RESEARCH ARTICLE

Hyperbaric Oxygen Therapy Increases Brain-Derived Neurotrophic Factor as well as Decreases Systemic Immune-Inflammatory Index and Systemic Inflammatory Response Index in Autism Spectrum Disorder

Verna Biutifasari[1,2], Ni Komang Sri Dewi Untari[3], Pramita Anindya Nugraheni[4,5], Ronald Pratama Adiwinoto[6], Djatiwidodo Edi Pratiknya[7], Vendra Setiawan[8], Hartono Kahar[9], Betty Agustina Tambunan[9,*]

[1]Clinical Pathology Sub-Specialist Doctor Education Program, Department of Clinical Pathology, Faculty of Medicine, Universitas Airlangga/ Dr. Soetomo General Academic Hospital, Jl. Prof. Dr. Moestopo No.47, Surabaya 60132, Indonesia
[2]Department of Clinical Pathology, Faculty of Medicine, Universitas Hang Tuah, Komplek Barat RSAL Dr. Ramelan, Jl. Gadung No. 1, Surabaya 60244, Indonesia
[3]Department of Hyperbaric, Naval Health Institute (LAKESLA) Drs. Med. R. Rijadi Sastropanoelar, Phys, Jl. Sarwajala No.2, Surabaya 60155, Indonesia
[4]Departement of Pediatric, Faculty of Medicine, Universitas Hang Tuah, Komplek Barat RSAL Dr. Ramelan, Jl. Gadung No. 1, Surabaya 60244, Indonesia
[5]Sub Department of Pediatric, Naval Center Hospital Dr. Ramelan, Jl. Gadung No.1, Surabaya 60244, Indonesia
[6]Department of Community Medicine. Faculty of Medicine, Universitas Hang Tuah, Komplek Barat RSAL Dr. Ramelan, Jl. Gadung No. 1, Surabaya 60244, Indonesia
[7]Department of Marine Health, Faculty of Medicine, Universitas Hang Tuah, Komplek Barat RSAL Dr. Ramelan, Jl. Gadung No. 1, Surabaya 60244, Indonesia
[8]Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Universitas Surabaya, Jl. Raya Kalirungkut, Surabaya 60293, Indonesia
[9]Department of Clinical Pathology, Faculty of Medicine, Universitas Airlangga/Dr. Soetomo General Academic Hospital, Jl. Prof. Dr. Moestopo No.47, Surabaya 60132, Indonesia

*Corresponding author. Email: betty-a-t@fk.unair.ac.id

Received date: Oct 1, 2024; Revised date: Nov 18, 2024; Accepted date: Nov 20, 2024

Abstract

BACKGROUND: Neuroinflammation and immune dysregulation are frequently viewed as contributing factors of autism spectrum disorder (ASD). Brain-derived neurotrophic factor (BDNF) is involved in the maintenance of neuron viability, as well as in neuron differentiation. Meanwhile, Systemic Immune-Inflammatory Index (SII) and Systemic Inflammatory Response Index (SIRI) are basic hematological indices used to assess inflammation and immune status. Hyperbaric oxygen (HBO) is known to enhance cerebral blood flow and reduce inflammation, however, not many studies have observed the its effect on BDNF level, SII, and SIRI in ASD subjects; therefore, this study was performed.
METHODS: Fifteen ASD subjects were involved in this study and received HBO therapy 10 times within a 2-week period. The HBO therapy was performed by letting the subjects got into an isolated chamber filled with 100% oxygen and 1.3 ATA pressure for 60 minutes. Pre- and post-therapy blood samples were taken from subjects. BDNF level was measured with Enzyme Linked Immunosorbent Assay (ELISA), while neutrophils, monocytes, lymphocytes and platelets were measured by hematology analyzer for the calculation of SII and SIRI.
RESULTS: Post-therapy BDNF level was higher than pre-therapy (1.84 ng/mL *vs.* 1.46 ng/mL; p=0.039). The increased in BDNF suggested reduced neuroinflammation and enhanced connections between neurons. Both post-therapy SII (672.4 *vs.* 359.4; p=0.005) and SIRI (1.3 *vs.* 0.7; p=0.009) were significantly lower than pre-therapy indexes. Decreased in SII and SIRI signified a reduction in neuroinflammation.
CONCLUSION: HBO therapy increases BDNF level, also decreases SII and SIRI in ASD subjects. These results suggest that HBO has an effect on neuroinflammation, specifically in ameliorating inflammation.
KEYWORDS: autism spectrum disorder, BDNF, SII, SIRI, hyperbaric oxygen therapy

Indones Biomed J. 2024; 16(6): 534-9

Introduction

Autism spectrum disorder (ASD) is a neurodevelopmental disorder with primary symptoms of impaired social communication and interaction, as well as repetitive and restricted behaviors and interests.(1,2) According to the Center for Disease Control and Prevention (CDC), the frequency of ASD has been rising each year, increasing from 1/154 children in 2000 to 1/54 children in 2016.(1) ASD is recognized for having various factors contributing to its development and accompanying conditions. The causes of ASD may involve genetic and environmental factors, including dysfunction of the immune system. However, the correlation between immune system and aberrant neural circuits in alternating behavior and communication characterized by ASD remains unknown.(3) Other than immune system, neuroinflammation is also frequently viewed as contributing factors of ASD.(4)

Brain-derived neurotrophic factor (BDNF) is a crucial neurotrophic factor involved in the management of neuroinflammation in ASD by reducing inflammation and protecting nerve cells. BDNF has important role in synaptic plasticity and nerve cell development.(5) The level of BDNF production has a prominent impact on neutron activity, which is closely linked to the field of learning and memory.(6) Depletion of BDNF has been associated with the level of neurological damage in neurological disorder, including ASD. It is reported that peripheral BDNF level inadvertently reflect the concentration of BDNF in brain.(7,8) The involvement of BDNF in autism impacts the development of brain through its neurotrophic effects.(9)

To assess inflammation and immune status, hematological testing is also commonly used. The simultaneous examination of neutrophil, monocytes, lymphocyte and platelets levels contributes to the determination of microinflammatory status through the Systemic Immune-Inflammatory Index (SII) and the Systemic Inflammatory Response Index (SIRI). Both inflammatory indexes are employed as predictors of alterations in cancer, cardiovascular, as well as inflammatory conditions. Alterations in these indexes reflect an alteration in the equilibrium between patient's inflammatory and immunological status. SII and SIRI are considered as comprehensive biomarkers that are easily accessible and validated across a wide range of studies.(10,11)

Screening, diagnosis, and early therapy implementation are crucial factors to achieve the best therapeutic outcomes in reducing symptoms and promoting social adaptation for individuals with ASD.(2,12) In individuals with ASD, there is a reduction in regional cerebral blood flow in the bilateral frontal lobe, temporal lobe, limbic system, and basal ganglia.(13) Hence, therapies specifically targeting the neuroinflammation could be potential for ASD treatment.

Various modalities of therapies have been given to ASD patients to reduce neuroinflammation, such as exercise, anti-inflammatory agents, and hyperbaric oxygen (HBO). HBO therapy is known to be able to enhance cerebral hypoperfusion, reduce brain inflammation, and lower oxidative stress in individuals with ASD.(13,14) HBO therapy also enhances the blood serum's oxidative capacity through diffusion, correcting hypoxia and decreasing tissue edema.(15) Even though it was reported that BDNF was utilized as a diagnostic marker to track the progress and improvement of ASD after HBO therapy (16), however, not many studies have been conducted to observe the effect of HBO therapy on BDNF, SII, and SIRI, and evaluate how these aspects of therapy may ameliorate neuroinflammation in ASD subjects. Therefore, this study was performed.

Methods

Study Design and Subjects Recruitment

This was a quasi-experimental study with pre- and post-therapy design conducted in Marine Health Institute/ Lembaga Kesehatan Laut (LAKESLA) TNI AL Drs. Med. R. Rijadi Sastropanoelar, Phys, Surabaya, Indonesia during May to June 2023. Fifteen ASD patients aged ≤18 years old were involved as subjects in this study. Subjects who had chronic illnesses, lack of nutrients, or had physical limitations were excluded from the study. Subjects would also be excluded from the study during any emergency situations and if the subject's family declines to continue the HBO therapy. Informed consents were obtained from the subjects' parents. This study followed the Helsinki Declaration and World Health Organization-Council for International Medical Sciences (WHO-CIOMS) ethical guidelines. The protocol of this study was ethically approved by Ethical Committee of LAKESLA (No. 07/EC/LKS/V/2023).

HBO Therapy and Blood Sample Collection

ASD subjects received HBO therapy 10 times within a 2-week period. The subjects were exposed to high pressure air in an isolated chamber for 60 minutes, with 100% oxygen

(O_2) levels and a pressure of 1.3 ATA, continuously. The HBO therapy sessions were conducted during the afternoon. For the measurement of BDNF and the haematological parameters, blood samples from subjects were taken twice; once taken before the first HBO session for the pre-therapy analysis, and once taken immediately following the final HBO session for the post-therapy analysis.

Measurement of BDNF

The collected blood samples were placed into the serum separator tube (SST) and then centrifuged at 3000 revolutions per minute (RPM) for 15 minutes. The serum was promptly isolated and kept as a combined sample at a temperature of -20°C. The BDNF level was analyzed using sandwich Enzyme Linked Immunosorbent Assay (ELISA) with Human Brain Derived Neurotrophic Factor, BDNF ELISA Kit (Cat. No. E1302Hu; BT LAB, Jiaxing, China), with the sensitivity of 0.023 ng/mL and detection range of 0.05-10 ng/mL. Forty µL of serum sample was added to a well that had been pre-coated with human BDNF antibodies. The addition of biotinylated human BDNF would bind BDNF to the sample. Streptavidin-horseradish peroxidase (HRP) was introduced and would be attached to BDNF antibodies that have been labeled with biotin, and then washed. The addition of substrate solution would result in color change that was proportional to the amount of human BDNF present. After the stop solution was added to halt the reaction, the absorbance was then measured using a single ELISA HumaReader HS (HUMAN Diagnostics Worldwide, Wiesbaden, Germany) at a wavelength of 450 nm.

Calculation of SII and SIRI

Approximately 1 mL of blood sample were drawn using the anticoagulant ethylenediaminetetraacetic acid (EDTA) tube for complete blood count tests using an automated hematology analyzer Sysmex XN-3000 (Sysmex, Kobe, Japan). The analysis of leukocyte count (neutrophils, monocytes, lymphocytes) was conducted using flow cytometry with a 633 nm semiconductor laser. Examination of cell size, intracellular data, and nucleic acid elements was performed by utilizing forward scattered light, side scattered light, and side fluorescent light. Meanwhile, the platelet count was determined using the direct current sheath flow technique. The obtained neutrophils, monocytes, lymphocytes, and platelets value were used for the calculation of SII and SIRI, with following formula:

$$SII = (Platelet \times Neutrophil)/Lymphocyte$$

$$SIRI = (Neutrophil \times Monocyte)/Lymphocyte.$$

Results

Subjects' Characteristics

From 15 ASD subjects receiving HBO therapy, 80% of the subjects consist of male, with most of the subjects were within the 6-10 years old age range (53.3%). No subjects had the history of ASD in their family (Table 1).

Though not significantly, HBO therapy reduced white blood cells/leukocytes level from 11.22±4.30 to 10.23±3.10 mm^3, indicating the reduction of neuroinflammatory conditions in ASD subjects. Not only leukocytes, HBO therapy also decreased the neutrophil (39.41±28.12 to 35.62±24.28%) and platelets (301.12±255.30 to 248.24±205.76 mm^3) levels in ASD subjects compared to pre-therapy (Table 2).

HBO Therapy Increased BDNF Level and Decrease SII and SIRI

Pre-therapy BDNF level in ASD subjects ranged from 0.1-5.5 ng/mL, with an average of 1.46±1.30 ng/mL. While, after the HBO therapy, there were significant increase (p=0.039) in BDNF level, with range of 0.1-5.6 ng/mL and an average of 1.84±1.50 ng/mL (Table 3). ASD subjects receiving HBO therapy experienced improved BDNF level due to the increased oxygen levels under pressure, which resulted in enhanced cerebral blood flow and decreased neuroinflammation.

Even though there was no significant difference between the platelet and leukocytes component pre- and post-therapy; however, as composite scores incorporating the main peripheral blood parameters related to inflammation, there were significant decreases of SII and SIRI after HBO therapy (p=0.005 and p=0.009, respectively) (Table 3).

Table 1. Characteristics of ASD subjects receiving HBO therapy (n=15).

Characteristics	n (%)
Gender	
Male	12 (80)
Female	3 (20)
Age (years)	
0-5	4 (26.7)
6-10	8 (53.3)
11-15	2 (13.3)
16-18	1 (6.7)
History of ASD in the family	
History	0 (0)
No history	15 (100)

Tabel 2. Hematologic parameters in ASD subjects pre- and post-therapy (n=15).

Parameters	Mean±SD		*p*-value
	Pre-therapy	Post-therapy	
Leukocyte (mm^3)	11.22±4.30	10.23±3.10	0.354
Neutrophil (%)	39.41±28.12	35.62±24.28	0.060
Monocyte (%)	4.75±6.03	5.94±5.46	0.245
Lymphocyte (%)	27.48±27.56	28.92±3.10	0.982
Platelet (mm^3)	301.12±255.30	248.24±205.76	0.115

Means were compared with paired sample t-test.

These results suggested that both SII and SIRI might be integrated inflammation indicators in ASD subjects.

Discussion

BDNF is beneficial as a potential indicator of neuroplasticity since it can readily pass through the blood-brain barrier. Serum BDNF concentrations directly mirror the brain's BDNF concentration. The effectiveness of therapeutic interventions in ASD subjects can be measured by monitoring BDNF levels. Elevated BDNF levels are typically linked to improved cognitive function, memory, and mood.(7,9) The results of current study showed a significant increase in BDNF level post-therapy (p=0.039), supporting the role of HBO in improving neuroplasticity in ASD patients.(17) The finding of this study shows lower BDNF level compared to previous study, that found BDNF level in autism patients to be 4.02±1.27 ng/mL.(18) The causes of variations in BDNF levels might be due to the variations in clinical characteristics, like age and gender distribution, or the types of BDNF samples utilized in various studies. BDNF is utilized as an indicator of neuroplasticity in individuals with ASD, which can be affected by age, diet, nutritional status, exercise, circadian rhythm, and characteristics of intestinal microbiota.(19) In this study, since the HBO therapy session was conducted in the afternoon, this might affect BDNF level due to the subjects' circadian rhythm, resulting in decreased effectiveness of HBO therapy, which results in small increase of BDNF level.

Hypoperfusion in ASD is mainly observed in about 75% of cases in temporal lobe regions, which are linked to alterations in ASD behavior. It is anticipated that HBO will enhance hypoperfusion in the region, leading to improved clinical outcomes by increasing oxygen solubility in plasma. This will results in the improvement of tissue perfusion, particularly in the brain, and reduction of neuroinflammation.(20) Oxidative stress and dysfunction in the mitochondria of the brain will lead to a reduction in BDNF expression, particularly in the hippocampus. Stimulation of hyperoxygenation by 100% at high pressure enhances hippocampal neurogenesis and provides protective effects against brain injury and ischemia. Hence, administering HBO might boost the production of neurotrophic factors, including BDNF, and reduce the proinflammatory cytokines and oxidative stress parameters while boosting blood flow to the brain in individuals with ASD.(21,22)

ASD is also significantly impacted by systemic inflammation. Chronic neuroinflammation increases neutrophil and monocyte levels, triggering prolonged inflammatory immune responses.(23) In ASD patients, elevated pro-inflammatory cytokines will the activation of neutrophils.(24) Meanwhile, neurological defect is mainly linked to the functioning of platelets. The increment of platelet were found in ASD cases where mammalian target rapamycin (mTOR) activation raises megakaryocytes.

Table 3. BDNF Level, SII, and SIRI pre- and post-therapy (n=15).

Parameters	Mean±SD		*p*-value
	Pre-therapy	Post-therapy	
BDNF (ng/mL)	1.46±1.30	1.84±1.50	0.039*
SII	672.40±508.40	359.40±224.60	0.005*
SIRI	1.30±1.20	0.70±0.44	0.009*

*Significant if p<0.05; Means were compared with paired sample t-test.

(25,26) Though not significant, however the results of this study, showed reduction in neutrophil and platelets after HBO therapy in ASD subjects, suggesting that this might be due to the reduction of inflammation. Besides being inflammation parameters, neutrophils, lymphocytes, monocytes, and platelets are also the fundamental hematological parameters to determine SII and SIRI. The results of current study indicate that HBO reduced systemic inflammation, which is shown by the significant reduction of SII (p=0.005) and SIRI (p=0.0009). Study on SII and SIRI in individuals with necrotizing pneumonia suggests that these markers are reliable predictors of hospitalization duration and prognosis. SII is also a useful indicator of inflammation, comparable to C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR).(27) Additionally, the decrease of SII is also related to the inflammation reduction.(28)

HBO is a viable alternative treatment for individuals with ASD. The results of this study showed that this treatment yields significant results, including significantly ameliorated inflammations. However, it is important to note that while some studies have reported improvements in cognitive and behavioral outcomes following HBO therapy, others have found no significant changes in these areas since behavioral aspects should be validated by psychological parameters. HBO therapy also needs to be used cautiously due to some potential side effects. Reported possible side effects include injury in middle ear, sinus/paranasal, dental barotrauma, central nervous system, and oxygen toxicity. (15) HBO therapy session performed in a limited area might create stress, particularly in individuals with ASD.(1)

Unfortunately, in this study, the type of ASD patients was not distinguished (typical or atypical ASD). Oxidative stress markers, as well as other factors affecting the examination of BDNF including age, diet, nutritional status, physical activity, circadian rhythm, and gut microbiota characteristics are also not measured or considered. Future research should explore those factors that might contribute to discrepancies of results while understanding the full potential of HBO therapy as a treatment for ASD. Since this study only involved few numbers of subjects, further study with a more extensive group of ASD patients is suggested.

Conclusion

HBO therapy increases BDNF level, also decreases SII and SIRI in ASD subjects. These results suggest that HBO has an effect on neuroinflammation, specifically in ameliorating inflammation, and is a potential option for ASD treatment.

Acknowledgments

We acknowledge all participants and their parents for supporting and cooperating with this study.

Authors Contribution

VB and BAT were involved in conceptualizing and planning the research. NKSDU, PA, and DEP performed the sample and data acquisition/collection. VB, RPA and VS calculated the experimental data and performed the analysis. VB and BAT drafted the manuscript and designed the figures, as well as aided in interpreting the results. All authors took parts in giving critical revision of the manuscript.

References

1. Podgórska-Bednarz J, Perenc L. Hyperbaric oxygen therapy for children and youth with autism spectrum disorder: A review. Brain Sci. 2021; 11(7): 916. doi: 10.3390/brainsci11070916.
2. Catherine Lord, Mayada Elsabbagh, Gillian Baird JVV. Autism spectrum disorder. Clin Child Neurol. 2020; 392(10146): 275–92.
3. Ohja K, Gozal E, Fahnestock M, Cai L, Cai J, Freedman JH, *et al.* Neuroimmunologic and neurotrophic interactions in autism spectrum disorders: relationship to neuroinflammation. Neuro Molecular Med. 2018; 20(2): 161–73.
4. Eissa N, Sadeq A, Sasse A, Sadek B. Role of neuroinflammation in autism spectrum disorder and the emergence of brain histaminergic system. Lessons also for BPSD? Front Pharmacol. 2020; 11: 886. doi: 10.3389/fphar.2020.00886.
5. Tanjung ND, Wahono NA, Mudjihartini N, Prijanti AR. Maternal zinc diet impairs learning and memory in offspring rats through the CREB/BDNF pathway. Indones Biomed J. 2024; 16(3): 228–36.
6. Aryana IGPS, Hapsari AAAR, Kuswardhani RAT. Myokine regulation as marker of sarcopenia in elderly. Mol Cell Biomed Sci. 2018; 2(2): 38–47.
7. Kasarpalkar NJ, Kothari ST, Dave UP, Dave UP. Brain-derived neurotrophic factor in children with Autism Spectrum Disorder. Ann Neurosci. 2014; 21(4): 129–33.
8. Elhamid SAA, Alkherkhisy MM, Kasem RE. Assessment of brain-derived neurotrophic factor levels in serum of children with autism spectrum disorders. Middle East Curr Psychiatry. 2024; 31(1): 18. doi: 10.1186/s43045-024-00403-y.
9. Naegelin Y, Dingsdale H, Säuberli K, Schädelin S, Kappos L, Barde YA. Measuring and validating the levels of brain-derived neurotrophic factor in human serum. eNeuro. 2018; 5(2): ENEURO.0419-17.2018. doi: 10.1523/ENEURO.0419-17.2018.
10. Elmeazawy R, Ayoub D, Morad LM, EL-Moazen AMF. Role of systemic immune-inflammatory index and systemic inflammatory response index in predicting the diagnosis of necrotizing pneumonia in children. BMC Pediatr. 2024; 24(1): 496. doi: 10.1186/s12887-024-04818-8.
11. Elmeazawy R, El Shall S, AbdElsamea MZ, Emara MH. Systemic

immune-inflammatory index and systemic inflammation response index in predicting renal impairment in children with type 1 diabetes mellitus. Egypt Pediatr Assoc Gaz. 2024; 72(1): 49. doi: 10.1186/s43054-024-00290-2.

12. Hodges H, Fealko C, Soares N. Autism spectrum disorder: Definition, epidemiology, causes, and clinical evaluation. Transl Pediatr. 2020; 9(8): S55–65.
13. Halepoto DM, Al-ayadhi LY, Salam AAA. Therapeutic use of hyperbaric oxygen therapy for children with autism spectrum disorder. J Coll Physicians Surg Pak. 2014; 24(7): 508–14.
14. Rossignol DA, Rossignol LW. Hyperbaric oxygen therapy may improve symptoms in autistic children. Med Hypotheses. 2006; 67(2): 216–28.
15. Soetjipto, Murbani ID, Harnanik T. Hyperbaric oxygen ameliorates the expression of tumor growth factor-β and malondialdehyde in pristane-induced lupus nephritis mice model. Indones Biomed J. 2023; 15(1): 54–60.
16. Meyer M. The science journal of the lander is hyperbaric oxygen therapy effective for treating autism? Is hyperbaric oxygen therapy effective for treating autism? The Science Journal of the Lander College of Arts and Sciences. 2020; 13(2): 65–73.
17. Saghazadeh A, Rezaei N. Brain-derived neurotrophic factor levels in autism: A systematic review and meta-analysis. J Autism Dev Disord. 2017; 47(4): 1018–29.
18. Meng WD, Sun SJ, Yang J, Chu RX, Tu W, Liu Q. Elevated serum brain-derived neurotrophic factor (BDNF) but not BDNF gene Val66Met polymorphism is associated with autism spectrum disorders. Mol Neurobiol. 2017; 54(2): 1167–72.
19. Barbosa AG, Pratesi R, Paz GSC, dos Santos MAAL, Uenishi RH, Nakano EY, *et al.* Assessment of BDNF serum levels as a diagnostic marker in children with autism spectrum disorder. Sci Rep. 2020; 10(1): 17348. doi: 10.1038/s41598-020-74239-x.
20. Martin R, Srivastava T, Lee J, Raj N, Koth KA, Whelan HT. Using hyperbaric oxygen for autism treatment: A review and discussion of literature using hyperbaric oxygen for autism treatment: A review and discussion of literature. Undersea Hyperb Med. 2015; 42(4): 353–9.
21. Daniels AM, Mandell DS. Explaining differences in age at autism spectrum disorder diagnosis: A critical review. Autism. 2016; 18(5): 583–97.
22. Choi J, Kwon HJ, Seoh JY, Han PL. Hyperoxygenation ameliorates stress-induced neuronal and behavioral deficits. Exp Neurobiol. 2021; 30(6): 415–29.
23. Arteaga-Henríquez G, Lugo-Marín J, Gisbert L, Setién-Ramos I, Martínez-Gallo M, Pujol-Borrell R, *et al.* Activation of the monocyte/macrophage system and abnormal blood levels of lymphocyte subpopulations in individuals with autism spectrum disorder: A systematic review and meta-analysis. Int J Mol Sci. 2022; 23(22): 14329. doi: 10.3390/ijms232214329.
24. Zhao H xiang, Yin S sha, Fan J gang. High plasma neopterin levels in Chinese children with autism spectrum disorders. Int J Dev Neurosci. 2015; 41: 92–7.
25. Padmakumar M, Van Raes E, Van Geet C, Freson K. Blood platelet research in autism spectrum disorders: In search of biomarkers. Res Pract Thromb Haemost. 2019; 3(4): 566–77.
26. Farmer CA, Thurm AE, Honnekeri B, Kim P, Swedo SE, Han JC. The contribution of platelets to peripheral BDNF elevation in children with autism spectrum disorder. Sci Rep. 2021; 11(1): 18158. doi: 10.1038/s41598-021-97367-4.
27. Nicoară DM, Munteanu AI, Scutca AC, Brad GF, Asproniu R, Jugănaru I, *et al.* Evaluating the diagnostic performance of systemic immune-inflammation index in childhood inflammatory arthritis: A focus on differentiating juvenile idiopathic arthritis from reactive arthritis. Biomedicines. 2023; 12(1): 65. doi: 10.3390/biomedicines12010065.
28. Winker M, Stössel S, Neu MA, Lehmann N, El Malki K, Paret C, *et al.* Exercise reduces systemic immune inflammation index (SII) in childhood cancer patients. Support Care Cancer. 2022; 30(4): 2905–8.