Chapter 16
Sleep in Neurological and Neurodevelopmental Disorders

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Abstract Sleep problems are highly prevalent in children suffering from diverse neurological diseases. There is a close relationship between the degree of brain abnormality and impaired ability to generate physiological sleep-wake cycles and normal sleep architecture. This chapter summarizes clinical features and management of sleep pathologies in different neurological diseases. Cerebral palsy and neurodevelopmental disorders such as mental retardation, motor coordination disorder, developmental dysphasia, and learning disabilities are reviewed, as well as attention deficit/hyperactivity disorder and autism spectrum disorders. Attention is focused on sleep complaints in chromosomal abnormalities and various genetic programming malformations of the nervous system. Sleep disturbances can be a leading symptom (increasing with the severity of the disease) in many neurometabolic and/or neurodegenerative diseases. Children suffering from neuromuscular diseases are at increased risk of sleep-related breathing disorders, and their management has a substantial role in the patients' life longevity.

Keywords Sleep disorders • Cerebral palsy • Neurodevelopmental disabilities • Mental retardation • Autistic spectrum disorders • Chromosomal abnormalities • Neurometabolic and neuromuscular diseases

Introduction

Sleep quality in children is extremely important for brain development and synaptic plasticity during further life. There is considerable evidence that different sleep stages have a role to play in learning and memory and in the development of

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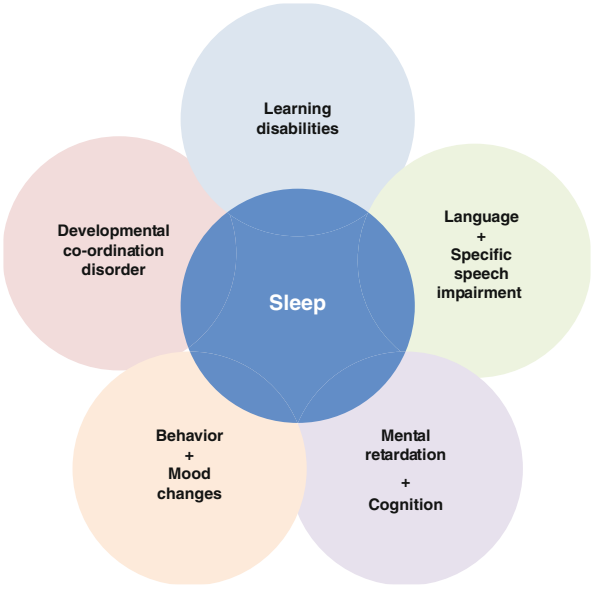


Fig. 16.1 Sleep and its disorganization are connected with all intellectual functions including cognition, learning disabilities, language, and developmental dysphasia, with developmental coordination disorder as well as behavior and mood changes

neuronal plasticity. However, the consequences of sleep disorders in structural and functional damaged brain structures are connected not only with intellectual capacity, but they influence mood changes, such as irritability, aggression, and depression, leading frequently to hyperactivity and conduct problems. Relationships between sleep and these functions are closely interconnected (Fig. 16.1).

Sleep disturbances in children with brain damage are highly prevalent and have different etiologies and medical, neurologic, and psychiatric comorbidities. Furthermore, unlike age-related sleep disturbances in typically developing children, sleep disorders in patients with neurodevelopmental disorders tend to be chronic, lasting into adolescence or adulthood.

The clinical picture of sleep disorders in these children could be directly linked to the brain damage, to a specific genetic syndrome, to hormonal and neurotransmitter dysfunction, or to altered perception of the "zeitgebers" (light-dark cycle, dietary schedule, maternal inputs, etc.) [1]. Sleep problems have a major impact not only on the child, but they affect the whole family's health and well-being.

Cerebral Palsy

Cerebral palsy (CP) affects approximately 1 in 500 live-born infants (more frequently in the developing countries), and the main risk is prematurity. The condition is nonprogressive and arises most commonly as the result of perinatal asphyxia and

hypoxic-ischemic encephalopathy or intraventricular hemorrhage. The location of injury predicts the type of motor symptoms; the clinical picture is usually divided in four groups: diplegia, hemiplegia, quadriplegia, and dyskinesia [2, 3].

Children with CP are at increased risk of sleep disturbances for their motor involvement, as well as for a high association with different comorbidities. Severe developmental delay and mental retardation accompany CP in 31 %, seizure in 21 %, and blindness in 11 % patients [4]. Patients with more severe CP have a greater likelihood of sleep dysfunction. Spasticity, contractures, limitation of movement, and associated pain due to a high degree of functional motor impairment contribute to abnormal positioning during sleep. Severe CP can be associated with scoliosis and restricted lung volume and at risk for sleep-related hypoventilation. Abnormalities of the structure and tone of the upper airways may contribute to obstructive sleep apnea. The prevalence of sleep-disordered breathing is underrecognized and undertreated. Respiratory disorders, severe motor disability, seizures, and intellectual status may be associated with unexpected death during sleep in affected children [5].

Comorbid epilepsy strongly correlates with sleep disorders: nocturnal seizures disrupt sleep continuity, while certain antiepileptic drugs alter the sleep structure and, at the same time, influence daytime alertness. Blindness or severe visual impairment can affect the timing and maintenance of sleep through their effect on melatonin secretion and the lack of light perception. Intellectual disability and behavioral problems predispose to inconsistent bedtime routine and poor sleep hygiene [6, 7]. Romeo et al. [2] found in a detailed study of 165 children with CP that almost half of them (42 %) suffer at least from one sleep disorder. The most frequent complaints were sleep initiation and maintenance disorders (22 %), followed by sleep-wake transition disorder such as hypnic jerks, rhythmic movement disorder, hyperkinesias and bruxism (15 %), sleep breathing disorders (14 %), disorders of excessive somnolence 13 %, and disorders of arousal including sleepwalking, sleep terrors, and nightmares (10 %). There was no significant difference in the questionnaire data (Sleep Disturbance Scale for Children, SDSC) among the four classical types of CP. However, a group of dyskinetic CP children that is connected with structural or functional lesion of basal ganglia presented a more significant score for sleep-wake transition disorder (represented mainly by sleep-related movement disorders) than other children with hemiplegia, quadriplegia, or diplegia. The authors found also a significant correlation with sleep disorders and active epilepsy, mental retardation, and severity of motor CP involvement [2].

Anatomical factors such as upper airway hypotonia, adenotonsillar hypertrophy, glossoptosis, and midface anatomy or mandibular alterations, together with abnormal central control of respiration, can aggravate obstructive sleep disorder. Scoliosis and restricted lung volumes may increase the risk of sleep-related hypoventilation. A questionnaire-based survey of 233 children with CP found habitual snoring in 63 % and sleep apnea in 19.7 % [8]. In another study Wiggs et al. [9] found that 14.5 % of the 173 children with CP had a pathologic score for sleep-related breathing disorders on the Sleep Disturbance Scale for Children.

A few studies on sleep organization in children with CP showed abnormal sleep EEG pattern, absence or alteration of phasic sleep EEG events, difficult differentiation

of stages NREM and REM, extremely low incidence of sleep spindles or presence of "extreme spindles," or an abnormally high percentage of wake after sleep onset [10].

No sleep interventions specifically designed to improve sleep of children with CP are reported in the literature, and only melatonin remains a commonly prescribed drug for disturbed sleep in children with CP. Treatment of OSA with adenotonsillectomy or CPAP may improve sleep and quality of life in children with CP [11].

To sum up, sleep disorders are common in children with CP, and different factors, such as motor or cognitive impairment, behavioral problems, or epilepsy, are important risk factors for the development of sleep disorders. Parenting children with CP is associated with an increased risk of psychological stress developing in the primary caregivers, usually the mothers. Children's sleep disturbances are, therefore, frequently connected with poor maternal sleep quality and depression [12]. The optimal management in children with CP is based not only on the determination and therapy of the physical features of the disease itself; the diagnosis and treatment of comorbid sleep disorders are very important too. A combination of pharmacological treatment (including melatonin), behavioral intervention, and respiratory support should be involved in the complex care.

Neurodevelopmental Disorders

Mental Retardation

Sleep problems are reported to occur in 13–86 % of individuals with intellectual disabilities depending on the study design, participant characteristics, and definition of sleep problems [14]. The most prevalent problems include setting difficulties, long sleep latencies, night waking, and shortened sleep duration with early morning waking. There is a trend for sleep problems and daytime sleepiness to occur more frequently with more severe levels of mental retardation. Besides altered macrostructure, changes were found also in the sleep microstructure, particularly in cyclic alternating pattern (CAP) [14].

Recent studies on the relationship between CAP and cognitive and memory performances support the idea that EEG slow components (A1) play a role in sleep-related cognitive processes and could obviously be altered in mental retardation [15]. In two groups of children with mental retardation, i.e., fragile X (fraX) and Down syndrome, CAP analysis showed a decrease of CAP rate in slow-wave sleep (SWS) and a decreased A1 index (EEG slow oscillations) and an increase of A2 and A3 percentages (i.e., arousals) in both groups, compared to normal controls. Similar results were found in children with autistic spectrum disorder and mental retardation. Therefore, it seems that the decrease in the CAP rate and in A1 mainly in SWS represents a sleep microstructural pattern typical of intellectual disability [16].

However, there is a controversy about whether sleep problems in mentally retarded children are related more to their general medical problems and brain lesions rather than to the mental retardation itself. Some recent studies [17] strongly support the hypothesis that general medical conditions are mainly coresponsible for the sleep patterns in mentally retarded children.

Mental retardation has a wide spectrum of clinical diagnoses. Tietze et al. [18] found, in a cohort of 214 children with severe mental retardation and sleep disturbances, that 25 % of them were children with cerebral palsy, 13 % with genetic syndromes, and 11 % with metabolic disorders. However, the diagnosis was either not established or was caused by a global developmental delay almost in one-third of the whole patients' cohort.

The relationship between sleep and optimal cognitive and physical function is bidirectional. Sleep problems in developmentally disabled children are associated with a number of associated clinical outcomes: poor communication and academic skills, poor self-help skills, incontinence, daytime behavioral problems, and epilepsy [3]. Blankenburg et al. [19] recommended a specific questionnaire (SNAKE) for the diagnosis of sleep disturbances in children with severe psychomotor impairment. The questionnaire evaluates symptoms and consequences of sleep disturbances, as well as conditions that are known to have a direct or indirect impact on sleep in affected children. It takes into account the patient's impaired or limited perception, intellectual ability, limited behavioral repertoire, motor impairment due to underlying disease, and the environmental impact of the disease that makes it less conducive to sleep (e.g., nursing care, artificial ventilation, etc.). The questionnaire is based on the ICSD-2 classification for sleep problems, and it should be completed by parents or nursing personnel over a 4-week period of child's sleep.

Sleep problems are often complex and usually difficult to treat in individuals with mental retardation. The management of sleep disorders in mentally retarded children should include an early intervention program [20] and a pharmaceutical approach with different drugs, with melatonin as the most widely used medicine. Melatonin is increasingly prescribed to many children with mental retardation using a wide range of doses and demonstrating efficacy in improving sleep quality by reducing sleep-onset latency or by slightly increasing total sleep time. These effects appear to be stronger in children with visual impairment, mental retardation, attention deficit, and autism [21].

A meta-analysis of nine randomized and placebo-controlled trials including a total of 183 individuals with neurodevelopmental disorders showed that melatonin decreases sleep latency by a mean of 34 min, increases total sleep time by a mean of 50 min, and less significantly decreases the number of awakenings per night [22]. A recent placebo-controlled study in 146 children (aged 3–15 years) with intellectual disability showed similar results [23].

In spite of the heterogeneity of the studies, regarding patient groups, melatonin preparations, dosage, and timing of administration, the results of different studies [13, 21] indicate that melatonin is effective and safe in the treatment of sleep problems in intellectually disabled individuals.

Developmental Coordination Disorder

Children with developmental coordination disorder experience significant difficulty in the performance of every body's movement skills (particularly clumsiness) in the absence of obvious neurological, sensory, or intellectual impairment. The condition has a reported prevalence of at least 2 % in population studies [24]. The biological background is currently unknown; however, it is frequently found in children with a history of perinatal risk factors (e.g., low birth weight), and genetic factors probably play an important role, too. Affected children show more sleep disturbances than the healthy ones. Particular problems include bedtime resistance, parasomnias, and daytime sleepiness [25]. Scabar et al. [26] found in six out of eight children with severe type of this disorder rolandic spikes during sleep and propose a close link between developmental coordination disorder, so-called benign rolandic epilepsy, and specific language impairment.

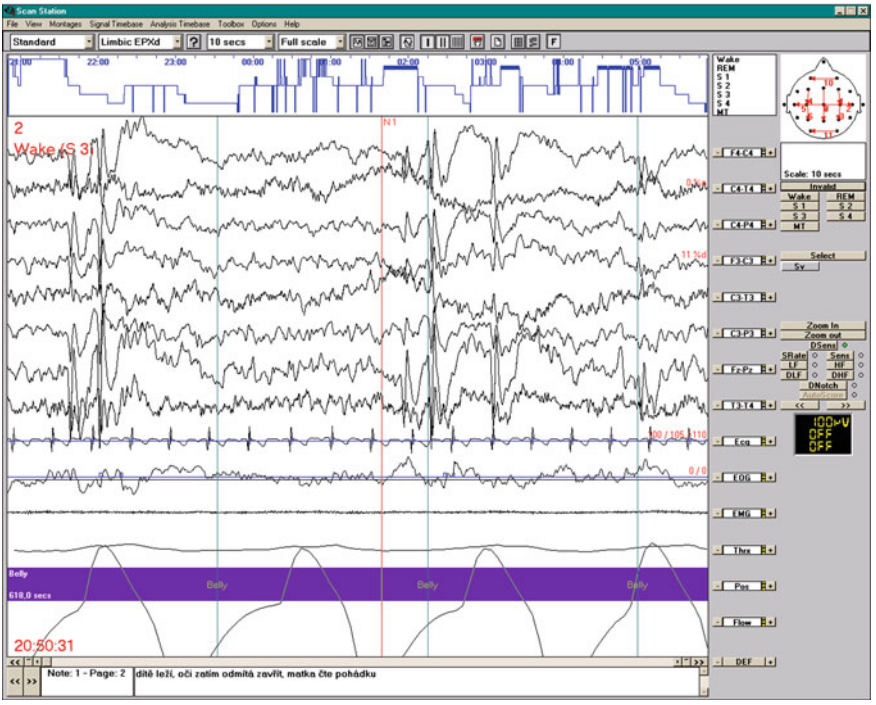
Specific Language Impairment (Developmental Dysphasia)

Specific language impairment includes both developmental expressive and receptive language disorder and affects 3–5 % children's population. The resulting language difficulties interfere with social communication and with successful performance of daily activities including school results. Neurological findings are usually normal; however, a mild hypotonia can be seen. The disorder is very frequently associated with developmental coordination and learning disabilities; neuroimaging abnormalities and EEG changes have been observed, too [27].

Dlouha and Nevsimalova [28] examined a group of 100 children with specific language impairment (69 boys, 31 girls, mean age 6.3 ± 1.2 years). Most of them had signs of mild coordination disorder, borderline or mild decrease intellectual capacity was found in nine children, and learning disabilities (dyslexia, dysgraphia) had developed in 21 out of 33 school children. Epileptic discharges were found in 48 cases in waking EEG, and polysomnography verified epileptiform discharges in 20 out of 26 children (77 %) (Fig. 16.2). In one case, even continual spike-wave discharges during sleep (electrical status epilepticus during sleep, ESES) were found. Severe epileptiform discharges during sleep were seen as a neurophysiological continuity leading to neurocognitive impairment and particularly language disorder in a wide spectrum of diseases including benign rolandic epilepsy and Landau-Kleffner syndrome [29].

Fig. 16.2 A 7-year-old girl with developmental dysphasia. (**a**) Generalized epileptic discharges during wakefulness before nocturnal polysomnographic recording starts. (**b**) Stage 1, NREM sleep with sharp wave discharges predominating above the left centro-temporo-parietal regions

a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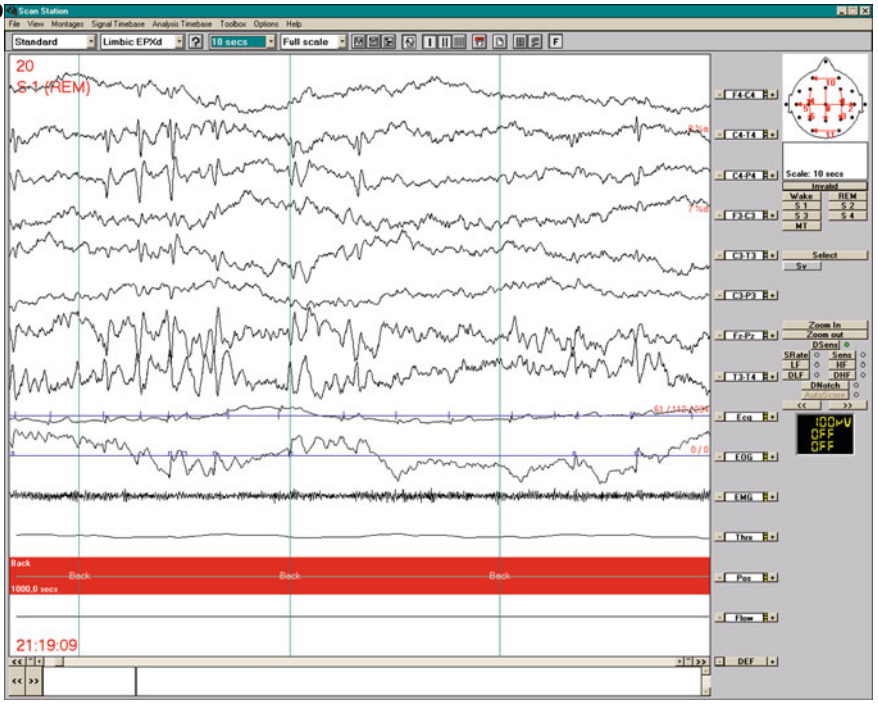
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Learning Disabilities

Learning disabilities (dyslexia, dysgraphia, dysorthographia, dyscalculia) affect up to 5–7 % school children, and they are frequently associated with other developmental disorders. The most frequent learning disability is developmental dyslexia. It is characterized by a difficulty in accurate and/or fluent world recognition and by poor spelling and decoding abilities. Although sleep plays a key role in the processes of learning and memory, almost no studies are available on sleep in children with this disorder. Bruni et al. [30] found a clear increase in spindle activity and sigma power (11–15 Hz frequency) while examining nocturnal sleep in 19 children with developmental dyslexia. A relationship was found between increased sleep spindle activity and the severity of dyslectic impairment, supporting an important role of NREM sleep and spindles in sleep-related neurocognitive processing.

Furthermore, CAP analysis revealed an increase in total CAP rate and EEG slow oscillation (A1) index in stage N3. A correlation analysis between CAP parameters and cognitive-behavioral measures showed a significant positive correlation between the A1 index in N3 with Verbal IQ, full-scale IQ, and Memory and Learning Transfer reading test, while CAP rate in N3 was positively correlated with verbal IQ [30]. In order to explain this finding, the authors hypothesize that to overcome reading difficulties, dyslexic subjects overactivate thalamocortical and hippocampal circuitry to transfer information between cortical posterior and anterior areas. The overactivation of the ancillary frontal areas may account for the CAP rate modifications and mainly for the increase of CAP rate and the A1 index in N3 that seem to be correlated with IQ and reading abilities [30].

Attention Deficit/Hyperactivity Disorder (ADHD)

ADHD is a highly prevalent childhood-onset neuropsychiatric condition, with an estimated worldwide prevalence of approximately 5 % in school-age children. The syndrome is defined by a persistent and age-inappropriate pattern of inattention, hyperactivity-impulsivity, or both. ADHD is frequently comorbid with other neurodevelopmental disorders including coordination disorder, specific language impairment, and learning difficulties [31].

As many as 70 % of children with ADHD have been reported having mild to severe sleep problems including sleep-onset insomnia (the most often reported problem), bedtime resistance, night awakenings, difficulties in morning awakenings, sleep disorder breathing, and daytime sleepiness [32]. Objective studies showed that children with ADHD had significant differences vs. control children for sleep-onset latency, apnea-hypopnea index, sleep efficiency, and higher levels of daytime sleepiness on the Multiple Sleep Latency Test (MSLT) supporting the hypothesis of disorders of vigilance in ADHD [33, 34]. Both subjective and objective sleep/alertness alteration presented in ADHD children [35, 36] are suggested to

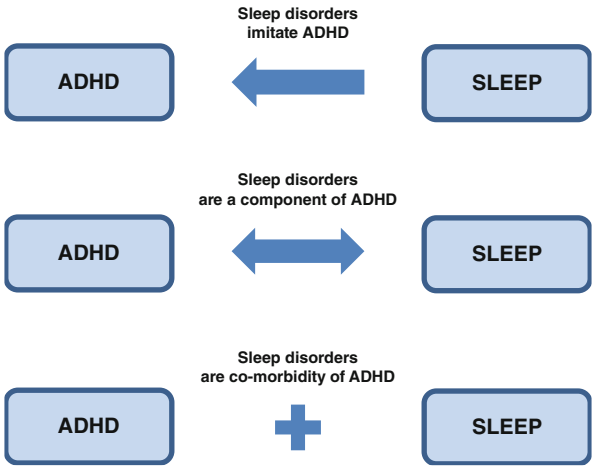

Fig. 16.3 A comprehensive view on a relationship between sleep disturbances and attention deficit/hyperactivity disorder (ADHD) (Adapted from Owens et al. [37]). Sleep disturbances may imitate ADHD, may be a component of ADHD, and/or may be a comorbidity of ADHD

be a result of changes in the micro- rather than macro-sleep architecture [33]. Generally speaking, the relationship between sleep disturbances and ADHD is very complicated [37]. Sleep disturbances may mimic ADHD, may be the consequence, or may contribute to ADHD – like phenotypes, as Fig. 16.3 illustrates. Several comorbid sleep disorders – particularly periodic limb movements (PLMs) and restless leg syndrome (RLS) – take part in the clinical picture of ADHD.

The next chapter (17) brings a more comprehensive view of sleep disorders in ADHD and its comorbidities.

Autistic Spectrum Disorders

Autistic spectrum disorders (ASD) are a set of neurodevelopmental disorders characterized by varying degrees of impairment in communication skills, social interaction, and restricted, repetitive, and stereotyped patterns of behavior. The prevalence varies between 0.2 and 0.7 % in the whole population [38, 39].

Parental surveys show a 50–80 % prevalence of sleep problems in children with ASD mainly represented by insomnia [40]. Sleep disturbance in these children seems to be correlated with aggressive behavior, developmental regression, internalizing problems [41], and anxiety and sensory over-responsibility [42]. Sleep disorders were reported either in ASD children with severe mental retardation or in high-functioning subjects [40].

Children with a history of developmental regression have a more disturbed sleep pattern than children without regression [43] and demonstrate a higher degree of

sleep disruption either at a macrostructural or microstructural level [38, 44]. Circadian abnormalities in ASD children might be a result of genetic abnormalities related to melatonin synthesis and its role in modulating synaptic transmission. In ASD, there is an overall reduction in nocturnal melatonin secretion or a delay in its secretion at night. Low levels of melatonin and/or its urinary metabolic derivatives correlate with sleep problems and autistic behaviors [45]. This is probably the cause of the difficulties in falling asleep and of the irregular sleep-wake rhythms [46]. Recently, a bifurcation of the sleep-wake cycle with increased sensitivity to external noise and short sleep duration causing irregular sleep-onset and wake-up times has been suggested [43].

Several studies have demonstrated effectiveness of behavioral interventions for sleep-onset and maintenance problems [39]. C*o*nsistent sleeping environment and routine should be maintained to help the child relax down to sleep. The management of sleep disturbance in ASD children depends on the type of sleep disorder, but behavioral therapy associated to melatonin supplementation is the most used since ASD children have endogenous melatonin deficiency [47].

A more detailed description of sleep studies in ASD is described in the next chapter (17).

Chromosomal Abnormalities and Microdeletion Syndrome

Sleep problems are highly prevalent in children suffering from diverse genetic syndromes featured by autosomal, gonosomal, and/or microdeletion changes. The main sleep characteristics involve nocturnal sleep complaints (mainly night awakenings and sleep apnea); however, also tiredness or even excessive daytime sleepiness has been reported [48].

Down Syndrome

Down syndrome is one of the most common autosomal abnormalities occurring in 0.9 per 1000 live births, its probability being directly proportional to increasing maternal age. Typically phenotypic features are accompanied by delayed psychomotor development with generalized hypotonia and impaired cognitive performance. The most frequent cause rests in trisomy chromosome 21, translocation of the long arm of an extra chromosome 21 to chromosome 14 or 22, and/or mosaicism of trisomy 21.

The leading sleep complaints are sleep-related breathing disorder and insomnia. The prevalence of obstructive sleep apnea (OSA) is higher than 50 %, the obstruction being caused by an anatomically narrow upper airway due to midfacial and mandibular hypoplasia, relative macroglossia, glossoptosis, and frequent adenotonsillar hypertrophy. Other factors predisposing to OSA include obesity and

generalized hypotonia with upper airway muscle malfunction. However, changes were found also in the sleep architecture. The patients have a reduced quantity of REM sleep and decreased REM sleep density. Sleep fragmentation and arousals independent of respiratory events and PLMs and even RLS have also been reported. Daytime sleepiness is therefore a consequence of poor nocturnal sleep quality. From the therapeutic point of view, management of OSA as well as behavioral methods is usually recommended to decrease sleep problems [49, 50].

Recently, the practice parameters from the American Academy of Pediatrics recommended to discuss with parents, at least once during the first 6 months of life, symptoms of obstructive sleep apnea, uncommon sleep positions, frequent night awakening, daytime sleepiness, and behavior problems [51].

Fragile X Chromosome

Fragile X chromosome is the most common cause of sex chromosomal abnormalities with a rate of occurrence 1:4000 live births in males. It is the most frequent cause of inherited mental retardation in boys due to X-linked trinucleotide repeat disorders (Xq27.3). The characteristic face features (elongated face, large ears, and protruding jaw) are accompanied by macroorchidism. Cognitive and language features comprise a deficit consistent with the level of mental retardation; behavioral changes include increased social avoidance, anxiety, and hyperactivity [52].

Very few studies evaluated the presence of sleep disorders in patients with fragile X. Kronk et al. [53] reported a prevalence of 32–50 % of significant sleep problems with the more frequent complaints represented by sleep-onset difficulties and frequent awakenings during the night.

Data obtained from the Fragile X Clinical and Research Consortium Database (FXCRC) showed that 27 % of parents reported sleep problems in affected children, and also OSA has been reported to be a frequent complaint [54]. A variable sleep duration and sleep fragmentation are sporadically observed [49]. Some sleep studies showed a correlation between REM sleep deficit and the level of mental retardation [52].

In an interesting study, Gould et al. [55] found increased levels of melatonin across the circadian cycle in young fragile X individuals, possibly explaining the difficulties in maintaining consistent sleep and increased number of night wake episodes. Clonidine has been reported to have a beneficial effect on hyperactivity and abnormal sleep patterns [56]; behavioral therapy was also used with a benefit [57].

Prader-Willi Syndrome

Prader-Willi syndrome (PWS) is a genetic disorder affecting in 1:10,000–25,000 live births. The genetic defect is linked to a deletion in the paternally inherited chromosome 15q11–q13 in 70–75 % of individuals, to a maternal uniparental disomy in

20–25 % of cases, and to abnormal methylation of the imprinting center on chromosome 15 in 1–2 %.

PWS is characterized by obesity, small status, hyperphagia, hypogonadism, mental retardation, and behavioral disorder. The most frequent sleep complaints include breathing disorders, particularly OSA, and daytime sleepiness. The risk factors for OSA are obesity and mass loading of the chest wall, facial dysmorphism, and hypotonia. Abnormality of central respiratory control also predisposes to central apneas.

OSA seems to be a feature that appears during development; in fact, infants with PWS, when compared with older children, were more likely to experience central sleep apnea than obstructive events [58]. With age obesity increasing and OSA emerging, a recent review analyzing 14 studies in children with PWS reported an OSA prevalence of 79.91 %: 53.07 % had mild, 22.35 % moderate, and 24.58 % severe OSA. Adenotonsillectomy was found to be effective in reducing OSA for some children, but residual OSA was present in the majority of cases after surgery [59].

Although OSA may have a role in decreased vigilance during the day, excessive daytime sleepiness (EDS) is primary caused by hypothalamic dysfunction. Decreased level of hypocretin-1 in the cerebrospinal fluid [60] can support a potential involvement of hypothalamic dysfunction.

Different polysomnographic studies have been carried out to evaluate sleep in PWS subjects showing a decrease of sleep and REM latency and the presence of sleep-onset REM periods (SOREMPs), corroborating the hypothesis of a primary disorder of vigilance [61].

Reviewing the relevant literature, Camfferman et al. [62] found EDS in 74 out of 110 cases and cataplexy-like symptoms in 13 out of 63 patients. However, no convincing correlation was found between OSA severity and EDS.

Growth hormone (GH) therapy in children with PWS may determine hypertrophy of tonsils or adenoids, increase OSA, and may be responsible for sudden death in PWS subjects [63]. A recent paper, however, showed a decrease in the respiratory disturbance index and the central apnea index. The authors [63] concluded that long-term GH treatment in patients with PWS is generally safe and recommended annual polysomnography and adenotonsillar evaluation.

CPAP (or BiPAP) is commonly prescribed for sleep-disordered breathing, while most patients benefit from modafinil to counteract excessive daytime sleepiness [62].

Angelman Syndrome

Angelman syndrome (AS) is a neurodevelopmental genetic disorder caused by the absence or loss of function of the maternally inherited allele at the 15q11-q13 domain; it occurs in 1:12,000–20,000 individuals and accounts for 6 % of all children with severe cognitive disability and epilepsy [64]. AS is called “happy puppet

syndrome" because of the patients' characteristic jerky movements, happy disposition, and frequent laughter. Microcephaly, severe mental retardation, and epileptic seizures accompany the clinical picture [65].

A variety of sleep abnormalities are reported including prolonged sleep latency, frequent nocturnal awakenings, involuntary movements, bruxism, snoring, and a higher rate of parasomnias (enuresis, sleep terrors, sleepwalking) [66]. Nocturnal sleep time is reduced and some children have abnormal sleep-wake cycles with short periods of diurnal and nocturnal sleep [49].

Polysomnographic studies showed a reduction in sleep efficiency and in REM sleep, while the percentage of SWS was found to be significantly higher, due to the presence of the 1–3 Hz bursts that represent the typical EEG pattern of the syndrome. No respiratory abnormalities were found; however, a tendency to an increase in the periodic limb movement index (PLMI) was observed [67].

In children with AS, treatment with sleep hygiene, behavioral therapy, associated with melatonin was documented to be effective. Melatonin before bedtime promotes less fragmented sleep and helps to regulate sleep-wake cycles [68]. A recent research in children with AS reported that the nighttime serum melatonin levels were significantly low in AS patients and with delayed melatonin peak showing the delayed sleep phase syndrome (DSPS) [69].

Williams Syndrome

Williams syndrome (WS) is a disorder marked by an unusual elfin-like facies, hyperacusis, infantile hypercalcemia, and significant physical and mental retardation. The condition is caused by a heterozygous deletion in chromosome 7q11.23 and its incidence is estimated at 1:10,000.

There are only few studies dealing with sleep problems in these patients. While in children the attention has been focused on night sleep complaints and predominantly on PLMs [70], Goldman et al. [71] used actigraphy to examine overnight sleep pattern in 23 adolescents and young adults and completed their sleep data with a structured questionnaire: although free to spend 9 h in bed, nearly all the subjects were tired and almost 80 % were sleepy during the day.

Smith-Magenis Syndrome

Smith-Magenis syndrome (SMS) is characterized by mental retardation with distinctive behavioral characteristics, dysmorphic features, and an abnormal circadian pattern of melatonin ascribed to an interstitial deletion of chromosome 17 (17p11.2). The prevalence is estimated at 1:25,000 live births [72].

Sleep disturbances are seen in 65–100 % cases, and all affected children display a phase shift in their circadian rhythm of melatonin secretion. Prominent sleep

problems include early sleep onset, repeated and prolonged awakening during the night, and early sleep offset. Most patients exhibit morning tiredness, temper tantrums when tired, and naps during the day (Fig. 16.4).

Actigraphic studies indicated a sleep disturbance that begins as early as 6 months of age, with fragmented sleep and reduced 24-h sleep compared with healthy control subjects [73]. This finding was corroborated by polysomnographic studies which revealed reduced sleep time in virtually all SMS patients [74].

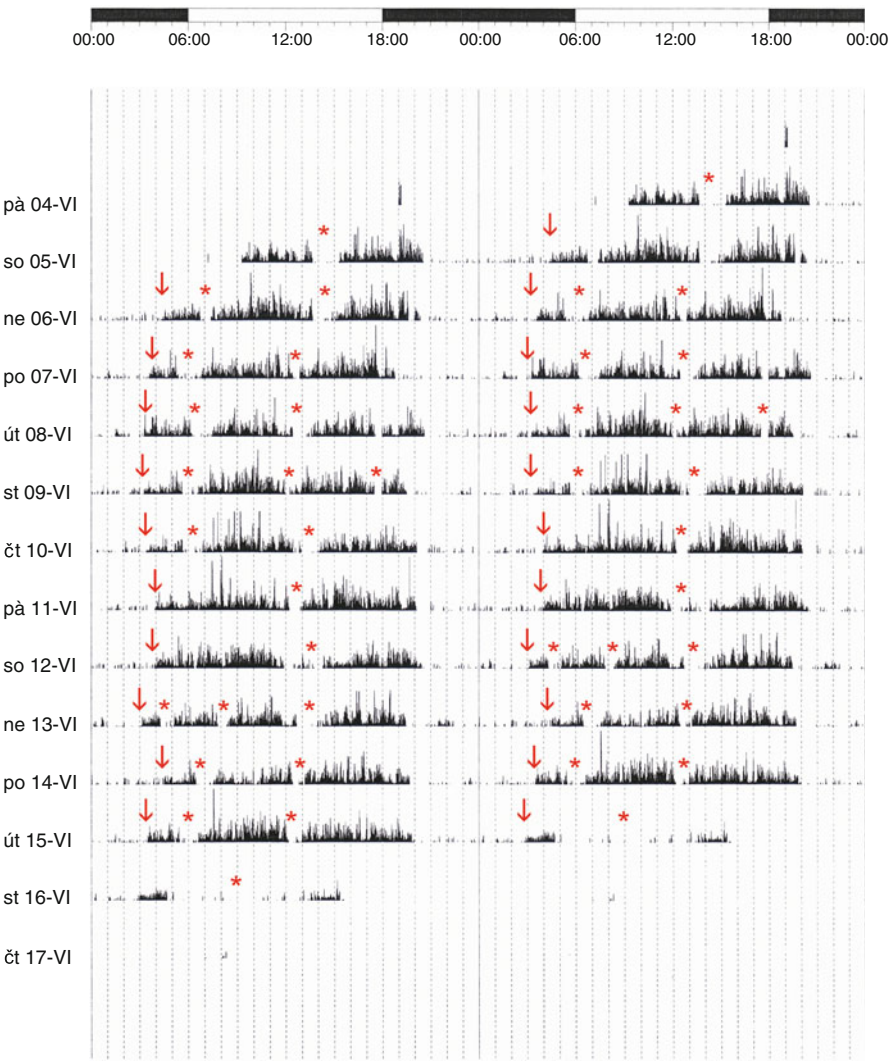

Fig. 16.4 A 7-year-old boy with Smith-Magenis syndrome: the actigraphic recording shows early awakenings from nocturnal sleep (marked by *arrowheads*) and many excessive daytime sleep attacks (marked by *asterisks*)

The disorder of circadian rhythm in SMS is related to disturbed regulation of downstream circadian clock genes and explains sleep disturbance and abnormal daytime behavior with hyperactivity. The mechanism of the quantitatively normal, but rhythmically abnormal, melatonin secretion is, as yet, unknown [75]. A series of studies have found that 96 % of SMS children had inverted endogenous melatonin secretion, peaking in the day rather than at night [76, 77]. The best recommended treatment is a combination of evening melatonin administration and morning β1-adrenergic antagonist (acebutolol) to reduce the daytime production of this hormone [78].

Rett Syndrome

Rett syndrome (RS) is a severe neurological disorder with an incidence of 1:10,000 girls. It is one of the most frequent causes of mental retardation in female patients. It is generally caused by mutation in the MECP2 (methyl-CpG binding protein 2) gene (Xq28). Almost 300 mutations have been recorded [79]. The disorder is characterized by progressive intellectual and neurological impairments beginning after apparently normal psychomotor development. Early signs of RS typically manifest at the age of 6–18 months. Characteristic features comprise microcephaly, stereotyped hand movements (hand-wringing or washing), severely impaired language functioning, autistic behavior, regress of motor and intellectual functions, epilepsy, and attacks of breathing disturbance during wakefulness.

Several studies show that sleep patterns are changed from infancy. The affected girls sleep longer during the day and, on the other hand, wake and laugh in the middle of night. Their sleep onset is very irregular and total daytime sleep remains prolonged instead of showing the normal age-related physiological decline. The immature sleep pattern seems to be a consequence of arrested brain development. Frequent daily napping has been reported almost in 80 % of affected patients and found to increase with the age [80].

Polysomnographic studies revealed lower sleep efficiency, long sleep-onset latency, and short total sleep time, but also increased wakefulness after sleep onset (WASO), decreased REM sleep, fewer spindles, and K complexes similar to other forms of mental retardation [81, 82]. Alterations in sleep architecture including tonus changes in NREM as well as REM sleep were found [83, 84]. Patients with RS commonly show irregular breathing during wakefulness consisting of episodes of hyperventilation interspersed with breath-holding spells, sometimes associated with severe oxygen desaturation.

Respiratory disturbances during the night are very frequent [85–87]. Hagebeuk et al. [86] found in a group of 12 RS girls combined central and obstructive apneas in five patients, in another three prevailed central apnea, and in further two obstructive one. Only two cases showed normal respiratory functions.

A recent study showed, in a sample of more than 300 cases followed over 12 years, that the prevalence of any sleep disturbance was very high (more than 80 %) and decreased with age (less common in individuals aged more than 18 years) [88].

Night laughing represented the most frequent problem occurring in 60–88 % of younger girls followed by night screaming.

Behavioral insomnia and nighttime behaviors in RS are usually treated with a combination of behavioral treatments and oral melatonin (2.5–7.5 mg) that reduced mean sleep latency [89, 90].

Management of breathing sleep disorder is necessary almost in all RS cases, sometimes including 1–2 h per day of continuous positive airway pressure (CPAP) while awake.

Coffin-Lowry Syndrome

Coffin-Lowry syndrome is a rare disorder characterized by moderate to severe mental retardation, facial dysmorphism, tapering digits, and skeletal deformity. The gene is located on Xp22.2 [91]. The characteristic features are stimulus-induced drop episodes, accompanied by sudden loss of muscle tone, and induced by unexpected tactile or auditory stimuli. No epileptiform activity was proven in any reported case. Drop attacks are not induced by emotion (as in true cataplectic attacks), and recovery is immediate. The attacks last only a few seconds and always lead to fall. The pathophysiology of these cataplexy-like drop attacks remains unclear [92]. Sleepiness has not been described in any case. Treatment with conventional antiepileptic medication proved ineffective. Sporadically clomipramine and/or tiagabine – a potent GABA-uptake inhibitor – was used with a benefit [92, 93].

Norrie Disease

Norrie disease is a rare X-linked microdeletion syndrome (Xp11.3–p11.4) characterized by infantile blindness, pseudotumorous retinal dysgenesis, and ocular atrophy. It is associated commonly with mental retardation, sensorineural deafness, dysmorphic features, and occasionally with atonic seizures. Sleep studies are extremely rare. Vossler et al. [94] described three boys with this syndrome and found them to have cataplexy and abnormal REM sleep with no other signs of narcolepsy. The authors verified the congenital absence of monoamine oxidase (MAO) in these patients and suppose its indirect responsibility for cataplexy and REM sleep disturbance.

Some other congenital syndromes such as *Möbius*, *Pierre-Robin*, *Treacher-Collins*, *Goldenhar*, *and/or centrofacial dysgenesia* also belong to neuroembryological and/or genetic programming malformations of the nervous system. Their difficulties are primarily connected with upper airway obstruction and subsequent sleep disorder breathing difficulties. Noninvasive breathing support (BiPAP) followed by individually chosen surgical treatment manages usually a necessary benefit.

Neurometabolic Diseases

Metabolic and/or degenerative diseases affecting the central nervous system usually result from a single mutant gene coding for an enzymatic protein mostly involved in the catabolic pathway. The defective gene in metabolic diseases is normally expressed in one or more organs (not necessarily in the nervous system), where chemical analyses of tissues often have a diagnostic value. Most of them belong to the group of lysosomal or so-called storage diseases [95].

Storage lysosomal diseases are characterized by an accumulation of undergraded macromolecules within lysosomes. The most common representatives are the glycogen storage diseases – glycogenosis (Pompe disease), mucopolysaccharidosis and mucolipidosis, glycoproteinosis together with sphingolipidosis, and neuronal ceroid lipofuscinosis. Almost all are autosomal recessive inherited diseases; the combined prevalence of all lysosomal storage diseases is 1:6600–1:7700 live births [95].

Pompe Disease

Pompe disease results from acid α-glucosidase deficiency; its incidence is estimated at 1:40,000 individuals. The infantile form is usually fatal before the age of 2 years, and the juvenile form progresses more slowly, but all patients develop involvement of respiratory muscles – predominantly of the diaphragm. Enzyme replacement therapy is the only causal treatment improving significantly the prognosis and diminishing breathing difficulties. Obstructive sleep apnea and hypoventilation are common without causal treatment in both patients' groups, and noninvasive ventilation support is indicated [96, 97].

Mucopolysaccharidosis

Mucopolysaccharidoses are heterogeneous syndromes consisting of mental and physical retardation, typical facies features with the large head, multiple skeletal deformities, hepatosplenomegaly, and clouding of the cornea in Hunter and Hurler syndrome. The syndrome comprises seven major entities, which are distinguishable by their clinical picture, genetic transmission, enzyme defect, and urinary mucopolysaccharide pattern.

OSA is the most common sleep disorder in all types. Upper airway obstruction has multiple causative factors, and progressive respiratory disease may severely affect morbidity and mortality [98]. Children are more severely affected than adult patients [99]. Retropalatal and retroglossal spaces were found to be significantly smaller in children than in adults. Adenoid hypertrophy was found to have a significant role to play in all examined children.

The most frequent and probably specific sleep disturbances have been found in the commonest mucopolysaccharidosis, Sanfilippo syndrome. These patients have extremely irregular sleep pattern, with several sleep episodes of variable duration and irregular round-the-clock distribution [100]. Guerrero et al. [101] examined urine melatonin excretion in 12 patients with Sanfilippo syndrome and found a significantly lower melatonin excretion at night and significantly higher concentration in the morning with keeping a slightly higher level also during the day compared to the controls. Analysis of the circadian rhythm alteration may explain the cause of sleep disorders found in these patients, and melatonin can be recommended as a benefit treatment.

Niemann-Pick Disease

Niemann-Pick disease is a heterogeneous syndrome comprising different forms (A–D). However, its type C (NP-C) with sphingomyelinase activity deficit is one of the most frequent recessively inherited lysosomal storage sphingolipidoses. The prevalence is 1:150,000, and about 95 % of NP-C patients have mutation in NPC1 gene (18q11). Three main clinical forms are distinguished: infantile with early onset and rapid progression, late infantile/juvenile with slower progression, and variant with a late onset. The most common late infantile/juvenile form is characterized by vertical supranuclear ophthalmoplegia, cerebellar ataxia, dystonia, dysarthria, dysphagia, and intellectual deterioration. Cataplexy is a frequent symptom, and spleen enlargement or hepatosplenomegalia is expressed in all patients.

Several sleep studies [102–105] were done in NPC1 patients. Night sleep is interrupted with frequent arousals, disorganized, shortened, and of low efficiency. The MSLT shows shortened mean sleep latency (independent of the presence or absence of cataplexy). A decreased value of CSF hypocretin was found to be independent of the presence of cataplexy. Vankova et al. [102] found in five NP-C patients altered sleep patterns including sudden increase in muscle tone during delta sleep, electroencephalographic sigma activity connected with rapid eye movements and muscle atonia, presence of alpha-delta sleep, and atypical K complexes as well as spindle activity. All patients exhibited fragmentary myoclonus (Fig. 16.5).

According to Vanier [106] only about 10 % of NPC1 cases have clinically evident cataplectic attacks. However, cataplexy as a leading sleep disorder symptom was recently described by many authors [104, 107, 108]. Nevsimalova and Malinova [109] found cataplexy in four out of nine patients with late infantile and in one out of three patients with infantile NP-C form, while cataplexy was absent in juvenile or adult cases. Cataplectic attacks were found more frequently in children than in adults also by further authors [110]. Therefore, Challamel et al. [111] recommend to rule out NPC1 disease in all children with frequent cataplectic attacks.

Miglustat® represents a new possibility of NP-C treatment; its benefit was exceptionally observed also on cataplectic attacks [112].

Neuronal Ceroid Lipofuscinosis

Neuronal ceroid lipofuscinosis (NCL) is characterized by the accumulation of autofluorescent storage material within lysosomes, leading to neuronal death. The major clinical subtypes are infantile, late infantile, early juvenile, juvenile, and the adult forms, all transmitted in an autosomal recessive manner [95].

Late infantile neuronal ceroid lipofuscinosis is one of the most common variants. It is caused by a genomic defect in chromosome 11p15.5, the Finish variant of late infantile NCL, which is also known as the early juvenile form of 13q22. Clinical features include progressive visual failure, intellectual deterioration, cerebellar

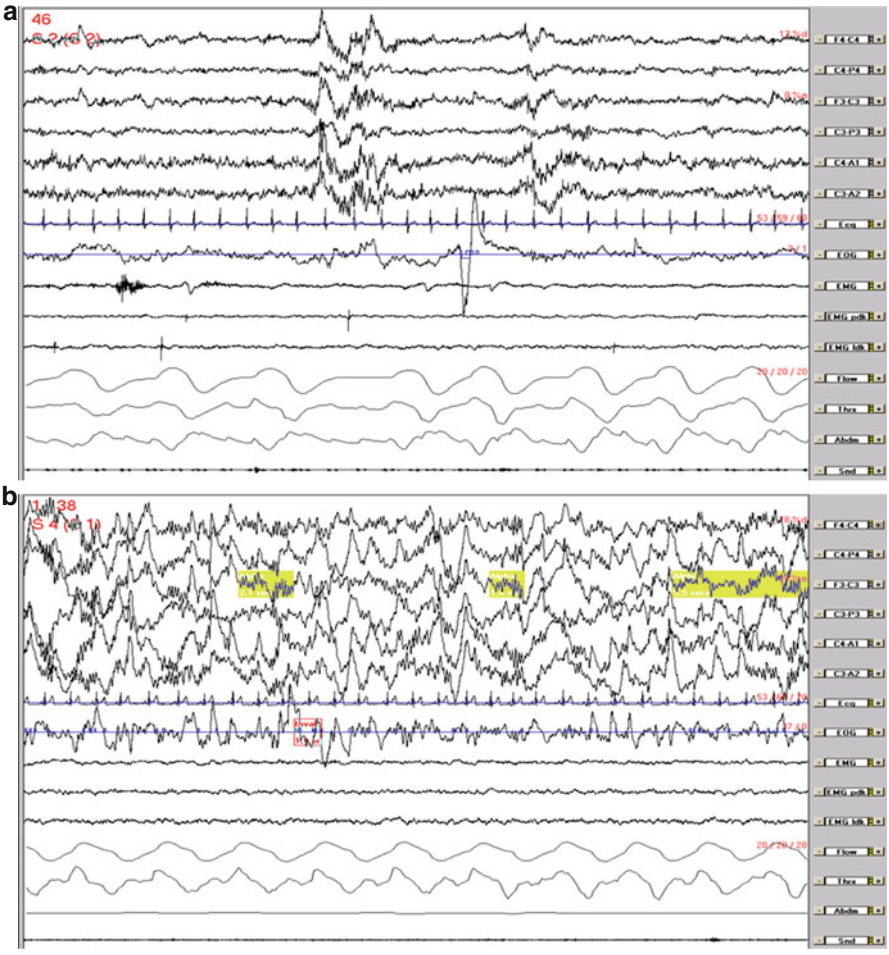

Fig. 16.5 A 14-year-old girl with Niemann-Pick disease type C. (**a**) REM sleep with rapid eye movements, muscle twitches, and sigma activity. (**b**) NREM sleep, stage 3 with diffuse penetration of alpha rhythm. (**c**) Alpha-delta sleep. (**d**) NREM sleep, stage 2 with fragmental myoclonus

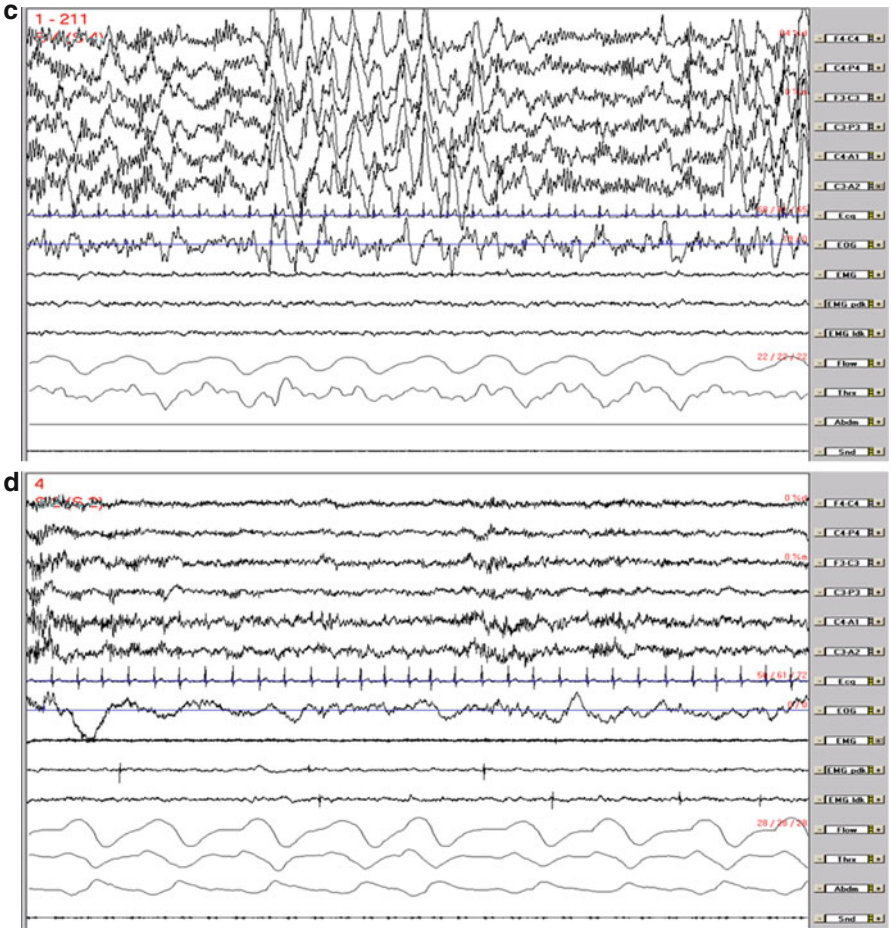

Fig. 16.5 (continued)

symptoms with ataxia, epilepsy, and frequent myoclonic jerks. Clinical decline leads to coma vigile and premature death. Sleep studies [113] show in the initial phase an excess of night sleep and frequent daytime naps. Later on, the longest sleep period was frequently shifted into daytime hours. Fragmented diurnal rest activity patterns with no distinct rhythm are seen during disease progression. The internal circadian timing system may be damaged also due to visual deterioration.

Juvenile neuronal ceroid lipofuscinosis is mapped to chromosome 16p12.1. Its clinical features include progressive loss of vision, usually leading to blindness between 8 and 13 years of age, intellectual deterioration, extrapyramidal and cerebellar symptoms, and epilepsy. Common sleep disturbances are reported in more than half of the patients. The most typical are daytime sleepiness [114], settling problems, nocturnal awakenings, and nightmares. Polysomnography showed

significantly reduced total sleep time, sleep efficiency, percentage of REM sleep, and NREM stage 2. Treatment with melatonin before bedtime may help to slightly improve the circadian rhythm [114].

Neuromuscular Diseases

Neuromuscular diseases include a wide spectrum of motor unit diseases starting with the affection of motor neuron in the brainstem and spinal cord and spinal muscular atrophies (SMA), continuing through myasthenic syndromes, congenital myopathies, muscle dystrophies, and myotonic syndromes, and ending with Charcot-Marie-Tooth (CMT) disease, called also as hereditary motor and sensory polyneuropathy (HMSN).

Patients suffering from neuromuscular diseases are at an increased risk of sleep-disordered breathing (SDB) disorders such as OSA and hypoventilation, as well as central sleep apnea. SDB increases particularly due to diaphragmatic weakness and can precede abnormalities during wakefulness by months to years. Hypoventilation becomes more severe as the disease progresses, but SDB can be seen in some cases still in early stages of neuromuscular diseases (Fig. 16.6). Sleep-related hypoxemia is predominantly seen in REM sleep, because of the loss of accessory muscle contribution to breathing in coping with diaphragmatic weakness. REM-related desaturations are also frequently associated with recurring apnea and hypopnea. These apneas are most commonly central origin, but obstructive apnea can develop if upper airway muscle contraction is impaired [115]. Later on, SDB appears also during NREM sleep. A decrease in blood oxygen saturation can reach a value between 60 and 80 %, a quantity connected with compensatory increased breathing effort and nocturnal awakening reactions. Noninvasive nocturnal breathing support is the adequate treatment for SDB in all the types of neuromuscular diseases [116].

Nocturnal sleep-related ventilatory alterations lead to sleep inertia in the morning with headaches, daytime somnolence, fatigue, and inappropriate napping. Children are also at higher risk for developing complications as pulmonary hypertension, cor pulmonale, and neurocognitive dysfunction that impair their quality of life and may lead to significant morbidity and increased mortality [115, 117].

Spinal Muscular Atrophy (SMA)

Spinal muscular atrophy is transmitted by an autosomal recessive gene and manifested by widespread muscular denervation and atrophy. The incidence is 1:10,000–25,000. Three main clinical variants exist in children: infantile (SMA 1) with the most rapid course, intermediate (SMA 2) which makes approximately one-half of all cases, and juvenile (SMA 3) with much slower progression. All forms are caused by mutations in a survival motor neuron gene 1 (SMN1) located at chromosome 5q11.2–q13.3 [118].

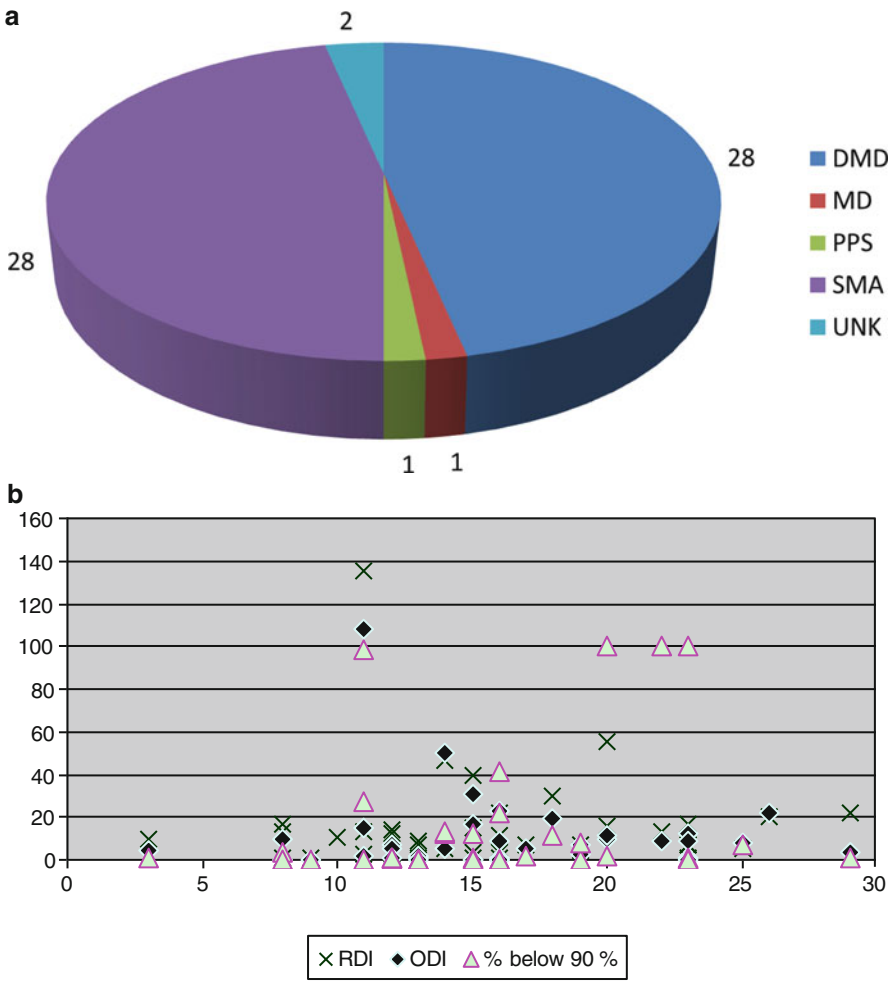

Fig. 16.6 Neuromuscular diseases followed-up in our Prague Sleep Center (Kemlink D. et al., unpublished data). (**a**) A survey of a cohort of 60 children, adolescents, and young adults with neuromuscular diseases: *DMD* Duchenne muscle dystrophy, *MD* myotonic dystrophy, *PPS* post-poliomyelitic syndrome, *SMA* spinal muscular atrophy type 2 and 3. (**b**) An age-related polysomnographic (PSG) respiratory findings in 34 patients from the abovementioned cohort. *RDI* respiratory disturbance index, *ODI* oxygen desaturation index, *% below 90 %* the percentage of the total recorded time spent below 90 % of oxygen saturation level. The graph shows no age-related dependence on the severity of the patients' respiratory parameters

There are very few studies of sleep patterns in patients with SMA and especially in subjects with SMA1. In a polysomnographic study of 32 neuromuscular patients, four with a form of SMA, sleep architecture revealed an increase in stage 1 sleep coupled with a decrease or absence of REM sleep [119]. Another study on seven SMA children (six with SMA type 1.5–1.8, one with SMA type 2) showed impaired

sleep architecture, in whom nocturnal noninvasive ventilation (NIV) resulted in a significant improvement of sleep architecture with higher sleep efficiency, increased deep sleep, longer REM sleep, and significantly fewer EEG arousals [120].

A recent study on SMA1 patients indicates the presence of an abnormal sleep microstructure in SMA1 patients, characterized by a reduction of A2 and A3 CAP subtypes (corresponding to arousals). The authors hypothesize that SMA1 patients have reduced arousability during NREM sleep, which could be interpreted as additional evidence of central nervous system involvement in this disease and might represent an additional risk factor for the premature death of these patients, which is frequently attributed to the rapid progress of weakening of muscles and respiratory failure [121].

SDB is a classical feature particularly in SMA 1 and 2. The intercostal muscles in these cases are more affected than the diaphragm, resulting in paradoxical breathing (inspiratory efforts cause the rib cage to move inward as the abdomen moves outward). Thoracoabdominal asynchrony is present during the inspiratory and expiratory phases in both REM and NREM sleep [122].

In the past 20 years, NIV has been used as a standard method for increasing the duration and quality of life of the affected children. Nocturnal sleep architecture is consolidated and daytime functioning improves. Both the growth and development of lung parenchyma are positively influenced, and chest wall deformity either slows down growing or starts reversing its progression [115, 123].

Congenital Myasthenic Syndromes

The congenital myasthenic syndromes represent a group of heterogeneous disorders that can be classified into presynaptic, synaptic, or postsynaptic according to the site of the transmission defect. The manifestations can be severe from birth with weak cry, congenital hypotonia with generalized weakness, and feeble suck or can combine in various degrees ptosis, ophthalmoparesis, easy fatigability, and proximal pattern of muscle weakness.

The presence of sleep hypoventilation syndrome has been reported [115], and therefore, polysomnographic evaluation and NIV positive pressure ventilation can be indicated.

Congenital Muscular Dystrophies

Congenital muscular dystrophies are genetically and clinically heterogeneous group of autosomal recessive disorders, presenting with muscle weakness and hypotonia at birth or within the first few months of life. The diagnosis is possible at the molecular level; the course of disease is usually slowly progressive.

Patients are at risk of SDB including central apneas/hypopneas, awakenings, as well as of poor quality of sleep and epileptic seizures. Pinard et al. [124] examined

sleep structure in a group of 20 children and adolescents and found frequent awakenings with decreased total sleep time and decreased REM duration in all the cases. Increased apnea-hypopnea index was noticed in 13 out of 20 children, and in a half of the patients (10 out of 20) nocturnal paroxysmal activity was found. Association of nocturnal paroxysmal activity with apnea-hypopnea syndrome was noticed in eight of these ten children. Systematic screening of SDB and sleep quality should be, though, a part of routine management.

Duchenne Muscular Dystrophy

Duchenne muscular dystrophy (DMD) is the most frequent progressive muscular dystrophy in childhood. It belongs to a group of dystrophinopathies, resulting from mutation in the dystrophin gene, located on the short arm of the X chromosome (Xp21) and transmitted in a sex-linked recessive manner. The incidence of DMD of approximately 1:3000 up to 1:6000 male births [118] makes it the most widespread neuromuscular disease. The clinical picture includes classic myopathic features (difficulty in climbing stairs, rising from the floor, progressive muscle wasting with increased lordosis, and diminished tendon reflexes). In contrast to general atrophy, there is striking pseudohypertrophy of the calves. At about the age of 10–12 years, the children start being wheelchair bound and developing cardiomyopathy. After the introduction of the palliative steroid therapy, the median age for the loss of ambulation has increased by approximately two years. However, the prognosis depends also on respiratory care. Over the past 20 years, improvement in ventilatory support and multidisciplinary care has improved the survival rate of DMD patients till their 30s [125].

Signs of early respiratory insufficiency are usually first detectable in sleep; hence, polysomnographic examination is indispensable there. Annual monitoring is recommended if vital capacity declines to <65 %; the patients should undergo twice yearly a visit to a pulmonary and cardiology pediatric specialists and somnologist after confinement to a wheelchair, after their vital capacity falls below 80 % and/or after the age of 10 years [115]. Increased risk for SDB includes hypopnea, central and obstructive apnea, and hypoxemia. Suresh et al. [126] presume a bi-phase presentation SDB, with OSA found in the first decade and hypoventilation more commonly seen at the beginning of the second decade. However, the patients' sleep can also be influenced by medication and/or physical factors. Disorders of initiating and maintaining sleep were significantly more frequent in children treated by steroids. The need to start a career where immobility forms to obstacle seems to be a major burden on the quality of sleep, and sleep disturbances are strongly associated with immobility [125]. Gradually increasing number of nocturnal awakenings leads to daytime sleepiness and morning headaches and can contribute to cognitive impairment. Although SDB treatment with NIV support is very important, the treatment should take into account its complexity as the aim to improve quality of life and reduce the high morbidity and early mortality associated with DMD.

Myotonic Dystrophy

Myotonic dystrophy, particularly type 1, is the most frequent adult-onset muscular dystrophy characterized, besides clear neurological symptoms, by fatigue and daytime sleepiness [127]. The inheritance is autosomal dominant with amplification of a trinucleotide repeat localized at the chromosome 19q13.2. The clinical severity depends on the number of repeats. The congenital form is usually related to a maternal transmission and shows the greatest number of repeats. Facial diplegia and dysmorphic craniomandibular structures aggravate respiratory difficulty. Mixed central and obstructive apneas have been reported in children with congenital myotonic dystrophy [115].

Besides the presence of frequent central apnea, not only in REM sleep but occurring throughout all the sleep stages, and less frequent obstructive events [128], there is impairment of neural respiratory control indicated by abnormal response to hypoxia and hypercapnia, which is due to the CNS involvement. The excessive daytime sleepiness, often described in children with the initial stage of the myopathy, is probably independent of the apnea-hypopnea index, oxygen desaturations, or sleep fragmentation, occurring because of the direct effect of CNS lesions as indicated by the cognitive and neuropsychological deficits [129].

Charcot-Marie-Tooth Disease (CMT)

CMT represents a widely heterogeneous group of diseases as regards the genetic background, mode of transmission, and clinical and neurophysiological manifestation. As the most common form, CMT1 is characterized by progressive peroneal muscular atrophy and transmitted as a rule by an autosomal dominant trait of inheritance. Their prevalence is 3.8 per 10,000 in population, with most cases located at the chromosome 17p11.2 [95]. The clinical picture varies from very mild up to the quite severe wheelchair-bound handicapped phenotype.

Restrictive pulmonary impairment has been described in association with phrenic nerve dysfunction, diaphragm dysfunction, or thoracic cage abnormalities. Sleep disturbances may be associated with paresthesia, muscle cramps, or RLS. Fatigue, and reduced sleep quality, has been described in adult patients; the references about children are scarce. Sleep apnea was found to be common in CMT patients, and the apnea-hypopnea index correlated with disease severity. Since causative treatment for CMT is not available, sleep-related symptoms should be recognized and treated in order to improve quality of life [130]. Bi-level positive airway pressure (BiPAP) is more appreciate treatment than positive airway pressure (CPAP). The prominence of peripheral neuropathy as a cause of the RLS in CMT may justify treatment with neuropathic medication (e.g., gabapentin) better than dopaminergic agents [131].

Conclusions

Sleep disturbances in children with neurodevelopmental disabilities are highly prevalent and tend to be chronic. A specific sleep phenotype could be characteristic of a particular disorder and can represent a clinical clue for the diagnosis.

The clinical evaluation of children with neurodevelopmental disabilities should always comprise a detailed investigation of sleep problems, disturbances, and complaints reported by parents. Also the contributing factors to sleep disorders should be analyzed (either psychiatric or medical) in order to choose the best treatment for sleep disorders that are often overlooked and considered as a minor issue in relation to the general condition of the child. A comprehensive awareness of sleep disorders in these patients becomes essential for the appropriate recognition and effective treatment.

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