CURRENT TOPIC

Recognition and management of narcolepsy

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Perhaps as many as 5% of adults are excessively sleepy to a clinically relevant extent.¹ The comparable figure for children is not known, but sleepiness is associated with many different conditions and, although a neglected topic, it can be the cause of serious psychological and social disadvantage.² Narcolepsy is by no means the most common cause of excessive sleepiness. Nonetheless, it is not the rarity once supposed, and poses special problems of recognition and management, especially in young people. The purpose of this article is mainly to review the clinical picture of narcolepsy in children and adolescents, emphasising the need for paediatricians, child psychiatrists, and others to take a wide view of the ways in which the condition can show itself. The clinical picture is often very different from that of the fully developed narcolepsy syndrome in adults. It is, therefore, at particular risk of either being overlooked or misconstrued.

Narcolepsy in general

Narcolepsy is a neurological disorder, the main classic feature of which is excessive sleepiness during the day, with recurrent episodes of irresistible sleep (sleep attacks). In its fully developed form the “narcolepsy syndrome” also includes sudden loss of muscle tone in response to strong emotion (cataplexy), vivid dream-like experiences before falling asleep (hypnagogic hallucinations) or on waking (hypnopompic hallucinations), and episodes of inability to move after waking in the morning (sleep paralysis). Estimates for the occurrence of the non-sleepiness (“ancillary”) components of the syndrome are: cataplexy (all cases where cataplexy is required for the diagnosis of narcolepsy; however, others accept that in about 20% of cases cataplexy is not present), hypnagogic or hypnopompic hallucinations (50–60%), and sleep paralysis (40%). These symptoms occur in various combinations and less than half of those with narcolepsy develop all four of them. In narcolepsy, overnight sleep is generally disrupted, causing some degree of persistent tiredness. Additional symptoms can include automatic behaviour (complicated behaviour in a sleepy state with impairment of consciousness), poor memory and concentration, and visual disturbances such as blurred vision and diplopia.

Narcolepsy has been viewed as primarily a disorder of rapid eye movement (REM) sleep mechanisms. Each of the classic tetrad of symptoms represents a main feature of this

form of sleep: sleep attacks (sleep), cataplexy and sleep paralysis (atonia of the skeletal musculature), hypnagogic and hypnopompic hallucinations (dreaming). In narcolepsy, these aspects become dissociated and intrude into wakefulness. However, the physiopathogenesis of narcolepsy seems to be more complicated than this, with evidence of non-REM (NREM) sleep and possibly circadian sleep wake rhythm abnormalities. Basic neurochemical mechanisms are not yet well defined.³

There are ill understood associations between narcolepsy and obstructive sleep apnoea, periodic limb movements in sleep, and REM sleep behaviour disorder. Genetic influences are prominent in narcolepsy, but environmental factors, such as stress or illness, also affect the severity of symptoms. Narcolepsy is a lifelong illness. Medication is usually needed, as well as other supportive measures, such as advice on various aspects of living.

Features of narcolepsy in young people

In comparison with adult narcolepsy, the condition in children has received little attention, in spite of the fact that Yoss and Daly discussed the topic as long ago as 1960.⁴ Since then a number of limited accounts have been published including some based on small series of cases or individual patients^{5–15} and, in the past few years, fuller accounts.^{16–22} Kavey²³ and Kashden and colleagues²⁴ have written specifically about the psychosocial aspects of narcolepsy in children and adolescents. Although these accounts (very likely affected by referral bias) form the still limited research interest that has been taken in young people with narcolepsy, collectively, they probably provide a fairly balanced view, which needs to be conveyed to a wide range of clinicians. The following is an outline of the picture that is emerging. Further details are provided in the recent fuller descriptions just mentioned.

Prevalence

This is uncertain partly because of variable diagnostic standards but, even so, the condition cannot be the rarity often supposed. The figure usually quoted for adult narcolepsy in the USA is 4–10/10 000 (the figure is much higher for Japan and much lower for Israel). Assuming comparable rates in the USA and the UK, this represents at least 250 000 Americans and about 20 000 cases in the UK.²⁵ There is general agreement that at least half the cases begin

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in childhood although, as discussed shortly, the condition is usually not diagnosed until much later, if correctly diagnosed at all.

Age of onset

Perhaps curiously for a condition that often appears to have a genetic and immunological basis, the reported age of onset of narcolepsy is very wide, from early childhood to at least middle age. The youngest patient in the series described by Guilleminault and Pelayo²² was 2.1 years at the time of diagnosis. Peak age of onset is about 14 years. Chalamel and colleagues¹⁶ pooled the information from three studies involving a total of 235 adult patients with narcolepsy, and reported that 34% presented their first symptoms before the age of 15 years (a lower proportion than other authors have claimed), 16% before 10 years, and 4.5% before 5 years of age.

Presentation

A confident diagnosis of childhood narcolepsy is possible if excessive daytime sleepiness (including sleep attacks) develops suddenly, combined with cataplexy, sleep paralysis, and hypnagogic hallucinations, together with the abnormalities of sleep physiology characteristically seen in adults—rapid onset of sleep and the early appearance of REM sleep. However, this clear cut, classic picture seems to be unusual in the early stages of the disorder. The exact proportion of non-classic presentations is not clear, but a number of ambiguous presentations have been described, which have contributed to diagnostic confusion and delays (sometimes for years), with repeated referrals to different clinical services.

EXCESSIVE SLEEPINESS

This is the predominant complaint in most cases but it can take various forms. The adult picture of sleep attacks against a background of general sleepiness (caused by disturbed overnight sleep) is seen in only the minority of prepubertal patients. The first sign of sleepiness may consist of no more than wanting to sleep longer overnight. However, individual differences in sleep requirements make it particularly difficult to assess excessive sleepiness in very young children. Presumably, it is for this reason that features other than sleepiness were the presenting complaints in the children up to the age of 5 years in the series reported by Guilleminault and Pelayo.²² In a child of school age, a more obvious sign of sleepiness would be the persistence of regular daytime naps because these should normally cease by the age of 3–4 years. An important point emphasised by Dahl and colleagues²⁶ is that, especially in young children, sleepiness can take the form of an increase rather than a reduction in activity, with the presence of irritability, aggression, and attention deficit hyperactivity disorder symptoms.

CATAPLEXY

Opinions differ as to whether narcolepsy should be diagnosed in the absence of cataplexy and it remains something of an open question whether the absence of cataplexy

indicates a separate narcolepsy-like condition. In most cases, however, this feature develops after excessive sleepiness has appeared (perhaps years later), bringing the child's condition to medical attention for the first time because it is perceived as more abnormal than sleepiness. Sometimes the two develop together and, in a minority, cataplexy is the initial symptom. In either case, like excessive sleepiness, cataplexy can take various forms. At its most subtle, weakness causes the child to feel strange or unsteady without obvious external change. Otherwise, attacks may consist of slight observable weakness of the limbs, face, head, and neck causing the knees to buckle, the head or shoulders to drop, or the jaw to sag. Recognition is made less difficult when the child suddenly drops to the ground and is unable to move perhaps for several minutes. Combinations of these various manifestations are not unusual. Important diagnostic features are that emotion (often laughter but also other positive as well as negative experiences, such as fear) acts as a trigger, and that eye and respiratory movements are preserved even in the more dramatic forms.

SLEEP PARALYSIS AND HYPNAGOGIC AND HYPNOPOMPIC HALLUCINATIONS

These seem to be unusual in young patients but, when they occur (sometimes together) they can be very frightening. Very rarely they are the first symptom of the condition to appear. The dream-like and often vivid hallucinatory experiences are usually visual, but tactile and auditory forms are also described. Consciousness is preserved in these experiences and also during attacks of cataplexy.

OTHER ASSOCIATED TYPES OF SLEEP DISTURBANCE

Difficulty getting to sleep because of a fear of night-time experiences has already been mentioned. Frequent awakenings are also described, possibly associated with periodic limb movements, although reports of the occurrence of such movements in children with narcolepsy have been inconsistent. Night terrors and frequent nightmares have been described in a high proportion of cases. In contrast, automatic behaviour (said to be very common in adults with narcolepsy) and sleep apnoea (also linked to narcolepsy in adults) do not feature in reported series of young patients.

SECONDARY PSYCHOLOGICAL EFFECTS

These are common and may well overshadow their causes and mistakenly lead to referral for psychiatric or educational advice. Understandably, children often become fearful, embarrassed, and distressed in other ways (including feeling helpless) by the experiences that narcolepsy imposes on them. They may deny or conceal the condition.

Inappropriate reactions by parents, teachers, and other professionals (including physicians), as well as peers, based on misinterpretation of the narcolepsy symptoms or the child's reactions to them, and restrictions placed on recreational and social activities, make a

difficult situation worse. The problem is intensified by inappropriate or delayed diagnosis and treatment, which seem to be commonplace. Even when correct treatment is given this may itself cause further adverse effects.

Additional problems may arise from poor school progress caused by the effect of sleepiness on concentration, memory, and other aspects of cognitive function,²⁷ and the adverse psychological effects of persistently disrupted overnight sleep.²⁸ It is no surprise that in reported series of children with narcolepsy a range of serious psychological problems are consistently described, especially emotional lability, depression, difficult or aggressive behaviour, social withdrawal and isolation, and academic failure.

Misdiagnosis

The non-specific nature of the early features of narcolepsy, combined with the very limited awareness that the condition can start in these ways, leads to various misinterpretations.

The fact that the onset of narcolepsy can be triggered by emotional stress can itself be misleading. Psychiatric misdiagnosis features prominently in the published series including severe depression, conduct and oppositional defiant disorders, attention deficit hyperactivity disorder, conversion disorder (especially if cataplexy is not recognised as such), and even psychotic states if hypnagogic hallucinations are misconstrued. Medical misdiagnoses that have been reported include epilepsy and other neurological or medical disorders capable of causing hypersomnia.

Sometimes, a sleep disorder other than narcolepsy has been considered initially, for example terrifying hypnagogic hallucinations may be labelled "night terrors", or the child's fear of bedtime because of such frightening experiences may be thought of as the more usual childhood unwillingness to go to bed at the time preferred by parents. Problems getting up in the morning may also be misinterpreted as "difficult" behaviour, especially in adolescents with narcolepsy.

Misinterpretation of narcolepsy symptoms is not confined to the medical profession. The reported series indicate that teachers may well be critical of the child with narcolepsy because of their perception of narcolepsy symptoms as laziness, poor motivation, or difficult behaviour. Sometimes use of illicit drugs is suspected. Alternatively, even able children with narcolepsy may be considered in need of special educational provision because of the mistaken belief that they are intellectually limited. Such disapproval or misunderstanding may persist even after the diagnosis of narcolepsy has been made, indicating the need for much better appreciation of the nature of the condition. It is easy to see how such misjudgments can cause escalating conflict between children, or their parents, and school. However, some parents themselves may have misgivings about their child's symptoms, or they might be unsympathetic to the child's understandable difficulties and reactions to the condition.

Examples are given in the literature of how, as a consequence of failure to recognise not only the more subtle manifestations of narcolepsy, but even the more classic features, misinterpretation, equivocation, referral to psychological or educational services, or inappropriate medical investigations may extend over long periods, sometimes many years. In many cases, the true nature of the child's condition only came to light because a sleep disorders service was available for a further opinion. The shortage of such centres with a special interest in children is a problem, although a general improvement in awareness would help.

Clinical implications

- (1) Child health professionals should be aware that narcolepsy in young children is not a rarity and that they need to be familiar with its clinical features in both its classic and less obvious forms.
- (2) Narcolepsy should be suspected if a child's excessive sleepiness cannot be explained in other ways. Very many childhood sleep disorders are now recognised, grouped (with some overlap) according to the main presenting symptom: sleeplessness, excessive daytime sleepiness, and episodic disturbances of behaviour associated with sleep (parasomnias).^{29 30} The main cause of excessive sleepiness is insufficient sleep for various reasons, including mistiming of the sleep phase or irregular sleep patterns, especially in adolescence. Often, however, the problem results from disrupted overnight sleep, for such reasons as obstructive sleep apnoea, other medical disorders, and sometimes frequent parasomnias. Narcolepsy is the main example of disorders that are characterised by an intrinsic increase in sleep requirements. Other members of this group are "idiopathic hypersomnia" (where overnight sleep is prolonged and very sound, with great difficulty getting up in the morning, but without any of the clinical or polysomnographic features of the REM sleep abnormality seen in narcolepsy); and the Kleine-Levin syndrome, in which classically long periods of excessive sleepiness (associated with overeating, hypersexuality, and other behavioural abnormalities) alternate with periods of normality. It is important not to confuse sleepiness with weariness or fatigue (without an increased tendency to sleep) for which physical illness is a more likely explanation. It is also very relevant that the ancillary symptoms of narcolepsy occur in the general population as isolated phenomena (frequently in the case of hallucinatory phenomena and sleep paralysis) without being part of the narcolepsy syndrome.
- (3) As already explained, the early features of the narcolepsy syndrome can be both subtle and non-specific with a wide differential diagnosis including epilepsy, clumsiness, psychiatric disorder, and the various

causes of excessive daytime sleepiness other than narcolepsy. The possible difficulty of recognising the condition should not be underestimated, especially in young children or, indeed, older ones where the picture may have been obscured by psychological complications, which then dominate the clinical picture. Particularly careful scrutiny of both the present symptoms and the past sequence of events is required. Repeated clinical assessment may be needed before convincing features of the disorder come to light.

- (4) Once there is suggestive evidence of narcolepsy, standardised physiological sleep studies (polysomnography or PSG) are required for a definite diagnosis. These should involve overnight PSG (partly to exclude other causes of excessive sleepiness) combined with multiple sleep latency testing (MSLT), which is an objective measure of daytime sleepiness (see Kotagal²⁰ for further details of these procedures). In general, it is thought that children with narcolepsy will show the same abnormal features as adults—mainly they take an abnormally short time to fall asleep when taking daytime naps (short sleep latency), and have a tendency to go straight into REM sleep (sleep onset REM periods or SOREMPs). However, the classic PSG criteria for the diagnosis of adult narcolepsy might need to be relaxed somewhat for use with children, some of whom might not display the adult characteristics until later in the evolution of their condition. In particular, the mean sleep latency in children with narcolepsy may be less than seven to 10 minutes (rather than five minutes for adults), and some children do not initially show the two or more SOREMPs out of the five MSLT naps seen in adult patients. The high level of alertness during the day that is characteristic of older, prepubertal children may offset to some extent the excessive daytime sleepiness seen in other patients with narcolepsy. Unfortunately, PSG is not readily available and referral to a special centre will often be necessary. Even there, it is important that these procedures are performed with an understanding of the special considerations regarding children. Home PSG including MSLT has been used with adults for the diagnosis of narcolepsy, and shows good agreement with the results from laboratory recordings, except that fewer daytime SOREMPs were seen in patients investigated at home.³¹ Recordings at home are especially appropriate for children and could be used more widely. Normative data are now available at least for basic PSG variables,³² although not as yet for MSLT.
- (5) Human leucocyte antigen (HLA) typing is usually performed if narcolepsy is suspected, but its value is limited. Although type DQB1 0602 in particular is strongly associated with narcolepsy, its

specificity is restricted. However, a negative result appears to make the diagnosis of narcolepsy unlikely, although patients are described who are HLA DQB1 0602 negative and yet have the clinical and PSG features of narcolepsy. A variety of different conditions on the narcolepsy theme have been discussed by Parkes *et al.*³³

- (6) As part of the initial differential diagnosis, basic haematological tests and endocrine studies, together with electroencephalography and urine drug screen, may be appropriate, but further special investigations for narcolepsy itself have little part to play. At least, that is the usual view based on the general impression that “symptomatic” narcolepsy is rare.³⁴ Challamel and her colleagues¹⁶ have described examples from the literature and their own experience where childhood narcolepsy appears to have been associated with such conditions as Niemann Pick disease type C, diencephalic tumour, Tourette syndrome, Turner syndrome, thymoma, and precocious puberty. The authors suggest that the possibility of symptomatic narcolepsy should be seriously considered (and the appropriate investigations, such as neuroimaging, performed) in pre-teenage children with narcolepsy, especially when cataplexy is very prominent (including status cataplecticus), where classic PSG evidence is absent (accepting that this might be the case or early “idiopathic” narcolepsy), or where HLA typing is negative. It might be argued, however, that some of the cases proposed as examples of symptomatic narcolepsy, including some with Niemann Pick disease type C, should not be classified as narcolepsy because they lack the characteristic clinical and PSG features of this condition.²⁰ This issue is one of the aspects of childhood narcolepsy that needs further study, in addition to its characterisation compared with the better known adult forms.

Management

Detailed discussion of treatment and wider aspects of care of children with narcolepsy has been provided by Dahl,³⁵ Kotagal,²⁰ Brown and Billiard,³⁶ and also Guilleminault and Pelayo,²² who are particularly mindful of the need to combine pharmacological approaches with attention to the psychosocial issues concerning the child, family, and school. Some of the main points are as follows.

- (1) Early recognition and intervention are highly desirable. Narcolepsy (especially the excessive sleepiness component) is lifelong and therefore needs very long term care. However, the attention required is likely to be much greater and more complicated if there have been long delays in diagnosis, inappropriate treatments, and/or the accumulation of the secondary psychosocial and even psychiatric problems to which reference was made earlier.

- (2) The main specific aspect of care is medication, which is best reserved for children whose lives are being greatly affected by their narcolepsy. Methylphenidate and pemoline have often been prescribed. The main side effects of such stimulant drugs are headaches; features of overarousal such as agitation, tension, and anxiety; and gastrointestinal upset. Breaks from taking drugs at weekends and during holidays are important to avoid the development of tolerance. Dosage needs to keep pace with physical growth. Modafinil is a recent addition, licensed in the UK for use with patients age 12 years and above. It is unrelated to other central nervous system stimulant drugs and is said to have fewer adverse psychological effects, including less risk of abuse compared with traditional treatments.³⁷ Tricyclic drugs, such as clomipramine, has been the main treatment for cataplexy (and also hallucinations and sleep paralysis). Their main side effects are dry mouth, constipation, and urinary retention. Selective serotonin reuptake inhibitors, such as fluoxetine, are a recently introduced alternative. The use of tricyclic drugs and selective serotonin reuptake inhibitors has not been studied systematically in young patients with narcolepsy. Clomipramine is officially licensed for patients 12 years or older; fluoxetine for those age 18 and above. Preliminary attempts to improve the quality of sleep by means of benzodiazepine medication in adults with very disrupted overnight sleep have not produced improvements in daytime sleepiness. Unfortunately, non-compliance with recommended medication can be a serious problem, particularly in older children, possibly because of their unhelpful attitude to the condition, including denial and ambivalence on the part of the children and sometimes their parents.²²
- (3) In mild cases, an additional specific measure that might enable the use of medication to be avoided is the implementation of a programme of short planned naps once or twice a day (mid-afternoon is generally best). This requires careful planning with school to avoid the child being stigmatised as strangely different from other children.
- (4) General aspects of management include:
- Explanations to all concerned about the nature of narcolepsy, allaying in particular the idea that it is a character defect or other form of psychological disorder
 - Advice about schooling, choice of higher education, career, and other aspects of living such as driving regulations in the case of adolescents
 - Promotion of sleep hygiene including good sleep habits and routines
 - Children should be encouraged to lead an active and healthy lifestyle and adopt a positive outlook. Excessive weight gain should be avoided because obesity is thought to be closely linked with childhood narcolepsy

- Some families of affected children find mutual support groups very helpful.

Narcolepsy is a complicated condition requiring long term comprehensive care. General paediatricians and child psychiatrists in particular need to be mindful of the ways that it can present. As is true of the more complicated forms of epilepsy, management of narcolepsy needs special interdisciplinary provision to be effective and to prevent the potentially very serious developmental consequences of the condition.

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Think fuzzy and solve

Fuzzy logic could well be a description of what goes on in many a doctor's brain when the telephone rings at three in the morning but, more formally, it is a mathematical system introduced in 1965 which deals with imprecision, uncertainty, and partial truth. Since all of these attributes are part of the staple fare of medical practice most doctors would no doubt want to buy into such a system. In São Paulo, Brazil it was used to arrive at a successful measles mass vaccination strategy when they had a limited number of doses of vaccine available (Eduardo Massad and colleagues. *International Journal of Epidemiology* 1999;28:550-7).

The fuzzy logic system of decision making requires a set of goals, a set of possible actions, and a set of constraints, from which a decision can be made about the action that best satisfies the goals and constraints. The team in Brazil were faced with a rise in measles notifications despite a previously successful vaccination programme. They took as their goal the control of measles in children under 14 and considered 8 possible vaccination strategies. They obtained a series of constraints from an expert medical panel. Using fuzzy logic one strategy was chosen: selective vaccination of children aged 9 months to 6 years at fixed sites in the primary care network. The strategy proved successful in São Paulo city but a second mass vaccination campaign in the interior of the state was necessary 2 months later.

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