NARCOLEPSY: PROBLEMS OF DIAGNOSIS AND TREATMENT

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Narcolepsy (Gelineau's syndrome) is an unusual syndrome and that may be one of the reasons for difficulties in diagnosis; as in many aspects of life 'you only see what you know'. Among Gelineau's series of 14 patients was his wine merchant who may have fallen asleep over 200 times a day.[1]

The prevalence of narcolepsy in the UK has been estimated as between two and six per 10,000.[2, 3] It is viewed as a disorder of rapid eye movement (REM) sleep, with an initial period of REM sleep instead of the normal entry into sleep through a prolonged non-REM period; but there also seem to be abnormalities of non-REM sleep and possibly of circadian sleep/wake rhythms.[4] Normally, adults and children over the age of three months enter non-REM sleep with the appearance of REM sleep 60 to 90 minutes later.[5] A sleep onset REM period (SOREMP) is defined as REM sleep within 15 minutes of sleep onset, and although frequently present among children with narcolepsy, in some there may only be a delay lasting longer than 15 seconds between the onset of sleep and the appearance of the first epoch of REM sleep. Also, the sleep of most affected children is disturbed by frequent awakenings, increased wake time after sleep onset, increased time spent in Stage 1 non-REM sleep, and an increased prevalence of periodic leg movements; all may contribute to daytime sleepiness.[5]

CLINICAL FEATURES

The diagnosis of narcolepsy will usually be made on the clinical presentation of the condition.[4] Among children, the commonest age of onset of symptoms is around 14 years, but it can start in early childhood. In a meta-analysis of 235 patients derived from three series, in which the age of onset was known, 34% had developed symptoms before the age of 15, 16% before the age of 10, and 4·5% before the age of five years.[5, 6]

The most typical history is of a sudden onset of excessive daytime sleepiness, including irresistible attacks of sleep, combined with cataplexy, sleep paralysis and hallucinations, although the latter may not occur often.

Daytime sleepiness may not be as common among children as it is among adults, but in all sufferers it tends to occur in situations where anyone may feel sleepy, such as after a meal or when travelling on a bus, or listening to a dull lecture, when drowsiness may be difficult to resist. Cataplexy, which can occur before or after excessive sleepiness, consists of sudden muscular weakness of short duration and affecting both sides of the body. Its occurrence when typical is the only pathognomonic symptom of narcolepsy. The result of this can range from unsteadiness to a dramatic fall to the ground, but respiratory movements are not affected, and the condition is most often precipitated by emotions such as laughter and fear. As with sleepiness, it may be an exaggeration of the normal (hence the expression 'weak at the knees with laughter'). However, it has been suggested that cataplexy is different as it may be accompanied by such REM sleep-related events as face and limb muscle jerking.[7]

In adult life cataplexy can cause severe problems. For example, from personal experience, one such patient was a teacher who was in danger of losing his job. When he was about to discipline a recalcitrant pupil he would sink to the floor and have to remain there for a few minutes. The effect of this on the children can be imagined, and he was told he would have to resign if the episodes persisted. Another patient harpooned fish at a considerable depth. All was well if he missed, but if successful he briefly lost all muscle power.[8]

Other features of this symptom-complex, such as sleep paralysis and hypnagogic hallucinations, may be more common than is thought in childhood, due in part to difficulties in describing the symptoms or fear of doing so, and to their being attributed to other causes. One factor, which surely cannot be denied, is that they can be a terrifying experience.

Sleep paralysis can occur when falling asleep or on waking. The affected children find for a brief period that they cannot move or speak, and naturally this causes acute anxiety. To make matters worse this situation may be accompanied by hallucinations, although these may occur on their own: hypnagogic on falling asleep, hypnopompic on waking. These hallucinations are usually visual, and are more often than not in colour. They are usually of simple objects but can be of animals or humans. Auditory hallucinations can also occur, ranging from simple sounds to melodies and voices,[9] and they may be accompanied by the feeling of falling into an abyss.

Ohayon *et al.*[2] interviewed 4,972 people aged 15 to 100 to find out how common such hallucinations were in the general population. Hypnagogic hallucinations were reported by 37% and hypnopompic by 12·5%, and were significantly commoner among those with symptoms of insomnia, excessive daytime sleepiness or mental disorders.

The findings were considered to be much higher than expected, and far exceeded the number which could be explained by an association with narcolepsy.

Confusion on arousal from sleep can occur, and before a diagnosis is made this can cause conflicts with the parents in the rush to get children ready for school. Also, disturbed sleep during the night is likely to aggravate daytime sleepiness, and this in its turn can lead to behaviour and emotional disorders, and impaired progress at school – these symptoms are especially prominent in childhood.[10]

Childhood narcolepsy is often under-diagnosed[5] as hypersomnolence may not always be accompanied by cataplexy, sleep paralysis or hypnagogic hallucinations in the early stages. To illustrate the clinical features in prepubertal children Guilleminault and Pelayo[11] studied 51 children with narcolepsy and a mean age range of 7·9 years. Cataplexy was present in ten children, sleep paralysis in 38, and hypnagogic hallucinations in 30. On follow-up examination, all the children presented at least once with depressive symptoms. All the children had sleep studies, 31 exhibiting REM at sleep onset, and 46 children were human leukocyte antigen (HLA) Class II-positive for DQw6; 45 were also positive for DRw15. Poor memory can be a symptom, but rather than being a direct effect of narcolepsy is more likely to be due to the effects of sleepiness or of the treatment.[12]

CAUSES OF THE SYNDROME

Canine narcolepsy, which may be equivalent to the human form, is a useful model in which to study the latter, and it seems most likely that it is an interplay between genetic susceptibility, environmental and biochemical factors. The first is most probably an example of genetic heterogeneity, and the biochemical disturbance seems to consist in an imbalance between neurotransmitters. It has been shown that patients with narcolepsy compared with controls show significantly decreased levels of dopamine and indole acetic acid, a metabolite of tryptomine in the cerebro-spinal fluid; stimulants such as amphetamines are known to enhance dopamine release from presynaptic terminals. Also, selective dopamine D2 receptor agonists are capable of suppressing cataplexy which is thought to be due to facilitation of presynaptic projections into the noradrenergic system. A reduction of dopamine activity may be responsible for the periodic leg movements seen during the night sleep of sufferers from narcolepsy, who do respond to levodopa. However, it has been found that narcolepsy is not associated with alterations in dopamine D2 receptor density and affinity.[13]

Cataplexy, sleep paralysis and hypnagogic hallucinations are all REM sleep phenomena, and there is evidence of a cholinergic basis for them. The firing rate of nor-adrenergic neurons in the brain stem decreases during REM sleep, with an increase in the activity of cholinergic neurons in the pontine reticular formation, so that these symptoms do seem to be due to a catecholamine-cholinergic imbalance.[5]

Prior to the age of three months there is an abundance of REM sleep, and melatonin plasma levels are low. Then, with maturation of the pineal gland, the melatonin levels increase and the percentage of REM sleep declines, and it has been shown that pinealectomy in animals induces a narcoleptic-like pattern of REM sleep which resembles that of the newborn and is reversed by giving melatonin. It has therefore been suggested that narcolepsy can be viewed as a defect of REM organisation which may result from dysfunction of the pineal gland in infancy, and that there may be links to abnormalities of the immune system due to disruption of pineal melatonin functions which are found in narcolepsy.[14]

Much of the current understanding of the relationship between narcolepsy, genetics and orexin transmission has come from studies on a dog model and a 'knock-out' mouse model. Recently narcolepsy, and cataplexy in some instances, has been associated with dysfunction of this newly discovered hypocretin (orexin) peptide system due to a hypocretin receptor-2 gene mutation, and this may be a possible cause. Nishino *et al.*[15] measured immunoreactive hypocretin in the cerebrospinal fluids of nine patients with narcolepsy and eight controls. Hypocretin-1 was found in all controls, but none was detected in seven patients. In the other two patients it was found and this may have been due to a receptor-effector mediated deficiency. In the case of cataplexy this system may malfunction by removing a source of excitation from the locus coeruleus as diminished activity of this locus can lead to loss of muscle tone in animals. The mechanism that causes drowsiness is not so certain, but arousal levels can be reduced by hypocretin deficiency. Certainly hypocretin neurons in the lateral hypothalamus have diffuse projections to monoaminergic cell groups, and this neuropeptide has excitatory properties. However, it may be immune, or other mechanisms which damage the cells in these locations, and environmental factors may trigger the condition.[16]

There are certainly suggestions that narcolepsy may be an autoimmune disease, such as the association with HLA or other polymorphic genes, but there are arguments against this as no systemic or central nervous system evidence of autoimmune abnormalities have been found.[17]

Because hypocretins stimulate food intake in animals, it may be that this accounts for the increased body mass index found among sufferers from narcolepsy.[18]

THE DIAGNOSIS OF NARCOLEPSY

The diagnosis is most likely to be made when the clinical findings raise a suspicion of the condition. In view of the frequency of hypnagogic hallucinations in the general

population, Ohayon *et al.*[2] have suggested that a diagnosis based on hypnopompic hallucinations associated with daytime sleepiness and attacks of muscle weakness may be a better marker.

An ambulatory electroencephalogram (EEG) may occasionally be a useful screening test,[19] but the investigations most often used are the nocturnal polysomnogram (PSG) and the multiple sleep latency test (MSLT). During the first procedure, the EEG, eye movements, chin and leg electromyogram, respiratory effort, oral and nasal airflow, heart rate and oxygen saturation should be monitored. Folkerts *et al.*[20] have tested the results of polysomnographic findings in patients with narcolepsy and found them reliable. The use of respiratory measures in this test may not be necessary unless a sleep-related breathing disorder is suspected. The latter test is an objective measure of daytime sleepiness, with the provision of a series of five nap opportunities at two-hourly intervals, and provides information on the speed with which an individual falls asleep and on events during the sleep period. The EEG, eye movements, and chin electromyogram are monitored simultaneously.[5] If it is ever possible the diagnosis can be confirmed by using polysomnography and clinical examination during an attack of cataplexy, an REM-related phenomenon; as in narcolepsy this is always associated with the typical EEG correlates of REM sleep.[21]

Studies on various HLA can be helpful in establishing the diagnosis, especially DQB1 0602, although their value is limited due to their lack of specificity.[4] As mentioned Guilleminault and Pelayo[11] found most of the children they examined were positive for HLA DQw6 (DQw1) and HLA DRw15 (DR2). This has been confirmed by Wing *et al.*[22] among a Chinese population, and Mignot *et al.*[23] established a close HLA association among 509 patients with narcolepsy. Analysing the diagnostic value of typing for the narcolepsy-associated alleles, Planelles *et al.*[24] demonstrated a very high negative predictive value and this can be used to exclude the diagnosis of narcolepsy when this is in doubt. A study in the Czech Republic confirmed that, although there were genetic influences in many sufferers from narcolepsy, HLA susceptibility factors were not essential for the disease to develop.[25] However, these tests can lack sensitivity and specificity, and some may not be feasible in young children; clinical judgement remains crucial for the diagnosis of narcolepsy. Aldrich[26] has reviewed the clinical spectrum of narcolepsy and idiopathic hypersomnia and does not agree that the presence of cataplexy is essential for the diagnosis of narcolepsy. He suggests a classification into narcolepsy-cataplexy and hypersomnia with or without sleep-onset REM periods, but admits further research is needed.

The differential diagnosis will include hypersomnia related to obstructive sleep apnoea, the obesity-hypoventilation syndromes, epilepsy, ischaemic brain stem lesions, viral encephalitis, head trauma, cerebral tumours, multiple sclerosis, depression and drug abuse. As obesity and hypersomnia can be a feature of narcolepsy, the differential diagnosis of the Prader-Willi syndrome is an example.[27] A particular diagnostic feature was the finding that excessive daytime sleepiness in the Prader-Willi syndrome was associated with an increased amount and depth of sleep. Affected patients with such sleepiness (compared with those Prader-Willi patients without this, and with those with narcolepsy, obese patients and normal groups) showed a significant decrease in wakefulness and an increase in the percentage of sleep time and slow wave sleep, both during daytime and night time testing. In the Prader-Willi syndrome with excessive daytime sleepiness or shortened nocturnal REM latencies, there is also a unique alteration of the distribution of REM sleep in relation to controls. They showed a significant increase in the number of REM periods and a decreased average interval between these periods.

It is suggested that the findings in this syndrome are not akin to narcolepsy, or the result of obesity, but that the primary mechanism is a generalised 24-hour hypo-arousal, supported by the plasma levels of the cerebral inhibitory neurotransmitter GABA being increased to four to five times above normal. Gammahydroxybuterate given to patients with narcolepsy does decrease daytime sleepiness by, among other effects, an inhibition of GABA ketoglutarate transaminase.[28] Richdale *et al.*[29] confirmed the presence of excessive daytime sleepiness in patients with the Prader-Willi syndrome, and this led to behavioural disturbances, but there were very few other symptoms to suggest narcolepsy.

Narcolepsy can be mistaken for epilepsy, which is about ten times more common, especially when cataplexy occurs and when episodes are associated with muscle twitching and drowsiness. Also, hallucinations may well suggest temporal lobe epilepsy. If there are doubts, the multiple sleep latency test should be used. Typically, those with narcolepsy have a mean sleep latency of less than eight minutes and episodes of REM or dreaming sleep within ten minutes of sleep onset.[30]

One condition which may cause difficulties is 'idiopathic' hypersomnia, which is rarer than narcolepsy. This is recognised as a separate entity by the International Classification of Sleep Disorders, and as distinct from sleepiness following upper airway obstruction. It consists of prolonged nocturnal sleep, difficulty in waking up in the morning and excessive daytime sleepiness. Cataplexy does not occur, and sleep onset REM periods and an association with HLA are not found in this condition, but there is a strong genetic component. The most effective treatment is with modafinil.[31] A Parasomnia Overlap Disorder, with sleep walking and night terrors, has also been reported with some features of narcolepsy, but does not cause hypersomnia or cataplexy.[32]

In cases of idiopathic narcolepsy, as opposed to those which are 'secondary', there will be no evidence of a structural lesion. This was confirmed by Ellis *et al.*[33] with the use of proton spectroscopy which, in the case of the former, showed no evidence of loss of neurons or of gross biochemical abnormalities in the ventral pons. The use of the term 'secondary narcolepsy' may be ill-advised if all it means is the identification of a cause such as a cerebral tumour producing symptoms like undue sleepiness.

The difficulties of diagnosing narcolepsy in childhood have been emphasised, especially in the early stages, and the possibility of this condition should be considered when any child presents with daytime drowsiness. If at that time there are no associated symptoms, especially cataplexy, other causes will be considered. It will be particularly important to exclude upper airway obstruction, most frequently due to adenotonsillar hypertrophy, confirmed by overnight polysomnography.

TREATMENT

The main aim of treatment must be to prevent undue sleepiness during the daytime, and allow the patient to lead a normal life. Modafinil is now the preferred treatment for narcolepsy, especially in the case of teenagers and adults, and although not a stimulant, it does reduce sleepiness. Its exact mode of action is not known, although it may act on the hypothalamus in a different manner to the amphetamines and methylphenidate; and it does require an intact central α_1-adrenergic system. Unlike central nervous system stimulants, its action cannot be explained by dopaminergic activation. Its most common side-effects are headaches and nausea.

Two papers have been published by the US Modafinil in Narcolepsy Multicenter Study Group.[34, 35] In the first of these placebo-controlled, double-blind, randomised trials the efficiency and safety of modafinil was assessed. Over 200 patients with narcolepsy were given 200 or 400 mg of modafinil or a placebo for nine weeks, and some for a further period which was not blind; subjective and objective measurements of sleepiness were made. Modafinil reduced all measurements of sleepiness, and taken once daily was well tolerated with only mild to moderate side-effects such as headache and nausea. These were dose-dependant, and there was no evidence of tolerance developing over the period of the trial. In the second report similar results were recorded, but with a higher incidence of nausea and rhinitis. Using a dose step-up routine caused a lower incidence of adverse events. Also this drug was not associated with a major risk of withdrawal symptoms, nocturnal sleep disturbances and abuse potential, characteristic of stimulants which can be associated with this medication.

Ellis *et al.*[36] studied 12 subjects with narcolepsy and 12 controls. A single oral dose of modafinil, 400 mg, was given to eight subjects from each group, and a placebo to four from each. Functional magnetic resonance imaging was used to detect regional brain responses to changes in sensory stimuli. Although the number of subjects was small, and the changes slight, it was shown that low cortical activation levels in both subjects which were normal, and narcoleptics were increased following the administration of modafinil. The technique used may be a valuable addition to established studies of attention.

Besset *et al.*[37] treated 140 narcoleptic patients with modafinil over a period of up to 114 months with considerable success. Continuous treatment was slightly better than interrupted treatment, and dependency signs or significant side-effects were never observed. When the latter did occur they included nausea, headache, poor sleep and sweating. The trial of treatment with modafinil for excessive daytime sleepiness by Broughton *et al.*[38] confirmed that in a dose of 200–400 mg it was effective in reducing the number of daytime sleep episodes and periods of severe sleepiness, and it was well tolerated. Apart from the absence of short-term side-effects, the alerting properties of modafinil do not seem to be related to an alteration of hormone profiles.[39]

Previously the most frequently used drugs to achieve this end were central nervous system stimulants such as methylphenidate and amphetamines. Methylphenidate, given in a starting dose of 5 mg, was preferred to amphetamines because of its shorter half-life and lower incidence of adverse effects. It can be given by iontophoretic delivery.[40] Amphetamines are given once or twice daily in a starting dose of 2·5 mg, gradually increasing to the limit of tolerance; and there is no doubt that they can be effective, often within a matter of a few hours. Both do have a number of side-effects such as irritability, anxiety, nervousness, headache, psychosis, tachycardia, hypertension, nocturnal sleep disturbances, and tolerance and drug dependency,[33] and in the case of the latter possibly dental caries.[41] Pemoline has also been tried, but has a longer half-life and a slower onset of action.[12] It is less efficient but is well tolerated, although there is a risk of liver damage, and is not licensed in the UK. The starting does is 37·5 mg. Now the main use for these drugs may be as add-on therapy when a situation demands special alertness.

A number of other drugs, including tricyclic antidepressants, and selective serotonin re-uptake inhibitors in the case of cataplexy, have been tried. These include selegeline hydrochloride, 20 mg a day, used in a randomised, double-blind, placebo-controlled trial.[42] This is a monoamine oxidase inhibitor which shows a dose-dependent REM suppression, and an increase of REM latency and sleep latency, a dose-dependant reduction of cataplexies, as well as a reduction of daytime sleepiness, sleep attacks and number of naps. However, apart from REM suppression, the other effects lessen as treatment

proceeds. As has been mentioned, gamma-hydroxybutyrate, 26·4 to 52·4 mg per kg, reduces daytime sleepiness when given to patients with narcolepsy, and decreases episodes of cataplexy, sleep paralysis and hypnagogic hallucinations. In addition to inhibiting GABA ketoglutarate transaminase, it increases acetylcholine and dopamine in the brain, and depresses glucose utilisation but not oxygen consumption. It has a short half-life so that the patients wake up fully alert and refreshed, but unfortunately the drug effects can wear off after a while and sleepwalking can be a troublesome side-effect.

Other drugs used to treat cataplexy, sleep paralysis, and hypnagogic hallucinations in particular, include venlafaxine, aprotrytiline, imipramine, clomipramine and fluoxetine; and for nocturnal sleep disruption with periodic leg movements, clonazepam and levodopa.[14] A trial of treatment with melatonin may be of special interest.[43] Whatever drug treatment is given to patients with narcolepsy, frequent follow-up may be necessary to ensure compliance.[44]

Non-pharmacological approaches to the treatment of narcolepsy should also be considered especially in children,[45] as in view of the symptoms it is not surprising that emotional and behavioural problems are common. In particular there may be difficulties at school as a result of daytime sleepiness. Behavioural management can include structured sleep schedules with the opportunity to sleep in the afternoon, and at other strategic times, and dietary advice (to avoid obesity) can be useful. In fact, all aspects of the patient's lifestyle should be reviewed, and if associated symptoms such as anxiety and depression are marked, psychiatric opinion may be needed. Teachers will need to be told of the child's condition, and help given in the learning situation. A watch should be kept on possibilities such as bullying and social isolation.[46] Also, it will be important to give advice to adolescents about the dangers of sleepiness while driving, and patient help groups and associations dealing with the condition can be of value.

CONCLUSIONS

There are obvious difficulties in diagnosing narcolepsy at any age, but especially in childhood. The onset of symptoms is usually in late adolescence or in early adult life, but Heier[47] stresses that in about one-third of patients these occur before the age of 15 years, and reports three such patients, two aged five and one aged four and a half. If the correct diagnosis is not made, serious psychological and social problems can arise, particularly in the school situation, which in turn can cause difficulties in social adjustments later in life. This emphasises the importance of early treatment.

The discovery of canine or dobermann narcolepsy, with an autosomal recessive gene called canarc, provides an animal model for research, which may well help in elucidating the exact cause of this condition.[9] As emphasised by Guilleminault and Brooks,[48] the diagnosis and treatment of excessive daytime sleepiness presents particular difficulties, but also rewards, as it is so often remediable. Effective management may require special interdisciplinary provisions to ensure success.[4]

REFERENCES

1 Parkes D. Excessive daytime sleepiness. *Proc R Coll Physicians Edinb* 2001; **31:**50.
2 Ohayon MM, Priest RG, Caulet M *et al.* Hypnagogic and hypnopompic hallucinations: pathological phenomena? *Br J Psychiatry* 1996; **169:**459–67.
3 Billiard M. Narcolepsies. *Rev Prat* 1996; **46:**2428–34.
4 Stores G. Recognition and management of narcolepsy. *Arch Dis Child* 1999; **81:**519–24.
5 Kotagal S. Narcolepsy in children. *Semin Pediatr Neurol* 1996; **3:** 36–43.
6 Kotagal S. Sleep disorders in school-age children. *Indian J Pediatr* 1997; **64:**625–38.
7 Parkes JD, Chen SY, Clift SJ *et al.* The clinical diagnosis of the narcoleptic syndrome. *J Sleep Res* 1998; **7:**41–52.
8 Aird RB, Gordon NS, Gregg HC. Use of phenacemide (phenurone) in treatment of narcolepsy and cataplexy. A preliminary report. *Arch Neurol Psychiat* 1953; **70:**510–15.
9 Guilleminault C, Pelayo R. Narcolepsy in children. A practical guide to its diagnosis, treatment and follow-up. *Paediatr Drugs* 2000; **2:**1–9.
10 Dahl RE. The development and disorders of sleep. *Adv Pediatr* 1998; **45:**73–90.
11 Guilleminault C, Pelayo R. Narcolepsy in prepubertal children. *Ann Neurol* 1998; **43:**135–42.
12 Lenti C, Somajni F. Narcolepsy in an 8-year-old boy: neurologic psychiatric study. *J Child Neurol* 1998; **13:**405–7.
13 MacFarlane JG, List SJ, Moldofsky H *et al.* Dopamine D2 receptors quantified *in vivo* in human narcolepsy. *Biol Psychiatry*1997; **41:**305–10.
14 Sandyk R. Melatonin and maturation of REM sleep. *Int J Neurosci* 1992; **63:**105–14.
15 Nishino S, Ripley B, Overeem S *et al.* Hypicretin (orexin) deficiency in human narcolepsy. *Lancet* 2000; **355:**39–40.
16 Siegel JM. Narcolepsy: a key role for hypocretins (orexins). *Cell* 1999; **98:**409–12.
17 Mignot E, Tafti M, Dement WC *et al*. Narcolepsy and immunity. *Adv Neuroimmunol* 1995; **5:**23–37.
18 Schuld A, Hebebrand J, Geller F *et al.* Increased body-mass index in patients with narcolepsy. *Lancet* 2000; **355:**1274–5.
19 Genton P, Benlakhel K, Disdier P *et al.* Diagnostic de la narcolepsie-cataplexie: intérêt de l'enregistrement continu sous EEG ambulatoire. À propos de observations. *Neurophysiol Clin* 1995; **25:**187–95.
20 Folkerts M, Rosenthal L, Roehrs T *et al.* The reliability of the diagnostic features in patients with narcolepsy. *Biol Psychiatry* 1996; **40:**208–14.
21 Dyken ME, Yamada T, Lin-Dyken DC *et al*. Diagnosing narcolepsy through the simultaneous clinical and electrophysiologic analysis of cataplexy. *Arch Neurol* 1996; **53:**456–60.
22 Wing Y-K, Chen C-N, CKW Ho. HLA DR2 and DQ1 frequency among narcoleptic patients in Hong Kong Chinese. *Psychiatry Clin Neurosci* 1998; **52:**523–7.

23 Mignot, E, Hayduk R, Black J *et al.* HLA DQB1*0602 is associated with cataplexy in 509 narcoleptic patients. *Sleep* 1997; **20:**1012–20.

24 Planelles D, Puig N, Beneto A *et al.* HLA-DQA, -DQB and -DRB allele contribution to narcolepsy susceptibility. *Eur J Immunogenet* 1997; **24:**409–21.

25 Nevšímalová S, Mignot E, Šonka K *et al.* Familial aspects of narcolepsy-cataplexy in the Czech Republic. *Sleep* 1997; **20:**1021–6.

26 Aldrich MS. The clinical spectrum of narcolepsy and idiopathic hypersomnia. *Neurology* 1996; **46:**393–401.

27 Vgontzas AN, Bixler EO, Kales A *et al.* Daytime sleepiness and REM abnormalities in Prader-Willi syndrome: evidence of generalized hypoarousal. *Int J Neurosci* 1996; **87:**127–39.

28 Scharf MB, Lai AA, Branigan B *et al.* Pharmacokinetics of gammahydroxybuterate (GHB) in narcoleptic patients. *Sleep* 1998; **21:**507–14.

29 Richdale AL, Cotton S, Hibbit K. Sleep and behaviour disturbance in Prader-Willi syndrome: a questionnaire study. *J Intellect Disabil Res* 1999; **43:**380–92.

30 Zeman A, Douglas N, Aylward R. Narcolepsy mistaken for epilepsy. *BMJ* 2001; **322:**216–7.

31 Billiard M, Merle C, Carlander B *et al.* Idiopathic hypersomnia. *Psychiatry Clinl Neurosci* 1998; **52:**125–9.

32 Schenck CH, Boyd KL, Mahowald MW. A parasomnia overlap disorder involving sleepwalking, sleep terrors, and REM sleep behaviour disorder in 33 polysomnographically confirmed cases. *Sleep* 1997; **20:**972–81.

33 Ellis CM, Simmons A, Lemmens G *et al.* Proton spectroscopy in the narcoleptic syndrome. *Neurology* 1998; **50(Suppl 1):**S23–S26.

34 US Modafinil in Narcolepsy Multicenter Study Group Randomized trial of modafinil for the treatment of pathological somnolence in narcolepsy. *Ann Neurol* 1998; **43:**88–97.

35 US Modafinil in Narcolepsy Multicenter Study Group Randomized trial of modafinil as a treatment for the excessive daytime somnolence of narcolepsy. *Neurology* 2000; **54:**1166–75.

36 Ellis CM, Monk C, Simmons A *et al.* Functional magnetic resonance imaging neuroactivation studies in normal subjects and subjects with the narcoleptic syndrome. Action of modafinil. *J Sleep Res* 1999; **8:**85–93.

37 Besset A, Chetrit M, Carlander B *et al.* Use of modafinil in the treatment of narcolepsy: a long term follow-up study. *Neurophysiol Clin* 1996; **26:**60–6.

38 Broughton RJ, Fleming FAE, George CFP *et al.* Randomized, double-blind, placebo-controlled crossover trial of modafinil in the treatment of excessive daytime sleepiness in narcolepsy. *Neurology* 1997; **49:**444–51.

39 Brun J, Chamba G, Khalfallah Y *et al.* Effect of modafinil on plasma melatonin, cortisol and growth hormone rhythms, rectal temperature and performance in healthy subjects during a 36 h sleep deprivation. *J Sleep Res* 1998; **7:**105–14.

40 Singh P, Boniello S, Liu P *et al.* Transdermal iontophoretic delivery of methylphenidate HCL *in vitro*. *Int J Pharm* 1999; **178:**121–8.

41 Howe AM. Methamphetamine and childhood and adolescent caries (letter). *Aust Dent J* 1995; **40:**340.

42 Mayer G, Ewert Meier K, Hephata K. Selegeline hydrochloride treatment in narcolepsy. A double-blind, placebo-controlled study. *Clin Pharmocol* 1995; **18:**306–19.

43 Gordon N. The therapeutics of melatonin: a paediatric perspective. *Brain Dev* 2000; **22:**213–7.

44 Rogers AE, Aldrich MS, Berrios AM *et al.* Compliance with stimulant medications in patients with narcolepsy. *Sleep* 1997; **20:**29–33.

45 Garma L, Marchand F. Non-pharmacological approaches to the treatment of narcolepsy. *Sleep* 1994; **17(Suppl 8):**S97–S102.

46 Wise MS. Childhood narcolepsy. *Neurology* 1998; **50(Suppl 1):**S37–S42.

47 Heier MS. Narkolepsi hos barn-en dioagnostisk og terapeutisk utfordring. *Tidsskr Nor Loegeforen* 1998; **19:**2961–3.

48 Guilleminault C, Brooks SN. Excessive daytime sleepiness. A challenge for the practising neurologist. *Brain* 2001; **124:**1482–8.