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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

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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.