Paediatric Narcolepsy: A Rare and Easily Forgotten Diagnosis

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Abstract
Paediatric narcolepsy is a rare entity and remains under-diagnosed in many situations. This study presents the demographic and clinical features and laboratory findings of children diagnosed with narcolepsy in our hospital. It discusses the approach to investigating and managing these children. It is important that clinicians should be more aware of this condition, as without a diagnosis children may receive incorrect treatments or no treatment at all, for what after all is a potentially treatable condition.

Key words
Cataplexy; Paediatric; Multiple sleep latency test; Narcolepsy

Introduction

The term narcolepsy is derived from the Greek, "seized by somnolence". It is a rare but non-progressive neurologic disease. It is characterised by the classical tetrad, namely excessive daytime sleepiness (EDS), cataplexy, hypnagogic/hypnopompic hallucinations and sleep paralysis. Since its first description more than 100 years ago, it remains under-diagnosed. The prevalence in the adult population internationally is estimated to be around 1 in 2000. Data in the paediatric population are lacking.

According to the International Classification of Sleep Disorders, second edition (ICSD-2), narcolepsy is diagnosed by the following criteria:

Narcolepsy with cataplexy:
• Excessive daytime sleepiness occurring almost daily for at least three months
• Definite cataplexy, defined as a sudden transient loss of muscle tone triggered by emotion
• Should be confirmed by nocturnal polysomnography followed by an multiple sleep latency test (MSLT). The mean sleep latency time is less than or equal to eight minutes and two or more sleep onset rapid eye movement periods (SOREMPs) are observed following sufficient nocturnal sleep during the night prior to the test.
• Alternatively cerebrospinal fluid (CSF) hypocretin level should be less than or equal to 110 pg/ml or one third of mean normal control value.
• Excluding other causes

Narcolepsy without cataplexy:
• Excessive daytime sleepiness occurring almost daily for at least three months
• Typical cataplexy is not present
• The diagnosis must be confirmed by nocturnal polysomnography followed by MSLT. The mean sleep latency on MSLT is less than or equal to eight minutes and two or more SOREMPs are observed following sufficient nocturnal sleep during the night prior to the test.
• Excluding other causes
It has been estimated that the diagnosis of narcolepsy is delayed for more than 10 years after presentation in most cases. One should have more vigilance in looking for this condition, as it is treatable. It has also been widely accepted that it causes a huge socioeconomic impact in untreated cases. Reports of cases and series in children are also scarce. We hope this study will raise clinicians’ awareness of this condition.

**Method**

We used the keyword "narcolepsy" to search the electronic clinical correspondence database in Great Ormond Street Hospital NHS Trust, London, United Kingdom, which contained patient information from 1991 till the present. We identified nine cases of confirmed paediatric narcolepsy, aged 6-14. We performed a retrospective review of the demographics, presenting complaints, co-morbidities, diagnoses and treatments of those patients.

**Results**

**Demographics and Presenting Complaints**

There were two males (22.2%) and seven females (77.7%), aged from six to fourteen years (mean age 10.1 years) at the time of diagnosis. All presented with excessive daytime sleepiness, often with other associated complaints and co-morbidities. Most had their onset of symptoms several years prior to diagnosis. The longest time from symptom onset to diagnosis is seven years. He defaulted after an initial assessment in 2001 and was re-referred in 2008. All patients were suspected to have narcolepsy after the initial assessment in our hospital and relevant tests were arranged in the first visit. Demographic and clinical information of the subjects are summarised in Table 1. Figure 1 shows the time from symptom onset to diagnosis in these patients.

**Classical Narcoleptic Symptoms and Other Associated Symptoms**

Five subjects (55.5%) had cataplexy, which all experienced as sudden loss of tone associated with laughter or emotional outburst. They are all described as sudden generalised weakness or give-way on emotions or laughter. Two (22.2%) had sleep paralysis and two also had hypnagogic hallucinations. Only one of the nine subjects had all four classical symptoms (excessive daytime sleepiness, cataplexy, hypnagogic hallucinations and sleep paralysis) on presentation. One subject had three classic symptoms on presentation. Seven subjects (77.7%) had other associated symptoms: six of them had disruptive sleep pattern and four of them had weight gain. One adolescent girl was also found to have insulin resistance and polycystic ovarian syndrome and another girl also suffered from growth hormone deficiency.

Brain tumours are considered as major differential diagnoses in subjects with associated endocrine disorders. Epilepsy, hypothyroidism and Obstructive Sleep Apnoea Syndrome (OSAS) were also considered in some subjects. But the presenting features of most of the subjects are pointing to narcolepsy and tests are directed towards that diagnosis. No clinical features are suggestive of inherited disorders.

**Body Mass Index and Blood Pressure**

Mean body mass index (BMI) was 23.9 (16.7-36.2). All subjects but one had normal blood pressure on presentation. One of the subjects had a borderline high blood pressure on presentation and would be followed up on that.

**Investigations Before Polysomnography+Multiple Sleep Latency Test**

Five had a sleep electroencephalography (EEG), of which three were reported as normal; of the two abnormal EEGs, one was reported as a disrupted sleep pattern and the other as less rapid eye movement (REM) sleep. No subjects had CSF hypocretin level measured. Six had their HLA typing done, four patients were positive to DQB1*0602 and one result was pending at the time of study. One of them was human leukocyte antigen (HLA) negative. Magnetic resonance imaging (MRI) brain was performed in eight cases and CT brain was performed in one case. All of the brain scans were normal.

Some tests are ordered individually, such as thyroid function tests and trypanosomal titre. They were all normal.

**MSLT Features**

MSLT results were available in eight out of nine cases. MSLT was booked and pending in one case, which was also included as a confirmed case because excessive daytime sleepiness and cataplexy were present. All MSLTs were preceded by overnight polysomnography (PSG). There was no abnormality such as sleep disordered breathing or sleep apnoea in all PSGs. Six out of eight cases have MSLT features of narcolepsy. Mean sleep
<table>
<thead>
<tr>
<th>Sex/Age</th>
<th>Presenting complaint</th>
<th>Associated features</th>
<th>Other features</th>
<th>Approximate years from symptom onset to diagnosis</th>
<th>BMI</th>
<th>Sleep EEG</th>
<th>HLA typing</th>
<th>PSG+ MSLT</th>
<th>Treatment</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 M/14</td>
<td>EDS</td>
<td>Nil</td>
<td>Disrupted sleep, sleep talking</td>
<td>7</td>
<td>24.8</td>
<td>Disrupted sleep</td>
<td>Negative</td>
<td>3/3</td>
<td>Modafinil</td>
<td>Good</td>
</tr>
<tr>
<td>2 F/14</td>
<td>EDS</td>
<td>Cataplexy, hallucinations, sleep paralysis</td>
<td>Weight gain, insulin resistance, PCOS</td>
<td>3</td>
<td>36.2</td>
<td>Normal</td>
<td>Not available</td>
<td>No</td>
<td>Modafinil</td>
<td>No response</td>
</tr>
<tr>
<td>3 F/9</td>
<td>EDS</td>
<td>Cataplexy</td>
<td>Disrupted sleep, weight gain, hyperphagia, growth hormone deficiency</td>
<td>1</td>
<td>20.7</td>
<td>Normal</td>
<td>Not available</td>
<td>3/5</td>
<td>Methylphenidate</td>
<td>Good</td>
</tr>
<tr>
<td>4 F/7</td>
<td>EDS</td>
<td>Cataplexy, hallucinations</td>
<td>Nil</td>
<td>1</td>
<td>19.7</td>
<td>N/A</td>
<td>Not available</td>
<td>3/4</td>
<td>Nil</td>
<td>Not applicable</td>
</tr>
<tr>
<td>5 M/14</td>
<td>EDS</td>
<td>Nil</td>
<td>Disrupted sleep, weight gain, sleep talking</td>
<td>1</td>
<td>27.1</td>
<td>N/A</td>
<td>DQB1 *0602</td>
<td>3/3</td>
<td>Modafinil</td>
<td>Good</td>
</tr>
<tr>
<td>6 F/6</td>
<td>EDS</td>
<td>Cataplexy</td>
<td>Disrupted sleep</td>
<td>1</td>
<td>17.7</td>
<td>N/A</td>
<td>Pending</td>
<td>0/5</td>
<td>Nil</td>
<td>Not applicable</td>
</tr>
<tr>
<td>7 F/6</td>
<td>EDS</td>
<td>Nil</td>
<td>Disrupted sleep, nightmares</td>
<td>1</td>
<td>16.7</td>
<td>Less REM sleep %</td>
<td>DQB1 *0602</td>
<td>2/5</td>
<td>Methylphenidate</td>
<td>Good</td>
</tr>
<tr>
<td>8 F/14</td>
<td>EDS</td>
<td>Sleep paralysis</td>
<td>Nil</td>
<td>2</td>
<td>20.3</td>
<td>N/A</td>
<td>DQB1 *0602</td>
<td>3/4</td>
<td>Nil</td>
<td>Not applicable</td>
</tr>
<tr>
<td>9 F/7</td>
<td>EDS</td>
<td>Cataplexy</td>
<td>Disrupted sleep, weight gain, increased appetite</td>
<td>2</td>
<td>31.8</td>
<td>Normal</td>
<td>DQB1 *0602</td>
<td>Not available</td>
<td>Modafinil</td>
<td>Pending</td>
</tr>
</tbody>
</table>

*Concurrent intake of modafinil; **Disturbed by unfamiliar environment

BMI: body mass index; EDS: excessive daytime sleepiness; EEG: electroencephalography; HLA: human leukocyte antigen; MSLT: multiple sleep latency test; PCOS: Polycystic Ovarian syndrome; PSG: polysomnography; REM: rapid eye movement; SOREMP: sleep-onset rapid eye movement sleep period
latency was 5.6 minutes (range from 2.4-11.2 minutes). Two or more SOREMPs were found in six cases. The case with the classical tetrad had a negative MSLT (MSLT 11.2 minutes with no SOREMPs) with the concurrent intake of modafinil. Although patient 6 did not have any SOREMPs in MSLT, she was considered to have the diagnosis because of the presence of cataplexy. Her sleep was disturbed by unfamiliar environment during PSG+MSLT testing. Patient 7 was also considered to be positive. Although the mean sleep latency was more than 8 minutes, 2 SOREMPs were detected. The diagnosis was made by the treating neurologist, after considering the clinical features and the positive HLA typing.

**Pharmacological Treatment**

Six subjects received stimulant treatment. All were initially treated with modafinil for excessive daytime sleepiness and none of them received sodium oxybate. No treatment was directed to cataplexy.

The outcome after treatment was recorded from the clinic letters from follow-up. It was the impression from both the families and the clinicians. Two of them showed a positive response to modafinil. In two cases the treatment was changed to other stimulants with good response. One of them was prescribed modafinil and was pending clinic follow up. The reason why three patients failed modafinil is not completely clear. Excluding compliance issue, there may be individual difference in drug response.

**Discussion**

It is well known that diagnosing paediatric narcolepsy is difficult. It is reasonable to suspect under-diagnosis as we only identified nine cases over 20 years from our clinical correspondence database. There was insufficient data to calculate the true prevalence in the population served by our centre. The classical combination of symptoms is rare in children and symptoms may be non-specific and easily misinterpreted. Moreover, the current gold standard, MSLT, is validated for children older than eight years old. Four subjects were younger than 8 years old in this study. The MSLT results had limitations and are interpreted in an individual basis. The diagnosis could only be made after considering other clinical and laboratory features e.g. presence of cataplexy and positive HLA typing. For that reason, other tests are being developed to aid diagnosis.

The single most important aspect of diagnosis is the clinical history. This is especially true for narcolepsy without cataplexy, in which classical cataplexy is absent. There is a range of differential diagnoses for excessive daytime sleepiness. Diagnosis of narcolepsy relies heavily on the establishment of hypersonmolence and its associated symptoms. Older children can describe excessive daytime sleepiness quite reliably. A sleep log, which includes sleep time, wake time, numbers of naps, description of sleep quality etc, can be enormously helpful in young children and their parents.
The classic tetrad of narcolepsy rarely presents in paediatric narcoleptics. Indeed in a series of cases, no subjects had sleep paralysis. A similar phenomenon is observed in our study. Childhood cataplexy, on the other hand, also has its own characteristics, apart from the classical description. Serra et al described the features of cataplexy in a series of paediatric narcoleptics. Forty-three percent of them have a fall during an attack. Knee, head and jaw were the most commonly involved body parts, followed by eyelids, arms and trunk. The usual triggers e.g. emotion, laughter, were not always present. Dhondt et al presented a case of paediatric narcolepsy with partial facial cataplexy.

Guilleminault et al described the clinical features of fifty-one childhood narcoleptics. The presenting complaints for those younger than five years old were unexplained abrupt falls onto the ground, aggressive behaviour, abrupt dropping of objects and sleep disturbance. Narcoleptics aged five to ten presented with repetitively falling asleep in class, inarousable in the morning with excessive napping, falling in school, learning difficulties and behavioural problems. Narcoleptics aged ten to twelve presented with excessive daytime sleepiness, abrupt falls and school failure.

There are other clinical features outside the classic tetrad. It had been shown that childhood narcoleptics were more likely to be obese, thus having higher risk of OSAS. Mean BMI of our subjects approach the overweight range. Three of them have BMI over 25. Fragmented nocturnal sleep was commonly seen in childhood narcoleptics and caused disruptive change in sleep cycle and daytime performance. REM sleep behaviour disorder and precocious puberty were also reported in childhood narcoleptics. These findings are well reflected in this study.

There are clinical scales to describe daytime sleepiness objectively. The Epworth Sleepiness Scale and Stanford Sleepiness Scale are good examples. The Epworth Sleepiness Scale is a well-known self-rated scale to measure daytime sleepiness in adults. It was first introduced in Australia in 1991. The scales consist of a series of questions to rate sleepiness in daytime activities. They generally show good sensitivity and specificity to narcolepsy in adults. But there are very few correlation studies for paediatric populations.

A modified version of the Epworth Sleepiness Scale for children was developed because some of the activities described in those scale would not happen in children, e.g. driving a car, or causing arousal e.g. watching TV. But there is no good evidence that the paediatric form correlates well with paediatric cases. Chan et al did show a low sensitivity of the Modified Epworth Sleepiness Scale Score in children with a high apnoeic-hypopnoeic index.

The Paediatric Daytime Sleepiness Scale (PDSS) was developed specifically for paediatric population. It consists of eight self-administered questions to describe how sleepy he/she was in daytime activities. It correlates well with excessive daytime sleepiness in more severe sleep disorders. A recent study by Yang et al showed that a Chinese version of PDSS is useful to screen for daytime sleepiness caused by narcolepsy.

There are also questionnaires to help to identify excessive daytime sleepiness objectively in children, namely childhood sleep habits questionnaires and paediatric sleep questionnaires. However they are developed mainly for research purpose and their clinical use is unproven.

Physical examination should include measurement of body mass index and blood pressure, though it is unusual to have an abnormal physical examination. It is important to look for secondary causes of narcolepsy. The most common secondary causes of narcolepsy in children were inherited disorders (e.g. Niemann-Pick disease type C and Prada-Willi syndrome), tumours and head trauma. It is reported that up to one-fifth to one-third of paediatric narcolepsy were secondary in origin. It is prudent to carefully exclude secondary causes in history, physical examination and the use basic blood tests and brain imaging. One uncommon but specific finding in physical examination is the loss of deep tendon reflex during cataplexy.

Nocturnal PSG followed by MSLT remains the gold standard of the diagnosis of narcolepsy with or without cataplexy. It has specific practice parameters and standards.

- The test is sensitive to sleep deprivation and circadian effect.
- The test has not been validated as a diagnostic test in children younger than eight years old.
- Normal and abnormal ranges of sleep latencies have not been established when these tests are administered at times other than the hours between 8am and 6pm.
- The patient must be free of drugs that influence sleep for at least 15 days (or at least five times the half life of the drug and longest acting metabolite).
- The sleep-wake schedule must have been standardised for at least seven days before the PSG testing; and nocturnal PSG should be performed on the night immediately preceding the MSLT to rule out other sleep disorders that could mimic the diagnostic features of narcolepsy.
Moreover, the test may be difficult to interpret if the patient failed to sleep for an adequate time in the PSG. It may also be difficult to keep patients awake before and between MSLT naps. Unfortunately it does not correlate well with the clinical scales e.g. Epworth Sleepiness Scale. In our study most of our patients fulfilled the MSLT diagnostic criteria. The ones who did not meet it might be due to the concurrent intake of modafinil or the sleep disturbance by unfamiliar environment.

A MSLT is time and labour-consuming. As it has its limitations and pitfalls, other adjunctive tests are developing to aid narcolepsy diagnosis.

Since 1980s, researchers have found a close association between narcolepsy and certain HLA haplotypes. Among those, DQB1*0602 has the closest association with narcolepsy. It is present in about 90% of patients with narcolepsy with cataplexy among different populations. But it is also present in about a quarter of the normal population. So it has a good sensitivity but poor specificity in picking up narcolepsy with cataplexy. DQB1*0602 is used as an adjunct in diagnosing narcolepsy and other central hypersomnia. This association was also the basis of the underlying autoimmune mechanism of the disease.

Unfortunately, the association is almost not present in those without cataplexy. Only 40-50% of patients with narcolepsy without cataplexy were positive for DQB1*0602.

In keeping with a presumed autoimmune mechanism, it has been found that CSF hypocretin level is a specific marker for narcolepsy with cataplexy. Hypocretin is a neuropeptide primarily secreted in the hypothalamus. In 2002, researchers had noted undetectable level of CSF hypocretin in 2 prepubertal narcoleptics. After that, there were numerous studies of the hypocretin model. It is now thought that narcolepsy is caused by an immune destruction of hypocretin-secreting neurones, though detailed the pathophysiological mechanism is not well delineated. It had been shown that CSF hypocretin drops rapidly after destruction of the associated neurones, much earlier than the appearance of clinical symptoms. CSF hypocretin measurement has been adopted in the clinical setting. It has a test sensitivity similar to HLA DR2 typing, but it is much more specific than HLA typing. For that reason, it was included as one of the diagnostic criteria for narcolepsy with cataplexy in ICSD-2 in 2005. The test has an obvious drawback for the need of a lumbar puncture. It is useful in young subjects who have problem with MSLTs.

Low CSF hypocretin levels in narcoleptics without cataplexy were not observed though. They were also usually DR2 negative on HLA typing. This exemplifies the difficulty in diagnosing narcolepsy without cataplexy. Thus narcolepsy with cataplexy is thought to be a more homogenous entity, with specific HLA association and low CSF hypocretin. Narcolepsy without cataplexy, along with other central hypersomnias e.g. idiopathic hypersomnia, represents a heterogeneous group of diseases with various presentations. A simple algorithm for diagnosing and treating narcolepsy is given in Figure 2.

Strategies for the treatment of narcolepsy with or without cataplexy in children are mainly extrapolated from adult studies. Clinicians should make sure that patients and their families have a clear understanding of the diagnosis and its consequences. The treatment should aim at relatively normal daily routines with suitable modifications. Regular naps in the daytime could be a good adjunct of treatment, though it might not be adequate as a primary treatment option.

Traditional stimulants such as amphetamines and the novel "awaking" agent modafinil have become a standard treatment of EDS of narcolepsy in adults. Clinical data in children are still very limited, though these drugs appear to be effective in younger age-groups with good tolerability. It is currently not licensed for children younger than 12 years old. The treatment options for childhood narcoleptics are mainly off-label. There are some reports to support the use of modafinil in childhood narcoleptics and attention deficit hyperactivity disorder with good results and minimal side effects. Many clinicians prefer modafinil over traditional stimulants because modafinil has a better side effect profile. A reasonable approach would be to try modafinil first, and then switch to other stimulants if there is no clinical response. There are no head-to-head trials comparing the efficacy of modafinil and traditional stimulants in children.

Sodium oxybate, which had an undesirable reputation in the past, is licensed to treat narcolepsy with cataplexy in adults only. It is also used to treat childhood narcolepsy, especially in severe cases. Its side effect profile limits its use in paediatric population.

Cataplexy responds best to agents with noradrenaline reuptake blocking property. Therefore off-label use of tricyclic antidepressants is commonly used as treatment for childhood cataplexy, such as clomipramine and imipramine. There is no systemic clinical trial of anti-cataplectic agents in children. Moller and Ostergaard used venlafaxine, a serotonin and noradrenaline reuptake blocker, as the treatment for narcolepsy with cataplexy and hypnagogic hallucinations, and showed a favourable response.
There are very few studies on the prognosis of narcolepsy. In a series of 20 paediatric narcoleptics, half of the treated patients showed good response to medications. 6 out of the 20 patients had residual daytime sleepiness on follow up. More studies are required to clarify the natural history and prognosis of this condition.

In summary, childhood narcolepsy is a rare but potentially treatable disease. It has been underrecognised and underdiagnosed. Clinicians should have a high index of suspicion for this entity, and be aware of the difficulty in recognising narcoleptic symptoms in childhood.

References