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Sleep disorders in children with cerebral palsy

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Recent studies on children with cerebral palsy indicate that this population is at a higher risk of sleep disorders. Although sleep dysfunction seems to be frequent in cerebral palsy, there are few studies assessing sleep dysfunction and its risk in children. Also, the prevalence of sleep apnea has not been formally assessed in children with cerebral palsy. Risk factors for sleep dysfunction include comorbid epilepsy, mental retardation, visual impairment and degree of functional motor impairment. Contractures and spasticity can adversely contribute to positioning during sleep. We analyzed motor, cognitive and functional impairment, as well as the existence of comorbidity and results of brain imaging and electroencephalography in 21 children with cerebral palsy and correlated them with the presence of sleep disorders. Sleep disorder was evaluated by electroencephalography/polysomnography. About 57% of children in our study had sleep disorders. The most common motor impairment was spastic diplegia. Most children had periventricular hyperintensities and cortical atrophy on neuroimaging. Difficulty in initiating and maintaining sleep (microarousals), fragmented sleep, and sleep breathing disorders were frequently identified problems and were evaluated by polysomnography. Children with abnormal electroencephalography had more sleep disturbances than those with normal electroencephalography. Disorders of initiation and maintenance of sleep were more frequent in children with spastic quadriplegia. It is known that the consequences of sleep disorders in children affect both the child and the family. Prospective studies in a larger sample and proper methodology are needed to determine whether improvement in sleep quality of children with cerebral palsy leads to improvement in their life quality.

Keywords: cerebral palsy; sleep disorders; sleep apnea syndromes; epilepsy

INTRODUCTION

Cerebral palsy (CP) is a static neurodevelopmental disorder featured by motor dysfunction with or without associated encephalopathy. It affects 2 to 2.5/1000 live births (1). It is the result of perinatal asphyxia and hypoxic ischemic encephalopathy or intraventricular hemorrhage during the perinatal period. Subsequent periventricular white matter damage may culminate in periventricular leukomalacia. The location of brain injury predicts the type of motor symptoms: injury in the periventricular white matter results in spasticity, injury of the basal ganglia results in extrapyramidal symptoms (athetosis, dystonia), and involvement of cerebellum results in hypotonia and/or ataxia. In addition, any child with CP may have intellectual disorders, sensitive, visual and hearing, which added to the motor changes, may have repercussions in different ways in their function (2-5).

Classification of cerebral palsy

In 1998, a collaborative European network of cerebral palsy registers and surveys was formed. The aim of this network entitled Surveillance of Cerebral Palsy in Europe (SCPE) was to develop a central database of children with CP in order to monitor trends in birth weight specific rates, to provide information for service planning, and to provide a framework for collaborative research. For epidemiological purposes,

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classification systems of CP based on clinical findings were most widely used. Although there is no entirely satisfactory classification that takes into account the etiology, clinical features and extent of functional disability, there is continuing development and modifications of CP classifications; revised definitions and classification of cerebral palsy were proposed in 2005 (6, 7) and 2007 (8).

Sleep in humans and functional neuroanatomy

Sleep affects many processes in the body including immune system function, energy metabolism, learning, memory, appetite regulation and gene expression (9-14). *Gais et al*. suggest that sleep enhances creativity by facilitating mental restructuring that is critical to insight (15). Regulation of the sleep-waking cycle is complex (16-19). The ascending arousal system includes multiple ascending projections from the brainstem, hypothalamus, thalamus and basal forebrain with interplay among neurotransmitter systems to maintain the waking state (16-19). Beside wakefulness-promoting actions of acetylcholine, dopamine and norepinephrine, recent studies indicate that serotonin, histamine and orexin (also called hypocretin, in the lateral hypothalamic area) also promote wakefulness. Sleep-promoting regions in the anterior hypothalamus utilize the GABA and galanin to inhibit wake-promoting regions in the hypothalamus and brainstem during slow wave sleep. Brainstem regions inhibited during wakefulness and NREM sleep become active during REM sleep. Ascending projections from cholinergic neurons in the brainstem (laterodorsal tegmental and pendunculopontine areas) activate the thalamus, which activates the cortex. Descending projections from this area inhibit motor neurons, producing atonia. Further complexity has been introduced by the recognition of somnogens (sleep-promoting substances) that accumulate during wakefulness. Synthesis of adenosine (which appears to directly inhibit wake-promoting neurons) increases during periods of high metabolic demand (e.g., seizures, ischemia). Information on how circadian rhythms are generated at molecular level comes mainly from studies in mice. The mechanism depends on controlled coexpression of specific clock genes, the Period (Per1, Per2 and Per3) and the Cryptochrome (Cry1 and Cry2) genes. The protein products of all these oscillate over the 24-hour cycle by inhibiting their own promoters operating in an intricate negative feedback loop. Permanently attached to these promoters is a heterodimer of two transcriptional activator proteins, CLOCK and BMAL1 (20).

Sleep in children with cerebral palsy

Sleep abnormalities are frequently associated with both primary psychiatric disorders and traumatic brain injuries. Recent studies on children with CP indicate that this population is at a higher risk of sleep disorders. Although sleep dysfunction seems to be frequent in CP, there are few studies assessing sleep dysfunction and its risk in children (21). Also, the prevalence of sleep apnea has not been formally assessed in children with CP. Functional impairment seems to correlate with the number and severity of reported sleep disorders in children with CP. Risk factors for sleep dysfunction include comorbid epilepsy, mental retardation, visual impairment and degree of functional motor impairment. Visual impairment because of abnormal light perception affects the retinohypothalamic tract and the ability to adequately respond to the circadian influence of dark-light cycle. Sleep disorders are occurring in about 50% of children with CP and visual impairment (22, 23). These children offen have fragmented sleep and frequent nocturnal awakenings. Difficulty in initiating and maintaining sleep, sleep-wake transition, and sleep breathing disorders are the most frequently identified problems. Contractures and spasticity can adversely contribute to positioning during sleep. Sleep related breathing disturbances consist of obstructive sleep apnea and include irritability, habitual snoring, increased nocturnal awakenings, mouth breathing, opistotonic posturing and obstructive apnea. A component of central apnea may coexist. There is also the risk of sleep related hypoventilation due to scoliosis and restricted lung volumes. Bulbar involvement contributes to the crowding of oropharynx and arching of the palate further increasing the risk of sleep disturbed breathing. The findings in these children may include nocturnal and diurnal hypoxia and hypercarbia. Hypercarbia is caused by decreased minute ventilation (alveolar volume/respiratory rate) due to the issues in CP such as central hypotonia, kyphoscoliosis, craniofacial anomalies, swallowing dysfunction, gastroesophageal reflux disease (GERD), muscle relaxant medications, poor cough, chronic lung infections, bronchiectasis, tracheostomy with chronic colonization, medications that suppress respiratory drive, and other medical problems such as asthma or seizures.

It is essential to be timely aware of the sleep disorder in the child with CP. At outpatient visits or during hospitalization, some routine questions about sleeping habits of the child with CP should always be part of the interview. Sleep logs and actigraphy are helpful in a child with circadian rhythm abnormalities. Although it is not always available in daily practice, overnight polysomnography is the most useful tool for diagnosing sleep disorders and for further follow up of the management and therapy applied. Instead of overnight polysomnography, prolonged video electroencephalography (EEG) in sleep can also provide useful information on the child's sleep.

Nonpharmacological interventions for sleep disorders in CP usually include feeding regimen modification, optimizing control of secretions, asthma, GERD, repositioning, chest physiotherapy, cough assist in middle of the night, positive airway pressure, slowed nocturnal feeds, in smaller and more frequent boluses. So far, pharmacological therapy for sleep disorders in children with CP has included different types of medications, e.g., melatonin, chloral hydrate, barbiturates, benzodiazepines, non-benzodiazepine hypnotics, tricyclic antidepressants, neuroleptics, antiepileptics (gabapentin, pregabalin, tiagabin), and herbal medicine (24).

PATIENTS AND METHODS

We retrospectively analyzed data on 21 children with CP at our Children's Hospital during one-year period (December 2011 to November 2012). All children had at least one EEG in sleep recorded (EEG during natural sleep, EEG after sleep deprivation or overnight polysomnography). In all children, the type of motor dysfunction was described. The existence of visual dysfunction, mental retardation, epilepsy or other comorbidity was evaluated. Besides EEG findings, computed tomography (CT) or magnetic resonance imaging (MRI) of the brain and other findings relevant to the diagnosis of CP and its classification were collected. The presence, type and severity of sleep disorders were evaluated by EEG/polysomnography using video monitoring, while the possibility of existing sleeping issues was collected retrospectively from non-validated pediatric sleep questionnaire in our Unit for Sleep Disorders in Children. Results of our sleep questionnaire and its validation were not the subject of interest of this study and are not shown here. Overnight polysomnography included EEG (6 channels or more), left and right electrooculography, nasal thermistor, snoring detector, chin and leg electromyography (EMG), electrocardiography (ECG), thoracic and abdominal plethysmography, pulse oximetry, and video/audio monitoring.

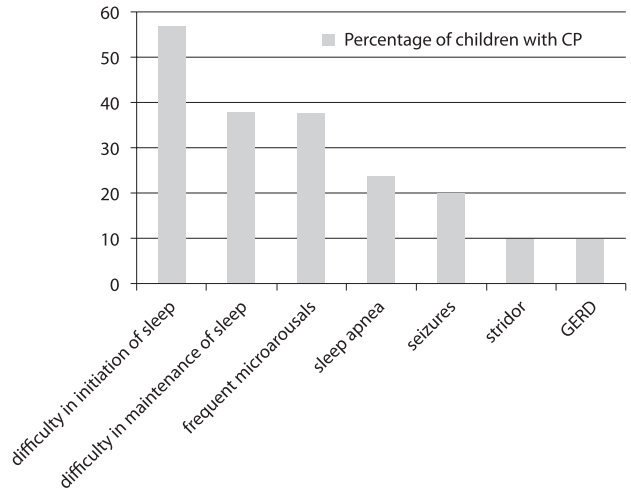
Statistical analysis in this study included the probability (p) with the level of confidence set at $p<0.05$. Numeric values were expressed as absolute values and percentages. Due to the small study sample, statistical significance of differences between children with and without epilepsy, with and without normal EEG, with and without visual disturbances, and the variable of sleep disorder was analyzed by Fisher exact test.

RESULTS

The study population included 21 children with CP: 15 (71%) male and 6 (29%) female, mean age 8.52 (SD 4.42, range 2.0-8.0) years. Selected clinical characteristics and findings of 21 patients with CP are shown in Table 1.

The most common motor impairment was spastic diplegia: 12/21 children had spastic diplegia, 7/21 had spastic quadriplegia and 2/21 had hemiplegia. Gross Motor Function Classification System Level I was appropriate for 6 children, Level II for 6 children, Level III for 2 children, Level IV for 2 children and Level V for 5 children. Out of 21 children, 11 (52%) had epilepsy and 10 (48%) had some degree of mental retardation. Most children had periventricular hyperintensities on T2-weighted and FLAIR MRI scans (12/21), and cortical atrophy (8/21).

About 57% (12/21) of children in our study had sleep disorders. Difficulty in initiating and maintaining sleep (microarousals), sleep-wake transition, and sleep breathing disorders were frequently identified problems (Figure 1). Children with abnormal EEG had more sleep disturbances than those with normal EEG (Fisher exact test, two-tailed, $p<0.016$), but active epilepsy was not significantly associated with the presence of sleep disorder (Fisher exact test, two-tailed, $p<0.153$). Disorders of initiation and maintenance of sleep were more frequent in children with spastic quadriplegia (Fisher exact test, two-tailed, $p<0.0006$). Children with visual impairment had significantly more sleep disturbances than those without it (Fisher exact test, two-tailed, $p<0.037$). All children with epilepsy were under antiepileptic therapy. Seven were under monotherapy with lamotrigine (n=2), valproic acid (n=4) and carbamazepine (n=1). Four children were under polytherapy with topiramate/phenobarbital; lamotrigine/clonazepam; lamotrigine/valproic acid; and difetoin/phenobarbital/zonegran/clobazam. Three children were under melatonin substitution because of disorders of initiation and maintenance of sleep.



Legend: percentage of children with cerebral palsy; difficulty in initiation of sleep; difficulty in maintenance of sleep; frequent microarousals; sleep apnea; stridor; GERD = gastroesophageal reflux disease

FIGURE 1. **The frequency of different sleep disorders and night issues in 21 children with cerebral palsy according to EEG/polysomnography and additional findings (24-hour pH-metry)**

TABLE 1. Selected clinical characteristics and findings of 21 patients with cerebral palsy

Patient no.	Age (yrs)	Sex	Motor impairment	Contractures (Y/N)	Mental retardation	Visual impairment (Y or N)	Sleep disorder	Comorbitidy	EEG	Brain ultrasound/magnetic resonance imaging/ computerized tomography	Antiepileptic therapy
1	12	M	Spastic paraparesis	Y	N	Y	Diffuculty to fall asleep, frequent awakenings	N	Frontal slowing in sleep	Periventricular hyperintensities	0
2	5	M	Left hemiparesis	Y	Y	Y	Snoring, difficulty to breath, adenoids	N	Dysrhythmic	Right periventricular vertical zones with reduction of white matter	0
3	6	M	Spastic paraparesis	N	N	N	N	N	Bilateral centrofrontal asynchronous focus	N	0
4	8	F	Tetraparesis	Y	Y	Y	Insomnia, difficulty to fall asleep, frequent arousals, sleep apnea, no REM sleep, stridor	Epilepsy, severe microcephaly	Low voltage	Thin corpus callosum, diffuse cerebellar and cerebral atrophy	Lamotrigine, clonazepam
5	4	M	Paraparesis	N	N	N	Insomnia, difficulty to fall asleep, frequent arousals	Anorexia	Left centrofrontal focus	Bilateral periventricular parietooccipital discrete hyperintensive changes	0
6	4	M	Paraparesis	N	N	Y	N	Hypofunction of the left kidney	Normal	N	0
7	2	F	Paraparesis	N	N	N	N	N	Normal	Hypoxic-ischemic changes bilateral frontal grade 2	0
8	6	M	Hemiparesis left	N	N	N	N	N	Normal	N	0
9	8	M	Paraparesis	N	Y	N	Insomnia	Epilepsy, autistic spectrum	Right centrofrontal focus	N	Valproic acid
10	18	M	Tetraparesis	Y	Y	Y	No slow wave sleep, sleep apnea, stridor	Pudenz after tuberculosis meningoencephalitis	Multifocal	Cortical atrophy,state after hydrocephaly – Pudenz valve	0
11	11	F	Paraparesis	N	N	N	N	Epilepsy	Focal right temporoparietal and left centroparietal	Periventricular hypoxia, cystic leukomalacia	Lamotrigine, valproic acid
12	13	M	Paraparesis	N	N	N	N	Epilepsy	Dysrhythmic right centroparieto-temporal	Hyperintensities on T2/FLAIR, in both thalami	Carbamazepine
13	14	F	Tetraparesis	Y	Y	Y	Insomnia, psychoorganic changes	Epilepsy	Focal	Cortical atrophy	Valproic acid
14	15	M	Tetraparesis	Y	Y	N	Difficulty to fall asleep, and maintenance of sleep	Epilepsy, severe microcephaly	Normal	Severe cortical atrophy	Valproic acid
15	7	F	Tetraparesis	N	Y	N	Difficulty to fall asleep and maintenance of sleep	Epilepsy	Paroxysmally dysrhythmic, focal occipitally	Leukomalacia, periventricular hyperintensities	Valproic acid, lamotrigine

TABLE 1. Selected clinical characteristics and findings of 21 patients with cerebral palsy (cont.)

16	8	M	Paraparesis	N	Y	N	Y	Epilepsy	Focal right centrotemporo-parietal, mirror focus left	Hypoxic-ischemic changes in the white matter, nodose ectopy of grey matter - right frontally	Valproic acid, lamotrigine
17	2	f	Paraparesis	N	N	N	N	N	Normal	Left periintraventricular hemorrhage grade III, right grade II	N
18	10	M	Paraparesis	N	N	N	N	ADHD	Normal	Developmental venous anomaly parasagittal right in the frontal lobe	Lamotrigine
19	10	M	Tetraparesis	Y	Y	Y	Seizures, sleep apnea, insomnia, difficulty to fall asleep	Epilepsy	Diffuse dysrhythmic with slowing	Cortical atrophy	Topiramate, phenobarbital
20	4	M	Tetraparesis	Y	Y	Y	Sleep apnea, seizures	Epileptic encephalopathy	Diffuse slowing	Leukoencephalopathy	Difetoin, phenobarbital, zonisamide, clobazam
21	12	M	Paraparesis	N	N	N	N	N	Normal	Periventricular leukomalacia, occipital demyelination	N

Legend: Y = yes, N = no

DISCUSSION

As in most other studies, in our study the most common motor impairment was spastic diplegia (25-28), although there are previous and recent studies reflecting changes in the epidemiology of different topographic types of CP (29-31).

The incidence of epilepsy in our group was comparable or even higher than that reported from other studies in children with CP (32), but unlike some authors (23), we did not prove significance of active epilepsy in sleep disorders and CP. Our study pointed to the value of EEG abnormalities in children with sleep disorders. This can implicate that the existence of interictal EEG discharges without active epilepsy may be attributed to the impairment of functional status in children with CP and abnormal EEG findings, and thus, be a risk factor for sleep disorders. This can be supported by the fact that all children with mental retardation in our study had sleep disorders and that 9 of 10 children with mental retardation also had an abnormal EEG finding. We can argue that risk factors for sleep disorders in children with CP in our study were mental retardation, quadriplegia, abnormal EEG and visual impairment. *Kotagal* also concludes that obstructive apnea, decreased ability to change body position, and interictal epileptiform discharges are prevalent in the sleep of patients with severe CP, and contribute to its disruption (33).

Psychological disturbances are seen in 50% of hemiplegic children with CP compared with 15% of children in general population (34, 35), contributing to sleep disorder. As in the study by *Newman et al*., the most frequently identified problems in our study were difficulty in initiating and maintaining sleep, sleep-wake transition, and sleep breathing disorders (23).

In order to timely evaluate sleep disorder, it is worth to take some data about usual duration of nighttime sleeping, time needed to fall asleep, daily naps, possible parasomnias or other paroxysmal events during the night. It is also useful for parents to complete sleep questionnaire and underline the issues in the sleep of their child by filling the boxes with offered answers "yes" or "no", or to have the possibility to check the box as "often", "sometimes" or "never", when they are asked about the frequency of sleeping issues. It gives the possibility to recall the sleeping problems because sometimes parents tend to forget sleeping issues when they visit doctor for being used to it at home. Some studies evaluated the life quality of CP patients by using lifestyle assessment questionnaire; CP and the sleep should also be measures of the child's quality of life (36). Sleep disorder affects not only the child with CP, but also his/her family.

The prevalence of sleep disorders in our children with CP was similar to that reported by other authors (32-36, 38). The most frequent sleep issues in general population usually consist of snoring, sleep deprivation, sleep apnea, parasomnias and insomnia (23, 24, 39). In comparison to general population, children with CP tend to have a higher risk of sleep disorders. Polysomnography studies usually reveal longer sleep and REM latency, low percentage of REM, and slow wave sleep and fragmented sleep in children with epilepsy (32-36, 38), and our group of patients also showed similar changes in sleep architecture. We can argue that motor disability and contractures contributed adversely to frequent microarousals and sleep fragmentation in our four children with CP (Table 1).

In order to benefit from videoEEG in sleep, it is useful to record at least one sleep cycle and to determine the time till the REM sleep and duration of different phases of sleep. There is a need for at least 1.5-2 hours of EEG sleep recordings, in order to record one sleep cycle. We suggest performing overnight polysomnography in all children with CP who have suspected sleep disordered breathing, convulsions, or other paroxysmal events during sleep.

Three children in our study were under melatonin substitution. Melatonin supplementation can be useful in these children. It is a natural compound with a phase setting effect on sleep. It is the hormone of darkness as the detection of darkness by visual receptors drives the hypothalamus to stimulate the pineal gland *via* sympathetic pathways to increase melatonin secretion. Up to 80% of children have response to a 3 mg melatonin use at bedtime with a reduction in delayed sleep onset, nocturnal awakening, and early arousal with minimal side effects (37, 38). Our children with CP had only partial success with melatonin, possibly because of noncompliance of their parents.

Two-thirds of children with CP and epilepsy in our study were under monotherapy. Valproic acid was the most frequent antiepileptic therapy, alone or in combination, and the second one was lamotrigine. Mainly, anticonvulsants decrease sleep latency and improve sleep continuity. Nevertheless, we have to be aware of the fact that valproic acid and phenobarbital can cause sedation and drowsiness, lamotrigine can increase REM sleep, but may cause insomnia, which also holds for etosuximide, and finally, gabapentin and pregabalin are known to increase slow wave sleep. The newer drug on the market, felbamate, causes insomnia in 9% of epileptic population (39). We suggest that all of these antiepileptics be carefully evaluated in terms of sleep disorders in each child with CP and epilepsy before introduction. Medications that improve the sleep-wake cycle may also decrease spasticity and improve daytime behavior. Hypnotics are effective for a short period, but lose their effect in a few days due to the tolerance (40).

CONCLUSION

Each child with CP is unique and may suffer from sleeplessness for different reasons. Identifying the underlying pathophysiological processes is a key to resolve the problem and to take proper intervention. It is well known that the consequences of sleep disorders in children are broad and affect both the child and the family. In our study, the main risk factors for sleep disorders in the child with CP were mental retardation, quadriplegia, abnormal EEG and visual impairment. Since this study had some limitations due to the small sample size, heterogeneous age group, and short follow up period, there is the need of prospective studies to determine whether improvement in the sleep quality of children with CP leads to the improvement of their life quality.

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Autori su popunili *the Unified Competing Interest form na www.icmje.org/coi_disclosure.pdf (dostupno na zahtjev)* obrazac i izjavljuju: nemaju potporu niti jedne organizacije za objavljeni rad; nemaju financijsku potporu niti jedne organizacije koja bi mogla imati interes za objavu ovog rada u posljednje 3 godine; nemaju drugih veza ili aktivnosti koje bi mogle utjecati na objavljeni rad./*All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work.*

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SAŽETAK

Poremećaji spavanja u djece s cerebralnom paralizom

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Prethodna istraživanja u djece s cerebralnom paralizom pokazuju da ta populacija ima povećan rizik za poremećaje spavanja. Iako su poremećaji spavanja u djece s cerebralnom paralizom česti, samo nekolicina istraživanja procjenjuje poremećaj spavanja i rizik za njih u djece sa cerebralnom paralizom. Isto tako ne postoji formalna evaluacija prevalencije apneje u spavanju u djece sa cerebralnom paralizom. Rizični čimbenici poremećaja spavanja uključuju epilepsiju, mentalnu retardaciju, oštećenje vida i stupanj funkcionalnog motoričkog oštećenja. Kontrakture i spastičnost mogu pogoršati pozicioniranje tijela u spavanju. U ovom smo radu analizirali motoričke, kognitivne i funkcionalne smetnje, kao i komobiditet te nalaze neuroslikovnih pretraga i elektroencefalografije u 21-og djeteta sa cerebralnom paralizom i korelirali ih s prisutnim poremećajima spavanja. Poremećaj spavanja evaluirali smo putem elektroencefalografije/polysomnografije. Oko 57% djece u našoj studiji ima poremećaj spavanja. Najčešći motorički poremećaj je spastična diplegija. Većina djece ima periventrikularne hiperintenzitete i kortikalnu atrofiju na neuroslikovnim pretragama. Poteškoće u uspavljivanju, održavanju sna (mikrobuđenja), fragmentirano spavanje i poremećaji disanja u spavanju bili su najčešći problemi koje smo evaluirali putem polisomnografije. Djeca s promijenjenim elektroencefalografskim zapisom imala su više poremećaja spavanja nego ona s normalnim EEG-om. Poteškoće započinjanja i održavanja spavanja bile su češće u djece sa spastičnom kvadriplegijom. Poznato je da posljedice poremećaja spavanja u djece utječu na njih, ali i na obitelj. Postoji potreba za prospektivnim studijama, uz veći uzorak i razrađenu metodologiju da bismo odredili dovodi li poboljašanje kakvoće spavanja u djece sa cerebralnom paralizom i do poboljšanja kvalitete života.

Ključne riječi: cerebralna paraliza; poremećaji spavanja; apneja u spavanju; epilepsija