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ЕЖЕМЕСЯЧНЫЙ НАУЧНЫЙ ЖУРНАЛ

Медицинские новости Грузии

საქართველოს სამედიცინო სიახლენი

GEORGIAN MEDICAL NEWS

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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.

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Содержание:

METHIONINE SULFOXIDE REDUCTASE A AND NEUROTRANSMISSION ENZYMES IN AUTISM SPECTRUM DISORDER AND DYSTOCIA RELATED AUTISTICS

Othman Q. Abdulhameed*, Luay A. Al-Helaly.

Department of chemistry, College of Science, University of Mosul, Mosul, 41002, Iraq.

Abstract.

Methionine sulfoxide reductase A (MsrA) is an antioxidant enzyme that repairs the oxidation of methionine residues in proteins and free methionine in autism spectrum disorder (ASD). The present study aimed to assess the level of MsrA and neurotransmission enzymes in ASD individuals. Results confirmed that ASD associated with significant ($P<0.05$) reduction of MsrA and modulated mission enzymes. The role of MsrA as repair enzyme should be taken into account for study the activity of brain enzymes and proteins in ASD including ASMT that has a role in melatonin problems production in ASD due to higher AANAT level. The influence of MsrA also should be studied with MAT in mice to give more evidence.

Key words. Autism, dystocia, methionine, methionine adenosyl transferase. methionine sulfoxide reductase.

Introduction.

Autism spectrum disorder (ASD) is a neurodevelopmental complication that makes their individuals characterised by inability in social interaction and communication as well as restrictive and repetitive features in behaviour [1]. Genetic, environmental aspects, immune, inflammation, metabolic, and oxidative stress (OS) were suggested as the origin in the pathogenesis of ASD [2]. The association between OS and ASD neural problems was proposed by neurobiologists then targeted as for therapeutic [3]. Elevated OS may not serve as a cause but results in advanced clinical symptoms of ASD. During normal physiological function, antioxidants serve the main purpose of removing ROS, which can lead to cell apoptosis as a signal molecule if there is no balance between ROS and antioxidants as shown in ASD people [4,5]. Various studies, as well as meta-analysis research, indicated that plasma and brain GSH levels decreased in ASD and were linked to the severity [6,7].

Alterations in superoxide dismutase and catalase activities were reported in the brain and plasma result in unequal hydrogen peroxide and superoxide [8]. ASD individuals show increased superoxide in blood, cerebellum and immune cells that enhances production of H_2O_2 by SOD and peroxynitrite in the presence of nitric oxide. Methionine residues or free methionine is able to be oxidized through exposure to peroxynitrite [9], so we investigate the activity of methionine sulfoxide reductase A (MsrA) as a potential biomarker in the blood serum in addition to the important role of MsrA in elimination of H_2O_2-induced OS in eukaryotic especially in lens and fibroblasts cells [10]. The MsrA regulates the OS caused by oxidants-induced methionine sulfoxide formation within amino acids sequence of proteins or free methionine [11]. Free methionine or methionine residue exhibits an antioxidant system in normal cellular level of MsrA while causes a protein modification followed by loss its function when MsrA in abnormal level [12]. As reported in aging, Alzheimer's disease (AD) and Parkinson's disease (PD), methionine oxidation is increased, so MsrA plays a crucial role, additionally some diabetes patients show two oxidized methionine of albumin [13,14]. On the other hand, mitochondrial dysfunction in the central nervous system (CNS) of ASD patients that was suggested by different studies, results in a decline in development and impairment in learning and behaviours. In this situation neurotransmitters give evidence about the abnormalities in the neurons [15,16].

The regulation of social behaviour, reward, emotion, learning, social cognition, and movement control is aided by important neurotransmitter called dopamine and psychiatric and neurological disorders have been linked to dopamine [17]. According to some authors, dopaminergic transmission changes could lead to a decreased desire to engage in social activities, as the brain of autistic individuals may find these activities unsatisfying [18]. The frontal cortex in the brain holds particular importance as it affects mood cognitive, mood, planning and inhibition of behaviors, thinking, emotion, and short-term memory, and includes the degradation of dopamine that is related to COMT, which is an enzyme use S-adenosylmethionine in metabolizing the catechol amines by methylation process. In the pathophysiology of many neurological and psychiatric disorders, the COMT enzyme has a major role [19]. The COMT Val158 allele is a gene associated with increased activity that is associated with lower cognitive function and a higher risk of developing psychiatric disorders, While the Met allele COMT shows decreased activity and has been linked to aggression like in schizophrenia [20]. The enzyme activity is not dependent only on the allelic shape but also the metabolism of its several cofactors, their transport, stimulation, breakdown, related polymorphic enzyme functions and the metabolite related receptor functions [21]. A correlation was discovered between COMT genotypes, levels of dopamine, and ASD severity observed in 52 ASD individuals [22].

In regarding, MAT is an enzyme that produces s-adenosylmethionine from the substrate, methionine. S-adenosylmethionine is a co-substrate which serves as methyl donor molecule in different pathways especially in COMT reaction, Studies showed that this chemical was reduced in the serum of ASD individuals [23]. It was decreased in ASD in several body fluids [24]. So, we introduce this enzyme due to its relationship with COMT and also MsrA.

Sleep problems can disrupt social behavior in ASD patients, causing emotional irritability, self-harm, and attacks on others, which in turn worsens the sleep pathology. In different study, melatonin supplements support the daily behaviour of ASD individuals and sleep problems [25]. Low melatonin levels have been observed in (ASD) patients and melatonin system plays a role in the ASD progression [26]. Melatonin, a neurohormone

that controls the circadian rhythm of the body, is released by the pineal gland, which is a small endocrine gland, and is affected by dark and light environments. Melatonin is essential for regulating the sleep/wake cycle, but it has also been proven to have powerful anti-inflammatory and antioxidant capabilities, which are linked to immune responses and neural protection [27].

Therefore, the focus of our study was on estimating the level of MsrA and several new neurotransmission related enzymes (GAD67, COMT, AANAT, MAT and MAOA) to determine the state of neurotransmission in ASD patients including dystocia related ASD patients.

Materials and Methods.

Two groups, ASD group (n=35) against control group (n=25) with various age (5-28 years) were conducted to measure the biochemical parameters in blood serum. We also divided the autism group into two groups with idiopathic group and dystocia-related ASD group after asking the parents of autistics. The serum isolation process involved leaving gel tubes containing blood samples at room temperature for a few minutes before centrifuging at 3000 g for 15 minutes. We obtained blood samples from individuals with ASD by supporting Ibn Sina Teaching Hospital and Al-Salam Teaching Hospital, as well as private special needs schools in Mosul city while the Central Blood Bank and schools were responsible for the control group during the last three months of 2023.

The main enzyme (MsrA) was determined by Ellman's reagent spectrophotometric method in which thioredoxin in vivo is replaced by dithiothreitol (DTT). An inorganic phosphate determination method using green malachite was conducted to measure the activity of methionine adenosyl transferase while benzylamine was used as substrate for the activity of monoamine oxidase A using the oxidative deamination method. GAD67, COMT and AANAT measurement used ELISA kit method that we obtained by ELK Biotechnology with cast number (ELK3676), (ELK3245) and (ELK5237), respectively.

Statistical Analysis: The t-test was used to statistically analyze using IBM SPSS Statistics software (V28, USA), the data presented as mean and standard deviation (SD).

Results.

The serum levels of ASD are in an alteration compared with control group. MsrA and MAT are decreased significantly (391.21±24.068) and (38.13±3.776) with control group (485.13±38.05) and (52.67±5.58) respectively. MAOA is also in significant decrease (574.90±28.984) with control (631.44±35.58) while GAD67, COMT and AANAT increased in ASD (1.639±0.067), (4.28±0.421), (4.57±0.343) compared with control group (0.43±0.073), (3.55±0.460), (3.47±0.416), respectively (Table 1).

The serum levels of GAD67 are increased significantly in dystocia related-ASD (1.398±0.319) compared with idiopathic group (0.943±0.338). MAT and MAOA serum levels are significantly decrease (27.43±2.88), (522.78±55.22) compared with idiopathic group (43.76±3.153), (608.62±30.34), respectively (Table 2). Good positive significant relationship between MsrA and MAT as well as MAT and AANAT in the control group. However, this relationship was not observed in individuals with ASD as shown in (Table 3).

Discussion.

The purpose of this study was to examine biochemical parameters that take into account various factors, particularly interactions between them. Due to the lower activity of MAT in ASD individuals, important considerations are suggested.

Regarding methionine, the lower activity of MAT in ASD may be related to insufficient methionine. Here we investigated the importance of MsrA, and it is highlighted by its inability to scavenge methionine sulfoxide in ASD compared to observation in normal persons, where it is observed that MsrA and MAT are more active, and there is a good positive correlation between them, which is lacking in ASD. S-adenosylmethionine and

Table 1. *Antioxidant enzyme and neural pathways enzymes in ASD compared with control.*

Biochemical parameters	**Control**	**ASD**
MsrA(U/L)	485.13±38.05*	391.21±24.068
GAD67(ng/ml)	0.43±0.073	1.639±0.067*
COMT(ng/ml)	3.55±0.460	4.28±0.421*
AANAT(ng/ml)	3.47±0.416	4.57±0.343*
MAT(U/L)	52.67±5.58*	38.13±3.776
MAOA(U/L)	631.44±35.58*	574.90±28.984
Data expressed as mean±SD *indicates significant difference at(P≤0.05) using 2-sample t-test		

Table 2. *Antioxidant enzyme and neural pathways enzymes in dystocia related-ASD group compared with idiopathic group.*

Biochemical Parameters	**Dystocia**	**Idiopathic**
MsrA(U/L)	381.77±20.40	396.17±35.523
GAD67(ng/ml)	1.698±0.319	0.943±0.338*
COMT(ng/ml)	3.934±0.529	4.457±0.579
AANAT(ng/ml)	4.364±0.534	4.416±0.455
MAT(U/L)	27.43±2.88	43.76±3.153*
MAOA(U/L)	522.78±55.22	608.62±30.34*
Data expressed as mean±SD *indicates significant difference at(P≤0.05) using 2-sample t-test		

Table 3. *The correlations between the enzymes in ASD and control individuals.*

		Correlation of ASD				**Correlation of Control**			
		COMT	**AANAT**	**MsrA**	**MAT**	**COMT**	**AANAT**	**MsrA**	**MAT**
COMT	Pearson Correlation	1	0.086	0.239	-0.127	1	0.374	-0.184	0.356
	Sig. (2-tailed)		0.651	0.240	0.538		0.104	0.413	0.113
AANAT	Pearson Correlation	0.086	1	0.284	0.060	0.374	1	0.282	0.718**
	Sig. (2-tailed)	0.651		0.143	0.760	0.104		0.193	0.0001
MsrA	Pearson Correlation	0.239	0.284	1	0.324	-0.184	.282	1	0.469*
	Sig. (2-tailed)	0.240	0.143		0.093	0.413	.193		0.028
MAT	Pearson Correlation	-0.127	0.060	0.324	1	0.356	0.718**	0.469*	1
	Sig. (2-tailed)	0.538	0.760	0.093		0.113	0.0001	0.028	

neurotransmission processes are impacted by this situation, because it serves as the methyl donor molecular in multiple pathways, such as melatonin production and dopamine inhibition via COMT [28]. On the other hand, Melatonin system is characterized by the involvement of multiple neurotransmitters. The influence of abnormally synthesizing melatonin is seen in ASD through the upstream neurotransmitters that contain serotonin and other related proteins [29]. The serotonin-NAS-melatonin pathway disruptions have been recently demonstrated to be highly sensitive and may serve as a promising biomarker for diagnosing ASD [30]. According to the general consensus, AANAT is the enzyme that is responsible for limiting the rate of melatonin synthesis, while ASMT is partially responsible for the rate-limiting role at night [31]. AANAT concentration in ASD could indicate the accumulation of N-acetyl serotonin (NAS) that was reported by Hodge, et al. (2014) [32], and the need of melatonin production enhances the releasing of this enzyme due to it is the rate determining step. A sharp positive correlation was observed between AANAT and MAT in the control group, but not in ASD patients, this may relate to the role of MAT in disruption of melatonin pathway that provides SAM in the methylation of NAS if we assume that AANAT level reflects the level of NAS the substrate of ASMT in addition to indirect role of MsrA. Lower activity of MAOA may also enhance AANAT for metabolize higher level of serotonin.

According to our results, elevated GAD67 in ASD may indicate the imbalance GABA neurons. GAD67 is the rate limiting step of GABA synthesis, so lower GABA level enhances this enzyme to be more activity especially that GAD67 is important for basal GABA within neurons, The role of GABA inhibition on neurons through neurodevelopment may be affected by GAD67 [33]. The level of glucose within brain may cause elevation in glutamate production that may results in more GAD67 activity, particularly increased glutamate levels result in neurotoxicity and damage to target neurons [34]. Different studies in animals suggest the role of GAD67 in cognitive, brain development and emotional behaviour [35,36], and all of this present in ASD individuals so it should be targeted in therapeutic.

Most of the synaptic activity and intracellular signalling in the brain is accounted for by glutamate (Excitatory) and GABA (Inhibitory) [37]. Healthy function of neurotransmission requires a balance between excitatory and inhibitory (E/I) signals that is crucial for proper neuronal firing and synaptic transmission. Dysfunction of inhibitory GABAergic circuits has been proposed as a cause for both disorders suggesting that the excitation/inhibition imbalance resulting from neurodevelopmental defects in GABAergic circuitry might represent a common pathogenetic mechanism for these disorders [34].

The GAD67 is a critical enzyme used by neuron cells to synthesise GABA from glutamate and modulate its developmental, balancing, and activity-dependent modulation [38]. Changes in GAD67 levels and activity are easily able to affect the amount of GABA present in cells and vesicles. As the rate-limiting factor for this synthesis, it is accountable for over 90% of GABA production [39]. Neurodevelopmental disturbances can arise from disruptions in GABAergic inhibition, which helps to brain rhythm and activity of the neurons during growth.

Antioxidative activity was demonstrated by glutamate decarboxylase 67 released by astrocytes as a result of elevated glutathione synthesis and release when compared with control astrocytes [40]. The other enzyme which can impact cognitive, and learning is COMT, and its increased level inhibits dopamine in striatum of mice [22]. Due to decreased MAOA level in ASD, dopamine may be in higher levels in within neurons and this stimulates COMT to be released in higher concentration for inhibition. Overproduction of COMT may be related to gene expression that prevents dopamine to reach the required level within neurons [41]. These alterations in COMT were observed in mice effects on behaviour and increased the danger of psychiatric disease [20].

On the hand, Several ASD risk factors are associated with fetal hypoxia events, which have been identified as a common mechanism. The brain experiences hypoxia in many pathological conditions throughout life, such as perinatal hypoxia-ischemia encephalopathy. The development and function of the brain is impacted by hypoxia in an age-dependent way. In rats, hypoxia exposure has been demonstrated to result in neurodevelopmental problems. Clinical studies have shown that ASD development is strongly influenced by pregnancy and birth problems caused by hypoxic-ischemic damage in which perinatal rats were exposed to hypoxia-ischemia for 12 hours, which caused social disorder, anxiety and dysregulation in emotion [42,43].

Maternal immune activation also is the environmental factor that is most commonly associated with the onset of ASD [44]. An immune response is provoked by it, and the offspring are afflicted with neuro-inflammation and OS, which can cause direct or indirect damage to the placenta and brain of fetal during embryonic steps [45,46].

The results of dystocia-related ASD children showed a significant decrease in MAOA and MAT compared to

idiopathic individuals, while GAD67 showed a significant increase. This suggests that there has been an alteration in neurotransmission problems among the two groups of the same disease. More damage may be occurred in GABAergic neurons affected by dystocia, in which there is sharp decrease of GABA represented by elevated in GAD67, also methylation process by s-adenosylmethionine may be affected more. While no alterations were observed in MsrA, COMT and AANAT.

MAOA deficiency may result in aggressive feature in the behaviour of ASD patients compared to the control, in dystocia-related ASD children may refer to the increased sensitivity to this feature [47]. A significant number of autistic individuals had hyperserotonemia in serum and whole blood, but outside the brain and the possibility for used this biomarker for ASD diagnosis [48]. We introduce AANAT for these reasons as a biochemical parameter to know its role and give an indication about the synthesis of melatonin and catabolism of serotonin, beside AANAT, we also introduce MAOA that is also a crucial enzyme for the breakdown of serotonin and catecholamines in order to know its role in implication of serotonin. During early developmental stages, MAOA and A/B knockout (KO) mice exhibit high levels of serotonin. MAOA deficiency in humans and mice leads to elevated serotonin levels in the blood and brain, especially in the early post-natal period, and an extreme propensity to reactive aggression and behavioral alterations. Findings indicate that the neurochemical imbalances caused by MAOA deficiency (either on its own or with a lack of MAOB) could lead to a range of abnormalities similar to symptoms observed in ASD patients [49,50]. According to a study on migraine and Alzheimer's disease, compared to ASD, MAOA levels in blood serum were found to be higher, potentially indicating higher H2O2 production and oxidative stress [51].

In overall, Accumulation of MO that may effect on the methionine metabolism in the brain and liver especially in producing S-Adenosylmethionine (SAM) is related to decreased activity of MsrA. Accumulation of oxidized methionine residues that cause modifications to enzymes or proteins results in loss of function. In connection with this, neuronal proteins were significantly damaged compared to postmortem brains of Alzheimer's disease patients and aging rats due to decreased MsrA activity [13] and as reported by several studies, decreased activity of MsrA refer to Aging, regardless of any illness due to protein oxidation and dysfunction are enhanced in this situation [52]. Finally, stem cells might find application in autism [53], through immune regulation [54] and stem cells hypoxia tolerability [55].

Conclusion.

The role of MsrA as repair enzyme should be taken into account for study the activity of brain enzymes and proteins in ASD including ASMT that has a role in melatonin problems production in ASD due to higher AANAT level. The influence of MsrA also should be studied with MAT in mice to give more evidence.

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