GEORGIAN MEDICAL NEWS

ISSN 1512-0112

NO 7-8 (340-341) Июль-Август 2023

ТБИЛИСИ - NEW YORK

ЕЖЕМЕСЯЧНЫЙ НАУЧНЫЙ ЖУРНАЛ

Медицинские новости Грузии

საქართველოს სამედიცინო სიახლენი

GEORGIAN MEDICAL NEWS

Monthly Georgia-US joint scientific journal published both in electronic and paper formats of the Agency of Medical Information of the Georgian Association of Business Press. Published since 1994. Distributed in NIS, EU and USA.

GMN: Georgian Medical News is peer-reviewed, published monthly journal committed to promoting the science and art of medicine and the betterment of public health, published by the GMN Editorial Board since 1994. GMN carries original scientific articles on medicine, biology and pharmacy, which are of experimental, theoretical and practical character; publishes original research, reviews, commentaries, editorials, essays, medical news, and correspondence in English and Russian.

GMN is indexed in MEDLINE, SCOPUS, PubMed and VINITI Russian Academy of Sciences. The full text content is available through EBSCO databases.

GMN: Медицинские новости Грузии - ежемесячный рецензируемый научный журнал, издаётся Редакционной коллегией с 1994 года на русском и английском языках в целях поддержки медицинской науки и улучшения здравоохранения. В журнале публикуются оригинальные научные статьи в области медицины, биологии и фармации, статьи обзорного характера, научные сообщения, новости медицины и здравоохранения. Журнал индексируется в MEDLINE, отражён в базе данных SCOPUS, PubMed и ВИНИТИ РАН. Полнотекстовые статьи журнала доступны через БД EBSCO.

GMN: Georgian Medical News – საქართველოს სამედიცინო სიახლენი – არის ყოველთვიური სამეცნიერო სამედიცინო რეცენზირებადი ჟურნალი, გამოიცემა 1994 წლიდან, წარმოადგენს სარედაქციო კოლეგიისა და აშშ-ის მეცნიერების, განათლების, ინდუსტრიის, ხელოვნებისა და ბუნებისმეტყველების საერთაშორისო აკადემიის ერთობლივ გამოცემას. GMN-ში რუსულ და ინგლისურ ენებზე ქვეყნდება ექსპერიმენტული, თეორიული და პრაქტიკული ხასიათის ორიგინალური სამეცნიერო სტატიები მედიცინის, ბიოლოგიისა და ფარმაციის სფეროში, მიმოხილვითი ხასიათის სტატიები.

ჟურნალი ინდექსირებულია MEDLINE-ის საერთაშორისო სისტემაში, ასახულია SCOPUS-ის, PubMed-ის და ВИНИТИ РАН-ის მონაცემთა ბაზებში. სტატიების სრული ტექსტი ხელმისაწვდომია EBSCO-ს მონაცემთა ბაზებიდან.

WEBSITE

www.geomednews.com

К СВЕДЕНИЮ АВТОРОВ!

При направлении статьи в редакцию необходимо соблюдать следующие правила:

1. Статья должна быть представлена в двух экземплярах, на русском или английском языках, напечатанная через **полтора интервала на одной стороне стандартного листа с шириной левого поля в три сантиметра**. Используемый компьютерный шрифт для текста на русском и английском языках - **Times New Roman** (**Кириллица**), для текста на грузинском языке следует использовать **AcadNusx.** Размер шрифта - **12**. К рукописи, напечатанной на компьютере, должен быть приложен CD со статьей.

2. Размер статьи должен быть не менее десяти и не более двадцати страниц машинописи, включая указатель литературы и резюме на английском, русском и грузинском языках.

3. В статье должны быть освещены актуальность данного материала, методы и результаты исследования и их обсуждение.

При представлении в печать научных экспериментальных работ авторы должны указывать вид и количество экспериментальных животных, применявшиеся методы обезболивания и усыпления (в ходе острых опытов).

4. К статье должны быть приложены краткое (на полстраницы) резюме на английском, русском и грузинском языках (включающее следующие разделы: цель исследования, материал и методы, результаты и заключение) и список ключевых слов (key words).

5. Таблицы необходимо представлять в печатной форме. Фотокопии не принимаются. **Все цифровые, итоговые и процентные данные в таблицах должны соответствовать таковым в тексте статьи**. Таблицы и графики должны быть озаглавлены.

6. Фотографии должны быть контрастными, фотокопии с рентгенограмм - в позитивном изображении. Рисунки, чертежи и диаграммы следует озаглавить, пронумеровать и вставить в соответствующее место текста **в tiff формате**.

В подписях к микрофотографиям следует указывать степень увеличения через окуляр или объектив и метод окраски или импрегнации срезов.

7. Фамилии отечественных авторов приводятся в оригинальной транскрипции.

8. При оформлении и направлении статей в журнал МНГ просим авторов соблюдать правила, изложенные в «Единых требованиях к рукописям, представляемым в биомедицинские журналы», принятых Международным комитетом редакторов медицинских журналов - http://www.spinesurgery.ru/files/publish.pdf и http://www.nlm.nih.gov/bsd/uniform_requirements.html
В конце каждой оригинальной статьи приводится библиографический список. В список литературы включаются все материалы, на которые имеются ссылки в тексте. Список составляется в алфавитном порядке и нумеруется. Литературный источник приводится на языке оригинала. В списке литературы сначала приводятся работы, написанные знаками грузинского алфавита, затем кириллицей и латиницей. Ссылки на цитируемые работы в тексте статьи даются в квадратных скобках в виде номера, соответствующего номеру данной работы в списке литературы. Большинство цитированных источников должны быть за последние 5-7 лет.

9. Для получения права на публикацию статья должна иметь от руководителя работы или учреждения визу и сопроводительное отношение, написанные или напечатанные на бланке и заверенные подписью и печатью.

10. В конце статьи должны быть подписи всех авторов, полностью приведены их фамилии, имена и отчества, указаны служебный и домашний номера телефонов и адреса или иные координаты. Количество авторов (соавторов) не должно превышать пяти человек.

11. Редакция оставляет за собой право сокращать и исправлять статьи. Корректура авторам не высылается, вся работа и сверка проводится по авторскому оригиналу.

12. Недопустимо направление в редакцию работ, представленных к печати в иных издательствах или опубликованных в других изданиях.

При нарушении указанных правил статьи не рассматриваются.

REQUIREMENTS

Please note, materials submitted to the Editorial Office Staff are supposed to meet the following requirements:

1. Articles must be provided with a double copy, in English or Russian languages and typed or compu-ter-printed on a single side of standard typing paper, with the left margin of **3** centimeters width, and **1.5** spacing between the lines, typeface - **Times New Roman** (**Cyrillic**), print size - **12** (referring to Georgian and Russian materials). With computer-printed texts please enclose a CD carrying the same file titled with Latin symbols.

2. Size of the article, including index and resume in English, Russian and Georgian languages must be at least 10 pages and not exceed the limit of 20 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.

4. Articles must have a short (half page) abstract in English, Russian and Georgian (including the following sections: aim of study, material and methods, results and conclusions) and a list of key words.

5. Tables must be presented in an original typed or computer-printed form, instead of a photocopied version. **Numbers, totals, percentile data on the tables must coincide with those in the texts of the articles.** Tables and graphs must be headed.

6. Photographs are required to be contrasted and must be submitted with doubles. Please number each photograph with a pencil on its back, indicate author's name, title of the article (short version), and mark out its top and bottom parts. Drawings must be accurate, drafts and diagrams drawn in Indian ink (or black ink). Photocopies of the X-ray photographs must be presented in a positive image in **tiff format**.

Accurately numbered subtitles for each illustration must be listed on a separate sheet of paper. In the subtitles for the microphotographs please indicate the ocular and objective lens magnification power, method of coloring or impregnation of the microscopic sections (preparations).

7. Please indicate last names, first and middle initials of the native authors, present names and initials of the foreign authors in the transcription of the original language, enclose in parenthesis corresponding number under which the author is listed in the reference materials.

8. Please follow guidance offered to authors by The International Committee of Medical Journal Editors guidance in its Uniform Requirements for Manuscripts Submitted to Biomedical Journals publication available online at: http://www.nlm.nih.gov/bsd/uniform_requirements.html
http://www.icmje.org/urm_full.pdf
In GMN style for each work cited in the text, a bibliographic reference is given, and this is located at the end of the article under the title "References". All references cited in the text must be listed. The list of references should be arranged alphabetically and then numbered. References are numbered in the text [numbers in square brackets] and in the reference list and numbers are repeated throughout the text as needed. The bibliographic description is given in the language of publication (citations in Georgian script are followed by Cyrillic and Latin).

9. To obtain the rights of publication articles must be accompanied by a visa from the project instructor or the establishment, where the work has been performed, and a reference letter, both written or typed on a special signed form, certified by a stamp or a seal.

10. Articles must be signed by all of the authors at the end, and they must be provided with a list of full names, office and home phone numbers and addresses or other non-office locations where the authors could be reached. The number of the authors (co-authors) must not exceed the limit of 5 people.

11. Editorial Staff reserves the rights to cut down in size and correct the articles. Proof-sheets are not sent out to the authors. The entire editorial and collation work is performed according to the author's original text.

12. Sending in the works that have already been assigned to the press by other Editorial Staffs or have been printed by other publishers is not permissible.

Articles that Fail to Meet the Aforementioned Requirements are not Assigned to be Reviewed.

ავტორთა საყურადღებოდ!

რედაქციაში სტატიის წარმოდგენისას საჭიროა დავიცვათ შემდეგი წესები:

1. სტატია უნდა წარმოადგინოთ 2 ცალად, რუსულ ან ინგლისურ ენებზე,დაბეჭდილი სტანდარტული ფურცლის 1 გვერდზე, 3 სმ სიგანის მარცხენა ველისა და სტრიქონებს შორის 1,5 ინტერვალის დაცვით. გამოყენებული კომპიუტერული შრიფტი რუსულ და ინგლისურენოვან ტექსტებში - **Times New Roman (Кириллица)**, ხოლო ქართულენოვან ტექსტში საჭიროა გამოვიყენოთ **AcadNusx.** შრიფტის ზომა – 12. სტატიას თან უნდა ახლდეს CD სტატიით.

2. სტატიის მოცულობა არ უნდა შეადგენდეს 10 გვერდზე ნაკლებს და 20 გვერდზე მეტს ლიტერატურის სიის და რეზიუმეების (ინგლისურ, რუსულ და ქართულ ენებზე) ჩათვლით.

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

5. ცხრილები საჭიროა წარმოადგინოთ ნაბეჭდი სახით. ყველა ციფრული, შემაჯამებელი და პროცენტული მონაცემები უნდა შეესაბამებოდეს ტექსტში მოყვანილს.

6. ფოტოსურათები უნდა იყოს კონტრასტული; სურათები, ნახაზები, დიაგრამები - დასათაურებული, დანომრილი და სათანადო ადგილას ჩასმული. რენტგენოგრამების ფოტოასლები წარმოადგინეთ პოზიტიური გამოსახულებით **tiff** ფორმატში. მიკროფოტოსურათების წარწერებში საჭიროა მიუთითოთ ოკულარის ან ობიექტივის საშუალებით გადიდების ხარისხი, ანათალების შეღებვის ან იმპრეგნაციის მეთოდი და აღნიშნოთ სურათის ზედა და ქვედა ნაწილები.

7. სამამულო ავტორების გვარები სტატიაში აღინიშნება ინიციალების თანდართვით, უცხოურისა – უცხოური ტრანსკრიპციით.

8. 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. ტექსტში კვადრატულ ფჩხილებში უნდა მიუთითოთ ავტორის შესაბამისი N ლიტერატურის სიის მიხედვით. მიზანშეწონილია, რომ ციტირებული წყაროების უმეტესი ნაწილი იყოს 5-6 წლის სიღრმის.

9. 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.

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

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.

GEORGIAN MEDICAL NEWS
No 7 (340) 2023

Содержание:

GEORGIAN MEDICAL NEWS
No 7 (340) 2023

THE RELATIONSHIP BETWEEN THE DURATION OF REMISSIONS AFTER THE ONSET, THE SEVERITY OF THE RELAPSES AGAINST THE BACKGROUND OF DIFFERENT DURATION OF THE RELAPSING STAGE AND THE NATURE OF THE PROGNOSIS IN SECONDARY-PROGRESSIVE MULTIPLE SCLEROSIS

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Abstract.

Work objective: To study the relationship between the duration of remission after the onset, the severity of relapses against the background of different duration of the relapsing stage (RS) and the nature of the prognosis in the secondary progressive multiple sclerosis (SPMS) using clinical and mathematical analysis.

Material and research methods: Patients with different prognosis for SPMS; neurological examination using The Expanded Disability Status Scale (EDSS); a survey method. Mathematical methods: 'contingency tables 2x2' (determining the significance of the connection between a pair of two indicators - different duration of remission after the onset and RS in four groups of patients), Yule's Coefficient of Association (determining the magnitude of differences between the group and the studied indicator), a permutation test (defining clinical indicators on RS, which significantly differed in mild and severe relapses).

Research results: Pairwise comparison in four groups of patients with different duration of remission after the onset and RS in SPMS showed that long-term remission after the onset and prolonged RS delay the transition of RS into secondary progression (SP). Short duration of these indicators revealed the opposite prognostic tendencies, indicating the further progression of the disease. The presence of severe relapses on RS in SPMS is predominantly associated with unfavorable prognostic indicators on RS and indicates the initiation of the transition into SP.

Conclusion: Accordingly, the duration of remission after the onset, the severity of relapses against the background of different durations of RS should be regarded as prognostic clinical markers that play a key role in the switch of RS to SPS in SPMS. The results obtained should be used to assess the current clinical situation and timely prescribe an appropriate pathogenetic therapy on RS.

Key words. Multiple sclerosis, secondary progressive course, prognosis, remission after the onset, severity of relapses, relapsing stage, Yule's coefficient, contingency tables, permutation test.

Introduction.

Prognosticating in secondary progressive multiple sclerosis (SPMS) results from the interaction of various clinical indicators that characterize the disease course stages. Thus, a logical question arises whether the transformation of a recurrent course (RC) into a secondary progressive one is inevitable, or these are two different types of the course with different pathogenetic mechanisms of formation? [1-8].

Unlike RC, which is relatively stable and generally favorable in 10-15% of patients, SPMS is characterized by an accelerated accumulation of neurological deficit and an increase in the degree of disability with the formation of a final unfavorable prognosis in the vast majority of patients [1,9-13].

At the same time, some patients should be given a relatively "benign" prognosis as an indefinite one, which has characteristic features, the leading ones of which are a long relapsing stage (RS), slow progressive accumulation of neurological deficit during the secondary progression stage (SPS), an adequate response to various methods of pathogenetic and symptomatic therapy [10,13,14,15,16].

The paths along which the SPS is formed are of strategic importance for different prognosis options in SPMS. Repeat clinical analysis has shown that this stage forms and develops in two ways. Pathway 1 is more common and begins after a relapsing stage of varying duration; path 2 follows immediately after clinical remission after onset, bypassing RS. Therefore, the pathway 1 is regarded as more favorable due to the inclusion of such temporary stages of the disease as remission after the onset of various durations and RS, which temporarily prevent the formation and slow down the development of SPS. Pathway 2, which has no RS, is characterized by an accelerated formation of a persistent neurological deficit and a furthermore unfavorable course of the disease [10,14].

Long-term remission after the onset has been generally accepted to be an important criterion for the further benign course of the disease [17]. However, this statement, based on the clinical experience of previous generations of neurologists, is in conflict with recent studies, which, taking into account the introduction of neuroimaging research methods (MRI), indicate a continuous wave-like activity of the demyelinating process. Therefore, in the vast majority of patients, the so-called clinical remissions, which due to the MRI-revealed radiological activity proceed as pseudo-remissions, represent a stage in the subclinical course of MS. The longer this process proceeds, the more likely it causes depletion and disruption of adaptive-compensatory mechanisms due to the lack of adequate and timely pathogenetic therapy. This fact significantly increases the likelihood of further adverse courses of the disease in this category of patients [12,15,18,19].

The transformation of RC into SPMS requires a complex selective structural reorganization of various clinical indicators in RS (its duration, the rate of formation of neurological symptoms in different relapses, the severity and duration of relapses, the duration and completeness of clinical remissions between relapses, the dynamics and degree of accumulation of neurological deficit, according to the EDSS). The leading role

among these indicators belongs to the duration of RS and the severity of relapses [10,18,19,20].

With this in mind, the objective of this research was to study the relationship between the duration of remission after the onset, the severity of relapses against the background of different durations of RS, and the nature of the prognosis in SPMS using clinical and mathematical analysis.

One hundred patients with secondary-progressive stage (SPS) were examined. Eighty patients with relapsing stage (RS) were examined as a control group when analyzing the severity of recurrent course (RC). Therefore, in Table 5, " Significant differences between the frequency of clinical indicators in patients with severe and mild (and/or moderate) RS relapses in RC", the number of patients with severe relapses (n=15), and mild relapses (n=65). A total of 80 patients.

Using the “2x2 contingency tables” (method of statistical analysis), the significance of the relationship between a pair of two indicators characterizing the clinical features of the course of remissions after the onset and RS according to the $\chi 2$ test was compared and assessed. The groups were distinguished taking into account the frequency of these indicators, for each of which non-random differences in their frequency were determined in the considered pairs of groups. The magnitude of the differences between the group and the studied indicator was assessed using the coefficient of colligation, which in this case was a correlation coefficient. With the help of a permutation test (method of statistical analysis) in SPMS and RC, clinical indicators were determined that significantly differed in RS in mild (and/or moderate) and severe relapses [10,21-24].

Correlations between two indicators, the duration of remissions after the onset and the duration of RS, was compared in the following groups of SPMS patients:

- group 1 – short (and/or medium) remission after the onset and short (and/or medium) recurrent stage (46 people).
- group 2 – long remission after the onset and long recurrent stage (14 people).
- group 3 – short (and/or medium) remission after the onset and long recurrent stage (26 people).
- group 4 – long remission after the onset and short (and/or medium) recurrent stage (14 people).

Various prognosis outcomes were grouped as follows. Groups 1 and 4 had approximately the same distribution of prognosis outcomes that practically coincides with the distribution for all patients. While in group 2 the distribution of outcomes is “reverse”, with more common uncertain prognosis with the same proportion as in groups 1 and 4. In group 3, on the contrary, an unfavorable prognosis significantly prevails. All other cases, based on this table, show trends only (Table 1).

Considering these data using the contingency method, according to the $\chi 2$ test, we obtain a correlation between groups and percentages of the outcome of the final prognosis that is statistically significant ($p<0.01$). Since the differences in the duration of remission after the onset and the duration of RS in different groups are presented in various combinations, it can be assumed that these two factors are associated with the distribution of patients according to the nature of the prognosis in these four groups and that this distribution is not random.

To test this assumption, using the $\chi 2$ test, we assessed the relationship between the distribution of prognosis outcomes for the combined groups with one factor: groups with different duration of remission after the onset (1+3 and 2+4) and groups with different duration of RS (1+4 and 2+3). The first four-field table corresponds to the differences in the duration of remission after the onset (1+3) and includes all patients with short remissions after the onset and (2+4) with long remissions. The second four-field table corresponds to the differences in the duration of RS: (1+4) - short and (2+3) - long (Table 2).

Applying the $\chi 2$ test to two tables showed a weak correlation in the first case (1+3 and 2+4) and no correlation in the second (1+4 and 2+3). This indicates that only the combination of these two factors significantly predetermines the final outcome of the prognosis. Obviously, the outcome of the prognosis is also influenced by other signs that either themselves depend on the duration of remission and/or RS, or act independently. In order to identify "candidates" for this role, intergroup pairwise differences were analyzed.

Table 3 shows the clinical indicators, which correspond to a fairly large (0.7 or more) coefficient of colligation.

The absolute value of the coefficient of colligation (0.7 and more) indicates significant differences in its distribution between the studied groups. The (+) sign of the coefficient of colligation means that it is more common in group 1 of the compared pair, while (-) represents an alternative option.

It has been shown that long-term remission most often occurs after a mild (groups 1-2) or moderate (groups 2-3) onset, which is rapidly formed (groups 3-4). RS after long-term remission, in general, proceeds favorably and is characterized by mild (3-4 groups), short or medium-term relapses (2-4 groups), alternation of different rates of formation of clinical symptoms in relapses (2-4), long-term remissions between relapses (2-4 groups). Thus, long-term remission after the onset should be regarded as a favorable prognostic clinical marker for the further course of the disease.

Long-term RS, as well as post-onset long-term remission, is characterized by favorable prognostic indicators. These include

Table 1. *The nature of the prognosis and the duration of remissions after the onset and recurrent stage in 4 groups of patients with SPMS.*

Group	**Unfavorable prognosis (n=58)**	**Undefined prognosis (n=42)**
Group 1 (n=46)	56.5	43.5
Group 2 (n=14)	42.8	57.2
Group 3 (n=26)	69.2	30.8
Group 4 (n=14)	57.1	42.9

Note: n - number of patients

Table 2. *Prognosis for combined groups of SPMS patients with different duration of remissions after the onset and recurrent stage.*

Group	**Unfavorable prognosis**	**Undefined prognosis**
1+3	61	39
2+4	50	50
1+4	57	43
2+3	50	50

mild and moderate onsets (groups 2-3), short relapses (groups 2-3), long-term remissions and alternation of remissions of different duration between relapses (groups 2-3). Despite the predominance of the final unfavorable prognosis, a longer RS improves the quality of life of these patients, postponing SPS. With a short and/or medium remission after the onset of RS, the course is ambiguous. A less aggressive course was observed in the subgroup of patients with remission after the medium onset. The structure of the RS was dominated by gradual formation of short and mild relapses (groups 1-2 and 1-3), which alternated with complete and long remissions (groups 1-2 and 1-3). Subgroup 2 with a short remission after the onset has less favorable RS with a predominance of long-term relapses (groups 1-4) and their tendency to worsen and lengthen (groups 1-3 and 1-4).

In the case of short and/or medium RS opposite prognostic trends also prevailed. On the one hand, the subgroup of patients with medium RS more often had mild onsets (groups 1-4), short (1-3 and 1-4 groups) and mild (1-3) relapses, full-fledged (groups 1-2) and long-term (1-2 and 1-3) clinical remissions between relapses (1-2 groups). These indicated a more favorable course of the disease. On the other hand, the subgroup of patients with short RS more often had long-term relapses (groups 1-4) with their further lengthening and aggravation (groups 1-3). With such a structural configuration of indicators, conditions were created that contributed to the depletion of compensatory reserves, which led to an increased risk of SPS development.

The patients with mild (and/or moderate) and severe relapses were grouped based on the clinical characteristics of relapses of varying severity, which occurred in a different sequence during the course of RS and, as a rule, alternated with each other. Mild relapses were characterized by rapid formation of clinical symptoms, a short duration (no more than 3-4 weeks), mono- or oligosyndromic symptoms with minimal signs of

Table 3. *Pairwise correlation (using contingency tables) between clinical indicators in 4 groups of SPMS patients.*

Indicator	**Coefficient of colligation (0.7 and more)**
Gradual symptom formation in RS relapses (groups 1 and 2)	+0.70
Alternation of different rates of symptom formation in relapses as the course progresses in RS (groups 1 and 2)	+1.0
Complete remissions between RS relapses (groups 1 and 2)	+0.77
Long remissions between RS relapses (groups 1 and 2)	+0.77
Alternation of remissions of different duration between RS relapses (groups 1 and 2)	+0.70
Short RS relapses (groups 1 and 3)	+0.70
Mild RS relapses (groups 1 and 3)	+0.79
Tendency to aggravation of RS relapses (groups 1 and 3)	+0.79
Tendency to aggravation of RS relapses (groups 1 and 3)	+0.75
Tendency to lengthening of RS relapses (groups 1 and 3)	+0.70
Long remissions between RS relapses (groups 1 and 3)	+0.87
Mild onset (groups 1 and 4)	-0.75
Short RS relapses (groups 1 and 4)	-0.73
Long RS relapses (groups 1 and 4)	+1.00
EDSS (groups 1 and 4)	-1.00
Moderate onset (groups 2 and 3)	+0.78
Alternation of different rates of symptom formation in RS relapses (groups 2 and 3)	-1.00
Mild onset (groups 2 and 4)	-0.72
Short RS relapses (groups 2 and 4)	-0.78
Medium RS relapses (groups 2 and 4)	-0.78
Alternation of different rates of clinical symptom formation in RS relapses (groups 2 and 4)	-1.0
Long clinical remissions between RS relapses (groups 2 and 4)	-1.0
Alternation of clinical remissions of different duration between RS relapses (groups 2 and 4)	-0.72
Rapid formation of clinical signs of the onset (groups 3 and 4)	-0.72
Mild RS relapses (groups 3 and 4)	-0.81
Short RS relapses (groups 3 and 4)	-0.95
Long clinical remissions between RS relapses (groups 3 and 4)	-1.0

Table 4. *Significant differences between the frequency of clinical indicators in patients with severe and mild (and/or moderate) RS relapses in SPMS.*

Indicator	**Patients with severe relapses (n=54)**	**Patients with mild (and/or moderate) relapses (n=46)**
RS relapse worsening	**92.6±5.1**	60.9±14.1
Long RS relapse	**82.5±10.1**	47.8±14.4
RS relapse lengthening	**92.6±5.1**	65.2±13.8
Alternation of different rates of formation of RS relapses	**81.5±10.4**	34.8±13.8
Short remissions between RS relapses	**81.5±10.4**	56.5±14.3
Moderate duration of remission after the onset	25.9±11.7	**52.2±14.4**
Short RS relapses	48.1±13.3	**73.9±12.7**

Note: n - number of patients

Table 5. *Significant differences between the frequency of clinical indicators in patients with severe and mild (and/or moderate) RS relapses in RC.*

Indicator	**Patients with severe relapses (n=15)**	**Patients with mild (and/ or moderate) relapses (n=65)**
RS relapse worsening	**60.0±24.8**	16.9±9.1
RS relapse lengthening	**60.0±24.8**	20.3±9.7
Undefined prognosis	**66.7±23.8**	27.6±10.9
Moderate duration of remission after the onset	6.7±12.6	**47.0±12.1**
Mild RS relapses	40.2±24.8	**86.4±8.3**
Favorable prognosis	23.5±11.3	63.2±14.2

Note: n - number of patients

a rapidly regressing neurological deficit. Moderate relapses were characterized by oligo- or polysyndromic symptoms, predominantly developing at a gradual pace, the formation of a moderate neurological deficit with its further gradual regression over 2 or more months. In severe relapses, slow formation of severe polysyndromic clinical symptoms prevailed, followed by partial regression and gradual transformation (within 3 or more months) into short, unstable, and incomplete remissions [12,15,19,20].

Groups with mild (and/or moderate) relapses in SPMS showed a significant predominance of the average duration of remission after the onset and short RS relapses. Patients with severe RS relapses mostly had long-term relapses, alternation of different rates of relapse formation, worsening and lengthening of relapses, short remissions between relapses (Table 4).

The group of patients with a favorable prognosis in RC had no severe relapses accompanied by medium remission after the onset and mild relapses throughout the entire course of RS. In case of severe RS relapses, the uncertain prognosis prevailed, which was associated with such clinical indicators as worsening and lengthening of relapses (Table 5).

Thus, the study of comparative pairwise analysis of four groups of patients revealed complex and ambiguous correlations between different durations of prognostically important clinical indicators, i.e., clinical remission after the onset and RS in SPMS. It has been shown that long-term clinical remission after the onset plays a key role in the subsequent relatively benign course of SPMS. A prolonged RS for the final prognosis generally had a positive effect, postponing the transformation into SPMS. The greatest difficulty for assessing the prognosis was the interpretation of indicators that have short and medium remissions after the onset and a short and medium RS. For these indicators, directly opposite prognostic trends were found, indicating that medium remissions and medium RS turned out to be more favorable, and the short duration of these indicators was an unfavorable clinical marker of the further course of the disease.

The severity of RS relapses in SPMS and the MSRC should also be considered as a diagnostic indicator selectively associated with other clinical indicators that occur during clinical remission after the onset and in RS. For the group of patients with mild relapses in RS, the value of timely diagnosis of SPMS is not significant enough as it is close to the similar group of patients with RC. This circumstance can lead to an incorrect interpretation of the further course of the disease in this category of patients. Severe RS relapses in this type of course, on the contrary, may indicate the onset of transformation into SPS.

The presence of severe RS relapses in RC allows us to regard the further prognosis as uncertain, i.e., more unfavorable, and testify to the further possible formation of SPMS.

Thus, the duration of remission after the onset, the severity of relapses with different durations of RS should be regarded as prognostic clinical markers that play a key role in transforming RS to SPMS. The results of this study should be used to assess the current clinical situation and timely prescribe adequate pathogenetic therapy for RS.

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