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Level of S100B protein, neuron specific enolase, orexin A, adiponectin and insulin-like growth factor in serum of pediatric patients suffering from sleep disorders with or without epilepsy

Marek Kaciński[1], Bogusława Budziszewska[2], Władysław Lasoń[2], Anna Zając[1], Barbara Skowronek-Bała[1], Monika Leśkiewicz[2], Alicja Kubik[1], Agnieszka Basta-Kaim[2]

[1]Chair of Pediatric and Adolescent Neurology, Jagiellonian University, Medical College, Wielicka 265, PL 30-663 Kraków, Poland

[2]Department of Experimental Neuroendocrinology, Institute of Pharmacology, Polish Academy of Sciences, Smętna 12, PL 31-343 Kraków, Poland

Correspondence: Bogusława Budziszewska, e-mail: budzisz@if-pan.krakow.pl

Abstract:
Background: Paroxysmal sleep disorders in children are important from both pathophysiological and clinical point of view. Correct diagnosis is crucial for further management. The aim of the present study was to identify peripheral markers of paroxysmal sleep disorders in children, which could improve diagnostics of these disorders. We compared serum levels of several putative biomarkers of neurological disorders, such as S100B protein, neuron specific enolase (NSE), orexin A, adiponectin, and insulin-like growth factor 1 (IGF-1) in pediatric patients suffering from sleep disturbances with those who additionally to parasomnia revealed also epilepsy.
Methods: Fifty six children from 1 month to 18 years of age hospitalized in the Pediatric Neurology Clinic, Chair of Children and Adolescent Neurology, participated in this study. Polysomnographic diagnostics was indicated due to sleep disturbances. Examination was performed with the use of polysomnography and videoelectroencephalography Grass device. Blood samples were taken before registration of sleep, after 2.5 h of sleep or 0.5 h after occurrence of clinical seizures. Concentrations of S100B protein, NSE, orexin A, adiponectin, and IGF-1 were measured by specific ELISA methods.
Results: The obtained data showed that serum S100B level was significantly increased in children with epilepsy and clinical seizure attacks as compared to patients with parasomnia only. A tendency to enhanced serum S100B level was also seen in epileptic children without clinical seizures during polysomnographic recording. The level of orexin A was significantly decreased in epileptic children without seizures as compared to the hormone level in parasomnic patients, but was elevated in patients who experienced seizures during polysomnographic examination. As S100B is regarded to be a marker of blood brain barrier leakage and astrocyte damage, the data suggest an increase in BBB permeability in epileptic children, especially during seizure fits. Furthermore, the enhanced S100B serum level without changes in NSE activity may be interpreted rather as an evidence of the elevated secretion of this protein during seizures than of the damage of brain tissue. In contrast to S100B and orexin A level, serum concentration of adiponectin and IGF-1 as well as NSE activity did not significantly differ between the studied groups.
Conclusion: Out of the five putative biomarkers measured, blood concentration of S100B and orexin A may be helpful in differentiating parasomnic pediatric patients with and without epilepsy.

Key words:
parasomnias, epilepsy, polysomnography, S100B protein, neuron specific enolase, orexin A, adiponectin, insulin-like growth factor 1

Introduction

Sleep disorders in children occur frequently and are characterized by complex symptomatology and only partially unraveled etiopathogenesis [19]. Also diagnosis and rational therapy of these disorders constitutes to be a major problem for clinicians. Parasomnia in children may be reflected by such symptoms as late falling asleep, sleep fragmentation associated with the occurrence of moon walking, teeth chattering, excessive daytime sleepiness, talking when sleeping, night anxiety. Some parasomnias, like obstructive sleep apnea-hypopnea syndrome (OSAHS), a sleep disorder caused by respiratory disturbance during sleep are life-threatening conditions. Recurrent sleep disturbances persistently occur in various sleep phases (REM, non-REM). Furthermore, almost 30% of epileptic attacks in children are connected with sleep, and apnea is one of many epileptic symptoms [10]. Therefore, the proper diagnosis and differentiation of epilepsy from sleep disturbances unconnected with seizure phenomena is of pivotal significance for efficient pharmacotherapy [17]. Polysomnographic monitoring allows for diagnosis of epileptic attacks occurring during sleep, parasomnia and some sleep disturbances evoked by causes beyond the nervous system e.g., of respiratory, ENT (ear-nose-throat) and gastric origins [7, 32]. However, limited availability of polysomnography, its high costs and time consuming procedure encourage to seek biochemical serum markers for initial diagnosis of the patients. Our earlier attempts to find specific and sensitive markers of sleep disturbances of different etiology (cytokines, ICAM-I, cortisol and DHEA) failed to bring satisfactory results [13–15]. The lack of sufficient knowledge of pathophysiology of sleep disorders and involvement of specific neurotransmitters, hormones and neuropeptides and cytokines in sleep modulation do not help to solve this problem. Of many biochemical endogenous agents which may reflect malfunctioning of the central nervous system, the serum levels of S100B protein and neuron specific enolase deserve special attention, since some data suggest that neurodegenerative processes may aggravate some sleep disorders [12]. The S100B is a calcium binding protein, which at low nanomolar concentrations stimulates neurite growth and promotes neuronal survival, whereas at higher concentration can induce apoptosis. Because this protein occurs mainly in astrocytes, its elevated concentration in CSF or serum is regarded as a marker of astrocyte damage [27]. On the other hand, neuronal enolase, a glycolytic enzyme, is considered to be a specific biomarker of neuronal injury. The studies on measurement of serum concentrations of S100B and neuron specific enolase (NSE) in patients with OSHAS, but not in other sleep disorders yielded unequivocal results [3, 12]. Moreover, some data showed that epileptic seizures increased S100B concentration and NSE activity, thus one can expect that these proteins can differentiate sleep disorders with and without accompanying epilepsy [20, 24, 25].

Orexins are highly expressed in the lateral hypothalamus and orexin-containing neurons projecting to the brain structures critically involved in the regulation of sleep, food and water intake, sleep and wakefulness and cognitive behaviors. It is well-established that dysfunction of orexin system is associated with pathomechanism of narcolepsy and possibly with other sleep disturbances [5]. Importantly, Sakurai et al. [28] found that orexin A concentrations were significantly lower in patients with OSAHS. Orexins are also engaged in the regulation of neuronal excitability and seizures, although the reports on these effects are controversial. Some authors reported that intracortical injection of orexin A or orexin B induced epileptic seizures in rats [9]. Moreover, intracortical orexin injection enhanced the hyperexcitable and hypersynchronic cortical epileptic activity induced by focal application of penicillin-G [18]. In contrast, Doreulee et al. [6] showed that orexin-A decreased duration/amplitude of multiple discharges of pop-spikes and inhibited spontaneous epileptiform afterdischarges induced by bicuculline methiodide in CA1 in rat hippocampal slices. As far as clinical studies are concerned, the decreased cerebrospinal fluid orexin A in patients after repetitive generalized tonic-clonic seizures was reported and significance of this effect in postseizure somnolence was postulated [26]. Additionally, since metabolic disturbances are frequently connected with sleep and epileptic disorders, apart from orexins, also other regulators of metabolic processes, e.g., adiponectin and insulin-like growth factor 1 (IGF-1) deserve attention. In OSAHS patients, the serum adiponectin and IGF-1 levels were found to be lower than in healthy control subjects [21, 33]. Therefore, the aim of the present study was to compare serum levels of the abovementioned putative biomarkers of neurological disorders i.e., S100B protein, NSE, orexin A, adiponectin and IGF-1 in pediatric patients suffering from sleep disturbances with those who additionally to parasomnia revealed also epilepsy.

Materials and Methods

Fifty six children with sleep disorders hospitalized in the Pediatric Neurology Clinic, Chair of Children and Adolescent Neurology in the years 2009–2011 were enrolled into the study. Patients were in the age ranging from 1 month to 18 years. Polysomnographic examination was performed with the use of polysomnography and videoelectroencephalography Grass device in the Clinical Electrophysiology Laboratory of the Chair of Children and Adolescent Neurology. The examination comprised simultaneous recording of digital EEG tracing, child behavior during sleep, respiratory and cardiologic parameters, oculomotor muscular activity. Based on these recordings, an objective diagnosis of sleep disorders and sleep phases (REM, NREM) can be made. Intravenous access was established in every child in case sleep disorders occurred and pharmacological treatment was needed. Blood samples for biochemical analysis were taken after parental consent was given. The first sample was taken before registration of sleep, the second after 2.5 h of sleep or 0.5 h after occurrence of clinical seizures during sleep.

Evaluation of orexin level was performed in 49 children with paroxysmal sleep disorders, including 14 children with parasomnias, 25 with epilepsy and 10 with clinical epileptic seizures recorded during sleep. Enolase, S100B protein, adiponectin, and NGF-1 were evaluated in 56 children, including 16 with parasomnias, 29 with epilepsy and 11 with recorded clinical epileptic seizures.

Plasma levels of S100B, NSE, orexin A, adiponectin and IGF-1 were measured using a commercial enzyme-linked immunoassay kits and each assay was carried out in duplicate. S100B level was determined using sandwich ELISA (Human S100B ELISA kit, Bio-Vendor Research and Diagnostic Products, RD192090 100R), neuron specific enolase by NSE ELISA kit (Demeditec Diagnostics GmbH, DE2353), adiponectin by Human Adiponectin ELISA kit (BioVendor Research and Diagnostic Products, RD195023100) and insulin-like growth factor 1 by IGF-1 ELISA kit (Demeditec Diagnostics GmbH, DE4140). The minimal measurable concentrations for these detection systems are 15 pg/ml for S100B, 1 μg/l for NSE, 0.1 μg/ml for adiponectin and 1.29 ng/ml for IGF-1. Plasma orexin A was measured using enzyme immunoassay kit (Phoenix Pharmaceuticals Inc., California, USA, EK-003-30) after the extraction by Sep-Pak C18 cartridges, according to the manufacturer's instruction. Sensitivity of orexin A assay was 0.01 ng/ml.

Statistical analysis

The data are presented as the mean ± SEM. The significance of differences between the means was evaluated by the Duncan's test following a one-way analysis of variance.

Results

The ELISA study showed that S100B serum level was significantly increased in children with epilepsy and clinical seizure attacks as compared to that in patients

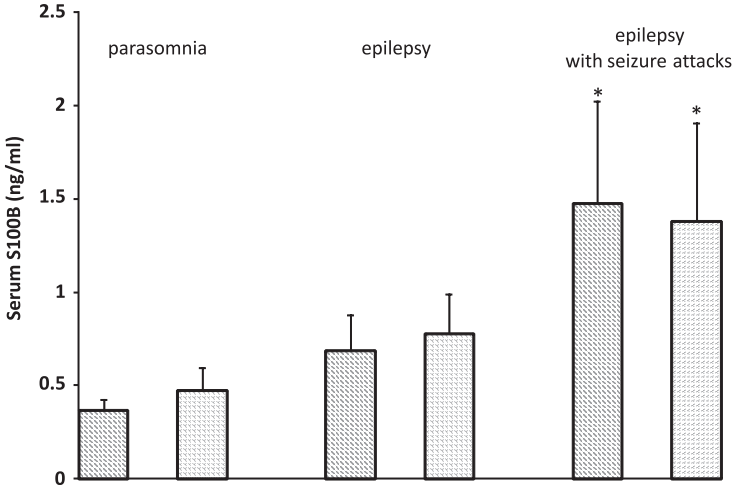

Fig. 1. Serum level of S100B in patients with parasomnia, epilepsy and epilepsy with seizure attacks during polysomnographic recording. Blood samples were taken before (first, lined bar) and after polysomnographic recording or 30 min after seizure episode (second, squared bar); * $p < 0.05$ *vs.* parasomnia group

Tab. 1. Serum level of neuronal specific enolase (NSE), adiponectin and insulin-like growth factor (IGF-1) in patients with parasomnia, epilepsy and epilepsy with seizure attacks during polysomnographic recording. Blood samples were taken before and after polysomnographic recording or 30 min after seizure episode

	NSE		Adiponectin		IGF-1	
	Before polysomnographic recording	After polysomnographic recording	Before polysomnographic recording	After polysomnographic recording	Before polysomnographic recording	After polysomnographic recording
Parasomnia	47.05 ± 12.47	49.81 ± 12.27	20.62 ± 1.93	21.9 ± 2.35	158.14 ± 18.12	171.5 ± 26.84
Epilepsy	34.68 ± 7.56	32.51 ± 6.56	18.44 ± 2.04	18.73 ± 2.39	154.96 ± 17.22	164.51 ± 20.70
Epilepsy with seizure attacks	24.71 ± 7.68	20.71 ± 8.54	20.12 ± 2.82	22.06 ± 2.18	165.58 ± 28.25	128.67 ± 21.79

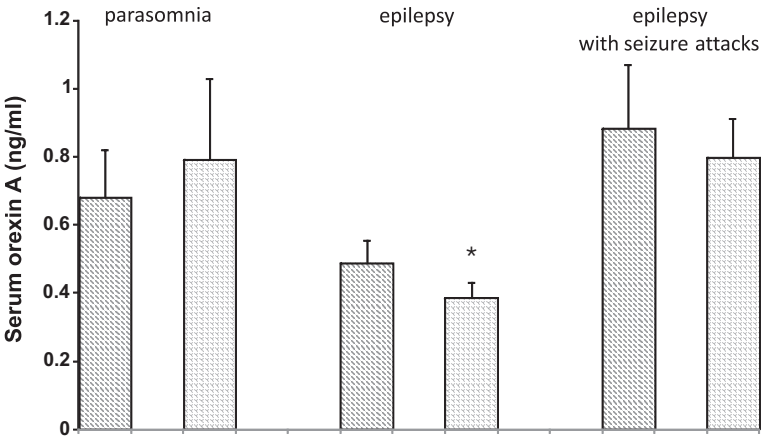

Fig. 2. Serum level of orexin A in patients with parasomnia, epilepsy and epilepsy with seizure attacks during polysomnographic recording. Blood samples were taken before (first, lined bar) and after polysomnographic recording or 30 min after seizure episode (second, squared bar); * $p < 0.05$ *vs.* groups with parasomnia and epilepsy with seizure attacks

with parasomnia only (Fig. 1). The increase in S100B level could be observed before and after polysomnographic recordings. A tendency to enhanced serum S100B level was also seen in epileptic children without clinical seizures in blood samples collected before and after polysomnographic recording, but these effects did not reach statistical significance. The measurement of NSE serum level, a marker of neuronal injury, did not reveal any significant differences between the studied group of patients, independently of the time of blood collection (Tab. 1). The serum level of orexin A was significantly decreased in epileptic children without seizures as compared to the hormone level in parasomnic patients, but was elevated in patients who experienced seizures during polysomnographic examination (Fig. 2). However, significant effects were found only in blood samples collected after, but not before polysomnographic recording or a seizure attack. The serum concentration of adiponectin and IGF-1 did not significantly differ between the studied groups (Tab. 1).

Discussion

This study attempted to find a useful serum biomarker for screening diagnosis of children with sleep disturbances with or without epilepsy. The measurement of five endogenous substances apparently involved in

sleep regulation and other functions of the central nervous system was conducted in pediatric patients admitted to the clinic because of paroxysmal sleep disorders. For bioethical reasons it was not possible to enroll into this study also healthy children as a control group, and this fact limits interpretation of the obtained results. Nevertheless, we found that there were significant differences between the groups in 2 of 5 measured potential biomarkers. The most important result of this study was demonstration that the serum level of S100B protein was elevated in epileptic patients which experienced a seizure attack during polysomnographic recordings in comparison to those children with parasomnia only. S100B protein is expressed mainly in astrocytes, and to a lesser extent in oligodendrocytes and ependyma. Elevated serum or CSF level of this protein is often observed in patients with traumatic brain injury, hemorrhagic and ischemic stroke, but also in psychiatric diseases, e.g., schizophrenia and major depression [29, 31]. A higher S100B serum level in stroke or in chronic neurodegenerative diseases, e.g., Alzheimer's disease is regarded as a marker of glia cell damage, but in these conditions also elevated NSE level, a marker of neuronal injury can be observed [4, 22, 30]. In contrast to brain damage, in schizophrenia or depression one can observe only increase in S100B, but not in neuronal enolase. This is interpreted as the increased secretion of this protein rather than an indication of neuronal damage and can be associated with acute phase of these psychiatric diseases. The question arises regarding functional significance of the changes in S100B serum concentration. In relation to this, the preclinical study showed enhanced epileptogenesis in S100B knockout mice [8]. Therefore, the elevated S100B level can be an adaptive response, which prevents development of susceptibility to seizures. However, such mechanism may be connected only with some particular kinds of epilepsy. Indeed, negative results were reported with regard to the changes in serum S100B level in children with febrile seizures. Thus, simple febrile seizures were not associated with an elevation in serum S100B levels [2]. Also Mikkonen et al. [23] found that S100B concentrations was not predictive of the clinical severity of the febrile seizures or their recurrence. Regarding alterations of S100B concentrations in sleep disorders, Braga et al. [3] observed that serum S100B level was higher in OSAHS patients than in the control group, whereas serum NSE was similar in both groups. An indirect evidence for S100B involvement in sleep regulation was provided by Iskesen et al. [11], who found that patients with elevated S100B values had more sleep disturbances after cardiac surgery than patients with normal S100B values. In the present study, the increased serum S100B level without simultaneous elevation in NSE may reflect a higher permeability of blood-brain barrier (BBB) in the pediatric patients in periods preceding or following the seizure attack. It is a matter of debate whether S100B can be perceived as a good marker of BBB integrity or whether it may easily cross the barrier [29]. Thus, it is difficult to state if elevated serum S100B level reflects an increase in its synthesis/release or merely changes in the BBB permeability. In favor of the latter interpretation is the observation of an increased serum orexin A level in patients with epileptic attacks, despite that in patients with epilepsy but without seizures recorded during polysomnography the level of this hormone was decreased. Such increase in BBB permeability may explain the increase in the concentration of the hypothalamic neuropeptide, orexin A in serum during epileptic seizures. This peptide, besides its role in sleep regulation, was shown to inhibit epileptic activity. Therefore, a lower concentration of the peptide in children with epilepsy may contribute to their higher susceptibility to seizure occurrence. One can assume that if the release of orexin A and S100B during seizures is associated with enhanced synthesis of these proteins in the brain, this may indicate that it is a part of endogenous neuroprotective/anticonvulsant system. Other authors found that the orexin level in CSF of patients after repetitive generalized tonic-clonic seizures was decreased and postulated that this effect might be engaged in the mechanism of somnolence after seizures [26]. It has been found that destruction of orexin-producing neurons results in narcolepsy, and this finding stirred interest in the role of this hormone in sleep pathophysiology. The elevated blood level of orexin A was proposed to be a biological marker of the severity of OSAHS in children [1]. In contrast, Sakurai et al. [28] reported that plasma orexin A concentration was lower in adult patients with OSAHS. Because in our study no healthy control group was enrolled, it is not possible to draw a firm conclusion whether the level of this hormone is changed in children with sleep disorders. Sleep disturbances are often associated with metabolic disorders, especially it was noted that the decreased sleep duration can lead to the increased prevalence of obesity

and diabetes [16]. Adiponectin and IGF-1 are known to be involved not only in metabolic processes, but also in sleep regulation and pathomechanism of seizures. Therefore, serum levels of adiponectin and IGF-1 were also measured in the present study. We did not observe any differences in the adiponectin and IGF-1 levels in any of the groups studied, which could be due to the lack of overweight patients in our study group. Other authors found decrease in both of these hormone plasma levels in OSAHS patients [21, 33]. It should be mentioned here that OSAHS is associated with more serious hypoxia-related changes in the brain than milder forms of sleep disorders.

In summary, the analysis of serum levels of S100B protein, NSE, orexin A, adiponectin, and IGF-1 revealed that measurement of blood S100B and orexin A concentrations may be helpful in differentiating parasomnic pediatric patients with and without epilepsy.

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