Narcolepsy with cataplexy in children

Liliane Parise, Virginie Dupont, Roxane Rossignol

CHU Tivoli, Department of Pediatrics, Sleep unit for children and adolescents, La Louvière, Belgium

lparise@chu-tivoli.be

Keywords

Narcolepsy, cataplexy, children, excessive somnolence

Abstract

Narcolepsy with cataplexy is a rare chronic condition without cure that can be controlled if treated adequately. The disease often starts in childhood and adolescence. Excessive daytime somnolence is the main symptom for which parents consult in somnology. Cataplexy, which corresponds to loss of tonus without loss of consciousness can appear later.

Other less specific symptoms can be identified such as hallucinations at sleep onset or at wake-up time, sleep paralysis and disturbed night time sleep.

The disease has major repercussions on school life and family life. Treatment with stimulants is required, together with good sleep/wake hygiene, treatment of the co-morbidities, psychological support of the child and his family and eventual school measures to allow for uncontrolled excessive daytime somnolence.

Rapid identification and treatment of the disease increases the chances of better integration in society as it will favor completion of studies and normalize professional life.

Introduction

Narcolepsy is one of the central hypersomnias which include type 1 narcolepsy with cataplexy, type 2 narcolepsy without cataplexy, idiopathic hypersomnia and Kleine-Levin syndrome (1). In this article, we will focus on narcolepsy with cataplexy.

It is estimated that one third of pediatric cases of narcolepsy develop the first symptoms before the age of 15, 50% before the age of 20. Narcolepsy with cataplexy is rare before the age of 4. Different studies have shown that cataplexy is present in 50 to 70% of narcoleptic children. The child has excessive daytime sleepiness and an irrepressible need to sleep, even in unusual situations, favored by inactivity and boredom. The negative consequences on social life and learning can be very significant.

Confronted with hypersomnia, differential diagnosis should be made based on the case's history, data from sleep diaries and sleep questionnaires and additional examinations. Hypersomnia secondary to neurodegeneration, more frequently found in children whose disease begins at very young age, must be excluded.

Epidemiology

Based on the number of annual births in France, the incidence of the disease is estimated at 0.05%.

Clinical case

The first consultation toke place when the girl is 6 years old. Rapid weight gain had been noted in the past year. Her BMI rose from 21 to 27. She had been complaining of fatigue during the day for two months. She was referred to the sleep consultation because she sleeps in class.

In her antecedents, allergic rhinitis treated by an antihistamine (stopped because of excessive daytime sleepiness) is mentioned. Her sleep is described as restless and of poor quality with great difficulty waking up in the morning. There is no ronchopathy. During the consultation, she falls asleep in her chair. Awake, she has sagging chin and eyelids.

The adapted somnolence scale is 20 (abnormal above 15). At this stage, a night polysomnography followed the next day by sleep onset latency tests are scheduled. The sleep registration shows a total sleep time of 397minutes, in which the child falls asleep in REM sleep in 1 minute. Sleep is divided by 4 waking periods each followed by falling asleep in REM (SOREM – Sleep Onset Rapid Eye Movement). Sleep is restless. There is no sleep apnea syndrome.

Latency tests: 5 out of 5 sleep onset are in REM sleep, in less than a minute. The medical work up is completed by HLA typing which shows the presence of the DQB10602 allele found in narcolepsy. There is no profile of neurodegeneration on MRI. The biology is normal. Lumbar puncture is not carried out.

At the 2nd consultation, the child describes loss of muscle tone, especially during laughing episodes. She describes hallucinations on falling asleep and nightmares. She continues to gain weight. The diagnosis of narcolepsy with cataplexy is retained. Treatment with modafinil is started as well as dietary management. A systematic nap on return from school is implemented.

Nine months after the start of treatment, the nights are better and getting up is spontaneous. She still exhibits drowsiness after school recess, episodes of cataplexy at laughter, and hallucinations at sleep onset. Weight gain is not stabilized. Given the persistence of drowsiness and the inability to increase modafinil, the treatment is increased by 18 mg of methylphenidate SR (sustained release) in the morning. This leads to a disappearance of drowsiness and a marked improvement in school results.

Additional work up was carried out with an endocrinology assessment that did not show any signs of early puberty, and a psychological work up that showed normal cognitive capacities. The treatment by psycho-stimulants motivated a cardiac assessment which came back normal. The weight gain motivated the prescription of an annual polysomnography in order to exclude sleep apnea syndrome.

For a few months, parents adhered to dietary monitoring and the child lost weight. Her BMI fell from 35 to 32. However, faced with the persistence of certain symptoms (hallucinations and cataplexies), an opinion was requested from the reference center for child narcolepsy in Lyon, France . On their advice, venlafaxine (an antidepressant with an effect on hallucinations and cataplexy) is added to the treatment. The overall evolution was favorable. Unfortunately, 6 months later, the dietary support was abandoned and the child regained weight.

Discussion (2)

Since the work published in the early 2000s, it has been established that narcolepsy with cataplexy is due to destruction of orexin A / hypocretin 1 neurons of the lateral hypothalamus. This neuropeptide is a mediator of the arousal system.

Early development of the disease, before puberty, is not exceptional.

Excessive daytime sleepiness is the most consistent and debilitating symptom. It is essential to differentiate between fatigue and sleepiness, which can be difficult in young children. One must think about the disease when a child falls asleep in an unusual situation and when his total sleep time over 24 hours increases compared to children of his age and / or when naps re-appear after the age of 7 or before if they had been abandoned. Unlike in adults, these naps are not necessarily refreshing. The narcoleptic child does not increase his time spent in bed.

Abnormal sleepiness can lead to behavioral and attentional disturbances and impact schooling even though these children may have normal intellectual potential. Difficulties are often encountered with the teacher who does not understand what is going on.

The negative views of other children, especially if a significant weight gain is associated, can lead to a loss of self-esteem or even depression. It is important to take these aspects into account when providing treatment.

Cataplexy is the second most common symptom of the disease. It is a sudden loss of muscle tone, often related to pleasant emotions such as laughter. The prospect of a reward can trigger the attack of cataplexy. In children, this symptom is inconstant and may not be described by parents.

It may also appear late in relation to drowsiness (several years) and present, at the onset of illness, in the form of facial hypotonia with drooping eyelids, sagging lower face, opening of the mouth and protrusion of the tongue. Facial movements can be observed. Video can help with diagnosis.

The other less frequent symptoms, such as hallucinations on falling asleep (hypnagogic) or on awakening (hypnopompic) and sleep paralysis are difficult to objectify, especially in young children. The older child will talk about nightmares and not being able to get up in the morning while awake. Only 13% of children would present the complete tetrad of narcolepsy (3)

The narcoleptic child has difficulty maintaining sleep with frequent awakenings and possible periodic leg movements.

In 60% of children under 10 years of age, the disease is associated with significant and rapid weight gain. This symptom can be a warning sign and precede the onset of excessive daytime sleepiness by several months. These children have a BMI above 25, and various studies have shown a lower basal metabolic rate than normal. A hypothesis to try to explain this weight gain calls into question the dysregulation of orexin, which plays a role in the regulation of sleep and vigilance but also in the regulation of eating behaviors (4).

There is not always an increase in food intake, but studies have shown a change in eating behavior, in an effort perhaps to control drowsiness by changing meal times and by eating at night, resulting in an unstructured diet. The inactivity associated with hypersomnia worsens the situation. Rapid weight gain could be responsible for some cases of early puberty (5).

It is in narcoleptic-obese children that we observe the most absenteeism from school: they are drowsy, their weight gain is rapid (10 to 20 kg), cataplexy attacks start earlier. 30% of them show signs of depression. It is also in these patients that one will follow the possible appearance of a syndrome of sleep apnea. However, it seems that, despite the obesity, this syndrome is not very frequent thanks to a good tonicity of the airways.

Triggering factors

Environmental factors could play a role in promoting an inflammatory process. Significant stress, H1N1 influenza vaccination, viral infection, beta-hemolytic streptococcal infection have been implicated in various studies. At the genetic level, narcolepsy with cataplexy is one of the diseases most associated with HLA class 2. There is therefore a strong autoimmune component. A study published in Nature in 2018 reinforces the hypothesis of the autoimmune origin of the disease. In this study, narcoleptic patients have an increased level of certain T lymphocytes which could attack neurons producing hypocretin (6).

Familial cases are rare, where predisposition is more likely than direct transmission. A study in France in 1994 showed 7.4% of family cases; within these, only 9% could correspond to a genetic susceptibility within the family.

Diagnosis

Diagnosis is difficult and requires a careful history to rule out sleep deprivation, phase delay, toxic substance abuse in adolescents, depression, symptoms suggesting sleep apnea syndrome. It is necessary to question the taking of drugs such as antihistamines and certain analgesics.

A sleepiness scale adapted to the child makes it possible, on the basis of 10 simple questions, to assess sleepiness in different situations. When dealing with a young child, it is important to rule out secondary narcolepsy.

Complementary examinations (7,8)

Polysomnography followed by sleep onset latency tests constitute the reference examinations making it possible to objectify the clinical criteria. A 24-hour sleep diary for 3 weeks before the polysomnography is requested in order to quantify sleep and its distribution. It is useful to exclude sleep deprivation.

During the recording of the night's sleep, narcoleptic children fall asleep with a latency of often less than 10 minutes and in REM sleep for 50% of them. Sleep is fragmented by many spontaneous awakenings or in connection with periodic movements of the legs.

The presence of a sleep apnea syndrome does not exclude the diagnosis of narcolepsy. Latency tests are carried out the day after the polysomnography: this is the recording of 5 naps of 20 minutes every 2 hours. In children, 2 sleep onsets in REM sleep or an average sleep onset latency less than or equal to 8.2 minutes are reliable markers for the diagnosis of pediatric narcolepsy (8). These characteristics may be absent at the onset of illness in children. If necessary, the latency tests will be repeated after some time.

In 85 to 100% of narcoleptic patients the HLA DQB 10602 allele is found.

An HLA DQB10602 positive patient has a high probability of developing the disease. However, this is not an absolute criterion because it is present in 20% of people without symptoms. Its absence has a negative predictive value for patients with atypical cataplexies.

HLA typing can be a good examination if we want to avoid lumbar puncture. A hypocretin-1 dosage of less than 110 pg / ml in the cerebrospinal fluid is pathognomonic for childhood narcolepsy (9). Although a specific biomarker, the dosage of hypocretin may not be conclusive at the onset of disease. It will then be necessary to re-check one to two years later.

MRI of the brain is necessary to exclude secondary narcolepsy; it is always carried out in young children.

Co-morbidities (10)

- Attention deficit with hyperactivity disorder is found to be twice as important in narcoleptic patients.
- Sudden weight gain and obesity, especially if the disease begins before 10 years.
- Sleep apnea syndrome especially in the presence of significant weight gain.
- Sleepwalking, nightmares.
- Periodic leg movements.
- Anxiety, depression: 25% have signs of depression. They have a more hallucinations and sleep paralysis. Depression has a major impact on the quality of life.

In the presence of obesity and attention deficit hyperactivity disorder, it is important to question sleep in order to exclude narcolepsy.

Management (11)

Although not curable, narcolepsy can be treated effectively with different approaches. It will be necessary, above all, to ensure a healthy lifestyle and regular sleep-wake rhythms. A nap after returning from school is essential. During school time, 1 or 2 scheduled 20-minute naps may be recommended but rarely accepted. It is essential to inform teachers and to propose arrangements for the child's working time.

Psychological support for the child and his parents is advised. It will help the child to accept his illness, his constraints and the difficulties of everyday

life. Parents may find themselves helpless when confronted with their child's disease, not knowing how to help and support.

Drug treatment (12,13)

The treatment must consider co-morbidities.

Currently, in Belgium, three molecules are available to treat narcolepsy in children. To treat excessive daytime sleepiness, psycho-stimulating drugs such as modafinil and methylphenidate can be used. Venlafaxine acts on cataplexy, hallucinations and sleep paralysis.

Other molecules are available for adults but not yet for young people under 18, sodium oxybate acts on all symptoms including weight. A study published in the Lancet Child Adolescent Health in 2018 validated sodium oxybate as a treatment for narcolepsy in children (14). It is not approved in Belgium for children and adolescents up to the age of 18.

Pitolisant which stimulates vigilance and wakefulness was approved in Belgium in 2018 as a 2nd line treatment for adult patients with narcolepsy.

A study is underway in children, and the results look promising. Well tolerated, it acts on alertness and cataplexy.

Solriamfetol is a new psychostimulant which, in January 2020, was approved by the European Commission to improve wakefulness and reduce drowsiness in adults with narcolepsy. Safety and efficacy in young people under 18 has not yet been proven.

Follow-up

- Cardiac check-up before starting the psycho-stimulating treatment, then once a year. - Blood pressure and general growth monitoring.
- Neuro-cognitive assessment and attentional tests to rule out learning problems.
- Endocrinological check-up once a year as there is a risk of early puberty especially in girls (17% especially if the disease starts early).
- Metabolic check-up once a year: obese narcoleptic children have an 18% risk of developing metabolic syndrome, hepatic steatosis or type 2 diabetes.

Finally, if some symptoms or complaints remain after correct treatment of narcolepsy, there could be an undiagnosed underlying problem such as a sleep apnea syndrome or an upper airways resistance syndrome.

Conclusion

Narcolepsy with cataplexy is a chronic and debilitating disease which begins in childhood in 30% of subjects. There is frequently a delay in the onset of symptoms, and incomplete forms of the disease are frequent in young age in both clinical manifestations and electrophysiological signs.

Cataplexy can be delayed for several years. Children may also be seen with cataplexy and normal levels of hypocretin at lumbar puncture. In this case, it will be necessary to control it at a later stage.

Excessive daytime sleepiness is usually the reason for consultation, but sudden unexplained weight gain may also be the reason. Both symptoms will need to be addressed fast, as untreated drowsiness leads to school absenteeism in 26% of cases and school failure in 36% of cases. Bullying is not uncommon.

The early diagnosis allows the establishment of treatment and family and school support.

Care should be taken to make the differential diagnosis between fatigue and drowsiness.

In young children, secondary narcolepsy should always be excluded.

Lumbar puncture is not systematic in Belgium as the sample must be sent to the Netherlands or France and the cost is not reimbursed. However, in case of doubt, it must be done.

When the symptoms are well controlled, the child will develop favorably, particularly at the level of schooling. A study carried out within the reference center for child narcolepsy in Lyon showed that there was no difference between the population of narcoleptic patients and a control population.

Conflict of interest

The authors have no conflict of interest to declare.

REFERENCES:

1. American Academy of sleep médecine. International classification of sleep disorders, third version
2. Lecendreux M., Dauvilliers Y., Arnulf I., Franco P. Narcolepsy with cataplexy in the child : clinical evaluation and therapeutical management. Rev Neurol (Paris) 2008;164:646-57
3. Challamel MJ, Mazzola ME, Nevsimalova S. and al, Narcolepsy in children,Sleep 1994; 17 : 17-20
4. Kotagal S, Krahn LE, Slocum N. A putative link between childhood narcolepsy and obesity. Sleep Med 2004;5:147-150
5. Plazzi G, Parmeggiani A, Mignot E. Narcolepsy-cataplexy associated with precocious puberty. Neurology 2006; 1577-1579
6. Latorre D, Kallweit U, Armentani and al. Tcells in patients with narcolepsy target self-antigens of hypocretin neurons. Nature 2018; 562:63-68
7. Pizza F, Franceschini C, Peltola H and al. Clinical and polysomnographic course of childhood narcolepsy with cataplexy. Brain 2013; 136 : 3787-3795
8. Pizza F, Baratean L, Jaussent I and al. Validation of Multiple Sleep Latency Test for the diagnosis of pediatric narcolepsy type 1. Neurology 2019; 93
9. Arii J, Kanbayashi T, Tanabe Y and al. CSF hypocretin-1 levels in childhood narcolepsy and neurologic disorders. Neurology 2004; 63 : 2440-2442
10. Lecendreux M, Lavault S, Lopez R and al. Attention deficit/ Hyperactivity Disorder symptoms in pediatric narcolepsy; a cross sectional study. Sleep 2015; 38:1285-1295
11. Lopez R, Arnulf I, Drouot X, Lecendreux M, Dauvilliers Y. Consensus. Prise en charge des patients hypersomniaques : quelle stratégie? Médecine du sommeil. 2017;14:119-124
12. Lecendreux M. Pharmacological management of narcolepsy and cataplexy in pediatric patients. Pediatr. Drugs 2014; 16: 363-372
13. Barateau L, Lopez R, Dauvilliers T, Treatment options for narcolepsy, CNS Drugs 2016; 30: 369-379
14. Plazzi G, Ruoff C, Lecendreux M, Dauvilliers Y, and al. Treatment of pediatric narcolepsy with sodium oxybate : a double-blind placebo-controlled, randomized- withdrawal multicentre study and open-label investigation. Lancet Child Adolesc.Health 2018; 2: 483-494