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ЕЖЕМЕСЯЧНЫЙ НАУЧНЫЙ ЖУРНАЛ

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საქართველოს სამედიცინო სიახლენი

GEORGIAN MEDICAL NEWS

No 3 (156), 2008

This issue is dedicated to the memory of the prominent Georgian pediatrician Professor Irakli Pagava (1918-1988)

The editor of the issue: Karaman Pagava

Журнал посвящается видному грузинскому педиатру профессору Ираклию Карамановичу Пагава (1918-1988)

Редактор номера: Пагава К.И.

ЕЖЕМЕСЯЧНЫЙ НАУЧНЫЙ ЖУРНАЛ

ТБИЛИСИ - НЬЮ-ЙОРК

"Georgian Medical News" is a Georgian-Russian-English-German monthly journal and carries original scientific articles on medicine and biology, which are of experimental, theoretical and practical character.

"Georgian Medical News" is a joint publication of GMN Editorial Board and The International Academy of Sciences, Education, Industry and Arts (U.S.A.).

"Georgian Medical News" is included in the international system of medical information "MEDLINE" which represents the central electronic database of the world medical scientific literature. The journal is stored in the funds of US national library. It is listed in the catalogue of The Central Scientific-Medical Public Library of Russian Federation and world-wide catalogues: "*Ulrich's International Periodicals Directory"* and *"Medical and Health Care Serials in Print".* Articles from the bulletin are under review of *scientific and technological informative journal of the Russian Academy of Sciences.*

"Georgian Medical News" - ежемесячный научно-медицинский рецензируемый журнал, в котором на русском, английском и немецком языках публикуются оригинальные научные статьи экспериментального, теоретического и практического характера в области медицины и биологии, статьи обзорного характера, рецензии; периодически печатается информация о проведенных научных мероприятиях, новшествах медицины и здравоохранения.

"Georgian Medical News" является совместным изданием с Международной Академией Наук, Образования, Искусств и Естествознания (IASEIA) США.

"Georgian Medical News" включен в международную систему медицинской информации "MEDLINE", которая является центральной электронной базой данных мировой медицинской научной литературы. Журнал хранится в фондах библиотеки конгресса США; входит в каталог Государственной Центральной научно-медицинской библиотеки Российской Федерации и Всемирные каталоги *Ulrich's International Periodicals Directory и Medical and Health Care Serials in Print.* Статьи из журнала реферируются в реферативном журнале *Всероссийского института научной и технической информации Российской академии наук (ВИНИТИ РАН)* и хранятся в его базе данных по медицине.

"Georgian Medical News" - არის ყოველთვიური სამეცნიერო სამედიცინო რეცენზირებადი ჟურნალი, რომელშიც რუსულ, ინგლისურ და გერმანულ ენებზე ქვეყნდება ექსპერიმენტული, თეორიული და პრაქტიკული ხასიათის ორიგინალური სამეცნიერო სტატიები მედიცინისა და ბიოლოგიის სფეროში, მიმოხილვითი ხასიათის სტატიები, რეცენზიები.

"Georgian Medical News" წარმოადგენს ერთობლივ გამოცემას აშშ-ის მეცნიერების, განათლების, ინდუსტრიის, ხელოვნებისა და ბუნებისმეტყველების საერთაშორისო აკადემიასთან (IASEIA) ერთად.

"Georgian Medical News" შეყვანილია სამედიცინო ინფორმაციის საერთაშორისო სისტემა "MEDLINE"-ში, რომელიც წარმოადგენს მსოფლიოს სამედიცინო სამეცნიერო ლიტერატურის ცენტრალურ ელექტრონულ მონაცემთა ბაზას. ინახება აშშ-ის კონგრესის ბიბლიოთეკის ფონდებში; შესულია რუსეთის ფედერაციის სახელმწიფო ცენტრალური სამეცნიერო ბიბლიოთეკის კატალოგსა და საერთაშორისო კატალოგებში *"Ulrich's International Periodicals Directory"* და *"Medical and Health Care Serials in Print"*. ჟურნალში გამოქვეყნებული სტატიები რეფერირდება *რუსეთის მეცნიერებათა აკადემიის სამეცნიერო და ტექნიკური ინფორმაციის ინსტიტუტის* რეფერატულ ჟურნალში და ინახება მედიცინის მონაცემთა ბაზაში.

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With computer-printed texts please enclose a diskette carrying the same file titled with Latin symbols.

2. Size of the article, including index and resume, must be at least 5 pages and not exceed the limit of 10 pages of typed or computer-printed text.

3. Submitted material must include a coverage of a topical subject, research methods, results, and review.

Authors of the scientific-research works must indicate the number of experimental biological species drawn in, list the employed methods of anesthetization and soporific means used during acute tests.

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3. სტატიაში საჭიროა გაშუქდეს: საკითხის აქტუალობა; კვლევის მიზანი; საკვლევი მასალა და გამოყენებული მეთოდები; მიღებული შედეგები და მათი განსჯა. ექსპერიმენტული ხასიათის სტატიების წარმოდგენისას ავტორებმა უნდა მიუთითონ საექსპერიმენტო ცხოველების სახეობა და რაოდენობა; გაუტკივარებისა და დაძინების მეთოდები (მწვავე ცდების პირობებში).

4. ცხრილები საჭიროა წარმოადგინოთ ნაბეჭდი სახით. ყველა ციფრული, შემაჯამებელი და პროცენტული მონაცემები უნდა შეესაბამებოდეს ტექსტში მოყვანილს. ცხრილები, გრაფიკები – დაასათაურეთ.

5. ფოტოსურათები უნდა იყოს კონტრასტული; სურათები, ნახაზები, დიაგრამები - დასათაურებული და ტუშით შესრულებული. რენტგენოგრამების ფოტოასლები წარმოადგინეთ პოზიტიური გამოსახულებით. თითოეული სურათის უკანა მხარეს ფანქრით აღნიშნეთ მისი ნომერი, ავტორის გვარი, სტატიის სათაური (შემოკლებით), სურათის ზედა და ქვედა ნაწილები. სურათების წარწერები წარმოადგინეთ ცალკე ფურცელზე მათი N-ის მითითებით. მიკროფოტოსურათების წარწერებში საჭიროა მიუთითოთ ოკულარის ან ობიექტივის საშუალებით გადიდების ხარისხი, ანათალების შეღებვის ან იმპრეგნაციის მეთოდი.

6. სამამულო ავტორების გვარები სტატიაში აღინიშნება ინიციალების თანდართვით, უცხოურისა – უცხოური ტრანსკრიპციით; კვადრატულ ფჩხილებში უნდა მიუთითოთ ავტორის შესაბამისი N ლიტერატურის სიის მიხედვით.

7. სტატიას თან უნდა ახლდეს ავტორის მიერ გამოყენებული სამამულო და უცხოური შრომების ბიბლიოგრაფიული სია (ბოლო 5-8 წლის სიღრმით). ანბანური წყობით წარმოდგენილ ბიბლიოგრაფიულ სიაში მიუთითეთ ჯერ სამამულო, შემდეგ უცხოელი ავტორები (გვარი, ინიციალები, სტატიის სათაური, ჟურნალის დასახელება, გამოცემის ადგილი, წელი, ჟურნალის №, პირველი და ბოლო გვერდები). მონოგრაფიის შემთხვევაში მიუთითეთ გამოცემის წელი, ადგილი და გვერდების საერთო რაოდენობა.

8. სტატიას თან უნდა ახლდეს: ა) დაწესებულების ან სამეცნიერო ხელმძღვანელის წარდგინება, დამოწმებული ხელმოწერითა და ბეჭდით; ბ) დარგის სპეციალისტის დამოწმებული რეცენზია, რომელშიც მითითებული იქნება საკითხის აქტუალობა, მასალის საკმაობა, მეთოდის სანდოობა, შედეგების სამეცნიერო-პრაქტიკული მნიშვნელობა.

9. სტატიის ბოლოს საჭიროა ყველა ავტორის ხელმოწერა, რომელთა რაოდენობა არ უნდა აღემატებოდეს 5-ს.

10. სტატიას თან უნდა ახლდეს რეზიუმე ინგლისურ და რუსულ ენებზე არანაკლებ ნახევარი გვერდის მოცულობისა (სათაურის, ავტორების, დაწესებულების მითითებით და უნდა შეიცავდეს შემდეგ განყოფილებებს: შესავალი, მასალა და მეთოდები, შედეგები და დასკვნები; ტექსტუალური ნაწილი არ უნდა იყოს 15 სტრიქონზე ნაკლები) და საკვანძო სიტყვების ჩამონათვალი (key words).

11. რედაქცია იტოვებს უფლებას შეასწოროს სტატია. ტექსტზე მუშაობა და შეჯერება ხდება საავტორო ორიგინალის მიხედვით.

12. დაუშვებელია რედაქციაში ისეთი სტატიის წარდგენა, რომელიც დასაბეჭდად წარდგენილი იყო სხვა რედაქციაში ან გამოქვეყნებული იყო სხვა გამოცემებში.

აღნიშნული წესების დარღვევის შემთხვევაში სტატიები არ განიხილება.

Contents:

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REMEMBERING PROFESSOR IRAKLI PAGAVA (1918-1988)

Oniani[1] T, Manjavidze[2] N, Pagava[2] K.

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Prominent pediatrician, corresponding member of the Academy of Sciences of Georgia, Honored Scientist, Doctor of Medical Sciences, Professor Irakli Pagava has made an appreciable contribution to the development of Georgian medicine.

His scientific interests covered following areas: age-related physiology, experimental medicine, medical geography, medical and psychological border-line problems, problems of premorbid or disease-preceding states, history of medicine, scientific fundamentals of diagnostics and treatment of different diseases in childhood [1].

Already in 1940s I. Pagava was studying frequency of different non-infectious diseases in regions of Georgia. Afterwards, under his guidance a large-scale research was carried out in our country on prevalence and incidence of allergy, revealing modulating factors. This served to some extent as a basis for elaboration of principles of Georgia's medical mapping.

I. Pagava studied physiology of respiration at the early stages of ontogenesis, in newborns and infants in norm and pathology, peculiarities of external and tissue breathing in eutrophic and dystrophic children. He distinguished different stages of breath disturbance in infants' pneumonia. On the basis of the massive epidemiological studies he was one of the first to present us the normatives of arterial blood pressure for adolescents. He established dynamics of cardiovascular parameters since newborn period including the adolescence, peculiarities of functioning of hemato-encephalic barrier, brain biochemistry and cerebrospinal fluid in healthy eutrophic and dystrophic infants.

I. Pagava paid great attention to the problem of the so-called premorbid. Already in 1950s while determining normatives of arterial pressure in adolescents he singled out a group of children with labile arterial pressure, hyperreactors and expressed an opinion that these children might develop morbus hypertonicus in the future. This opinion was confirmed later on by his own investigations (he studied catamnesis of these teenagers) as well as by other authors. Nowadays there is no doubt that the significant part of the adult hypertension starts in the childhood. He also expressed an opinion and proved it later that a variant of constitutional anomaly: exudative-catharral diathesis might be considered as a premorbid of allergic diseases and even collagenoses. Nowadays this statement is also generally accepted. I. Pagava was one of the first to call for strict individualization of preventive vaccinations as in some cases they act as triggers for immunopathological reactions and corresponding diseases. Together with his disciples he carried out multiple researches in order to investigate how the immunological relationship between mother and foetus and specifically the ABO blood groups incompatibility affect child's health. He looked for the risk factors including topology of connective tissue which predetermines allergic predisposition in the adolescent's organism.

In former Soviet Union Irakli Pagava was one of the first who commenced to investigate psycho-neurosomatic relationships in pediatric clinic. Together with co-workers he laid the foundation for detection of psychological disturbances in different internal diseases in children and adolescents and establishment of their importance in etiopathogenesis of various nosological entities. He emphasized the psychological aspects of hypogalactia. Irakli Pagava's investigations on significance of Dimitri Uznadze's "Mood" phenomenon (in the frame of D. Uznadze's "set" theory) in pathogenesis and modulation of clinical signs in somatic and especially in infectious-allergic diseases in children are of high priority.

I. Pagava is author of numerous personalia, incl. monography dedicated to the famous public figures in medicine. In these articles he conveyed to us a mosaic but very informative picture of the newest history of the Georgian medicine. In the textbook "Children's Diseases" (Volume 1) a separate chapter is dedicated to the history of pediatrics in Georgia. Taking into account the affluence of facts, depth of the analysis and a volume, it can be considered as a separate, independent work culminating a large part of the research in this field up to our days.

While drawing a creative portrait of Irakli Pagava, one can not omit his pedagogical activities. During about 50 years he was a lecturer and then Professor of the Tbilisi State Medical Institute and working with youth was always one of his priority activities. His lectures-workshops,

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practical lessons, case studies, rounds were particular and attracted attention not only due to the high professionalism, comprehensive coverage, but also due to the innovative and original approach and artistic form. Gifted with oratorical skills and inner artistry, he was implementing the noble principles of deontology inconspicuously but efficiently. He was supervisor and consultant, impartial opponent and reviewer of up to 40 theses for the scientific degrees of Candidate of Medical Sciences and Doctor of Medical Sciences. His books "Manual of Pediatrics" and especially "Children's Diseases" (in 2 volumes) have become table books for many generations of Georgia's physicians and students.

Irakli Pagava was excellent practitioner too. He was attended by patients from all regions of Georgia, from different places of the former Soviet Union with complicated and rare diseases, resistant to the treatment. His erudition, extensive clinical experience, ability to pay attention to particularities and to interpret the facts which might have seemed inessential at first sight, intuition, knowledge of the modern therapeutical approaches but at the same time cautious, reserved and sometimes even skeptical approach towards them, ability to initiate quickly a contact with ill children and their parents, outstanding bedside manner, making a precise diagnosis and flawless determination of the treatment regimen: all this contributed to his success as diagnostician and physician and correspondingly to his popularity.

He described a new diagnostic sign in juvenile chorea: inability to restrain the palpebral reflex. He discovered a phenomenon of disappearance of cerebrolytic ability of cerebrospinal fluid in tuberculous meningitis that has quite a diagnostic significance. In 1948 he published a paper about the usage of corticosteroids in treatment of collagenoses. He proved scientifically the effectiveness of air-therapy in the respiratory diseases.

He studied in details influence of some resorts of Georgia such as Kobuleti, Borjomi, Bakhmaro on the reactivity of child's organism. Their indications and contra-indications were established. There was shown a positive effect of bathes with Tbilisi sulfuric water in the treatment of child rheumatic diseases.

It can be stated with the whole responsibility that in Georgia during almost 4 decades (1950-80s) no event in pediatrics took place, no issue related to the children health, development and care was solved without Irakli Pagava acting as an initiator, performer, or consultant. Founding of the Institute of Pediatrics (later Irakli Pagava's name was given to this institution), local, all-union and international pediatric congresses and conferences, circuit sessions, organizing Pediatric scientific Associations in Batumi and Sokhumi, actualities of children health care, opening and modernization of children hospitals and departments, of laboratory of problematic puberty, of psychological centre and of the center of pediatric acupuncture and laser therapy, leading the work of scientific-certification councils in pediatrics: everywhere he has made a considerable contribution.

Acting for the country and nation, Irakli Pagava did not limit himself to pediatrics or medicine only. He participated actively in the work of the regulatory commission of Georgian literary language, which was established by the government regulation. He was one of the leaders of the demographic commission at the Georgian Academy of Sciences. He dedicated a work "Many children are immortality of the nation" to this very painful topic.

Multiple articles in mass media, interviews, radio and TV appearances, lectures at the society "Tsodna" ("Knowledge"), activities in Tbilisi, Senaki, Martvili public universities – everywhere and every time he covered the most vital issues – demography, children's upbringing, hygiene, school and adolescent. He performed duties of the member of the editorial board of the Soviet Union Medical Encyclopedia, actively collaborated with the Georgian Encyclopedia, with the newspaper "Public education", was member of the editorial board of the journal "Soviet Medicine".

It is remarkable and even symbolic, that in 1987 at the congress of Georgian pediatricians, just one month before his death, I. Pagava did a presentation "Ilya Chavchavadze [leader of the national-liberating movement in Georgia in XIX century] on child health and upbringing". And the last interview with him, published after his death in February 1988, which might be considered as his testament was titled "On shaping a full-fledged person".

During his whole life Irakli Pagava worked without sparing himself for development of Georgian science and medicine, for the benefit of the younger generation. The scientific results achieved by him are considerable and some of them are even of the first priority. The problems highlighted by him such as premorbid, puberty, complementary medicine, immune relationship between mother and foetus, psychosomatic and somatopsychic conjunctions, are quite current even for the present-day pediatrics.

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SUMMARY

REMEMBERING PROFESSOR IRAKLI PAGAVA (1918-1988)

Oniani[1] T, Manjavidze[2] N, Pagava[2] K.

[1]Georgian Academy of Sciences; [2]Tbilisi State Medical University, Georgia

A short review of scientific-pedagogical and public activities of Professor Irakli Pagava, prominent Georgian pediatrician is presented.

РЕЗЮМЕ

ПАМЯТИ ПРОФЕССОРА ИРАКЛИЯ КАРАМАНОВИЧА ПАГАВА (1918-1988)

Ониани[1] Т.Н., Манджавидзе[2] Н.Ш., Пагава[2] К.И.

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В работе представлен краткий обзор научно-педагогической и общественной деятельности видного грузинского педиатра профессора И.К. Пагава.

НАУКА

AUTISM, THE BIG UNKNOWN

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Autism Spectrum Disorders (ASD) are described as lifelong neuro-developmental disorders due to neurobiological conditions [1,2]. Indeed, ASD is a broad concept that includes phenotypes related with the three main characteristics of autism - early onset of impairments in social interaction and communication and unusual, stereotyped behaviours - as defined by L. Kanner in 1943 [3].

DSM-IV-TR and ICD10 are the two major classifications that provide some criteria for the ASD diagnosis, although there are some overlaps between them, DSM-IV is more extensive for clinical diagnosis and ICD10 for population epidemiological studies [4-6]. The DSM-IV- TR includes as ASD diagnostic categories Autistic Disorder, Pervasive Development Disorder Not Otherwise Specified, Rett's Syndrome, Asperger's Syndrome and Childhood Disintegrative Disorder [7,8].

ASD are usually followed by a high degree of disability and dependence because they have very specific needs of support related specially with communication; also many times mental retardation and challenging behaviour are co-morbid with these disorders. It is important that paediatricians are able to recognize the signs and symptoms of autism spectrum disorders and have a strategy for assessing them systematically as well as able to manage the different situations that could be presented with ASD children and their families.

Epidemiology

A possible increase in time trend prevalence has been described in the last years. A review [9] of prevalence studies has contributed to explaining some of the influences on variation among prevalence estimates. The reasons for these differences have been postulated to be the inclusion of less restricted criteria for ASD diagnosis - changes in diagnostic criteria and development of the wider concept of the autistic spectrum - the different methods used in epidemiological studies; an increasing awareness among physicians and parents of ASD symptoms and the availability of services, rather than possible unidentified new environmental influences or risk factors. In spite of it all, the possibility of a real prevalence increase cannot be ruled out (Table 1).

The last prevalence report published [9] describes the prevalence and characteristics of children with ASD in the first CDC studies (2000 and 2002) [10,11] based on the ASD surveillance program among 8 years-old children. The resulting prevalence (using the 2000 and 2002 combined denominator 47,726) was 6.2 per 1,000 children (95% CI 5.1-7.1), where boys were more commonly affected than girls (3.1:1).

Table 1. ASD epidemiological studies

Study Authors	Population	Age	Location	Results	
Bertrand et al.2001	8,896	3-10 y.o.	Brick Township, New Jersey	40.5 per 10,000	
Baird et al. 2005	16,235	18m	South East Thames Health Region	Typical autism: 30.8 per 10,000 (95 percent CI: 22.9–40.6) PDDNOS: 27.1 per 10,000 (95 percent CI: 19.7–36.4).	
Chakrabarti S & Fombonne E 2001 & 2005)	15,500	2.5-6.5 y.o.	Staffordshie, England.	PDD: 62.5 per 10,000 (95 percent CI: 50.8–76.3) AS: 8.4 (95 percent CI: 4.5–14.3) per 10,000. PDD-Nos: 36.1 (95 percent CI: 27.3–46.9) per 10,000	
CDC (2007)	--	8 y.o.	6 states of USA	Range: From 1 ASD / 222 to 1 ASD / 101	AVERAGE: 6.6 and 60.7 per 10,000 1 ASD / 101
CDC (2007)	407,578	8 y.o.	14 states of USA	Range: From 1 ASD / 303 to 1 ASD / 94	
Joyce S.(2008)	25,000	8 y.o.	SC ADDM (South California Autism and Developmental Disabilities Monitoring Program)	60.2 per 10000 children (using the 2000 and 2002 combined denominator 47,726) (95% CI 5.6–7.0)	

The rapid change in prevalence of ASD from 4/10,000 to 62/ 10,000 children in the last 20 years continuous calling the attention of scientific community. Although criteria set and awareness to define autism have changed over the years, these changes could not explain major differences in reported prevalence over time.

The causes and contributing factors for autism are poorly understood and the mechanisms of pathogenesis have yet to be delineated. Contrary to early beliefs that autism resulted from bad parent–child interactions [12], it is now widely accepted that aberrant brain development underlies autism pathogenesis [13-16].

ASD are heterogeneous in terms of aetiology, age of onset, manifestation of symptoms, outcome, and co-morbidity and disability with other disorders and there is no unique risk factor that unifies the understanding of the causation of autism [17].

Genetic studies have been intensively developed during the last 5-10 years but with unequal results. Several markers have been identified in most of the chromosomes although chromosome 2, 7 and 15 and very recently chromosome 11p12–p13 [18] and lastly the chromosome 16 [19] are showing the most prominent and interesting findings. Other studies have been focused on inborn metabolic errors because in some metabolic rare diseases the prevalence of autism features is high [20].

Environmental causes such as chemical exposures to heavy metals as well as persistent organic pollutants (POPs) [21], and side effects from drugs as well as virus infectious, perinatal factors and some congenital malformations [22] have been suggested as potential causes for autism. It is likely that further understanding will require consideration of critical windows during gestation and possibly early infancy, as well as interactions between genetic or epigenetic predisposition and environmental factors [17].

Biotechnological progress in all of these areas as well as cooperative research among environmentalists and genetic scientists will lead to promising results on the etiological research of autism in the next future [21,23].

Autistic disorder is the most severe form of autism spectrum disorders (ASDs). Approximately 70% of individuals with autistic disorder have some degree of mental retardation, and about half are nonverbal or have very impaired speech. Research has shown that children with autism and their families have compromised quality of life (QOL) [24] most individuals with autism cannot live independently as adults [25] and these disorders are always linked to a considerable the public health burden. Burden of Disease (BoD) is an important measurement and a good health indicator that summarizes two important pieces on health information: premature mortality and life lived with disability, allowing the quantification of the lost health in the population and the comparison between different populations [26].

Although a higher mortality risk has been observed in autism compared with the general population, there are no deaths caused directly by the condition. Elevated death rates are due to several causes, including seizures, accidents and respiratory diseases among people with severe learning disability [27-30].

Surveillance and screening

The present lack of reliable data in respect of the ASD prevalence adversely affects the identification and development of pan-European strategies that could assist to provide to families an earlier diagnosis, a better access to appropriate treatment and a good estimate of the societal and family costs.

A European project funded by DG SANCO entitled "European Autism Information System – EAIS" [31] is now being developed in order to address the need of early detection and the changes in the ASD prevalence across the European countries. Its main mission is to improve the quality of life of children, adults and families affected by ASD, through early diagnosis of the condition and the creation of a reliable information system on ASD for Europe, which will promote the development of government policies to facilitate appropriate and effective treatments and services.

For the time being, although retrospective reports suggest that most parents identify ASD symptoms before 18 months of age [32] and that a diagnosis of autism can be reliably made between 2 and 3 years of age, ASD diagnoses are often delayed until mid-childhood. Child Neurology Society practice parameter on screening and diagnosis of autism suggests that the following "red flags" are absolute indications for immediate evaluation [33]:

no babbling or pointing or other gesture by 12 months;
no single words by 16 months;
no 2-word spontaneous (not echolalic) phrases by 24 months;
loss of language or social skills at any age.

General developmental screening tools are appropriate for using with unselected primary care populations and are likely to detect ASD in many young children because of associated language and cognitive delays, but they do not differentiate children with ASD from those with other developmental disorders, and data are not available on sensitivity for detection of ASD. Tools to screen specifically for ASD also have been designed (Table 2).

Table 2. Selected Screening Measures

Instrument/ Author	Age	Time to complete	Sensibility/ Specificity	Availability
CHAT. Baron-Cohen et al., 2000	18m	5min.	0.38/0.99	www.autismresearchcentre.com/tests/chat_test.asp
M-CHAT. Robins et al., 2001	16-30m	5-10min.	0.87/0.99	www.firstsigns.org/downloads/m-chat.pdf; www.firstsigns.org/downloads/m-chat_scoring.PDF
CAST Scott et al, 2002	4-11y.o.	10min.	0.88-1.0	www.autismresearchcentre.com/tests/cast_test.asp
PDDST-II. Siegel B., 2004	12-48m	10-15min.	0.92/0.91	PsychCorp/Harcourt Assessment(www.harcourtassessment.com)
CHAT-23. Wong et al., 2004	18-24m	---	0.84/0.85	--

The M-CHAT [34], was designed as a screening tool to detect high risk ASD children. Although this tool is broadly used, there is not enough information about the feasibility and validity in a population-based study. At the moment, the Spanish ASD Study Group [35] is involved in the transcultural adaptation of this tool into Spanish language, adopting the original MCHAT criteria and a refining procedure for the phone call after agreement with the authors.

Clinical signs and diagnosis

Whereas severe social skills deficits and restricted, repetitive, and stereotyped patterns of behaviour, interests, and activities are core features of all ASD, significant language delays are characteristic of only AD and PDDNOS. One of the most challenging aspects in recognizing ASD are the wide heterogeneity of features in individual children. There is no pathognomonic feature; however, a few of the early social deficits (eg, delayed or absent joint attention) seem to be fairly reliable red flags for ASDs. The autism spectrum encompasses an extremely heterogeneous phenotype with indistinct end points, especially at the mild end of the spectrum. The severity of each of the core deficits varies significantly among children with ASDs.

Some cases are detected because of a developmental regression; approximately 25% to 30% of children with ASD begin to say words but then stop speaking, often between the ages of 15 and 24 months [36].

There is ongoing debate over whether a categorical or dimensional conceptualization is appropriate for ASD. The difficulty of such categorical conceptualization, or indeed a bimodal conceptualization, is that the definition of the case may be somewhat arbitrary [37]. Thus, a dimensional conceptualization of ASD is now commonly invoked.

The diagnosis of autism as distinct from other develop-

mental disabilities requires a comprehensive multidisciplinary approach [33]. The evaluation should include measures of parental report, child observation and interactions, and clinical judgment. Assessments should include cognitive, adaptive behaviour and specific autism diagnostic measures (Table 3).

Table 3. Selected diagnosis instruments

Aspects Evaluated	Type of test	Instrument/ Author	Age
Autism symptoms	Parents interview	GARS (Gilliam, 1995)	3-22 y.o.
		ADI-R (Le Couteur et al., 1989;Lord et al. 1994)	>18m. (mental age)
	Observation Instrument	CARS (Schopler et al., 1988)	>24m.
		ADOS-G (DiLavore, Lord & Rutter, 1995)	>36m. (mental age)
Speech/Language Development	Parents interview	MacArthur Communicative Develpment Inventories (MCDI; Fenson et al.,1993)	
	Observation Instrument	Communication and Symbolic Behaviour Scales (CSBS; Wetherby & Prizant,1993)	It is applicable for non verbal children
Cognitive Development	Observation Instrument	Bayley Scales ofInfant Development II (1993)	<42m.
		Leiter-Revised (Roid & Miller, 1997)	
		Merril-Palmer R (Roid y Sampers, 2004)	
Adaptative Behaviour Level	Parents interview	Vineland Adaptative Behavior Scales (Sparrow et al., 1984)	0-18 y.o.

Treatment

The National Research Council recommends intervention at the time the diagnosis is initially suspect [38].

Due to the inexistence of an aetiology based intervention for Autistic Spectrum Disorders (ASD) families and professionals are exposed to diverse and sometimes conflictive recommendations when they have to decide the most adequate alternative for treatment. For the first time in Spanish and updated to 2007 an ASD Study Group from the National Institute of Health Carlos III has analyzed and reviewed more than 20 different interventions summarizing scientifically afterwards treatment guidelines for this population [39]. At this time there is not a treatment algorithm with an accurate available evidence. In general, based recommendations of each intervention are in the weaker degrees of EBM classifications. Nevertheless, there is widespread agreement to stress that education, with special incidence in the development of communication and social competence, with community support are the main means of treatment nowadays. Depending on individual needs, this can be complemented, with medication, behavioural approaches and cognitive behavioural therapy for associated psychological problems in persons with higher cognitive level.

Support to families and community empowerment are essential elements for the quality of life of persons with ASD.

It is clear that the road ahead is very challenging. ASD is now the second most frequently occurring serious developmental disability in the United States after mental retardation [9]. Paediatricians should become concerned if children show deficits or delays in milestones or if behaviours typical of ASD are observed during an office visit. A variety of general developmental screening tools are available to practitioners. In an ideal world, developmental surveillance would be practised by paediatricians from infancy and families would not have to wait long periods for diagnostic assessments.

It is also very important that paediatricians know how to deal with the difficulties that these disorders could present. In the same way, they must be aware of local resources that can assist in making a definitive diagnosis and in managing, ASD.

It is argued that research into autism has a priority in the broader field of developmental psychopathology because it carries the promise of throwing light on causal mechanisms that apply beyond the syndrome of autism [40].

In conclusion, there are several difficulties and challenges to understand the magnitude of ASD such as a better case definition, the prevalence of the disorder, the social consequences of this disability, the need of good screening and diagnostic tools and new medical and educational interventions. Despite major difficulties autism research should continue to offer hope. It will help to direct decisions by policymakers, raise interest among researchers, and help to develop better and a wider range of evidence-based intervention techniques.

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SUMMARY

AUTISM, THE BIG UNKNOWN

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Autism is a common disorder of childhood. Yet, it often remains unrecognized and undiagnosed until or after late preschool age because appropriate tools for routine developmental screening and screening specifically for autism have not been available. Paediatricians have an important role in early recognition and evaluation of autism spectrum disorders because they usually are the first point of contact for parents. It is important that paediatricians are able to recognize the signs and symptoms of autism spectrum disorders and have a strategy for assessing them systematically. But paediatricians have also a role in chronic management of these disorders. The objective of this paper is to show a general view of the autism spectrum disorders (ASD) state of knowledge nowadays as well to stress the need of early detection and treatment of these disorders in order to improve better evolution and prognosis.

Key words: autism, autism spectrum disorders, epidemiology.

РЕЗЮМЕ

АУТИЗМ – БОЛЬШОЕ НЕИЗВЕСТНОЕ

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Аутизм достаточно частое заболевание у детей. Однако, часто остается нераспознанным и недиагносцированным вплоть до или после позднего дошкольного возраста ввиду того, что необходимые методы для скрининга нарушений развития и, в особенности, специфичных для выявления аутизма недостаточно доступны. Педиатры играют значительную роль в раннем распознавании и оценке спектра нарушений, характерных для аутизма, так как они первыми контактируют с родителями. Весьма важно, чтобы педиатры умели распознавать признаки этих нарушений и имели стратегию их систематической оценки. В то же время педиатры должны уметь обеспечивать постоянный контроль этих нарушений. Цель статьи - представить современное состояние вопроса, подчеркнуть значение ранней диагностики для успешного лечения болезни и прогноза.

ЛЕЧИТЬ ИЛИ НЕ ЛЕЧИТЬ ПОДРОСТКОВ С СИНДРОМОМ ВЕГЕТАТИВНОЙ ДИСТОНИИ?

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Синдром вегетативной дистонии (СВД), в том числе у детей и подростков, в настоящее время определяется как нарушение вегетативной регуляции работы внутренних органов (сердечно-сосудистой системы, органов пищеварения, дыхания, желез внутренней секреции и др.), сложного взаимодействия сегментарных, надсегментарных и автономных местных вегетативных структур [4,5].

Вопрос о сути СВД и его наиболее распространенном варианте нейроциркуляторной дистонии (НЦД) у детей не имеет однозначного восприятия в педиатрической среде, а тем более у специалистов разных направлений. В дискуссии, развернувшейся на страницах журнала «Педиатрия» [8]. СВД рассматривается преимущественно как пограничное состояние между здоровьем и болезнью, своего рода континуум переходных состояний.

СВД в медико-биологическом плане рассматривается как отклонение уровня здоровья, с точки зрения статистики – заболевание (фиксируется выборочно), в клиническом отношении - функциональное состояние. Диагноз верифицируют как первичную соматоформную дисфункцию вегетативной нервной системы (МКБ Х- F45), нейроциркуляторную астению (G 90), гипотензию (I 95) или как вторичный синдромокомплекс в результате психоэмоциональных воздействий, травм, перенесенных соматических заболеваний, эндокринной перестройки. СВД – обязательный компонент так называемых пограничных состояний у подростков – расстройств адаптации, хронического стресса, заболеваний на стадии начальных или субклинических проявлений, неврозов, «малых» психических расстройств, диатезов и т.д. [1,7,9].

В подростковой практике чаще приходится сталкиваться с полиорганным вариантом или непосредственно с СВД. Нередки случаи изолированного поражения отдельных органов или систем. Типичным представителем последних является НЦД – частное проявление дистонии автономной нервной системы, при котором имеются дизрегуляторные изменения преимущественно в сердечно-сосудистой системе.

На практике применяется клиническая классификация СВД, предложенная еще в 1986 году Белоконь Н.А., Кубергер М.Б. [2]. Но на практике у подростков чаще диагностируют и соответственно корригируют изолированные клинические варианты СВД, такие как вегетативная астения конституционально обусловленная, НЦД, синдром нейрогенной гипервентиляции, венозные церебральные дисрегуляции, функциональная диспепсия, дисфункция билиарного тракта, синдром раздраженного кишечника, нейрогенный мочевой пузырь и др.

Типичными клиническими маркерами СВД признаны цефалгии, кардиалгии, «кишечная колика», термоневроз, синкопе, вестибулопатия, метеочувствительность, десинхроноз. Все эти состояния, наблюдаемые в подростковом возрасте, обычно характеризуются разнообразной, длительной, трудно купируемой медикаментозными средствами, клинической симптоматикой.

Вегетативно-сосудистая дисфункция у подростков часто протекает на фоне дисморфогенеза, что касается как артериальных, так и венозных дисциркуляций, определяющих характер сосудисто-мозговой недостаточности [13]. Обязательно исключают малые аномалии развития сердца, прежде всего пролапс митрального клапана и др. [3].

Комплекс исследовательских методик, используемый у подростков для выявления СВД, достаточно обширен. Ведь СВД – диагноз исключения. Поэтому в круг обследования обычно включают психоневрологические, кардиологические, уронефрологические, гастроэнтерологические и, по показаниям, иные исследования. Не следует забывать о возможности атипичного течения инфекционных заболеваний. Среди обязательных методик - кардиоинтервалография и функциональные тесты с физической нагрузкой. Диагностическое значение имеет определение у детей и подростков с вегетативными дисфункциями содержания оксида азота в периферической крови [11].

В окончательном варианте необходимо решить, кто из специалистов будет курировать больного. Предпочтительно, чтобы эту миссию выполнял врач-педиатр или семейный доктор; узкие специалисты привлекаются к составлению схемы этапной терапии и профилактики. Исключение - первичная кардиальная, психоневрологическая или гастроэнтерологическая патология. По мнению Румянцева А.Г. и Панкова Д.Д. [14], чтобы исключить «бег» больного СВД по специалистам следует готовить врача-вегетолога.

Вопрос в заголовок статьи вынесен не случайно: лечить или не лечить подростков. Все связано воспринимает ли врач СВД как болезнь или нет. Не все врачи серьезно оценивают последствия проблемы переходных состояний, считая СВД своего рода болезнью роста. Однако, создание устойчивых патогенных систем (УПС) в высших отделах нервной системы в подростковом возрасте легко воспроизводимо в более старшем. Поэтому следует признать необходимость обследования и своевременного лечения таких подростков. Однако возникает другая проблема – «не залечить».

В большинстве случаев лучше идти по схеме постепенного увеличения лечебных нагрузок, т.е. начинать с малых, лучше немедикаментозных назначений. Но при наличии серьезных клинических проявлений (синкопе, симпатикоадреналовые или вагоинсулярные кризы), ограничиться немедикаментозными назначениями вряд ли удастся, поэтому используют преимущественно другой принцип: «от большого к малому».

Лечение всегда комплексное и учитывает исходный вегетативный тонус. Включает строгий режим дня, полноценный отдых, рациональное питание, регулирование физических и умственных нагрузок, психотерапию, физиотерапию, фитотерапию, медикаментозное лечение (транквилизаторы, нейролептики, нейрометаболические стимуляторы). Лечебная помощь при вегетативных кризах у детей учитывает характер криза.

Таблица 1. Неотложные и плановые назначения при вегетативных кризах у детей

Симпатикоадреналовый криз	Вагоинсулярный криз
Психотерапия и седативная фитотерапия	Психотерапия и седативная фитотерапия
Транквилизаторы – седуксен, реланиум	Амизил
Сонапакс	Адаптогены – настойка элеутерококка, женьшеня и др.
Седуксен+сонапакс	Беллоид, беллатаминал
Пирроксан	Антигистаминные препараты (при аллергии)
Обзидан (0,5-1 мг/кг-разовая доза)	Атропин п/к

Таблица 2. Методы физиолечения детей, больных СВД

Процедуры	Ваготония	Симпатикотония
Лекарственный электрофорез на воротниковую зону	5% р-р Са хлорида 1% р-р кофеина 1% р-р мезатона	2% р-р эуфиллина 2% р-р папаверина 4% р-р Mg сульфата 1% р-р дибазола
ПеМП	-	+
Электросон	Импульсный ток с частотой до 100 Гц	Импульсный ток с частотой до 10 Гц
Терморелаксация в альфа-капсуле	-	+

Таблица 3. Методы водолечения детей, больных СВД

СВД / Методы	Ваготония	Симпатикотония
Ванны	Кислородные Солено-хвойные Жемчужные С настоями из березового, смородинового листа, белокопытника	Углекислые Сульфидные Йодо-бромные Сухие радоновые Шалфейные С настоями из мяты, хвои, валерианы, с сушеницей (ножные)
Души	Циркулярный Игольчатый Контрастный Струевой Душ Шарко Подводный душ-массаж (старший возраст)	Пылевой Дождевой Циркулярный Веерный

В «межприступный период» на основе сохранения рационального режима дня методики выбора: адаптогены, ноотропные средства, коэнзим Q, санация хронических очагов инфекции, неспецифические средства воздействия и т.д. В последние годы большое значение придают коррекции внутриклеточного энергообмена у детей с нарушениями вегетативного гомеостаза, причем в качестве средств рекомендуется комплексное применение пантогама и элькара [12].

Для восстановления регуляторных функций необходимы полноценный сон, занятия гимнастикой, ЛФК, массаж. Режим питания включает: кратность, разнообразие продуктов, контроль водной нагрузки, обязательные витамины и микроэлементы, при необходимости назначают лечебные столы. Исключают высококалорийные продукты.

В детской практике используется широкий набор альтернативных методов лечения СВД, что во многом определяется возможностью лечебной базы и наличием обученных специалистов. К базисным методам лечения относятся:
физиотерапия (водолечение, электросон, лазеротерапия, электрофорез лекарственных веществ и др.);
кинезитерапия (ЛФК, массаж и др.);
мануальная терапия и остеопатия, рефлексотерапия-иглоукалывание;
энтеросорбция, «галотерапия», сенсорная комната, альфа-капсула, стоунтерапия;
фитотерапия, гомеопатия;

апи-, гирудо-, иппотерапия;
лечебная педагогика, психосоматическая медицина, биологическая обратная связь;
санаторно-курортное лечение, метеопрофилактика, закаливание и др.

Выбор конкретной методики физио- и, особенно водолечения, определяется характером вегетативных изменений сердечно-сосудистой системы у больного ребенка (таблица 2 и таблица 3).

Седативная терапия обычно базируется на средствах растительного происхождения. Препараты выбора: валериана, пустырник – обычно экстракты, травы – экстракт пассифлоры жидкий, зверобоя – негрустин, комбинированные средства – санасон, персен, дормиплат, новопассит, а также фитосборы – шалфей, боярышник, валериана, пустырник, зверобой и др. комбинации, фиточай, коктейли, бальзамы.

Поскольку при СВД часто регистрируется повышенная метеочувствительность, то практическое значение имеет применение специальных мер метеопрофилактики, включая баротренировки [6, 10].

Выделим необходимые условия для эффективного восстановительного лечения детей и подростков с СВД, используемые в условиях клинической практики:
выполнение индивидуальной программы терапии, учитывающей особенности болезни, конституции, реактивности организма, в том числе переходных состояний;
строгое и последовательное выполнение комплекса режимных и лечебных мер, включая восстановительный период (использование санаторно-курортных факторов);
профилактика «рецидивов» и участие в индивидуальной программе оздоровления.

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SUMMARY

IS THERE ARE NEEDS TREATING THE ADOLESCENTS WITH SYNDROME OF VEGETATIVE DYSFUNCTION?

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Article presents the pathogenesis aspects and clinical data of adolescents with syndrome of vegetative dysfunction. The authors observe the structure of different clinical forms, reflect on conditions and situation, when adolescents needs a stable complex of etiopathogenetic therapy to control autonomic nervous system dysfunction.

Key words: adolescents, syndrome of vegetative dysfunction, nervous system.

РЕЗЮМЕ

ЛЕЧИТЬ ИЛИ НЕ ЛЕЧИТЬ ПОДРОСТКОВ С СИНДРОМОМ ВЕГЕТАТИВНОЙ ДИСТОНИИ?

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В статье представлены патогенетические аспекты и клинические проявления у подростков с синдромом вегетативной дистонии. Описывается структура различных клинических форм, обсуждаются обстоятельства, при которых подростки нуждаются в комплексе этиопатогенетических мероприятий с целью нормализации дисфункции автономной нервной системы.

ASSESSMENT OF TRAUMATIC BRAIN INJURY AND ANTERIOR PITUITARY DYSFUNCTION IN ADOLESCENTS

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Traumatic brain injury (TBI) is a non-degenerative, non-congenital insult to the brain from an external mechanical force causing temporary of permanent neurological dysfunction, which may result in impairment of cognitive, physical and psychosocial functions [5,6].

The overall incidence of TBI in developed countries is about 200/100.000 population per year [17]. The highest incidence of TBI is among subjects aged 15-24 years. Incidence rate for males is almost twice that for females, with the highest male:female ratio occurring in adolescence and young adulthood (1.2:1 and 4.4:1, respectively).

Data from the Italian Ministry of Health show that approximately 300-500 per 100.000 Italians are admitted to hospital each year for either TBI or subarachnoid haemorrhage with an annual mortality of 20 per 100.000; 90% of these TBI are of medium severity [2].

Approximately 50% of TBI in adolescents are the result of motor vehicle, bicycle falls and sports accidents.

TBI has been associated with hypopituitarism and precocious puberty. Hypopituitarism may be either partial or complete and its clinical manifestation may be mild, moderate or severe depending on the number of pituitary hormones affected, rapidity of its onset and age of the patients.

In adults, the prevalence of specific pituitary deficits observed in TBI patients with pituitary dysfunction is as follows:

- growth hormone deficiency (mean: 30.1%; range 14.6% - 60%);
- gonadotrophin deficiency (mean 28.8%; range 2.1% - 62.5%);
- corticotrophin deficiency (mean 18.5%; range 0 – 44.8%);
- thyrotrophin deficiency (mean 18.5%; range 3.6% - 31%).

Nearly 75% of patients have an isolated hormonal deficiency, 21.9% a multiple deficits and 3.4% of patients have panhypopituitarism [5,6]. Diabetes insipidus (DI) is present in 2.7% of patients.

The frequency of these complications in adolescents and young adults is not yet well known. From a systematic review of the literature we found only few case reports or small case series highlighting a link between TBI and the occurrence of hypothalamic-pituitary hormone abnormalities [1,10-12,16,17,19,20].

Aimaretti et al [4] studied a population of adolescents and young adults 3 and 12 months after TBI. At 3 months, hypopituitarism was present in 34.6%. Total, multiple and isolated deficits were present in 8.6, 4.3 and 21.7%, respectively. DI was present in 8.6% patients and mild hyperprolactinemia in 4.3%. Unlike the previous study in adult population, the follow up at 12 months after TBI demonstrated a substantial stability of the pituitary alteration or normal pituitary function.

Recently, Bondone et al [7] studied the occurrence of hypothalamic-pituitary dysfunction (HHD) in 65 patients (age: 10-18 years) hospitalized in the Neurosurgical and Intensive Care Unit of Regina Margherita Children's Hospital (Turin): 22 patients have been evaluated within the first 72 hours from TBI, 43 patients 1 year or more after TBI. Among the 22 patients evaluated in the acute phase of TBI, 6 (27%) had HHD: 2 had low T3 syndrome, 2 cerebral salt wasting syndrome and 2 both the conditions. Among the 43 patients evaluated 1 or more years after TBI, 6 (14%) had HHD: 3 had GH deficiency, 1 ACTH deficiency, 1 LH e FSH deficiency, 1 precocious puberty [7].

In the past, the risk of developing pituitary dysfunction was considered as strictly dependent on the severity of TBI, particularly when associated with skull and facial fractures, cranial nerve injury and a prolonged period of unconsciousness [8,10]. Nevertheless, some patients with mild TBI may develop a HHD [1,13,17].

Classification of the severity of head injury

The Glasgow Coma Scale (GCS) is the most widely used clinical classification of TBI severity [18]. GCS is based on the patient's response to various stimuli (Table 1). Clinical severity of TBI is also defined by duration of loss of consciousness, loss of memory for events immediately before or after the accident and identified intracranial lesions [5].

Table 1. Glasgow Coma Scale score

Eye-opening response	
Spontaneous	4
To speech	3
To pain	2
No response	1
Verbal response	
Oriented	5
Confused conversation	4
Inappropriate words	3
Incomprehensible words	2
No response	1
Best upper limb motor response	
Obeys commands	6
Vocalizes pain	5
Withdraws	4
Abnormal flexion to pain	3
Abnormal extension response to pain	2
No response	1

A GCS score ≤ 8 indicates severe TBI, whereas 9 to 12 indicates moderate TBI and 13 to 15, mild TBI. One of the limitation of GCS is that it can be 15 (normal) even after a mild TBI. As a result, using the GCS score as an assessment of injury severity in this group is difficult.

Table 2 classifies the severity of intracranial injuries on the basis of the child's history and the findings at physical and neurological examination. The inclusion of the GCS provides more information to assist in triage, treatment and prediction of outcome.

Table 2. Classification of severity of intracranial injury

MILD	Asymptomatic. Mild headache Three of fewer episodes of vomiting Glasgow Coma Scale score of 13 to 15 Loss of consciousness for less than 5 minutes
MODERATE	Loss of consciousness for 5 minutes or more Progressive lethargy Progressive headache Vomiting protracted (more than three times) or associated with other symptoms Post-traumatic amnesia Post-traumatic seizure Multiple trauma Serious facial injury Signs of basal skull fracture Possible penetrating injury or depressed skull fracture Suspected child abuse Glasgow Coma Scale score of 9 to 12
SEVERE	Glasgow Coma Scale score of 8 or less Focal neurologic signs Penetrating skull injury Palpable depressed skull fracture Compound skull fracture

The GCS score and cranial computed tomography (CT) are the current gold standards for assessment of injury severity after pediatric TBI. To address limitations of GCS score and TBI in mild head trauma recent studies have focused on the use of serum biomarkers of brain injury, such as neuron-specific enolase and S100B, released from the neurons and glial cells, after brain injury [15].

History-taking and physical and neurologic assessment. The most important personal history information includes mechanism (if known), time of occurrence of the injury, level of consciousness after TBI, subsequent mental status, the occurrence of post-traumatic seizures, and intervention before arrival [22].

These procedures are invaluable to determine the severity of the intracranial injury, to identify those at risk for secondary injury and to identify injuries to other regions that may contribute to illness and death [18,22].

Nevertheless, clinical reports may be inconsistent and hence unreliable. Fortunately the progression of symptoms provides invaluable information to assist the physician for the clinical evaluation. A brief seizure at the time of injury may not be clinically significant and may necessitate therapy. However, one or more prolonged seizures associated with cardiorespiratory compromise necessitates prompt treatment. Many children will vomit two to three times after even a minor head injury. However, protracted vomiting and retching associated with other symptoms or signs indicate a more severe head injury. Amnesia, irritability, lethargy, pallor or agitation may also indicate severe injury [18,22].

Table 3 may help clinicians for the physical and neurological examination.

Table 3. Features of physical and neurologic examination of adolescents with head trauma

Physical examination	Determination of vital signs Investigation for signs of skull fracture Hematotympanum Periorbital or postauricular ecchymosis Cerebrospinal fluid otorrhea or rhinorrhea Depressed fracture or penetrating injury
Neurologic examination	Glasgow Coma Scale score Pupillary reflexes Cranial nerve examination Movement of extremities

Pathophysiology of head injuries.
The pathophysiology of head injuries can be subdivided into two types: primary and secondary injury.

The injury directly caused by the mechanical force of the trauma is called primary injury. This type of injury is due to shear force, direct contact, and tissue penetration.

Secondary injury is created by the body's response to the primary insult. In secondary injury excitation neuropeptides, cytokines, free radicals, metabolic and oxygenation insufficiencies cause further tissue damage.

Both primary and secondary injury can be focal or diffuse. Focal injury tends to be caused by contact forces, whereas diffuse injury is more likely to be caused by non-contact, acceleration-deceleration and rotational forces. Rotational acceleration-deceleration can induce shearing injury of the axons, with disruption of the white matter and widespread damage, most likely vasogenic. Shearing injury is most often seen in midline structures of the brain and may represent a possible mechanism of hypothalamic-pituitary dysfunction in TBI [14,18].

It is important to realize that unlike injuries in other parts of the body, injury to the brain occurs within a confined volume, the intracranial space. The intracranial space is made up of three components: brain volume (90%), blood volume (5%) and cerebral spinal fluid volume (5%). Initially, as the brain swells in response to injury, the increase in brain volume is accommodated by a reduction of cerebral spinal fluid volume, and then blood volume. However, in the finite space of the calvarium, the mass effect caused by acute brain edema and hemorrhage may reach a point at which this volume can no longer be accommodated. Intracranial hypertension, or elevated intracranial pressure is harmful as it can decrease cerebral perfusion, inciting further hypoxia and cell death [14,18].

Assessment of pituitary function.
Different autopsy studies have reported in 26%-86% of patients, who died from TBI, an injury to the hypothalamus, pituitary gland or pituitary stalk. Structural abnormalities in the hypothalamus and the pituitary commonly include anterior lobe necrosis, posterior lobe haemorrhage or stalk laceration. Trauma-mediated vascular injury to the hypothalamus may be the basis of the TBI-mediated hypopituitarism, although pituitary lesions are also a prominent factor.

Hypothalamic lesion have been reported in > 50% of head trauma cases, affecting hypothalamic nuclei and resembling the lesions found in ruptured cerebral aneurysms. Pituitary function is at particular risk because of the vulnerable physiologic location of the gland within the sella turcica as well as its delicate infundibular hypothalamic structure and its fragile vascular supply.

At present, there are no studies that suggest injuries of a certain type or in a certain location are more likely to produce hypopituitarism [3,5,6,8,13,14].

Although the correlation between the autopsy and the biochemical results is unknown, the autopsy [3] and func-

tional studies [5,6] are sufficient to justify a systematic evaluation of patients with TBI.

Anterior pituitary hormone abnormalities may remain stable, may improve or deteriorate in the first 6-12 months following head injury. Therefore, a periodic endocrine evaluation and monitoring in patients with head trauma are recommended.

Agha and Thompson [3] have proposed a follow-up plan for patients with TBI, which is summarized in figure.

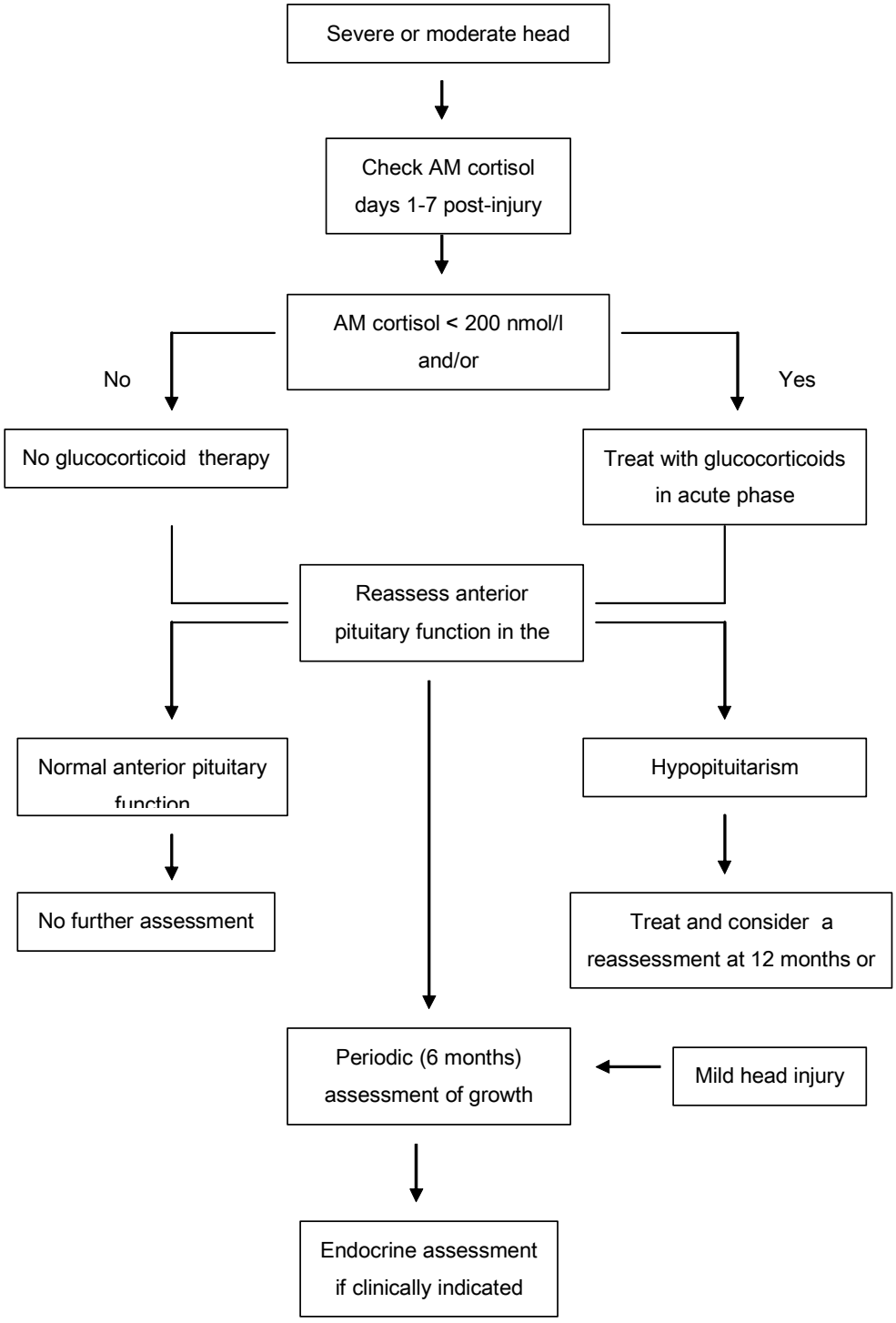

Figure. Suggested algorithm for growth and endocrine assessment in adolescents after traumatic brain injury (from reference 3, modified)

Traumatic brain injury-induced hypopituitarism in adults are more common than previously thought. The paucity of clinical reports relating to adolescents with past-TBI induced hypothalamic-pituitary-dysfunction suggests that this phenomenon might be less common that that observed in adults. Such a difference may be due to different selection criteria and diagnostic procedures, but also to the reduced susceptibility of adolescents to the mechanical vascular damage of pituitary and stalk. Coma severity ,depressed cranial fractures and bad outcome don't apparently represent risk factors for HHD, on the contrary, cerebral lesion on CT scan might have a prognostic relevance for endocrine sequelae [7]. In the last 25 years, in our Unit a pituitary dysfunction was established in 3 patients during childhood and adolescence (one patient had a precocious puberty, one patient had a gonadal dysfunction and one patient had a partial growth hormone deficiency). In all patients the TBI was classified as severe (unpublished data, 2008).

Kabi International Growth study (KIGS) support this hypothesis. Over a 20-years period (1986-2006) only 141 cases were registered as having GH deficiency secondary to TBI compared to 23.722 registered with idiopathic GH deficiency (KIGS - unpublished data, 2006).

The physiopathological basis of hypopituitarism is lacking. Nevertheless, necrotic, hypoxic, ischemic and shearing lesions are at the hypothalamus and/or the pituitary are likely important factors. The subjects at highest risk appear to be those who have suffered a moderate or severe trauma.

Clinical signs of anterior hypopituitarism are often subtle and may be masked by sequalae of TBI. Therefore, post-traumatic anterior pituitary dysfunction may remain undiagnosed and, possibly, aggravate symptoms of brain injury.

In conclusion, adolescents with moderate-severe traumatic brain injury should be screened for endocrine deficiencies so that replacement therapy can be initiated not late in order to avoid potential fatal endocrine crisis, to optimized medical intervention and endocrine outcome of patients [1,3,9,13].

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SUMMARY

ASSESSMENT OF TRAUMATIC BRAIN INJURY AND ANTERIOR PITUITARY DYSFUNCTION IN ADOLESCENTS

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Data from the Italian Ministry of Health show that approximately 300-500 per 100.000 Italians are admitted to hospital each year for either TBI or subarachnoid haemorrhage with an annual mortality of 20 per 100.000; 90% of these TBI are of medium severity. Traumatic brain injury-induced hypopituitarism in adults are more common than previously thought. The paucity of clinical reports relating to adolescents with past-TBI induced hypothalamic-pituitary-dysfunction suggests that this phenomenon might be less common that that observed in adults. In the last 25 years, in our Unit a pituitary dysfunction was established during childhood and adolescence in 3 patients (one patient had a precocious puberty, one patient had a gonadal dysfunction and one patient had a partial growth hormone deficiency). In all patients the TBI was severe (unpublished data, 2008). The physiopathological basis of hypopituitarism is lacking. Nevertheless, necrotic, hypoxic, ischemic and shearing lesions are at the hypothalamus and/or the pituitary are likely important factors. The subjects at highest risk appear to be those who have suffered a moderate or severe trauma. Clinical signs of anterior hypopituitarism are often subtle and may be masked by sequalae of TBI. Therefore, post-traumatic anterior pituitary dysfunction may remain undiagnosed and, possibly, aggravate symptoms of brain injury. Moreover it may, if undiagnosed, lead to potentially fatal endocrine crisis. Therefore, adolescents with moderate-severe traumatic brain injury should be screened for such endocrine deficiencies so that replacement therapy can be initiated to optimized the rehabilitation and outcome.

Key words: traumatic brain injury, pituitary dysfunction, adolescents.

РЕЗЮМЕ

ОЦЕНКА ТРАВМАТИЧЕСКОГО ПОВРЕЖДЕНИЯ МОЗГА И ДИСФУНКЦИИ ПЕРЕДНЕЙ ЧАСТИ ГИПОФИЗА У ПОДРОСТКОВ

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Согласно данным Министерства здравоохранения Италии в год примерно 300-500 больных на 1000000 населения поступают в больницы по поводу травматического повреждения мозга (ТПМ) или субарахноидального кровоизлияния, смертность 20 на 1000000. У 90% больных ТПМ отмечается состояние средней тяжести. Полагают, что гипопитуитаризм, обусловленный ТПМ, у взрослых встречается чаще, чем считалось ранее. Малочисленность клинических сообщений касательно подростков с гипоталамо-гипофизарными нарушениями, обусловленными перенесенными ранее ТПМ, позволяет предположить, что в данной возрастной группе этот феномен встречается реже, чем у взрослых. За последние 25 лет в нашем отделе наблюдались три подобных случая у детей и подростков (один пациент был с преждевременным половым созреванием, один – с гонадальной дисфункцией и еще один – с частичным дефицитом гормона роста). Во всех случаях ТПМ было тяжелым (неопубликованные данные, 2008). Физиопатологической основой гипопитуитаризма является дефицит. Тем не менее, некротические, гипоксические, ишемические и сдвиговые повреждения таламуса и/или гипофиза должны играть важную роль. Лицами с высоким риском видимо являются те, которые перенесли тяжелую или средней тяжести травму. Клинические признаки переднего питуитаризма часто весьма слабо выражены и могут маскироваться последствиями ТПМ. Вследствие этого, посттравматическая передняя питуитарная недостаточность может оставаться недиагносцированной и, возможно, отягощать симптоматику повреждения мозга. Кроме этого, будучи недиагносцированным, данное состояние может привести к потенциально фатальному эндокринному кризису. Таким образом, подростки с умеренным/тяжелым ТПМ должны пройти скрининг на наличие такой эндокринной недостаточности и, при необходимости, получить замещающую терапию. Это позволит оптимизировать реабилитацию и улучшить исход.

COENZYM Q10 IM KINDESALTER: NACHWEISMETHODIK, REFERENZWERTE UND KRANKHEITSBEZOGENE VERÄNDERUNGEN

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1. Einleitung

1.1.Oxidativer Stress

Die oxidative Schädigung durch freie Radikale spielt in der Pathogenese zahlreicher Erkrankungen eine wichtige Rolle [20,43]. Freie Radikale sind hochgradig instabile Substanzen, die im menschlichen Organismus durch den Sauerstoffwechsel der Mitochondrien, durch die Phagozytose bei entzündlichen Prozessen sowie durch die Aktivierung oxidativer Enzyme bei Sauerstoffmangel im Gewebe hervorgerufen werden [20]. Zum Schutz des Körpers vor freien Radikalen hat die Natur ein komplexes Abwehrsystem von antioxidativen Substanzen entwickelt [26]. Die vermehrte Bildung freier Radikale führt bei Insuffizienz dieser Antioxidantien zur oxidativen Schädigung des Gewebes (oxidativer Stress) [43]. Tiefgreifende Funktionseinschränkungen des zellulären Stoffwechsels bis hin zum Zelltod können die Folgen sein [44].

1.2.Coenzym Q10

Im Bereich der lipophilen Zellbestandteile und der Lipoproteine gilt das Antioxidans Coenzym Q10 in seiner reduzierten Form als effektiver Inhibitor einer oxidativen Schädigung [15]. Im Gegensatz zu anderen lipophilen Antioxidantien wie α-Tocopherol und β-Karotin wird Coenzym Q10 sowohl über die Nahrung zugeführt [23] als auch im Körper selber synthetisiert [14]. Die Substanz besitzt zusätzlich eine wichtige Rolle bei der Energiegewinnung in der Atmungskette der Mitochondrien [16]. Coenzym Q10 kann aufgrund der ringförmigen Chinonstruktur Elektronen aufnehmen und abgeben und somit zwischen Donator- und Akzeptorzentren von katalytischen Proteinen der Atmungskette zirkulieren. So werden Elektronen von Komplex I und Komplex II auf Komplex III transferiert. Aufgrund seiner Doppelfunktion besitzt CoenzymQ10 eine Sonderstellung in der Gruppe der Antioxidantien. Es kann vermutet, dass CoenzymQ10 aufgrund dieser Doppelrolle bei radikalvermittelten Erkrankungen eine Schlüsselfunktion besitzt.

1.3.Coenzym Q10-Spiegel bei definierten Krankheitsbildern

In zahlreichen Untersuchungen wurden bei verschiedenen Krankheitsbildern erniedrigte CoenzymQ10-Spiegel im Plasma nachgewiesen (Tabelle 1). Es ist ungeklärt, inwieweit diese erniedrigten Plasmawerte Ursache oder Folge der Erkrankungen sind. Oxidativer Stress und mitochondriale Dysfunktion werden als ursächlich diskutiert. Auch bei Patienten mit unklaren mitochondrialen Erkrankungen wurden erniedrigte CoenzymQ10-Spiegel in Muskelgewebe und Fibroblasten nachgewiesen. Postuliert wird bei diesen mitochondrialen Erkrankungen ein primärer Coenzym Q10-Mangel, der sich in Abhängigkeit von Klinik und Coenzym Q10-Gehalt in Muskelgewebe und Fibroblasten in 2 Formen manifestiert (Tabelle 2).

Tabelle 1. Krankheiten, bei denen erniedrigte CoenzymQ10-Spiegel nachgewiesen wurden

-	Mevalonazidurie (Hubner et al . 1993) (21)
-	Mitochondriale Enzephalopathien (Beal et al. 2002) (5)
-	Kardiomyopathien (Mortensen et al. 1989) (32)
-	Phenylketonurie (Artuch et al. 1999) (3)
-	ARDS (Cross et al. 1990) (11)
-	Mammakarzinom (Jolliet et al. 1998) (22)
-	parenterale Ernährung (Okamoto et al. 1986) (39)
-	neuronale Ceroidlipofuscinose (Westermarck et al. 1997) (52)
-	Therapie mit Statinen bei Hyperlipidämie (Langsjoen et al. 2003) (25)
-	EPH-Gestose (Teran et al. 2003) (49)
-	Asthma bronchiale (Gazdik et al. 2002) (18)

1.4.Therapiestudien mit CoenzymQ10

Aufgrund der antioxidativen und bioenergetischen Eigenschaften von CoenzymQ10 wurden zahlreiche Studien bei neurologischen Erkrankungen durchgeführt, in denen die therapeutische Wirksamkeit dieser Substanz untersucht worden ist . Diese Studien betreffen insbesondere diejenigen Krankheitsbilder, bei denen mitochondriale Dysfunktion und oxidativer Stress in der Pathogenese eine zentrale Rolle spielen (neurodegenerative Erkrankungen, Mitochondriopathien, Migräne).

Tabelle 2. Myopathie-Typ und Ataxie-Typ als Manifestationsformen des primären CoenzymQ10-Mangels bei mitochondrialen Erkrankungen

Manifestationsform	Klinik	CoenzymQ10-Messungen
Myopathie-Typ Ogashara et al. 1989 [38] Sobereira et al. 1997 [45] Boitier et. al. 1998 [8] Di Giovanni et al. 2001 [13]	Muskelschwäche Myoglobinurie Cerebrale Dysfunktion (Epilepsie, Retardierung) Biopsie (ragged red fibres) Erhöhtes Laktat und CK	Plasma: normal Fibroblasten: normal Muskelgewebe: erniedrigt
Ataxie-Typ Musumeci et al . 2001 [34] Naini et al. 2003 [35]	Cerebelläre Ataxie Cerebelläre Atrophie Muskelschwäche	Plasma: nicht gemessen Fibroblasten: erniedrigt Muskelgewebe: erniedrigt

In mehreren Kasuistiken wurde die Anwendung von CoenzymQ10 bei Mitochondriopathien (Morbus Leigh, MELAS) beschrieben [1,2,50]. Es konnte gezeigt werden, dass die Verabreichung von CoenzymQ10 die pathologisch erhöhten Laktatspiegel im Plasma senkt und das klinische Beschwerdebild verbessert. Als ursächlich für den beobachteten therapeutischen Effekt wird vermutet, dass die orale Supplementierung der Substanz zu einer verstärkten Oxidation der reduzierten Coenzyme in der mitochondrialen Atmungskette führt. Es wird diskutiert, dass der so gesteigerte Elektronenfluss die Einzelkomponenten der Atmungskette stimuliert und die verbliebene Restfunktion der Energiegewinnung durch die oxidative Phosphorylierung optimiert [10]. Zusätzlich wird die antioxidative Wirksamkeit der Substanz als ursächlich für die therapeutischen Effekte vermutet. Basierend auf den in Einzelkasuistiken erzielten Ergebnissen sind Studien durchgeführt worden, in denen die therapeutische Wirksamkeit einer oralen Supplementierung von CoenzymQ10 bei Mitochondriopathien untersucht worden ist [9,27]. Die zuvor beschriebene therapeutische Wirksamkeit von CoenzymQ10 konnte in diesen Studien nicht bestätigt werden. Mitochondriale Dysfunktionen spielen auch in der Pathogenese von neurodegenerativen Erkrankungen eine wichtige Rolle. So konnte bei Patienten mit Morbus Parkinson eine erniedrigte Komplex I Aktvivität in der Atmungskette der Mitochondrien nachgewiesen werden. In einer Doppelblindstudie bei Patienten im Frühstadium der Erkrankung wurde eine signifikante Verbesserung der klinischen Symptomatik nach Einnahme von CoenzymQ10 beschrieben [42]. Bei Patienten mit Chorea Huntington wurde bei Verabreichung von CoenzymQ10 kein therapeutischer Effekt beobachtet [6]. Die therapeutische Wirkung von CoenzymQ10 ist auch bei Patienten mit Migräne untersucht worden. Bei der Migräne wird ein gestörter Energiestoffwechsel im zentralen Nervensystem als ursächlich diskutiert. So lassen NMR-spectroscopische Untersuchungen vermuten, dass ein Defizit der mitochondrialen Energiereserven im pathophysiologischen Konzept der Migräne eine wichtige Rolle spielt [4]. Sandor und Mitarbeiter haben in einer Doppelblindstudie über 3 Monaten CoenzymQ10 verabreicht und eine signifikante Abnahme der Schmerzattacken in der Studiengruppe im Vergleich zur Placebogruppe beschrieben [41].

2. Problemstellung und Ziel des Forschungsprojektes

CoenzymQ10 wurde in der Behandlung verschiedener prooxidativer Erkrankungen angewendet. In Kasuistiken beobachtete Therapieeffekte konnten durch Studien jedoch nicht bestätigt werden [1,9]. Zudem zeigen verschiedene Studien bei dem gleichen Krankheitsbild widersprüchliche Ergebnisse [24,33].

Prädiktive Kriterien für einen CoenzymQ10-Therapieresponse konnten aufgrund der bisher durchgeführten Untersuchungen nicht formuliert werden. Während bei Erwachsenen zahlreiche Publikationen bezüglich Nachweismethodik, Referenzwerte und Therapiestudien vorliegen [19,40,46], ist die Bedeutung von CoenzymQ10 im Kindesalter weitgehend unerforscht.

Damit der praktisch tätige Arzt die Verabreichung von CoenzymQ10 in die Therapiekonzepte der für ihn relevanten Krankheitsbilder und Patienten einordnen kann, müssen fundierte physiologische, pathophysiologische und pharmakologische Daten vorliegen, die die Identifizierung derjenigen Patienten ermöglicht, die von einer Therapie mit dieser Substanz profitieren. Diese Voraussetzung gilt insbesondere für den Bereich der Pädiatrie, da die hier zu behandelnden Patienten aufgrund der Wachstums- und Reifungsprozesse von der Geburt bis zur Adoleszenz wechselnden physiologischen und pathophysiologischen Bedingungen unterworfen sind. Im Mittelpunkt des Forschungsprojektes stand daher die Einordnung der Substanz CoenzymQ10 in das pathophysiologische Konzept pädiatrischer Krankheitsbilder. Wesentliche Schwerpunkte waren die Entwicklung einer Nachweismethodik, die Ermittlung altersabhängiger Referenzwerte, die Beurteilung krankheitsbezogener Veränderungen im CoenzymQ10-Status sowie die Modellentwicklung zur Testung pharmakokinetischer und pharmakodynamischer Eigenschaften von CoenzymQ10.

3. Ergebnisse

3.1.Methodenenwicklung und Referenzwerte im Kindesalter
Es wurden Methoden zur Messung von CoenzymQ10 mittels HPLC und elektrochemischer Detektion in Plas-

ma [28], Erythrozyten [36] und Thrombozyten [37] entwickelt (siehe Abbildung 1). Gewebeproben, die es ermöglichen, den CoenzymQ10-Spiegel intrazellulär zu messen, sind nur unter besonderen Bedingungen (diagnostische und therapeutische Eingriffe mit Gewebeentnahme) realisierbar. In der Pädiatrie erscheint daher die Untersuchung der zellulären Bestandteile des Blutes sinnvoll, um intrazelluläre Spiegel von CoenzymQ10 zu bestimmen. Die Analyse von CoenzymQ10 in Erythrozyten (Zellen ohne Mitochondrien) und Thrombozyten (Zellen mit Mitochondrien) bietet zudem die Möglichkeit, Wechselwirkungen von intrazellulären Kompartimenten und umgebendem Plasma zu untersuchen. Es wurden Methoden entwickelt, die ein geringes Probevolumen benötigen und somit die Voraussetzung für die Durchführung kindgerechter Studien bilden.

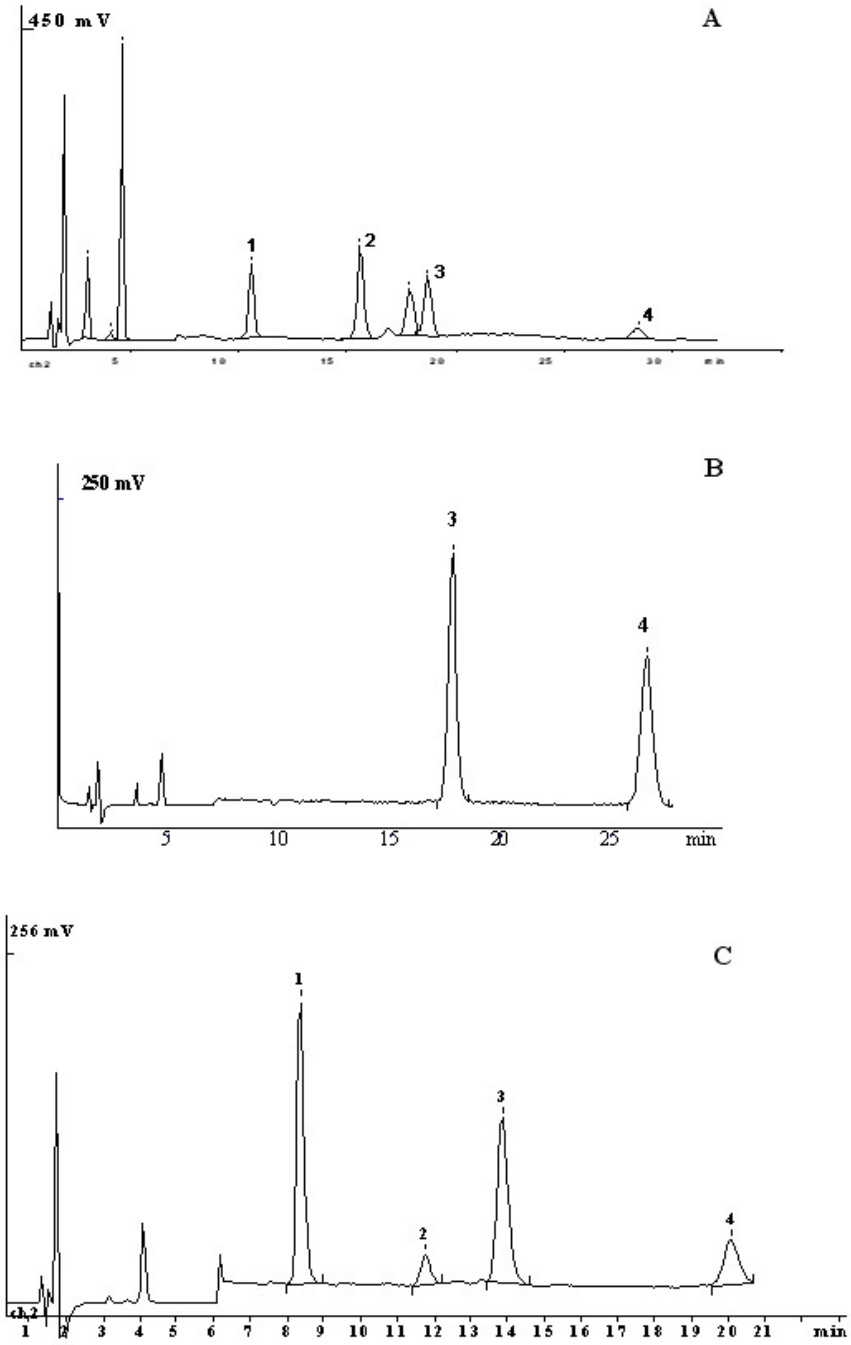

Abbildung 1. Chromatogramme einer gesunden erwachsenen Person zur Messung von CoenzymQ10 in Plasma (A), in Erythrozyten (B) und in Thrombozyten (C). Als interner Standard wird CoenzymQ9 verwendet [reduziertes CoenzymQ9 (1), reduziertes CoenzymQ10 (2), oxidiertes CoenzymQ9 (3), oxidiertes CoenzymQ10 (4)]

Im Vergleich zu bisher publizierten Methodiken [48] liegt das erforderliche Plasmavolumen zur Bestimmung von CoenzymQ10 mit 10µl Plasma im Bereich der unteren Norm und kann im Rahmen einer kapillären Blutentnahme gewonnen werden. Das erforderliche Blutvolumen für die intrazelluläre Bestimmung von CoenzymQ10 in Erythrozyten und Thrombozyten liegt mit 2ml EDTA-Blut deutlich unter dem Probevolumen anderer Methodiken [48].

Mit der entwickelten Messmethodik wurde der CoenzymQ10-Gehalt im Plasma bei klinisch gesunden Kindern (n=271) gemessen und es wurden altersbezogene Normwerte ermittelt [29] (Abbildung 2). So zeigen sich die CoenzymQ10-Plasmaspiegel bei der Geburt deutlich erniedrigt. Sie steigen im Säuglingsalter an und fallen im Kleinkindes- und Schulkindesalter ab, um sich den Normwerten des Erwachsenenalters anzunähern.

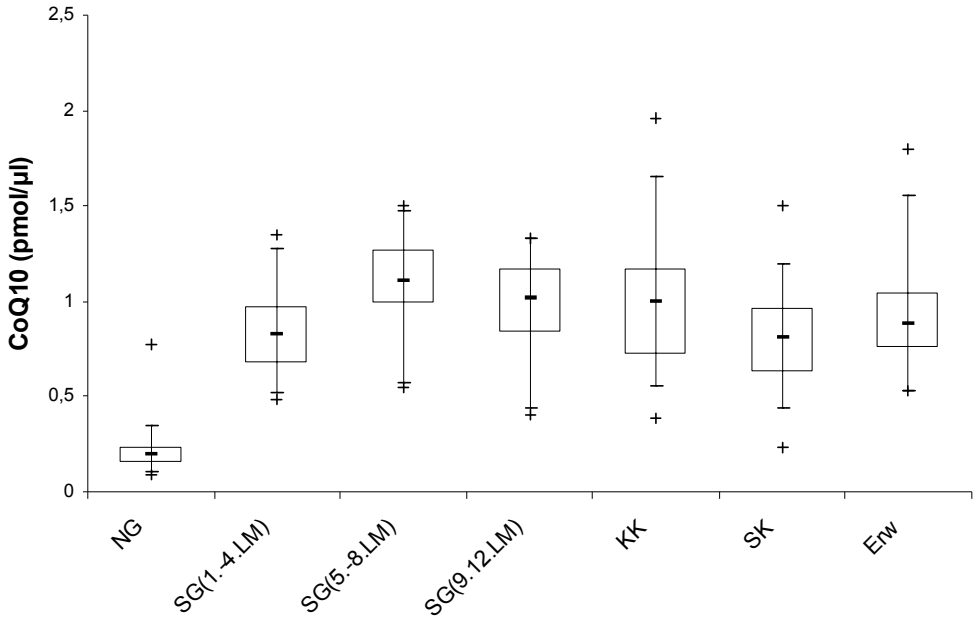

Abbildung 2. Vergleich von CoenzymQ10-Plasmaspiegel bei gesunden Neugeborenen (NG / n=72), Sòuglingen (SG/n=85), Kleinkindern (KK/n=60), Schulkindern (SK/n=54) und Erwachsenen (Erw/n=45)

3.3. CoenzymQ10-Plasmaspiegel bei Erkrankungen im Kindesalter

In dem hier vorgestellten Forschungsprojekt wurde bei Kindern mit definierten Krankheitsbildern (Hepatitis, Hyperthyreose [31], Adipositas [30], akute lymphatische Leukämie) der CoenzymQ10-Spiegel im Plasma gemessen. Die Plasmaspiegel bei Kindern mit Adipositas und bei Kindern mit akuter lymphatischer Leukämie zum Zeitpunkt der Diagnosestellung zeigten sich normwertig. Bei Kindern mit Hyperthyreose [31] und Hepatitis konnten erniedrigte CoenzymQ10-Plasmaspiegel nachgewiesen werden.

3.3.1. Hyperthyreose

Die zentrale Rolle der Mitochondrien in der Radikalgenerierung lässt vermuten, dass die Erhöhung des zellulären Energiestoffwechsels im Rahmen pathophysiologischer Prozesse zu einer erhöhten Produktion freier Radikale in der mitochondrialen Atmungskette und folglich zu oxidativem Stress führt. Insbesondere Krankheitsbilder mit hyperthyreoter Stoffwechsel-lage führen zur oxidativen Schädigung zellulärer Strukturen [7]. Aufgrund seiner Doppelfunktion als Elektronendonator in der Atmungskette und Antioxidans in den mitochondrialen Membranen wird vermutet, dass CoenzymQ10 eine zentrale Rolle im mitochondrialen Stoffwechsel und dessen Protektion besitzt. Die CoenzymQ10-Plasmaspiegel wurden bei 12 Patienten in hyperthyreoter und euthyreoter Stoffwechsellage gemessen und mit einem Normkollektiv gesunder gleichaltriger Kinder (n=52) verglichen. Die CoenzymQ10-Plasmaspiegel bei hyperthyreoter Stoffwechsellage waren im Vergleich zum Normkollektiv signifikant erniedrigt (Median: 0,46 pmol/µl , Interquartilsrange: 0,39-065 pmol/µl versus Median: 0,79 pmol/µl, Interquartilsrange: 0,62-0,92 pmol/µl, $p<0,0005$ Mann-Whitney-U-Test). Es zeigt sich ein signifikanter Anstieg der CoenzymQ10-Plasmaspiegel bei den Patienten nach Erreichen der euthyreoten Stoffwechsellage (Median 0,46pmol/µl, Interquartilsrange: 0,39-0,65 pmol/µl versus Median 0,74 pmol/µl Interquartilsrange: (0,67-0,92), $p<0,05$, Wilcoxon-Paar-Test).

3.3.2. Hepatitis

Untersuchungen weisen daraufhin, dass die CoenzymQ10-Konzentration im Plasma maß geblich durch die Leberzellen reguliert wird, in denen CoenzymQ10 synthetisiert, reduziert und über die Lipoproteinen ausgeschleust wird [14,47]. Es kann vermutet werden, dass bei Erkrankun-

gen der Leber die CoenzymQ10-Konzentration im Plasma verändert ist. Die CoenzymQ10-Plasmaspiegel wurden bei Patienten mit akuter Hepatitis A (n=11) und chronischer Hepatits B (n=14) und Hepatits C (n=9) bestimmt. Die Resultate wurden mit einem Normkollektiv gesunder gleichaltriger Kinder (n=114) verglichen. Im Vergleich zum Normkollektiv (Median :0,85 pmol/µl, Interquartilsrange: 0,67-1,12 pmol/µl) zeigen sich der CoenzymQ10-Plasmaspiegel bei Patienten mit Hepatitis A (Median 0,44 pmol/µl, Interquartilsrange: 0,39-0,55 pmol/µl, $p<0,05$ Mann-Whitney-U-Test) und Hepatitis C (Median 0,66 pmol/µl, Interquartilsrange 0,49-0,78 pmol/µl, $p<0,05$ Mann-Whintney-U-Test) signifikant erniedrigt.

3.4. Modelle für die Testung pharmakokinetischer und pharmakodynamischer Eigenschaften von CoenzymQ10 Zahlreiche Untersuchungen zeigen, dass nach oraler Aufnahme von CoenzymQ10 die Plasmaspiegel rasch ansteigen [51]. Die intrazelluläre Aufnahme von CoenzymQ10 in die verschiedenen Organe des menschlichen Körpers ist jedoch weitgehend unerforscht. Die Messung der Gewebespiegel durch Biopsieentnahme unter CoenzymQ10-Therapie ist in der klinischen Routine kaum durchführbar. Es stellt sich daher die Frage, ob die Isolierung von Blutzellen die Möglichkeit bietet, die dort gemessenen intrazellulären Spiegel als *in vivo* Modell für ein Therapiemonitoring der intrazellulären CoenzymQ10-Aufnahme zu nutzen.

Gesunden Erwachsenen wurde über 14 Tage CoenzymQ10 in einer Dosierung von 3mg/kg Körpergewicht/Tag verabreicht und der CoenzymQ10-Gehalt in Plasma, Erythrozyten und Thrombozyten vor Beginn der Studie, nach 5 Stunden und nach 14 Tagen gemessen. Die Resultate sind in Tabelle 3 dargestellt. Die Gabe von CoenzymQ10 führt zu einem signifikanten Anstieg der Konzentrationen im Plasma und in den Thrombozyten. Die CoenzymQ10-Spiegel in Erythrozyten zeigen sich unbeeinflusst von der oralen Substitution. Darüberhinaus wurden die CoenzymQ10-Konzentrationen in Plasma und Thrombozyten miteinander verglichen (siehe Abbildung 3). Die CoenzymQ10 Werte in Plasma und Thrombozyten zeigen eine positive Korrelation. Abbildung 3 zeigt ebenso, dass bei denjenigen Probanden, bei denen ein CoenzymQ10-Plasmaspiegel von über 3pmol/µl unter der Substitution gemessen wurde, die parallel gemessenen thrombozytären Spiegel an CoenzymQ10 allesamt höher waren (Median 380pmol/10^9 Zellen, Range 272-538 pmol/10^9 Zellen) als die thrombozytären Spiegel bei Plasmaspiegeln unter 3pmol/µl (Median: 200pmol/10^9Zellen, Range: 103-250 pmol/10^9Zellen). Die Auswertung dieser Studie konnte zeigen, dass oral verabreichtes CoenzymQ10 selektiv von den mitochondrienhaltigen Zellen des Blutes, den Thrombozyten, aufgenommen wird, wobei der Schwellenwert der Plasmakonzentration für die intrazelluläre Aufnahme im Bereich von 3pmol/µl liegt.

*Tabelle 3. CoenzymQ10-Gehalt im Plasma, Thrombozyten und Erythrozyten nach oraler Gabe von 3mg/kg Kцrpergewicht/Tag bei 12 klinisch gesunden Erwachsenen. Dargestellt ist der Median und der IQR (*ANOVA $p<0,05$)*

	1 Stunde vor der 1. Gabe	**5 Stunden nach 1. Gabe**	**Nach 14 Tage**
CoQ10 im Plasma (pmol/µl)	0,98 (0,78-1,04)	1,21 (0,99-1,40)	4,32 (3,06-4,52) *
CoQ10 in Erythrozyten (pmol/10^9 Zellen)	29 (25-30)	31 (29-33)	30 (26-33)
CoQ10 in Thrombozyten (pmol/10^9 Zellen)	204 (175-239)	180 (150-226)	346 (218-413) *

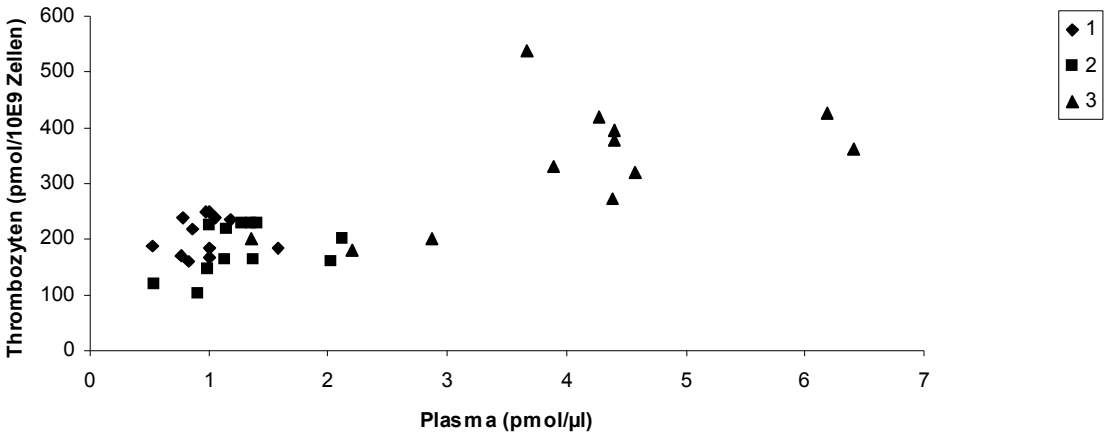

Abbildung 3. Vergleich der CoenzymQ10-Spiegel in Plasma und Thrombozyten. Alle Messpaare wurden unabhɔngig vom Datum der Abnahme miteinander verglichen ($r = 0,6$, $p< 0,0000001$, Spearman-Rangkorrelation-Test). (1=1 Stunde vor der 1. Gabe , 2=5 Stunden nach 1. Gabe, 3=nach 14 Tagen)

CoenzymQ10 wird bei zahlreichen Erkrankungen mit oxidativem Stress und mitochondrialer Dysfunktion angewendet. Die hier erzielten Resultate sind jedoch nicht einheitlich. So konnten Therapieeffekte, die in Kasuistiken beschrieben worden sind, durch Studien nicht bestätigt werden. Auch zeigen verschiedene Studien, die bei dem gleichen Krankheitsbild durchgeführt worden sind, widersprüchliche Ergebnisse. In zahlreichen dieser Untersuchungen wurden weder CoenzymQ10-Spiegel in Plasma und Gewebe noch biochemische Marker als Zielgröß en der therapeutischen Effektivität einer CoenzymQ10 Substitution bestimmt. Auch in der täglichen Praxis sind bei der Beurteilung eines präventiven oder therapeutischen Effektes insbesondere bei chronischen Erkrankungen lange Beobachtungszeiträume notwendig und erschweren somit die Einordnung der CoenzymQ10-Substitution in bestehende Therapiekonzepte. Die zusätzliche Entwicklung von pharmako-kinetischen und pharmakodynamischen Modellen für ein Therapiemonitoring ist dabei möglicherweise hilfreich, um im Rahmen zukünftiger Behandlungskonzepte ein thera-peutisches Ansprechen und somit CoenzymQ10-Therapieresponder zu erkennen.

Ziel der Studie war es, bei gesunden Probanden unter Gabe von CoenzymQ10 pharmakokinetische und pharmakodynamische Parameter zu bestimmen. Zur Beurteilung der Pharmakokinetik wurde die Konzentration an CoenzymQ10 in Plasma und Thrombozyten bestimmt. Zur Beurteilung der Pharmakodynamik wurde die oxidative Schädigung der DNA in Lymphozyten mit dem Comet-Assay gemessen. Über 28 Tage wurde 12 gesunden Erwachsenen CoenzymQ10 in einer Dosierung von 3mg/kg-Körpergewicht/Tag verabreicht. Vor Beginn der Studie, nach 14 Tagen , nach 28 Tagen sowie 12 Wochen nach Beendigung der CoenzymQ10-Gabe (nach 112 Tagen) wurde venös Blut entnommen, um die geplanten Messungen (CoenzymQ10 in Plasma und Thrombozyten, COMET-Assay) durchzuführen.

Die Ergebnisse sind in Abbildung 4 dargestellt. Nach zweiwöchiger Substitution mit CoenzymQ10 haben die Plasmaspiegel einen Konzentrationsanstieg erreicht, der im weiteren Verlauf der Substitution nicht mehr signifikant gesteigert werden kann. 12 Wochen nach Absetzen der CoenzymQ10-Substitution sind die Spiegel auf das Ausgangsniveau abgefallen. Die thrombozytären Spiegel sind nach zweiwöchiger Substitution mit CoenzymQ10 ebenfalls signifikant angestiegen, ein Effekt, der nach weiteren 2 Wochen Substitution noch steigerungsfähig ist. Obwohl die thrombozytären Spiegel 12 Wochen nach Beendigung der Substitution abgefallen sind, sind sie im Vergleich zu den intrazellulären Spiegeln zu Beginn der Studie weiterhin signifikant erhöht. Nach vierwöchiger Gabe von CoenzymQ10 ist eine signifikante Abnahme der DNA-Schädigung in den Lymphozyten zu beobachten. Auch nach Absetzten der CoenzymQ10-Substitution findet sich weiterhin eine signifikante Abnahme der oxidativen Schädigung im Vergleich zu den Werten zu Beginn der Studie.

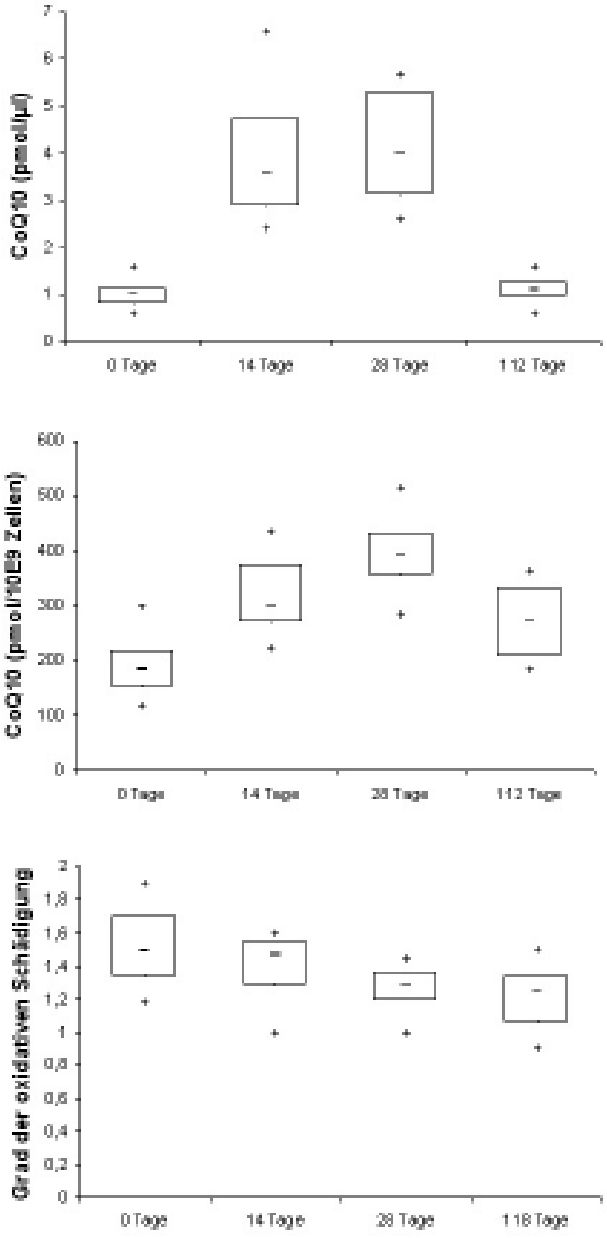

Abbildung 4. CoenzymQ10-Spiegel im Plasma und Thrombozyten sowie Grad der oxidativen Schòdigung in Lymphozyten bei 10 gesunden Erwachsen unter oraler Gabe von 3 mg/kgKцrpergewicht/Tag nach 14 und 28 Tagen sowie 12 Wochen (= 112 Tage) nach Beendigung der Substitution

CoenzymQ10 wird in klinischen Studien verabreicht, um in den Organen zu wirken, bei denen eine intakte mitochondriale Funktion und Energiegewinnung eine wichtige Voraussetzung ist (Gehirn, Myokard, Muskulatur). Bei der Modellentwicklung für ein Therapiemonitoring ist jedoch nur die Verwendung von Surrogaten möglich, um

pharmakologische und pharmakodynamische Funktionen auf zellulärer Ebene zu erfassen. Die Verwendung von Blutzellen bietet die Möglichkeit, derartige Untersuchungen im Kindesalter durchzuführen. Inwieweit jedoch die hier beobachteten Effekte die Wirkung in den Zielorgane reflektieren, ist zurzeit unklar. Die Schwellenwerte der Plasmakonzen-trationen für die intrazelluläre Aufnahme scheinen im Bereich von 3pmol/µl zu liegen. Es bedarf jedoch weitergehender Untersuchungen, in denen Surrogatmessungen mit klinischen Parametern insbesondere bei chronischen Erkrankungen verglichen werden. Nur derartige Studien können die Qualität von Surrogatmodellen beurteilen. Die hier entwickelten Modelle bieten dabei möglicherweise einen Ansatz.

4. Zusammenfassung

Die im Rahmen des Forschungsprojektes gesammelten Daten bieten einen sinnvollen Beitrag zur Beurteilung von CoenzymQ10-Mangelzuständen und zur Planung und Durchführung von Therapiestudien mit CoenzymQ10 im Kindesalter. Die entwickelte Nachweismethodik ist aufgrund der geringen Probevolumina kindgerecht und auch im Rahmen von Multizenter-studien praktikabel. Die ermittelten altersbezogenen Normwerte bieten eine sinnvolle Richtlinie zur Beurteilung von CoenzymQ10-Mangelzuständen, wobei insbesondere die Reifungsprozesse im Neugeborenen- und Säuglingsalter berücksichtigt werden. Bei den verschiedenen Erkrankungen im Kindesalter konnten so wesentliche pathophysiologische Einflussgröß en für den CoenzymQ10-Gehalt im Plasma definiert werden. Aufgrund der entwickelten Nachweismethodik kann der CoenzymQ10-Gehalt in Plasma und Blutzellen im Rahmen zukünftiger Therapiestudien ethisch vertretbar gemessen werden. Die so erhobenen Daten ermöglichen den retrospektiven Vergleich der gemessenen CoenzymQ10-Konzentrationen mit dem Therapieansprechen. Die Bestimmung von CoenzymQ10 in Plasma und Blutzellen während der Therapie bietet zusätzlich die Möglichkeit, die individuelle Dosierung für den einzelnen Patienten in Abhängigkeit von dem angestrebten Plasmaspiegel und dem Schwellenwert für die intrazelluläre Aufnahme in Thrombozyten festzulegen. Die Messung der oxidativen DNA-Schädigung im Comet-Assay in den Lymphozyten ermöglicht zudem ein pharmakodynamisches Monitoring auf intrazellulärer Ebene im Rahmen der Therapiestudien.

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SUMMARY

COENZYME Q10 IN CHILDHOOD: DETECTION METHODS, REFERENCE VALUES AND DISEASE-RELATED CHANGES IN THE COENZYME Q10 STATUS

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The lipophilic antioxidant coenzyme Q10 is an effective inhibitor of oxidative damage. Furthermore coenzyme Q10 is involved in electron transport related to the mitochondrial respiratorial chain. Because of this double function coenzyme Q10 has become a special role in the group of antioxidants. Little is known about coenzyme Q10 in healthy and sick children.

The aim of the study was to determine the role of coenzyme

Q10 in the pathophysiological concept of pediatric diseases. At first a HPLC-method for the detection of coenzyme Q10 in plasma, erythrocytes and platelets was developed and age-related reference values for children were established. Based on these reference values the CoQ10 status was measured in different pediatric diseases. By this way various conditions for low coenzyme Q10 plasma values in children could be defined. Furthermore there were different in vivo models developed to define pharmacokinetic and pharmacodynamic characteristics of coenzyme Q10.

The established methods and measured data might be a helpful contribution for estimating coenzyme Q10 deficiency and for planning therapeutical studies with coenzyme Q10 in childhood.

Key words: coenzyme Q10, oxidative damage, pediatric diseases.

РЕЗЮМЕ

КОЭНЗИМ Q10 У ДЕТЕЙ: МЕТОДЫ ОПРЕДЕЛЕНИЯ, РЕФЕРЕНТНЫЕ ВЕЛИЧИНЫ И СВЯЗАННЫЕ С БОЛЕЗНЬЮ ИЗМЕНЕНИЯ

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Липофильный антиоксидант коэнзим Q10 является эффективным ингибитором окислительных повреждений. Более того, Q10 вовлечен в транспорт электронов, связанный с митохондриальной респираторной цепью. Из-за этой двойной функции коэнзим Q10 приобрел особое значение в группе антиоксидантов. Мало известно о коэнзиме Q10 у здоровых и больных детей.

Целью исследования было определение роли коэнзима Q10 в патофизиологической концепции педиатрических болезней. Впервые был разработан HPLC-метод для определения коэнзима Q10 в плазме, эритроцитах и тромбоцитах, получены возрастные референтные данные для детей. Коэнзима Q10 статус определялся при различных педиатрических болезнях. Были установлены состояния, при которых уровень коэнзима Q10 был низким. Кроме этого, были разработаны различные in vivo модели для определения фармакокинетических и фарамакодинамических характеристик коэнзима Q10.

Установленные методы и результаты соответствующих исследований могут способствовать определению дефицита коэнзима Q10 и планированию терапевтических исследований с коэнзимом Q10 в детском возрасте.

COMPARATIVE EFFICIENCY OF DIAGNOSTICS AND TREATMENT FOR HELICOBACTER PYLORI INFECTION IN CHILDREN

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Helicobacter pylori (H.pylori) is one of the most common pathogens in humans which cause the diseases of the upper gastrointestinal tract (UGIT) [4,7,9,12,14,20]. During the last years in Ukraine we have observed an increase in the prevalence of chronic gastroduodenal diseases both in adults and children. The frequency of these diseases has increased more than 1.5 times for the last 3 years and reached 160 per 1000 children's population. For this reason they account for the large part of the diseases in children and teenagers [17-19].

The most common diseases among children are the gastroduodenal illnesses associated with H. pylori. The different clinical presentations, the influence of daily life conditions, and the family genetics are the reasons for why H. pylori is considered the infectious disease with characteristics of uncontrolled epidemic in our country. The role of H. pylori in the development of chronic gastroduodenal diseases is well known around the world; however there is a lack of information about the prevalence of H. pylori in children and teenagers in the countries like Ukraine [5,19,23]. There are no reports about the virulence and pathogenicity of H. pylori strains, the modes of transmission in children, and the role of family and school environment in the transmission. The optimal protocols of eradication therapy are still vague, because of the regional patterns of antibiotic resistance of H. pylori. Asymptomatic chronic erosive gastritis, ulcer disease, stomach dyspepsia requires the development of new algorithms for diagnosis and treatment, planning surveillance in a regional scale, especially in countries with a considerable economic deficit [6,10,11,20,23].

In spite of considerable experience in studying of various aspects of H. pylori infection questions of epidemiology, the degree of pathogenicity of regional strains, routes of transmission in children, and the optimal treatment methods have not been clarified and still represent a matter of debates [2,15,18,21].

The leading role of H. pylori in ulcer disease, gastritis, non-ulcer dyspepsia, and gastric cancer has been confirmed. The connection between H. pylori and the development of reflux-esophagitis and ulcers which are induced by using non-steroid anti-inflammatory medicines is less clear. However, it is proved that H. pylori could be found in 90-100% of patients with duodenal ulcers and in 85-90% with gastric ulcers [3,5,19].

The investigations reported from different countries proved the high prevalence of H. pylori infection in both adults and children. According to the data of the last year the prevalence of H. pylori colonization in the adult population of Ukraine is about 80-85% but in children's population this value has not been established yet. However there are reasons to predict that it could be high enough around 40-70% depending on child's age. The frequency of H. pylori infections increases with the age of the child. According to the data of Russian researchers H. pylori infection of 5-6 years old children in Russia is about 40-45%, and in 14-15 years old children it reaches the level of adults - 65-70%. The figures are substantially different in other countries. According to the literature H. pylori colonization of schoolchildren is around 4,2% in Belgium, 28,9% in Italy, 63% in Czech Republic, 70% in Russia, 80,6% in Benin, 84% in India, and 96% in Albania. In developed countries, such as the USA, Germany, Sweden, Japan, the prevalence of H. pylori in child's age is lower, although with age it increases. The high prevalence of H. pylori in Ukraine can be explained by low socio-economic status of the population, unsatisfactory living conditions, peculiarities of feeding, insufficient hygienic skills, low level of sanitary education, and poor organization of medical care [5,12,20].

A systematic control of H. pylori infection in the leading countries of the world (such as the USA, Japan, countries of Western Europe) reduced its prevalence in children's population that in turn caused the decrease of frequency of stomach cancer, ulcer disease and gastroduodenitis. In Ukraine we can see steady increase in incidence of these diseases. The problem is that the treatment of children begins too late, in 1-3 years after the appearance of the first symptoms of the diseases. No less important is underestimation by the children's parents of the gastrointestinal child's complaints, insufficient information of pediatricians and family doctors about the role of H. pylori in the development of chronic gastrointestinal diseases in children. The situation is complicated due to use of outdated equipment, lack of possibilities for modern diagnostics, absence of clear national recommendations and standards of treatment, lack of prevention and control measures for these pathologies [4,5,16].

The inadequate plans of treatment and reduction of doses and duration of taking medications very often result in insufficient efficiency of eradication treatment in children. The situation is complicated by the high cost of noninvasive methods to control efficiency of eradication [8,22,23].

According to our data children from socially unfavorable families the number of which is rather considerably high in Ukraine are the most vulnerable to infecting and further development of the disease. In such families we can find low local immunity in children, lack of hygienic skills, overcrowding of flats and high frequency of parents infections. Taking all this into account one of the most important task is to conduct educational work in those families which has to be based on the results of our own local research. Thus, in spite of the high prevalence H. pylori in Ukraine and substantial increase of the incidence of H. pylori associated diseases we do not have the real possibilities for its timely diagnosis, treatment and prevention [5,19,23].

The way to improve treatment outcomes is the optimal combination of medicines for eradication therapy. According to generally accepted recommendations the treatment must be simple, have a good tolerance, accessible on costs and eradication effect has to exceed 80%. However treatment patterns suggested for adults have being constantly modified and not always can be used in pediatric patients. In 2000 the special European commission worked out the main principles of consensus of H. pylori diagnostics and eradication in children which were practically changed in various countries. The first Ukrainian recommendations for diagnosis and therapy of chronic stomach and duodenal diseases in children were proposed in Kyiv in 1999. They have being permanently modified because of the local peculiarities of H. pylori sensitivity to antibiotics and insufficient possibilities for laboratory evaluations. That is why the regional standards of investigation of patients with chronic UGIT diseases and H. pylori eradication are needed. They should take into account both the availability of laboratory and instrumental facilities and regional peculiarities of H. pylori sensitivity to antibacterial medicines [6,8,11,13,18,22,24]. We elaborated our first regional guidelines in 2000.

In spite of that our data suggest that almost the half of children visit qualified pediatric gastroenterologist only in 1.5-2 years after disease onset. Also fiber gastroduodenoscopy (FGDS) is performed only in 10-15% of the patients. Biopsy material is undertaken morphological study very rarely and only in isolated cases tests are performed to elicit the presence of H.pylori. Often it leads to to inef-

fective treatment and development of recurrences within a year after the treatment has been employed. Even among pediatric gastroenterologists a widespread opinion exists that only diffuse gastroduodenitis and ulcerous lesions require complete triple- or quadrotherapy while mild gastroduodenitis limited to few areas of the stomach or duodenum and associated with H.pylori require monotherapy or therapy with 2 drugs.

During the last 8 years the Department of Faculty and Hospital Pediatrics at Lviv National Medical University together with the Departments of General Medicine and Microbiology was involved into the work for development of diagnostics and treatment of H. pylori-associated diseases in the Western region of Ukraine. From the very beginning our researchers proposed a family approach to diagnostics and treatment of this infection. At first, the results of our research were published in Polish Journal «Pediatria Wspolczesna Gastroenterologia, Hepatologia and Zywienie Dziecka» [15] and were reported in the USA (Georgetown Conference Centre, Washington DC, 2002) at the "Children's Environmental II: A Global Forum for Action" [16].

To increase the efficiency of diagnostics and treatment of children with chronic diseases of UGIT associated with H.pylori by introducing the methods of early disease diagnosis, studying of clinical course features, and introduce the effective methods of noninvasive diagnostics and contemporary protocols of eradication therapy.

The study was carried out at several steps. First of all we have performed the primary screening of children (by the method of questionnaire) to identify the children with upper gastrointestinal complaints. The next stage was in-depth physical examination of these children at school setting to find out objective symptoms, which could confirm upper gastrointestinal diseases. Then we carried out the instrumental and laboratory investigation of the selected children to verify the diagnosis of upper gastrointestinal diseases and its etiology. After that the children with upper gastrointestinal diseases were arranged into two groups: colonized with H. pylori and those who were not. The last step was to investigate the efficiency of different methods of H. pylori diagnostics and protocols of eradication therapy in children with H. pylori-associated diseases based on clinical data and patterns of H. pylori antibiotic resistance.

At the first step of work the interviewing was conducted involving 17480 schoolchildren of 1-11 forms. The numbers of boys and girls were nearly equal.

According to the questionnaires it was found out that about 13% of schoolchildren live in incomplete families (with substantial increase in higher forms: from 9,9% to 14,7%, $p<0,001$), 8,6% – in hostels, 14,6% children and parents considered their socioeconomic conditions as unsatisfactory. 55,4% children did not have a separate room, 18,5% – separate table for work, 14,2% – separate bed. One-third of schoolchildren have a dog or a cat at home which can be the potential source of H.pylori and helminthic infestation.

Analyzing the health condition of schoolchildren family members we found that most of them had chronic diseases of UGIT (32,6 %) comparing to morbidity due to diseases of respiratory system – 32 %, cardiovascular system – 28,7 % ($p<0,01$), and urinary system – 24,3 % ($p<0,001$). These data confirm the wide prevalence of gastroduodenal diseases in the population and indicate necessity of systematic measures directed against them to be taken for both children and their household.

The important risk factor in such diseases development was the violation of adequate children's nutrition. From our questionnaire 13,3% of schoolchildren had irregular nutrition and 17,7% showed unsatisfactory diet by its quality. Almost 2,5% of schoolchildren ate only twice a day, and a general number of such kids grew threefold in senior forms. Practically, every fifth schoolchild ate nothing at school, where he or she stayed most of the day. Among first-class boys and girls only 25,5% used school dinners but among graduating pupils – 3,9%. The most popular kind of food was a sandwich which was brought by 2/3 children to school. Every second schoolchild had a harmful habit to eat just before sleep.

The main complaints of all age's schoolchildren were typical for gastroduodenal disorders. The most frequent complaint identified in 71% of children was abdominal pain. Almost a half of pupils complained on disturbance of appetite, periodic nausea, and regurgitation. The typical complaints were motility disorders of UGIT: epigastric burning, feeling that meal heavily swallows, bitter or sour taste in oral cavity. Prevalence of such complaints was substantially increased among the children of higher forms, which meant the increase of the pathology of digestive system prevalence with age.

Other complaints were headache, dizziness, fatigue, sweating, cold sensation in the limbs, changes of face colour at agitation. Prevalence of these symptoms was also increased in pupils of higher forms.

At the next step of the research, we selected children with probable pathology of the digestive system by specially developed computer analytic system.

Among pupils selected for positive findings in screen-questionnaire and at examination, we could not confirm functional or organic disorders of UGIT in 38% of pupils.

In 23% of children there were clear clinical and/or instrumental signs of motility disorders such as duodenogastric and/or gastroesophageal refluxes. In 39% of selected schoolchildren we defined the organic changes of mucous membrane (GM) of UGIT which were typical for gastroduodenitis, gastritis or ulcer disease. 81% of them were associated with H.pylori.

To study endoscopic, morphologic and clinical features of the course of chronic diseases of UGIT associated with H.pylori comparing to similar diseases of other etiology we formed 2 groups of children. Into the main group we included 120 children (mean age – 12,52±1,83 years) with the inflammatory UGIT diseases associated with H.pylori. Into the group of comparison we included 20 children (mean age – 12,40±2,06 years) with the UGIT diseases which were not associated with H. pylori.

The spectrum of diseases in children from the main group was represented by chronic diffuse gastroduodenitis with increased acidity in relapse (65%) and chronic isolated gastroduodenitis (35%), 10,8% of children had duodenum ulcer and in 13,3% we diagnosed erosive gastroduodenitis. In the comparison group the spectrum of diseases based on main diagnoses was following: chronic diffuse gastroduodenitis with increased secretory function in relapse – 70% and chronic local spotty gastroduodenitis – 30%.

Having interviewed schoolchildren and elicited their social and domestic features we compared them to the similar outcomes in children of the main group and group of comparison. Analyzing the condition of residence we identified that children with helicobacteriosis more frequently lived in unsatisfactory conditions, in hostels or in incomplete families.

There was more chronic UGIT diseases (81,7%) in other family members in children from the main group and children from comparison group (30,5%, $p<0,001$) that confirms domestic origin of helicobacteriosis. Such a conclusion was supported by significant correlation between revealed colonization with H.pylori and presence of UGIT disease in family members ($r =+0,42$).

Our studies defined the necessity to improve organization of medical supervision of children with gastroduodenal pathology by pediatric gastroenterologist. In spite of the fact that most of the children had typical for chronic disorders of UGIT complaints only 13 children (10,8%) from the main group had underwent endoscopy and none of them had had target biopsy of gastric mucosa or H.pylori test. As a result children did not receive adequate treatment.

In the study we determined a similarity of clinical diseases manifestation in children of the both groups. At the same time, children with helicobacteriosis had rarely mild disease (respectively, 7,5% vs. 40%, $p<0,001$) and more frequently had recurrent abdominal pain (45,8% vs. 20,0%, $p<0,05$). Symptoms of UGIT motility disorders were very marked: sour reflection (87,5% vs. 65,0%, $p<0,01$), epigastric burning (43,3% vs. 15,0%, $p<0,05$), early satiation with food (53,3% vs. 25,0%, $p<0,05$), feeling of discomfort in epigastrium (respectively, 52,5% vs. 10,0, $p<0,001$). At physical examination children with helicobacteriosis substantially more frequently had an unpleasant smell from a mouth (77,5% vs. 30,0%, $p<0,05$), moderate dryness of skin (28,5% vs. 5,0%, $p<0,05$), muscular defense of the anterior abdominal wall at deep palpation (respectively, 55,8% vs. 30,0%, $p<0,05$). There was no difference in the frequency of the other symptoms between the 2 groups.

The all children in the both groups were investigated with EGDS supplemented with target biopsy of gastric mucosa in the antral and fundal parts of the stomach, and simultaneous gastric pH measurement. With EGDS we found a similar visual picture in the both groups of children which was characterized by motility disorders (change of retraction, presence of refluxes, functional insufficiency of cardiac part of the stomach, gastroesophageal prolapse, not fully closed pylorus), inflammatory changes (hyperemia of gastric mucosa, increase volume of secretory mucus). More secretions were found in the esophagus of children from the control group (respectively, 50,0% vs. 26,7%, $p<0,05$), while in the children from the main group there was significantly more gastric mucus (respectively, 94,2% vs. 65,0%, $p<0,001$). We observed destructive changes of gastric mucosa and duodenum (erosions, ulcers) only in children of the main group, but the number of these cases in our study was insufficient to reach statistically significant difference.

At morphological study of biopsy materials of gastric mucosa taken from the antral part of the stomach, all children of the main group had certain inflammatory changes while in the group of comparison such changes were found only in 65% of children ($p<0,001$). Degree of inflammatory process was substantially higher in children with helicobacteriosis. In children from the main group there was considerable local infiltration by lymphocytes, neutrophiles, and cellular polymorphism. Some of them had a mixed local spotty character of gastric mucosa infiltration. In 4 children of the main group we observed lymph follicles with germenative centers typical for helicobacteriosis [12]. The other changes of antral gastric mucosa, local atrophy of glands, polyp like changes of GM, local intestinal metaplasia, and congestion were similar in the both group.

In biopsy samples taken from the fundus of the stomach of children from the main group there was greater activity

of inflammatory process with more frequent lymphatic and neutrophil infiltration, local intestinal metaplasia of gastric epithelium. The other morphological changes of GM in the fundal part were not different in the both groups of children.

Thus, considerable degree of inflammation of GM, massive infiltration of mucus membrane with cellular elements, formation of follicular lymphoid hyperplasia, local intestinal metaplasia must alert physician to think about the disease of H.pylori etiology.

Nowadays diagnostics of H.pylori infections in children is based on the data obtained by various methods which differ each from other by the degree of invasiveness, additional equipment used, time required, specificity and sensitivity [1,4,7,12,16]. For the last time morphological investigation is the most important diagnostic method of H.pylori infection which is considered as a "gold standard" of this bacteria identification [12]. According to our data, the presence of H.pylori was determined in biopsy samples of antral part in 103 children (85,8%) and in biopsy materials from fundal part in 61 child (50,8%) that corresponds to the findings of other authors. Negative results of combined fundal and antral biopsy were documented in 5 (4,17%) children of the main group suggesting the high sensitivity of this method (~ 96%). It is useful to note that in some children of the main group H.pylori was identified only in biopsy materials of fundal part of GM that necessitates not only antral but fundal biopsy also.

Until now EGDS has been an important invasive method of diagnostics of UGIT chronic diseases associated with H. pylori. One third of our children from the main group did not have the clear endoscopic signs of helicobacteriosis despite the presence of infection proven by histological investigation and ELISA.

We used the print smears of GM taken from the areas of maximal hyperemia and edema. Positive diagnosis of helicobacteriosis was documented only in 67 children (55,8%) of the main group that questions the value of this method as a main diagnostic tool taking into account a high percent of errors and availability of more sensitive and specific assays for verification of the diagnosis.

CLO-test and bacteriological method also had low sensitivity (respectively 70,8% and 60%) that substantially limited their use in practice of pediatric gastroenterologist.

Enzyme linked immunosorbent analysis of RIDASCREEN® for Helicobacter by which we determined the presence of antibodies (IgG) against H.pylori in the blood serum showed positive result in 112 children (93,3%) with helicobacteriosis. Express method employing one-step strip-test for assaying of anti-helicobacter antibodies in capillary blood showed positive result in 110 children (91,7%). Results of express method were insignificantly less accurate than the results obtained by ELISA but this method was more acceptable in routine practice of pediatric gastroenterologist, pediatrician or family physician. Sensitivity of 92% is considered enough for wide use of the method and its simplicity as well as a possibility to get prompt result make it very comfortable.

At the same time we noted that its use in children younger than 10 years brought the increase of negative results which is probably associated with features of immune system in this age. Last time we started to use the test systems for immunochromotographic detection of H.pylori antigens (Cito Test H. Pylori Ag) in excrements. The results were positive in 93% of infected children independently of age. It is simple and comfortable for use.

Comparing sensitivity and convenience of different methods for H.pylori determination one can make a conclusion that a very sensitive method of H.pylori infection diagnostics is a morphologic method which has some flaws because of its invasiveness. Modern non-invasive methods of diagnosis with use of ELISA and immunochromotographic reactions have a sensitivity which is close to the "gold standard" and may be used in clinical practice decreasing the need for EGDS. Method Cito-Test-H.pylori-Ag is very promising and convenient for diagnostics.

In order to determine the effectiveness of various protocols of eradication therapy, their tolerability and complications 120 children where divided into 4 groups depending on given particular protocol of treatment. The group 1 comprised of 30 children who took de-nol (colloid bismuth subcitrate) + flemoxin-solutab (amoxiciline) + clarytromicin (fromilid) (DFC); the group 2 - 30 children who took de-nol + flemoxin solutab + furazolidon (DFF); the group 3 - 30 children who took proton pump inhibitor (PPI) nexium + flemoxin-solutab+clarytromicin (NFC); the group 4 - 30 children who took de-nol + flemoxin-solutab + claritromicin + nexium (DFCN).

Duration of the treatment lasted 7 days and medication doses were as follows: de-nol - 8 mg/kg/24 hours - 2 intakes, flemoxin solutab - 50 mg/kg/24 hours - 2 intakes, clarytromicin (fromilid) - 7,5 mg/kg/24 hours - 2 intakes, furazolidon - 8 mg/kg/24 hours - 3 intakes, nexium - 0,5 mg/kg/24 hours – once in the evening.

Prescribing therapy we followed a «family approach» to diagnosis and treatment of helicobacter-associated children's illness which was implemented into the practice of gastroenterologists in our region for the first time. This approach gave us an opportunity to eliminate the bacteria in household and prevent possible re-infection in children after complete eradication being achieved.

Dyspepsia and abdominal pain were frequent and prevalent findings in helicobacteriosis together with signs of motility disorders of UGIT and weakness. Evolution of pain in the groups of children depended on the therapy received, localization of pain, and timing to meals. In group 1 feeling of pain decreased on 5,64±0,23 day and pain relived on 7,80±0,31 day from the beginning of treatment. In children of the group 2 the decrease and disappearance of pain occurred within the similar period of time. Children treated with nexium (group 3) had faster disappearance of pain in comparison to 2 groups above. In the group of children received quadrotherapy we documented similar to group 3 dynamics of pain. It was also faster than in groups 1 and 2.

The similar dynamics was observed for the group of clinical symptoms suggestive to motile disorders of UGIT such as heartburn and pain in the chest, belching and hoarseness of voice in the morning.

Summarizing the observation of disease clinical course we can make a conclusion that in each group there was a decrease in frequency of complaints and relief from symptoms of illness. In groups of patients where eradication therapy included bismuth based drug (1st and 2nd group) and antibiotics eradication of pathologic symptoms was slower and there was no considerable difference between these two groups. In sub-groups where eradication therapy included PPI timeframe for resolution of pathologic symptoms was faster.

An important component in the assessment of therapy efficacy is tolerability, frequency and severity of adverse events and complications resulting in finishing of the treatment.

In general the all medications mentioned above were well tolerated with no complications or adverse effects seen in any group. At the same time breakdown of adverse events differed. The lowest frequency of adverse events (33,3%) was in the group 1 and highest - 53,3% was in the the group 4. In the 2nd and the 3rd groups side effects were documented in 14 cases (46,7%) (Table 1).

Table 1. Frequency of side effects in children on eradication therapy

Data	1st group n=30	2nd group n=30	3rd group n=30	4th group n=30
Total	10	14	14	16
Mild	9	12	13	12
Moderate	1	2	2	4
Severe	0	0	0	0
Nausea	3	9	4	3
Vomiting	0	1	0	0
Change of taste	1	1	1	1
Diarrhea	4	1	8	7
Dizziness	0	0	0	1
Eruption, itching	0	1	1	1
Dryness in mouth	0	0	0	1

Grading adverse events we used the following criteria: mild - symptoms present but do not change behavior of a child; moderate - symptoms present and change behavior of a child, but do not require stopping the treatment; severe - symptoms present and are so severe that advocate finishing treatment.

Some purgative effect observed in the 1st, 3rd and 4th groups of children may be explained by prokinetic action of macrolides and reaction to PPI. The most frequent side effects in the 2nd group of children were mild nausea likely because of taking of furazolidon. There were no constipation or flatulence, increase in pain syndrome, or disturbance of sleeping.

We determined effectiveness of eradication therapy in 1,5 month after finishing it by means of non-invasive highly informative method of diagnostic of antigens H.pylori in feces - "H.pylori Stool antigens test".

According to our data the most effective was quadrotherapy effectiveness of which reached 93,3%. We failed to achieve eradication in 2 of 30 children from the group 4 although there was clinical improvement in the both cases. The probable cause of that was longstanding disease or prior repeat courses of monotherapy with de-nol, metronidazol, and furazolidon.

In the group of children where triple therapy was employed with de-nol and two antibiotics we had got good results - 86,7% of successful eradication. The lowest eradication rate was achieved in the group 2 where we applied furazolidon (DFF) - 80%. Changing de-nol to nexium did not change the frequency of eradication in the group 3 where it was 86,7% (Table 2). Taking into account that effectiveness of eradication therapy must be more than 80% it is better to use protocols with DFC, NFC, DFNC. Protocols employed nexium were better but more expensive and with more side effects.

Table 2. Effectiveness of different schems of medicines for eradication of H.pylori

Groups	Schemes of medicines	Effectiveness (%)
1	De-nol+ Flemoxin + Clarithromicine	86,7%
2	De-nol+Flemoxin+Furazolidon	80%
3	Nexium+ Flemoxin + Clarithromicine	86,7%
4	De-nol+ Flemoxin + Clarithromicine+Nexium	93,3%

Children with successful eradication of H.pylori as tested in 1,5 month after finishing therapy repeated antigens H.pylori studies in 6 and 12 months. In six months we got negative results in all children who had negative results at their first check of eradication status but 6-10% of children showed recurrence of mild UGIT motility disorders with heartburn, eructation, bad appetite, fast stomach filling sensation. In 12 months situation changed. In each group we found children with positive reaction to H.pylori. From the first group - 2 children (7,7% of successful eradication cases), from the second group - 3 children (12,5%), from the third group - 2 children (7,7%), from the fourth group - 1 child (3,6%). One may think that reappearance of antigens of H.pylori in feces may be caused by re-infection. All those children were from the families where household refused treatment despite the fact that some family members had symptoms characteristic to chronic UGIT diseases.

It is interesting to note that effectiveness of eradication therapy in a subgroup of 14 children with poor compliance (dose missing, incomplete course of therapy) was only 50%. The repeated eradication course of quadrotherapy was available for 7 children but only in 4 cases we gained eradication. These data emphasized the crucial importance of compliance (proper dosing, frequency and length of treatment) in preventing of antibiotic resistance and increasing of eradication rate.

According to significant prevalence of symptoms and signs suggestive to UGIT motility dysfunction (clinical data and results of endoscopy examination), possible disorders of gut friendly flora at the background of the disease, and antibacterial therapy, deficit of water-soluble vitamins in children with chronic pathology of UGIT, all children were prescribed to receive prokinetic motylium (domperidon), probiotics (Lactobacteria GG (LGG)+Bifido-bacteria) and polivitamin-mineral medicine Multitabs for the period of three weeks. Prescribing of rehabilitation therapy contributed to fast normalization of children condition.

The study proved the necessity of making early diagnosis in children with chronic gastroduodenal pathology which is quite prevalent among schoolchildren. Typically, schoolchildren produce complaints with characteristic patterns for functional and organic disorders of UGIT. Such children do not apply for qualified medical care for a long time but if even they receive it, it is insufficient. All mentioned above influence the success of further treatment. Screen for those children using interviewing with questionnaires allows selecting the individuals with symptoms and signs suggesting probable pathology of UGIT. Use of ELISA and immunochromatographic methods allows diagnosing of helicobacteriosis with a high degree of reliability which makes invasive EGDS unjustified for routine use in children with gastroduodenal pathology. In the case of performing EGDS it is imperative to make target biopsy GM at fundal and antral areas of the stomach.

Management of children with helicobacteriosis of UGIT should consist of eradication therapy and rehabilitation treatment. Eradication therapy requires strict compliance to eradication protocol and "family approach" to diagnosis and treatment. Most effective protocol for eradication of H.pylori is quadrotherapy which is indicated to children with erosive gastroduodenitis or ulcer disease of the stomach or duodenum. The best protocol of triple therapy comprised of de-nol, flemoxine, clarythromicin and was optimal on cost/effect ration and frequency of adverse events.

Obligatory condition for success was examination of the household and their simultaneous treatment in the case of eliciting of H.pylori carrier state. In the high risk families which members were not treated the risk of re-infection is increased.

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SUMMARY

COMPARATIVE EFFICIENCY OF DIAGNOSTICS AND TREATMENT FOR HELICOBACTER PYLORI INFECTION IN CHILDREN

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The prevalence of chronic gastroenterological diseases among schoolchildren is high and the incidence of those diseases is growing up. The article is devoted to study of diagnostic, clinical features of Helicobacter pylori associated chronic diseases of upper digestive tract in children. With a help of screening-questioning of school children the age prevalence of main, gastroduodenal-specific complaints has been determined, their social and everyday life peculiarities have been investigated. Comparative efficacy of the main invasive and non invasive Helicobacter pylori diagnostic techniques among children has been determined. With the help of qualitative Helicobacter pylori stool antigen test the comparative efficacy of different methods of eradication therapy based on using bismuth containing drugs and the proton pump inhibitors were studied. The eradication therapy tolerability and side effects profile have been investigated.

Key words: helicobacter pylori, gastrointestinal diseases, diagnostics, treatment, eradication.

РЕЗЮМЕ

СРАВНИТЕЛЬНАЯ ЭФФЕКТИВНОСТЬ ДИАГНОСТИКИ И ЛЕЧЕНИЯ HELICOBACTER PYLORI-ИНФЕКЦИИ У ДЕТЕЙ

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Частота хронических гастроэнтерологических заболеваний у детей школьного возраста растет. Статья посвящается диагностике и клиническим особенностям Helicobacter pylori-ассоциированных хронических болезней верхнего отдела желудочно-кишечного тракта у детей. С помощью опроса детей школьного возраста, позволяющего проводить скрининг, была установлена возрастная частота важнейших специфических для желудочно-кишечного тракта симптомов, были определены социальные и бытовые особенности у детей, имеющих соответствующие жалобы. Определялась сравнительная эффективность инвазивных и неинвазивных диагностических методов для выявления Helicobacter pylori. При помощи качественного теста на наличие антигена Helicobacter pylori в кале была определена сравнительная эффективность различных методов эрадикационной терапии, основанной на применении лекарств, содержащих висмут, и ингибиторов протонной помпы. Представлены данные о переносимости лечения и характере побочных реакций.

ANALYSIS OF CLINICAL EXPERIENCE OF USING FORMULA NUTRILON FOR BOTTLE FEEDING OF THE FIRST YEAR OF LIFE IN UKRAINE

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It is already well known that an optimum feeding behaviour belongs to the leading factors which determine the health of children and adults, their physical and psychic development. In many researches it was observed that correlation exists between nutrition and frequency of appearance and severity of infectious diseases [10,11,22,26,30,36,49]. Yet in 1968 in the monograph of Chandra R.K. "The relation between immunology, nutrition and disease in elderly people" it was confirmed that malnourished people are more susceptible to infections. An attempt to explain this dependence was done in the monograph; however the only progress of immunology during the last decades clarified the pathogenetic mechanisms of these processes [11].

For the first time the term "immunonutrition" was used in 1992 by Daly J. in the article devoted to the metabolic and immunological aspects of enteral nutrition enriched with arginin, nucleinic acids and ω-6-fatty acids in patients after surgical interventions [14]. Later it was found that specially adopted nutrition causes changes of phagocytosis and neutrophil bactericidal activity, total amount of neutrophils, lymphocytes, activated T-lymphocytes, NK-cells, immunoglobulins A,M,G and γ-interferon production in adults and children with various diseases and pathological states [6,13,17,26,31,34].

Accumulation of new data confirms a thesis that infants' nutrition has long-lasting outcomes for health and plays an important role in prevention of a group of chronic non-infectious diseases in adults and influences the function of physiologic systems of child in the future. Children fed inappropriately to their physiological needs have increased frequency and severity of intestinal and other infections and high risk of premature death. Besides that, the lack of nutrients or their disproportion causes failure to thrive, decrease of cognitive function, immune disorders, appearance of allergic reaction, improper realization of genetic potential for child development, change of structure of cellular membranes and receptors, appearance of pathologic intestinal biocenosis [3,4,7,8,30,32,37,45].

Immunity is an important and dynamic system which constantly synthesizes new molecules and compounds, provides high level of cell proliferation and differentiation, maintains a tissue uniqueness, protects our organism from penetration of extraneous proteins and biopolymers, keeps under control humans genetic program by destruction of transformed and old cells, determines the course of infectious, inflammatory, autoimmune and allergic processes [17].

More often immune system is referred as a system of endogenous nutrition. One of the basic function of immunity is disintegration of highly-molecular organic compounds to the primary molecules (amino acids, monosaccharides, fatty acids, lipids, nucleic acids) and providing of effective and complete reutilization of nutriments, appeared in the course of vital processes (dead cells and products of their decomposition, microorganisms, incompletely digested food) [10,17].

From this position, it could be defined that the unique system of cells nutrition in the organism includes 3 subsystems: exogenic digestive system, immune system and intracellular system of disintegration. Their concordance is provided by signal molecules: molecules of immunoglobulins, molecules of major histocompatibility complex and heat shock molecules [17,36].

The immune system of stomach and bowels has got the name of gut associated lymphoid tissue (GALT). It is localised along the surface of stomach and bowels in the lamina propria and includes isolated and grouped lymphoid follicles (Peyer's patches), lymphoid tissue of appendix, tonsils, mesenteric lymph nodes. From the last data, 60-70% of immune cells in child's organism are localised in the gastro-intestinal tract [17,22].

Immunomodulative effect of nutrients in the GALT carries out at subcellular, cellular and intercellular levels of cooperation. It is realised by the change of intestinal flora, properties of cellular membrane and activation of membrane's enzymes, adjusting of receptors expression and affinity, activation of receptor-dependent signal systems or initiation of additional signals in a cell, modulation of transcription factors and cellular cycle, change of gene expression, immunoglobulins, cytokines, regulation of apoptosis [6,17,13,22].

A total surface of mucosal membrane of gastro-intestinal tract is approximately 300 m^2. It is an important barrier, which protects our organism from penetration of pathogenic microorganism from contaminated food and water. Mucous membrane of gastrointestinal tract is an organ with complicated structure, metabolic and regulatory functions which consists of glycomucoproteins, immune cells, immunoglobulins, lysozyme et al. Mucosa is covered by

adhesive microorganisms which not only take part in the processes of food detoxication, immunomodulation and fermentation but also influence on mucus quality and amount. Unspecific protective factors which help to maintain homeostasis of the organism include: the components of saliva, acid of gastric juice, bile, mucus and adequate bowel's peristalsis. The main defence of mucous membranes is considered an antigen-specific secretory IgA [17,22].

Isolated lymphoid follicles contain mainly B-lymphocytes, some T-helpers, and T-suppressors. Peyer's patches are divided into three areas: dome (consists of lymphocytes, macrophages, plasma cells and M-cells, responsible for antigen absorption and transport to the inside of lymphoid follicle), B-cellular area (localized under a dome, contains plenty of B-cells - precursors of IgA producers) and T-cellular area (contains mainly subpopulations of T-lymphocytes). An antigen delivered to the dome of lymphoid follicle by M-cells is released, caught by antigenpresenting cells, disintegrated and presented to T-lymphocytes. As a result there is recognition of antigen. B-lymphocytes which carry superficial IgM switch to the synthesis of IgA. In inductive part of mucosa there are immunocompetent cells which provide initial immune answer. After migration to effector areas (first of all - Lamina propria of mucous membrane) specific T- and B-lymphocytes provide an accumulation of effector cells, responsible in the future for cellular and humoral forms of immune answer. Appendix also contains lymphoid follicles covered by M-cells. Mesenteric lymph nodes contain mainly B-lymphocytes, which are precursors of IgA producers. There is recognition of antigens, caught in bowels, in the mesenteric lymph nodes [17].

In the GALT antigen contacts with T-cells and B-lymphocytes - precursors of plasma cells, which produce IgA. Lymphokines secreted by T-cells switch B-lymphocytes from IgM to IgA production, following by clonal B-cells proliferation and maturation to plasma cells. It is complicated process with involvement of Th2-lymphocytes subclass, interleukins (IL-4,IL-5, IL-6 et al), transforming growth factor β. Mature and prepared to the IgA production B-lymphocytes, through lymphatic vessels and ductus thoracicus get into systemic circulation and spleen. After that they settle in the mucous membranes of different organs, mainly in the place of cells sensibilisation ("homing" effect). Such settling apart is important for the young children and provides protective effect in condition of weaker immune defence. Lamina propria is a place for the synthesis of antigenspecific IgA and polipeptide (joined-chain or j-chain) which is the connecting chain of these immunoglobulins. Then 2 molecules of IgA connected by j-chain (dimer) unite with glicoprotein, secretory component, which stabilizes secretory IgA and reliably protects it from the action of proteolytic enzymes of intestinal juice. IgA complex is packed in cytoplasm vesiculae, transported and released on apical part of mucosa epithelium [17].

Polimeric secretory IgA (sIgA) is able to neutralize effectively viruses, bacteria and their toxins, enzymes. It can partly block the processes of viral and bacterial adhesion to the epithelial cells of mucosa, viral attachment to cellular membranes and inhibit intracellular replication of viruses. It is proved that sIgA enhances activity of phagocytes and lymphocytes, induces significant cytotoxic effect to pathogenic bacteria. The basic role of sIgA is fastening of food and other allergens and infectious agents which can pass epithelium barrier and cause allergic reactions or infectious disease [17,36].

Besides that, in mucosa there are localized intraepithelial gamma- and delta-T-lymphocytes which are considered to be the first link of defence. After stimulation these lymphocytes can differentiate into T-helper (CD4+) or T-killer (CD8+) cells. After antigen stimulation gamma- and delta-T-lymphocytes produce various cytokines, which stimulate growth of epithelial cells, destroy harmful germs (including intracellular) and own unviable epithelial cells. Probably, chronic course of some diseases is related to the primary lack of gamma- and delta-T-lymphocytes [17,22].

Intestinal immune system performs 2 important and antagonistic functions: defence against pathogenic microorganisms (IgA-antibodies and cellular-mediated response) and suppression of immune reaction against food proteins and bacterial components of intestinal microflora [22].

For today several factors have been considered responsible for child's immune response: genetic predisposition to immune disorders (carriers of antigens HLA-DW), transfer of antibodies in the prenatal period and with breast milk, duration of breastfeeding. Important are also the nature of antigen, its dose, frequency of introduction, chemical structure, absorption, pressing, age of child at the first contact with an antigen, penetration of gastrointestinal tract mucosa, state of local immunity and intestinal microflora [17,22].

Maternal milk is an optimum natural regulator of these processes. For today various immunoactive components of breast milk are known which can be divided into several groups according to their action. The first group is presented with antibacterial compounds: secretory immunoglobulins, lactoferrin, lysozyme, lactoperoxidase, nucleotides, antibodies, k-casein and α-lactalbumin, haptocorrin, mucins, lactadherin, free secretory component, oligosaccharides and prebiotics, fatty acids, maternal leucocytes and cytokines, sCD14, complement and complement receptors, β-defensins, toll-like receptors, bifidus factor, tolerance/priming compounds (cytokines: IL 10 and

TGFβ; anti-idiotypic antibodies). The second group contains immune development compounds: macrophages, neutrophils, lymphocytes, cytokines, growth factors, hormones, milk peptides, long-chain polyunsaturated fatty acids, nuckleotides and adhesion molecules. The next group includes anti-inflammatory compounds: cytokines (IL 10 and TGFβ), IL-1 receptor antagonist TNFα and IL-6 receptors, sCD14, adhesion molecules, long-chain polyunsaturated fatty acids, hormones and growth factors, osteoprotegerin [1,5,19,28,33,35,42]. And it yet not complete list of immunoactive components of breast milk! Normal microflora of gastrointestinal tract is an important part of human ecosystem which plays an important role in the immunophysiologic regulation of many processes, directed to the maintenance of immunologic homeostasis. Intestinal microflora has received more and more attention over the last few years 45, [3,9,12,20,24,25,29, 43,45,46]. Evidence has clearly demonstrated that the establishment of indigenous microflora is fundamental for [33, 38]:
generation of immunophysiological regulation in terms of both protection against infection agents and acquisition of immune tolerance;
the non-immunological protective function of the intestinal system - gatekeeper;
a variety of nutritive and metabolic activities of the gastrointestinal system [23,26,30].

Development of the microbiota in the newborn GI tract depends on the original inoculum, the immediate living environment and early feeding practices. Before birth the infant is sterile. During vaginal delivery the natural colonization of the infant starts with bacteria mainly from the vaginal and intestinal flora of the mother [3,33,49].

For the further development of infant's intestinal flora the diet plays a very important role. Bifidobacteria dominate in the intestinal flora of breastfed infants shortly after birth. During artificial feeding without prebiotics the intestinal flora considerably change: the quantity of bifidobacteria and lactobacilli decreases meantime the numbers of opportunistic microorganisms and various bacterial associations increase, what is typical for dysbiosis and mature intestinal microbiota. As a consequence, within a few weeks the intestinal flora becomes different in breastfed and formula fed infants [5,20,21,37].

The species and concentration of bacteria vary from the stomach to the intestine and colon. In the proximal small bowie and stomach, most of the bacteria are aerobic and gram-positive, and the concentration is low, about 10^3 to 10^4 colony-forming units (CFUs)/mL of luminal content. In contrast, within the colon, bacterial concentration increases sharply, reaching 10^{11} to 10^{12} CFUs/mL of luminal content. More then 400 different species of bacteria reside there, the dominant species are anaerobes [24,31,45,49].

Yet in 1900 Tissier proved that bifidobacteria are predominant in intestinal flora of breastfed infants [47]. The prebiotic concept, developed by the Gibson and Roberfoid in 1995 [23], is now firmly established. Human milk is a true prebiotic, and its neutral oligosaccharides are known as the main "bifidus factor" [7]. Besides 7% lactose, human milk contains approximately 1% neutral oligosaccharides. Therefore, these oligosaccharides make up a large part of human milk composition, similar to the proteins level [5]. Prebiotic oligosaccharides are configured in such a way that the small intestinal enzymes cannot hydrolyses them for absorption. Accordingly, they enter the colon intact and provide the "preferential food" for certain colonizing bacteria through the process of fermentation [19].

Prebiotics which can be supplied naturally (brest milk) or be used as food additives (galactooligosaccharides) are non-digestible oligosaccharides which enter the colon and are fermented to change the colonic environment and stimulate the increased proliferation of certain commensal bacteria, bifidobacteria and lactobacillus, which function as probiotics to stimulate intestinal host defences [22,32,33]. This indirect effect of prebiotics, e.g. an altered colonic milieu leading to stimulus of bifidobacteria and lactobacillus proliferation, has been considered as the primary role for prebiotics as a health-promoting dietary supplement. However, more recently several studies have suggested that prebiotics can also have a direct effect on the GULT that does not require the proliferation of commensal probiotic [22].

A great clinical experience of using of oligosaccharide-containing formulas produced by Nutricia company (Nutrilon, Nutrilon Hypoallergic, Nutrilon Comfort for children before 6 months of life and senior) has been accumulated in Ukraine. These formulas contain mixture of oligosaccharides (galactooligosaccharides [GOS] and fructooligosaccharides [FOS] with 9:1 ratio) in the concentration 0,8g/100 ml [37].

In the study of Prof. V.D.Ott and co-authors positive effects in infants fed with formula "Nutrilon-1" (34 children) were established in comparison with the control group (22 children): improved child's behaviour, frequency of defecation, faecal pH, metabolic processes in bowels mucosa, multiplied bifidobacteria and lactobacilli in faeces. Follow-up examination of children biochemical tests allowed making conclusion that this formula not only provides all essential nutrients, but also has positive influence on the functional condition of gastrointestinal tract, normalizes intestinal microbiota and metabolic processes in intestinal mucosa. That is why it could be defined as formula for functional nutrition [39].

Research of Nyankovskyy S.L. and Ivahnenko O.S. was devoted to the investigation of influence of oligosaccha-

ride-containing formulas on establishment of intestinal biocenosis in infants of the first year of life. The study included 40 children: 14 children (average age – 3,2±1,1 months) fed with "Nutrilon-1" formula, 16 children (average age – 7,1±1,4 months) fed with "Nutrilon-2" formula, and 10 children fed with a standard formula without oligosaccharides. The authors found that artificial feeding is followed by dysbiotic changes and progressive diminishing of the quantity of bifidobacteria, lactobacillus, normal E.Coli and multiplying the numbers of aerobic and opportunistic bacteria. Administration of formulas with oligosaccharides during 3 months allowed attaining the reliable increase in numbers of bifidobacteria and lactobacilli, positively influenced establishment of intestinal microbiota making formula feeding as effective as breastfeeding. The results of stool analysis in these children approached the same results as in breastfed infants [36].

Tishchenko V.A. and co-authors in their research which included 20 new-born infants demonstrated that breastfed children and infants who received the formula enriched with oligosaccharides had the same qualitative, quantitative and functional tolerance and also quantitative characteristic of intestinal microbiota [48].

In their study with involvement of 23 children of the first 2 months of life, Prof. T.M. Klimenko and co-authors demonstrated that feeding with "Nutrilon-1" formula results in the decline of faces pH promotes the growth of acidophilic bacteria and warns surplus growth of pathogenic flora [27]. In the research performed by Dorofeyeva G.D. and co-authors in 20 children of the first year of life it was established that using of formula with oligosaccharides effectively ceases dyspepsia, meteorism, peristaltic disorders, promotes body weight increase, normalizes the number of bifidobacteria, however insufficiently inhibits the growth of hemolitic E.Coli [15]. In another research these authors observed 32 children fed with oligosaccharide-containing formulas. The aim of the study was to further investigate the influence of formula feeding with prebiotics on intestinal microbiota in children of the first year of life suffering from intestinal dysbiosis. The researches showed that during observation period the incidences of dyspepsia, meteorism, and peristaltic disorders reduced, body weight increased, sensibilization to food and bacterial allergens and allergic symptoms diminished, quantity of bifidobacteria increased and amount of opportunistic flora decreased (Proteus, Klebsiella, Enterobacter) [16].

Arayev L.N. and co-authors studied an efficiency of oligosaccharide-containing formula in 20 children of the first year of life. It was proved that in comparison with the control group infants fed with this formula had positive dynamics of physical development, stool improvement, augmentation of bifidobacteria and lactobacilli, decrease of lactosonegative and hemolytic species of E.Coli and quantity of opportunistic bacteria (Staphylococcus, Proteus, Citrobacter, Enterobacter) [2].

The data of Zolotareva S.G. and co-authors suggested that the use of formula with oligosaccharides in 11 children aged 6 months resulted in substantial increase of quantity of bifidobacteria, lactobcilli, nornal E.Coli and decline of amount of opportunistic flora, comparatively with children fed with the standard formula [50].

The research of Fedortsiv O.E. was devoted to the study of efficiency of formula "Nutrilon" for infants with malnutrition of I-II stages in a period of transitional and optimum feeding. There were involved 57 children at the age of 2-12 months from Ternopil Child's House. The results of dynamic study of body weight increase showed advantage of the formulas with oligosaccharides comparatively with formulas without oligosaccharides which were used in the control group [21].

The aim of research of Duka K.D. and Ilchenko S.I. was to evaluate the influence of oligosaccharide-containing formula on nutritional status and mucosal immunity of 52 infants from an ecologically unfavourable area. It was found that for artificial-fed children is typical suppressive orientation of immune reactions, lymphopenia, tense humoral immunity with relatively increased levels of IgG, IgA and IgE, low capacity for interferon synthesis, intestinal dysbiosis. According to researchers' data the use of mentioned formula during 3 months allowed to correct significantly insufficiency of immune defence [18].

Prohorov E.V. and co-authors studied the efficiency of formula "Nutrilon-1" in children with functional disorders of gastrointestinal system. The research involved 19 children of 2-6 months with different functional disorders of gastrointestinal tract: regurgitation syndrome, intestinal cramps, and functional constipations. The authors showed that the use of formula with oligosaccharide allows liquidating dysbiosis and improving immune resistance of children [40].

36 children of the first year of life fed with oligosaccharide-containing formula were included into research of Reznichenko Yu.G. and co-authors. 132 infants from the ecologically unfavourable city district were fed with a standard formula (control group). The results suggested that in comparison with the control group children fed with an enriched formula had 25-45% lower morbidity (malnutrition, acute respiratory infections, rickets, anaemia and intestinal dysbiosis) what had positive influence on baby's health [41].

The interesting results were obtained by Mukvich O.M. and Ott V.D. in the research comparing the levels of blood

cytokines, glycosaminoglycans, fucose and hexose in coprofiltrates in children with intestinal dysbiosis. 25 healthy breastfed infants of 1 to 5 months (control group), 85 children of the same age with stage II-III dysbiosis including 45 breastfed infants (group 2), and 40 children fed with prebiotic-containing formula "Nutrilon-1" (group 3) were under observation. The authors demonstrated some positive changes in children from the group 3 after a period of 2-3 weeks of enriched formula feeding: they became more quiet; meteorism, bubbling and abdominal pain on palpation reduced; sicky urges to defecation disappeared; faeces became soft and homogeneous; steatorea and aminorea diminished in 67,5% of infants. At the same time the reliable increase of bifidobacteria and lactobacillus concentration and tendency to decrease of opportunistic flora were noted. Data of this research suggested that children with intestinal dysbiosis develop immune response with macrophages involvement: the levels of proinflammative cytokines (IL-6, IL-6R, IL-8) rose and the concentration of antiinflammative cytokine (IL-4) declined as an evidence of Th1-lymphocytes activation. Children fed with oligosaccharide-containing formula has decreased level of proinflamative cytokines (IL-6, IL-6R, TNF) and increased level of IL-4, that means activation of Th2-lymphocites function, stimulation of humoral immunity and immunoglobulin synthesis. Despite cytokines level did not attain a norm, concentration of their active form (IL-6/IL-6R) after the feeding with formula "Nutrilon-1" didn't differ from control. The synthesis of protective fucoglycoproteins in formula-fed children with oligosaccharide and breastfed children was the same [34].

The analysis of mentioned above researches testify that the level of reliability of considerable part of them is insufficient. That is why the multicentral study aimed to estimate the effectiveness of formula "Nutrilon-1" with oligosaccharides in children of 1-3 months has been started in Ukraine. There are 6 centres participating in the study: Lviv (2 centres), Kyiv (2 centres), Donetsk (1 centre), Odesa (1 centre). 270 term babies are planned to be involved into the study. All participated children are randomized into 3 groups: 90 breastfed infants, 90 infants fed with oligosaccharide-containing formula starting from the first 2 weeks of life; and 90 infants fed with a standard formula without oligosaccharides starting from the first 2 weeks of life. The study has been designed to evaluate children's physical development, nutritional tolerance, levels of SIgA and Defensin in saliva, lysozyme in faeces and intestinal microbiota composition. The mentioned indexes and values are planned to be obtained at achievement of children's age of 1 month, 3 months and 1 year. On the basis of the achieved results the conclusion will be drawn about the possible influence of formula with oligosaccharides on baby's immunity, physical development and intestinal microbiota formation.

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SUMMARY

ANALYSIS OF CLINICAL EXPERIENCE OF USING FORMULA NUTRILON FOR BOTTLE FEEDING OF THE FIRST YEAR OF LIFE IN UKRAINE

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The article describes some current issues of bottle feeding of first year children. Human milk oligosaccharides play an important role in postnatal development of the intestinal flora and development of protective functions of child's organism. Dietary modulation of the intestinal microflora and immune response is one of the important problems in the nutritional sciences today. The present review summarizes the data of experimental research and clinical studies concerning the possible effects of probiotic mixture of galacto-oligosaccharides and fructo-oli-

gosaccharides in Ukraine. The data demonstrate that prebiotic oligosaccharides such as studied mixture provide beneficial effects for formula-fed infants. The results from several studies in Ukraine demonstrate that probiotic oligosaccharides stimulate the growth of bifidobacteria and lactobacilli, reduce the growth of pathogens, decrease faecal pH, normalize the stool consistency and modulate immune system as human milk does.

Key words: immunonutrition, oligosaccharides, intestinal flora, infants.

РЕЗЮМЕ

АНАЛИЗ КЛИНИЧЕСКОГО ОПЫТА ПРИМЕНЕНИЯ СМЕСИ NUTRILON ДЛЯ ИСКУССТВЕННОГО ВСКАРМЛИВАНИЯ ДЕТЕЙ ПЕРВОГО ГОДА ЖИЗНИ В УКРАИНЕ

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В статье описаны современные вопросы искусственного вскармливания детей первого года жизни. Олигосахариды грудного молока играют значительную роль в постнатальном развитии кишечной флоры и защитных функций детского организма. Диетическая модуляция кишечной микрофлоры и иммунного ответа является одной из значительных проблем современной нутрициологии. В представленном обзоре суммируются данные экспериментальных и клинических исследований, касающихся возможных эффектов пробиотических смесей галакто-олигосахаридов и фрукто-олигосахаридов в Украине. Данные свидетельствуют, что изученные смеси обеспечивают благоприятные эффекты у детей, находящихся на искусственном вскармливании. Согласно результатам нескольких исследований в Украине пробиотические олигосахариды стимулируют рост бифидобактерий и лактобацилл, ингибируют рост патогенных бактерий, снижают pH кала, нормализуют консистенцию стула и модулируют иммунную систему подобно грудному молоку.

EIN- UND DURCHSCHLAFPROBLEME IM KINDESALTER: GRUNDLAGEN DER SCHLAFREGULATION UND INTERVENTIONSMÖGLICHKEITEN

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Schwierigkeiten mit dem Einschlafen und dem Durchschlafen, d.h. dem Wiedereinschlafen nach einem Aufwachen in der Nacht, kommen bei Kindern häufig vor. In einer aktuellen Untersuchung von Patienten einer allgemeinpädiatrischen Klinik wurde gefunden, dass 20,6% der Vorschulkinder sowie 17,1% der Schulkinder betroffen waren [4]. Besonders fьr die Entwicklungsphasen des „späten Säuglingsalters" (7. bis 12. Lebensmonat) und des „Kleinkindalters" (2. bis 4. Lebensjahr) trifft zu, dass die Schlafproblematik in einem engem Zusammenhang mit der normalen physischen und psychischen Entwicklung steht.

Die Beratung von Müttern und Vätern, deren Kinder Ein- und/oder Durchschlafprobleme haben, erfolgt vielfach unter dem Motto „Jedes Kind kann schlafen lernen" [19]. Im folgenden sollen die wissenschaftlichen Grundlagen (Ontogenese des Schlafs) dargestellt werden, auf denen das Konzept des „Schlafenlernens" basiert. Dabei wird erkennbar, dass einerseits ein Teil der betroffenen Kinder von verhaltenstherapeutischen Interventionen profitieren wird, andererseits kein „Patentrezept" vorliegt, das in allen Fällen die gewünschte Veränderung des Ein- und Durchschlafverhaltens garantiert.

Elternratgeber, Elternzeitschriften und auch Artikel in Tageszeitungen, die Ratschläge im Sinne einer „Alltagspsychologie" geben, nehmen eine wichtige Vermittler-Funktion wahr [2,3,18]. Betroffene Eltern haben prinzipiell eine andere Perspektive als professionelle Helfer. Ärzte sind aufgrund ihrer Ausbildung in erster Linie als Experten für Krankheiten anzusehen. Ärztlicher Rat wird öfter gegeben als befolgt [14]. Ratschläge von Selbsthilfegruppen, von anderen betroffenen Eltern, erreichen manchmal eine höhere Akzeptanz. Diese Diskrepanz ergibt sich aus den unterschiedlichen Perspektiven des Beraters und des Rat-

suchenden; sie kann auch als Mangel an kognitiver Kongruenz bezeichnet werden [31]. Die Theorie der kognitiven Kongruenz (Cognitive congruence theory, Cornwall 1979) postuliert, dass sich Experten und Novizen durch verschiedene kognitive Strukturen unterscheiden. Deshalb ist ein Berater, der nicht den Experten-Status besitzt, besser in der Lage, Vorwissen, Erfahrungsmangel, Denkart, Sprachgebrauch etc. der Betroffenen in seine Beratung einzubeziehen [31]. Bei der Beurteilung des kindlichen Schlaf-Wach-Verhaltens gilt es, voreiliges Pathologisieren zu vermeiden und sich zunächst mit den normalen Entwicklungsvorgängen vertraut zu machen [16,28].

Allgemeine physiologische Grundlagen der Schlafregulation [6,17,34]

Schlafen und Wachen sind Ausdruck biologischer Rhythmen, die den 24-Stunden-Tag in Phasen der Ruhe und der Aktivität gliedern. Ein basaler Ruhe-Aktivitäts-Zyklus mit abwechselnden Phasen vermehrter und verminderter Aktivität (basic rest/ activity cycle (BRAC) nach Kleitman) wurde zuerst für den Wachzustand beschrieben. Es handelt sich um einen ultradianen Rhythmus mit einer Periodenlänge von 90-100 Minuten beim Erwachsenen. Dieser Rhythmus setzt sich während des Schlafens fort und gliedert den Schlaf in mehrere aufeinanderfolgende Non-REM/ REM-Zyklen. Die zirkadiane Periodik wird durch sogenannte innere Uhren erzeugt, die durch periodisch auftretende Auß enreize, sogenannte Zeitgeber, auf bestimmte Periodenwerte eingestellt werden (Synchronisation). Der Nucleus suprachiasmaticus des Hypothalamus wird als morphologisches Korrelat der inneren circadianen Uhr angesehen. Die Periodendauer des endogenen circadianen Rhythmus beträgt im Mittel 25 Stunden. Eine Zeitinformation durch die Sinneswahrnehmung von Umweltreizen, z.B. Wechsel von Helligkeit am Tage und Dunkelheit in der Nacht, ist für ein Entrainment auf eine Periodendauer von 24 Stunden erforderlich.

Beim Menschen ist der Schlaf nicht monophasisch, d.h. streng circadian, sondern biphasisch, d.h. semicircadian organisiert. Neben der nächtlichen Hauptschlafperiode ist beim Erwachsenen noch eine weitere am frühen Nachmittag, etwa halbwegs zwischen zwei Hauptperioden gelegene Episode mit vermehrtem „Schlafdruck" festzustellen. Dies ist die Tageszeit, in welcher im Verlaufe des Älterwerdens von Kindern die letzten „Naps" auftreten (Abb. 1). Es ist die Zeit, in der das charakteristische „postprandiale Tief" bei Gesunden auftritt, und die größ te Häufung von (krankhaften) Schlafanfall-Attacken bei Narkolepsie-Patienten zu beobachten ist.

Schlafontogenese [26]

Schlaf ist ein aktiver biologischer Prozess, in den zahlreiche neuronale Netzwerke einbezogen sind. Unter Berücksichtigung reifungsbezogener Aspekte des Schlafs wird deutlich, wie sich der Output dieser neuronalen Netze verändert. Am Ende der Fetalzeit kommt es zu wichtigen Fortschritten der funktionellen Hirnreifung, die sich während der ersten Lebensmonate fortsetzen. Dieser Entwicklungsfortschritt kann an folgenden Befunden abgelesen werden:
1. Powerspektrum des EEG: Das EEG-Powerspektrum zeigt im hochfrequenten Bereich eine Zunahme der Energie, die während des gesamten Entwicklungsganges von der Neonatalperiode, über das Säuglingsalter bis in spätere Phasen der Kindheit nachweisbar ist.
2. Arousalschwelle: Beim jungen Säugling sind die Arousalschwellen während des Schlafs erhöht.
3. Zirkadiane Rhythmik: Beim Neugeborenen und jungen Säugling werden die Schlafperioden häufig unterbrochen. Sie verteilen sich über den gesamten 24-Stunden Tag-Nacht-Zyklus. Mit zunehmender Ausreifung des Kindes nimmt die Fragmentierung des Schlafs ab (d.h. Abnahme der Arousalfrequenz). Die nächtlichen Schlafzeiten konsolidieren sich in der Regel im Laufe der ersten 2 bis 4 Lebensmonate. Im Alter von 12 Monaten bestehen noch 2 kurze Schlafperioden am Tage (Abb. 1).
4. Ultradiane Rhythmik
a. Periodendauer: Neugeborene haben eine kürzere Periodendauer (30-70 Minuten) des ultradianen Schlafzyklus (Abb. 2A). Beim älteren Säugling findet sich eine längere Periodendauer (75-90 Minuten), die sich den adulten Verhältnissen annähert (Abb. 2B).
b. Schlafstadienorganisation: Parallel zur Entwicklung vom Neonaten zum jungen Säugling kommt es zu einer Reorganisation des Schlafs, die eine veränderte Schlafarchitektur und ein verändertes elektroenzephalographisches Kontinuitätsverhalten umfaß t.

Referenzwerte [20]

Die Zeitstruktur und die quantitative Struktur des Schlafes sind bei Erwachsenen streng festgelegt und robust. Die Anteile der einzelnen Stadien, aufaddiert über eine ganze Schlafperiode, sind unter normalen Umständen (d.h. normale Lage der Schlafperiode im 24-Stunden-Tag) für ein Individuum, aber auch im Vergleich zwischen gleichaltrigen Individuen, die unter ähnlichen biologischen Bedingungen leben, relativ konstant.

In Abhängigkeit vom Lebensalter zeigen sowohl die Schlafmenge pro 24 Stunden (Tab. 1) als auch die Verteilung der Schlafphasen innerhalb des 24-Stunden-Tages (Abb. 1), die Anteile der Schlafstadien (Leicht-, Tief-, REM-Schlaf) an der Gesamtschlafzeit (Abb. 3) sowie die Verteilung der Schlafstadien im Verlaufe einer Schlafperiode einen typischen Entwicklungsgang (Abb. 4 u. 5) [1,22,24,29].

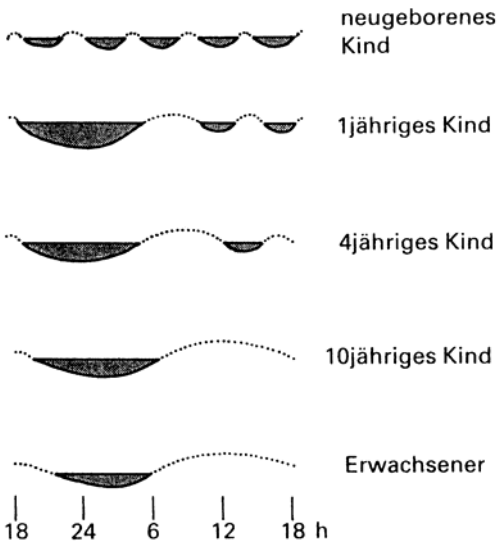

Abbildung 1. Verteilung der Schlafperioden über 24 Std. in verschiedenen Lebensabschnitten [24]

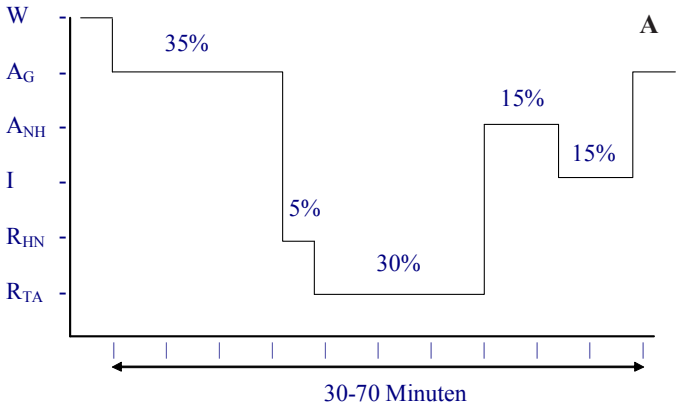

Abbildung 2A: Schematische Darstellung eines Schlafzyklus beim Neugeborenen [26]
W = Wach, AG = gemischtfrequenter Aktivschlaf, ANH = niedrigamplitudig-hochfrequenter Aktivschlaf, I = Indeterminierter Schlaf, RHN = hochamplitudig-niedrigfrequenter Ruhigschlaf, RTA = Tracé alternant, diskontinuierlicher Ruhigschlaf

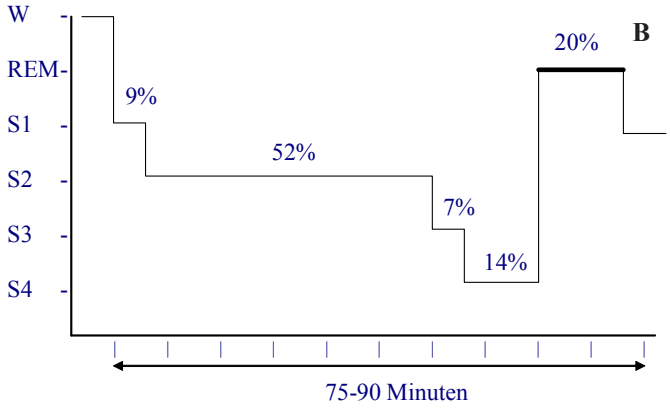

Abbildung 2B: Schematische Darstellung eines Schlafzyklus beim Erwachsenen. Die Zahlenangeben [15] entsprechen den durchschnittlichen Anteilen der Schlafstadien an der Gesamtschlafdauer. In Wirklichkeit besteht ein Nachtschlaf aus mehreren aufeinanderfolgenden Zyklen mit jeweils anderen prozentualen Anteilen von S1, S2, S3, S4 sowie REM. W = Wach, REM = Rapid eye movement-Schlaf, S1 und S2 = Leichtschlafstadien (NREM), S3 und S4 = Tiefschlafstadien (NREM)

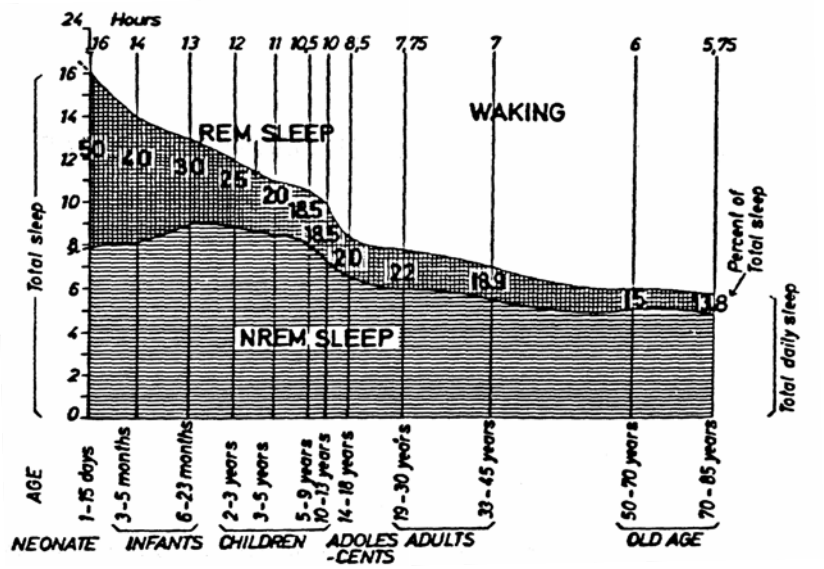

Abbildung 3: Anteile von REM- und Non-REM-Schlaf an der Gesamtschlafzeit in verschiedenen Lebensabschnitten [25]

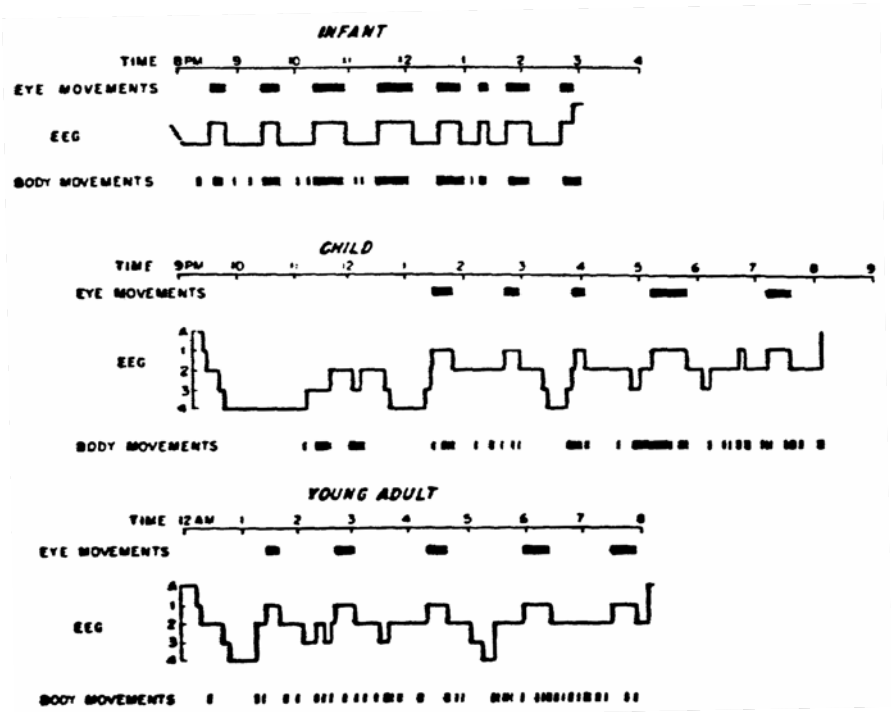

Abbildung 4: Zyklische Organisation der Schlafstadien (infant/ child/ young adult) [1]

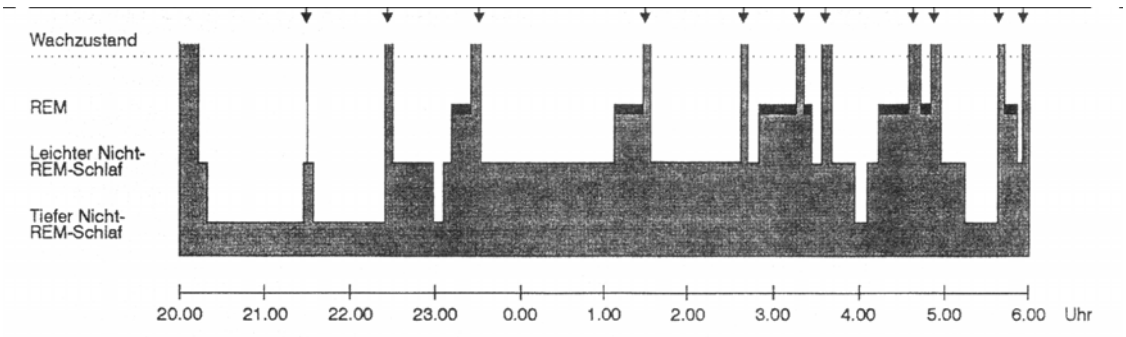

Abbildung 5: Typische nȍchtliche Schlafzyklenfolge beim Kleinkind [19]

Tabelle 1: Schlafdauer pro 24 Stunden in den ersten 5 Lebensjahren [5]

Alter [J.]		0,5	0,75	1	1,5	2	3	4	5
Anzahl der Kinder		115	73	91	86	315	319	332	280
	Jungen	58	36	47	44	156	164	168	142
	Mädchen	57	37	44	42	159	155	164	138
Gesamtschlaf [Std]									
	M	14,8	15,3	15,1	14,9	14,5	13,6	12,6	12,0
	SD	1,5	1,2	1,1	0,9	1,1	1,1	1,0	0,8
Nachtschlaf [Std]									
	M	11,3	11,9	12,5	12,4	12,3	12,1	11,8	11,8
	SD	1,1	1,1	0,9	0,8	1,0	0,9	0,8	0,8
Tagschlaf [Std] *									
	M	3,7	3,5	2,7	2,6	2,3	2,0	1,8	1,4
	SD	1,3	1,2	0,9	0,7	0,7	0,6	0,6	0,5
Häufigkeit des									
Tagschlafes [%]		100	99	98	99	96	75	54	21

** nur Kinder, die tagsьber noch schlafen*

J. = Jahre, M = Mittelwert, SD = Standardabweichung

Der Mittelwert der Schlafmenge pro 24 Stunden nimmt von 16 Stunden beim Neugeborenen auf 11 Stunden beim 5-Jährigen ab (Tab. 1). Die Standardabweichung ist mit 2 Stunden relativ groß [5,22]. Die Verteilung der Schlafphasen innerhalb des 24-Stunden-Tages zeigt beim Neugeborenen und jungen Säugling eine relativ regelmäßige Abfolge relativ kurzer Schlaf- und Wachperioden, unabhängig von Tag und Nacht [24]. Hingegen ist in der zweiten Hälfte des ersten Lebensjahres eine stärkere Synchronisierung durch äußere Zeitgeber bereits deutlich erkennbar. Die längste Schlafperiode fällt in die Nacht, die längste Aktivitätsperiode in den Tag. Die Häufigkeit kurzer Schlafperioden am Tage („Naps") nimmt bis zum Alter von 5 Jahren deutlich ab (Abb. 1). Der Anteil des Non-REM-Schlafes an der Gesamtschlafzeit (Abb. 3) steigt von einem Mittelwert von 50% beim Neugeborenen auf 80% beim 5-jährigen Kind an, der Anteil des REM-Schlafes nimmt von 50% auf 20% ab [22,25]. Die Abbildung 4 zeigt typische Verteilungsmuster der Schlafstadien in verschiedenen Lebensabschnitten: Beim Säugling regelmäßiger Wechsel zwischen ruhigem und aktivem Schlaf; beim Kind längere Zyklen mit der Differenzierung von verschiedenen Stadien des Non-REM-Schlafes; beim Adoleszenten ein später Schlafbeginn und geringer ausgeprägte Stadien des ruhigen Schlafes (Non-REM 3 und 4) sowie ein relativ höherer REM-Anteil. In Abbildung 5 ist ein typisches Hypnogramm des Kleinkindalters dargestellt. Tiefschlaf ist im ersten Zyklus ausgeprägt, tritt aber auch wieder gegen Morgen auf. Kurzes Aufwachen aus dem Leicht- und REM-Schlaf mit spontanem Wiedereinschlafen nach wenigen Minuten ist alterstypisch und kann mehrmals in der Nacht auftreten [19].

Varianten der Norm: Kurz- und Langschläfer; Morgen- und Abendtypen.

Für die Bewertung des normalen und gestörten Schlafs bieten altersbezogene Referenzwerte wichtige Orientierungsmarken [27,30]. In den letzten Jahren hat ein Umdenken stattgefunden. Der wesentliche Punkt in der Praxis ist die Frage, wann eine Therapie indiziert ist. Nicht die Schlafmenge, sondern die gestörte Tagesverfassung des Patienten wird heute als Entscheidungskriterium in den Vordergrund gerückt [12].

Allgemein bekannt sind die Normvarianten der Schlafdauer (Kurz- und Langschläfer) und die Normvarianten der Lage der Schlafperiode im 24-Stunden-Tag ("Eulen" und "Lerchen"). Beim Erwachsenen beträgt die mittlere Schlafdauer des gesunden Normalschläfers 8 Stunden (7 bis 9 Std.). Demgegenüber schlafen gesunde Langschläfer regelmäßig 8 bis 9,5 Std. und mehr, gesunde Kurzschlдfer schlafen regelmäßig weniger als 8 Std., häufig 7 bis 6,5 Std. und weniger. Diese Typen sind bereits in der Kindheit erkennbar [9].

Die individuelle zirkadiane Phasenlage ist ein normal verteiltes Merkmal (Chronotyp), dessen extreme Ausprägung als Morgen- und Abendtyp besondere Beachtung findet. Morgenmenschen ("Lerchen") gehen früh zu Bett und stehen in der Regel auch früh auf. Abendmenschen ("Eulen") gehen spät zu Bett und brauchen am nächsten Morgen entsprechend länger, bis sie leistungsfähig werden.

Die Betrachtung des kindlichen Schlaf-Wach-Verhaltens vor dem Hintergrund von (physischen und psychischen) Reifungs- und Entwicklungsvorgängen führt zu einer differenzierten Beurteilung, die zwischen „normal", „auffällig" und „pathologisch" unterscheidet. Als „auffällig" kann das gekennzeichnet werden, das von physiologischen Referenzwerten abweicht, dem gleichwohl kein

Krankheitswert zukommt. Im Hinblick auf therapeutische Interventionen ist eine weitere Unterscheidung wichtig: „Was ist tolerabel? Was ist behandlungsbedürftig?" Hier sind neben physiologischen Parametern zusätzlich psychosoziale (Belastungs-) Faktoren der betroffenen Familien zu berücksichtigen.

Psychologische Grundlagen der normalen frühkindlichen Entwicklung [9,13,33].

Für die Bewertung von Ein- und Durchschlafstörungen bei Säuglingen und Kleinkindern sind Grundkenntnisse über die Stadien der normalen Entwicklung der frühen Mutter-(Eltern-) Kind-Beziehung unerlässlich. Pathophysiologische Mechanismen der Insomnie bei Erwachsenen (intrinsische Schlafstörungen, Tabelle 2) können nicht auf kindliche Ein- und Durchschlafstörungen (extrinsische Schlafstörungen, Tabelle 2) übertragen werden. Die Dynamik der Beziehungen innerhalb einer Familie ist zu berücksichtigen [9]. Für Anwendungen in allen Bereichen der psychosozialen Gesundheit hat sich die Bindungstheorie (nach Bowlby) als sehr praktisch erwiesen. Die Interaktionen zwischen dem Säugling und seiner bemutternden Person lassen sich zunächst als externe Organisation des Säuglings beschreiben. Neugeborene und Säuglinge verfügen bereits über Fähigkeiten mit sozialem Charakter und zeigen aktives Verhalten. Zwischen der primären Bezugsperson (der Mutter) und dem Säugling entwickelt sich eine wechselseitige Kette von Handlungen, die ihren deutlichsten Niederschlag in dem Problem der Trennung von Mutter und Kind in bestimmten sensiblen Phasen der Entwicklung findet (Trennungsängste). Von psychoanalytischer Seite wird diese Phase als die orale Phase bezeichnet, angemessener wäre die Bezeichnung „Phase der Bindung". Die erste Bindung wird etwa um den siebten Lebensmonat entwickelt. Die physiologische Funktion des Schlaf-Wach-Rhythmus wird durch die Art und Güte der Versorgung in Abhängigkeit von den Bedürfnissen des Kindes geregelt. Mütterliche Feinfühligkeit muss in Zusammenhang mit der Eigenart des Kindes gesehen werden. Die Eigenart bzw. das Temperament des Kindes macht es der bemutternden Person leichter oder schwieriger, die Signale des Kindes zu verstehen, die geeigneten beruhigenden Verhaltensweisen zu finden (Selbstregulierung), und die Angemessenheit ihrer Reaktionen zu bewerten.

Tabelle 2: Klassifizierungsmöglichkeiten extrinsischer Schlafstörungen (nicht-organische Insomnie) bei Kindern entsprechend der Internationalen Klassifikation der Schlafstörungen, ICSD [12]

I. Dyssomnien
A. Intrinsische Schlafstörungen

B. Extrinsische Schlafstörungen
Inadäquate Schlafhygiene
Umweltbedingte Schlafstörung
Anpassungsbedingte Schlafstörung
Schlafstörung aufgrund mangelnder Schlafdisziplin
Einschlafstörung durch Fehlen des gewohnten Schlafrituals
Schlafstörung bedingt durch nächtliches Essen und Trinken

C. Störungen des zirkadianen Schlafrhythmus

II. Parasomnien

III. Schlafstörungen bei körperlichen/ psychischen Erkrankungen

Das zweite Lebensjahr ist durch eine Intensivierung der Bindung gekennzeichnet. Die Nähe der Mutter wird gesucht, weil sie Sicherheit bedeutet. Gleichzeitig machen sich in diesem Alter Autonomiebestrebungen des Kindes bemerkbar. Das Kind exploriert, inwieweit sich seine Umgebung beeinflussen lässt. Eine Ambivalenz von Abhängigkeitsbedürfnissen und Autonomiestreben kennzeichnet die normale Situation in diesem Alter. Ist der Vater nicht anwesend, kann die ausbleibende „Triangulierung" zu verschiedenen psychosomatischen Symptomen führen, u.a. Ein- und Durchschlafstörungen. Schlafstörungen können jeweils im Zusammenhang mit Erkrankungen, emotionalen Belastungen und Erwartungsspannung auftreten. In einer australischen Studie war die Wahrscheinlichkeit von Ein- und Durchschlafstörungen bei 6-12 Monate alten Kindern größer, wenn deren Mütter subklinische Zeichen der Depression aufwiesen [7,16]. Im Sinne eines Circulus vitiosus wird die emotionale Überforderungssituation der Mutter durch die kindlichen Schlafstörungen weiter verstärkt [8]. Die physiologische Regulation des Schlafes ist also in enger Abhängigkeit zur psychologischen Gesamtverfassung zu sehen.

Muss schlafen gelernt werden?

Gesunde Kinder durchlaufen im Rahmen ihrer normalen

Entwicklung die dargestellte physiologische Schlafontogenese; insofern gibt es für gesunde Kinder nichts zu lernen. Die endogene Schlaf-Wach-Regulation ist jedoch durch exogene Einflüsse leicht störbar. Deshalb sollten Eltern, Betreuer von Kindern (Erzieher (-innen), Hebammen, Kinderkrankenschwestern und –pfleger, Ärzte) die Entwicklung des kindlichen Schlaf-Wach-Verhaltens kennen bzw. lernen, um die normale Entwicklung in der richtigen Weise fördern und unterstützen zu können. Mit Blick auf die psychologischen Grundlagen der Schlafontogenese kann man sagen, dass Eltern und Kind lernen müssen, wie sie aufeinander reagieren und miteinander umgehen. Sicherlich beinhaltet das Familienleben gemeinsame Aktivitäten (am Tage), auch Konflikte, die dazu führen, dass „man sich aneinander reibt" oder die Emotionen wechselseitig „hochpuscht"; daneben ist es von wesentlicher Bedeutung, dass man (zur Nacht) auch miteinander zur Ruhe kommen kann.

Möglicherweise wurden diese Zusammenhänge in früheren Generationen intuitiv gewusst, heute fehlen vielfach die „traditionellen Ratgeber" der früheren Großfamilien. Moderne Lebensweisen in hochtechnisierten Gesellschaften und die damit verknüpften demographischen Veränderungen fördern einen Trend zur dysfunktionalen Familie [21]. Verunsicherte Eltern werden vielfach mit Ratschlägen überhäuft; gleichwohl mangelt es an der vertrauensvollen Beziehung als Grundlage für das Annehmen und Umsetzten der Empfehlungen.

Verhaltenstherapeutische Maßnahmen [32]

Wesentliche Voraussetzungen für eine wirksame Verhaltensmodifikation bestehen darin, dass die gewünschte kindliche Verhaltensänderung eingangs ausführlich mit den Eltern diskutiert wird, und dass beide Elternteile hinsichtlich der Behandlungsziele übereinstimmen müssen. Bei der Verhaltensmodifikation werden vornehmlich die Prinzipien der Löschung, d.h. der Beseitigung eines positiven Verstärkers (z.B. Aufgabe des nächtliches Schlafens der Mutter beim Kind), der positiven Verstärkung (Lob, Anerkennung oder ein kleines Geschenk für das Erreichen eines Zieles, wie z.B. erfolgreiches Durchschlafen), der Verhaltensformung und graduellen Annäherung (z.B. allmähliches Vorverlegen der abendlichen Schlafenszeit) und des Diskriminationslernens (z.B. Einsatz von Zu-Bett-Geh-Ritualen als dem Schlaf vorausgehende Bedingung) eingesetzt. Techniken der Verhaltensbeeinflussung, die sich an dem Erscheinungsbild des kindlichen Schlafproblems orientieren, sind in der Tabelle 3 zusammengefasst.

Tabelle 3. Techniken zur Beeinflussung kindlicher Einschlaf- und Durchschlafprobleme [32]

A. Behandlung von Kindern, die nicht allein einschlafen wollen
    1. Ankündigung des geplanten elterlichen Verhaltens
    2. Graduelles Ausblenden des bisherigen elterlichen Verhaltens
    3. Einsatz von Zubettgeh-Ritualen
    4. Spielobjekte

B. Behandlung von Kindern, die sich weigern, zu Bett zu gehen
    1. Festsetzung der Schlafenszeit
    2. Graduelle Vorverlegung der Schlafenszeit
    3. Festsetzung der Schlafenszeit in Kombination mit Vorgehen wie bei A. 1. bis 4.

C. Behandlung von Kindern, die nachts ins Bett der Eltern kommen
    1. Das Kind in das eigene Bett zurückbringen
    2. Verstärkung

D. Behandlung von Kindern, die nicht durchschlafen
    1. "Checking" bei Kleinkindern
    2. Verstärkung bei größeren Kindern
    3. Nachtlicht und Spielobjekte

Bei der Anwendung von verhaltenstherapeutischen Methoden sind Voraussetzungen von Seiten des Kindes zu beachten. Die „Checking"-Prozedur kommt in Frage für körperlich gesunde Kinder im Alter von mindestens 5-6 Monaten (Lebensalter=Entwicklungsalter) mit intakter Eltern-Kind-Beziehung [19]. Die „Freiburger Sanduhrmethode" [23] sollte nur angewandt werden, wenn das Kind älter als 12 Monate ist und **ü**ber hinreichende Trennungskompetenz verfügt.

Schlafbahnung [10,24].

Förderlich zur Schlafbahnung ist ein gut durchgelüftetes, angewärmtes Schlafzimmer, evtl. auch ein vorgewärmtes Bett, eine zweckmäßige, d.h. leichte Abendmahlzeit und – wesentlich – die abendliche Fernsehüberwachung [24]. Ernst u. Ernst [10] sprechen von Optimierung unzureichender äußerer Bedingungen (Schlafumgebung).

„Timing“ und „Ritual“ [11,24]

Durch Beobachtung des kindlichen Verhaltens erfassen die Eltern den Müdigkeitspunkt ihres Kindes. In Form eines Rituals läuft an jedem Abend ein stets gleichbleibender stufenförmiger Ablauf der Schlafvorbereitungen ab [24]. Frank u. Freisleder [11] empfehlen die Gestaltung des Tagesablaufs, gestützt auf ein Schlaf-Wach-Protokoll bzw. Schlaftagebuch. Solche elterlichen Aufzeichnungen bieten sowohl diagnostische Aspekte („Wer hat das Problem? Wie hoch ist die Motivation, etwas zu ändern?”) als auch therapeutische Aspekte (Versachlichung; Distanzierung von der Betroffenheit; Motivierung; Vergewisserung über das aktuelle Problem; Rechenschaft über den Verlauf; Dokumentation eines Erfolges; Rückversicherung). Im günstigen Fall helfen die Aufzeichnungen, die Eltern aus ihrer Hilflosigkeit herauszuholen und in ihrer Kompetenz als Kotherapeuten zu stärken.

Extinktionsmethode [19].

Kast-Zahn u. Morgenroth [19] beschreiben das Vorgehen, empfehlen es in dieser Form aber ausdrücklich nicht. Die gewohnten Einschlafhilfen des Kindes fallen weg. Wenn die Kinder schreien, bleibt die erwartete Zuwendung aus (Wegfall positiver Verstärker). Die Kinder lernen, dass sie auch auf Dauer mit Schreien nichts erreichen. Das „Einfach-schreien-lassen” führt nur bei konsequentem Durchhalten der Methode zum Erfolg, was bedeuten kann, dass die Kinder tatsächlich mehrere Tage hintereinander bis zum Einschlafen über einen langen Zeitraum durchschreien.

„Checking“ [32]

Bei dieser Vorgehensweise geht jeweils ein Elternteil nachts zum Kind, sofern dieses ruft oder weint, um ihm ein Gefühl der Sicherheit zu geben. Zugleich wird jedoch auch mit einer gewissen Bestimmtheit vermittelt, dass das Kind nicht hochgenommen wird, sondern vielmehr zum Schlaf zurückfinden soll. Sodann verlässt der Elternteil das Zimmer, auch wenn das Kind noch nicht eingeschlafen ist. Sofern das Kind weiter weint, erscheint der Elternteil erst nach wenigen Minuten wieder und wiederholt das Vorgehen, bis das Kind einschläft. Die Wartezeit, bis der Elternteil erneut zum Kind geht, wird allmählich von 5 Minuten auf 11 Minuten gesteigert. Bei konsistentem Handeln der Eltern, das sowohl Entschiedenheit wie Fürsorge ausdrückt, lernt das Kind innerhalb weniger Nächte, dass Weinen und Rufen nicht zu dem erwünschten Ergebnis führt, nachts aufzustehen oder den Kontakt mit den Eltern zu haben.

Kast-Zahn u. Morgenroth [19] sprechen von Extinktionsmethode mit Checking-Prozedur.

Freiburger Sanduhrmethode [23]

Rabenschlag [23] beschreibt ein Vorgehen, bei dem die Eltern ihr Kind mit einem Ritual zu Bett bringen (Dauer <30 Minuten). Wenn das Kind nachts ruft und weint, wird das Ritual in Kurzform (3 Minuten Dauer) wiederholt. Die Wartezeiten der Eltern werden von anfangs 3 Minuten in Verlaufe mehrerer Nächte auf 6 Minuten und schließ lich auf 9 Minuten gesteigert.

Psychotherapeutisches Vorgehen [10,22].

Wurden bereits Maß nahmen wie die schlafhygienische Beratung und die verhaltenstherapeutischen Behandlungen durchgeführt und wurde keine Besserung der kindlichen Schlafprobleme erreicht, so kann dies auf eine tiefergreifende Störung der psychosozialen Situation hinweisen [22]. In diesen Fällen sollte eine fundierte Erziehungsberatung und gegebenenfalls eine spezielle Psychotherapie (Spieltherapie, Familientherapie, Ehepaartherapie) eingeleitet werden. Hier rückt der finale Aspekt der kindlichen Schlafstörung und die Behandlung der gestörten Mutter-Kind-Beziehung in den Mittelpunkt der Betrachtung. Ernst u. Ernst [10] teilten die Störungen der Mutter (Eltern)-Kind-Beziehungen in drei Gruppen: Die erste Gruppe ist charakterisiert durch Verwöhnung und Überängstlichkeit, durch die die Kinder zu stark an die Mutter gebunden und in Unselbständigkeit gehalten werden. Die zweite Gruppe – Deprivation – umfasst die Kinder, die ihre Schlafstörungen aufgrund von Trennungen von den Eltern bekommen. Die dritte Gruppe ist die der Privation und umfasst all jene Kinder, die trotz Anwesenheit der Mutter entweder direkt vernachlässigt oder zwar viel, aber qualitativ „schlechte”, nicht kindgemäß e Zuwendung erhalten. Neben der Qualität der mütterlichen Zuwendung ist als weiterer Faktor das kindliche Temperament zu berücksichtigen. Die Behandlung der gestörten Mutter (Eltern)-Kind-Beziehung sollte dem ausgebildeten Kinder- und Jugendlichen-Psychotherapeuten vorbehalten bleiben [10]. Die medikamentöse Therapie kann zwar den Einstieg in die Psychotherapie erleichtern, jedoch niemals ersetzen; sie sollte daher die Ausnahme bleiben [10].

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SUMMARY

SLEEP PROBLEMS IN CHILDHOOD: BASIS OF SLEEP REGULATION AND INTERVENTION POSSIBILITIES

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In the article there is provided the up-to-date information about foundamentals of sleep regulation in childhood, sleep disturbances and treatment possibilities as well.

Key words: sleep, childhood.

РЕЗЮМЕ

ПРОБЛЕМЫ СНА В ДЕТСКОМ ВОЗРАСТЕ: ОСНОВЫ РЕГУЛЯЦИИ СНА И ВОЗМОЖНОСТИ ВМЕШАТЕЛЬСТВ

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В статье представлены современные данные об основах регуляции сна в детском возрасте, нарушениях сна, а также средствах лечения.

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FEEDING DIFFICULTIES IN CHILDREN AND ADOLESCENTS WITH CHRONIC ILLNESS

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1. Transitional feeding, weaning and associated problems
Eating and swallowing are such a natural, subconscious act that it is easy to forget that eating is a learned skill. It requires the coordination of the movement of at least 26 pairs of striated muscles in the mouth, pharynx and oesophagus by 5 cranial nerves, the brain stem and the cerebral cortex [1]. Unlike breathing, which is similar to feeding in that it is largely subconscious with some element of voluntary control, most of feeding is learned behaviour. While in the neonate feeding begins as a result of a range of reflexes (gag, phasic bite, tongue protrusion, rooting, suckling and swallowing reflexes) it later becomes a voluntary act with only the pharyngeal and oesophageal parts of the swallow remaining under reflex control. Transitional feeding from a predominantly sucking mode of feeding to mature solid food eating begins between 3 and 6 months of age. Growth in the upper digestive tract occurs as the mandible grows downwards and forwards and the hyoid bone and larynx move downwards. The sucking pads are gradually absorbed. All of these changes contribute to an enlargement of the buccal cavity which allows food to be manipulated between the tongue and the buccal wall. The gradual eruption of teeth allows the infant to progress towards eating harder and lumpier foods. So growth and maturation play a role in feeding development, but learning from experience is also crucial. An important aspect of learning is sensation and sensory feedback. This involves proprioception, touch, pressure, temperature, and taste. Other important factors contributing to learning are gross and fine motor development, the methods of food presentation, and cognitive development.

1.1. Weaning Failure
Weaning is the process whereby an infant becomes accustomed to an intake of solid food in preference to milk. This transitional phase may be associated with disorganization of feeding and infants are often seen to be agitated or unsettled at this stage. During this critical period infants are vulnerable to develop feeding difficulties. Feeding is a reciprocal process that depends not only on the abilities and characteristics of the infant but also those of their parent. Avoidance by parents of encouraging the infant to make the transition from milk to solids at this time may make the process considerably more difficult at a later time. Similarly, prolonged nasogastric tube feeding or any other noxious stimulus in the oro-pharynx during this period may be associated with weaning failure.

1.2 Infant feeding problems
There has been remarkably little research on the development of infant feeding problems. Seminal studies by Dahl and colleagues in Sweden on 50 infants meeting strict diagnostic criteria, however, have helped to identify the characteristics and consequences of infant feeding problems [2-5]. Feeding problems in this group had been ongoing for a mean duration of five months. The commonest problems were refusal to eat (56%), colic (18%) and vomiting (16%). The majority (86%) of infants was underweight and 14% were malnourished (> 2 SD below mean weight for age). Physical disorder (e.g. gastro-oesophageal reflux) was present in only 14% but in 6% this was a serious organic disease (e.g. congenital heart disease – see below). Follow up studies at 2 years showed that over a third of the refusal to eat group had a persistent feeding problem [4].

Problems with crying and feeding are two of the most common paediatric concerns of parents in early infancy. Colic is considered to occur when infants cry for three or more hours per day, for at least three days of the week, for at least three weeks [6]. Miller-Loncar and colleagues (2004) examined the relation between colic in infants between 6 and 8 weeks of age and feeding difficulties [7]. Compared with a control group infants with colic displayed more difficulties with feeding; including disorganized feeding behaviours, less rhythmic nutritive and non-nutritive sucking, more discomfort following feeds and lower responsiveness during feeding interactions. Not surprisingly perhaps, mothers in the colic group reported higher levels of parenting stress. These results suggest that feeding may be a reasonable area on which to focus interventions in the management of the infant with colic.

2. Oral-Motor Impairment
Oral-Motor Impairment may occur as a result of structural lesions (e.g. cleft lip and palate, macroglossia, Pierre-Robin syndrome, oesophageal atresia) or functional lesions (e.g. cerebral palsy, bulbar and pseudobulbar palsies, myopathies). In order to attain optimum oral-motor skill a child must have the ability to move oral and facial structures independently of the rest of the body. Poor control of posture, uncoordinated movements of the upper limbs, lack of independent mobility, visual, hearing and communication problems all contribute to feeding difficulties in disabled children.

2.1 Cerebral palsy
Severe disability is common in the graduates from neonatal intensive care units; the EPIcure study group evaluated children who were born at 25 or fewer completed weeks

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of gestation at the time when they reached a median age of 30 months and 49 percent were disabled with 23 percent meeting the criteria for severe disability [8]. Epidemiological studies have shown that these are the children who will encounter feeding difficulties. The North American Growth in Cerebral Palsy Project is a population-based study that evaluated the growth and nutritional status in children with moderate to severe cerebral palsy and found the majority (58%) had reported feeding problems [9]. The Oxford Feeding Study examined 440 children with cerebral palsy and feeding problems and found that 89% required assistance with feedings and there were other concerns such as frequent choking (56%), stressful and prolonged feeding (43%) and vomiting (22%) [10]. As has been outlined above, to feed effectively an infant needs to co-ordinate sucking, swallowing and breathing. Oral motor dysfunction is the primary cause of feeding difficulties in children with disabilities. Reilly et al (1996) noted that greater than 90% of children with cerebral palsy had clinically significant oral motor dysfunction [11]. Prolonged feeding times, drooling, coughing and choking with feeds and gagging are all signs of oral motor dysfunction. In one study of 271 children with cerebral palsy, the median length of time caregivers spent feeding per day was 2.5 hours with 28% (72/261) spending more than three hours a day on this activity alone [10].

Malnutrition results from long-term poor feeding. An American study of children with moderate or severe cerebral palsy found that 47% had a weight less than the 5th percentile for their age and gender, 27% had triceps skinfold thickness less than 10th percentile and 68% had height less than the 2.5th percentile [12]. The study also identified an association between low fat stores in children with cerebral palsy and increased hospitalisation, missed school days, physician visits, days spent in bed and an inability to perform usual activities. A British study of 100 disabled children found that only one-fifth regularly achieved the estimated average requirement for energy intake [13].

Enteral feeding via gastrostomy tube is increasingly being used in disabled children with oral-motor dysfunction and feeding problems to provide nutrition. Moreover, tube feeding is more likely to be initiated in those children with severe disability [13] and reports from various groups have indicated that both growth and nutritional status improve following enteral feeding [14-17]. In a systematic review of gastrostomy feeding in disabled children, however, Samson-Fang and colleagues concluded that there is considerable uncertainty about its safety and efficacy [18]. Since then a longitudinal, prospective, multi-centre cohort study designed to measure the outcomes of gastrostomy tube feeding in children with cerebral palsy has been reported [19]. In this study, statistically significant and clinically important increases in weight gain and subcutaneous fat deposition were demonstrated following gastrostomy feeding. Fifty seven children with cerebral palsy (28 female; median age 4 years 4 months, range 5 months to 17 yrs) and undernutrition were assessed prior to gastrostomy placement and at 6 and 12 months afterwards. The main reason for referral for gastrostomy tube insertion was their nutritional status for the preceding 12 months. Outcome measures included growth/anthropometry and nutritional intake, general health and complications of gastrostomy feeding. At baseline, half of the children were more than 3 standard deviations below the average weight for their age and sex, when compared to the standards for normal children. Weight increased substantially over the study period; the median weight z score increased from -3.0 pre-gastrostomy placement to -2.2 at 6 months and -1.6 at 12 months. Weight gain was accompanied by significant increases in skin fold thickness indicating deposition of subcutaneous fat. Minor complications (e.g. gastrostomy site infection) were common, but serious complications following gastrostomy tube insertion were rare. Almost all parents reported a significant improvement in their child's health following this intervention accompanied by a significant reduction in time spent feeding. This reduction in time feeding is one component (along with increased ease of drug administration and reduced concern about their child's nutritional status) of an improvement in the quality of life in carers of children with cerebral palsy that is associated with the introduction of gastrostomy tube feeds. This has been demonstrated in a prospective cohort study aimed to evaluate the impact of gastrostomy-tube feeding on caregiver Quality of Life in carers of children with cerebral palsy [20].

3. Chronic disease

It is important to recognise that chronic disease in any organ system in a child can be associated with poor feeding. Thus, anorexia is a consequence of chronic inflammatory diseases such as inflammatory bowel disease and of the metabolic derangement that accompanies chronic renal failure. Dysphagia secondary to the oesophagitis secondary caused by gastro-oesophageal reflux is a common cause of poor feeding [21]. Bronchopulmonary dysplasia (BPD), a chronic lung disease of preterm babies with antecedent respiratory distress syndrome, ventilatory barotrauma and oxygen toxicity is characterised by varying degrees of prolonged oxygen dependency. Infants with BPD can experience significant feeding difficulty, possibly secondary to tachypnoea interfering with suck coordination. As discussed in Section 1, optimal oral feeding occurs when a regular rhythmic relationship exists between suck, swallow and respiration. It has been shown using simultaneous digital recordings of pharyngeal and nipple (teat) pressure that this normal developmental pattern is disrupted in infants with BPD [22].

3.1 Congenital heart disease

Feeding an infant is an interactive process that facilitates

social, emotional and culturally based skills. Children with congenital or acquired cardiac disease frequently require supportive regimes with regard to feeding in order to maintain weight, resulting in altered experiences for both the child and family

Difficulties with feeding are common in children with congenital heart disease (CHD).Both decreased energy intake and increased energy requirements in this group contribute to malnutrition [23,24]. Cameron et al (1995), for example, investigated nutritional status in 160 hospitalized children with congenital heart disease and showed that acute and chronic malnutrition occurred in 33% and 64% of the patients respectively [24].

For most parents feeding of infants and children with CHD poses significant difficulties, is time consuming and associated with considerable anxiety [25,26]. Moreover, having a child with congenital cardiac disease producing difficulty in feeding has a strong negative impact on the whole family. The feeding pattern of children with CHD is characterized by a large variation in caloric intake. When heart failure is mild the infant commonly overfeeds, and fluid and sodium overload disturb cardiac haemodynamics, leading to decompensation of heart failure and decreased intake [27]. The magnitude of the growth disturbance is generally related to the anatomical lesion but children with cyanotic heart disease accompanied by pulmonary hypertension are the most severely affected in terms of nutrition and growth. Anorexia also accompanies malnutrition and further compromises the patient's condition. Dyspnoea and tachypnoea in patients with congestive heart failure lead to propensity for fatigue and decreased intake. In congestive heart failure a form of "stagnant anoxia" occurs caused by sluggish capillary blood flow within the tissues, which leads to cellular hypoxia. Chronic hypoxia may contribute to the feeding problem in cardiac patients. Heart disease causes an increase in cardiac and respiratory work. Decreased intake caused by anorexia combined with increased respiratory effort results in a greater nutrient deficit. The malnutrition associated with CHD varies in severity from mild undernutrition to failure-to-thrive and can significantly affect the outcome of surgery increasing morbidity and mortality. Children with heart disease may need as much as 50% more calories than normal children in order to achieve normal growth. A combination of these factors predisposes the infant to malnutrition and growth failure.

Adequate nutrition is thus crucial to the management of children and infants with cardiac disease. Maintenance of an adequate caloric intake, in order to achieve sustained growth, is often not possible without nutritional support. Such support can come in the form of caloric supplementation [28] or continuous enteral feeding [29] with or without percutaneous endoscopic gastrostomy tubes [30,31].

3.2. Cystic fibrosis

Good nutritional care is also an essential part of the management of the child with cystic fibrosis (CF) and is one of the major factors contributing to the improved longevity of such children. Energy requirements vary but can be in excess of 150% of the daily recommended value for the normal child and this may pose a significant challenge or parents as they try to meet these requirements. A number of studies have highlighted that children with CF are at risk of developing behaviour problems during mealtimes [32-34]. Behavioural therapy has been shown by meta-analysis of several studies to be as effective as oral supplementation and enteral and parenteral feeding in improving weight gain in young people with CF [32]. Duff and colleagues (2003) used the Behavioural Paediatric Feeding Assessment Scale (BPFAS) to study feeding behaviour problems in children with CF in the UK [34]. In children aged 5 to 12 years there were significantly more problematic disruptive child behaviours and inappropriate parental responses in the CF group than in the control group. Typical disruptive child behaviours observed during mealtimes in this study included no enjoyment of eating, poor appetite, reluctance to come to mealtimes, preferring to drink rather than eat, eating snack food but not eating at mealtimes, and trying to negotiate foods to be eaten. Duff et al report that these behaviours seem to lead to frustration and unhappiness for parents and result in ineffectual and counterproductive strategies (e.g. coaxing) during mealtimes [34]. In view of the fact that there is a high prevalence of feeding behaviour problems in pre-pubertal children with CF it is important that preventive and reactive interventions, tailored to the child's developmental age, continue throughout childhood.

3.3. Type 1 Diabetes

Adolescent girls with type 1 diabetes encounter several difficulties which may affect their disease. Early puberty is associated with decreased insulin sensitivity during the growth spurt and sexual maturation [35]. Whereas, in the later stages of puberty as growth diminishes insulin sensitivity increases. The adolescent years are often characterised by deterioration in the metabolic control of diabetes and it is not uncommon for adolescent girls particularly to be overweight. These changes coincide with the peak period of risk for the development of eating disorders. The cycle of weight loss and then weight gain that accompanies the onset and treatment of diabetes may increase body dissatisfaction and the drive for thinness in vulnerable adolescent females. Management strategies which impose dietary restraint and an intentional disregard of the natural promptings of hunger and satiety may activate dietary dysregulation and disturbed eating patterns. Early studies in this area have been confounded by their small size and conflicting results but more recent research has confirmed the risks for the development of eating disorders in young women with type 1 diabetes.

Engstrцm and colleagues (1999) studied 89 adolescent females (aged 14-18 years) with type 1 diabetes and compared them with age-matched healthy controls [36]. They used the Eating Disorder Inventory a Likert-type self-report questionnaire which tracks symptoms associated with eating disorders and showed highly significant differences between the diabetes group and the control group on the Drive for Thinness subscale. Fifteen diabetic girls (16.9%) scored above the cut-off level for disturbed eating behaviour compared with 2 control girls (2.2%) ($p<0.01$). The commonest abnormality encountered in this study was binge eating and purging behaviour (self-induced vomiting or insulin omission). These observations were confirmed and extended in another study by Jones et al (2000) who studied 356 diabetic females (aged 12-19 years) and 1098 age-matched controls [37]. Using Diagnostic and Statistical Manual of Mental Disorders (DSM IV) criteria they found that eating disorders were twice as common (OR 2.4) in those with type 1 diabetes. Moreover, diabetics with eating disorders had higher HbA_{1c} concentrations than those without eating disorders. It is not surprising, therefore, that patients with type 1 diabetes and eating disorders have more long term diabetic complications. Such patients have been shown to have an increased prevalence of retinopathy, microalbuminuria and painful neuropathy when compared with those diabetics without an eating disorder [38,39].

Some young women utilise their insulin-dependency as a potent means of weight control and induce urinary calories wasting either by insulin omission or under dosing [36,40]. Such behaviour is more likely to occur in those who also have an eating disorder [37]. The importance of this is that insulin omission worsens glycaemic control, increases the risk of microvascular complications and in adolescents has been identified as the primary cause of recurrent diabetic ketoacidosis [41].

Family relationships play an important part in the development of eating disorders in adolescent girls with diabetes. In eating disturbed diabetic girls, Maharaj et al (1998) have identified dysfunctional family environments characterised by poor communication, mistrust of parents responsiveness to their needs and consequently greater feelings of anger and hopelessness [42]. Moreover, eating disturbances in girls with diabetes are significantly associated with heightened weight and shape concerns in their mothers [42].

4. Neurodevelopmental disorders

Developmental disorders characterised by communication difficulties are often accompanied by eating problems. Two conditions, autism and Rett syndrome will suffice as examples.

Autism is a developmental disorder characterised by severe deficits in social interaction and communication along with stereotypic behaviour patterns. The unusual eating patterns and feeding difficulties of children with autism (which is more common in boys) has long been recognised. They often have an extremely limited food repertoire occasionally with apparent craving for certain foods. Research in this area is limited but Williams and colleagues (2000) undertook a parent survey of the eating habits of 340 autistic children [44]. Two thirds of respondents considered their child to be a “picky” eater. The commonest behavioural problems reported were unwillingness to try new foods, mouthing objects, and rituals surrounding eating. Other problems were licking objects, smelling and throwing food and pica. According to Kinnell (1985), 60% of his series of 70 autistic patients exhibited pica [45].

Rett syndrome may be confused with autism but arises from a mutation in the transcription regulating gene MECP2 on the X chromosome; it occurs almost exclusively in girls. Feeding problems are common in Rett syndrome in which there are characteristic oropharyngeal abnormalities [46,47]. Videofluoroscopic studies of feeding in girls with Rett syndrome have shown reduced movements of the mid and posterior tongue, with premature spillover of food and liquid from the mouth into the pharynx and laryngeal penetration of liquids and solid food during swallowing [48,49]. Air swallowing has also been noted as a problem in these patients [50].

4.1. Behavioural Disorders

Feeding difficulties are some of the most common behavioural disturbances in young children. An estimated 24% of 2 year old, 19% of 3 year old and 18% of 4 year old children are reported by their parents as having problems with feeding [51].These problems can range from nuisance behaviour (messy, disruptive mealtime behaviour) to total food refusal and life-threatening malnutrition. Any of the organic diseases referred to above can have an additional psychological and behavioural component which should also be addressed for successful management. It is important to note that there is a clear association between parental behaviour and child feeding behaviour. Sanders and colleagues (1993) using standardised family mealtime observations noted that parents of feeding-disordered children were more negative and coercive in their feeding practices and engaged in higher levels of aversive instruction giving, aversive prompting, and negative eating related comments than parents of non-problem eaters [52]. Dahl et al (1986) found that four factors were highly significant in predicting feeding problems in infants (1) feeding problems in the parents during their own infancy, (2) great anxiety experienced by the mother during pregnancy,(3) breast-feeding problems experienced by the mother and (4) ill health in the mother [3]. These studies provide support for the recommendation that evaluation of the feeding relationship should be an essential part of the

diagnostic study of any child with feeding problems and for treatment methods that directly alter parents' feeding practices.

5. Conclusion

Much of the interaction between an infant and its parents surrounds feeding and thus early feeding experience is important to the psychological development of the child. This fundamental aspect of life is reflected in the interconnectedness of the words "nourish", "nurture" and "nurse". Feeding thus plays a central role in the life of the child not only in relation to their growth but also in its contribution to their social integration. Problems with feeding can cause a major disruption to normal growth and development. In addition, they can pose additional complications for the child coping with a chronic disease. To protect the child from the adverse effects of these complications requires great patience and skill on the part of parents and clinicians alike.

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SUMMARY

FEEDING DIFFICULTIES IN CHILDREN AND ADOLESCENTS WITH CHRONIC ILLNESS

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Good health demands good nutrition and in the child it is reflected in normal growth. Children who cannot or do not eat properly often become unwell and do not grow. This becomes a source of great concern and anxiety for their parents. Several chronic illnesses in children impair normal feeding; this article aims to describe the interrelationship between eating and disease in children with reference to some common conditions. The effects of childhood eating disorders on parents and families will also be considered.

Key words: childhood eating disorders, eating and disease, children.

РЕЗЮМЕ

ТРУДНОСТИ ПИТАНИЯ У ДЕТЕЙ И ПОДРОСТКОВ С ХРОНИЧЕСКИМИ БОЛЕЗНЯМИ

Салливан П.Б.

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Хорошее здоровье требует хорошего питания, у детей оно отражается в нормальном росте. Дети, которые не питаются или не имеют возможности питаться правильно, часто болеют и не растут. Это становится источником озабоченности и беспокойства родителей. В статье рассматриваются взаимосвязь между нарушением питания и болезнями. Описывается также действие нарушения питания у детей на родителей и семью.

ADOLESCENT MEDICINE: FROM CLINICAL PRACTICE TO PUBLIC HEALTH

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Why do we need adolescent medicine?
There is compelling evidence both in the field of clinical care and epidemiology that this stage of life is unique and requires special approaches and skills. Adolescence, usually defined as the period extending from ten to nineteen years, is a unique phase of rapid biological psychological and social changes [15]. Chiefly, the psychological process of adolescence totally modifies the position of the adolescent within his family as well as the doctor-patient relationship. The adolescent process is marked by progressive changes in cognitive and intellectual abilities which have to be assessed before giving any piece of information or advice to the young patient. But above all, the two major challenges of adolescent are first the gaining of autonomy, the individuation process on one hand, and the shaping of one's identity [16]. The identity achieved person is one who has come to a firm sense of self after engaging in a long search full of exploration. In order to come to a sense of identity, teens must engage in exploration. They must try out new ways of thinking and behaving. As a result of this, adolescents will test their body, searching new sensation, engaging in strenuous sports, or substance use, and adolescents suffering from a chronic condition may play with the dosages of their medication, thus jeopardizing their health status or even lead to treatment failure.

Thus, the health care provider must tailor his investigation and messages to his patient's stage of development, comply with his rights, such as a right for confidentiality, but at the same time secure good relationship with his parents and family. One good way to preserve the adolescent's search for autonomy is to let him participate actively in the search for adequate solution to his problems. Young people often help us very efficiently to find proper answers to their situation and health treatment.

There are other reasons for developing adolescent medicine as a special field of interest, which are linked with the nature of their health problems, which has greatly evolved over the last fifty years [1]. Among major threats to health in Europe and around the world, assessed in terms of disability adjusted life years (DALY's), there are issues such as unsafe sex, substance use, physical inactivity [6], which all are linked with behaviors acquired during adolescence or young adulthood. In other terms, physicians have to not only look at young people as patients, but as persons who shape their health habits and adopt more or less healthy behavior. From childhood to adolescence, there is a strong shift from medical issues to psychosocial challenges. From ten to fourteen years, besides injuries, infections play an important role around the world, probably less in our countries, but from fifteen years on, the major challenges lies in the field of mental health, injuries especially traffic injuries, sexual life including STI's, and substance use.

Besides mortality rates or DALYs, there are other important indicators which can be used to assess adolescent health such as surveys in which young people themselves are asked to report on their own health perceptions problems and health care utilization. A few years ago, Pagava & colleagues have published the results of the first survey on adolescent health run in Georgia [12,14]. Georgian adolescents aged 12 to 19 years are less numerous to smoke regularly than in other countries: 10.4% of Georgian adolescents 15-17 years old report that they are currently smoking. However, around 25% of boys reported to have smoked cannabis at least once, especially those living in a city. Also, around 10% of the participants in the survey had been drunk more than 1 or 2 times in their life, and 20% had been involved in a fight because they had consumed alcohol. One lesson that one get from nearly all national surveys is that although the majority of respondents say they feel in good health, a substantial proportion, when asked more precisely whether they suffer from specific problems indicated worries and burdens in the field of stress, depression, love affairs, or nutrition [3].

How can physicians address these issues at an individual level?
Every encounter between an adolescent and a health care provider should not only focus on the reason for consultation or the main complaint but also should be an occasion to explore the adolescent health broadly. As stated recently [5], "relying on therapeutic interventions to address health problems after they occur is a costly strategy and does not address the need to reduce the number of youth who develop these health problems. Primary care physicians have an important role to play in promoting adolescent health through a strategy of providing health guidance to adolescents and parents, screening, and promoting immunizations". The GAPS recommendations developed by the American Medical Association constitute a good example of preventive strategies which can be implemented in the clinical setting [4]. Goldenring and colleagues [7] have described several year ago an excellent acronym which summarizes the main areas which should be covered by such an investigation, the acronym HEEADSSS (table 1). This systematic investigation cov-

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ers the important areas of the home environment and school environment as well as relationships with parents, teachers and peers. It also explores leisure activities such as sport and hobbies as well as eating patterns. In most industrialized countries currently, physicians are allowed to explore the use of substance as well as sexual experiences, provided they guarantee the adolescent both privacy and confidentiality.

Table 1. The various issues to be covered when exploring an adolescent's lifestyles (HEAAEDSSS)

Home
Education, Eating
Activities
Drugs
Sexuality
Safety
Suicide

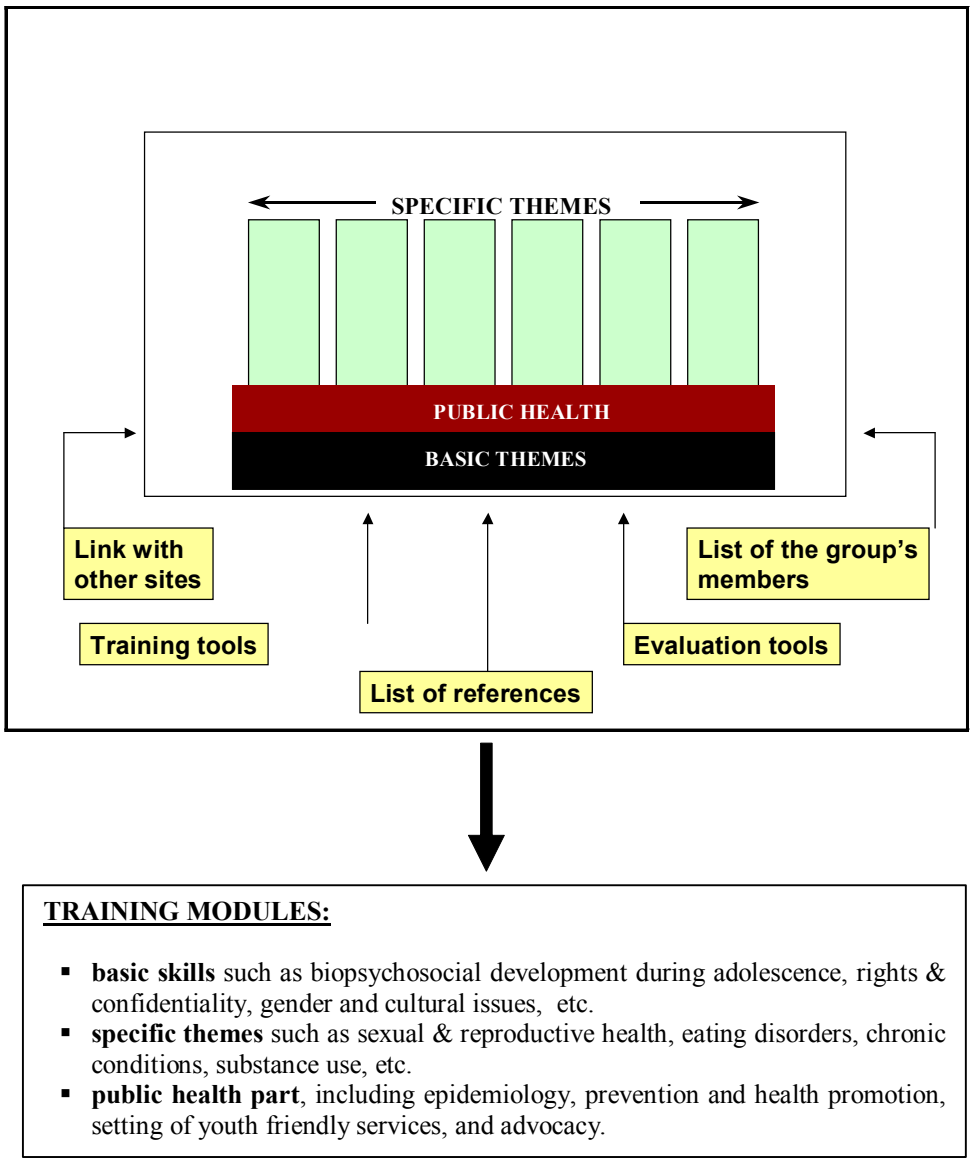
One of the main obstacle to the proper care of adolescents however is linked with the difficulty that physicians and health care structures have in complying with the adolescents' expectation in terms of the value of the reception and the quality of care. Recently, the World health organization has developed the concept of adolescent friendly services [11]. What is interesting in this concept is that it was developed with the assistance of adolescents and youth leaders themselves and that it applies to developed as well as developing countries (table 2). Several sets of conditions underlie youth friendly services in the field of policies, of environment and of procedures. Friendly policies involve the guarantee of confidentiality and, as far as possible, an easy access to provisions of services even for those who are from under privileged areas or who are uninsured. Friendly procedures include easy access to the health professional, such as early registration or drop-in hours, short waiting time as well as a strong linkage with the surroundings of the patient and with social services providers, if needed. Youth friendly services involve youth friendly staff, that is the availability of professionals who are not only technically competent but who can provide a warm supportive environment promoting a respectful and trusting relationship. Finally, environmental measures such as easy access, appealing premises increase the appeal of health care structure. In fact, such youth friendly environment can be offered everywhere. A pediatrician's office can become user friendly and some of them have designed a special waiting room and special hours for young people. In large cities, health professionals have set-up out reach centers, often in conjunction with social agencies, to attract young people who would not otherwise come to the hospital or in more official health centers. The school is a particularly interesting setting for offering basic health counsels or care for under privileged adolescents. Finally comes the Academic center, such as the ones developed in Switzerland, U.K. Greece or Portugal.

Table 2. Some of the ingrredients of adolescent friendly health service (AFHS)

POLICIES	Fulfil the right of adolescents Address the special needs of vulnerable adolescents No stigmatization (ethnicity, social status, etc.) Confidentiality guaranteed Affordability of services
PROCEDURES	Easy access Easy registration Short waiting time
HEALTH CARE PROVIDERS	Technically competent Communication skills Adequate time Provide information and support Evidence-based approach
ENVIRONMENT	Convenient location Convenient opening hours Outreach activities Link with the community
YOUTH PARTICIPATION	Young people consulted / youth council Young people's satisfaction surveyed Young people disseminating information

Training paediatricians and general practitioner: a necessity. There are no vaccines against unsafe sex, nor do we have medication with help young people with chronic disorders to adapt successfully to their environment. One important answer to the challenge of adolescent health lies in an adequate training of health professionals. A recent survey conducted among primary care physicians in Switzerland [9] assesses the perceived importance of several areas in the field of adolescent medicine as well as the perceived training needs. Among the top-ten subjects for which pediatricians strongly feel they need to be trained, the most important are functional symptoms, growth and puberty disorders, family conflicts, mental health, eating disorders or substance use. As an answer to the challenge of teaching adolescent medicine and health challenge, we have set up, four years ago, a project named Euteach, or European Training Effective Adolescent Care and Health) [13]. Its purpose was to select and propose a set of knowledge, attitudes and skills essential for the care of adolescents, and to provide faculty teachers with a comprehensive training curriculum. This modular instrument has been developed by sixteen physicians from eleven European countries and with various professional specializations, including a representative from Georgia, Prof. K. Pagava. It is freely available on the web and consists of thematic modules, each containing detailed objectives, learning approaches, examples and evaluation methods. It covers the main teaching areas in the field (table 3). Five international courses, so-called "Euteach summer school" have already been set-up in Switzerland, using the euteach curiculum as a tool. This training program is funded by private funds and supported by the World Health organisation, UNICEF, UNFPA and the European Confederation of Specialists in Paediatrics.

Table 3. Content of the euteach website



Answers from the field of public health.
As stated before, the answers to the health problems of young people do not lie exclusively in curative approaches and there are a number of initiatives that can be developed outside the field hospitals and of other health care settings. Schools remain one of the most important settings for health promotion and preventive interventions for young people. Adolescents, up to the age of 15 to 18 years, spend just under half their waking hours in school. Many of the most important relationships outside the family are with peers and teachers. It is for this that many prevention and health promotion interventions have been designed for use within the school setting. These include: Programs aimed at increasing physical activity, often with a nutrition component. The available evidence suggests that programs extending outside the school zone and involving the parents are more effective than those targeting the pupils only [18]. Drug education has been a major focus of earlier school based interventions. Effective programs have tended to adopt approaches which promote other life and social skills and extend beyond a single year of intervention [17].The issue of sexual education is a tough issue, especially in countries which do not have any tradition in the field. It is important to underline the fact that carefully designed interventions such as those based on sound theoretical frameworks have had positive effects on the adoption of safe sex behaviours, without increasing the percentage of young people engaging in active sexual life [8].

The extension of health education to health promotion led the World Health Organisation to develop the concept of health promoting school (HPS (World Health Organization 1993) [19]). The network of HPS currently involves more than 35 countries. Schools commit to establishing a healthy physical and social environment. Youth participation such as setting up pupils' councils, or mediation sessions in case of conflict, and the use of life skills interventions are encouraged. Parents are invited to participate in some of these activities where feasible. The effect of such strategies for health education and promotion has been subject to several large scale evaluations and meta-analyses [10] which show that programs should be sustained, multi-faceted, and have the commitment of the head of the school to provide appropriate training to the staff and to work in a holistic way. An excellent example of this approach was the Gatehouse project [2], a multilevel systemic program focusing on promoting social inclusion of students with a view to promoting mental health and diminishing health risk behaviors. Reductions in health risk behaviors over four years ranged from around 25% for substance use and socially disruptive behaviors to around 50% for levels of very early sexually activity.

Other promising strategies to promote the health of young people include media campaigns, and the adoption of policies outside the health sector. For instance, injury prevention lies largely in the adoption of speed limits, low accepted levels of alcoholemia for those driving a vehicle. The struggle against obesity should include large scale measures such as restricting access to soft drinks and improving the content of what is served in facilities hosting young people (e.g. the schools). Easy access to condoms and family planning centres are effective ways to improve the adoption of safe sex behaviors by young people. Among initiatives that extend beyond a health focus, one is the Millennium Development Goals (www.un.org/millenniumgoals/) which was adopted by the UN General Assembly in 2000 and which provides a framework for cooperation across the UN agencie. The MDGs aim at reducing extreme poverty, and as far as adolescent health is concerned, they focus on HIV prevention and the prevention of mortality in the young mothers.

Forty years ago, neonatology emerged from the field of pediatrics as a particular discipline requiring specific settings and skills. Adolescent medicine is now coming of age. Investing in the health of young people is a sound strategy in countries such as Georgia, who face an important societal transition as well as still a lack of resources.

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SUMMARY

ADOLESCENT MEDICINE: FROM CLINICAL PRACTICE TO PUBLIC HEALTH

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In most countries, adolescent health problems have shifted from pure medical conditions to more psychosocial burdens such as injuries and violence, substance use, unsafe sex and chronic conditions including under nutrition or obesity. This new situation requires specific actions which have to take into account the specificities of the bio psychosocial development of the adolescent. Youth friendly services offering adequate environment and policies as well as carefully trained physicians represent one answer to the health needs of adolescents. Another lies in the development of school prevention and health promotion. Finally, policies aiming at securing a safe environment represent an effective mean to improve the health of adolescents.

Key words: adolescent health problems, psychosocial burdens, bio psychosocial development.

РЕЗЮМЕ

ПОДРОСТКОВАЯ МЕДИЦИНА: ОТ КЛИНИЧЕСКОЙ ДИСЦИПЛИНЫ ДО ПРОБЛЕМЫ ОБЩЕСТВЕННОГО ЗДРАВООХРАНЕНИЯ

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В большинстве стран в проблематике охраны здоровья подростков произошел значительный сдвиг: место чисто медицинских нарушений (болезней) занимают психосоциальные состояния, такие как повреждение и насилие, применение наркотиков, небезопасный секс и хронические состояния, включая недостаточное питание и ожирение. Эта новая ситуация требует специфических акций, которые должны учитывать специфику био-психо-социального развития подростков. Система медицинской помощи, дружественная к молодежи, включающая адекватные среду оказания медицинской помощи и политику, а также хорошо обученный персонал, представляет ответ на вызовы, касающиеся здоровья подростков. Помимо этого, соответствующим ответом могут служить проведение превентивных мероприятий в школе и поддержка здоровья. Наконец, политика, имеющая своей целью организацию безопасной среды обитания, является эффективным средством улучшения здоровья подростков.

NEW APPROACH TO ESTIMATE DIFFERENT DRUGS AND/OR OTHER MEDICAL INTERVENTIONS EFFECTIVENESS BASED ON FUZZY LOGIC PRINCIPLES

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Administration of any medical intervention needs antecedent proofs, evidences of its efficacy. As a rule the clinical trials should be performed in patients in whom the tested interventions, incl. drugs are intended to be used (adults, elderly, women, pregnant women, adolescents, children, infants, newborns etc.). Clinical trials aiming at the definition of efficacy and effectiveness of the treatment are based on the formation of two groups, control

and study ones. Study subjects are randomly included in one of these groups to be assigned to receive the study treatment or a placebo/standard treatment. The main requirement is for the above-mentioned groups to be congruous, similar as much as possible. The conclusion on the efficacy of the tested treatment depends on the estimation of the statistical difference between disease outcomes in the groups.

Though this approach is generally accepted, it has some negative sides as well. First of all one must take into account the bioethical aspects: if the drug is good, why to deprive of it the patients who only due to the chance got into the control group. If the drug is not useful why to use it at all.

Secondly it is extremely difficult if ever possible to form the analogous groups. The study subjects – patients / volunteers are so individual that the whole averaging, homogenization of groups seems to be a utopia. The diseases' course is also different. Very often different concomitant diseases are present. All subjects may have a lot of distinctive signs, which are sometimes rather difficult to reveal, but potentially affecting the action of the intervention. One has to have in mind that the human organism per se is a very complex system with fuzzy manifestations of well- and ill-being. Subsequently, in general almost all problems in medicine are filled with imperfect information. Patients and especially their care-givers cannot describe exactly what has happened to them or how do they feel, their information is subjective, exaggerated, underestimated, or incomplete. Doctors and nurses do not formulate exactly what they observe, misinterpretation of clinical findings by physical examination can occur, and the signs may be overlooked. Laboratories report results with some degree of error, and exact borderline between normal and pathological is often unclear. The same can be said about the instrumental investigations too. There are not comprehensive and precise data how the human body is functioning. The data about how disease alters it are also not sufficient, likewise the precise mechanisms of drug action. Accordingly, the prognosis remains one the most difficult diagnostic tasks.

In the face of the uncertainty concerning the revealed symptoms and signs as well as the uncertainty concerning their relation to a disease entity, it is nevertheless crucial that the physician determines the diagnostic label that will entail the appropriate therapeutic regimen [4, 7]. Naturally fuzzy logic allows modeling the uncertainty and vagueness inherent to the above-described medical problem. The theory of fuzzy sets was introduced by Lotfi Zadeh in the 60th of the last century as the means to model the uncertainty within natural language. Fuzzy sets have imprecise boundaries and therefore gradual transition from membership to non-membership of an element in the fuzzy set.

It is interesting to mention that the seminal paper of Lotfi Zadeh [8], a point of departure of the fuzzy logic development, was motivated by the discrepancies between the strict mathematical techniques and real situations in biology and medicine, and, in general, humanistic systems: "... mainstream mathematical techniques - aimed as they were, and still are - at the analysis of mechanical systems, did not provide effective tools for the analysis of biological, or, more generally, humanistic systems in which human judgment, perceptions and emotions play an important role". Since that time fuzzy logic attachedly serves medicine [1,5,6]. Applications of fuzzy set theory are medical diagnoses, fuzzy controllers for various medical devices, fuzzy pattern recognition and image processing for analysis of X-ray images and other visual data, and fuzzy decision making for determining appropriate therapy [4].

On the basis of the above-mentioned we considered it expedient to suggest a new approach for performing of clinical trials using fuzzy logic principles. We are not going into the mathematical details of the theory; just try to describe the application of fuzzy logic for our problem in general.

The whole clinical description of the patients included in the trial will be given. Besides the personal data, all peculiarities incl. unchangeable ones, at least for the period of the trial (e.g. age, gender, presence of chronic conditions etc.) [independent variables] and changeable ones (which are supposed to be improved by the treatment) [dependent variables] will be put in. The parameters will be described by the statistical means and by fuzzy sets as well. The latter ones, as they are, allow modeling of expressions as e.g. *bad appetite, high temperature, high irritability etc.* It can be done on the basis of the expert opinion or taking into consideration different observations.

The minute description of all treatment interventions, incl. intake of the tested drug (if the patient does not receive the tested drug, it can be described as taking the medicine of zero dosage) will also be put in.

After specified periods from the beginning of the treatment the indices of the changeable parameters are defined and put in. Then we propose to use the fuzzy cluster analysis method. Given a finite set of data X, the problem of clustering in X is to find several cluster centers that can properly characterize relevant classes of X. In the fuzzy cluster analysis, these classes are required to form a fuzzy partition of X such as the degree of association is strong for data within blocks and weak for data in different blocks. On the basis of the fuzzy cluster analysis method the positive or negative tendencies of drug action will be assessed. Thereby it will be established whether the drug is effective or not and in what conditions.

The fuzzy logic mechanism uses the easily described rules. They have IF-THEN form and are easily interpreted by any physician. The set of such rules is called a fuzzy rule base: IF (a set of conditions are satisfied) THEN (a set of consequences can be inferred). For example, a rule can take the following form: IF (an antibiotic is applied during three days in a case of community-acquired pneumonia), THEN (temperature is normalised). The antecedents and consequents of these IF-THEN rules are associated with fuzzy concepts. Thus, the fuzzy system based on the rules can be explained (which is very important when dealing with physicians) and adjusted by means of tuning the rules. It is not an easy task to build such set of rules for a particular problem. However the description of all possible situations can be considered without information gaps because fuzzy logic knowledge is interpreted as a set of elastic or equivalently fuzzy constraint on a collection of variables [3]. The rules are a collection of information about the problem. To push them to work for a decision making, as in our case, the fuzzy inference mechanism should be used. Inference is viewed as a process of propagation of elastic constraints. A rough explanation how this inference works can be done as follows. The information about a patient to be treated is compared with information contained in the rule base and on the basis of the aggregated information a conclusion is drawn. In general a conclusion itself is also a fuzzy set, i.e. its every element represents a membership degree and can be considered as an advice which action to choose: in our case – administer or not to administer the drug. What we have described can be considered as a fuzzy expert system striving for the evaluation of the different methods of treatment and the prediction whether a particular patient can be treated by a particular drug successfully. The general scheme is represented on the fig. as follows.

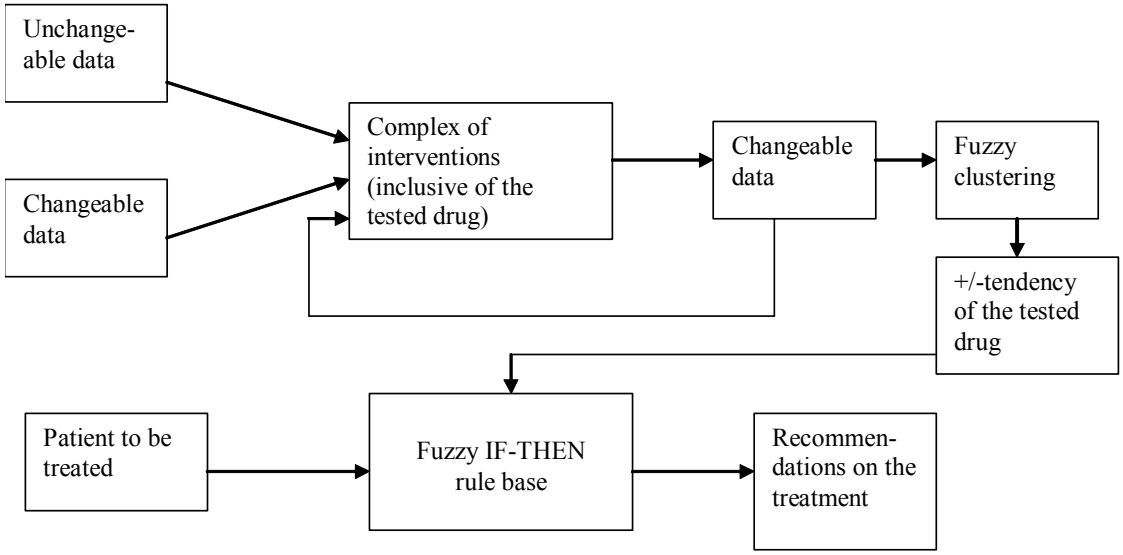

Fig. The scheme of the usage of fuzzy logic for clinical (treatment) trial

We do not touch such important parts of each fuzzy system as fuzzyfication, the inference mechanism, defuzzyfication, composition of fuzzy relations, etc. All these components of the rigorous theory of fuzzy set are visible and understandable for a physician which is not a specialist in mathematics and computer science. Moreover, most of the medical staff who has already worked with fuzzy systems noted that the fuzzy systems were close to their process of thinking and they were satisfied with obtained results that had helped them to make a decision [1, 2]. Therefore we suppose that the proposed approach can be used successfully as an additional method for estimation of effectiveness of different drugs and/or other medical interventions and prognosis of their efficacy in a particular patient.

We suggest also that this method can be used for the evaluation of the individualised therapy (first of all in complementary medicine, e.g. in acupuncture, psychotherapy, homeopathy etc.), when the physician is varying the complex of therapeutic interventions based on his/her intuition, experience, number of subjective and objective factors, permanent estimation of the state of the patient in order to receive the best possible result. We would like to mention also, that this approach seems to be universal and it could be used for the assessment of the effectiveness and prediction of the output of any interventions, not only in the area of medicine.

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SUMMARY

NEW APPROACH TO ESTIMATE DIFFERENT DRUGS AND/OR OTHER MEDICAL INTERVENTIONS EFFECTIVENESS BASED ON FUZZY LOGIC PRINCIPLES

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A new approach for the evaluation of the efficacy of drugs and/or other medical interventions is proposed. It is based on the principles of fuzzy logic, particularly on fuzzy sets, fuzzy cluster analysis and fuzzy expert system.

Key words: drugs, medical interventions, fuzzy logic.

РЕЗЮМЕ

НОВЫЕ ПОДХОДЫ ДЛЯ ОПРЕДЕЛЕНИЯ ЭФФЕКТИВНОСТИ ЛЕКАРСТВ И/ИЛИ ДРУГИХ МЕДИЦИНСКИХ ВМЕШАТЕЛЬСТВ С ИСПОЛЬЗОВАНИЕМ ПРИНЦИПОВ НЕЧЕТКОЙ ЛОГИКИ

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Предлагается новый подход для оценки эффективности лекарств и/или других медицинских вмешательств. Он основывается на принципах нечеткой логики, в частности, нечетких множеств, нечеткого кластерного анализа и нечеткой экспертной системы.

NETWORK IN PEDIATRIC RHEUMATOLOGY: THE EXAMPLE OF THE PEDIATRIC RHEUMATOLOGY INTERNATIONAL TRIALS ORGANISATION

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The pediatric rheumatic diseases (PRD) are rare conditions associated with substantial morbidity, consequence on the quality of life, and monetary costs. Many studies of the impact and outcome of PRD have shown that this group of diseases is associated with greater morbidity and monetary cost than previously thought [1]. For example, long term outcome studies of children with juvenile idiopathic arthritis (JIA) report that, after a mean follow-up of 15 years, the majority of the patients continue to experience some difficulties in daily living activities, and that moderate to severe pain is still present in 30% of the patients [2-4]. There is also evidence of cumulative organ damage in patients with juvenile systemic lupus erythematosus (JSLE) [5].

Certainly childhood chronic illnesses with high levels of morbidity should be the target of intense research aimed at ameliorating and/or curing the disease. However, conducting clinical trials in PRD has proven difficult for a host of reasons.

Due to the rarity of the diseases the only possibility to gather a sufficient number of patients to obtain clinically and statistically valid results in a reasonable period of time, is to perform multi-centre studies on an international scale. The ethics of conducting any placebo-controlled trial, even in adults, has recently come under intense debate [6-8]. Parents often refuse entry into studies because they are uncomfortable with the prospect of their child being assigned by chance to placebo. Securing funding for conducting clinical trials in PRD has always been difficult since the pharmaceutical industry has little interest in funding these trials due to the small potential market.

Drugs available for the treatment of PRD have been used in new dosages, new routes of administration, and new

combinations. Unfortunately, data regarding the safety and effectiveness of these new treatment regimens tends to be from small, open, anecdotal, uncontrolled, non-randomized case series. Examples include the use of high dose MTX in recalcitrant JIA [9,10] and of MTX usage in juvenile dermatomyositis [11]. Many of these new approaches to management may represent improvements over existing standards, but without larger, systematic trials the data must remain suspect.

The history of collaborative research in pediatric rheumatology.

The Pediatric Rheumatology Collaborative Study Group (PRCSG).

Founded in 1973 by Dr Earl Brewer and lead in the following years by Drs. Edward H. Giannini, and Daniel J. Lovell, the purpose of the PRCSG is to foster, facilitate, and conduct high quality research in the field of pediatric rheumatology in North America. The activities of the PRCSG are governed by written bylaws and oversight and long range planning is provided by the PRCSG Advisory Council. The PRCSG Coordinating Center is located in Cincinnati, Ohio, USA.

The main focus of the PRCSG in its early years was related to clinical trials of non-steroidal anti inflammatory drugs (NSAID) in juvenile rheumatoid arthritis (JRA) [12.]

Their pioneering methodological works for the conduct of clinical trials (13-17) set the basis for the further development of evidence-based collaborative research in PRD.

Indeed, in the ensuing years the PRCSG started the work in the field of disease modifying anti rheumatic drugs (DMARDs) [18] that lead to the demonstration of the ineffectiveness of penicillamine, hydroxychloroquine [19] and auronafin [20] in the treatment of severe JRA. It should be noted that to reach an adequate sample size for the above mentioned trials it was necessary to establish an international collaboration between the United States and the former Soviet Union.

Their seminal work lead to a significant impact in the current clinical practice of the pediatric rheumatology community, especially after the publication of the methotrexate (MTX) trial [21] in JRA, that demonstrated the efficacy of this drug at the dosage of 10 mg/m^2/week. Since 1992 MTX indeed has become the drug of first choice for the treatment of JRA patients whose disease is resistant to NSAIDs.

The PRCSG more recently developed a randomized withdrawal study design in collaboration with the Food and Drug Administration (FDA) that has been accepted by regulatory agencies throughout the world as an acceptable study design for use in evaluation of new therapies for children with JIA. This study design was succefully used by the PRSCG in performing the first trial of a biologic therapy in JIA [22].

The Pediatric Rheumatology International Trials Organisation (PRINTO).

The Pediatric Rheumatology International Trials Organization (PRINTO) was founded by Alberto Martini and Nicolino Ruperto in 1996, and initially included 14 European countries (now more countries with more than 250 centres world wide) [23,24]. PRINTO aims are to facilitate and co-ordinate the development, conduct, analysis, and reporting of clinical trials and outcome assessment standardization in children with PRD. PRINTO was founded with the idea to perform clinical trials for the PRD with or without the support of pharmaceutical companies. In general, if a study is not supported by a pharmaceutical company the design is that of a randomized, actively controlled, and open label clinical trial. If the study is supported by a pharmaceutical company and is part of a clinical development program which aims for marketing an agent, more classic design are used.

PRINTO is composed of academic, clinical centers actively engaged in the research/clinical care of children with PRD. PRINTO actually is composed of the most esteemed pediatric rheumatology researchers outside the US. PRINTO has four main vertical structures: the Advisory Council that provide leadership and guidance for PRINTO research activities; the International Coordinating Centre whose main task it to facilitate the flow of logistic and scientific details needed to design, launch and manage multi-centered, multi-national, collaborative studies; the National Coordinating Centres (one per country) whose tasks are to facilitate the participation of the greatest number possible of individual centers, and to provide the translation of all the forms to be completed by the parents/patients; and finally the individual clinical sites that constitute the main support structure to obtain a critical mass of data for on-going and future research.

In recent years the PRINTO and the PRCSG have worked closely in various international collaborative projects detailed below.

The ACR pediatric 30 definition of improvement for JIA.

Up until the late 1990's, the assessment of clinical response in JIA/JRA was not standardized. Multiple measures of outcome were in use and different trials used different endpoints. Some of these endpoints had low validity characteristics and were insensitive to change, some were redundant, and some were non-reliable (poor reproducibility). Additionally, there was little consensus about the amount of change in endpoints which signifies clinically important improvement or worsening. This lack of standardization led to inefficient trials that required larger than

necessary sample sizes, an increased risk of statistical error, possible reporting bias, multiple or ambiguous interpretations of the results, and an inability to compare multiple therapies using meta-analytic techniques.

The main aim of this first combined effort conducted by the PRCSG and PRINTO under the guidance of Dr Giannini E.H., was to develop a standardized core set of measures and a definition of improvement for the evaluation of response to therapy in JRA that would be accepted by the international community.

There are 6 validated outcomes measures in the JIA core set [25,26] that measures different domains of disease activity: the number of joints with active arthritis, the number of joints with limited range of motion; the physician global evaluation of disease activity; the parent assessment of child's overall well-being; a functional assessment tool; the Westergren erythrocyte sedimentation rate (ESR). To be classified as improved a patient must demonstrate at least 30% improvement from baseline in at least 3 of any 6 JIA core set variables with no more than 1 of the remaining variables worsened by more than 30%. The definition of improvement allows researchers and clinicians to dichotomize patients into responders or non-responders.

After its publication [26], the definition of improvement was adopted by the FDA as the primary outcome for all clinical trials involving children with JIA, and subsequently officially recognized by the American College of Rheumatology (ACR) and renamed the ACR Pediatric 30 [27].

The Methotrexate trial in JIA.
After the trial published by Giannini et al [21] methotrexate became the disease-modifying-agent of first choice in polyarticular course JIA. For children who did not respond to 10 mg/m^2/week it became common practice to use higher dose MTX, up to 30 mg/m^2/week (10), but no randomized trial had confirmed this hypothesis. Knowledge of the optimal dosage of MTX in term of efficacy and safety is central to disease management, PRINTO, supported by the European Union (Contract BMH4 983531), conducted a randomized, open label standard-of-care trial to evaluate the MTX efficacy and safety profile in intermediate versus higher dose for polyarticular course JIA patients who failed to improve on standard dose MTX. The trial shows that the plateau of efficacy of MTX in JIA is reached with the parenteral administration of 15 mg/m^2/week and that further increase in dosage is not associated with any additional therapeutic benefit [28].

From a methodological point of view, the trial was built on the current "standard of care" in such a way that the cost of insurance coverage, the medication, clinic visits, and laboratory monitoring, were paid by the usual method of cost reimbursement for clinical care in each participating country. The amount of data collected, in addition to that from routine follow-up, was minimal, and all investigators volunteered their time and effort. The study received no pharmaceutical industry support.

The next steps were to launch clinical trials in Europe and to prepare standardized tools for the outcome assessment of children with PRD to be used internationally among nations with different languages and cultures.

The quality of life project for PRD.
One particular problem for the conduct of international studies was the availability of parent's/patient's reported outcome for functional ability and quality of life assessment. Thanks to the European Union (Contract BMH4 983531) PRINTO has been able to cross-culturally adapt and validate 2 questionnaires; the Childhood Health Assessment Questionnaire (CHAQ) for functional ability assessment in JIA and juvenile dermatomyositis (JDM), and the Child Health Questionnaire (CHQ) for health related quality of life evaluation for all PRDs. The project enrolled 6,644 subjects (3,235 patients with JIA and 3,409 healthy children), with 32 validated version of the CHAQ and CHQ now available (29-31). The CHAQ is now the functional assessment tool used for nearly all trials in JIA (22;28), and the CHQ for quality of life assessment papers (32-35).

Disease activity and damage assessment in JSLE and JDM.
Once the problem of a standardized approach for the evaluation of response to therapy in JIA, was resolved, the logical follow-up study was to conduct a similar project for 2 other chronic PRDs, JSLE and JDM. With a second grant from the European Union (contract n° QLG1-CT-2000-00514) PRINTO, with collaboration with PRCSG, has been able to propose validated core sets for the evaluation of disease activity and damage (36-38) and also definitions of improvement to be used in future clinical trials in JSLE (39) and JDM (paper in preparation). A total of 295 patients with JDM and 556 patients with JSLE were collected from 41 countries. These project have been officially endorsed by the ACR and the European League Against Rheumatism (EULAR) and are now know as PRINTO core set (37) and PRINTO/ACR definition of improvement for JSLE (39) and PRINTO/ACR/EULAR core set for JDM (38).

A website for families of children with pediatric rheumatic diseases.
Collaborative research is usually set up with the objective to answer specific scientific questions but also the social aspect of research has to be taken into account, and in particular the needs of the parents. The actual large availability of the use of the internet allows families to access medical information quickly and easily, but this informa-

tion is often not standardized, inaccurate and unreliable. To address this problem, PRINTO in collaboration with the Paediatric Rheumatology European Society (PRES), and again supported by the European Union (contract 2001CVG4-808) has recently finished a project with the goal to prepare a website, directed to families and health professionals, containing consensus defined information about PRD (in the format of frequently answered questions), the list of pediatric rheumatology centers, and the list of family help associations. All information is available and has been translated into the languages of all the countries belonging to the PRINTO network (www.pediatric-rheumatology.printo.it) (40).

Research Training in paediatric rheumatology.
Good collaborative clinical research requires qualified people around the world able to conduct studies in a standardized fashion (41). PRINTO, with another grant from the European Union (Contract no AML/B7-311/97/0666/II-0246-FI), has set up a research training programme in pediatric rheumatology, to support mainly Latin America recipients (Argentina, Brazil, Chile, Costa Rica, Cuba, or Mexico). For the 24 Latin American recipients the course will take place in Genoa in Italy, Paris in France, Utrecth in the Netherlands, Goteborg in Sweden, and London in United Kingdom. The project will also allow 4 trained pediatric rheumatology fellows from Genoa, Italy to spend some months in Latin America (Buenos Aires in Argentina, Rio de Janeiro and Botucatu in Brasil, Mexico City in Mexico) to standardise the outcome assessment of patients participating to common collaborative studies [5,33-36,42-46].

The clinical remission criteria for JIA.
In the last years PRINTO and PRCSG have worked with the North America recently founded Childhood Arthritis and Rheumatology Research Alliance (CARRA), in order to develop draft criteria for inactive disease and clinical remission for select JIA categories.

Draft criteria for inactive disease include: no active arthritis; no fever, rash, serositis, splenomegaly, generalized lymphadenopathy attributable to JIA; no active uveitis; normal ESR or C-Reactive Protein (CRP); and a physician's global assessment of disease activity rated at the best score possible for the instrument used. Six continuous months of inactive disease define clinical remission on medication, while 12 months off medication define clinical remission off medication [47].

The pediatric rule.
Most, if not all of the PRD drugs are used off label in most countries worldwide, meaning that no indication for pediatric use is reported on the drug label [48-50].

The paucity of controlled trials in childhood prompted passage of legislation that gives regulatory authorities such as the Food and Drug Administration (FDA) [49] (the Pediatric rule recently renewed until 2012), and more recently by the European Union [51] the power to require pharmaceutical sponsors to perform and support trials of new agents in children. As a result of such US and EU legislation several clinical trials, supported entirely by pharmaceutical industries, have been completed in children with JRA [22,52-54], others are currently running very effectively and others are in development.

The creation of big international trial networks such as PRINTO and PRCSG, the definition of internationally recognized and standardized outcome measures and definitions of improvement for JIA, JSLE and JDM, the cross-cultural adaptation and validation of quality of life instruments, the adoption of adequate legislative measures (pediatric rule), have created the basic premises for the best future assessment of the efficacy of new treatments for the PRD. Therefore, children with rheumatic diseases now have the same rights of adults to be treated with drugs whose safety and efficacy have been assessed.

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SUMMARY

NETWORK IN PEDIATRIC RHEUMATOLOGY: THE EXAMPLE OF THE PEDIATRIC RHEUMATOLOGY INTERNATIONAL TRIALS ORGANISATION

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The pediatric rheumatic diseases (PRD) are rare conditions associated with important sequelae on the quality of life and long term outcome. The research aimed at studying new therapeutic approaches is difficult because of logistic, methodological and ethical problems.

To face these problems 2 international networks; the Pediatric Rheumatology Collaborative Study Group (PRCSG) and the Paediatric Rheumatology International Trials Organization (PRINTO) have been founded. The 2 networks have the goal to promote, facilitate and conduct high quality research for the PRD. In particular they have been able to standardize the evaluation of response to therapy in juvenile idiopathic arthritis (JIA), juvenile systemic lupus erythematosus, and juvenile dermatomyositis, to draft clinical remission criteria in JIA, and to provide cross-cultural adapted and validated quality of life instruments like the Childhood Health Assessment Questionnaire, and the Child Health Questionnaire, into 32 different languages.

In this paper we reviewed how the creation of large international trial networks such as PRINTO and PRCSG, the definition of internationally recognized and standardized outcome measures and definitions of improvement, the validation of quality of life instruments, the adoption of adequate legislative measures (pediatric rule), have created the basic premises for the best future assessment of the PRD. This progress now offers children with PRD the same opportunities as adults to be treated with drugs whose safety and efficacy have been assessed through legitimate scientifically valid investigations.

Key words: pediatric rheumatic diseases, quality of life.

РЕЗЮМЕ

ОРГАНИЗАЦИЯ ПО ПРОВЕДЕНИЮ МЕЖДУНАРОДНЫХ КЛИНИЧЕСКИХ ИССЛЕДОВАНИЙ В ОБЛАСТИ РЕВМАТОЛОГИИ

Руперто Н., Мартини А. для Организация по проведению международных клинических исследований в области педиатрической ревматологии (PRINTO)

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Педиатрические ревматические болезни (ПРБ) являются редкими состояниями, обусловливающими тяжелые исхо-

ды и значительно ухудшающими качество жизни. Исследования, имеющие целью разработку новых лечебных подходов, затруднены из-за наличия логистических, методологических и этических проблем.

В ответ на эти вызовы были созданы две международные сети – Группа по совместным исследованиям в области педиатрической ревматологии [Pediatric Rheumatology Collaborative Study Group (PRCSG)] и Организация по проведению международных исследований в области педиатрической ревматологии [Paediatric Rheumatology INternational Trials Organization (PRINTO)]. Эти две сети имеют целью способствовать, облегчать и проводить высококвалифицированные исследования по ПРБ. В частности, им удалось стандартизировать оценку ответа на лечение при ювенильном идиопатическом артрите (ЮИА), ювенильной системной красной волчанке, ювенильном дерматомиозите, создать проект критериев клинической ремиссии при ЮИА, обеспечить кросс-культурально адаптированный и валидированные инструменты для оценки качества жизни [Childhood Health Assessment Questionnaire (CHAQ) и Child Health Questionnaire(CHQ)] на 32-х языках.

В статье указывается также, что организация больших международных сетей, таких как PRINTO и PRCSG, разработка интернационально признанных и стандартизированных измеримых определений исходов болезни, валидация инструментов для измерения качества жизни, принятие адекватных законодательных мер (педиатрических правил) - создали предпосылки для наилучшей оценки ПРБ. Этот прогресс предоставляет сейчас детям с ПРБ те же возможности, что и взрослым, лечиться лекарствами, безопасность и эффективность которых определяется посредством научно обоснованных валидных исследований.

SPERMATOGENESIS IN YOUNG ADULT PATIENTS WITH β-THALASSAEMIA MAJOR LONG-TERM TREATED WITH DESFERRIOXAMINE

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Thalassaemias are caused by under-production of α or β chains of adult haemoglobin. Homozygous β-thalassaemia (TM) causes intractable anaemia requiring blood transfusion for life and daily subcutaneous infusion of iron chelating agents [7,15,16].

In our Centre we follow regularly 180 patients with TM and intermedia (mean age 39.9 years), and more than 150 patients are referred yearly for an haematological or endocrine evaluation.

Compliant patients achieve adulthood and many of them hope for marriage and to have a family. Therefore the question of fertility potential in this adult group of patients has become paramount.

We report the semen parameters, endocrine functions and serum zinc levels in a group of young adult TM patients, who stared chelation therapy early in life.

Material and methods. In the last four years we studied semen parameters (count, motility and morphology), endocrine markers of testicular function (LH, FSH, total and free testosterone) and serum zinc levels in 12 fully mature TM patients (testicular volume between 15-25 ml, measured with Prader orchidometer).

All patients were referred to the Endocrine and Adolescent Unit of the Department of Reproduction and Growth of St Anna Hospital, Ferrara (Italy) for an assessment of their potential fertility. Their mean age was 24.8±2.6 years.

All patients reached spontaneously full pubertal development, they were no smokers and showed no symptoms or signs of genital infections.

The diagnosis of β-TM was made on the basis of clinical and laboratory findings.

All patients were regularly transfused from the time of diagnosis with the aim to keep the overall mean haemoglobin (Hb) level at 12.0 g/dl and the overall Hb level not less than 9 g/dl.

To minimize transfusional iron overload, desferrioxamine mesylate (DFX) (Desferal, Biofuture Pharma) was given subcutaneously by a small portable syringe driver pump over 8-10 hours, at night. The recommended DFX dose was 30-45 mg/kg body weight (5-6 times/week).

Compliance with chelating therapy was adequate or good (at least 4-5 times/week) in 72% of patients.

The degree of iron overload was assessed by measurement of serum ferritin and the concomitant presence of organ and endocrine dysfunctions were evaluated as previously described. [4]

Laboratory methods.
Blood glucose levels were measured by the local clinical chemistry laboratories. Serum concentrations of FSH and LH were measured by chemiluminescence (ADVIA Centaur, Bayer and IMX, Abbot Laboratories, USA); serum testosterone and free testosterone by chemiluminescence and radioimmunoassay (ADVIA Centaur, Bayer and Diagnostic Products Corporation, Los Angeles, USA); serum FT4 and TSH were measured by chemiluminescence (Chiron Diagnostics, Norwood, USA); calcium homeostasis was evaluated by standard methods and intact parathyroid hormone (PTH) was measured by immunometric assay (Immulite DCP, los Angeles, USA); plasma cortisol and adrenocorticotrophin (ACTH) were measured by sequential immunometric assays (Immulite DCP, Los Angeles, USA); iron overload was measured by serum ferritin levels, using a chemiluminescence system (Sanofi, Pasteur, France).

Semen samples were collected by masturbation after 3-5 days of abstinence and analysis was performed according to WHO guidelines. [17] After liquefaction, the seminal parameters were determined. Patients with abnormal seminal analysis were retested and the mean of values was calculated.

Plasma zinc levels were measure with a Perkin-Elmer model 306 atomic absorption spectrophotometer by modification of the method of Scudder et al. [12] The result are expressed in мmol/l.

The results of LH, FSH, total and free testosterone were compared with those obtained in 13 normal adults with comparable testicular size.

Informed consent was obtained from all patients on controls.

Statistical analysis was carried out by Mann Whitney U-test (a p value below 0.05 was chosen as the limit of significance).

Linear regression was used to evaluate correlations between variables.

Results and their discussion. Six TM patients had a normal sperm count, motility and morphology while the remaining patients had oligospermia (sperm concentration $<20x10^6$/ml) and/or asthenospermia (motility <40%).

Basal serum gonadotrophins (LH and FSH), total and free testosterone levels did not differ significantly from those found in the control subjects (Table 1).

Table 1. Laboratory detail (serum LH, FSH, T and free T) in β-thalassaemia major patients and in control subjects

Subjects examinated	LH mUI/ml	FSH mUI/ml	T ng/ml	Free T ng/ml
Thalassaemia major patients (no. 12)	3.7±1.2	3.1 ±1.7	614±239	25.2±7.3
Controls (no. 13)	3±1	3.5±1.3	637±148	26.7±10.8
p	n.s.	n.s.	n.s.	n.s.

Legend: LH=serum luteinising hormone; FSH=serum follicle stimulating hormone; T=serum total testosterone; Free T=serum free testosterone; ns=not significant

At the time of study serum ferritin levels ranged from 240 to 3055 ng/ml (mean 1139±810 ng/ml; normal values 32-176 ng/ml) and liver enzymes: serum alanine transaminase (ALT) and serum γ-glutamyl transpeptidase (γGT) ranged from 10 to 194 IU/l (mean 55.8±42.9 IU/l; normal range 7-40 IU/l) and from 7 to 73 IU/l (mean 33.9±19.6 IU/l; normal range 6-65 IU/l), respectively.

Serum zinc levels (mean 14.7±1.3 μmol/l) were in the normal range (11.1-17 μmol/l).

No associated cardiac or endocrine complications (diabetes, hypothyroidism, hypo-parathyroidism) were found in all TM patients.

We could not find any correlation between semen parameters, serum total and free testosterone, plasma zinc, serum ferritin and seminal parameters.

Nevertheless we observed that serum ferritin levels were lower in TM patients with abnormal seminal parameters (count and motility) compared to TM patients with normal seminal parameters (mean serum ferritin 543±224 ng/ml vs. 1276±874 ng/ml; p <0.01) (Table 2).

No statistical difference was found in serum zinc level between the two groups of TM patients (14.2±1.2 μmol/l vs. 14.9±1.8 μmol/l).

There are a number of reasons for the assessment of gonadal function in adult males with TM.

Firstly, subcutaneous chelation therapy with DFX has prolonged the survival of patients [4,5,7,16]. In our Centre, 70% of TM patients now enter in puberty normally with the assurance of a greater longevity and with the prospect of future marriage.

Table 2. Main laboratory features in 6 thalassaemic patients with abnormal seminal parameters

Case no.	ALT (IU/ml)	γGT (U/ml)	Plasma zinc (mol/l)	Serum ferritin (ng/ml)
1	17	18	11.9	280
2	16	45	13.7	480
3	40	30	15	240
4	54	48	15.1	805
5	20	54	14.4	720
6	10	10	15.1	734

Normal range: Serum alanine transaminase [ALT] = 7-40 IU/l; Serum gamma glutamyltranspeptidase [γGT] = 6-65 IU/l; plasma zinc = 11.5-17 μmol/l; Serum ferritin = 32-176 ng/ml

Secondly, studies on semen analysis in long-term iron chelated TM patients are scanty [3,8,9,14].

Thirdly, seminal parameters may change over the time and DFX chelation therapy may have an adverse effect on spermatogenesis and/or sperm function [9].

In addition, zinc deficiency has been reported in most TM patients [1,2,12]. Zinc is important in several aspects of male reproduction. Zinc concentrations are very high in the male genital organs compared with other tissues and body fluids, particularly in the prostate gland, which is largely responsible for the high zinc content in seminal plasma [10,11,13].

All of our patients were found to have normal hormonal parameters and 50% had normal sperm count, motility and morphology according to WHO criteria [17]. Two patients (16.6%) had oligospermia and four (33.3%) oligoasthenospermia.

Their serum ferritin levels were significantly lower compared to group with normal sperm count. None of these patients suffered from chronic liver disease or any endocrine complication.

Although the plasma zinc levels in our TM patients were in the normal range, oral zinc supplementation for 4 months in one oligoasthenospermic patient (Table 2, case no. 1) resulted in a normal sperm count (from 18 x 10^6/ml to 39 x 10^6/ml(while the motility remained unchanged.

We have not tested zinc seminal level in our patients. Therefore, further investigations are required to evaluate the possible negative effects of DFX chelation in relation to zinc status and spermatogenesis in TM patients on regular chelation therapy.

In conclusion, it may be claimed that persistently good iron chelation therapy with DFX ensure normal sexual development. However, to achieve a low serum ferritin level an excellent and consistent therapy is needed, and this raises the possibility that DFX may have an adverse effect on seminal parameters (sperm count and/or motility).

Moreover, further studies are needed to evaluate if these adverse effects can be reduced or prevented and if the damage of spermatogenesis is persistent.

Although the relationship between zinc concentrations in seminal fluid and seminal parameters have not yet clarified [6], zinc supplementation should be considered as an effective adjuvant therapy in well chelated oligoasthenospermic TM patients.

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SUMMARY

SPERMATOGENESIS IN YOUNG ADULT PATIENTS WITH β-THALASSAEMIA MAJOR LONG-TERM TREATED WITH DESFERRIOXAMINE

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Since the introduction of hypertransfusion and intensive iron chelation therapy, patients with homozygous β-thalassaemia major (TM) achieve adulthood. Many patients grow and develop normal hoping for marriage and to have a family. Therefore the question of fertility potential in this adult group of TM patients has become paramount. We report the semen parameters, the endocrine functions and serum zinc levels in 12 young adult TM patients. Their mean age was 24.8 years. Six patients (50%) had a normal sperm count, motility and morphology. While the remaining patients had oligospermia (sperm concentration $<20x10^6$/ml) and/or asthenospermia (motility <40%). Basal serum gonadotrophins [LH and FSH], total and free testosterone and serum zinc did not differ significantly from those found in 13 normal adults with comparable testicular size. At the time of the study serum ferritin levels ranged from 240 to 3055 ng/ml (mean 1139 ng/ml). No correlations were found between semen parameters, serum total and free testosterone, plasma zinc, serum ferritin and seminal parameters. Nevertheless we observed that serum ferritin levels were lower (mean 543 ng/ml) in TM patients with abnormal seminal parameters (count and motility) compared to TM patients with normal seminal parameters (mean serum ferritin 1276 ng/ml; $p<0.01$). In conclusion, impairment of semen parameters may be a negative effect of intensive chelation therapy. Clearly, further investigations are required to evaluate if these adverse effects can be reduced or prevented, and if the existing spermatogenesis damage is reversible.

Key words: homozygous β-thalassaemia major, oligospermia, asthenospermia, semen parameters, intensive iron chelation therapy.

РЕЗЮМЕ

СПЕРМАТОГЕНЕЗ У МОЛОДЫХ ВЗРОСЛЫХ БОЛЬНЫХ С БОЛЬШОЙ β-ТАЛАССЕМИЕЙ ДЛИТЕЛЬНОЕ ВРЕМЯ ЛЕЧЕННЫХ ДЕСФЕРРИОКСАМИНОМ

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После внедрения гипертрансфузии и интенсивной хелатотерапии железа, пациенты с гомозиготной большой β-талассемией (БТ) стали достигать взрослого возраста. У многих пациентов появляются нормальные желания создать семью и иметь детей. Вследствие этого вопрос о фертильном потенциале в этой группе взрослых людей с БТ приобретает первостепенное значение. Мы приводим материалы о характеристике семени, эндокринных функциях и уровне цинка в сыворотке у 12 молодых людей, больных БТ, средний возраст которых составил 24.8 лет. У 6 (50%) пациентов число сперматозоидов, подвижность и морфология были в норме. В то время как у остальных отмечались олигоспермия (концентрация спермы $<20x10^6$/ml) и/или астеноспермия (подвижность <40%). Базальный уровень гонадотропинов (LH и FSH), общий и свободный тестостерон и сывороточный цинк не отличались существенно по сравнению с показателями 13 здоровых взрослых мужчин, имеющих сопоставимые размеры тестикул. На момент исследования уровни сывороточного ферритина варьировали в пределах от 240 до 3055 нг/мл (средняя - 1139 нг/мл). Не было найдено корреляции между показателями семени, концентрациями общего и свободного тестостерона, цинка и ферритина в сыворотке. В то же время мы обнаружили, что уровень сывороточного ферритина был ниже (средняя – 543 нг/мл) у больных с БТ с нарушением показателей семени (число и подвижность) по сравнению с теми больными, у которых эти показатели были в пределах нормы (средняя – 1276 нг/мл; $p<0.01$). Можно заключить, что нарушение параметров семени может быть следствием интенсивной хелатной терапии. Очевидно, что необходимо проведение дальнейших исследований для выяснения могут ли быть эти побочные реакции редуцированы или предотвращены, а также обратимы ли существующие нарушения сперматогенеза.

НЕЙРОИММУННАЯ РЕГУЛЯЦИЯ ПРИ БРОНХИАЛЬНОЙ АСТМЕ У ДЕТЕЙ

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Бронхиальная астма (БА) представляет собой всевозрастающую социально-экономическую проблему здравоохранения во всем мире [1-2].

Распространенность аллергических болезней в разных регионах Азербайджана колеблется в пределах 2,1-4,6%, причем большую долю среди них занимает бронхиальная астма.

В последние десятилетия в развитии и формировании патогенеза бронхиальной астмы наряду с иммунологическими процессами, являющимися основой аллергических реакций, большое значение приобретают нейроиммунные механизмы [4], так как в осуществлении нейроиммунного контроля за деятельностью различных систем большое значение придается регуляторным нейропептидам [5,6]. Вероятность нейроиммунного взаимодействия подтверждается тем, что некоторые субпопуляции иммунных клеток обладают специфическими нейропептидными рецепторами, а также способны к синтезу и накоплению отдельных нейропептидов.

Установлено, что связывание нейропептидов с мембранными рецепторами иммунокомпетентных клеток приводит к специфической активации аденилат- или гуанилатциклазы. При этом наблюдается изменение внутриклеточной концентрации циклических нуклеотидов [6].

В легких нейропептиды могут высвобождаться из периферических нейросекреторных клеток, расположенных в гладкой мускулатуре дистальных отделов дыхательных путей [7-8]. В легких обнаружено более 10-и регуляторных нейропептидов, среди которых наиболее изучены субстанция Р, нейрокинин А и вазоактивный интестинальный пептид (ВИП).

Необходимо подчеркнуть, что нейрогенное воспаление с участием нейропептидов может сопровождать и усугублять уже имеющееся аллергическое воспаление, инициатором которого является реагинзависимая реакция [5,9].

Среди трансмиттеров в системе нервного контроля за тонусом бронхиального дерева значимое место занимают нейропептиды - субстанции Р и нейрокинин А.

Высвобождение этих нейропептидов из окончаний чувствительных нехолинергических нервов оказывает сосудорасширяющее действие, способствует де-грануляции тучных клеток и и усилению секреции простагландинов [11]. Высвобождение этих нейропептидов способствует формированию бронхоспазма.

ВИП, который является важным регулятором бронхиального тонуса, наиболее мощным эндогенным бронходилататором из известных в настоящее время и способен противодействовать бронхоспазму при астме. ВИП, как и β2-агонисты, повышает уровень цАМФ в дыхательном эпителии [10].

Целью данного исследования явилось определить содержание вышеназванных нейропептидов в сыворотке крови у детей с бронхиальной астмой и изучить их действие в зависимости от степени тяжести заболевания.

Материал и методы. Под наблюдением находилось 80 детей в возрасте от 2 до 14 лет (72 мальчика и 8 девочек) с бронхиальной астмой. У 44-х больных отмечалось среднетяжелое течение болезни, у 36-и больных - тяжелое.

У всех наблюдавшихся нами больных диагностирована атопическая форма БА, у всех был повышен уровень общего иммуноглобина Е. Его колебания составляли от 205 до 470 МЕ.

Специальные методы исследования включали определение содержания субстанции Р, нейрокинина А и вазоактивного интестинального пептида в плазме крови детей, больных БА различной степени тяжести.

Определение уровня нейропептидов проводили иммуноферментным методом с помощью анализаторного набора «Стат Фах» («Пенинсула лабораториес Инъ», США).

Результаты и их обсуждение. У детей со среднетяжелой бронхиальной астмой (44 больных) уровень субстанции Р, в среднем, составил 3,07±0,12 нг/мл, а нейрокинина А - 2,32±0,10 нг/мл ($p<0,001$). По сравнению с нейропептидами уровень ВИП у больных среднетяжелой БА был, в среднем, 0,209±0,021 нг/мл. У детей, страдающих тяжелой формой БА отмечались более высокие концентрации субстанции Р - 4,36±0,29 нг/мл ($p<0,001$) и нейрокинина А – 2,67±0,11 нг/мл ($p<0,05$). При тяжелом течении БА

отмечалось более низкое содержание ВИП - 0,132 ±0,009 нг/мл по сравнению со среднетяжелым течением заболевания (p<0,01).

Таким образом, изменения содержания вазоактивного интестинального пептида, который является медиатором неадренергической нервной системы в легких, имели противоположный субстанции Р и нейрокинину А характер в динамике заболевания (таблица).

Таблица. Показатели ВИП, субстанции Р и нейрокинина А у больных БА в динамике заболевания

Показатели	Группы		
	Контрольная (n=10)	**Среднетяжелая (n=44)**	**Тяжелая (n=36)**
ВИП (нг/мл)	0,987±0,123 (0,31-1,60)	0,209±0,021 (0,1-0,66)	0,132±0,009 (0,03-0,2)
p		<0,001	<0,001
p_1			<0,01
Субстанция Р (нг/мл)	1,28±0,20 (0,3-2,1)	3,07±0,12 (1,6-4,6)	4,36±0,29 (2,2-9,4)
p		<0,001	<0,001
p_1			<0,001
Нейрокинин А (нг/мл)	1,08±0,17 (0,2-1,9)	2,32±0,10 (1,4-4,56)	2,67±0,11 (1,86-4,98)
p		<0,001	<0,001
p_1			<0,05

p - по сравнению с контролем ; p_1- по сравнению со среднетяжелой группой

Наиболее высокие значения уровня субстанции Р и нейрокинина А рассматриваются в настоящее время как основной медиатор нейрогенного воспаления. Эффекты нейрогенного воспаления, проявляющиеся в процессе заболевания, влияют на его тяжесть и течение.

Дисфункция в системе вазоактивного интестинального пептида может возникнуть вторично в процессе хронического воспаления дыхательных путей. Так как ВИП является важным регулятором бронхиального тонуса, наиболее мощным эндогенным бронходилататором из известных в настоящее время, он противодействует бропхоспазму при астме.

Полученные данные свидетельствуют об участии нейропептидов в патогенезе бронхиальной астмы у детей. Активация воспалительных реакций, сочетание аллергического и нейрогенного воспаления характерные для бронхиальной астмы, приводят к освобождению субстанции Р и нейрокинина А, что способствует ускорению разрушения вазоактивного интестинального пептида. Снижение ВИП и накопление субстанции Р и нейрокинина А в легких, по всей вероятности, инициируют многие из патофизиологических реакций, свойственных бронхиальной астме (спазм гладкой мускулатуры, отек слизистой оболочки бронхов, гиперсекрецию слизи), усугубляют хронический воспалительный процесс в легких.

Таким образом, изучение нейроиммунной регуляции иммунного гомеостаза при бронхиальной астме является одним из принципиальных вопросов прикладной и научной иммунологии и может быть дополнительным критерием эффективности проводимого лечения.

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SUMMARY

NEUROIMMUNE REGULATION IN CHILDREN WITH BRONCHIAL ASTHMA

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80 children aged from 2 to 14 years,72 boys and 8 girls, 44 with moderate and 36 with severe form of atopic bronchial asthma were investigated. Substance P, neurokinin A and vasoactive intestinal peptide (VIP) were defined in blood plasma. In comparison with the control group, children suffering from bronchial asthma showed statistically significant ($p<0,001$) increase of substance P and neurokinin A and decrease of VIP.

Analogous changes were observed by comparison of data received from children with moderate and severe asthma. Received data indicate the participation of neuropeptides in pathogenesis of bronchial asthma in children.

Key words: bronchial asthma, vasoactive intestinal peptide.

РЕЗЮМЕ

НЕЙРОИММУННАЯ РЕГУЛЯЦИЯ ПРИ БРОНХИАЛЬНОЙ АСТМЕ У ДЕТЕЙ

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Под наблюдением находилось 80 детей в возрасте от 2 до 14 лет (72 мальчика и 8 девочек) с атопической бронхиальной астмой (БА). Из 80-и детей с БА у 44-х больных имело место среднетяжелое течение болезни, у 36-и - тяжелое. Определялось содержание субстанции Р, нейрокинина А и вазоактивного интестинального пептида (ВИП) в плазме крови. По сравнению с контролем у всех больных отмечалось статистически достоверное ($p<0,001$) увеличение содержания субстанции Р и нейрокинина А и уменьшение ВИП. Аналогичные результаты были получены при сравнении тех же показателей у больных тяжелой и среднетяжелой формами БА ($p<0,01$). Полученные данные свидетельствуют об участии нейропептидов в патогенезе бронхиальной астмы у детей.

SIMULATED-PATIENT-BASED PROGRAMS FOR TEACHING COMMUNICATION WITH ADOLESCENTS: THE LINK BETWEEN GUIDELINES AND PRACTICE

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Adolescents are regarded in general as healthy young people, but still 10-15% suffer from chronic illnesses, 20-30% develop obesity, 5% suffer from eating disorders, and a lot more are engaged in risk behaviors, such as tobacco smoking, alcohol and drug abuse, violence and unprotected sexual behaviors resulting in unplanned pregnancies and sexually transmitted diseases [1]. Adolescent medicine has emerged as a subspecialty with the recognition that teenagers have special health needs related to their physiological as well as their psychosocial development. The critical health issues of adolescence include reproductive health, injury, substance use, mental health, violence, obesity and access to health care [2].

Physicians are frequently positioned in the front line of teenage health care, either in primary care facilities (pediatricians and family physicians), or in hospitals as well as in specialty clinics (gynecology, gastroenterology, nephrology, pulmonology, etc).

While the clinical approach to most health problems characteristic to adolescents may be quite straight forward, the communication with the adolescent patient and frequently also with his or her parents, requires unique skills on behalf of the physician. Adolescents frequently tend not to share personal issues with their health care providers either because they deny the health hazards related to these issues (e.g. cigarette smoking, or unprotected sex),

or because they do not wish to share confidential matters with adults identified as part of the rules forming system [1]. Moreover, the presence of a parent during the medical encounter may increase the reluctance of the adolescent patient to provide a complete history. Utilizing a thorough system review that includes both physical and psychosocial items as well as inquiry about risky behaviors, in the absence of the parents, may disclose hidden agenda that significantly contributes to the clinical condition (e.g. restriction in food intake resulting in secondary amenorrhea, physical and sexual abuse presenting as severe abdominal pain). Chronically ill adolescents, who are typically more involved in risk behaviors, including non-compliance with their medical treatment, as compared to healthy adolescents [3] require special attention of the health care provider. Likewise, within the military service adolescents may wish to hide medical issues that might hamper their promotion in the army, while others may wish to exaggerate health complaints for the sake of secondary gains. These characteristics create difficulties for health care professionals in civilian as well as in military frameworks, in communication with adolescents.

Guidelines for obtaining information regarding adolescents' risk behaviors and other psychosocial issues have been developed and their use has improved physicians' attention toward a variety of adolescent health issues [4-6]. However, these guidelines do not provide the necessary tools for optimal communication with adolescents. Communication skills are best obtained in role-play models where either colleagues or actors simulate the patients' roles [7-9].

Table. Average and range of scores (1-6) for the items in the feedback questionnaire (1- very little or very poor, 6- very much or very good)

	N=96	
Item	**Average Score**	**Score Range**
General contribution	5.4	5.1 – 5.7
Actors performance	5.8	5.5 – 6.0
Gaining communication skills	5.5	5.1 – 6.0
Facilitators contribution	5.7	5.3 – 6.0
Video recording contribution	5.5	5.2 – 5.9
Logistics	5.8	5.6 – 6.0
Recommend inclusion of SP programs in training	5.8	5.7 – 6.0

Simulation-based medical education (SBME) is a rapidly growing field in addressing patient safety through quality-care training [10-12]. SBME offers a safe and "mistake forgiving" environment where trainees can learn from their errors without the risk of harming real patients [13]. The training is learner oriented, and enables consideration of the trainees' needs, deficiencies, and their pace of learning, without the ethically disturbing use of actual patients that is associated with traditional bedside teaching. SBME provides a hands-on empirical educational modality, enabling controlled proactive exposure of trainees to both regular and complex scenarios. Another important benefit of SBME is the reproducible, standardized, objective setting provided for both formative assessment (debriefing) [14] and summative assessment (testing) [15-16]. The medical literature is scant of publication addressing the use of simulated patients in training physicians in adolescent medicine, and the experience with simulated patients in training programs in adolescent medicine is limited.

The Israel Center for Medical Simulation Experience.
Training programs to improve physicians' communication skills with adolescents have been developed at the Israel Center for Medical Simulation (MSR). MSR is an international leader in the innovative and evolving field of medical simulation and patient safety. Founded in 2001 at the Chaim Sheba Medical Center, MSR's multi-modality approach enables multi-disciplinary training to health care professionals in a wide variety of over sixty vital courses, through hands-on practice in simulated medical environments. By replacing the real medical environment, MSR takes a unique approach toward improving patient safety, emphasizing essential aspects such as teamwork and communication skills, through extreme and challenging medical conditions with fidelity sufficient to achieve suspension of disbelief on the part of the trainee [17]. MSR trained over 27,000 health care professionals between the years 2002-2007.

In 2003 a unique simulated-patient-based program was developed to train practitioners in communication with adolescent patients and their parents [18]. Between 2003 and 2007, 470 physicians, including 233 primary care pediatricians and family physicians, 94 pediatric residents, 44 pediatricians in adolescent medicine post-graduate courses, 34 gynecologists and 65 physicians from military recruitment centers were trained at MSR in 40 one-day courses, on common adolescent health issues that require unique communication skills on behalf of the clinician, utilizing the simulated-patient-based programs. Typical adolescent health related scenarios presenting at the

physician's office included: Iron deficiency anemia due to dysfunctional uterine bleeding presenting as fatigue and social withdrawal; physical abuse by a parent presenting as recurrent abdominal pain with normal laboratory evaluation; approaching an adolescent girl who has been raped; disclosure of unprotected sexual relations followed by recommendations for birth control and sexually transmitted infection prevention; pregnancy presented as secondary amenorrhea; approaching an adolescent female who requires pelvic examination for the first time; explaining normal pubertal development to a mentally retarded adolescent girl; approaching eating disorders in an adolescent patient; exacerbation of asthma in an adolescent patient with poor compliance in preventive care, who discloses recent cigarettes smoking; approaching an adolescent patient with recent onset of a malignant condition; approaching the parents and the adolescent who discloses commencement of drug abuse.

For each training day at MSR for up to twelve participants, eight scenarios were prepared with actors who were well trained to perform as standardized adolescent patients or parents of adolescents. The scenarios were performed in four rooms designed to look like regular physicians' offices. Microphones and one-way mirrors enabled the observation of the physician-standardized patient (SP) encounters, and video cameras recorded the encounters for further analysis during debriefing sessions. Four scenarios were exercised 3 times in the morning sessions and 4 different scenarios were exercised 3 times in the afternoon sessions, thus enabling each participant to encounter with SPs at least twice during the training day and to observe 4 other encounters. Following both the morning and afternoon exercises the encounters were discussed with all participants utilizing the video recordings. These debriefing sessions were lead by facilitators experienced both in adolescent medicine and in SP-based programs. The last hour of the day was devoted to summary and feedback from the participants, including an anonymous structured Likert scale questionnaire. The feedback questionnaire included 7 topics: The general contribution of the day to the approach toward adolescents; The actors' performances; The acquisition of communication skills with adolescents; The contribution of the facilitators in the debriefing sessions; The contribution of video recording in the debriefing sessions; The logistics of the training day organization; and the need to include such simulation-based programs in training curricula for physicians. Altogether, 470 physicians were exposed to 3760 encounters with simulated adolescent patients, in 940 of which they actively communicated with the SPs.

Feedback From Trainees.

The average and range of the scores of a sample of 96 feedback questionnaires filled by physicians from various disciplines in medicine trained in 9 groups at MSR is presented in Table 1. Excellent feedbacks were obtained regarding all questionnaires' items, with scores raging from 5.1 to 6.0 (out of 6) per item. The highest scores (5.7-6.0) were related to the need to include simulation-based programs in physicians' training curricula of the disciplines where adolescents are included among the patient populations of these physicians.

The simulated-patient-based program that was applied in MSR to train 470 physicians from different disciplines in communication with adolescent patients proved to be successful. Therefore, an initiative is planned to integrate such programs in all residency curricula in pediatrics, family medicine, and gynecology under the auspice of the Academic Council of the Israel Medical Association.

Further studies are required to investigate the short and the long-term impact of such programs on participating physicians.

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SUMMARY

SIMULATED-PATIENT-BASED PROGRAMS FOR TEACHING COMMUNICATION WITH ADOLESCENTS: THE LINK BETWEEN GUIDELINES AND PRACTICE

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Adolescents frequently tend not to share personal issues with their health care providers, thus communication with the adolescent patient and frequently also with his or her parents requires unique skills on behalf of the physician. Guidelines for obtaining information regarding adolescents' risk behaviors and other psychosocial issues that have been developed, do not provide the necessary tools for optimal communication with adolescents. Communication skills are best obtained in role-play models where either colleagues or actors simulate the patients' roles. Simulation-based medical education offers a safe and "mistake forgiving" environment that enables consideration of the trainees' needs, without the use of real patients that is associated with traditional bedside teaching.

Training programs to improve physicians' communication skills with adolescents have been developed at the Israel Center for Medical Simulation (MSR). Between 2003 and 2007, 470 physicians were trained at MSR in 40 one-day courses. These courses dealt with common adolescent health issues that require unique communication skills on behalf of the clinician, utilizing the simulated-patient-based programs. At each training day up to 12 physicians were exposed to 8 typical adolescent health related scenarios simulated by professional actors in rooms equipped with video facilities and one-way mirrors. Following the encounters with the simulated patients, the different scenarios were discussed in debriefing group sessions with experienced facilitators utilizing the encounters' video recording. Feedbacks from participants in the programs were excellent, emphasizing the need to include simulation-based programs in physicians' training curricula.

Key words: communication skills, adolescent patient, training programs, role-play models.

РЕЗЮМЕ

ПРОГРАММЫ ДЛЯ ОБУЧЕНИЯ КОММУНИКАЦИИ С ПОДРОСТКАМИ С ИСПОЛЬЗОВАНИЕМ МНИМЫХ БОЛЬНЫХ: СВЯЗЬ МЕЖДУ МЕТОДИЧЕСКИМИ РЕКОМЕНДАЦИЯМИ И ПРАКТИКОЙ

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Подростки часто не делятся личными проблемами с лицами, оказывающим им медицинскую помощь, поэтому коммуникация с пациентами подросткового возраста, а также с их родителями требует специальных навыков. Существующие методические рекомендации по получению информации, касающейся рискового поведения подростков и других психосоциальных вопросов, не предоставляют необходимых способов для оптимальной коммуникации с подростками. Коммуникационные навыки в наилучшей мере приобретаются в процессе ролевых игр, в которых коллеги или актеры играют роль пациентов. Медицинское образование, основанное на использовании мнимых больных, предлагает безопасную и «прощающую ошибки» среду, которая позволяет учитывать потребности обучающихся без использования реальных больных, что проводится при традиционном обучении у постели больного.

В Израильском центре для медицинской имитации разработаны обучающие программы, позволяющие улучшить коммуникационные навыки врачей с подростками. За 2003-2007 гг. в данном центре обучены 470 врачей на 40 однодневных курсах. На этих курсах рассматриваются наиболее частые проблемы здоровья подростков, которые требуют особых коммуникационных навыков со стороны врачей, использующих эти курсы. В течение дня обучения до врачам представляют по 8 сценариев, связанных со здоровьем подростков, осуществляемых профессиональными актерами в помещениях с видеооборудованием и прозрачными только с одной стороны зеркалами. Вслед за встречами с мнимыми больными различные сценарии обсуждаются на групповых сессиях с опытным методистом с использованием видеозаписи встреч. Участники курсов высоко оценивают эту программу и подчеркивают необходимость внедрения подобных программ в курс обучения врачей.

NUTRITIONAL PROTEIN INTAKE IS ASSOCIATED WITH BODY MASS INDEX IN YOUNG ADOLESCENTS

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Obesity has reached epidemic levels in all age groups [11,46] so that preventing and treating obesity has become a major public health concern. Twenty five percent of children in the US are overweight and 11% are obese. The most recent German Health Interview and Examination Survey for Children and Adolescents [30] showed that 6.4% of the 7-10 year old children and 8.5% of the 14-17 year old adolescents are obese. Data for children collected in the Health Survey for England in 1998 showed that between 1994 and 1998, the prevalence of overweight children grew from about 13 to 20%. Reports on the rising trend in obesity are available for most developed, and also for many developing countries. In urban areas of Egypt, the prevalence of overweight women has risen to 69.9%, in Mexico to 65.4%, and even in the very poorest countries, overweight has become a major problem particularly in the lower social strata [35].

Obesity results from the imbalance of energy intake and energy expenditure. Energy intake has increased across all age groups [6,39]. The US Department of Agriculture factbook 2001-2002 (cited by Rigby 2005) provides evidence that the "average American" consumes about 530 Kcal per day more – an almost 25% increase in energy intake – compared with 30 years ago. The reasons for the increase in nutritional energy are manifold. Whereas characteristic food intake patterns did not consistently associate with body mass index [52,53], the overall increased availability of food supplies, increasing portion size, eating away from home, and consuming a variety of high-energy dense foods were considered responsible for the increase in energy intake [16,18,23,39]. The more food is served, the more people overeat [33].

Energy expenditure has decreased. The displacement of physical activity by sedentary behaviours is a significant co-factor for the development of obesity. Since 1985, when Dietz and Gortmaker found a significant association between the time spent watching television and the prevalence of obesity, there has been broad consensus that particularly TV watching associates with weight gain. Pendola and Gen [41] described an inverse relationship between population density and auto use as well as higher BMI scores for respondents reporting high levels of auto use for the work/school commute and trips to the grocery store.

Apart from the increase in energy intake and the decrease in energy expenditure, the proportion of macronutrient intake has also changed with a substantial decline in the percentage of energy from nutritional fat, and an increasing energy intake from sweetened beverages [40]. The present investigation focuses on the interaction between body mass index and protein. This relation has considerably less well been studied than the relation between BMI and the intake of nutritional fat and carbohydrate. In most Western diets, the protein energy percentage varies around some 15 percent. Protein is an essential compound of everyday food, and popular notion associates nutritional protein with health improvement. Particularly since recent literature suggests high protein diets to be beneficial for weight loss [31,32] which will be discussed later, protein-rich food has been favoured, and its consumption has substantially increased since many years. In Germany, the annual per capita meat production doubled since 1950 and reached almost 100 kg/a by now. The annual per capita production of milk has been stable since 1970 at some 70 litre, but the per capita production of cheese also doubled since 1970, and reached 20 kg/a. Since 1970, the per capita poultry production increased from 8 to 14 kg/a [14]. Adding all meat, dairy and poultry products results in an average per capita purchase of 85 gram/d animal protein (Hermanussen, unpublished). Similar data were reported from the Netherlands [4] and from the UK [42].

In spite of some early reports that protein intake was consistently high in obese children at all ages [8], the association between the rising consumption of protein and the rising prevalence of obesity has largely been neglected even in the recent literature. First in 1995, Rolland-Cachera and co-workers quantified the relation between nutritional protein and body weight. Protein intake at the age of 2 years was positively correlated with BMI at 8 years ($r=0.17$, and when adjusted for BMI at 2 years and for parental BMI, the correlation increased to $r=0.22$). The authors detected less convincing correlations between BMI and energy ($r=0.16$), and no correlation between BMI and fat intake and BMI and carbohydrates ($r=0.02$, and -0.07 respectively). It was concluded that protein at the age of 2 years was the only macronutrient that significantly associated with fatness development patterns. Similar results were published by Gunnarsdottir and Thorsdottir [17], and Scaglioni and co-workers [49]. Agostoni and co-workers (2005) stated that protein intake beyond the limit of 14% energy in 6-24 months old infants, will lead to overweight in young children. Kemper and co-workers [26] investigated fat mass in males and females, aged between 12-28 years of the Amsterdam Growth and Health Longitudinal Study and found an Odds Ratio of 1.5 (1.2-1.8) with the

daily intake of proteins. We report additional evidence supporting an effect of nutritional protein on body mass index.

Material and methods. 7182 three-day weighing and nutritional protocols and anthropometric data of the DONALD (Dortmund Nutritional and Anthropometrical Longitudinally Designed) Study were obtained and re-analyzed from the Forschungsinstitut fьr Kindererndhrung (Research Institute for Child Nutrition) Dortmund, Germany. DONALD is an open cohort study investigating the relations between feeding behaviour, food consumption, growth, development, nutritional status, metabolism and health from birth to adulthood since 1985 [29]. The protocols were obtained from 1028 healthy children and adolescents aged 2 to 18 years (51.3% girls, 48.7% boys), measured between 1985 and March 2006.

Mean daily intake of energy, carbohydrates, fat, protein and the amino acid glutamate were evaluated for each subject using the FKE (Forschungsinstitut fьr Kindererndhrung Dortmund) nutritional data base, and from national and international food tables [10,50,54]. Mean daily intakes were correlated with BMI standard deviation (BMI-SDS).

Results and their discussion. Mean daily energy intake ($r=0.060$, $p>0.1$), and the absolute daily intake of fat ($r=0.031$, $p>0.1$), and carbohydrate ($r=0.050$, $p>0.1$) were independent from BMI standard deviation scores (BMI-SDS). However, a significant interaction between BMI-SDS and the mean absolute daily intake of all protein ($r=0.143$, $p<0.0001$), and animal protein ($r=0.151$, $p<0.0001$) was found. When expressing macronutrient intake as percentage of daily energy intake, the fat and carbohydrate correlations remained insignificant with $r=-0.040$, and $r=-0.037$, respectively, whereas the correlation between BMI-SDS and all protein ($r=0.203$, $p<0.0001$), and animal protein ($r=0.163$, $p<0.0001$) further increased. The correlation depended on age (Figure 1), and reached maxima in the group of 10-12 year old boys ($r=0.31$, $p<0.0001$), and girls ($r=0.36$, $p<0.0001$), i.e., protein intake explained up to 13% of the BMI variance in young adolescents. The figure clearly indicates the propensity at early pubertal age, to become obese when consuming elevated amounts of protein.

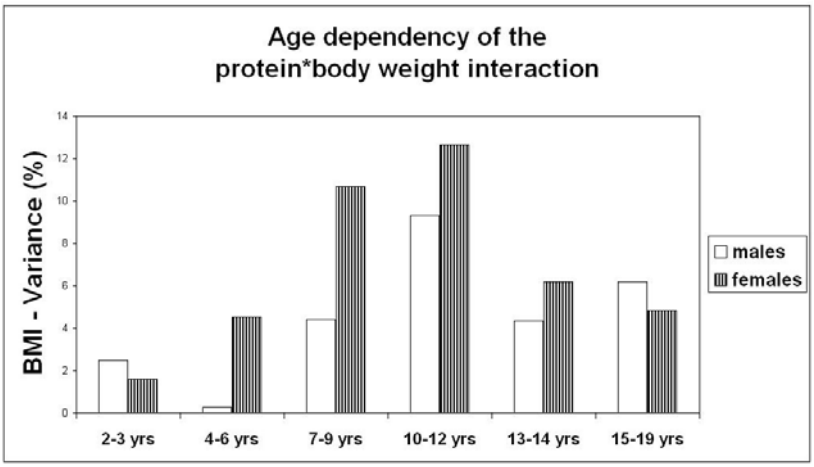

Fig 1. Nutritional protein significantly contributes to body mass index (BMI) variance in an age dependent manner. Bars indicate the percent of BMI variance that is explained by protein intake (percent of total energy intake). The interaction is strongest in pre- and early pubertal females (age groups 7-9, and 10-12 years) and males (age group 10-12 years)

Evidence has accumulated that protein consumption stimulates weight gain at the population level. This concept seems to contradict current opinion in respect to weight loss following high protein diets, and needs commenting. It is true that very high protein diets (with protein contributing to much more than 25% of energy intake) exhibit a number of metabolic effects. They stimulate postprandial thermogenesis and the sensation of fullness, suppress appetite and at the individual level, lead to negative energy balance [9,24,32,34]. These effects are even stronger in ketogenic low-carbohydrate diets [25,55], and appear to be independent of the leptin and ghrelin regulation [56], i.e., the effects of very high protein diets appear to bypass major paths of the physiological regulators of appetite. Recent evidence suggests a key role of the amino acid leucin that directly suppress food intake via hypothalamic mTOR signalling [7], and might explain the satiating effect of the popular very high protein weight loss diets.

These mechanisms however, are not relevant at the population level as the average protein consumption of modern populations, never contributes to more than 25% of its total energy intake. What makes protein so interesting?

Following regular food processing that already partially hydrolyses nutritional protein, intraluminal pancreatic

proteases further digest protein into oligopeptides (some 70%) and free amino acids (some 30%) [27]. Though under ordinary circumstances most amino acids should undergo rapid intestinal metabolism [43,44], free amino acids may bypass their intestinal metabolism. In 1983 it was shown that monosodium glutamate penetrates into the human circulation [51]. Bergstrцm and co-workers [3] showed that the serum levels of most amino acids increased following a protein rich meal. Also the brain levels of several amino acids increase following ingestion of protein-containing meals [15].

Glutamate is the most common amino acid in animal protein and accounts for some 16% of meat protein, and some 20% of milk protein weight. The per capita consumption of this amino acid in everyday food has markedly increased in recent years. Infants who consume up to 5 g/kg body weight (BW) of protein per day [28] consume as much as 1 g/kgBW/day of GLU. Glutamate not only serves as the physiological ligand of the taste receptor umami, the dominant taste of food containing L-GLU, like chicken broth, meat extracts, ageing cheese; the amino acid glutamate is the major excitatory neurotransmitter and in this function, is deeply involved in various hypothalamic regulation including eating behaviour. We recently linked obesity, voracity and growth hormone deficiency, to chronic over-consumption of glutamate [19-22], and reported that blocking the glutamate-gated Ca^{2+} ion channel of the NMDA receptor by Memantine significantly suppresses appetite not only in rodents, but also in human binge-eating disorder [21].

How much protein do we need? Millward [36] and Millward and Jackson [37] revised current recommendations for safe protein/energy ratios both in children and in adults. They concluded that minimum requirements may approach the upper range of the obligatory metabolic demands of daily amounts of some 0.3 to 0.5 g protein per kg body weight, equivalent to some 4 to 6% of energy, in adult subjects. Already in 1988, Beaton and Chery (1988) revised protein requirements of infants and suggested 1.1+/-0.1 - 0.2 g/kg/d to be a more reasonable estimate than the FAO/WHO/UNU estimates of 1.47+/-0.26 g/kg/d for infants aged 3-4 months. Agostoni and co-workers [1] considered 7-8% of energy in the 4-month exclusively breastfed infants, and up to the maximum acceptable levels of 14% of energy in 12-24-month-old infants safe. They stated that only when protein supply represents less than 6% and energy is limited, fully breastfed infants are likely to enter a status of negative nutrient balance. Reeds and Garlick [45] discussed the dietary requirements for protein, nitrogen and individual indispensable amino acids and calculated that over the age range of 6-24 months, a minimum protein-energy ratio of 6.3% was desirable.

These limits are way below current dietary protein consumption, and we are concerned that modern nutritional protein loads will cause unwelcome amino acid signalling and on the long run, result in voracity and weight gain. We strongly suggest reconsidering the recommended daily allowances of nutritional protein, to abstain from popular very high protein diets, and particularly from adding the flavouring agent monosodium glutamate.

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SUMMARY

NUTRITIONAL PROTEIN INTAKE IS ASSOCIATED WITH BODY MASS INDEX IN YOUNG ADOLESCENTS

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Preventing and treating obesity has become a major public health concern. Obesity results from the imbalance of energy intake and energy expenditure. Energy intake has increased, energy expenditure has decreased in recent years. In addition, the proportion of macronutrient intake has changed with a substantial decline in the percentage of energy from nutritional fat, and an increase in energy from sweetened beverages. We focus on the interaction between body mass index and the recent population wide increase in protein consumption.

7182 three-day weighing and nutritional protocols and anthropometric data of the DONALD (Dortmund Nutritional and Anthropometrical Longitudinally Designed) Study from 1028 healthy children and adolescents, aged 2 to 18 years (51.3% girls, 48.7% boys), measured between 1985 and March 2006, were obtained and re-analyzed.

Mean daily energy intake ($r=0.060$, $p>0.1$), and the absolute daily intake of fat ($r=0.031$, $p>0.1$), and carbohydrate ($r=0.050$, $p>0.1$) were independent from BMI standard deviation scores (BMI-SDS). However, a significant interaction between BMI-SDS and the mean absolute daily intake of all protein ($r=0.143$, $p<0.0001$), and animal protein ($r=0.151$, $p<0.0001$) was found. When expressing macronutrient intake as percentage of daily energy intake, the fat and carbohydrate correlations remained insignificant with $r=-0.040$, and $r=-0.037$, respectively, whereas the correlation between BMI-SDS and all protein ($r=0.203$, $p<0.0001$), and animal protein ($r=0.163$, $p<0.0001$) further increased. The correlation depended on age and reached maxima in the group of 10-12 year old boys ($r=0.31$, $p<0.0001$), and girls ($r=0.36$, $p<0.0001$).

Protein intake explained up to 13% of the BMI variance in young adolescents. We strongly suggest reconsidering the recommended daily allowances of nutritional protein, to abstain from the popular very high protein diets, and particularly from adding the flavouring agent monosodium glutamate.

Key words: protein intake, glutamate, body mass index, appetite control, obesity.

РЕЗЮМЕ

ПРИЕМ БЕЛКОВ В ВИДЕ ПИЩИ ВЛИЯЕТ НА ИНДЕКС МАССЫ ТЕЛА У МОЛОДЫХ ПОДРОСТКОВ

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Превенция и лечение ожирения является значимой проблемой общественного образования. Ожирение развивается в результате дисбаланса между получением энергии и ее расходом. В последние годы получение энергии увеличивается, а расход уменьшается. Следует добавить также, что соотношение между макронутриентами изменяется, имеет место существенное снижение процента количества энергии, получаемой от пищевых жиров, и увеличивается процент количества энергии, получаемой от сладких напитков. Мы делаем акцент на определение взаимодействия между индексом массы тела и наблюдаемым выраженным повышением потребления белков в популяции.

Были получены и заново проанализированы материалы исследования DONALD (Dortmund Nutritional and Anthropometrical Longitudinally Designed), в период между 1985 г. и мартом 2006 г. Материалы включали в себя антропометрические данные 1028-и здоровых детей и подростков, в возрасте от 2 до 18 лет и 7182-х протоколов с указанием результатов взвешивания и приема пищи в течение 3-х дней.

Среднее получение энергии ($r=0.060$, $p>0.1$) и абсолютное получение жиров ($r=0.031$, $p>0.1$) и углеводов ($r=0.050$, $p>0.1$) не зависели от баллов стандартной девиации индекса массы тела (BMI-SDS). В то же время была обнаружена существенная связь между BMI-SDS и средней абсолютного приема всех белков ($r=0.143$, $p<0.0001$) и животных белков ($r=0.151$, $p<0.0001$) за день. Когда выражали прием макронутриентов в виде процента к приему энергии за день, корреляции с жирами и белками оставались несущественными ($r=-0.040$ и $r=-0.037$ соответственно), в то время как корреляции между BMI-SDS и общими и животными протеинами далее усиливалась ($r=0.203$, $p<0.0001$ иг$=0.163$, $p<0.0001$, соответственно). Корреляция зависит от возраста и достигает максимума в группе мальчиков и девочек 10-12 лет ($r=0.31$, $p<0.0001$ и $r=0.36$, $p<0.0001$, соответственно).

Прием белков объясняет до 13% колебаний индекса массы тела у молодых подростков. Мы считаем необходимым пересмотреть рекомендации по приему белков, отказаться от популярных диет с их высоким содержанием и, в особенности, от добавления мононатриевого глютамата – вещества, придающего вкус пище.

CLINICAL AND PSYCHOLOGICAL CHARACTERISTICS OF SCHOOL ADAPTATION

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Last decades life conditions bring adaptive systems in children to deal with a significant exam. The adaptation procedure with ever changeable environment is considered as combined action results of adaptation and compensation. The structural body transformation takes place according to the changes accruing in external or internal world during adaptation. But during compensation to protect the unity of the body all structural and functional abilities are limited to the certain condition [2,6,8].

The adaptation procedure to impact an egzo- and endogenetic factors mainly is carried out by means of hypothalamus and reticular-limbic complex. One of the important unit in psycho-physiological disadaptation is disintegration in relationship of emotional, vegetative and cerebral systems and diminished adequate adaptive reactions. In this case higher hierarchal level systems are starting to work and not only biological but also physiological and social functions are deranged [1,7,9] in a child organism.

We can notice serious problems in adaptation to the schooling in 60-76% of the of primary school age children: decrease of interest towards learning, lack of organization, carelessness, confusion, aggressiveness, and complex relations with mates, etc [4,10]. In general, school disadaptation is a multifactor process which influences negatively on a child's organism, changes her/his activity, causes decrease of working ability, alteration of intellectual functions and violates the procedure of proper personality development of a child [3,5]. All above -mentioned provide actuality of problem if we consider wide distribution of disadaptative syndrome.

Aim of the study: Clinical and psychological characteristics of adaptation ability and disadaptation violation in primary school age children.

Material and methods. The research covered 120 practically healthy 6 – 8 y -young school age - (70 girls and 50 boys) children. The school selection and subject of study, after the preliminary identification, was performed under the randomization method (simple, random selection-with ballot – box).

All of them studied at secondary school. The end of the study year was chosen as a research period.

The criteria for inclusion in the research were: the primary school age (6-8); a child study at secondary school at the moment of the start of research; parent's consent for children psychological study and full anamnesis data provision.

The criteria for exclusion from the study were: co-existing somatic or neurotic pathologies that could cause school disadaptation; established adjacent neurotic-psycho disorders.

The cross sectional, one moment research was done that covered estimation of child mental development and academic results; readiness for school and school disadaptation study according to D Stot's "Map of Observation"; Determination of adaptive potential and vegetative nervous system functional state was performed by specifically for children adapted charts.

A special chart-questionnaire for children was filled in, that included early anamnesis, information about micro - social environment, family conditions, psychomotor development characteristics and so forth. Additional information was obtained from policlinic documentation; conversations with parents and teachers were held. The questioning methods by phone calls and interviews were used as well.

Data were processed with statistic analyses method (program system SPSS – 11v).

Results and their discussion. Three age groups were determined from under observation of 6 – 8 y. 120 children where equal number of children was included. One year study period covered 6 years of age 40 children (boys 17(14%), girls 23(19%)); Two years study period, 7 years of age – 40 children (boys 18(15%0, girls (22(18%)); Three years study period covered 8 years of age 40 children (boys 15 (13%), girls 25 (21%)).

In yearly development history pre- and perinatal pathologies were detected in 46% of researched patients, including 30% different types of pregnancy injuries. The further psychomotor development of children went according to the age. In many cases the existence of the residual organic syndromes were noticed. In 25% of cases the conflicts among the members of the family and family disharmony were revealed; 27 children grew up in divorced families. From the studied contingent 56% of the pupils (67 children) were practically healthy and well adapted to the school assignments. In the rest cases different forms

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and degrees of disorder of the school disadaptation were revealed: contingent components of disadaptation – academic results, secondary school abilities, habits and knowledge decrease, was revealed especially in the children at second form (14%). Emotional personal disorder towards teaching – passive abilities, protest reactions, negative attitude to the teachers and generally school, was revealed in the children at second and third form (18%), but behavior repeated and hard corrected disorders – negative reactions, regular violation of disciplines, school "vandalism", were mostly found out in the children at third form (12%).

To estimate readiness for school and school disadaptation data we used the "Map of Observation" by D.Stot's mainly teachers and parents took part in filling in it. Providing the age of the children, 8 syndromes out of 15 units of "Map of Observation" were selected that was distributed according to the age (6 – 7 – 8 yy).

Distrust to new people (25% - 16% - 11%), confusion to adults (30% - 24% - 225), confusion to children (27% - 21% - 15%), aggressive attitude to adults (18% - 19% - 27%), agitation (15% - 25% - 28%), emotional tension (38% - 21% - 20%), aggressive attitude to children (12% - 12% - 11%), neurotic symptoms (6% - 14% - 17%), respectively.

Distrust to new people, confusion to adults and children, emotional tension were excessive in the children at the first form. At the increase of the age aggressive attitude to adults, confusion and neurotic symptoms were prevailed.

Semiotics of the vegetative function was revealed in 65 children. It was ascertained that in the children of the children of primary school age dysfunction of the digestion tract (70%), easy tiredness (65%), headache (55%), sleep disorder (42%), palpitation (39%), heavy sweatiness (27%), limb dump and marble color (12%), were noticed. 25% of the first form children had vegetative dysfunction, and at the forth form mentioned index increased to 41%.

On the basis of the received results, the significant role of the pre- and perinatal pathology in primary school age was revealed in formation of the school disadaptation and relatively less social factors. Along the growth increased anxiety for micro social and family problems especially in boys were marked.

The revelations of the school disadaptation must be considered as a tense functional state of the adaptive barrier, which still is not a pathological procedure and is underway within the psycho adaptation mechanism.

Thus, the received results enabled us to reveal the school disadaptation characteristics in young children, causative aspects of formation and age-specific characteristics. The mentioned must be taken into the consideration during the elaboration of the school disadaptation prevention and complex rehabilitation actions.

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SUMMARY

CLINICAL AND PSYCHOLOGICAL CHARACTERISTICS OF SCHOOL ADAPTATION

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70 girls and 50 boys – totally 120 practically healthy children were examined; Three age-specific groups with equal number of children were chosen. Goal of the research was to evaluate the adaptation ability and analyse the disadaptive derangements in primary school age children. Cross-sectional, one moment research was carried out according to D. Stot's "Map of Observation". Adaptive potential determination and evaluation of vegetative nervous system functional state was done. Special charts for children were filled in. 56% of pupils were practically healthy and well adapted to school obligations. In the rest of cases different degree and form of school dysadaptation derangements were revealed. The dysadaptation contingent with cognitive function was seen in 14% of children. Emotional attitude derangements to learning process was revealed in 18% of chil-

dren.; and hard to cope with the derangements correction in behavior was seen in 12% of children. The study results enabled us to reveal different types of school dysadaptation in primary school age children as well as to study the main reasons for their formation on the basis of age-specific characteristics. The above-mentioned fact should be taken into consideration while elaborating complex rehabilitation actions and school disadaptation prevention.

Key words: primary school age, adaptation ability, adaptive potential.

РЕЗЮМЕ

КЛИНИКО-ПСИХОЛОГИЧЕСКАЯ ХАРАКТЕРИСТИКА ШКОЛЬНОЙ АДАПТАЦИИ У ДЕТЕЙ МЛАДШЕГО ШКОЛЬНОГО ВОЗРАСТА

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Работа посвящается оценке адаптационной способности и анализу дизадаптационных нарушений у школьников младшего возраста, Была использована «карта наблюдений» по Д. Стоту. 56% школьников были практически здоровыми и хорошо адаптированы к учебному процессу. В остальных случаях выявлены дизадаптации различной степени и формы. При этом: дизадаптации в форме нарушения когнитивной функции наблюдались у 14% детей, эмоциональная лабильность к учебе - у 18%, трудность при коррекции нарушения поведения - у 12% детей. Выявленные данные указывают на различные типы школьной дизадаптации у детей младшего школьного возраста, что диктует необходимость исследовать основные причины их формирования с учетом специфичных возрастных особенностей. Полагаем, что полученные данные следует учитывать при разработке комплексных реабилитационных мероприятий и превенции школьной дизадаптации.

HEMATOLOGIC RESPONSE TO HYDROXYUREA THERAPY IN CHILDREN WITH β-THALASSEMIA MAJOR

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β-thalassemia is a common single-gene disorder and poses an important public health problem in many countries, Georgia is among them [1,8,11]. β+-thalassemia gene frequency in Georgia averages 0,019 (3,79% gene carriers) [1,2].

Augmentation of fetal hemoglobin (HbF) synthesis can reduce the severity of β-thalassemia by improving the inbalance between α-globin and non-α-globin chains [10,12]. Pharmacological agents such as Hydroxyurea (HU) have been known to cause induction of HbF, but the efficacy of this treatment in β-thalassemia patients is unclear [3-7,9,13-15].

This study was undertaken to evaluate the clinical and hematologic responses in six, school-aged, transfusion-dependent patients with β+-thalassemia phenotype to treatment with HU during 5 years in Georgia.

Material and methods. Six patients with β+-thalassemia phenotype were enrolled in the study from September 2001 to October 2006. The diagnoses of β+-thalassemias major were made based on the clinical, hematologic and hemoglobin electrophoresis profiles. Each patient was transfusion-dependent from early childhood (from 6 month to 2 years) and splenectomized (from 3 years to 6 years).

The patients - three boys and three girls, ranged in age from 8 years to 13 years (average 9,8 years). All of them were treated in the Hematology Department of the Pediatric Clinic of the Tbilisi State Medical University with regular follow-up ever 3-4 weeks. All patients and their parents were informed about the possibility of side-effects and complications during therapy with HU. After informed consent was obtained, baseline and serial hematologic tests and measurements were performed. Complete blood count (CBC), microscopic examination of the blood smear, and reticulocyte count were determined by conventional methods. Percentages of HbF and HbA_2 were obtained by elution after electrophoresis in cellulose acetate. The hematologic parameters were determined weekly, during the first 2 months of therapy, and then monthly intervals. HbF

was measured at the beginning, after 1,2 and 5 years of treatment. Serum ferritin was determined using a radioimmunoassay method.

All six patients were treated with HU. At 10 days before the start of the therapy, patients received the next in turn transfusion with washed red cells, because at the beginning of the treatment a steady-state value of the Hb was to be 90 mg/L or higher. The starting dose was 5 mg/kg per day (5 days/week) given orally, once a day. The dose was adjusted upward at increments of 5 mg/kg per day at intervals of 12-24 weeks until hematologic toxic effects were noted (Leukocyte count $<2x10^9$/L, platelet count $<80x10^9$/L and absolute reticulocyte count <50,000/ML). The maximal average tolerable dose was 15 mg/kg per day.

Statistical analysis was performed with MICROSTA software (Ecosoft, Inc).

Results and their discussion. After the first 5 months of therapy, blood transfusions were given at intervals of 4-5 weeks. During the next six month, patients needed red cell transfusion at intervals of 6-8 weeks. During this period, the patients "felt better and had more energy". Hepatomegaly decrease or change in liver size was not observed. After 1 year of HU therapy, the transfusions were stopped in three cases. Their total Hb level stabilized and then increased. Two patients had significantly decreased need for transfusions (every 4-5 months), but their Hb level did not change from those recorded pretreatment. One patient continued to receive transfusions at intervals of 6-8 weeks. His Hb level decreased slowly from that recorded pretreated.

HbF level rose in all patients, but the response was variable. The level of HbF increased from 60% to 85% in patient 1, from 38%-68% in patient 5 and from 16% to 52% in patient 6. Thus, increase of HbF levels in three patients was significant (25%, 30% and 36% respectively), and there children became completely transfusion-free. The rise in HbF levels was not as marked in the other three patients (17%, 10,3% and 3%, respectively). We were able to classify three categories of HU response: a good response in patients who shifted from monthly blood transfusion to a stable transfusion-free condition at an average Hb level of more than 100 mg/L, a moderate response in patients who remained transfusion-dependent, but at longer intervals (4 months or more) and no response in patient, who after treatment for 1 year remained at the same level of transfusion-dependence.

Levels of serum ferritin decrease during HU treatment, which was particularly convincing in cases, when red cell transfusions stopped. In other cases, there was little decrease. There was an important decrease in reticulocyte count in cases, when the transfusions were stopped.

Hematological parameters before, after 1 and 5 years of HU treatment are presented in Table 1.

Table 1. Hematological parameters before, after 1 and 5 years of HU treatment

Patient No	Age (yr) /sex	Before therapy				After 1 years			After 5 years			
		Hb (mg/L)	Rt (%)	HbF (%)	Ferritin (ng/ml)	Hb (mg/L)	Rt (%)	HbF (%)	Hb (mg/L)	Rt (%)	HbF (%)	Ferritin (ng/ml)
1	12/F*	90.0	8.5	60.0	894.0	98.0	7.6	75.0	102.0	5.8	85.0	595.0
2	13/M	90.0	4.7	10.0	826.0	88.0	4.4	12.5	90.0	4.4	27.0	816.0
3	8/F	100.0	2.7	6.2	814.0	90.0	1.8	10.4	100.0	2.0	16.5	798.0
4	8/M	90.0	9.0	9.0	448.0	80.0	8.4	10.0	80.0	5.8	12.0	444.0
5	10/F*	96.0	7.0	38.0	410.0	100.0	7.0	60.0	102.0	6.4	68.0	350.0
6	8/M*	100.0	9.0	16.0	520.0	102.0	8.7	20.0	108.0	4.7	52.0	350.0

*Rt - reticulocytes, HbF - fetal hemoglobin; * - good response to HU therapy (HbF > 20%)*

Five children were treated for more than 5 years with no further major variation in levels of Hb. At the most recent follow-up, three patients had gone more than 5 years without transfusions. During this time their level of Hb remained between 100 gm/L and 108 mg/L.

There was no serious complication of treatment with HU. Total leukocyte count, absolute neutrophil count, and platelet count remained normal in all patients, even through an erythropoietic toxic reaction occurred in one patient at a dose 15 mg/kg per day, resulting in an acute drop in Hb and reticulocyte levels to below baseline levels. Administration of HU was then stopped, and the Hb levels increased before a return to baseline. Further treatment with HU was given at the dosage of 5 mg/kg per day. There were no complications.

Our results demonstrated that in children with high HbF levels, the HU therapy is more effective than it is in children with low baseline HbF levels. So, HbF has prognostic importance, and low baseline HbF levels (below 15%) were predictors of poor response. Thus, HU could be particularly useful in countries such as Georgia, where supplies of blood and chelating agents are limited.

Decreased levels of serum ferritin after treatment with HU suggested improvement in iron balance and these patients will use less Desferal (the decrease of ferritin is connected mostly with reducing or stopping the hemotransfusions).

We note, that HU has a more general role in augmenting globin synthesis, increasing β–globin in some β+-thalassemia phenotype patients who maintain the capacity to express normal β–globin chains.

The side-effects of HU depend on the dose. No significant side-effect was observed with this low-dose, long-term HU regimen, and regular hematological analyses showed no evidence of marrow toxicity.

Thus, it may concluded that low doses (5-10 mg/kg per day, 5 days/week) of HU after 12-18 months of therapy may correct the anemia and can eliminate or minimize the transfusional needs in children with β+-thalassemia major in cases when the patient's baseline HbF level is 15% and more and its increase during the treatment is to above 20%.

The main problem is to discover how enhance the oxygen release of HbF in future.

Our results raise cautious optimism that β+-thalassemia major patients may benefit from treatment with HU.

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SUMMARY

HEMATOLOGIC RESPONSE TO HYDROXYUREA THERAPY IN CHILDREN WITH β-THALASSEMIA MAJOR

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β-thalassemia major is the most common monogenic hereditary blood disease in children. β+-thalassemia major gene frequency in Georgia averages 0,019 (3,79% gene carriers). Hydroxyurea (HU) has been known to cause induction of fetal hemoglobin (HbF), but the efficacy of this treatment in β-thalassemia patients is still unclear.

This study was undertaken to evaluate the clinical and hematologic responses in patients with β+-thalassemia to treatment with HU during 5 years in Georgia.

Six children, aged 8 years to 13 years with transfusion-dependent β+-thalassemia phenotype were enrolled in a trial to assess the response to HU therapy. Hemoglobin, reticulocyte count, HbF and ferritin were evaluated. The starting dose of HU was 5 mg/kg per day (5 days week) given orally once a day. Response to therapy was evaluated at 1, 2, and 5 years of treatment.

Clinical improvement and rise in the HbF levels was observed in all patients. We report three cases of a remarkable response to treatment with HU in which the red cell transfusion was stopped after 1 year of treatment, and the patients became completely transfusion-free for more than 5 years. A moderate response was seen in two patients, who remained transfusion-dependent, but at longer intervals. There was no serious complication of treatment with HU.

Long-term HU therapy may correct the anemia and can elimi-

nate or minimize the transfusional needs in children with β+-thalassemia major in cases, when the patient's baseline HbF level is ≥15% and its increase during the treatment is up to 20%.

Key words: β+-thalassemia major, Hydroxyurea, fetal hemoglobin (HbF).

РЕЗЮМЕ

ГЕМАТОЛОГИЧЕСКИЙ ОТВЕТ НА ТЕРАПИЮ ГИДРОКСИМОЧЕВИНОЙ У ДЕТЕЙ С БОЛЬШОЙ β-ТАЛАССЕМИЕЙ

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β-талассемия является одной из наиболее распространённых моногенных врожденных заболеваний крови у детей. Частота встречаемости гена β+-талассемии в Грузии, в среднем, составляет 0,019 (3,79% - носители гена). Препарат гидроксимочевина (ГМ) в настоящее время известен как каузальный индуктор фетального гемоглобина (HBF), однако, механизм его действия при лечении β-талассемии до конца не ясен.

Целью исследования явилась оценка клинических и гематологических результатов лечения больных большой β+-талассемией гидроксимочевиной в Грузии.

Для оценки результатов лечения ГМ в течение 5-и лет под наблюдением находились 6 больных трансфузия-зависимой β+- талассемией в возрасте от 8 до 13 лет. Изучались показатели гемоглобина, HBF, ферритина и количество ретикулоцитов. Стартовая доза ГМ составила 5 мг/кг/сут энтерально, один раз в день (5 дней в неделю). Оценку результатов терапии проводили спустя 1, 2 и 5 лет.

Улучшение клинического состояния и повышение уровня HBF наблюдали у всех больных. Особенно следует выделить 3-х пациентов, у которых был получен оптимальный результат: через год после начала терапии ГМ, полностью исчезла необходимость в трансфузии эритроцитарной массы и им не требовалась гемотрансфузия более 5-и лет. Умеренный эффект наблюдался у 2-х пациентов, которые нуждались в гемотрансфузии, однако с более длительными интервалами. Серьезных осложнений при применении ГМ не наблюдалось.

Длительная терапия с применением ГМ способствует коррекции анемии и устраняет в целом или снижает до минимума необходимость в гемотрансфузиях у детей с большой β+- талассемией в случаях, где уровень HBF≥15% и в процесее лечения повышается до 20%.

EXPERT DIAGNOSIS IN TALL STATURE: EDITS 1.1 DIAGNOSTIC SOFTWARE EFFICACY

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Tall stature, which may be defined as height above the 97th percentile, is present in case of many pediatric disorders and bears much importance in terms of physical, emotional and social well-being of affected individuals; diagnostic approach to overgrowth and tall stature related disorders is of particular importance for clinical medicine [2,8,15,35].

It is noteworthy, that many cases of overgrowth and tall stature syndrome fall on a share of the so called rare diseases [16]; the prevalence of the latter being less than 0.07 or 0.05%, according to the US and European definitions; being rare, these clinical conditions constitute a serious diagnostic jig-saw for the majority of regular medical professionals not specializing in the field and lacking the relevant experience. However, this expertise gap may be filled by the usage of computerized tools created with the aim of simulating human reasoning.

The progress in the application of artificial intelligence, computer sciences and information processing techniques has resulted in the development of various medical expert systems [13,14,20,32,33], particularly for application in pediatrics [11].

It is noteworthy, that in 2006 the seemingly first expert system for diagnosing of disorders and syndromes manifested by tall stature was created: An Expert System for Differential Diagnosis of Tall Stature Syndrome [18], version 1.0. Recently, in 2007 it was further developed into the subsequent version [17], version 1.1, now called EDITS (Expert Diagnosis In Tall Stature).

However, the efficiency of the aforecited diagnostic software remains to be researched. It would be also helpful to compare it to the efficiency of other diagnostic computer

databases, like POSSUM, SYNDROC and LDDB [7,19, 28,29], which have some information about tall stature related syndromes in their knowledge base along with data about many other dysmorphological disorders.

Our goal was to evaluate the last available version of a specialized expert system for the differential diagnosis of the tall stature syndrome (EDITS 1.1).

Materials and methods. EDITS version 1.1 was evaluated by making it diagnose sets of clinical and laboratory criteria published as case reports in medical scientific literature, and analyzing the results obtained.

The case reports were selected randomly by means of the National Center for Biotechnology Information online database PubMed. Names of the syndromes were used as keywords, while search results were limited to "Links to free full text" and "Case Reports" as "Type of Articles". Retrieved works were sorted for the ones containing the best description of the case. In an attempt to imitate the real-life clinical situation no preference was given to cases with "standard" clinical presentation. The rarity of the diseases/syndromes that may manifest tall stature varies a lot [16]. So, for the extremely rare syndromes (only up to 10-15 cases published) we had to consult the seminal papers. Less rare disorders with tens of published cases as well as relatively common rare diseases with hundreds of reported and published cases were represented by the case reports found by means of PubMed.

After retrieving the case reports, the cases' data were collected. In all cases the tall stature (unspecified) diagnostic criterion was added if not already specified in the case report in order to make the case applicable to the expert system. The data were input into the EDITS 1.1. The results constituted a list of the top five most-probable diseases/syndromes, ranked in the order of likelihood along with their probability; the presence, if any, of the correct diagnosis on the list generated by the expert system was registered, as well as its likelihood rank and numerical probability.

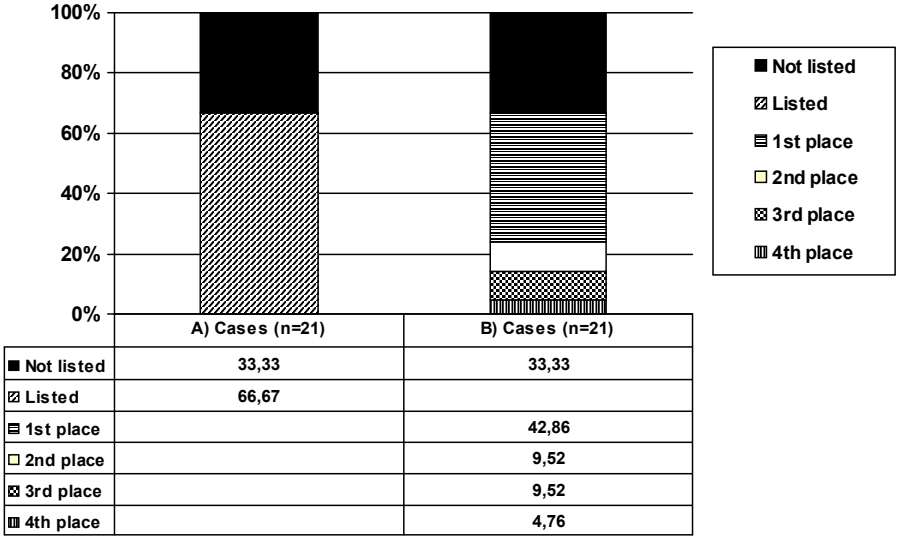
Obtained results were analyzed and compared to those of other expert systems.

Results and their discussion. 21 cases of 12 diseases were processed (Table). In 14 cases out of 21 (66.67%) the diagnosis established by the authors (referral diagnosis) of the case reports was included in the top five most probable diagnoses listed by the expert system. In 8 cases (38.10%) the referral diagnosis was ranked the first by the expert system, and in one more case the authors of the case report were suggesting two alternative diagnoses: Marshall-Smith syndrome and Weaver syndrome; the expert system ranked Marshall-Smith syndrome as the first diagnosis, and Weaver syndrome as the third diagnosis; therefore we may conjecture that the referral diagnosis was ranked the first in 9 cases and not 8 out of 21 (42.86%). The referral diagnosis was ranked the second in 2 cases out of 21 (9.52%), the third also in 2 cases (9.52%) (ignoring the case when one of the referral diagnoses was ranked the third, while another one was ranked the first), the fourth in 1 case (4.76%).

Table. Evaluation of EDITS 1.1. Case report sources, disease or syndrome names, correct diagnosis ranks and its probabilities are listed

Source	Disease/syndrome	Correct Diagnosis (Rank, if listed)	Probability
22: family 602, the older brother	Mental retardation, X-linked, marfanoid habitus	not listed	
22, family 576	Mental retardation, X-linked, marfanoid habitus	2nd	0.75
26	Perlman syndrome	not listed	
21	Perlman syndrome	not listed	
36	Zunich-Kaye syndrome	1st	99.93
27	Zunich-Kaye syndrome	1st	78.36
4	Weaver syndrome	4th	<0.01
30	Weaver or Marshall-Smith syndrome	1st (Marshall-Smith) 3rd (Weaver)	97.27 0.04
25	Simpson-Golabi-Behmel syndrome	1st	100.00
24	Proteus syndrome	not listed	
3	Proteus syndrome	not listed	
6	Klinefelter syndrome	1st	99.72
34	Klinefelter syndrome	3rd	18.32
1	Beckwith-Wiedemann	1st	99.93
12, case 2	Beckwith-Wiedemann	1st	100.00
10	Bardet-Biedl	1st	100.00
9	Bardet-Biedl	1st	99.97
31	Bannayan-Riley-Ruvalcaba	3rd	<0.01
5	Bannayan-Riley-Ruvalcaba	not listed	
23, case 3	Sotos	not listed	
23, case 2	Sotos	2nd	<0.01

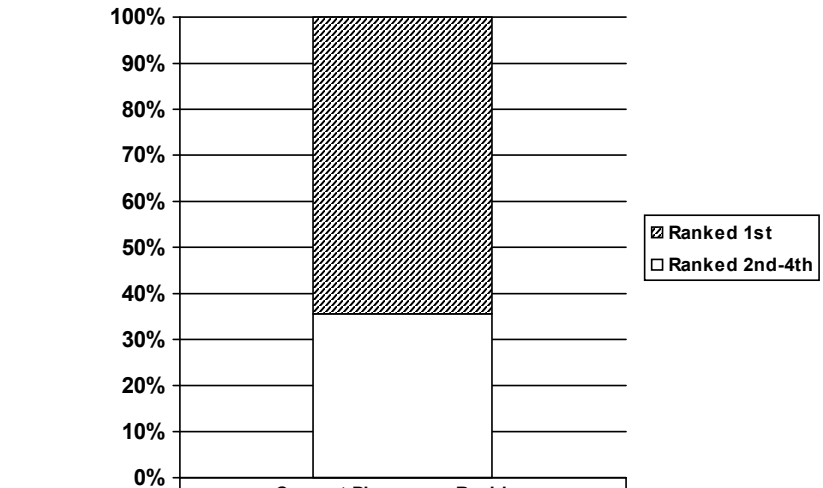
The evaluation results are summarized in Fig. 1.



	A) Cases (n=21)	B) Cases (n=21)
Not listed	33,33	33,33
Listed	66,67	
1st place		42,86
2nd place		9,52
3rd place		9,52
4th place		4,76

Fig. 1. EDITS v. 1.1 evaluation results: A) Listing the referral (correct) diagnosis among the top five most probable diagnoses. B) Percentage of different ranking of the referral (correct) diagnosis

In 64.29% of all the cases when the correct diagnosis was put on the top five list, the correct diagnosis ranked first (Fig. 2).



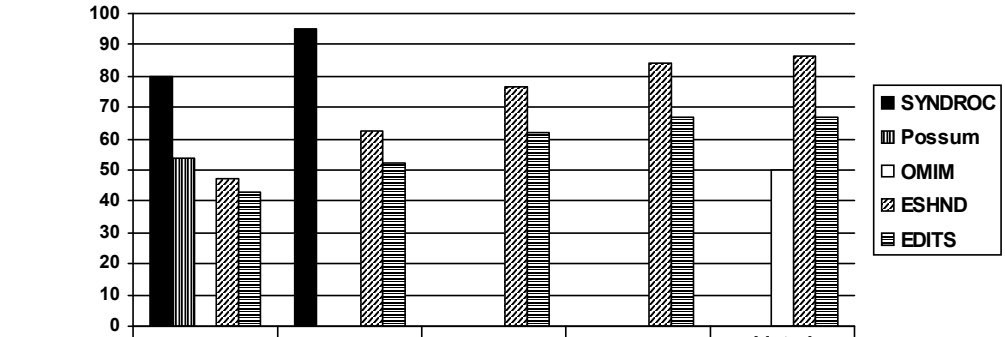
	Correct Diagnoses Ranking
Ranked 1st	64,29
Ranked 2nd-4th	35,71

Fig. 2. The percentage of the correct diagnosis ranked first in the total number of correct diagnoses put on the top five answers list generated by EDITS 1.1

The overall result, in terms of efficiency of EDITS 1.1 (the condition is diagnosed, or better say listed among the top five most probable diagnoses in 66.67%, two thirds of cases) is not ideal, but seems to prove that the software is not a purely theoretical plaything: despite the limited sample size and certain limitations imposed by using the literary data instead of first-hand clinical cases, it showed a certain practical value and can be freely applied in the clinical practice as an auxiliary tool supporting a physician.

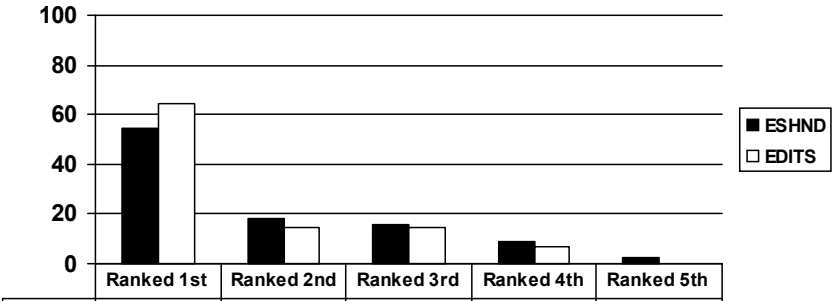
The efficacy of this expert system is more or less in line (Fig. 3) with that demonstrated by other more general diagnostic software programs like SYNDROC and POSSUM (Pictures of Standard Syndromes and Undiagnosed Malformations), or a "bibliographic database" like OMIM

(On-line Mendelian Inheritance in Man) [19,29]. For instance, the percentage of "correct" (referral, in our case) diagnoses ranked first was 80% for SYNDROC (applying both pseudo-Bayesian method and an heuristic approach), in contrast to 43% of EDITS, which nevertheless proved to be a more or less close match to POSSUM results: 54% [19,28]. SYNDROC, ranking correct diagnoses among the top two answers in 95% of cases is far ahead of EDITS doing that only in 52% of cases; however, as already mentioned, the latter ranks the correct diagnoses among the five top answers in 66.67% of cases, and thus has an advantage to OMIM, who does that in "above 50%" of cases [28,29].



	Ranked 1st	Ranked among top 2	Ranked among top 3	Ranked among top 4	Listed (ranked among top 5)
SYNDROC	80	95			
Possum	54				
OMIM					50
ESHND	47,06	62,75	76,47	84,31	86,27
EDITS	42,86	52,38	61,9	66,66	66,66

Fig. 3. Efficacy of SYNDROC, POSSUM, OMIM, ESHND and EDITS expert systems. Percentage of different ranking of the correct diagnosis



	Ranked 1st	Ranked 2nd	Ranked 3rd	Ranked 4th	Ranked 5th
ESHND	54,55	18,18	15,91	9,09	2,27
EDITS	64,29	14,29	14,29	7,14	0

Fig. 4. Efficacy of EDITS and ESHND expert systems. Percentage of the correct diagnoses ranked 1st, 2nd, 3rd, 4th and 5th in the total number of correct diagnoses put on the top five answers list generated by the expert system

The comparison with the Expert System for Differential Diagnosis of Hereditary Neuromuscular Diseases in Children [20] seems to be of a particular interest (Fig. 3). The latter, conventionally called ESHND, and the EDITS employ the same algorithm, and the creators of ESHND took part in elaboration of the early version of EDITS [18]. Therefore it is quite remarkable that the former showed somewhat better results than the latter (last version 1.1): correct diagnoses ranked first in 47% of cases vs. 43%, ranked among the three top answers in 76% vs. 62%, ranked among the top five answers in 86% vs. 67% (Fig. 2). Sharing the same algorithm, these two expert systems differ in terms of the knowledge bases and the essence of the clinical material formalized [17,18,20]. ESHND is based on the knowledge base of 7 experts and comprises 306 diagnostic criteria for 26 diseases [20], whereas EDITS 1.1 is based on the knowledge base of 5 experts and comprises 824 diagnostic criteria for 81 diseases or syndromes [17]. On the other hand, ESHND is dealing with a limited number of relatively well-researched and common dis-

eases, while EDITS focuses on a much bigger number of "orphan" rare disorders, being generally less common and less researched, with few exceptions; these diseases or syndromes are also mainly hereditary and should be therefore less variable in terms of clinical and laboratory indices, but current medical knowledge on them appears to be less organized. The creators of EDITS faced a challenge of formalizing much vaster data array comprising ambivalent and even multivalent and sometimes also mutable indices, and this should have predisposed in our opinion the diminished efficacy of EDITS compared with ESHND. One the other hand, the moderate efficacy of EDITS may demonstrate the limitations of the algorithm employed in these two expert systems.

EDITS 1.1 was sufficiently reliable in terms of adequacy of the list of the top five most probable diagnoses provided: the correct diagnosis was ranked first in 64.29% of all the cases when the correct answer was listed within the top five suggestions (Fig. 2). By this indicator, EDITS 1.1 seems to be somewhat more efficient than ESHND. Being more powerful (yielding a correct diagnosis within the top five answers in 86% vs. 67% of EDITS 1.1), the latter is less precise, ranking the correct answer first in only 54.55% of the cases when the correct answer is listed within the top five answers, whereas for EDITS 1.1 this index is equal to 64.29% (Fig. 4).

We would like to note that due to the limited sample size the obtained results are of a preliminary nature only and should serve as a basis for further, more expanded research.

Moreover, one has to bear in mind that confronting different diagnostic software sometimes designed for different purposes easily leads to a pitfall of matching the incongruous data, and an adequate meta-analysis becomes impossible. For more trustworthy results, one would have to test the general, multi-syndrome SYNDROC and POSSUM expert systems in diagnosing the tall stature manifested disorders only, and the uniform data should be input in case of all the expert systems brought into comparison; that means feeding the same cases into both SYNDROC and POSSUM and EDITS. The areas the EDITS and the ESHND are designed for are quite distinct. However, they employ the same algorithm, and that makes ESHND a certain etalon to match the following versions of EDITS with.

The evaluation of EDITS 1.1 highlighted the need to optimize the differential diagnostics process for the disorders sharing some clinical indices, like say 14 diseases/syndromes with marfanoid features (Boileau; Elmer; Clunie; Cotlier; Merghoub; Saul; Somlo; Stevenson; Tamminga; Furlong; Houlston; Mental retardation, X linked, marfanoid habitus; Marfanoid mental retardation syndrome, autosomal syndromes; Marfan disease): specific individual characteristics should be more thoroughly represented in the knowledge base.

Evaluation of the EDITS 1.1 diagnostic software showed that this expert system exceeds the framework of a theoretical research and constitutes a useful practical tool for differential diagnosis of diseases / syndromes that may be manifested by the tall stature syndrome: it provides the correct diagnosis in 66.67% of cases.

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SUMMARY

EXPERT DIAGNOSIS IN TALL STATURE: EDITS 1.1 DIAGNOSTIC SOFTWARE EFFICACY

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EDITS (Expert Diagnosis In Tall Stature) expert system version 1.1 was evaluated by making it diagnose sets of clinical and laboratory criteria published as case reports in medical scientific literature, and analyzing the results obtained. The case reports were selected by means of the PubMed database. Processing the input data yielded a list of the top five most-probable disorders, ranked in the order of likelihood along with their probability. 21 cases of 12 diseases were processed. In 14 cases out of 21 (66.67%) the referral diagnosis was included in the top five most probable diagnoses listed by the expert system. In 64.29% of all the cases when the correct diagnosis was put on the top five list, the correct diagnosis ranked first. The efficacy of EDITS 1.1 is in line with that demonstrated by SYNDROC, POSSUM, OMIM and the Expert System for Differential Diagnosis of Hereditary Neuromuscular Diseases in Children. EDITS 1.1 diagnostic software proved to be a useful practical tool for differential diagnosis of disorders that may be manifested by the tall stature syndrome.

Key words: expert system, tall stature, diagnostics.

РЕЗЮМЕ

ЭКСПЕРТНАЯ ДИАГНОСТИКА ПРИ ВЫСОКОЙ СТАТУРЕ – ЭФФЕКТИВНОСТЬ ДИАГНОСТИЧЕСКОЙ ПРОГРАММЫ EDITS 1.1

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Для определения эффективности экспертной программы EDITS (Expert Diagnosis In Tall Stature - Экспертная диагностика при высокой статуре), версии 1.1 ее использовали для диагностики наборов клинико-лабораторных данных, опубликованных в виде клинических случаев в научной медицинской литературе. Клинические случаи были отобраны при помощи базы данных PubMed. Обработка введенных данных давала список из пяти наиболее вероятных диагнозов перечисленных согласно их вероятности с указанием оной. Был обработан 21 случай 12-и болезней. В 14-и (66.67%) случаях указанный в литературе диагноз попал в первую пятерку наиболее вероятных диагнозов, генерированную экспертной системой. В 64.29% всех случаев, когда правильный диагноз попадал в первую пятерку, он указывался на первом месте как самый вероятный. Эффективность EDITS 1.1 соотносится с эффективностью SYNDROC, POSSUM, OMIM и Экспертной системы для дифференциальной диагностики наследственных нейромускулярных заболеваний у детей. Подтвердилось, что диагностическая программа EDITS 1.1 относится к числу полезных практических инструментов для дифференциальной диагностики заболеваний, которые могут манифестироваться синдромом высокой статуры.

GENERAL MOVEMENTS IN INFANTS WITH AUTISM SPECTRUM DISORDERS

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General Movements (GMs) are a distinct movement pattern carried out spontaneously without external stimulation. They can be observed in fetuses as young as 9 weeks gestational age until the end of the second month postterm [8]. GMs till the age of 8 weeks postterm are referred to as writhing movements. They are of small to moderate amplitude and of slow to moderate speed. Fast and large extensor movements may occasionally break through. These movements are elliptical in form [8]. At the age of 6 to 9 weeks post term (usually around 9th week) the form and character of GMs change into a fidgety pattern and this pattern remains until 16-20 weeks. Fidgety movements are circular movements of small amplitude and moderate speed and variable acceleration in all directions of neck, trunk and limbs. They are continual in the awake infant except during focused attention. They may be concurrent with other gross movements. [4,5,8,14,15].

There are three main abnormalities of GMs in the writhing movement period: *Poor Repertoire* is characterized with monotonous sequence of the successive movement components; movements of the different body parts do not occur in the complex way as seen in normal GMs. Cramped-Synchronised GMs look rigid and lack the normal smooth and fluent character; all limb and trunk muscles contract and relax almost simultaneously. Chaotic GMs occur in a chaotic order without any fluency or smooth appearance; the movements of all limbs are of large amplitude and consistently abrupt in appearance. Fidgety movements are judged as abnormal if they are Absent or Abnormal. Abnormal fidgety movements look like normal fidgety movements but with moderately or greatly exaggerated amplitude, speed and jerkiness [8,15].

There are several prerequisites indispensable in order to assess GMs in the proper way. The infant should lie in supine position with naked arms and legs. The room temperature should be appropriate. If GMs are assessed retrospectively by videos, recordings should be preferably performed during active wakefulness. It is contraindicated to continue recording during prolonged episodes of fussing and crying, and during drowsiness and episodes of hiccupping, or when the infant is sucking on a dummy. Every possible interference by an observer (parents, examiner) or presence of any toy in the immediate surroundings should be avoided. In any case, the observer must be able to see the infant's face to make sure e.g. that jerky movements are not due to crying [8,15].

The neurological assessment of the integrity of the central nervous system by means of observation of GMs has been proved to be a robust method with high inter-scorer agreement and test-retest reliability [8]. The sensitivity of the method averages 94.5%, specificity depends on the age. It is a quick, non-invasive, non-intrusive and cost-effective method with high reliability and high validity. It is of great importance in early evaluation of neurological deviations leading to cerebral palsy or other developmental deficits later on. It has been shown that the GM assessment can be used to early and specifically predict cerebral palsy [15] in preterm infants, including those with a chronic lung disease [4], or in infants with neonatal cerebral infarction [9], or in term infants with a hypoxic-ischaemic encephalopathy [14]. In addition, abnormal GMs were predictive for minor neurological deficits such as attention deficit hyperactivity disorder [10]. Recently, abnormal GMs were also described in infants who were later diagnosed as Rett syndrome [7].

Autism Spectrum Disorder (ASD) is a neurodevelopmental disorder involving a life-long deficit in several aspects of the social and communicative behavior. The complexity of this disorder poses many questions about its biological bases: children with ASD lack the neurophysiologic equipment to engage in the most fundamental aspects of inter-subjective behavior, such as making eye contact, responding to others and understanding what other people think and feel. Core early domains of social impairments include social orienting, joint attention and face recognition. These social impairments suggest that ASD is related to dysfunction of early developing brain systems involved in social cognition [1,6].

As there is not yet found a clear biological marker of the disorder, diagnosis of ASD must be inferred from behavior. Diagnosis in infancy and early childhood is troublesome because of behavioral likeness between autism and other developmental disorders, the frequent comorbidity of mental retardation with ASD, and the wide range of individual differences in the first years of life [11,12]. In spite of this, several researchers consider early detection an accessible aim and a fundamental goal.

At first glance, signs of atypical development are not clearly observable in the first months of life and the distinction between them and normal variations in temperament and personality is not reliable. Most of the data about early signs come from parental reports of their child's development in the first years of life. However, parental reports present several limitations and biases. Another method is the prospective follow-along study, involving direct observations of children with developmental concerns or of siblings of children with autism. The principal problem is that a very large sample is required to find several children who develop autism [11]. Another option is the analysis of home-videos of children later diagnosed with ASD, and recorded by parents before they suspect anything unusual. The availability of home-videos of infants with ASD offers the possibility to overcome the lack of data regarding the first stages of life and to disclose some specific behavioral patterns of the development of social skills. Lower frequencies of responding to their own name and looking at people have been reported to be evident on home videos as early as 8 to 10 months [11]. Impairment in face processing and recognition may be initially evident just in a failure to attend to people's faces, an abnormality which might reflect abnormal neural representation of this process in the brain [13]. The lack of anticipation behaviors - such as opening of the mouth before receiving food or stretch their arms toward their mother before being taken by her – is well known, and might represent the difficulties of the ASD child to code others' intentions and to respond adequately.

The fact that infants with autism are often described as hypoactive or too good, account for the emphasis on the motor development in autism. Different studies showed that older children with autism have some Parkinsonian characteristics, but there is still controversy whether movement disturbances play an early central role in autism. A growing number of descriptions indicate that there are some specific motor features in infants who later develop ASD. In infancy, the movement disorders present in autism are clearest, not yet masked by other compensatory mechanisms and it is possible that they may vary according to the areas of the brain in which developmental delay or damage has occurred. Using Eshkol–Wachman movement notation, Teitelbaum et al. [16,17] presented evidence that abnormal movement patterns can be detected in ASD during infancy, suggesting that ASD can be diagnosed very early, independently of the presence of language. They hypothesize that the majority of movement disturbances in autism can be interpreted as infantile reflexes ''gone astray''; to be more precise, some reflexes are not inhibited at the appropriate age in development, whereas others fail to appear when they should. For instance, Teitelbaum and colleagues consider the absence of the head verticalization response as an early warning sign, maybe characteristic of ASD. The presence of this early signs may be also linked with precocious difficulties in making contact with mother's eyes.

The results of the main studies [3,16,17] indicating early motor abnormalities in infants and children with ASD, are summarized in Table.

Table. Motor development impairment in children with ASD

[3]	delays in the attainment of motor milestones clumsiness hyperactivity hand flapping choreoform movement of extremities poor balance poor coordination impaired finger-thumb opposition muscle tone and reflex abnormalities are also common repetitive and stereotypical movement of the body, limbs and fingers unusual gait patterns (poorly coordinated limb movements and shortened steps) poor performance of motor imitation tasks failure to use gestures for communicative purposes
[16,17]	persistent asymmetry lying on the stomach at the age of 4 months righting from supine to prone all of the segments of the body *en bloc* and not in a corkscrew fashion inability to maintain sitting stability by the age of 6 months and falling over like a log without even using any allied reflexes for protection deviations from the normal pattern of crawling relative akinesia while standing up at the age of 8-10 months walking – asymmetry, delayed development, sequencing instead of superimposition, strange positions of arm

The evidence of early motor signs in ASD and the validity of the observation of spontaneous movements, particularly GMs, for the neurological diagnosis in newborns and young infants have suggested a new study, whose aim was

to detect whether abnormalities in spontaneous motor activity can be observed already in the first months of life in infants with ASD.

Materials and methods. Participants. A retrospective study was performed by analyzing the family videos provided by parents of 20 children (male 17, female 3) later diagnosed with ASD. They were referred to the Unit for Pervasive Developmental Disorders of the Stella Maris Scientific Institute in Pisa (Italy) during the last 10 years and diagnosed by means of DSM criteria confirmed by a score above 30 on Childhood Autism Rating Scale (CARS). Home videos provided by parents of normally developing children (n=20; male 10, female 10) matched for age with the ASD subjects and recorded in similar conditions served as controls. In both groups three infants were recorded during their writhing movement period (from term age to 8 weeks), 13 infants during their fidgety movements (from 9 to 21 weeks post-term) and four infants during both age epochs.

In total, 70 video clips were used for the analysis where the infant was lying in supine position, with all limbs visible. The behavioural state was active wakefulness and the infant did not cry. The infants' age ranged from 6 to 21 weeks. The duration of sequences varied from 31 seconds to 3 minutes and 51 seconds.

Two independent observers, not aware of the infant's outcome (ASD or normal), assessed all videos applying the global GM assessment: normal, poor repertoire, cramped-synchronized or chaotic for the writhing movements; and normal, absent, or abnormal for the fidgety movements. In addition, the GMs and concurrent movements were analysed in details using the age-specific GM optimality scores [8]. The maximum score for the optimality list in the writhing movement period was 18 (minimum 8); in the fidgety movement period it was 28 (minimum 5).

SPSS 13.0 was used to analyze the data. Descriptive statistics and non-parametric tests were used. Cohen kappa was 0.614.

Results and their discussion. The majority (70.0%) of the sequences depicting ASD children were assessed as poor repertoire writing movements. In the control group poor repertoire GMs were seen in only 12.5% of the sequences. In the fidgety movement period 20.8% of sequences were evaluated as absent fidgety movements, and 29.2% as abnormal fidgety movements. By contrast, in the same age period the majority of the videos from control infants were rated as normal (88.9%), in 11.1% no fidgety movements were seen (Fig.1).

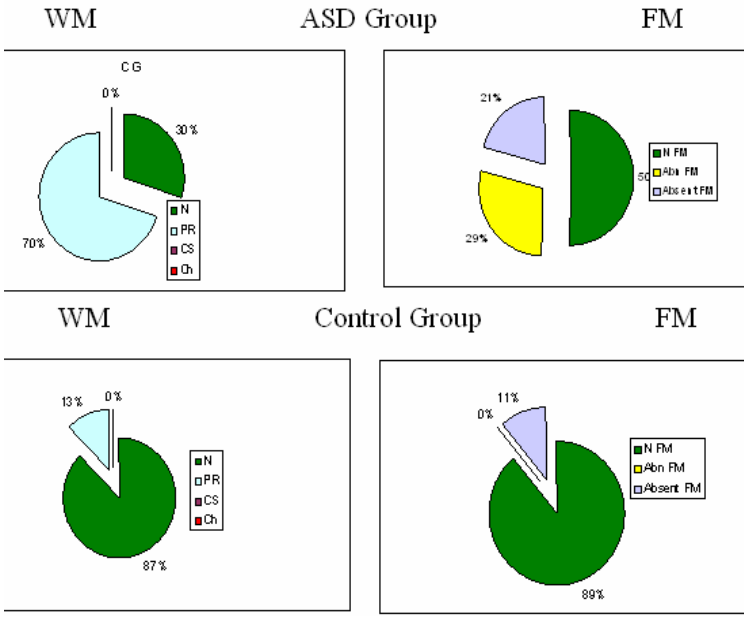

Fig. 1. Global assessment of general movements in ASD infants (n=20) and a control group (n=20)

From those four ASD children with available recordings from both, the writhing and the fidgety movement periods, one infant had normal writhing movements but developed no fidgety movements. Two infants with poor repertoire writhing movements developed normal fidgety movements. The remaining infant with poor repertoire writhing movements developed abnormal fidgety movements.

According to the Mann-Whitney U test there were significant differences between the ASD and the control groups' optimality scores ($p<0.001$). Both GM optimality scores were significantly lower in the ASD group compared to the control group (Fig. 2). A reduced optimality score was mainly due to a lack of variability in the sequences, amplitude, and speed (writhing movements, term-8 weeks) and a reduced quality of movements (3-4 months).

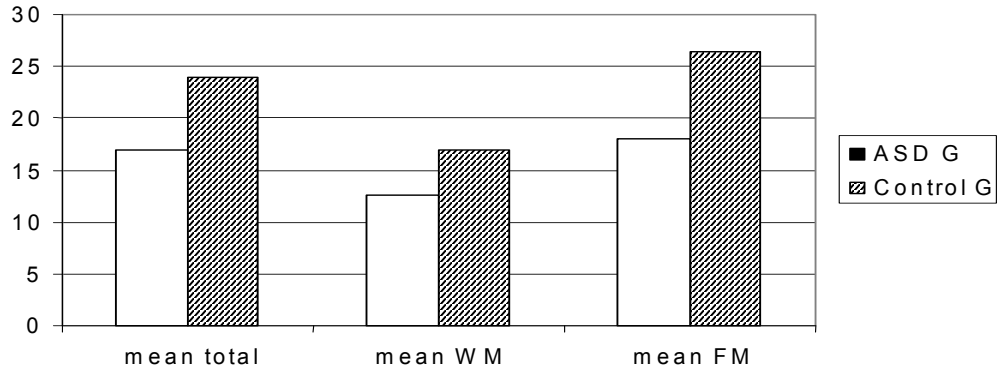

Fig. 2. Detailed assessment of general movements. Comparison of the motor optimality scores in the ASD (n=20) and the control group (n=20)

The results of our study indicate that infants with ASD show deviations from normal movement patterns. These findings are in the line with recent works of Teitelbaum et al and others suggesting that children with ASD show early motor impairment [2,3,16,17]. It is interesting that girls with Rett syndrome – a genetic disorder with autistic features - have similar abnormal GM patterns to our cases with ASD: they have been reported as having poor repertoire writhing movements and either no or abnormal fidgety movements [7].

The majority of autistic infants had an abnormal quality of GMs or even an absence of the age-specific fidgety movement pattern. In addition, the motor optimality scores were reduced in the ASD group compared to controls. These findings indicate that many cases with ASD have already an abnormal motor behavior before social and communicative skills become suspect. Spontaneous movements are the most relevant part of the neurological repertoire of infants in the first months of life. The obtained data may serve as a trigger to initiate more vast studies involving a larger number of family videos.

Our study has some limitations concerning the available duration of the videos of the ASD and consequently of the control group. In some cases, a poor repertoire of GMs may be wrongly judged as the video clip was too short. In the same line might be the judgment of an absence of fidgety movements. The video sequence might have ended just before the fidgety movements started. As the method can only be based on a retrospective video analysis of family recordings, we had to deal with the video sequences available. Although family videos from ASD patients are often available, frequently either they show infants at a later age than it is required for the GM assessment, or the sequence does not even meet the minimum of the requirements necessary to perform an adequate GM assessment [8].

For the above reasons, this research has to be considered as a pilot study, encouraging further research. It would be much advisable to proceed in this direction, as the early diagnosis of ASD is crucial for more fruitful intervention. If the finding of a qualitatively altered GM pattern in children later diagnosed as ASD will be confirmed, it would be advisable to put it as one of the early indicators for autism and to investigate the possible correlation with different clinical features of ASD. In fact, early movement disturbances can have an important role in the lack of initiative and in difficulties in being an active agent in purposeful interactions, contrasting the social activity expressed by a typical infant from birth.

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SUMMARY

GENERAL MOVEMENTS IN INFANTS WITH AUTISM SPECTRUM DISORDERS

Phagava[1] H, Muratori[2,3] F, Einspieler[4] C, Maestro[2] S, Apicella[2] F, Guzzetta[2] A, Prechtl[4] H.F.R, Cioni[2,3] G.

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General movements (GMs) are a distinct movement pattern carried out spontaneously without external stimulation and seen in fetuses of 9 weeks gestational age till 21 weeks postterm. GMs are helpful in the early diagnosis of an impaired central nervous system and the specific prediction of later neurological deficits. Autism spectrum disorder (ASD) is a neurodevelopmental disorder involving a lifelong deficit in several aspects of the social and communicative behavior. Recently there appeared studies proving that children with ASD demonstrate disorders of motor development.

To detect whether abnormalities in spontaneous motor activity can be observed already in the first months of life in infants with ASD.

A retrospective study was performed by analyzing the family videos provided by parents of 20 children (male 17, female 3) later diagnosed as ASD. Home videos provided by parents of a control group of healthy children (n=20; male 10, female 10) matched for age with the ASD subjects and recorded in similar conditions were also analysed. In total 70 sequences were studied. Two independent observers, blind of the infants' outcome (ASD or normal), assessed the cases applying a global and a more detailed assessment of GMs. Hence, the age-specific GM pattern (normal or abnormal) as well as motor optimality scores were determined for each video sequence. Cohen kappa was 0.614.

During the writhing movement period 70.0% sequences of infants with ASD showed poor repertoire GMs. In the control group, poor repertoire GMs were only seen in 12.5% of the sequences. In the fidgety movement period 20.8% of sequences were assessed as absent fidgety movements, 29.2% as abnormal fidgety movements. The large majority of the videos for the control cases were scored as normal (88.9%), 11.1% had no fidgety movements. According to the Mann-Whitney U test there were significant differences between the ASD and the control groups' optimality scores. The optimality scores were lower in the ASD group. The reduced optimality scores were mainly due to a lack of variable sequences, amplitude and speed of writhing GMs and an altered quality of fidgety and other spontaneous movements in the ASD group.

Infants with ASD had more often poor repertoire writhing GMs as well as abnormal or absent fidgety movements than control infants. These data encourage further studies involving a larger number of family videos.

Key words: neurodevelopmental disorder, general movements, autism, impaired central nervous system, infants, autism spectrum disorder.

РЕЗЮМЕ

ГЕНЕРАЛИЗОВАННЫЕ ДВИЖЕНИЯ У МЛАДЕНЦЕВ С ЗАБОЛЕВАНИЯМИ АУТИСТИЧЕСКОГО СПЕКТРА

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Генерализованные движения (ГД) представляют собой определенный двигательный паттерн, осуществляемый спон-

танно, без стимуляции извне и наблюдаемый у плода в периоде с 9-й недели гестационного возраста до 21-й недели после рождения. Оценка ГД является вспомогательным методом для постановки раннего диагноза поражения центральной нервной системы и позволяет предсказать неврологичекие дефициты, которые могут развиться позднее. Заболевания аутистического спектра (ЗАС) являются неврологическими расстройствами, которые характеризуются пожизненными нарушениями в социальном и коммуникативном поведении. Недавно появились новые данные, доказывающие, что дети, страдающие ЗАС, также демонстрируют нарушения моторного развития.

Целью исследования является возможность установления отклонений в спонтанной двигательной активности у детей с заболеваниями аутистического спектра уже в первые месяцы жизни.

Проведены ретроспективные исследования: анализ семейных видеозаписей, полученных от родителей 20 детей (17 мальчиков, 3 девочки), которым позднее поставили диагноз ЗАС, также проанализированы семейные видеозаписи здоровых детей (n=20; 10 мальчиков, 10 девочек) соответствующих по возрасту детям с ЗАС и записанных в аналогичных условиях. Рассмотрено всего 70 видеозаписей. Два независимых эксперта, не зная окончательного диагноза (ЗАС или норма) проанализировали случаи и дали свою оценку. Для каждой видеозаписи был установлен специфический для возрастной группы ГД паттерн (нормальный или ненормальный), а также была дана оценка оптимальности. Каппа Коэна равнялась 0.614.

В течение т.н. writhing периода 70.0% видеозаписей младенцев с ЗАС продемонстрировало бедный репертуар (poor repertoire) ГД. В контрольной группе, бедный репертуар ГД был всего лишь на 12.5% видеозаписей. В течение т.н. fidgety периода на 20.8% видеозаписей отмечалось отстутствие fidgety ГД, а на 29.2% отмечались анормальные fidgety движения. Большинство видеозаписей контроля были оценены как норма (88.9%), на оставшихся 11.1% не отмечались fidgety движения. По тесту Mann-Whitney U выявлены статистически значительные отличия между оценками оптимальности в группах ЗАС и контрольной. Оценка оптимальности была достоверно ниже в ЗАС группе. Низкая оценка оптимальности была вызвана, в основном, недостаточной вариабельностью, амплитудой и скоростью writhing ГД и измененным качеством fidgety и других спонтанных движений в ЗАС группе.

Младенцы с ЗАС чаще демонстрировали бедный репертуар writhing ГД, а также анормальные или отсутствующие fidgety движения по сравнению с младенцами контрольной группы. Полученные данные указывают на целесообразность продолжения исследований в данном направлении.

FAMILIAL MEDITERRANEAN FEVER IN ARMENIAN POPULATION

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Medical genetics concerns the relationships that exist between human genes, the variations and mutations that occur within this genes, and the phenotypes that result from these mutations. At least 5000 monogenic diseases have been documented in the Online catalogue of Mendelian Inheritance in Man (OMIM). The number of disease genes increases and now is over 1000. Many still remain to be described [3,18].

Center of Medical Genetics and Primary Health Care of Armenia has experience for many years in genetic testing of different inherited disorders. The main goal of genetic and clinical investigations is registration of frequency and structure of hereditary pathology in Armenian population. Detection of heterozygous carriers of recessive mutations and molecular investigation of several diseases such as hereditary autoinflammatory and neuromuscular disorders, mainly FMF, cancer, cystic fibrosis, birth defects, mental retardation, infectious diseases, as well as major mutations predisposing to venous thrombosis, etc. is carried out.

FMF is one of the crucial social and health care problems for Armenian population as historically endemic disease. Every week 35-50 new cases at the Center of Medical Genetics and Primary Health Care are registered.

FMF is characterized by recurrent episodes of fever and systemic inflammation. FMF as the nosological form was established by Siegal in 1945 [22]; its familial cases and lethal renal complications were described by Cattan and Mamou in 1951 [4]. The gene MEFV causing FMF was mapped to chromosome 16p13.3 by positional cloning [12,13] and >80 FMF-associated MEFV mutations have been identified. The 60 kb transcriptional unit in MEFV

interval was identified on the basis of genomic sequence analysis and exon trapping. Haplotype and mutational analyses showed ancestral relationships among carrier chromosomes that have been separated for centuries [15].

FMF is a prototype for several hereditary recurrent fever syndromes, also known as autoinflammatory syndromes with permanent genetic defects, accompanying with intermitted bouts of febrile serosites with focal organ, musculoskeletal system and skin involvement. FMF is the first disorder among different periodic inflammatory fevers caused by MEFV gene as one of attractive targets in Human Genome project, due to its defined regulatory role in the inflammatory response [15].

The mechanisms are specific for each type of these diseases. Among systemic autoinflammatory diseases there are the hereditary periodic fever syndromes, which include FMF and the following nosologies:

- TNF-RECEPTOR-ASSOCIATED PERIODIC FEVER SYNDROME (TRAPS, MIM 142680,) or FHF (FAMILIAL HIBERIAN FEVER) spreaded within non- Mediterranean origin populations. The type of inheritance of TRAPS is autosome-doninant. Mutations of TNF RSF 1A gene, located at the short arm of chromosome 12, affect the TNFRSF1A protein with cysteine substitutions (TNF receptor superfamily type 1A).

- Hyperimmunoglobulinaemia D (MIM 260920) or Dutch type periodic fever and periodic fever syndrome (HIDS), is characterised by the high serum level of immunoglobuline D, with a dominant mode of ingeritance. The deficiency of the mevalonate kinase enzyme is cased by mutations in the MVK gene localised on chromosome 12. MVK is the first committed enzyme of cholesterol biosynthesis.

Three cryopyrin-associated periodic syndromes with common signs like recurrent urticaria or urticaria-like eruption are caused by the mutations in CIASI gene (cold-induced autoinflammatory syndrome) localised on 1 chromosome. The CIASI gene encodes PYPAF1/cryopirin protein: Muckle-Wells syndrome is manifestated via characterised by urticaria and RA and nerve deafness.

Familial cold autoinflammatory syndrome/familial cold urticaria (FCAS/FCU) is the mildest clinical form.

Chronic infantile neurological cutaneous and articular/neonatal onset multisystemic inflammatory disease (CINCA/NOMID) is the most severe disease associated with neonatal skin rush, neurological and articular symptoms Diagnosis is based on the specific clinical and molecular-genetic data.

PFAPA syndrome of periodic fever, apthtous stomatitis, pharyngitis, cervical adenopathy. Syndrome of pyogenic arthritis with pyoderma gangrenosum and acne (PAPA) and Blau syndrome.

Amyloidosis (AA) remains a severe complication of these disorders apart from HIDS [10].

The main mutational "hotspots" of MEFV gene were identified at codons 694, 680, 148 [23]. Several classes of genes, responsible for the regulation of transcription, apoptosis, inflammatory response and the structural development of muscle cells are identified and express decreased functional levels in FMF patients [15]. Some upregulated genes involved in the defense and inflammatory responses also were found [14].

Mansfield et al. [19] proposed that the coding protein, pyrin or marenostrin, which is constituted of 781 amino acids and one of the members of nuclear factors family - homologous to the Ro52 antigen, regulates the inflammatory responses at the level of leukocyte cytoskeletal organization. Pyrin, the protein mutated in FMF, regulates caspase-1 activation and IL-1b production through interaction of N-terminal motif with ASC adaptor protein. This protein normally acts as a mediator in controlling inflammation and is produced inside neutrophils, eosinophils, monocytes with cytoskeleton. A mutated pyrin probably leads to uncontrolled inflammation. C-terminal B30.2 domain binds and inhibits the catalytic activity of caspase, and three common FMF-associated B30.2 mutations attenuate this effect [19].

FMF is unique in its susceptibility to the colchicine as the microtubule inhibitor. According to the data of D. Kastner et al. [15] the pyrin is co-localized within microtubules. Early cellular and molecular manifestation of FMF off colchicine includes increased protein's cleavage, upregulation of proinflammatory cytokines, including IL-12p70 and TNF and neutrophil activation.

Mutational study has revealed the strong correlations between the clinical severity and diagnostic criteria of the disease, including development of renal amyloidosis in individuals with different MEFV genotypes.

We participated at the creation of web-based International Project denoted "Meta-FMF" in 2000, composed of 12 experts in the field of FMF. This project, established by Prof. Isabelle Touitou [24] includes international collaboration between clinicians, geneticists, computer scientists and statisticians. The results of this project have revealed that some allele combinations at the MEFV locus contribute to severity of FMF manifestations, notably RA. In Armenia, Israel and Arabian countries, M694V homozygosity remained an aggravating factor for renal amyloidosis [24].

In the presented study MEFV mutations in FMF patients (homozygotes and compound heterozygotes) in compari-

son with healthy carriers of two mutations were investigated. The molecular analysis of MEFV mutations in a group of healthy individuals was performed to reveal the frequency of total carriers in Armenian population.

Material and methods. Present study provides the identification and distribution of twelve MEFV gene mutations in independent alleles among 7000 probands suffered from FMF collected from different regions of Armenia. An ongoing survey gives the information of frequency of MEFV mutations carriers and reveals genotype-phenotype correlation. The average age of the patients was 30.5 years. The male/female ratio is 1.16 which indicates the existence of reduced penetrance in females. The clinical diagnosis of FMF was performed according to the established clinical criteria by Livneh et al. in 1997 [17]. In order to determine the clinical differences between patients the criteria of severity scores were used.

Molecular testing was carried out to screen the MEFV gene mutations for diagnosis of patients with the clinical suspicion of FMF. For this purpose genomic DNA was isolated from peripheral blood using "Puregene kit" (Gentra System, USA).

Since 1998-2004 in our laboratory DNA was amplified by PCR technique with specific primers for MEFV gene region. The screening of MEFV gene mutations was realized by mutation-specific restriction-endonuclease assay for seven MEFV mutations from exons 2, 3, 5, 10. This study was performed for 4586 FMF patients.

Since 2004 the molecular-genetic diagnosis is carried out by PCR and reverse-hybridization method (Vienna Lab FMF Assay). We present the data of this assay for about 3000 patients.

The control investigations included the sequential analysis of all exons, was systematically carried out for each group of patients at the independent laboratories (Laboratory of Molecular Genetics, Head, Prof. Serge Amselem, Hospital Henri Mondor, Paris; and Primex Laboratory, USA, Dr. Erik Avanniss-Aghajani). These control investigations confirmed the correction of all results revealed in our laboratory.

Mutational analysis was also realized on 450 DNA samples obtained from control group of asymptomatic individuals.

The statistical analysis was performed using c2 and Fisher's tests.

Results and discussion. We have demonstrated that MEFV analyses has both diagnostic and prognostic values. Particular cases of inheritance should lead to a new ways for the management of FMF, including genetic counseling and therapeutic decisions in affected families [5].

Genetic investigation of the FMF mutations in group of 450 healthy individuals helped to reveal the extremely high overall carrier rate (0.21 or 1:5) in Armenia. We compared our data with the frequency of particular MEFV mutations and their distribution in different populations of the Mediterranean region [1,15,7,16,25].

The rate of carriers of FMF mutations in Armenians was as high as in North African and Iraqi Jews, Turks, but lower than in Ashkenazi Jews (1:4.5), Moroccan Jews (1:3.5) and Muslim Arabs (1:4.3) [8].

We have estimated the distribution of the most common MEFV gene mutations among healthy individuals, including M694V (4.7%); V726A (4.6%); M680I (1.8%); R761H (0.2%) in exon 10; F479L (0.4%) in exon 5; P369S (4.9%) in exon 3; E148Q (3.4%) in exon 2 [14].

We have revealed that the penetrance of MEFV gene mutations depends on the type of mutations involved in the pathogenesis of FMF in Armenian population. Among 450 controls we detected P369S rare mutation in complex alleles, suggesting that this mutation might ameliorate the phenotypic effect of exon 10 mutations. P369S mutation is the most common in the normal population (4.9%) but is less frequently represented in the patients (0.1%). Investigation of the frequency of mutations among FMF patients and healthy individuals suggests that E148Q mutation is associated with a mild phenotype, as well as P369S mutation was found in the most part of asymptomatic carriers. Evaluation of the phenotypic features depending from the presence of P369S mutation, showed the presence of seven patients with the FMF clinical picture: 4 heterozygous carriers for P369S mutation; two compound heterozygotes with P369S/E148Q mutations, and one patient with compound heterozygous mutations P369S/E148Q/M694V. In healthy individuals with P369S mutation we have found 9 heterozygotes, 3 compound heterozygotes (1 with P369S/F479L and 2 with P369S/E148Q), and 2 displayed complex alleles (P369S/E148Q/R761H; P369S/E148Q/M694V). This data confirms a reduced penetrance of P369S mutation.

The revealed results of this study allowed to identify specific MEFV mutations associated with severe or mild phenotypes of the disease.

In group of FMF patients the most common mutations are M694V (50.6%), followed by V726A (22.3%), M680I (18.7%), R761H (3.2%), M694I (0.4%); E148Q (2.2%), F479L (1.3%). 98.65% for Armenian FMF patients have the seven most common MEFV mutations. Approximately in 77% of these patients both alleles are mutated in exon 10.

The most part of FMF patients carries two mutations of MEFV (80.8%) compared with patients carrying only one mutation (18.5%) and patients with three mutations (0.7%). Common genotypes are M694V/M694V (20.9%), M694V/V726A (18%), M694V/M680I (12.7%), M680I/V726A (9.8%), M680I/M680I (3.4%), V726A/V726A (2.8%), M694V/R761H (2.8%). Some rare genotypes were found only in one patient (homozygous for F479L/F479L; V726A/R42W, etc.).

The screening of 12 mutations in MEFV gene in FMF patients with a clinical diagnosis of FMF (according to established criteria) indicated that almost 10% of patients have no mutated alleles. According to the "Tel Hashomer" diagnostic criteria, among these patients 98 cases are characterized as "probable FMF" with recurrent febrile attacks. These results indicate the possibility of existing FMF-like syndromes without MEFV mutations.

In collaboration with Prof. Amselem S. (France) we have revealed an unusual autoinflammatory syndrome that mimicked FMF, but with episodes triggered by generalized exposure to cold, and to further elucidate the controversial function of the PYPAF1 protein [14]. Mutations of this gene have been identified in three hereditary recurrent fever syndromes. In this patient presented with "FMF-like" episodes induced by cold, no disease-causing mutation was found in MEFV. A nonsense mutation (p.Arg554X) was identified in PYPAF1. This mutation resulted in a truncated protein lacking all leucine-rich repeats. Study of the wild-type and mutant PYPAF1 recombinant proteins revealed that PYPAF1 inhibited NF-κB proinflammatory pathways, and the identified mutation impaired this property [14].

Earlier in collaboration with the Laboratory of Prof. S.Amselem and with Dr. C.Cazeneuve we investigated a relatively homogeneous population of Armenian FMF patients with or without renal amyloidosis (RA). We have carried out the molecular analysis of the SAA1 and SAA2 genes coding serum amyloid proteins. Also we showed that the frequency of the M694V homozygous genotype in the group of patients with RA (51.1%) was significantly higher than in the group of patients without RA (18.9%, p=0.0001) (Cazeneuve C. et al., 2000). The risk of male patients to develop renal amyloidosis was four times higher than that of female patients. The results demonstrated that SAA a/a homozygous genotype was associated with a seven-fold increased risk for RA, compared with other SAA1 genotypes (OR=6.9, 95% CI=2.5-19.0). The presence of only one SAA1 a/a allele did not suggest an increased susceptibility to RA.

There were no significant differences in the frequency of other common genotypes between two groups of patients with and without RA. Our data are correlated to Booth's data [2] shown that the risk for the development of a secondary amyloidosis was higher in patients with rheumatoid arthritis or juvenile chronic arthritis when they carried the SAA1 a/a genotype ([5,6].

Due to the International Meta-FMF project we could compare our data with the FMF morbidity among other populations [24]. It was also confirmed that M694V mutation was a high risk factor in patients living in Armenia [6] and Israel [8].

We have revealed the complex FMF cases with following concurrent morbidity: epilepsy (M694V/M694V; V726A/M680I); Sjogren syndrome (M694V/M694V); monozygotic twins, heterozygous carriers for M680I mutation: one with FMF, and the other – non-FMF, but with epilepsy; bronchial asthma (M694V/V726A, V726A/M680I, M680I); b-thalassemia (M694V/M694V); hyperthyroidism (M694V/M680I); Tourette syndrome (M694V/M694V); ulcerative colitis (M694V/M694V); renal amyloidosis and multiple sclerosis (M680I/M680I). Neurological features are accompanied along with administration of colchicine. About 20% FMF patients (predominantly M694V homozygotes) had ankylosing spondilitis-like syndrome. For Armenian FMF children the onset of the disease via monoarthritis is peculiar phenomenon.

The daily treatment with colchicine was established by Goldfinger in 1972 [9]. RA, the most severe complication of FMF, leads to the progressive renal failure if the therapeutic treatment absent in affected individuals. In 90% of our cases, colchicine is effective to keep the inflammation under control. In our patients the colchicine largely prevents the development of RA in FMF. Moreover, our data suggest that adequate colchicinotherapy delayed RA progression in FMF/RA patients. However in a few cases the effect of colchicine remains controversial. We demonstrated that genotype may assist in prediction of the response to colchicine treatment given to children with RA.

In our group of FMF patients homozygous for M694V mutation not only present a more severe phenotype but also show a limited response to colchicine at the nephrotic stage of RA. In contrast, FMF patients with other genotypes still have a good chance to ameliorate of the nephrotic syndrome and to maintain renal function.

Based on our data concerning MEFV-homozygote, compound heterozygote, and symptomatic heterozygote patients, we have found, that resistance to colchicine may be caused by individual's response or endurance to the drug, non-efficient scheme of treatment, quality of the medication, and social behaviors such as smoking and alcohol consumption, etc.

Additional and common cited, problems in finding complex disease genes beyond the most obvious are complex

clinical, genealogical and genetic testing and publication bias. In the cases of multiple conflicting results and reports, meta-analysis across all published and our data, including the evidence for a functional consequence of the putative risk allele can help distinguish real disease genes.

Notwithstanding these difficulties, genetic analysis has laid the foundation for understanding a variety of disease mechanisms leading to autoinflammatory syndromes, including FMF. We have determined the symptoms associated with MEFV gene mutations in heterozygote patients, believed to be suffered from FMF, and compared them with affected homozygotes and compound heterozygotes. In this part of study 414 homozygotes, 980 compound heterozygotes, and 317 homozygotes have been analyzed (in collaboration with Dr. Mike M. Mouradian (UCLA, USA).

Our data indicate that the main homozygote cases are from M694V, V726A, M680I, and R761H mutations. When clinical symptoms of these mutations in heterozygote status are compared to homozygotes a strong correlation, over 90%, is observed. These correlations are of great importance since they take into account each clinically significant symptom and different combination of them, which cover almost all of the reported cases. In heterozygote patients the most prevalent and severe cases are caused by the presence of a single M694V mutation, which is associated with fever, abdominal, thoracic, and joint pain, skin symptoms, myalgia (protracted fibril), and amyloidosis.

However, less prevalent homozygous cases of the mutations such as V726A, M680I, R761H, and E148Q still cause clinically significant symptoms in heterozygote individuals and are treated with colchicine. We also have found that M694I and R42W mutations are only present in compound heterozygote patients. Therefore heterozygote individuals with M694I and R42W mutations have no clinical symptoms and they seem to be healthy. In Armenian population heterozygote individuals with M694V mutation suffer from the mild form of FMF. The same suggestion is, to a less extent, valid for V726A, M680I, R761H and E148Q heterozygote individuals.

We performed the genotyping of mutations of MEFV gene in 1250 pedigrees of families of probands with FMF. The pedigree analysis demonstrated the parent-to-offspring transmission of the mutations. The disease phenotype is explained by the heredity and mutational spectrum proved to be autosomal recessive in 91.5% and pseudo-dominant in 8.49% of all families.

Due to this study it is obvious that molecular testing is of prime necessity to confirm a diagnosis of genetic disorders, which is based on a set of non-specific signs. Therefore, it is important to continue this study on neighboring populations (Georgians, Iranians, etc.) in order to help those already affected, and try to prevent the spread of it.

On the basis of our results and recent data, we suggest that in some cases other factors along with MEFV genotype, such as environment or possibly other genetic factors play role in the determination of the severity of the inflammatory attacks in FMF. These data confirm that genetic analysis is essential in clinical practice, leading to new ways of managing FMF.

MEFV genotyping which is important to perform in the framework of a genetic counseling of the families of the probands, suffered from FMF, may reveal and identify affected individuals in pre-symtomatic phase, providing the possibility to start a therapy precociously.

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SUMMARY

FAMILIAL MEDITERRANEAN FEVER IN ARMENIAN POPULATION

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Familial Mediterranean Fever (FMF) is an inherited, recessively transmitted inflammatory condition usually occurred in populations from Mediterranean descent (Armenian, Arab, Jewish, Greek, Turkish and Italian populations). Identification of MEFV gene mutations has been of tremendous help for early diagnosis of most cases. The frequency of FMF is different. The prevalence of heterozygous carriers of one of the mutations of MEFV gene is as high as 1 in 5 healthy individuals in Armenia.

Genetic testing of this rare Mendelian disorder (MIM no 249100) is efficient for early and prenatal diagnosis of the disease, especially for atypic cases, for carrier screening and pregnancy planning since certain mutations have been shown to have significant correlation with renal amyloidosis (RA), the most severe possible manifestation of FMF. Also genetic testing is very important for colchicine therapy correction.

Twelve MEFV mutations are identified in 7000 Armenian FMF patients. Investigation of MEFV mutations in FMF patients (heterozygotes, homozygotes and compound heterozygotes) in comparison with healthy individuals has revealed the most frequent mutations and genotypes, and the information was received about the heterozygous carriers and genotype - phenotype correlation. In heterozygote carriers the most prevalent and severe cases are caused by the presence of a single M694V mutation.

Our results could confirm that the MEFV gene analysis provides the first objective diagnostic criterion for FMF (characterisation of the two MEFV mutated alleles in more than 90% of the patients). Molecular testing is also used to screen the MEFV gene for mutations in patients with a clinical suspicion of FMF. We also demonstrated the unfavourable prognostic value of the M694V homozygous genotype, and provided the first molecular evidence for incomplete penetrance and pseudo-dominant transmission of the disease. Overall, these data, which confirm the involvement of the MEFV gene in the development of FMF, should be essential in clinical practice, leading to new ways of managment and treatment of FMF patients.

Key words: FMF, MEFV gene mutations, genotype and phenotype correlations.

РЕЗЮМЕ

СЕМЕЙНАЯ СРЕДИЗЕМНОМОРСКАЯ ЛИХОРАДКА В АРМЯНСКОЙ ПОПУЛЯЦИИ

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Семейная средиземноморская лихорадка (MIM no249100) или периодическая болезнь (ПБ) является моногенным наследственным заболеванием воспалительной природы, которое, в основном, встречается среди представителей популяций Средиземноморского происхождения (арабы, армяне, греки, евреи, итальянцы, турки). Тип наследования ПБ, в основном, аутосомно-рецессивный. Генетика ПБ хорошо изучена на генеалогическом и молекулярно-генетическом уровнях. У пациентов всех стран обнаружены мутации в гене MEFV (MEDITERRANEAN FEVER), локализованном в коротком плече хромосомы 16p13.3. Частота болезни и бессимптомных носителей мутации может различаться в этносах и популяциях. В Армении распространенность носителей, в среднем, можно расценить как 1:5. Идентификация мутаций гена MEFV используется для ранней и точной диагностики ПБ. Генетическое тестирование является наиболее чувствительным способом подтверждения диагноза, выявления атипических вариантов, носителей мутаций, коррекции колхицинотерапии, а также рекомендуется для планирования семьи при наличии больных родственников. Показана достоверная и четкая корреляция спектра мутаций гена MEFV с развитием амилоидоза почек как наиболее грозного осложнения.

Мутации гена MEFV определены у 8500 больных ПБ армянской национальности. Определена зависимость фенотипа (клиническая картина заболевания) от генотипа (разных мутаций в одном и том же локусе). Заболевание вызывают двенадцать наиболее распространенных мутаций в гомозиготном и компаунд-гетерозиготном состояниях. Выявлено гетерозиготное носительство мутаций у больных ПБ, а также в группе здоровых лиц. Наиболее частая мутация M694V у гетерозиготных носителей, которая в гомозиготном и компаунд-гетерозиготном состояниях приводит к развитию наиболее тяжелых симптомов заболевания. На обширной выборке больных ПБ показано, что анализ мутаций MEFV является наиболее объективным диагностическим критерием прежде всего при наличии двух мутантных аллелей, что выявлено у более 98% пациентов. Продемонстрирована неблагоприятная прогностическая значимость некоторых мутаций, в частности, гомозигот по мутации M694V, в особенности, в сочетании с определенным изотипом мутаций гена SAA1. Вместе с тем, в ряде случаев нами обнаружена неполная пенетрантность некоторых мутаций, также псевдо-доминантный тип наследования в некоторых семьях больных.

Полученные данные подтверждают ведущую роль мутаций гена MEFV в развитии ПБ, необходимость и значимость молекулярных методов для ранней диагностики заболевания, разработки новых и эффективных способов лечения и слежения за состоянием больных.

A RARE CAUSE OF HEART FAILURE IN IRON-OVERLOAD THALASSAEMIC PATIENTS-PRIMARY HYPOPARATHYROIDISM

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The haemoglobinopathies are the most commonly inherited genetic disorders worldwide; some 240.000 infants suffering from them are born annually [11].

Homozygous β-thalassaemia (TM) results form an unbalanced rate of normal β-globin chain synthesis. This leads to ineffective erytropoiesis resulting in severe anaemia [1].

Optimal treatment consist of regular (every 3 to 4 weeks) red blood cell transfusions, in order to maintain a pretransfusional haemoglobin (Hb) level between 9-9.5 g/dl, and chelation therapy, to maintain the serum ferritin level below 1500 ng/ml [11].

Most of the complications of TM are attributable to iron overload. Excess of iron is toxic to the heart, liver and endocrine system. In TM, 70% of deaths are the result of cardiac failure or arrhythmia.

We report two TM patients with iron overload who developed heart failure as a consequence of hypocalcemia.

Case report. *Case 1*. A 18 years-old boy with TM was admitted to our Unit because of cardiac failure and arrhythmia. The patient had a documented past medical history of hypothyroidism, hypoparathyroidism and iron overload. He was not fully compliant to chelation therapy with desferrioxamine and to calcitriol. L-therapy [$1,25(OH)_2D$], apparently, was taken regularly.

On physical examination the patient had an irregular pulse rate of 110 beats/min, a systolic blood pressure of 90/40 mmHg. The neck vein were distended and cardiac auscultation revealed tachyarrhytmia. He had also hepato-splenomegaly.

Thyroid gland was not enlarged. Signs of tetany were not present while Chwostek's and Trousseau's signs were positive.

On emergency, the X-ray showed generalized cardiomegaly and evidence of pulmonary congestion, the electrocardiogram and echocardiogram revealed an atrial fibrillation with prolonged QTc interval (0.44s) and a left ventricular ejection fraction of 31%.

Initial laboratory investigations revealed reduced serum calcium (5.4 mg/dl; normal range 8.8-10-6 mg/dl), high inorganic phosphorous (9 mg/dl; normal range 2.5-4.5 mg/dl) and a undetectable PTH level.

Serum glucose, magnesium , thyroid function (FT4 and TSH) and renal function tests were normal. Liver enzymes

(ALT and γGT) were high (ALT = 86 IU/l, normal range 7-40 IU/ml; γGT=71 IU/l, normal range 6-65 IU/l).

The Hb level was 9.1 g/dl and serum ferritin level 3250 ng/ml (normal range 32-176 ng/ml). A diagnosis of cardiac failure, hypocalcemia due to hypoparathyroidism (HPT) and severe iron overload was made.

Intravenous calcium gluconate 10% along with oral calcitriol [1,25$(OH)_2$D: Rocaltrol 1 мg daily, in two divided doses] were given.

Clinical signs and hemodinamics improved considerably in the first 3 days of treatment and arrhythmia disappeared in 9 days.

The QTc interval decreased to 0.38s and the left ventricular shortening fraction increased to 38%. After 3 days, digoxins was added to the regimen and intravenous calcium gluconate was replaced with oral calcium supplementation.

He was discharged, after 12 days, with oral calcium, calcitriol (vitamin D) and L-thyroxine. Two and six months later the patient was admitted again with cardiac failure and in both occasions he confessed to having stopped calcium and calcitriol. The serum calcium levels were low (6.3 and 6.6 mg/dl, respectively). Intravenous calcium gluconate and oral calcitriol improved cardiac function after two and four days, respectively.

Restoration of calcemia resulted, after 6 weeks in an improvement of cardiac function (left ventricular ejection fraction 46%).

We concluded that the patient's heart failure was secondary to hypocalcemic myocardiopathy associated to severe iron-overload.

The reversal of cardiac dysfunction, in 3 different occasions, following normalization of serum calcium supported the dominance of hypocalcemia in the ethiology of the cardiac failure.

Case 2. A 22 years-old prepubertal patients with TM was admitted to our Unit because of congestive cardiac failure.

In the last six days she was unsuccessful treated, in another hospital, with digoxin and furosemide, but no improvement of heart failure occurred.

On examination, her temperature was 36.8°C, systemic arterial blood pressure was 90/50 mmHg, pulse rate was regular (115 beats/min) and respiratory rate was 25 breaths/min. Cardiac examination revealed a grade 2/6 apical holosystolic murmur. Chest auscultation revealed crackles at the basilar lobe. Liver edge was palpable 3 cm below the right costal margin. Chwostek's and Trousseau's signs were positive. Thyroid gland was not enlarged.

Initial laboratory investigations were significant for the following: haemoglobin level 8.2 g/dl, serum creatinine 1.2 mg/dl (normal range 0.7-1.3 mg/dl), total calcium 5.2 mg/dl (normal range 8.8-10.6 mg/dl), inorganic phosphorous 10.2 mg/dl (normal range 2.5-4.5 mg/dl), magnesium 2.1 mg/dl (normal range 1.8-2.6 mg/dl), albumin 36 g/l (normal range 35-50 g/l) and intact parathormone level was 11 pg/ml (normal range 10-55 pg/ml). Liver enzymes (ALT) was 120 IU/l (normal range 7-40 IU/l) and serum ferritin level was 9620 ng/ml (normal range 32-176 ng/ml).

The X-ray showed cardiac enlargement and the electrocardiogram revealed a prolonged QTc interval (0.45s).

Echocardiogram showed bilateral ventricular enlargement, generalized hypokinesia, moderate mitral and tricuspid regurgitation and a systolic dysfunction (ejection fraction 24.4%).

A diagnosis of congestive cardiac failure, hypoparathyroidism and severe iron overload was made.

She was treated with intravenous calcium gluconate, oral vitamin D (calcitriol), intensive iron chelation therapy (Desferal given subcutaneously), blood transfusions and diuretics (thiazides).

In the following 5-6 days, serum total calcium concentration slowly increased (7.1 mg/dl) and plasma inorganic phosphorous concentration decreased (7.3 mg/dl).

Restoration of calcemia resulted in clinical and cardiac improvement (left ventricular ejection fraction 38% after 3 weeks and 42%, after 4 weeks).

The patient was discharged after 34 days with oral calcium, vitamin D and subcutaneous chelation therapy (Desferal 40 mg/kg body weight, six times/week).

We concluded that the patient's congestive heart failure was precipitated by severe hypocalcemia, secondary to primary hypoparathyroidism.

Results and their ddiscussion. Hypocalcemia due to HPT is a late complication of iron overload in TM patients [3,4,6,7]. The Italian working group on endocrine complications in non endocrine diseases (Coordinator: V. De Sanctis) in 1994 reported a prevalence of HPT in 3.6% of 1661 TM patients. Their mean age at diagnosis was 18.7 years [6].

Hypocalcemia follows as a consequence of iron deposition in the parathyroids. The majority of patients have mild disease, with parasthesias, while in the more severe form tetany, seizures or cardiac failure may occur [5,11].

The biochemical abnormalities associated with HPT are hypocalcemia, hyperphosphatemia and reduced urinary calcium excretion. Alkaline phosphatise activity is usually normal or relatively low. PTH concentrations are low or undetectable [1].

Acute and chronic hypocalcemia has been associated with myocardial dysfunction in numerous studies and case reports [2,8,9].

Nevertheless hypocalcemic cardiopathy, due to HPT, is a very rare condition in TM patients. We found only one report of a 25 years-old man with TM who develop heart failure associated with HPT [9].

Calcium plays a key role in the maintenance and regulation of normal cardiac function. Extra-cellular calcium is indispensable for the contractile process since the sarcoplasmatic reticulum is unable to maintain a sufficient amount of calcium to trigger myocardial contraction [2,5,8,10].

In the last 20 years, we observed a hypocalcemic cardiopathy in 2 out of 38 (5.2%) severely iron-overloaded TM patients. Calcium supplementation and vitamin D induced correction of hypocalcemia and improvement of cardiac functions. The positive effects were quite clear in the case report 1. In fact, cardiac failure, which initially was resistant to conventional therapy, resolved with the correction of hypocalcemia. The recurrence of signs and symptoms, secondary to a poor compliance to the treatment (oral calcium and vitamin D), further on support these conclusions.

In conclusion, our observations stress the importance of a regular iron chelation therapy, adherence to treatment of endocrine complication and regular follow-up of TM patients with hypocalcemia.

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SUMMARY

A RARE CAUSE OF HEART FAILURE IN IRON-OVERLOAD THALASSAEMIC PATIENTS-PRIMARY HYPOPARATHYROIDISM

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Hypocalcemia due to hypoparathyroidism (HPT) is a late complication of iron-overloaded patients with β-thalassaemia major (TM). The majority of patients have mild disease with parasthesias, while in the more severe form tetany, seizures or cardiac failure may occur. In the last 20 years we observed heart failure in 2 out of 38 (5.2%) TM patients (aged 18 and 22 years) with hypocalcemia secondary to HPT associated to iron overload. Calcium supplementation and vitamin D induced correction of hypocalcemia and resulted in an improvement of cardiac function. Calcium plays a key role in the maintenance and regulation of normal cardiac function. Extra-cellular calcium is indispensable for the contractile process since the sarcoplasmatic reticulum is unable to maintain a sufficient amount of calcium to trigger myocardial contraction. In conclusion, our observations stress the importance of a regular iron chelation therapy, adherence to treatment of endocrine complication and regular follow-up of TM patients with hypocalcemia.

Key words: β-thalassaemia major, iron overload, hypocalcemia, heart failure.

РЕЗЮМЕ

РЕДКИЙ СЛУЧАЙ СЕРДЕЧНОЙ НЕДОСТАТОЧНОСТИ У ПАЦИЕНТА С ТАЛАССЕМИЕЙ ПЕРЕГРУЖЕННОГО ЖЕЛЕЗОМ – ПЕРВИЧНЫЙ ГИПОПАРАТИРЕОИДИЗМ

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Гипокальциемия, обусловленная гипопаратиреоидизмом (ГПТ), является поздним осложнением у больных боль-

шой β-талассемией, перегруженных железом. У большинства болезнь протекает легко с парестезией, тогда как в более тяжелых случаях могут проявиться тетания, судороги, сердечная недостаточность. За последние 20 лет мы наблюдали сердечную недостаточность у 2-х из 38-и (5.2%) пациентов с большой талассемией (в возрасте от 18 до 22 лет) с гипокальцемией, вторичной в отношении ГПТ, ассоциированного с перегрузкой железом. Добавка кальция и витамина Д обусловила коррекцию гипокальцемии и привела к улучшению сердечной функции. Кальций играет ключевую роль в сохранении и регуляции нормальной сердечной функции. Экстрацеллюлярный кальций является необходимым для контрактильных процессов, так как саркоплазматический ретикулум не в состоянии сохранять достаточное количество кальция, чтобы запустить мышечное сокращение. В заключение, наши наблюдения подчеркивают значение регулярной хелации железа, необходимость лечения эндокринных осложнений и регулярного мониторинга больных большой талассемией с гипокальциемией.

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