CLINICAL REVIEW

Narcolepsy in childhood

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Summary Narcolepsy is a chronic disease commonly diagnosed in middle adulthood. However, the first symptoms often appear in childhood and/or adolescence. Pediatric cases of narcolepsy are among the most often underrecognised and underdiagnosed diseases. This fact raises questions about the reasons for such diagnostic delay from the clinical point of view, and what kind of help can be expected from auxiliary diagnostic examinations. The aim of the review is to stress some specific features of the clinical picture in children, to discuss the role of auxiliary examinations at the onset of the disease including sleep studies, tests for human leukocyte antigens (HLAs), and cerebrospinal fluid hypocretin (Hcrt) measurement, and to draw attention to the most common cases of pediatric misdiagnosis. Frequent cataplectic attacks at an early age should lead to detailed clinical, neuroimaging and genetic examinations to rule out a secondary etiology. Beside the typical symptoms (excessive daytime sleepiness, cataplexy, sleep paralysis, hypnagogic/hypnopompic hallucinations), some additional features including obesity and nocturnal bulimia can appear. Also poor school performance and emotional disorder are common complaints. Treatment should start as early as possible to avoid the development of problems with progress at school, and close cooperation between school and family should be maintained.
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Introduction

Narcolepsy is a lifelong but non-progressive disease characterized by abnormal regulation of the sleep—wake cycle and increased penetration of rapid eye movement (REM) sleep. According to current international classification[1] narcolepsy is characterized by excessive daytime sleepiness, a condition typically associated with cataplexy (i.e., narcolepsy with cataplexy) and/or other REM sleep phenomena such as sleep paralysis and hypnagogic or hypnopompic hallucinations. Sleep attacks have a sudden onset sleep during the day, with sleep usually longer in children than in adults. Cataplexy is muscle weakness, often precipitated by intense emotion or excitement; it has a sudden onset, short duration and bilateral involvement. Hallucinations and sleep paralysis

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occur in the transitional period between wakefulness and sleep. Hallucinations cover visual, acoustic and sensory percepts; they are termed hypnagogic when they occur at sleep onset, and hypnopompic during awakening. Sleep paralysis is characterized by inability to move on waking for a period lasting seconds to minutes. Additional symptoms include disrupted nocturnal sleep and, at times, automatic behavior.

In children, cataplexy and other REM sleep phenomena can develop with some delay, and excessive daytime sleepiness may, at first, be the only clinical feature leading to the diagnosis of narcolepsy without cataplexy. Hence, important for the prognosis and severity of the disease are children's sleep studies and further auxiliary examinations, particularly tests for the human leukocyte antigen (HLA) haplotype and, if possible, for cerebrospinal fluid (CSF) hypocretin (Hcrt)-1 levels.[2]

Retrospective studies suggest that about half of the adults with narcolepsy had the onset of symptoms already in their youth,[3] but a large prospective series identified only 5% of the cases as prepubertal.[4] As a rule, diagnosis is established with a delay of more than 10 years,[5] and many cases remain underdiagnosed. According to the latest multicentric epidemiological studies,[6−8] the prevalence of narcolepsy—cataplexy is approximately 0.05% in the European as well as in the North American populations. Incidence and prevalence data for narcolepsy in children are lacking. One of the most important reviews of children's cases presented by Challamel et al.[9] based on literature and on their own series of 97 pediatric cases, found the mean age at onset to be 9 years, with 8% of the group aged 5 years or less.

Familial cases are well described and the risk of having a first-degree relative with narcolepsy—cataplexy is 1−2%, representing a 20- to 40-fold increase in the risk of having this disease.[10−12] According to some authors,[8] the age at onset clearly differentiates patients with a positive family history of narcolepsy who have an earlier onset from those without a family history, in whom the disease becomes manifest at a later age. Clinical and polygraphic findings may indicate that young age at onset is associated with increased severity of the condition with a higher frequency of cataplexy and decreased mean sleep latency on the multiple sleep latency test (MSLT). However, these results can be influenced by strong evidence of a progressive age-related decrease in the number of sleep-onset REM periods (SOREMPs) and a progressive increase in the mean sleep latency on MSLT as a function

of age. In their group of 383 unrelated narcoleptic patients who were divided into five age groups (the youngest ones under the age 21, the oldest ones over 65). Dauvilliers et al.[13] showed a linear and highly significant decrease ($p = 0.000002$) in the number of SOREMPs and an age-related progressive increase ($p = 0.002$) in the mean sleep latency on the MSLT. Similarly, further studies have shown that children with EDS and cataplexy have a markedly reduced sleep latency and a high prevalence of SOREMPs during the MSLT in comparison with adults.[4,14,15,19] This finding is also related to the severity of cataplexy as assessed from the clinical history, in which the disease, at first progressive, shows a declining frequency of cataplectic attacks later in older age.[13] These findings can also be explained as a possible feature of a slow ''burn-out'' of the basic pathophysiological mechanisms of the disease; accompanying complaints may abate after several years or rather decades of the disease duration. A further longitudinal follow-up of cases with childhood and adulthood onset is desirable.

Have pediatric cases a key role in the pathophysiology of narcolepsy?

One of the current pathophysiological models for narcolepsy—cataplexy involving an autoimmune-mediated destruction of Hcrt/orexin-containing neurons[16] points at the importance of early diagnosis of the disease. Some of the recent studies[17−19] have shown a favourable effect of autoimmune suppressive treatment using intravenous immunoglobulins (IVIGs) in early stages of the disease, but these were open labeled trials and all positive effects were reported subjectively, indicating a possible placebo effect. Other authors have not confirmed this experience with steroid treatment.[20]

A further feature that can support the co-existence of autoimmune mechanisms in narcolepsy—cataplexy is a remarkable association with the HLA system. More than 90% of Caucasian patients with a sporadic incidence of narcolepsy—cataplexy share a specific HLA DR2/15 allele, HLA DQB1*0602. Recent studies have shown that HLA DQA1*0102 and DQB1*0602 are primary susceptibility factors for narcolepsy.[12]

The advantage of blood HLA typing in children is in its non-invasive approach and in its high predictive value that helps in establishing the diagnosis. This examination has a lower pathognomonic value in familial cases in that it is less frequently expressed.[10]

However, no other inflammatory processes or immune abnormalities associated with narcolepsy have been found.[21] The systemic measurements of immune functions that have been studied show no abnormalities. The lymphocyte subpopulation, erythrocyte sedimentation rate, complement levels and C-reactive protein are all within the normal range even in very early stages of the disease. Anti-nuclear antibodies and all other tests for systemic autoimmune abnormalities have shown negative results. Similarly, cerebrospinal fluid analysis revealed an unincreased frequency of oligoclonal IgG bands. Nor did brain tissue histology support the hypothesis of autoimmune involvement. No signs of inflammation or lymphocyte accumulation were found.[12]

Up to now, the etiology of the focal neurodegenerative process affecting Hcrt neurons in the lateral hypothalamus remains unknown. Several animal models are now available in rodents, particularly knockout mice. The results show that Hcrt-2 knockout animals are less affected than Hcrt peptide knockout animals, thus pointing to a role for Hcrt-1 in increasing the severity of the phenotype.[22]

From the clinical point of view, it is known[23] that in non-narcoleptic subjects the Hcrt-1 level in CSF is stable from infancy up to old age. However, an undetectable Hcrt-1 level in the cerebrospinal fluid (CSF) is one of the most important diagnostic features of narcolepsy—cataplexy in children as well as in adults.[24—26] As follows from experimental studies[27], the decline of CSF Hcrt level in neurotoxically induced lesions of Hcrt neurons in rats starts very early (2—6 days after neurotoxin, hypocretin-2 saporin (Hcrt-2-SAP), is applied to the lateral hypothalamus), and this effect is permanent without any recovery. A loss of 73% of Hcrt neurons causes a 50% decline in CSF hypocretin; consequently, in narcoleptic patients with undetectable CSF, virtually all of the Hcrt neurons should be lost. If the hypothetic autoimmune role in the development of narcolepsy is accepted, the effect of immunosuppressive therapy in children with narcolepsy should depend on the earliest timing and on continual therapeutic management as in other autoimmune diseases. Another pathophysiological possibility relates to the damage done to Hcrt-containing neurons by some as yet unknown agents where autoimmune mechanisms may have only a supportive role to play. A possible role of prenatal nutritional factors, and/or toxic agents is suggested by some authors. The seasonal predominance of birth in narcoleptics suggests the role of early life environmental factors, interacting with genetic susceptibility to cause damage to the hypocretin system.[28]

Clinical signs and symptoms in different age groups

The diagnosis of narcolepsy in childhood raises several concerns. Concomitant cataplexy, sleep paralysis and hypnagogic and/or hypnopompic hallucinations are not always detected and, when present, may be difficult to recognize. Short periods of cataplexy may be mistaken for normal falls and/or misdiagnosed as atonic epileptic attacks. Daytime sleepiness may not be obvious to parents of very young children and may be missed before kindergarten.[4] Sleep behavior can more often be recognized by teachers as apathy and pathological sleepiness while the parents may misjudge the behavior of their child as normal napping. Prolonged nocturnal sleep, difficult awakening in the morning and aggressiveness prior to being awakened are commonly seen, too. However, sleepiness can be hidden behind other abnormal behavior such as irritability, aggressiveness or social withdrawal and shyness.[29]

Difficulties of diagnosis in infant and toddler cases

Narcolepsy in infants and toddlers is extremely rare and the diagnosis belongs to the most difficult ones due to atypical features, impossibility to describe any own feelings and lack of polysomnographic criteria.

The earliest age at onset was described by Hood and Harbord,[30] who followed-up a questionable case of infant narcolepsy with attacks of hypotonia appearing since the second week of life and marked, in the infant and toddler age, by excessive daytime sleepiness. Atypical features of this case included occasional transient hemiparesis following states of hypotonia and lasting up to a few hours, psychomotor delay and generalized tonic—clonic seizures of epileptic origin. The episodes of paroxysmal hypotonia were followed up to the age of 5 years, when they occurred approximately three times per week and could be induced by a strong emotional trigger such as laughing or crying. In contrast with an attempt at 15 months of age, where stimulants had no favourable effect, at the age of 5 years, significant improvement in daytime sleepiness was achieved with a dose of 10 mg of dexamphetamine given twice a day. The child was HLA DQB1*0602 positive, and a sleep study brought discrepant results.

Another case of infancy-onset narcolepsy, which was later recognized as the only case of hypocretin-deficient narcolepsy due to a mutation in the

hypocretin gene,[31,32] was described by Nevsimalova et al.[33] The boy's case history included perinatal risk factors with a slightly pronounced hypotonic syndrome during infancy. Cataplectic attacks, described by his parents as brief spells of head dropping provoked by laughter while the child was sitting in his pram, first appeared at the age of 6 months. Imperative sleep in spells lasting a few minutes up to 1 hour had also been observed from his infancy. From the age of 5 years, he had suffered from severe bulimia manifested mainly during the night. From puberty on, he had had states of hypnagogic hallucinations, sleep paralysis, automatic behavior and behavioral-disorder abnormalities. He also suffered from unquiet nocturnal sleep accompanied by slight periodic leg movements. Narcoleptic-tetrad symptoms were partially controlled with modafinil (previously methylphenidate) and fluoxetine (previously imipramine, clomipramine). He was found to be HLA DQBQ*0602 negative. Repeated MSLT showed extremely short sleep-onset latency with predominant SOREMPs. Similarly, nocturnal PSG recordings (and/or 24-h monitoring when the child was young) revealed fragmented sleep with SOREMPs. His CSF demonstrated four oligoclonal bands and an undetectable level of Hcrt-1. From the immunological point of view, an interesting finding of thymus enlargement on CT was made. Subsequent thymectomy revealed chronic inflammatory changes. Neuroimaging methods (CT, MR, PET) showed normal results.

A more typical case with excessive daytime sleepiness beginning at the age of 10 months was observed by Hayes.[34] Sharp and D'Cruz[35] described a case of a 12-month-old boy who had since infancy suffered from excessive sleepiness that showed improvement in response to non-pharmacological narcolepsy therapy. Another infancy or toddler-age onset of narcolepsy symptoms was described by Winter et al.[36] and Lent and Somajni.[37] Witmans and Kirk[38] drew attention to the fact that some ''clumsy'' children who would often fall and sometimes suddenly and intermittently refuse to walk can camouflage cataplectic attacks. They described a girl with specific episodes of collapses to the floor while playing and laughing and falling asleep soon afterward.

Specific features of narcolepsy in preschool and school children

In healthy children, physiological and scheduled daytime napping rapidly declines between the age of 18 months and 5 years.[39] On the other hand, overwhelming sleep attacks in young children suffering from narcolepsy are constant, usually of longer duration in comparison with adolescents or adults. In some patients chronic waxing and waning of drowsiness during the day with periodic superimposed sleep episodes can be observed. The children are sleepy in the kindergarten, during lessons at school, on their return home in the afternoon their naps can last up to 2—3 h and are generally non-restorative.[40,41] Owing to inattentiveness resulting from permanent sleepiness they have school problems including academic deterioration and poor social integration. Due to prolonged attacks of sleep, they have less time for play as well as for homework. In young children, restlessness and motor hyperactivity can sometimes overcome the drowsiness[42] and make behavioral problems.

Cataplectic attacks usually provoked by strong emotion (most often by laughter) are reported in 80.5% of idiopathic cases[9]; these are as common in childhood as later in life. However, cataplexy may not be present during the initial years of the disease and/or if it is present, it can, at first, be only sporadic. The children tend to attach little significance to this attack. Sometimes they may feel ashamed and this is where repeated, target-oriented questioning to obtain the anamnestic data is needed. In rare cases, an isolated appearance of cataplexy preceding excessive daytime sleepiness may pose a diagnostic problem as it can be misdiagnosed for astatic—myoclonic epileptic seizures.[33,4,29]

Additional REM sleep symptoms—hypnagogic hallucinations and sleep paralysis—have been observed in 39%, respectively, in 29% children presenting with idiopathic narcolepsy,[9] according to other authors[42] in more than 50%. The bizarre nature of hypnagogic hallucinations and sleep paralysis may confuse children who are then too embarrassed to discuss their problems; consequently, parents must sometimes help to clarify the child's experience.

Unlike adults, children suffering from narcolepsy often report sleep drunkenness (confusional arousals, sleep inertia). Parents may experience major conflicts with the child because of confusional arousals, particularly when the children are woken-up in the early morning for school.[42] Automatic behavior sometimes accompanying narcolepsy in children can imitate states of clouded consciousness of epileptic origin and can be misinterpreted for partial seizure epilepsy.

Nocturnal sleep disturbances appearing with vivid dreams and often with nightmares are very frequent in children and could be misdiagnosed as parasomnias. On the other hand, REM behavior disorder may appear even as one of the first

symptoms of the disease,[43] possibly in combination with the parasomnia overlap disorder.

Additional symptoms of childhood narcolepsy

Personality and behavioral changes

Narcolepsy even in its early stages affects also the patients' personality. Children and adolescents become more introverted, most of them with features of depression. Changes in their character comprise feelings of inferiority, sorrowfulness, emotional lability or sometimes irritability or even aggressiveness. Interpersonal conflicts are easy to arise within the family and at school.[44] Poor attention and concentration, and disciplinary problems due to sleepiness in class lead to false accusations of drug use. Daytime sleepiness frequently leads to impaired consolidation of memory, to decreased concentration and to executive dysfunction. Adults who have been diagnosed with narcolepsy frequently give a history of attention deficit disorder[45] owing to inattentiveness and sometimes also to hyperactivity superimposed on their sleepiness. Frontal lobe dysfunction from loss of affect control is a feature shared by both these conditions.

Stores et al.[46] compared in their multicentric study 42 children suffering from narcolepsy and 18 children with excessive daytime sleepiness alone. Both groups showed significantly higher rates of behavioral problems and depression in comparison with controls. Their quality of life was poorer and showed more educational problems.

Beside behavioral changes the children also appear to have emotional problems. Khatami et al.[47] recently described amygdala dysfunction in narcolepsy—cataplexy cases suggesting the involvement of limbic structures in affectivity modulation. These findings can help to explain specific personality changes occurring even in young patients. On the other hand, a ''narcoleptic personality'' may have a biological background and be supported by expression of genes involved in narcolepsy—cataplexy alone. These genes may have a role to play in the modulation of emotions[48] and in other character features.

Obesity

Obesity (sometimes accompanied by nocturnal eating disorder) is another frequently coexisting problem in childhood narcolepsy; it may occur in at least 1/4 of all children suffering from narcolepsy.[49,42] The tendency towards excessive weight gain is manifested relatively early in the course of the disorder.[50] Correlation of Hcrt and leptin metabolism seemed to help explain the pathogenesis of this symptom,[51] though a detailed study[52] failed to substantiate this suggestion. Data obtained from 370 subjects (111 healthy controls, 93 narcoleptic subjects with CSF Hcrt-1 deficiency, 72 narcoleptic subjects with normal CSF Hcrt-1 level, and 89 subjects with other sleep disorders) showed no difference in the serum leptin level. Similarly, the CSF leptin levels and the CSF leptin over serum leptin ratios were not different between groups. The data, therefore, gave no support to a role for leptin in mediating an increased body mass index (BMI) in narcolepsy. Another study devoted to eating disorders and metabolism in narcoleptic patients[53] revealed that narcoleptic patients have a lower basal metabolism than the controls, and although they eat less than the controls they have a tendency to being overweight. Both a lower metabolism and subtle changes in eating behavior (rather than in calorie intake) are responsible for the positive energy balance leading to increased BMI in adults and probably in pediatric narcoleptic patients as well.

Precocious puberty

Experimental studies suggest that the hypocretin system has a ramified brain and spinal projection, regulating not only autonomic functions, sleep and metabolism,[54] but playing also a major role in regulating the hypothalamo—pituitary—gonadal (HPG) axis.[55] A few cases of severe narcolepsy—cataplexy emerging in childhood in close coincidence with obesity and primary precocious puberty have been described.[56] The association of narcolepsy—cataplexy with obesity and precocious puberty may reflect a broadly based hypothalamic abnormality. Less probably, precocious puberty could be indirectly related to the rapid weight gain or metabolic dysregulation.

The importance of childhood narcolepsy due to medical condition (secondary, symptomatic cases)

Secondary (symptomatic) narcolepsy—cataplexy caused by a structural brain lesion is much more common in childhood than in adulthood involving 1/5 to 1/3 of all pediatric patients.[9,41] In comparison with idiopathic cases, the age at onset in

symptomatic ones is lower (6 years on average) with cataplexy as the predominant symptom. Up to 1/4 of the patients described in the relevant literature[9] have a history of status cataplecticus. The most extensive study of secondary cases was published by Nishino and Kanbayashi.[57] They collected 26 cases of childhood narcolepsy—cataplexy; the most frequent causes were inherited diseases and brain tumors (each group comprised 12 cases), only very rarely was the disease caused by some other condition (one case by head trauma, and one case by encephalitis). Summarizing the literary data, the authors found that 15 children suffered from symptomatic cataplexy or cataplexy-like isolated attacks.

While symptomatic cataplexy is frequently associated with non-hypothalamic structures, and the most frequent causes are inherited diseases (Coffin—Lowry syndrome, Norrie disease and Niemann—Pick disease), in symptomatic narcolepsy—cataplexy the hypothalamic region is affected as a rule. The most frequent structural abnormalities include brain tumors particularly in the suprasellar region, predominantly craniopharyngeomas[58] with Niemann—Pick disease type C prevailing among genetic diseases[59,60] followed by the Prader—Willi syndrome, more rarely by some other structural hypothalamic lesions caused by cerebral palsy, multiple sclerosis and/or less well-known neurological abnormalities.[9]

Careful history taking with neurological examination complemented by laboratory tests (including genetic examination) and neuroimaging methods (computerized tomography, CT or, better still, magnetic resonance imaging, MRI) should clarify the secondary etiology of the disease.

Diagnostic criteria for childhood narcolepsy

The diagnostic criteria in childhood cases vary with age. The diagnostic symptoms of narcolepsy are usually less typical in young children. Sleep studies have not yet been standardized. Daytime sleepiness may be difficult to recognize in early childhood, children can be misidentified as hyperactive, in the older ones as learning disabled, inattentive and lazy. Cataplexy in young age may be overlooked, disregarded as clumsiness or misdiagnosed as epileptic drop attacks.[29] Moreover, feelings during sleep paralysis and/or hypnagogic hallucinations cannot be explained by young children.

Bearing in mind behavioral problems in early childhood and possible manifestations of sleep disorders, pediatricians should include narcolepsy in their differential diagnosis. A clinical examination covering detailed anamnestic data and following auxiliary examinations is useful for diagnosis. A survey of the advantages and disadvantages of the recommended diagnostic procedures used in adults[22] and modified for children is given in Table 1.

Sleep diary and actigraphy

Sleep diary drawn in younger children by their parents and in older children by themselves should illustrate the amount of daytime and nocturnal sleep and exclude the irregularity caused by inappropriate regime and poor sleep hygiene. False excessive daytime sleepiness linked to the delayed (or advanced) sleep phase syndrome could be eliminated also by actigraphic recordings. Actigraphy seems to be a useful screening method in cases of children's narcolepsy illustrating repeated naps during the day.[40,41] In comparison with adult cases this method, if used in childhood, is better applicable with respect to the longer duration of sleep attacks during this period of life.

Polysomnographic studies

Daytime and overnight polysomnographic recordings

In toddlers and young preschool children, continuous daytime records using the ambulatory monitoring technique can serve as a useful diagnostic method instead of the multiple sleep latency test (MSLT). A minimum of three physiological parameters[61] should be recorded — electroencephalogram (EEG), electrooculogram (EOG) and chin electromyogram (EMG).

Long-term monitoring can exclude epileptiform discharges that are often thought of as starting the attacks and confirm SOREMPs accompanied by sleep attacks as an important feature of clinical diagnosis. Moreover, polygraphic monitoring can by chance detect cataplectic attacks as evidence of the narcolepsy syndrome. In symptomatic cases detailed EEG examination complemented with neuroimaging methods is necessary to specify the diagnosis of secondary narcolepsy.[2]

Overnight recordings eliminate other causes of excessive daytime sleepiness such as sleep disordered breathing and/or periodic limb movements. However, their presence does not rule out the presence of narcolepsy. These disorders can coexist in a significant minority of narcoleptic patients.[62] Overnight polygraphic sleep records also exclude parasomnias as a cause of fragmented and unquiet nocturnal sleep and/or verified REM behavior disorder as one of the possible symptoms of narcolepsy.[43]

Table 1 Advantages and disadvantages of diagnostic procedures in childhood narcolepsy

Parameters	Advantages	Disadvantages	Suggested indications
MSLT after nocturnal PSG Mean sleep latency < 8 min, 2 or >SOREMPs	Excludes concurrent disorder (SDB) Painless and available method	The method is not validated for preschool age and not applicable in younger age when long-term PSG monitoring is recommended False negative results can be obtained at the beginning of the disease False positive results can be found in adolescent sleep phase delay or in poor sleep hygiene with chronic sleep deprivation	School-age and adolescent children
CSF Hcrt-1 measurement Direct assay < 110 pg/ml	Highly specific and sensitive in cases with cataplexy In cases without cataplexy a possible development of cataplectic attacks can be predicted	Invasive and painful examination Method needs to be standardized in specific centers, not available everywhere Low sensitivity in cases without cataplexy	Infants, toddlers and preschool children when narcolepsy is suspected
HLA typing DQB1*0602 positive	Higly sensitive in cases with cataplexy In cases without cataplexy possible development of cataplectic attacks can be predicted	Low specificity Low sensitivity in cases without cataplexy	A positive finding can support diagnosis in early stages of the disease Method is available at any age including infants and toddlers

Multiple sleep latency test (MSLT); polysomnography (PSG); sleep-onset rapid eye movement periods (SOREMPs); cerebrospinal Fluid (CSF); hypocretin (Hcrt)-1; human leukocyte antigen (HLA); and sleep—disordered breathing (SDB).

Multiple sleep latency test (MSLT)

MSLT can occasionally be used in early preschool children, with more precise results obtained in school-age children.[63] However, normal values in children are different from those in adults. Particularly adolescents may develop physiological hypersomnia.[64] In preadolescents, a mean sleep latency of less than 10 min can be assumed as abnormal.[41] In some situations, children may become hypervigilant during the MSLT with marked alerting to minor stimuli, and MSLT can be invalidated by technical problems. Generally speaking, MSLT in children requires much more patience from technicians, and may sometimes need also a number of repeats.[42] Serial studies may be required in incipient childhood narcolepsy to establish a definitive diagnosis.[65]

In children as well as in adults, two or more episodes of SOREMPs are considered pathological. However, Huang et al.[66] observed a group of 35 children suffering from narcolepsy. Narcoleptics with cataplexy had a higher number of SOREMPs and much shorter mean sleep latency in MSLT than narcoleptics without cataplexy. The presence of two or more SOREMPs does not seems to be a sufficient diagnostic tool to identify narcolepsy in children when cataplexy is not present.

In most prepubertal cases described in the literature[4] SOREMPs during MSLT and nocturnal recordings are fully expressed, though in some early stage cases the polygraphic criteria may not have been met. The latency between clinical symptoms of narcolepsy and positive findings of SOREMPs in MSLT can last several months[25] up to, according to our own observation, several years, particularly in cases with a delayed development of cataplexy.

In prepubertal children and adolescents, narcolepsy may be misdiagnosed owing to the presence of short sleep latency, often accompanied by multiple SOREMPs on the MSLT as a result of chronic sleep deprivation and delayed sleep phase syndrome.[1]

Human leukocyte antigen typing

In children as well as in adults, HLA typing is a useful diagnostic tool. The presence of the DQB1*0602 haplotype makes the diagnostic

probability of narcolepsy much more likely, though DQB1*0602 negativity does not exclude it. Particularly, in children with multiple-case history in families, where the age at the disease onset used to be younger, negative HLA findings have no informative value.[10,21] The absence of DQB1*0602 in young children with sporadic narcolepsy may also indicate a symptomatic origin of the disease. HLA examination has a predictive value in children with excessive daytime sleepiness, though currently free from cataplectic attacks.[41] However, recent studies have shown also a protective HLA haplotype despite the presence of DQB1*0602 and a narcolepsy—predisposing haplotype other than DQB1*0602, in spite of the fact that HLA DQB1*0602 homozygosity doubles to quadruples the risk for narcolepsy.[67,21]

Hypocretin evaluation in cerebrospinal fluid

Kanbayashi et al.[23] showed that the CSF level of Hcrt-1 remains stable from early infancy up to old age; hence, an undetectable level of Hcrt-1 in CSF is a very valuable diagnostic marker in children. However, diagnostic lumbar puncture is an invasive method and some parents do not accept it in their child. Estimating the Hcrt-1 level from serum would be much more beneficial particularly in young children, but at the present time no positive results are available. In prepubertal children undetectable Hcrt-1 levels in CSF appear together with the first clinical manifestations of narcolepsy—cataplexy,[25] even before polysomnographic criteria are met. Experimental data support the fact[27] that the CSF Hcrt level starts declining nearly immediately after the loss of Hcrt-containing neurons in the lateral hypothalamus. How long a decreasing CSF Hcrt-1 takes to prepare the background for human narcolepsy—cataplexy to become manifest, and/or if it just joins the first symptoms of the disease, should be clarified. The outcome of such investigation could facilitate treatment management. The declining level of CSF Hcrt-1 is closely related predominantly to HLA positive cases.[68] The situation is even more complicated in HLA negative narcolepsy—cataplexy cases and/or in narcolepsy without cataplexy where CSF Hcrt-1 level is usually normal. Undetectable Hcrt level can be one of the factors predicting a later appearance of cataplexy, especially in children so far diagnosed only with isolated excessive daytime sleepiness.

Complementary tests excluding secondary (symptomatic) cases

Considering the large proportion of symptomatic cases, all children with suspected narcolepsy should be examined using neuroimaging methods. CT and/or, better still MRI should be used in all preschool and early school-age children to exclude brain tumors as a cause of the disease. In children with phenotypic features of the Prader—Willi syndrome and excessive daytime sleepiness the underlying diagnosis should be clarified by detailed genetic examination. Progressive neurological impairment together with intellectual decline accompanied by cataplexy and daytime sleepiness may point to a neurometabolic background of the disorder. In such cases, Niemann—Pick disease, type C should be excluded or verified by specific enzymatic examination, and NPC1 mutation by molecular genetic examination could be proved. Sudden drop attacks resembling cataplexy-like events should draw attention to the Coffin—Lowry syndrome.[69,70] Generally speaking, a high rate of cataplectic attacks, HLA negativity and detectable CSF Hcrt-1 level increase the probability of symptomatic cases. The greater our suspicion, the more detailed tests should be employed to specify the underlying complaint.

Differential diagnosis of childhood narcolepsy

Our diagnostic consideration is naturally influenced by age. In early childhood, excessive daytime sleepiness is not immediately recognized as abnormal before cataplexy appears.[4] Very often cataplectic attacks may be mistaken for seizures and, in particular, atonic seizures, or else drop attacks may be diagnosed instead of cataplexy.[29] The main distinguishing features are: retention of consciousness in cataplectic attacks and a history of episodes triggered by sudden, usually positive emotion (laugh, pleasure, awaiting a pleasant feeling). The child can remember these short episodes of cataplexy, as distinct from epileptic seizures he or she is not amnestic to such attacks. Frequent cataplectic attacks should always rule out a secondary etiology of the disease.

In preschool and early school children, the sleep-related breathing syndrome should first be excluded if excessive daytime sleepiness (or sleepiness camouflaged by hyperactivity) occurs alone. The most common causes comprise obstructive sleep apnea or, less frequently, upper airway resistance syndrome[29]: the clinical history of snoring and breathing pauses together with nocturnal polysomnographic examination should clarify this diagnosis. Excessive daytime sleepiness can be a consequence of head trauma, encephalitis, nocturnal seizures or, in coexisting epilepsy, an excessive dosage of antiepileptic drugs.

In adolescence, excessive daytime sleepiness can be a symptom of delayed sleep phase or just poor hygiene combined with sleep deprivation. Probably the most difficult distinction is that between narcolepsy and idiopathic hypersomnia. Particularly in cases of narcolepsy without cataplexy with delayed maturation of polysomnographic criteria (delayed appearance of multiple SOREMPs), distinguishing between these entities is nearly impossible. Naps of longer duration are quite typical of childhood, and non-refreshing feelings after awakening from the naps can be present in both entities.[71] Longitudinal clinical follow-up and repeated MSLT are necessary to confirm the diagnosis.

Atypical hypnagogic hallucinations in older children can be misdiagnosed as schizophrenia, while apathy and depressiveness accompanying children's narcolepsy may be mistaken for episodes of depression. On the other hand, pseudocataplexy, a phenomenon analogous to pseudoseizures, or simple malingering are also rarely referred to in adolescents.[72,73]

Treatment and management of pediatric cases

An autoimmune suppressive course of treatment (intravenously supplemented immunoglobulins) in the earliest stages of the disease is believed to be one of the most effective possibilities,[17–19] albeit in need of more clarification. On the other hand, there is no benefit in orally administered steroid treatment.[20]

According to generally accepted opinion,[4,42,41] there is no specific treatment for narcolepsy in children in comparison with adults. The most common medicaments used for children are modafinil,[74] atomoxetine and methylphenidate against sleepiness. Prescription of pemoline is now limited due to its hepato-toxicity and therefore it has been withdrawn in some countries. If cataplexy is the dominant symptom, venlafaxin, clomipramine and/or fluoxetine are usually prescribed. The recommended dosage should be based on body weight, and the initial dose should be of the lowest potency and highest efficacy. According to extremely rare experience from the earliest childhood,[30] any treatment with stimulants should be postponed to preschool age. In toddlers, the metabolic pathways involved in the processing of stimulants may not yet be fully matured.

According to the latest knowledge,[75] sodium oxybate in narcoleptic adolescents is relatively well tolerated and as effective as in adults. Sodium oxybate improves cataplexy, daytime sleepiness as well as fragmented nocturnal sleep. It seems to be an efficacious drug in the treatment of serious cases of narcolepsy—cataplexy in childhood. However, more experience of randomized, double blind placebo-controlled trials is still needed in children and therefore, in many countries sodium oxybate has so far been reserved for postpubertal children.

It is important to start the treatment in school age as early as possible to avoid academic problems. Nevertheless, any drug therapy must take into account possible adverse effects. The treatment thus balances avoidance of adverse effects, including tolerance, with the need to maintain an active life. Stimulant (and incidentally anticataplectic) medication represents only one component of the therapeutic program.

Some non-pharmacological interventions can enhance the therapeutic effect such as regular sleep—wake schedules and planned naps. At least two planned daytime naps at lunchtime and during the afternoon (between 4 and 5) are recommended in prepubertal and pubertal children to enhance refreshment, daytime alertness and performance.[76]

Children should be encouraged to participate in after-school and sports activities; similarly, a well-designed exercise program can have a stimulating effect. Adolescents should be counseled not to drive, use alcohol or engage in dangerous activities while drowsy. A close cooperation between school teachers and parents is desirable. Monitoring for emotional problems and depression, and providing appropriate career counseling is also important. Achieving optimal quality of life is the main target for the management of childhood narcolepsy.[42] However, more research is needed to improve the treatment of pediatric cases so as to keep this chronic disease under control. Children and their parents should be informed about the lifelong nature of the treatment.

Final remarks

Narcolepsy in childhood is one the most often underrecognised and underdiagnosed diseases. Increased daytime somnolence may sometimes be the only sign for a number of years; the sleep attacks become increasingly long, lasting up to hours; confusional arousals with features of sleep drunkenness may be present. Cataplexy may develop with delay, and in addition, some children are too embarrassed to discuss their symptoms, thus adding to the diagnostic difficulties. The narcoleptic tetrad is present only exceptionally. In some cases polygraphic criteria may be missing in the early stage of the disease. However, looking

for the HLA DQB1*0602 haplotype and undetectable CSF Hcrt-1 levels will greatly facilitate diagnosis. Beside the typical symptoms, some additional features including obesity and nocturnal bulimia may appear. Also poor school performance and emotional disorder are common complaints. Treatment should start as early as possible to avoid the development of problems with progress at school, and close parent—teacher cooperation should be maintained. In the future, childhood narcolepsy can be a key to our understanding of the pathogenesis of this disease.

Practice points

- Narcolepsy in childhood is one the most often underrecognised and underdiagnosed diseases. Pediatricians should be aware of its symptoms and send children to sleep specialists as soon as possible to prove or to rule out the diagnosis and to start with adequate treatment.
- Diagnosis should invariably be supported by complete polysomnographic examination including MSLT. Lack of SOREMPs does not disprove the diagnosis; longitudinal follow-up and additional tests (HLA, CSF Hcrt-1) are also needed.
- Childhood narcolepsy needs a lifelong treatment program that includes, beside medication, also behavioral treatments to avoid educational and personality problems.
- Early onset of frequent cataplectic attacks may point to a symptomatic etiology of the disease. Detailed neurological, neuroimaging (MRI, CT) and genetic tests are desirable to rule out any secondary cause.
- More clinical and therapeutic (including randomized trials) experience of childhood narcolepsy is needed to cope with the handicaps and to protect the child against the consequences of the disease.

Research agenda

- Childhood narcolepsy can be a key to our understanding of the pathogenesis of the disease. The effectiveness of immunosuppressive treatment in the earliest stages of the disease can help to clarify the substantial role of autoimmune processes in focal CNS hypocretin neurodegeneration.

- Follow-up CSF Hcrt-1 examination in the earliest stages of the disease, when excessive daytime sleepiness is the only symptom of narcolepsy and no SOREMPs are present on MSLT, can help answer the question of when hypocretin deficiency actually appeared.
- Randomized, double blind, placebo-controlled trials (similar to those in adults) should be undertaken to clarify the efficacy of the most recommended treatment (modafinil, sodium oxybate).
- The seasonal predominance of birth in narcoleptics suggests that early environmental factors may have influenced prenatal development. If this hypothesis is well founded, this influence should be more expressed in childhood cases.
- According to existing sporadic literary data, the earlier narcolepsy appears, the more severe the course of the disease is likely to be. Can age at onset really influence the further course of the disease? More evidence is obviously needed there.

Acknowledgements

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