ORIGINAL RESEARCH

Neurological Dysfunction and Serum Levels of IL-6 and IL-1β in Patients Undergoing Isoflurane Inhalation Anesthesia: A Correlation Study

Mingyu Xu, MM; Ling Han, BM; Jianbin He, MD; Lin Yuan, MM; Yalan Li, PhD

ABSTRACT

Objective • This study aims to explore the association between neurological dysfunction and serum levels of Interleukin-6 (IL-6) and Interleukin-1β (IL-1β) in patients undergoing isoflurane inhalation anesthesia.

Methods • This prospective observational study enrolled a total of 88 patients who underwent isoflurane anesthesia, between April 2019 and April 2020 in our hospital's operating room. The Mini-Mental State Examination scale (MMSE) was administered on the first preoperative day (T0), the 1st postoperative day (T1), the 3rd postoperative day (T2), and the 7th postoperative day (T3). Based on the MMSE score obtained on the 1st postoperative day, patients were categorized into the neurological dysfunction group (n = 23) and the normal group (n = 65). Serum levels of IL-6 and IL-1β were measured at T0, T1, T2, and T3, and their relationship with MMSE scores was analyzed.

Results • Compared to the normal group, the neurological dysfunction group exhibited significantly higher levels of serum IL-6 and IL-1β at all time points except T0, accompanied by notably lower MMSE scores ($P < .001$). Combined diagnostic parameters, including area under the curve (AUC) value, sensitivity, and specificity, showed improved performance compared to individual tests. Pearson correlation analysis revealed a negative correlation between serum IL-6 and IL-1β levels and MMSE scores ($r = -0.719, -0.408$, all $P < .05$).

Conclusions • Our findings highlight a correlation between neurological dysfunction and serum IL-6 and IL-1β levels in patients undergoing isoflurane inhalation anesthesia. These cytokines could serve as valuable indicators for the early detection of neurological dysfunction following anesthesia. (*Altern Ther Health Med.* 2023;29(8):315-319).

Mingyu Xu, MM, Associate Chief Physician; **Jianbin He, MD,** Attending Doctor; **Lin Yuan, MM,** Attending Doctor; Department of Anesthesiology, Shenzhen People's Hospital Affiliated to the Second Clinical College of Jinan University, Shenzhen, China. **Ling Han, BM,** Associate Chief Physician, Department of Anesthesiology, Shenzhen Luohu Maternal and Child Health Hospital, Shenzhen, China. **Yalan Li, PhD,** Chief Physician, Department of Anesthesiology, Overseas Chinese Hospital, The First Affiliated Hospital of Jinan University, Guangzhou, China.

Corresponding author: Yalan Li, PhD
E-mail: liyalan@jd120.org.cn

INTRODUCTION

Isoflurane, a widely utilized inhalation anesthetic in clinical settings,[1] is recognized for its efficacious analgesic and hypnotic properties. Its target sites encompass a broad distribution within the central nervous system, including the spinal cord, brainstem, diencephalon, and cortex.[1,2] The induction and emergence from isoflurane anesthesia are rapid, and its metabolic breakdown within the body is minimal. Furthermore, this anesthetic agent exerts suppressive effects on the circulatory and respiratory systems during deep anesthesia.[2] Owing to its reduced incidence of postoperative nausea and vomiting, isoflurane finds utility across diverse surgical procedures, such as cardiac surgery, cholecystectomy, and coronary artery bypass grafting. Importantly, isoflurane administration generally lacks sympathetic nervous system excitability and exhibits limited hepatotoxicity.[3]

Studies have indicated that isoflurane possesses the potential to trigger central neuronal apoptosis, thereby compromising nerve and memory functions. This phenomenon consequently escalates the susceptibility to neurological dysfunction.[4] Post-anaesthesia neurological dysfunction, a prevalent complication after surgical procedures, manifests as cognitive impairment or alterations in patients' cognitive states before or following surgery.[5] The advent of this complication not only extends hospital stays and escalates treatment expenses but also impairs patients'

quality of life due to enduring cognitive impairment.[6,7] Therefore, it is imperative to proactively investigate the etiological factors associated with post-anesthesia neurological dysfunction in patients subjected to isoflurane inhalation anesthesia. Such investigations are important in facilitating early identification and clinical intervention for neurological dysfunction in the postoperative phase.

Animal experiments have demonstrated that an elevation in brain levels of the proinflammatory cytokines IL-1β and IL-6 corresponds to conspicuous mental dysfunction and aberrant behavior.[8] Intensified IL-6 levels contribute to neutrophil chemotaxis towards sites of inflammatory injury and the subsequent release of excess inflammatory mediators. This, in turn, fosters the amplification of an inflammatory cascade, exacerbating inflammatory damage and inhibiting nerve cell repair. While IL-1β at physiological concentrations in the central nervous system presents neuroprotection against excitatory amino acid toxicity, excessive and prolonged IL-1β production causes harm to nerve cells.[8]

At present, there is no study to confirm the relationship between the above serum inflammatory factors and neurological dysfunction in patients with isoflurane inhalation anesthesia. This study thus focused on exploring the complex relationship among these three factors; the primary goal is to provide reliable evidence to support early clinical prevention and therapeutic strategies. The upcoming sections explain the methods and results of this study.

MATERIALS AND METHODS

Study Design and Subjects

A prospective observational study was conducted between April 2019 and April 2020, we included 88 patients who had received isoflurane anesthesia in our hospital's operating room. These patients were divided into two groups: one with neurological dysfunction (n = 23) and another with normal function (n = 65). The division was based on their MMSE scores on the first day after surgery. The neurological dysfunction group consisted of 12 males and 11 females, aged between 18 and 60 years, with an average age of (40.26 ± 10.82) years. In the normal group, there were 34 males and 31 females aged 18 to 60 years, with an average age of (41.38 ± 12.78) years. We found no significant differences in baseline characteristics between the two groups, which helped provide a solid foundation for our study. The Ethics Committee of our hospital approved this study, following the guidelines of the Declaration of Helsinki (2013),[9] and patients or their families provided informed consent before participating.

Inclusion and Exclusion Criteria

Inclusion criteria were as follows**:** (1) Patients who received isoflurane inhalation anesthesia; (2) Patients with normal coagulation function before surgery; (3) Patients with complete clinical data who could actively participate in the study. Exclusion criteria were as follows: (1) Patients with a history of nervous and mental system disorders; (2) Patients with cardiovascular conditions, anemia, or hyponatremia; (3) Patients with severe conditions such as pneumonia, endotoxic shock, or significant heart, kidney, and liver insufficiency; (4) Patients with other factors that might lead to neurological dysfunction; and (5) Patients with a history of allergies or contraindications to the drugs used in this study.

Serum Sample Collection and Analysis Procedure

Fasting venous blood samples (5 ml) were collected from the patients in the morning at T0, T1, T2, and T3. The blood was transferred to collection tubes (either test tubes or centrifuge tubes) without anticoagulant and allowed to clot at room temperature for 30-60 minutes naturally. Subsequently, the blood clot was gently separated along the tube's wall and placed at 4°C overnight for equilibration. Following this, a low-temperature and low-speed centrifugation for 10 minutes was carried out, separating serum as the supernatant.

The obtained supernatant was further subjected to centrifugation at 3000 r/min for 15 minutes (using a TGL-16M desktop micro-high-speed refrigerated centrifuge, model: 20180921, manufacturer: Jinan Olabo Scientific Instrument Co., Ltd., Origin: Shandong, China) at 4°C, with a centrifugal radius of 10cm. The resulting serum was then stored at -80°C for subsequent examination.

After rapid thawing of the stored serum samples, the enzyme-linked immunosorbent assay (ELISA) was employed to analyze the levels of IL-6 and IL-1β. The procedures were conducted in accordance with the kit's instructions (Shanghai Fusheng Industrial Co., Ltd., Shanghai, China).

Assessment of Neurological Dysfunction

Neurological dysfunction was assessed using the Mini-Mental State Examination (MMSE) score.[10] The MMSE evaluated various aspects of patients' cognitive function, including executive abilities, immediate memory, attention and calculation, delayed recall, linguistic skills, and visual-spatial awareness. The total MMSE score could reach a maximum of 30 points, and the assessment typically took 5-10 minutes to complete. A lower MMSE score indicated a more compromised mental state. An MMSE score of <26 was considered indicative of abnormal cognitive function.

Statistical Analysis

This study processed the data using SPSS version 26.0 software (IBM, Armonk, New York, USA). GraphPad Prism 7 software (GraphPad Software, San Diego, CA, USA) was employed for data visualization. Enumeration data and measurement data were subjected to χ^2 and t tests, respectively, and presented as [n(%)] and ($\bar{x} \pm s$)]. The clinical utility of IL-6 and IL-1β in diagnosing perioperative neurological dysfunction was assessed using receiver operating characteristic (ROC) curves. Additionally, Pearson correlation analysis was performed to ascertain the correlation between serum indices and MMSE scores. A significance level of $P < .05$ was considered indicative of statistical significance.

Table 1. Comparison of serum IL-6 level at different times in both groups ($\bar{x} \pm s$, pg/ml)

Groups	n	T0	T1	T2	T3
Neurological Dysfunction Group	23	14.61 ± 2.46	94.92 ± 5.89	77.25 ± 5.25	40.60 ± 4.51
Normal Group	65	14.72 ± 2.80	80.05 ± 4.50	63.29 ± 4.37	26.20 ± 3.56
t		0.048	7.790	10.492	10.859
P value		.957	<.001	<.001	<.001

Note: Serum IL-6 levels (pg/ml) were compared across various time points in both the Neurological Dysfunction Group and the Normal Group. The values presented are mean ± standard deviation ($\bar{x} \pm s$). Statistical analysis included *t* tests for each time point. Significance levels (*P*) are reported, with values < .001 indicating statistical significance.

Table 2. Comparison of serum IL-1β level at different times in both groups ($\bar{x} \pm s$, pg/ml)

Groups	n	T0	T1	T2	T3
Neurological Dysfunction Group	23	24.32 ± 3.73	33.94 ± 6.03	30.50 ± 1.89	24.51 ± 1.07
Normal Group	65	25.37 ± 3.47	27.66 ± 2.06	26.97 ± 1.54	21.42 ± 1.40
t		1.674	5.843	7.245	9.836
P value		.102	<.001	<.001	<.001

Note: Serum IL-1β levels (pg/ml) were compared at different time points for the Neurological Dysfunction and Normal Groups. The data are presented as mean ± standard deviation ($\bar{x} \pm s$). Statistical analysis included *t* tests for each time point. Significance levels (*P*) are reported, with values < .001 indicating statistical significance.

RESULTS

Comparing Serum Levels of IL-6 and IL-1β at Different Time Points in Both Groups

Compared to the normal group, the neurological dysfunction group exhibited significantly higher serum levels of IL-6 and IL-1β at all time points except T0 ($P < .001$). Please refer to Table 1 and Table 2 for detailed data.

Comparing MMSE Scores at Different Time Points Between the Two Groups

In contrast to the normal group, the neurological dysfunction group displayed noticeably lower MMSE scores at all time points except T0 ($P < .001$). See Figure 1 for detailed information.

Clinical Efficacy of Serum IL-6, IL-1β, and Combined Diagnosis for Neurological Dysfunction

The study findings revealed that the combined diagnosis exhibited higher values for the area under the curve (AUC), sensitivity, and specificity compared to single detection methods. For detailed results, refer to Figure 2 and Table 3.

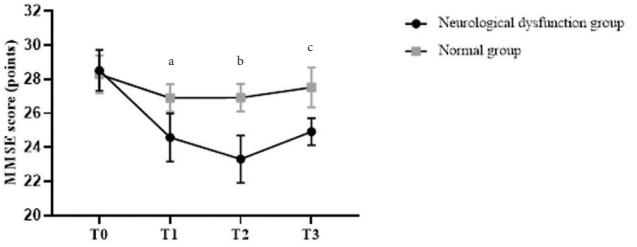
Correlation Between Serum IL-6, IL-1β, and MMSE Scores

Serum IL-6 and IL-1β demonstrated a negative correlation with MMSE scores, as demonstrated by Pearson correlation analysis (r = -0.719, P = -0.408, all $P < .05$). Further details can be found in Figure 3 and Figure 4.

DISCUSSION

Isoflurane, a commonly employed anesthetic, finds utility in the induction and maintenance of general anesthesia.[11] Its advantages include swift induction, manageable anesthesia depth, and the absence of pungent odor. These features render it highly suitable for surgical

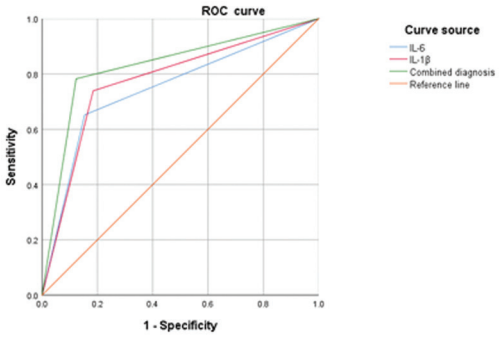
Figure 1. Comparison of MMSE scores at different times in both groups ($\bar{x} \pm s$).



[a]represented an apparent difference in the MMSE scores of patients at T1 in both groups (t = 7.773, $P < .001$).
[b]represented an apparent difference in the MMSE scores of patients at T2 in both groups ($t = 11.433$, $P < .001$).
[c]represented an apparent difference in the MMSE scores of patients at T3 in both groups ($t = 8.682$, $P < .001$).

Note: The transverse axis showed T0, T1, T2 and T3, and the vertical axis showed MMSE score (points). The MMSE scores at T0, T1, T2 and T3 in the neurological dysfunction group were (28.52 ± 1.20), (24.57 ± 1.41), (23.30 ± 1.40) and (24.91 ± 0.79), respectively. The MMSE scores at T0, T1, T2 and T3 in the normal group were (28.28 ± 1.11), (26.89 ± 0.81), (26.91 ± 0.80) and (27.51 ± 1.17), respectively.

Figure 2. ROC curve of serum IL-6, IL-1β and combined diagnosis of neurological dysfunction in patients with isoflurane inhalation anesthesia



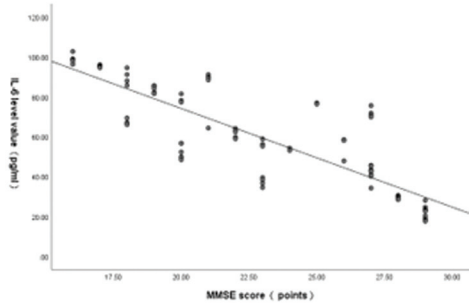
Note: The ROC (Receiver Operating Characteristic) curve visually portrays the diagnostic performance of serum IL-6, IL-1β, and the combined diagnostic approach in patients undergoing isoflurane inhalation anesthesia-related neurological dysfunction. The curve highlights the relationship between sensitivity and specificity for each diagnostic marker, aiding in determining optimal diagnostic thresholds.

Table 3. Clinical efficacy of serum IL-6, IL-1β and combined diagnosis of neurological dysfunction in patients with isoflurane inhalation anesthesia

Items	AUC Values	Standard Error	Asymptotic 95% Confidence Interval		Sensitivity (%)	Specificity (%)
			Upper Limit	Lower Limit		
IL-6	0.749	0.065	0.876	0.622	60.00	87.30
IL-1β	0.777	0.060	0.895	0.659	58.62	89.83
Combined Diagnosis	0.830	0.056	0.939	0.721	69.23	91.94

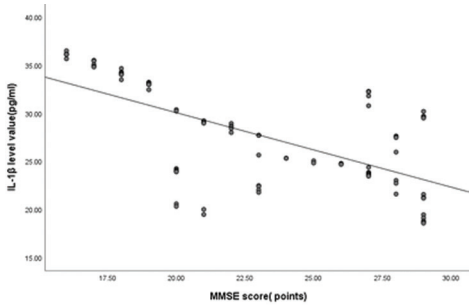
Note: This table illustrates the clinical effectiveness of serum IL-6, IL-1β, and combined diagnosis for assessing neurological dysfunction in patients undergoing isoflurane inhalation anesthesia. The area under the curve (AUC) values signify the discriminatory capacity of each diagnostic marker. Sensitivity and specificity percentages accurately depict the test's ability to identify positive and negative cases.

Figure 3. Correlation of serum IL-6 level and MMSE score in patients.



Note: The transverse axis showed the MMSE score (points), and the vertical axis showed the IL-6 level (pg/ml).

Figure 4. Correlation of serum IL-1β level and MMSE score in patients.



Note: The transverse axis showed the MMSE score (points), and the vertical axis showed the IL-1β level (pg/ml).

anesthesia induction and maintenance. Inhalation anaesthesia has become increasingly popular in anaesthesia research due to its ability to enhance airway humidity and temperature, reduce anesthetic gas loss, and minimize environmental pollution.[12]

Numerous studies have demonstrated that inhalation anesthetics can induce neuronal apoptosis, which can result in neurological dysfunction.[13-15] Researchers from other countries have also conclusded in their studies that isoflurane anesthesia can impair spatial learning function in rats. Neurological dysfunction around the time of surgery impacts patients' postoperative recovery, leading to extended hospital stays and heightened mortality rates, and places a financial and psychological strain on both patients' families and society at large.

The early identification of postoperative complications is important in enhancing patients' prognosis and quality of life. Serological indicators, a non-invasive diagnostic approach characterized by its straightforward procedure and wide acceptability, have emerged as a clinical diagnostic method for various diseases.[16,17] This study examined the correlation between serum IL-6, IL-1β, and neurological dysfunction among patients who underwent isoflurane inhalation anesthesia. Our findings offer evidence-based insights into the early prevention and treatment of neurological dysfunction and improvements in anesthesia efficacy after administering anesthesia.

Based on the study findings, it is evident that, except for T0, the neurological dysfunction group exhibited significantly elevated serum levels of IL-6 and IL-1β compared to the normal group ($P<.001$). This observation suggests the potential involvement of these serum inflammatory markers in the onset and advancement of neurological dysfunction following anesthesia. Inflammation represents a vital protective response of vascularized living tissues against injurious stimuli, forming a fundamental defense mechanism.[8-20]

Surgery can trigger the body's immune system, resulting in a robust inflammatory reaction. Peripheral inflammatory factors have the potential to induce inflammatory responses within the central nervous system, either directly or indirectly, and excessive inflammation is linked to the emergence of neurological dysfunction.[21] Among more than 30 recognized cytokines, IL-6 and IL-1β hold the status of classic pro-inflammatory cytokines.[22,23]

Some studies have examined the expression levels of inflammatory cytokines IL-6 and IL-1β in the hippocampus of rats subjected to partial hepatectomy using the Morris water maze. This behavioral experimental approach compels rodents like mice and rats to swim and learn to locate concealed water platforms. These experiments substantiated that surgical trauma could amplify and extend the cytokine response, particularly neuroinflammation, leading to alterations in neurological function.[24,25]

Utilizing the ROC curve, this study explored the diagnostic effectiveness of IL-6, IL-1β, and combined diagnosis for neurological dysfunction in patients undergoing isoflurane inhalation anesthesia. The findings revealed that the combined diagnostic approach exhibited higher values for AUC, sensitivity, and specificity compared to single detection methods. Moreover, serum IL-6 and IL-1β negatively correlated with MMSE scores, as evidenced by Pearson correlation analysis ($r = -0.719$, $P = -0.408$, all $P < .05$). These outcomes suggest a potential link between the presence and intensity of neurological dysfunction after isoflurane inhalation anesthesia and patients' serum levels of IL-6 and IL-1β.

Contribution and Limitations

This study has extended the understanding of the connection between neurological dysfunction and serum IL-6 and IL-1β levels in patients undergoing isoflurane inhalation anesthesia through rigorous clinical trials. This additional evidence offers valuable insights for the timely identification of perioperative neurological dysfunction and potential enhancements in surgical interventions.

The present study is subject to certain limitations that warrant consideration. Firstly, the utilization of relatively small sample size may limit the statistical inference and precision in the results of data analysis. Additionally, it is important to acknowledge that this study predominantly focused on young and middle-aged participant cohorts, excluding the investigation of potential effects in children and teenagers. The study's focus on a narrow age group might limit the applicability of the results to a wider range of age groups.

CONCLUSION

Our study confirms a remarkable correlation between serum IL-6 and IL-1β levels and the onset of neurological dysfunction following isoflurane inhalation anesthesia. The observed correlation highlights the potential utility of these serum markers as valuable indicators for early identification and evaluation of perioperative neurological dysfunction. These results contribute to refining clinical approaches and facilitating prompt interventions, ultimately improving patient outcomes and quality of care.

DATA AVAILABILITY

The data can be obtained from the author upon reasonable request.

CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

AUTHORS' CONTRIBUTION

All authors contributed equally to this study.

FUNDING

The authors received no financial support for the authorship or publication of this study.

REFERENCES

1. Chen SJ, Yuan XQ, Xue Q, Lu HF, Chen G. Current research progress of isoflurane in cerebral ischemia/reperfusion injury: a narrative review. *Med Gas Res*. 2022;12(3):73-76. doi:10.4103/2045-9912.330689
2. Anjana RR, Parikh PV, Mahla JK, Kelawala DN, Patel KP, Ashwath SN. Comparative evaluation of isoflurane and sevoflurane in avian patients. *Vet World*. 2021;14(5):1067-1073. doi:10.14202/vetworld.2021.1067-1073
3. Ruxanda F, Gal AF, Rațiu C, Miclăuș V, Rus V, Oana LI. Comparative immunohistochemical assessment of the effect of repetitive anesthesia with isoflurane and sevoflurane on rat liver. *Braz J Anesthesiol*. 2016;66(5):465-469. doi:10.1016/j.bjan.2015.09.007
4. Fang SY, Lee JS, Roan JN, Tsai YC, Lam CF. Isoflurane Impairs Motor Function Recovery by Increasing Neuroapoptosis and Degeneration During Spinal Ischemia-Reperfusion Injury in Rats. *Anesth Analg*. 2017;124(1):254-261. doi:10.1213/ANE.0000000000001704
5. Kapoor MC. Neurological dysfunction after cardiac surgery and cardiac intensive care admission: A narrative review part 1: The problem; nomenclature; delirium and postoperative neurocognitive disorder; and the role of cardiac surgery and anesthesia. *Ann Card Anaesth*. 2020;23(4):383-390. doi:10.4103/aca.ACA_138_19
6. Dhaya I, Griton M, Konsman JP. Magnetic resonance imaging under isoflurane anesthesia alters cortical cyclooxygenase-2 expression and glial cell morphology during sepsis-associated neurological dysfunction in rats. *Animal Model Exp Med*. 2021;4(3):249-260. doi:10.1002/ame2.12167
7. Lang SS, Vollmer E, Wu L, et al. A Retrospective Study of Neurological Complications in Pediatric Patients With Moyamoya Disease Undergoing General Anesthesia. *Anesth Analg*. 2021;132(2):493-499. doi:10.1213/ANE.0000000000004715
8. Fineberg AM, Ellman LM. Inflammatory cytokines and neurological and neurocognitive alterations in the course of schizophrenia. *Biol Psychiatry*. 2013;73(10):951-966. doi:10.1016/j.biopsych.2013.01.001
9. World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *JAMA*. 2013;310(20):2191-2194. doi:10.1001/jama.2013.281053
10. Jia X, Wang Z, Huang F, et al. A comparison of the Mini-Mental State Examination (MMSE) with the Montreal Cognitive Assessment (MoCA) for mild cognitive impairment screening in Chinese middle-aged and older population: a cross-sectional study. *BMC Psychiatry*. 2021;21(1):485. doi:10.1186/s12888-021-03495-6
11. Mohaghegh T, Yazdi B, Norouzi A, Fateh S, Modir H, Mohammadbeigi A. Effect of intravenous anesthesia with propofol *versus* isoflurane inhalation anesthesia in postoperative pain of inguinal herniotomy: a randomized clinical trial. *Med Gas Res*. 2017;7(2):86-92. doi:10.4103/2045-9912.208511
12. Lee S, Cho JS, Kim E, Kim Y, Lee J. Effects of Inhalation versus Total Intravenous Anesthesia on Postoperative Pulmonary Complications after Anatomic Pulmonary Resection. *J Chest Surg*. 2022;55(1):30-36. doi:10.5090/jcs.21.119
13. Kang W, Lu D, Yang X, et al. Sevoflurane Induces Hippocampal Neuronal Apoptosis by Altering the Level of Neuropeptide Y in Neonatal Rats. *Neurochem Res*. 2020;45(9):1986-1996. doi:10.1007/s11064-020-03028-9
14. Zou X, Sadovova N, Patterson TA, et al. The effects of L-carnitine on the combination of, inhalation anesthetic-induced developmental, neuronal apoptosis in the rat frontal cortex. *Neuroscience*. 2008;151(4):1053-1065. doi:10.1016/j.neuroscience.2007.12.013
15. Carton L, Auger F, Laloux C, et al. Effects of acute ethanol and/or diazepam exposure on immediate and delayed hippocampal metabolite levels in rats anesthetized with isoflurane. *Fundam Clin Pharmacol*. 2022;36(4):687-698. doi:10.1111/fcp.12764
16. Zhang A, Sun H, Wang X. Serum metabolomics as a novel diagnostic approach for disease: a systematic review. *Anal Bioanal Chem*. 2012;404(4):1239-1245. doi:10.1007/s00216-012-6117-1
17. Davis RL, Liang C, Sue CM. A comparison of current serum biomarkers as diagnostic indicators of mitochondrial diseases. *Neurology*. 2016;86(21):2010-2015. doi:10.1212/WNL.0000000000002705
18. Akdogan N, Dogan S, Incel-Uysal P, et al. Serum amyloid A and C-reactive protein levels and erythrocyte sedimentation rate are important indicators in hidradenitis suppurativa. *Arch Dermatol Res*. 2020;312(4):255-262. doi:10.1007/s00403-019-02014-8
19. Blanc RS, Kallenbach JG, Bachman JF, Mitchell A, Paris ND, Chakkalakal JV. Inhibition of inflammatory CCR2 signaling promotes aged muscle regeneration and strength recovery after injury. *Nat Commun*. 2020;11(1):4167. doi:10.1038/s41467-020-17620-8
20. Muñoz B, Schobel SA, Lisboa FA, et al. Clinical risk factors and inflammatory biomarkers of post-traumatic acute kidney injury in combat patients. *Surgery*. 2020;168(4):662-670. doi:10.1016/j.surg.2020.04.064
21. Madrid M, Brianza-Padilla M, Echeverría JC, Rivera-González R, Bojalil R. The Severity of Neurological Dysfunction in Preschool Children, Secondary to Damage Generated During the Perinatal Period, is Associated With a Pro-Inflammatory Pattern of Serum Molecules. *Front Immunol*. 2021;11:595309. doi:10.3389/fimmu.2020.595309
22. Alquisiras-Burgos I, Peralta-Arrieta I, Alonso-Palomares LA, Zacapala-Gómez AE, Salmerón-Bárcenas EG, Aguilera P. Neurological Complications Associated with the Blood-Brain Barrier Damage Induced by the Inflammatory Response During SARS-CoV-2 Infection. *Mol Neurobiol*. 2021;58(2):520-535. doi:10.1007/s12035-020-02134-7
23. Zhao T, Zhang K, Zhang Y, et al. Do proinflammatory cytokines play a role in clozapine-associated glycometabolism disorders? *Psychopharmacology (Berl)*. 2021;238(7):1979-1990. doi:10.1007/s00213-021-05824-9
24. Welcome MO, Mastorakis NE. The taste of neuroinflammation: molecular mechanisms linking taste sensing to neuroinflammatory responses. *Pharmacol Res*. 2021;167:105557. doi:10.1016/j.phrs.2021.105557
25. Liba Z, Nohejlova H, Capek V, Krsek P, Sediva A, Kayserova J. Utility of chemokines CCL2, CXCL8, 10 and 13 and interleukin 6 in the pediatric cohort for the recognition of neuroinflammation and in the context of traditional cerebrospinal fluid neuroinflammatory biomarkers. *PLoS One*. 2019;14(7):e0219987. doi:10.1371/journal.pone.0219987