

Symptoms of narcolepsy in children misinterpreted as epilepsy

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ABSTRACT – Differentiating an epileptic seizure from some other paroxysmal event is a common challenge in clinical practice. Many paroxysmal events mimic epileptic seizures and misdiagnosis can have disastrous consequences. Incorrectly identifying an event as an epileptic seizure can lead to unnecessary investigations and instigation of inappropriate treatment regimes. We report five patients referred to regional Paediatric Neuroscience Centres for investigation of events initially suspected of being epileptic seizures. All five patients were subsequently diagnosed as having narcolepsy. Suspected diagnoses were absence epilepsy (four patients), generalized epilepsy with atonic seizures (two patients) and focal epileptic seizures (two patients). Diagnostic confusion arose because lack of responsiveness due to excessive sleepiness was mistaken for epileptic absences, and cataplexy was confused with a variety of seizure types. In each case, videotape recording of clinical events aided in making the diagnosis of cataplexy. At presentation, all five children had excessive daytime sleepiness with cataplexy. Following correct diagnosis and appropriate management, an improvement in symptoms was reported in all cases. Narcolepsy/cataplexy should be included in the differential diagnoses of paroxysmal disorders, particularly if there are associated sleep symptoms or behavioural difficulties. It is important to take a sleep history when evaluating any disorder of the central nervous system. [Published with videosequences]

Key words: narcolepsy, cataplexy, epilepsy, differential diagnosis



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Misdiagnosis of epilepsy is common (Smith *et al.* 1999, Chadwick and Smith 2002). Prompt recognition of paroxysmal disorders that can mimic epilepsy is vital to prevent patients undergoing unnecessary and costly investigations, and clinicians instigating potentially harmful therapeutic regimes. The epilepsy specialist needs to have an equally expert awareness of all of the disorders that may mimic epilepsy. Where treatments for these “imitators of epilepsy” are available, this is even more important.

The International Classification of Sleep Disorders defines narcolepsy as “a disorder of unknown aetiology characterized by excessive daytime sleepiness that is typically associated with cataplexy and other rapid eye movement (REM) sleep phenomena such as sleep paralysis and hypnagogic hallucinations” (1990). An autoimmune basis for narcolepsy has been suspected for many years based on the well-established HLA association (Mignot *et al.* 2001). Approximately 85-100% of individuals with narcolepsy and ca-

cataplexy are HLA DQB1*0602 positive, however this HLA subtype is present in 24% of the general population (Mignot 1998). Therefore, this test is supportive but not diagnostic of narcolepsy. An increased risk of narcolepsy in siblings of affected individuals and concordance levels in monozygotic twins of 25-30% suggest a genetic and environmental interaction (Mignot 1998). The discovery that the neuropeptide hypocretin is undetectable or markedly reduced in the cerebro-spinal fluid (CSF) of individuals with narcolepsy, and the finding of absent hypocretin peptides in brain tissue from affected individuals, suggest a key role for hypocretin in the pathogenesis of narcolepsy and a possible autoimmune basis for the disorder (Nishino et al. 2000, Peyron et al. 2000, Thannickal et al. 2000, Mignot 2001). Hypocretin is a neuro-peptide implicated in regulation of the sleep-wake cycle. Further indirect evidence of a functional autoantibody in narcolepsy comes from a recent study in which IgG from patients with narcolepsy was injected into mice, resulting in altered smooth muscle responses to cholinergic stimulation (Smith et al. 2004). Cataplexy is a sudden reduction in muscle tone in response to a strong emotion.

Narcolepsy is an under-recognised disorder in paediatric practice; 30% of adults report symptom onset before 15 years (Challamel et al. 1994). The diagnosis is frequently delayed, and clinical events are often initially mistaken for epileptic seizures (Zeman et al. 2001). This paper describes the clinical features of five patients with narcolepsy/cataplexy whose symptoms were initially thought to represent epileptic seizures. Video recordings showing the paroxysmal events that were thought to be epileptic seizures are included.

Patients

Patients with narcolepsy/cataplexy were identified and those who had been given an initial diagnosis of epilepsy were included in the paper. All patients had excessive daytime sleepiness, falling asleep on numerous occasions during the day and in inappropriate places e.g. at the dinner table. They all had poor sleep quality at night with frequent arousals and extreme difficulty getting up in the morning. All patients were HLA DQB1*0602 positive.

Case 1. Video sequence 1

An eight-year-old girl presented to a district general paediatrician and was referred for an EEG. The EEG request stated *"12-week history of seizures, one-two per day, up to 40 in one week. Always triggered by fright, excitement, laughing. Three types of episode, tonic/clonic, tonic becoming hypotonic and left focal twitching with inability to hold head up"*. The EEG was reported as normal with a suggestion to request video-telemetry and imaging if episodes were that frequent. The video-EEG request was made, along with a request for neurological consultation.

The referring paediatrician felt that the patient had a history of epilepsy characterised by various seizure types including focal epileptic seizures. Twenty four-hour video EEG telemetry was performed, capturing one episode described as *"fell to the side, short fit, feet being tickled at the time"*. The ictal EEG was normal.

Detailed history-taking revealed that the child had excessive daytime sleepiness, first noted at the age of two years. All the paroxysmal events were triggered by strong emotion, most commonly laughter, and she had a history of hypnagogic hallucinations – *"seeing big hairy spiders on the bed"*. A clinical diagnosis of narcolepsy with cataplexy was made. Typical cataplexy, induced by laughter, was captured on videotape and a multiple sleep latency test was positive with four sleep-onset REM periods. Excessive daytime sleepiness (EDS) was managed with lifestyle changes including programmed daytime naps. Methylphenidate and dexamphetamine, prescribed for EDS, both produced excessive agitation, even at low doses, and had to be discontinued. Modafinil has proved partially effective in managing EDS. Medications for cataplexy, which have proved ineffective and have produced unacceptable side effects at low doses, include; clomipramine, imipramine, venlafaxine and gamma hydroxybutyrate. Fluoxetine produced a significant reduction in the cataplexy for six months; however the effect was not sustained and was not repeated on a subsequent trial of the medication. Despite her lack of response to pharmacological therapy, she has no significant mood or behavioral problems, and has good educational attainments at age 16.



Sequence 1

Cataplexy triggered by laughter. In this case, family members can be heard laughing in the background. At 15 seconds, the patient's head nods briefly, then arms and upper body slump, followed by knees buckling and the patient falls to the floor. The patient then appears to be unresponsive, lying motionless on the floor with eyes closed and mouth open. At 40 seconds, she opens her eyes and smiles. She then has further brief head nods as she is helped onto her feet before falling to the floor once again. Note that these episodes were captured by her parents when the clinician left the consulting room, allowing the patient to relax.

Case 2. Video sequence 2

This child presented to a paediatrician at the age of five with a two-year history of falls. The clinic letter states, *"His left leg would collapse and he would fall to the left... and on recent occasions his eyes have appeared to roll up-*

wards with the episodes". A diagnosis of focal epileptic seizures was made. Brain CT scan and interictal EEG were normal. Over the next few years he was tried on carbamazepine, sodium valproate and lamotrigine, with no reduction in the frequency of events. Throughout this time, various entries in his case sheets record: *"He is still having brief tonic-clonic generalised seizures, approximately one per month. He also has brief absence episodes occurring a couple of times a week"...* *"petit mal appears to be under reasonable control but still a couple of minor episodes."* Further standard and 24-hour EEG studies were normal. At the age of eight years he was referred for review of his *"refractory epilepsy"* to a senior child neurologist who initially commented, *"I am sure it is right that he has epilepsy despite normal EEGs and I think it is lesional in the light of his earlier symptomatology"*. MRI was normal. The "absences" were captured on 24-hour EEG and were shown to be non-epileptic. His mother described him as having a bad temper, with violent outbursts and a dislike of people staring at him. Concerns were expressed that the events had a psychological basis and medication was stopped. On the morning of the next hospital review, the attending neurologist had read a recently published review article on Narcolepsy in Pubertal Children (Guillemainault and Pelayo 1998), in which behavior and depressive symptoms were discussed. For the first time the mother was asked direct questions about her son's sleeping patterns and the presence of emotional triggers to his events. She clearly described excessive daytime sleepiness, falling asleep in unusual places during the daytime and events triggered by laughter and crying characterized by him falling to his knees or to the ground. He also had disturbed nighttime sleep and hypnagogic hallucinations. A diagnosis of narcolepsy with cataplexy was made. The diagnosis was confirmed by capturing an episode of cataplexy triggered by laughter on videotape. There was an improvement in symptoms, and adjustment to the condition following commencement of programmed daytime naps, psychological support and modafinil.



Sequence 2

Cataplexy induced by laughter, in this case by the patient's brother performing an amusing walk. At 13 seconds, the patient's knee suddenly buckles, his head is thrown back and he then collapses to the floor. There is a similar episode at 59 seconds, with buckling of the knees.

Case 3. Video sequence 3

This patient initially presented to local education services at the age of nine years, with concentration and attention difficulties. He had aggressive outbursts and low self-esteem. He was noted to have episodes of staring, several times per day, and brief head nods with facial twitching that his local paediatrician diagnosed as childhood absence epilepsy. Interictal EEG, 24-hour video-EEG telemetry and MRI were normal. On direct questioning he had a history of excessive daytime sleepiness and falling asleep in unusual places as well as sleep disturbance and sleep paralysis from age eight. A clinical diagnosis of narcolepsy with cataplexy was made. This was confirmed by capturing episodes of cataplexy triggered by laughter on videotape. Behavior, mood and schoolwork improved after the commencement of programmed daytime naps.



Sequence 3

This illustrates facial cataplexy, in this case triggered by the clinician telling a joke. Note the stepwise progression of cataplexy. The eyelids droop, mouth opens then the head nods forwards. Apparent facial twitching can be seen, caused by sequential loss then regaining of muscle tone.

Case 4. Video sequence 4

At age eight years, this boy presented to his local paediatrician with a four-month history of increasing daytime sleepiness, disturbed nocturnal sleep and a history of falling asleep in unusual places. He began to have episodes during which he would stare forwards and appear unresponsive. Sometimes there was associated facial twitching. He developed behavior problems with irritability, aggressive outbursts and low mood. The general paediatrician wrote *"absences, twitching and clumsiness late in the day and nocturnal disturbances could fit with juvenile myoclonic epilepsy"*. EEG and MRI brain were normal. He was referred to the Neurosciences Unit. He had all five features of narcolepsy, with excessive daytime sleepiness, cataplexy, hypnagogic hallucinations, sleep paralysis and disturbed nighttime sleep. He described particularly vivid hypnagogic hallucinations, frequently characterized by goblins or "orcs" from the *Lord of the Rings* films appearing in his bedroom. A multiple sleep latency test failed due to lack of cooperation. The clinical diagnosis was confirmed by a home videotape of cataplexy and by CSF analysis which showed undetectable hypocretin levels.



Sequence 4

In this clip the patient can be seen playing with a balloon. There is a very brief episode of knee buckling after two seconds from which the patient regains control. This is followed almost immediately by a collapse. The patient's mother can be heard asking him if he is OK. He then gets back up to his feet.

Case 5. Video sequence 5

This seven-year-old girl presented with a one-year history of increasing daytime sleepiness, facial twitching and collapse. She would fall to the floor and could remain motionless for several seconds. The episodes appeared to have a clear trigger, laughter or exercise, in about a third of cases. EEG studies awake and asleep were normal, as was brain CT. Despite normal neurophysiology, a diagnosis of epilepsy was suspected. A referral letter stated: *"My impression here was of a paroxysmal event and the first consideration of narcolepsy was rather knocked out of the options by the day time drop attacks. They suggested an epileptic background"*. Prescription of anti-epileptic medications was considered by a local paediatrician, however the diagnosis of narcolepsy was made after a child neurologist reviewed videotapes of collapses taken by her parents. It was clear that the episodes of collapse, not triggered by immediate preceding emotion, were associated with the anticipation of a strong emotion. The girl had been a regional diving champion but could no longer compete, as whenever she reached the diving platform she would collapse. The clinical diagnosis of narcolepsy with cataplexy was supported by a positive multiple sleep latency test. She showed clinical improvement following the commencement of programmed daytime naps, modafinil and immunoglobulin infusions.



Sequence 5

In this sequence, the patient is attempting to dance with her sister. Cataplexy is induced by the enjoyment of dancing. Numerous brief episodes of cataplexy can be seen, with brief head nods followed immediately by the upper body slumping. The patient then regains muscle tone. At 1 minute 55 seconds, the patient's sister induces laughter. The patient then collapses to the ground.

Discussion

The diagnosis of narcolepsy is made by the recognition of excessive daytime sleepiness and symptoms of abnormal REM sleep-related events such as cataplexy, sleep paralysis and hypnagogic hallucinations. Disturbed nighttime sleep, automatic behavior and short-term memory problems may occur (Okun *et al.* 2002). Cataplexy is the most specific symptom of the narcolepsy syndrome. In the absence of clear-cut cataplexy, diagnosis may be difficult. Objective measurements such as the multiple sleep latency test (MSLT) may be difficult to perform and are poorly validated in the paediatric population. The recent findings of reduced or absent cerebrospinal fluid hypocretin in most cases of narcolepsy with cataplexy, mean that estimation of this neuropeptide may aid diagnosis (Mignot *et al.* 2003).

Cataplexy is a sudden loss of muscle tone, triggered by strong emotion such as laughter or crying. Cataplexy can be considered an inappropriate intrusion of physiological REM atonia into the waking state. This loss of muscle tone usually starts in the face and proceeds in a downward fashion. Typically the mouth and face droop, followed by the upper body, trunk then lower limbs, sometimes resulting in the patient collapsing to the ground. Individuals may be able to exert a degree of control over the progression of the loss of tone, sometimes preventing themselves falling. Patient 1 is able to control her cataplexy during dancing classes by concentrating intensely. Although there is typically a caudal to rostral progression in the loss of tone, this may be asymmetrical at times, with one or other leg appearing to give way as described in patient 2. The variety in the degree and distribution of loss of tone in cataplexy can therefore be mistaken for different types of focal and generalized epileptic seizures. Facial cataplexy is associated with apparent twitching of the facial muscles as the patient loses, then regains control of facial muscles as seen in patient 3. This, combined with the lack of responsiveness associated with tiredness, can be confused with facial myoclonia associated with absences. This was noted in patient 4.

Once the diagnosis of epilepsy was made in patient 2, terms such as *"generalized tonic-clonic"* and *"petit mal"* were used throughout the case sheet without a clear explanation of what they meant to the physician. These terms are regarded as synonymous with epileptic seizures. Their use may have prevented a re-evaluation of the diagnosis in the absence of a recognizable epilepsy syndrome.

The identification of triggers is important in differentiating various paroxysmal events. In narcolepsy, triggers for cataplexy are usually strong emotions such as laughter or crying. However, the anticipation of emotion also seems to be important as illustrated by patient 5, who had loss of tone as she prepared to dive. In the same child, the fun or joy of dancing could trigger cataplexy, not the exercise

itself as was first suspected. The situation in which the events take place is also important. The parents of patient 1 clearly described events triggered by laughter. Attempts to recreate these situations by telling jokes in the consulting room proved unsuccessful until the clinician left the room and asked the parents to video the child playing with her siblings. A degree of familiarity with surroundings and a relatively relaxed state is often required for cataplexy to occur. In the same way, home video recording of events by parents can be of more use than attempting to capture events in unfamiliar environments such as hospitals.

Behavior, mood and school performance may be affected in childhood-onset narcolepsy as in many paediatric epilepsy syndromes. Parents of all five children reported mood disturbance including withdrawal from social activities, low self-esteem and sometimes aggressive outbursts. Adult quality of life studies comparing narcolepsy and refractory temporal lobe epilepsy have shown lower quality of life scores in the narcolepsy group (Broughton *et al.* 1984).

Making an early diagnosis of narcolepsy can be beneficial for the child and their family. Close correspondence with other health professionals and educational authorities has been useful in all five patients. Behavioral modification including programmed daytime naps, have been shown to be effective in narcolepsy. Medications such as modafinil can help promote wakefulness. Early diagnosis may be particularly important as treatment with intravenous immunoglobulin has been reported to alleviate symptoms in recent onset cases and as such, may have the potential to alter the course of the disease (Lecendreux *et al.* 2003). Although sleep problems are common in childhood, most physicians have little training in sleep medicine. Parents may not regard sleep problems, including daytime sleepiness, as possible symptoms of a medical disorder and as such may not volunteer information about sleep symptoms. Tools such as the Pediatric Daytime Sleepiness Scale may be useful in evaluating the clinical significance of daytime sleepiness (Drake *et al.* 2003). Taking a brief sleep history as part of the evaluation of all children with paroxysmal disorders may give valuable pointers to the underlying diagnosis. This history should include time to sleep in the evening, time to wake, history of sleep disturbance, daytime naps (including in inappropriate places), and loss of tone or "collapses" in response to strong emotion.

Conclusions

This series highlights some of the potential pit-falls associated with the diagnosis of paroxysmal disorders in childhood. Incorrect diagnosis of epilepsy may lead to inappropriate investigation and treatment. Identifying rare but potentially treatable causes of paroxysmal disorders may

also be delayed. This is especially important in childhood, a period of time crucial to the child's emotional, psychosocial and educational development. History taking, including sleep-related symptoms, remains the cornerstone of accurate diagnosis, but videotape analysis of events is also a useful tool. □

References

- Broughton RJ, Guberman A, Roberts J. Comparison of the psychosocial effects of epilepsy and narcolepsy/cataplexy: a case controlled study. *Epilepsia* 1984; 25: 423-33.
- Chadwick DW, Smith D. The misdiagnosis of epilepsy. *BMJ* 2002; 324: 495-6.
- Challamel MJ, Mazzola ME, Nevismalova S, *et al.* Narcolepsy in children. *Sleep* 1994; 17: S17-S20.
- Drake C, Nickel C, Burduvali E, *et al.* The pediatric daytime sleepiness scale (PDSS): sleep habits and school outcomes in middle-school children. *Sleep* 2003; 26(4): 455-8.
- Guilleminault C, Pelayo R. Narcolepsy in prepubertal children. *Ann Neurol* 1998; 43: 135-42.
- Lecendreux M, Maret S, Bassetti C, *et al.* Clinical efficacy of high dose intravenous immunoglobulin near the onset of narcolepsy in a ten-year-old boy. *J Sleep Res* 2003; 12: 1-2.
- Mignot E. Genetic and familial aspects of narcolepsy. *Neurology* 1998; 50: S16-S22.
- Mignot E. A commentary on the hypocretin/orexin system. *Neuropsychopharmacology* 2001; 25: S5-S13.
- Mignot E, Lin L, Rogers W, *et al.* Complex HLA-DR and -DQ interactions confer risk of narcolepsy-cataplexy in three ethnic groups. *Am J Hum Genet* 2001; 68: 686-99.
- Mignot E, Chen W, Black J. On the value of measuring CSF hypocretin 1 in diagnosing narcolepsy. *Sleep* 2003; 26: 646-9.
- Nishino S, Ripley B, Overeem S, *et al.* Hypocretin (orexin) deficiency in human narcolepsy. *Lancet* 2000; 355: 39-40.
- Okun ML, Lin L, Pelin Z, *et al.* Clinical aspects of narcolepsy-cataplexy across ethnic groups. *Sleep* 2002; 25: 27-35.
- Peyron C, Faraco J, Rogers W, *et al.* A mutation in a case of early onset narcolepsy and a generalized absence of hypocretin peptides in human narcoleptic brains. *Nat Med* 2000; 6: 991-7.
- Smith AJF, Jackson MW, Neufing P, *et al.* A functional antibody in narcolepsy. *Lancet* 2004; 364: 2122-4.
- Smith D, Defalla BA, Chadwick DW. The misdiagnosis of epilepsy and the management of refractory epilepsy in a specialist clinic. *QJM* 1999; 92: 15-23.
- Thannickal TC, Moore RY, Nienhuis R, *et al.* Reduced number of hypocretin neurons in human narcolepsy. *Neuron* 2000; 27: 469-74.
- Zeman A, Douglas N, Aylward R. Narcolepsy mistaken for epilepsy. *BMJ* 2001; 322: 216-8.