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Research Paper

Serum TLR2 and S100B in Substance Abuse: A Clinical Perspective

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ABSTRACT

Background: Substance abuse leads to blood-brain barrier dysfunction and activation of neuro-inflammatory pathways. However, the contribution of serum levels of Toll-like receptor 2 (TLR-2) and S100 calcium-binding protein B (S100B) to neuropsychological outcomes has not been clearly established. This study aims to explore the relationship between TLR-2 and S100B serum concentrations in individuals with substance abuse and their potential influence on neuropsychological results, specifically regarding the functioning of the frontal lobe.

Methods: This study involved 28 individuals who were diagnosed with substance abuse at Loghman Hakim Hospital's Toxicology Unit in 2022. Serum TLR-2 concentration and S100B levels, as neuroinflammatory markers, and the frontal assessment battery (FAB), as executive function markers, were measured.

Results: Substance abuse patients exhibited elevated levels of both TLR-2 and S100B. In drug addicts, a strong positive relationship was detected between serum levels of TLR-2 and S100B (r=0.742, P=0.0021) levels. Nevertheless, no significant relationship was found between FAB scores and serum concentrations of S100B and TLR-2.

Conclusion: This study reveals increased serum TLR-2 and S100B levels in individuals with substance abuse. However, these elevated levels did not appear to be associated with risk factors related to substance abuse or frontal lobe function.

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Introduction

Substance abuse refers to the detrimental or risky consumption of psychoactive substances, including alcohol and illegal drugs. This term covers the use of drugs in a manner that negatively impacts individuals and society, encompassing both physical and psychological addiction [1]. Physical dependence is a physiological adaptation to a substance, such as a drug or alcohol, typically marked by increased tolerance and the onset of withdrawal symptoms during extended periods without the substance. On the other hand, psychological dependence is the emotional need to consume a drug to enjoy its benefits or prevent the discomfort of its absence [2].

Drug abuse leads to enhanced permeability of the blood-brain barrier (BBB), resulting in a higher influx of peripheral toxins into the brain [3]. As a result, BBB dysfunction triggers the activation of neuroinflammatory pathways by elevating astroglial activity, subsequently leading to enhanced BBB permeability and increased vulnerability of the central nervous system (CNS) to foreign substances [4]. Toll-like receptors (TLRs) are pattern recognition receptors that play a crucial role in the innate immune response. This was achieved by identifying universally conserved molecular patterns that help in the early detection of pathogens [5]. TLRs found in the brain, especially those located on microglial cells, react to natural immune activators within the body, such as high-mobility group box 1 (HMGB1) and micro ribonucleic acid (miRNA). Various TLRs, HMGB1, and miRNAs are activated in the brain in response to stress, alcohol consumption, and abuse of other substances. The levels of these components are also elevated in the brains of patients with decreased alcohol consumption. Increased TLR-mediated immune signaling in the brain results in changes in epigenetic patterns, modifications to synaptic plasticity, and loss of neuronal populations. These processes contribute to cognitive and emotional dysfunctions [6]. Binge drinking during adolescence results in a lasting increase in the activation of innate immune danger signals (specifically, HMGB1/TLR) in the adult prefrontal cortex, which is associated with adult neurocognitive impairment [7].

In the TLR family, Toll-like receptor 2 (TLR-2) is pivotal in triggering glial cell activation and initiating neuroinflammatory responses. This underscores the significance of TLR-2 in the development of neurological disorders. TLR-2 has been identified as a novel factor contributing to CNS-related diseases, including multiple sclerosis (MS), Parkinson's disease, and Alzheimer's disease [8].

S100 calcium-binding protein B (S100B), a protein that binds calcium, is predominantly located in astrocytes within the nervous system. Its presence in bodily fluids is a dependable indicator of ongoing neural distress. Additionally, recent research suggests that S100B may serve as a damage-associated molecular pattern molecule, which, when present in high amounts, can initiate tissue responses to injury [9]. Individuals suffering from acute overdose of benzodiazepines exhibit elevated S100B levels [10]. Wedekind et al. investigated levels of S100B in patients with alcohol addiction. Their findings revealed a rapid decline throughout withdrawal treatment in alcoholism, which may be attributed to either a decrease in brain cell death or an increase in brain cell activity [11]. Furthermore, cannabis demonstrates neurotoxic effects, and elevated levels of S100B in the bloodstream may suggest neuronal damage in individuals with cannabis use disorder [12].

Many individuals with substance use disorders experience executive dysfunction, which is a prevalent problem. Studies have detected impairments in several cognitive areas, such as working memory, adaptability, decision-making, everyday life management, emotional control, and behavioral regulation [13]. The frontal assessment battery (FAB) was developed as a clinical assessment tool to quickly and conveniently evaluate frontal lobe impairments in diverse patients [14]. The FAB comprises six subtests, each designed to assess distinct facets of executive function thought to depend on the frontal cortex. These include conceptualization, cognitive adaptability, motor planning, interference management, inhibitory control, and environmental independence [15]. A neuroimaging study by Guedj et al. discovered a significant relationship between how well individuals performed the FAB task and blood flow in the brain's prefrontal cortex [16]. Individuals with substance dependence exhibited poorer performance on the FAB than the control group, and these FAB results were associated with performance on other tasks related to executive cognitive function [17]. However, the relationship between FAB and neuroinflammatory markers, especially substance abuse, has not been investigated.

This study aims to explore the possible correlation between blood levels of TLR-2 and S100B in patients with drug abuse, considering the type and duration of substance abuse. Furthermore, we aim to investigate the relationship between these biomarkers and frontal lobe function using a validated questionnaire.

Materials and Methods

Patients' recruitment and clinical evaluation

A descriptive correlational study was conducted at a university-affiliated referral toxicology center in Tehran City, Iran, with 28 participants referred for drug addiction.

Patients with a confirmed diagnosis of substance abuse, as determined by the clinical assessment, were enrolled. The study recorded the age, gender, and preexisting risk factors that could lead to suicide among patients, such as physical abuse, sexual abuse, family problems (e.g. divorce or disputes), academic failures, previous suicide attempts, and a family history of suicide. Additional clinical and demographic data were obtained from medical files. The exclusion criteria included individuals younger than 18 or older than 65 and individuals with concurrent neurological or medical disorders.

Childhood trauma questionnaire (CTQ)

CTQ is a widely recognized assessment tool consisting of 28 items created to gauge self-reported occurrences of childhood abuse and neglect. It has undergone thorough validation through psychometric evaluation [18].

FAB

FAB's reliability in Persian has been previously confirmed [19]. Each test question received a score between 0 and 3, leading to a total score between 0 and 18, indicating the level and seriousness of executive dysfunction. In this study, we assessed six elements of this evaluation: Similarities (evaluating conceptualization), lexical fluency (measuring mental flexibility), motor series "Luria" test (assessing programming ability), conflicting instructions (testing sensitivity to interference), Go-No-Go (evaluating inhibitory control), and pretension behavior (examining environmental autonomy).

The drug abuse screening test, 10-item version (DAST-10)

DAST-10 is a concise self-report questionnaire created to evaluate an individual's drug usage patterns and recognize potential issues associated with drug abuse [19]. Each query in the DAST-10 is answered with a simple "yes" or "no", and a point is assigned for every "yes" response. The cumulative score can vary between 0 and 10, with elevated scores indicating a greater likelihood of drug-related problems. Typically, suppose a person scores three or higher on the DAST-10. In that case, this suggests the need for further evaluation and assessment to determine if there are indications of substance abuse or dependence [20].

Blood collection and measurement of S100B and TLR-2 levels

Blood samples were collected from all patients within 24 h of admission, with each participant contributing five milliliters of venous blood. The blood samples were then centrifuged at 4000 ×g for 10 minutes at 4 ˚C. After centrifugation, the serum was separated immediately and stored in aliquots at -80 ˚C.

To measure serum S100B and TLR-2, we used a commercially available enzyme-linked immunosorbent assay (ELISA) kit from ZellBio GmbH (Ulm, Germany) following the manufacturer's instructions. This assay utilizes a biotin double antibody sandwich technology, and wavelengths of 450 nm were used to determine serum S100B and TLR-2 levels.

Statistical analysis

The study utilized the SPSS software, version 29, to conduct the analysis. The normal distribution of variables was assessed using the Kolmogorov-Smirnov test. Numerical variables are presented as Mean±SD, while categorical variables are expressed as frequencies and percentages. The relationship between serum biomarker concentrations and quantitative variables was evaluated using Spearman's correlation test. Significance was determined when $P<0.05$, following applying the Benjamini-Hochberg correction for multiple comparisons.

Results

As summarized in Table 1, the case group included 28 patients with drug addiction, 18 men and 10 women, with a mean age of 37.75±13.94 years. Among the 28 patients with drug addiction, 20(71.4%) consumed alcohol, and 18(64.3%) consumed tobacco (Table 1). Amphetamine, benzodiazepine, multidrug, and other drugs (lithium, organophosphorus, fluvoxamine, depakin) were used in five cases, accounting for 17.9% of total cases. Methadone and tramadol were used in four cases each, accounting for 14.3%.

Table 1. Clinical and demographic features of the study population (n=28)

Variables	Category	Mean±SD/No. (%)
Age (y)		37.75±13.94
Sex	Male	18(64.3)
	Female	10(35.7)
Education level	Elementary school	10(35.7)
	Diploma	12(42.9)
	Bachelor	6(21.4)
History of head trauma		5(17.9)
History of epilepsy		2(7.1)
Physical abuse		15(53.6)
Sexual abuse		7(25)
Dysfunctional family		21(75)
Academic failure		14(50)
Psychiatric problem in family		9(32.1)
History of suicide attempt		10(35.7)
Suicide in family		4(14.3)
Marital status		11(39.3)
Current employment		10(35.7)
Alcohol use		20(71.4)
Tobacco use		18(64.3)

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Table 2. The mean of neuropsychological task and biomarkers

Variables	Mean±SD
CTQ	43.92±9.81
FAB	12.71±3.08
DAST-10	5.46±2.45
TLR-2 (ng/mL)	10.37±1.44
S100B (ng/L)	75.54±13.37

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Abbreviations: CTQ: Childhood trauma questionnaire; FAB: Frontal assessment battery; DAST-10: Drug abuse screening test-10; TLR-2: Toll-like receptor 2; S100B: S100 calcium-binding protein B.

Table 3. Correlation between biomarkers and neuropsychological task

Variables	TLR-2		S100B	
	r	P*	r	P*
CTQ	0.3	0.2	0.3	0.1
FAB	0.1	0.7	0.1	0.6
DAST-10	0.05	0.7	0.06	0.8

*P adjusted with Benjamin–Hochberg.

Abbreviations: CTQ: Childhood trauma questionnaire; FAB: Frontal assessment battery; DAST-10: Drug abuse screening test-10;TLR-2: Toll-like receptor 2; S100B: S100 calcium-binding protein B.

The mean CTQ was 43.92±9.81, FAB was 12.71±3.08, and DAST-10 was 5.46±2.45. Serum S100B and TLR-2 concentrations were 75.54±13.37 ng/L and 10.37±1.44, respectively (Table 2). The relationship between serum TLR-2 levels and S100-B levels in individuals with drug addiction was statistically significant (r=0.765, P=0.001) (Figure 1). No normal distribution was observed between the variables; therefore, we applied the Spearman correlation. Our results showed no significant correlation between CTQ, FAB, and DAST10 and serum S100B and TLR-2 (Table 3).

Discussion

Substance abuse involves the overconsumption of substances that trigger the brain's reward system, resulting in the strengthening of certain behaviors. The the diagnostic and statistical manual of mental disorders, fifth edition (DSM-5), classifies various types of drugs into ten categories: Alcohol, caffeine, cannabis, hallucinogens, inhalants, opioids, sedatives, hypnotics, anxiolytics, stimulants, tobacco, and other substances [21].

S100B protein found in serum has been proposed as a reliable indicator of neuronal damage in the brain, making it a potential diagnostic tool for a range of neurological conditions, such as Alzheimer's disease, Parkinson's disease, MS, schizophrenia, and epilepsy [22]. Du et al. investigated the presence of S100B in protoplasmic astrocytes and myelinating oligodendrocytes during CNS development. They highlighted the possibility of using S100B as an alternative indicator of neurological conditions and their involvement in disease progression [23].

Our results showed increased levels of S100B and TLR-2 in drug abuse patients compared to those measured in previous studies in normal subjects [24, 25]. However, no significant correlation was found between serum S100B levels and risk factors associated with drug addiction. Furthermore, no significant correlation was observed regarding frontal lobe function as measured by the FAB questionnaire.

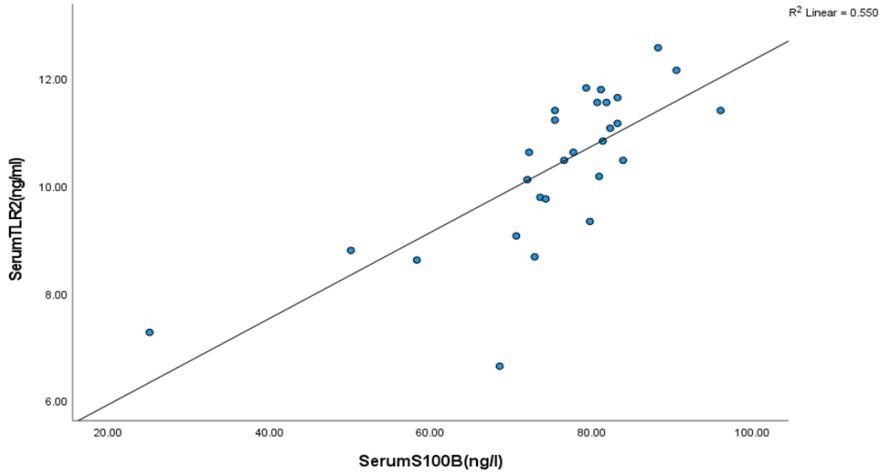

Figure 1. Correlation of serum S100B and TLR-2 levels in individual with drug addiction

S100B: S100 calcium-binding protein B; TLR-2: Toll-like receptor 2.

Consistent with our results, Liappas et al. found that S100B protein levels vary in alcohol-dependent individuals based on alcohol consumption [3]. Nonetheless, Bayazıt et al. discovered elevated S100B protein levels in individuals with cannabis use disorders, suggesting the possibility of harm to neurons [12]. Wedekind et al. observed a decline in S100B levels in female patients during alcohol withdrawal [11].

Based on our results regarding TLR-2 serum levels, no significant correlation was found between drug abuse-related risk factors and frontal lobe assessment. Furthermore, our results suggested a positive correlation between serum TLR-2 levels and S100-B levels in individuals with substance addiction. However, studies of TLR-2 in drug abuse are limited. Yi Li et al. conducted a survey of an animal model. They found that chronic treatment with morphine in primary neurons notably elevated the expression of TLR-2, as evidenced at both the messenger RNA and protein levels. They also suggested that inhibiting TLR-2 could prevent damage to neurons caused by opioids [2].

Our results showed no correlation between drug abuse risk factors or neuronal biomarkers and frontal lobe function, as measured by FAB. According to previous studies, substance-dependent individuals (SDI) exhibit neurocognitive dysfunction in executive domains related to frontal lobe function. Verdejo-García et al. examined the self-awareness of cognitive deficits in abstinent individuals and found poor awareness of deficits during drug abuse, potentially indicating frontostriatal involvement [2]. Moreover, Cunha et al., by using FAB in drug-dependent patients, found that SDI performed poorly on the FAB in abstract reasoning, motor programming, and cognitive flexibility [17]. Collectively, these results suggest that substance abuse is associated with frontal cognitive impairments. The small sample size in our study may explain the absence of a correlation between FAB and the measured variables.

Conclusion

These results reveal elevated levels of TLR-2 and S100B in individuals with substance abuse. A significant correlation has been observed between TLR-2 and S100B levels in patients with drug addiction. However, no significant correlations were observed between these biomarkers and risk factors related to substance abuse or frontal lobe function assessed by the FAB. While these results shed light on the potential neuroinflammatory involvement in substance abuse, further research with larger sample sizes and control groups is warranted to validate the utility of these biomarkers in this context.

Limitations

Our research encountered various limitations, such as a limited sample size resulting from a shortage of available ELISA kits and the absence of a control group. Moreover, we assessed only frontal lobe function using a questionnaire. It is advisable to conduct extensive multicenter research in the future to validate our findings and assess the practical applicability of neuronal biomarkers in individuals suffering from drug abuse. Additionally, a case-control study using more specific tools, such as functional and volumetric imaging, was conducted to evaluate frontal lobe function.

Ethical Considerations

Compliance with ethical guidelines

This study was approved by the Ethics Committee of the Shahid Beheshti University, Tehran, Iran (Code: IR.SBMU.RETECH.REC.1401.165). All ethical principles are considered in this article. The participants were informed of the purpose of the research and its implementation stages. They were also assured about the confidentiality of their information and were free to leave the study whenever they wished, and if desired, the research results would be available to them. A written consent has been obtained from the subjects. Principles of the Helsinki Convention was also observed.

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Authors' contributions

Conceptualization and methodology: Babak Mostafazadeh, Shahin Shadnia, Mahtab Ramezani, and Peyamn Erfantalab Evini; Data collection and writing the original draft: Faezeh Maghsudloo; Illustrations: Mitra Rahimi; Analytic calculations and numerical simulations: Leila Simani; Data acquisition: Somayeh Monjazeb and Fatemeh Abbaszadeh; Supervision: Hossein Pakdaman; Review, editing, and final approval: All authors.

Conflict of interest

The authors declared no conflict of interest.

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