NEUROLOGY 2000 AND BEYOND*

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The symposium was designed to give a practical, evidence-based approach to the common neurological problems faced every day in clinical practice (Table 1). In this article the key points made by the speakers are summarised.

TABLE 1

How do I manage?
Patients with suspected dementia
Patients with medically unexplained symptoms
Patients with multiple sclerosis who want beta interferon
Patients with epilepsy in pregnancy
Patients with chronic peripheral neuropathy

Sleep disorders
Narcolepsy
Night terrors, sleep walking and nocturnal seizures

Common but difficult problems
'Funny turns' and 'blackouts'
Abnormal movements

DEMENTIA

Dr Graham Lennox, Consultant Neurologist, Addenbrooke's Hospital, Cambridge, spoke on the clinical approach to diagnosing and treating suspected dementia.

At the bedside, two main patterns of dementia can be identified. In temporoparietal dementias, such as Alzheimer's disease (AD) and dementia with Lewy bodies (DLB), memory, language and parietal lobe problems (such as getting lost) are prominent, and treatment is likely to be limited. In frontotemporal dementias, such as those caused by frontotemporal degeneration (FTD), small vessel disease and structural lesions (such as hydrocephalus and tumour), impaired social judgement is common and there is a higher chance of finding a treatable cause. Concomitant depression and anxiety should always be sought and treated, as these may either be causative of, or associated with, cognitive complaints. Bedside tests of mental function should include tests of frontal function remembering that the mini-mental state examination (MMSE) was designed to test for AD and is not sensitive to other causes of dementia. Formal neuropsychological assessment, while valuable, is not essential. Investigations for metabolic causes or a space occupying lesion have a low yield but should be performed. The electroencephalogram (EEG) still has a role in diagnosis as it is usually abnormal in AD but invariably normal in frontotemporal dementia.

Typical AD presents with slow progressive forgetfulness and visuospatial dysfunction, sometimes with fine fingertip myoclonus but no other neurological signs. The diagnosis may have to be revised if progression is rapid or there are more florid neurological or psychotic features. DLB can present in a very rapid manner, even imitating Creutzfeldt-Jakob disease (CJD), although a slower course with fluctuation, visual hallucinosis, parkinsonism and neuroleptic sensitivity is more usual. The hallmarks of FTD are behavioural change with loss of insight, diminution and perseveration of speech, and a striking preservation of visuospatial function. By far, the commonest cause of FTD is that associated with motor neurone disease pathology and, perhaps surprisingly, Pick's disease is the least common.

Treatment that retards disease progress – neuroprotection – should be distinguished from symptomatic management. While there is some evidence that oestrogen and avoiding head injuries may offer some protection from AD, there is no drug that has yet been shown to retard disease progression. Evidence of microglial inflammation in AD is prompting treatment studies using anti-inflammatory and immunosuppressive drugs.

Neuroleptics are the most widely prescribed symptomatic treatment for dementia – even more so than for all other psychiatric disorders put together – yet the evidence suggests that they may actually shorten survival.[1] The newer cholinesterase inhibitors, donepezil, rivastigmine and tacrine (now only prescribed in the US) do confer a small symptomatic effect equating to a boost of 0.5 to 1 point on the MMSE. There are, however, undoubtedly patients that respond more significantly than this on clinical global impression ratings. For tacrine, 11 patients must be treated to obtain a *clinically measurable* response in one patient and 42 have to be treated to obtain a *marked* response in one patient.[2] Patients with DLB are more likely to be marked responders – hallucinosis and fluctuations being particularly treatment-sensitive symptoms. Relatively little data exist on the functional impact of these drugs, and there are no controlled data on carer burden and cost-effectiveness (e.g. delaying the time to severe dependency). However, guidelines have been drawn up for treatment in AD, which can also be applied to DLB.[3] Patients should have a reasonably secure diagnosis, MMSE between ten and 24 and a duration >6 months. An early review to check side-effects and a three month review to examine efficacy generally results in a lot of patients trying cholinesterase inhibitors but a substantial number being stopped early on when there is no response.

UNEXPLAINED SYMPTOMS

Dr Michael Sharpe, Senior Lecturer in Psychological Medicine, University of Edinburgh, spoke on managing medically unexplained symptoms in neurology.

Studies have shown that 50–70% of the most common

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symptoms in primary care do not have a basis in definable disease.[4] In a Neurology outpatients department, as in other specialities, 30% of patients have symptoms that are unexplained or largely unexplained by disease.[5] As a rule of thumb, the more symptoms a patient has, the more likely the presenting symptom remains unexplained. Compared to patients with explained symptoms, they are much more likely to have diagnoses of depression and anxiety and are at least as disabled on self-rated measures of physical and social functioning.[6] Their symptoms are likely to persist despite the fact that very few of these patients progress to a neurological disease.

Worth remembering when assessing and managing patients with unexplained symptoms:

- **Ask the patient what they think is wrong with them and ask them why they think that. Sometimes patients simply want specific reassurance tailored to a specific fear, for example about multiple sclerosis or having a brain tumour.**
- **Look for anxiety and depressive disorders remembering that these have somatic as well as psychological symptoms.**
- **Acute severe anxiety or panic is also common in this group; it is treatable and easy to miss if not asked about directly. Anxiety about disease is called hypochondriasis. Be careful of providing repeated reassurance to patients with hypochondriasis as this may be counterproductive.**
- **If antidepressants seem appropriate, explain their use in a way that is acceptable to the patient. For example, point out that they can improve symptoms such as pain and insomnia, and emphasise that they are not addictive.**
- **Cognitive behavioural therapy is useful for many unexplained symptoms.**
- **Look for a history of chronic multiple unexplained symptoms. A long history of this prior to the age of 30 may suggest somatization disorder which is best managed by containment, usually by the GP, to prevent iatrogenic harm and unnecessary cost.**
- **Finally, make sure you know what the patient and GP want from the consultation. Often the patient wants nothing more than to be listened to, and sometimes the GP simply wants the patient off their hands for a while.**
- **Detailed investigation, particularly if prolonged, in a partial attempt to reassure the patient can be potentially harmful.**

BETA INTERFERON AND MULTIPLE SCLEROSIS

Professor Alastair Compston, Professor of Neurology, Addenbrooke's Hospital, Cambridge, spoke on managing the patient with multiple sclerosis who wants beta interferon based on his own experience in the Interferon Clinic in Cambridge.

Three key areas need to be covered in a clinical discussion about interferon:

1. Expectations – often very high as a result of the degree of publicity the drug has received.
2. Efficacy – does it work?
3. Expense – since it costs £9,600 per patient per year.

At the outset, it is important to establish where the patient is in the clinical course of the disease. Do they have attacks of symptoms from which they recover *completely*? Are there residual symptoms? Most crucially of all, are they gradually getting worse? Acute events may indicate inflammation and electrical failure without significant demyelination. Disease *progression,* however, occurs because of axon degeneration in the absence of trophic support from myelin and oligodendrocytes. The key point here is that while the extent of axon degeneration is partly determined by the degree of inflammation, it will continue to take place *long after the inflammation has stopped*. It therefore does not seem logical to try to slow a neurodegenerative process in these patients with an immunological treatment.

The evidence for this scheme comes from studies on drugs such as the monoclonal antibody CAMPATH-1. This is a potent inhibitor of inflammation as measured by new clinical episodes and MRI lesions, but it does not stop progression that has begun *prior to treatment*.[7] In those patients that do progress, brain and spinal cord atrophy can be demonstrated to correlate with axonal loss measured using magnetic resonance spectroscopy.

Beta interferon inhibits the expression of molecules on the surface of antigen-presenting microglial cells thus inhibiting phagocytosis of myelin. However, its effects on the immune system are complex as, paradoxically, it also increases the phagocytic effect of microglia and enhances the release of pro-inflammatory mediators. Beta interferon is not conceptually different from other immuno-modulatory drugs that have been tried in MS but it has been tested much more thoroughly.

The three current interferon 'brands' have different construction, dosing regimens and methods of administration, but have broadly similar efficacy. Well-conducted randomised double-blind placebo-controlled trials have demonstrated that they each reduce relapse rates by about one third. This has a measurable effect on the amount of steroid courses and hospital admissions required in the course of the illness. Of course this includes both mild and more severe episodes, and so the impact of therapy is entirely different for someone with infrequent mild episodes versus someone with frequent episodes of moderate severity. Beta interferon also reduces, probably in a dose-responsive way, the rate of accumulation of new lesions in MS. It is this surrogate marker of disease activity that has perhaps excited the most attention about the drug.

A mild effect on disability was demonstrated in two trials of interferon in which this was not a primary outcome measure of the study.[8, 9] Because these trials may have underestimated the treatment effect, three subsequent studies have been designed to look specifically at this. A trial using betaferon (interferon ß-1b[10]) did demonstrate a small but definite effect on disability in secondary progressive disability although its methodology has excited some criticism. Analysis of the imaging in this study supports the hypothesis that those patients who benefited were the ones with inflammation in addition to disease progression. Another trial, using Rebif (interferon ß-1a[11]), has not demonstrated an overall effect despite claims about subgroup analysis.

The overall conclusion has to be that, pending the result of the final trial, beta interferon is not a drug that has a substantial effect on disability in patients

with multiple sclerosis. Clinically, this unfortunately means that patients with very mild symptoms, fixed disability or progressive disease are unlikely to benefit from beta interferon.

Adverse effects of beta interferon include an early flu-like illness and skin reactions, which occasionally can be very unpleasant, and a limiting factor in treatment. Other reactions such as thyroid disease and rarely anaphylactic reactions are emerging, but overall it seems to be a safe drug. A greater issue in long-term interferon treatment is the development of neutralising antibodies in 10–40% of patients, which can reduce its efficacy. This appears to be more likely for interferon ß-1b than interferon ß-1a, although antibodies appear to cross-react with different brands. This raises the possibility that premature commencement of interferon may limit its usefulness at a later stage as well as its potential benefits.

According to guidelines based on the principles above[12] only 15% of patients with relapsing-remitting or secondary progressive MS meet clinical criteria for treatment with beta interferon, i.e. they are over 18, can walk at least ten metres and have had two relapses in the last two years. In the future, further trials may demonstrate effects in much wider clinical scenarios. The introduction of the National Institute of Clinical Excellence (NICE) may help to eliminate geographical variation in prescribing practices and decide in which situations the drug is cost-effective. The pharmaceutical industry also has a role perhaps in pricing interferon equally between countries, and at a realistic level for the economy and health service of the UK.

Other therapies that deserve further study include intravenous immunoglobulin and plasmapheresis for rescuing a patient from a severe episode, mitoxantrone, and copolymer 1. Azathioprine seems to be at least as effective as interferon but is not as fashionable.[13]

Perhaps the most important aspect of discussing interferon is to ensure the patient feels they are not missing out on treatment that is going to make a radical difference to their condition, and that they have had a fair and open chance to discuss the issues involved.

EPILEPSY AND PREGNANCY

Dr Jim Morrow, Consultant Neurologist, Royal Victoria Hospital, Belfast spoke on epilepsy in pregnancy.

About 75,000 women of childbearing age suffer from epilepsy in the UK. This group has suffered historically, from a prohibitive stance with respect to pregnancy and child rearing. What is the evidence to guide us in managing the 5,000 pregnancies per year in the UK in this group?

Decisions about pregnancy in women suffering from epilepsy should be made prior to conception. Pre-conception counselling should wherever possible start at diagnosis, perhaps in a special pre-conception counselling clinic. Two special issues with regard to contraception are worth mentioning. Firstly, it is widely taught that for women taking carbamazepine and the oral contraceptive pill, an increase in the dose of oestrogen is sufficient to confer protection. This is not the case and barrier methods should also be advised. Secondly, although figures are debated, polycystic ovary syndrome may be particularly liable to occur on sodium valproate as compared to carbamazepine.[14]

In pregnancy, seizure frequency will improve in one third of patients, worsen in another third and the rest will stay the same. When epilepsy gets worse it may be because serum levels of the free anti-convulsant drug have fallen. No consensus exists on whether to pre-empt this with a change in drug dose but this is worthy of further study. Alternatively, epilepsy may worsen because of a unilateral maternal decision to stop drug therapy that may in itself be a risk factor for maternal mortality.

Women with epilepsy do not appear to have an increased risk of obstetric complications. However, haemorrhagic disease of the newborn occurs more frequently in mothers on hepatic enzyme-inducing drugs such as carbamazepine and topiramate. Mothers on these drugs should be given vitamin K in the last month of pregnancy and the neonate should receive it at birth.

The first step in pre-conceptual counselling is to review the diagnosis. The diagnosis of epilepsy may be incorrect in up to 20% of patients. Clearly if the patient has been seizure-free for some time then a trial without anticonvulsants maybe desirable. What about the risk of recurrent seizures during pregnancy? Fetal heart slowing during maternal seizures has been demonstrated and animal studies also support the idea that seizures are harmful but, surprisingly, firmer evidence is lacking. However, the possibility exists of trauma to the mother and fetus, as well as a possibility of increased miscarriage rate because of seizures. Despite the lack of evidence, many women will want to remain on treatment even if there is a possibility that they could withdraw.

What is the evidence that anticonvulsants cause fetal malformation? A meta-analysis[15] suggests that the risk of fetal malformation with maternal epilepsy on anticonvulsants is 4–9%, i.e. two to three times the risk without epilepsy. The risk of malformation is not increased in women who have epilepsy but are *not* on anticonvulsants. This may seem to exonerate epilepsy itself as the cause of malformations but it may simply reflect a group of mothers with mild or remitted epilepsy, or an incorrect diagnosis. A small amount of evidence exists that dose-response and peak-dose relationships exist between anticonvulsants and malformation risk. Polytherapy also appears more risky than monotherapy.

Which anticonvulsant should be prescribed? Johnson's meta-analysis[15] found no difference between monotherapy drugs but this was based on old studies and on sample sizes of less than 200 for carbamazepine and sodium valproate, which account for 90% of anticonvulsant prescriptions in the community. There is little evidence to guide practice with the newer drugs. In animal models of pregnancy lamotrigine and gabapentin look safer than older agents, but topiramate can cause limb abnormalities.

Neural tube defects are one of the commoner malformations linked with anticonvulsants – occurring ten times more commonly than the background rate with sodium valproate, for example. A number of large studies have demonstrated the general protective effect of folic acid but there are difficulties in assuming that this also protects against anticonvulsant-induced neural tube defects. The type of spina bifida seen with sodium valproate is different to that in the general population being lower in site and due to a failure of neural tube canalisation, not of folding. It therefore cannot automatically be assumed that this mechanism is folate dependent.

Dysmorphic syndromes and minor malformations can occur with any anticonvulsants. The real incidence is hard

to determine, partly because of the somewhat arbitrary way in which these children are clinically diagnosed unblinded to the mothers' drug history. Perhaps of more concern is the possibility that mothers on valproate may have a higher risk of having children with learning disabilities than mothers on other anticonvulsants.[16] The compelling need for more information in this area has prompted an observational national prospective register[17] which has already collected over 1,000 women with epilepsy during pregnancy (telephone 0800 389 1248 to register patients).

CHRONIC PERIPHERAL NEUROPATHY

Professor Richard Hughes, Professor of Neurology, Guy's, King's and St Thomas' School of Medicine, London, gave the William Ramsay Henderson Trust Lecture on the disabling and common problem of chronic peripheral neuropathy.

The first step in the diagnostic triage of neuropathy is to decide, with the aid of neurophysiological assessment, whether the problem is a multiple mononeuropathy, demyelinating or axonal peripheral neuropathy. A careful family history and childhood history, sometimes supplemented by examination for subtle signs in family members, helps to distinguish between hereditary and acquired disorders.

Multiple mononeuropathy occurs commonly in the context of diabetic, alcoholic or other metabolic neuropathy, but may indicate hereditary liability to pressure palsies (HLPP). Vasculitis is an important treatable cause in this group either as part of a systemic vasculitis, Sjögren's syndrome, or diabetes (which is now known to cause a vasculitic neuropathy).

If the neurophysiological assessments suggests demyelination, an increasing number of mutations have been discovered and can be tested for in order to establish hereditary causes. For example, duplication of the PMP22 gene on chromosome 17 results in Charcot-Marie-Tooth Disease type 1A whereas deletion of the same gene causes HLPP. If these are ruled out, the possibility of chronic inflammatory demyelinating polyradiculo-neuropathy (CIDP) should be considered, remembering that neurophysiological and clinical criteria now exist for this condition.[18] At this stage the possibility of paraprotein-associated or drug-associated (such as amiodarone) CIDP is worth remembering. Although the disease is rare with a prevalence of 0.5–1.25/100,000, 50% of patients have progressive disease and over half of patients can be expected to need expensive hospital treatments such as intravenous immunoglobulin and plasmapheresis.[19]

The evidence for effectiveness of treatment in CIDP is limited.[20] Prednisolone has been shown to improve impairment. Azathioprine has not been firmly demonstrated to be effective but is nevertheless routinely used by experts in the field. Plasma exchange has been shown in two studies to be superior to placebo but has been superseded by intravenous immunoglobulin. This is probably just as potent but more convenient to use, and is effective in up to two-thirds of patients. Improvement is more likely if treatment is begun early, but uncertainty about placebo response should sometimes be resolved by 'n of 1 trials' for individual patients.

Multifocal motor neuropathy is a subgroup of CIDP that is more common in men. It usually presents with upper limb weakness, cramps and fasciculation, and can be mistaken clinically for motor neurone disease. It is characterised by widespread conduction block, a normal CSF protein (in contrast to CIDP) and the variable presence of anti-GM1 antibodies. Two small trials suggest intravenous immunoglobulin is useful[21,22] and there are anecdotal reports of success with cyclophosphamide. Also anecdotally, steroids may make the condition worse.

Paraproteins associated with myeloma, Waldenström's macroglobulinaemia and benign monoclonal gammopathy of uncertain significance (MGUS) may all produce a demyelinating neuropathy. The POEMS syndrome of Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal gammopathy and Skin changes is worth looking out for. As these conditions are potentially treatable, patients with undiagnosed demyelinating neuropathy should have their paraprotein levels checked every year. In the presence of a paraprotein, consideration should also be given to a skeletal survey to look for a solitary myeloma.

The neuropathy seen in 50% of patients with an IgM paraproteinaemia usually produces a predominantly sensory, progressive neuropathy, sparing cranial nerves, and is often associated with a postural tremor. This is associated with antibodies to myelin-associated glycoprotein and is usually best left untreated as it is very slowly progressive.

The causes of axonal neuropathy should again be divided between hereditary and acquired. No genetic markers currently aid this diagnosis. Virtually every general medical condition can be associated with an axonal neuropathy. Careful enquiry should be made about alcohol, drugs and other toxins such as insecticides. Autonomic symptoms should be specifically asked about. Looking for thickened nerves and decreased muscle bulk of the *extensor digitorum brevis* is essential. A really thorough general medical examination including breast and rectal examination is also important. A thorough, staged laboratory work-up in which investigations of increasing complexity are performed should include tests for a paraneoplastic neuropathy.

If there is still no diagnosis then a lumbar puncture may be necessary. Nerve biopsy should be reserved as a last resort: biopsy should only be performed in patients with a densely analgesic area in whom aggressive treatment will be given if a treatable pathology is found. Patients should be made aware that there is a 10% risk of post-operative pain and only a 10% chance of finding a useful diagnosis. It should be done before the neuropathy is too severe and in a centre that can provide electron microscopy of the specimen. Diabetes remains the commonest cause of axonal neuropathy. The prevalence in diabetes is 14–63% and correlates to diabetic control, duration of diabetes, age and height of the patient.

After intensive investigation in tertiary centres, a quarter of patients with axonal neuropathy will remain undiagnosed.[23] The remainder typically have predominantly sensory, symmetrical and usually progressive symptoms and have been given the label of chronic idiopathic polyneuropathy of middle and old age. Although some will go on to suffer from other conditions, in most patients it is probably an age-related phenomenon. By extrapolation, this problem may affect 5–10% of the elderly population. Its origin may be pre-diabetic, toxic, genetic or, despite the lack of known antibodies, autoimmune (since an autoimmune axonal neuropathy has not yet been demonstrated).

General management should include footcare, stockings to avoid oedema, weight loss, sensible shoes, boots or orthoses, symptomatic treatment with tricyclic antidepressants, physiotherapy and occupational therapy.

EXCESSIVE DAYTIME SLEEPINESS

Professor David Parkes, Professor of Clinical Neurology, King's College Hospital, London, gave a precise account of excessive daytime sleepiness.

He dismissed laziness, boredom or psychiatric problems as potential causes, stressing that almost always there is an organic cause. Quantifying the degree of sleepiness (by using the Epworth scale[24]) is of paramount importance in history taking, and patients should contribute by keeping a sleep/wake diary for at least one week. The essential questions of the sleep/wake history are:

- What time do you go to bed?
- How long does it take you to fall asleep?
- How many times do you awake in the night?
- When do you wake up?
- How active are you during the daytime?

Other key elements include a medical history, family history and enquiry about alcohol and recreational drug use to help differentiate the narcolepsy syndrome from sleep fragmentation due to obstructive sleep apnoea, acromegaly, hypothyroidism, hypersomnias (e.g. Prader-Willi syndrome, Moebius syndrome), and secondary gain sought by amphetamine addicts. Professor Parkes dismissed idiopathic hypersomnia as a meaningless addition to the differential diagnosis, and more a reflection of diagnostic incompetence.

The history should be refined with a few investigations, in particular a urine drug screen if substance misuse is suspected. Professor Parkes felt that motor activity monitors ('actimiters'), and the printouts of rest activity that they produce, are cost-effective if worn for over a fortnight. He did, however, confess his personal bias against the use of polysomnography because the mean sleep latency time measurement gleaned does not appear to correlate with other behavioural measures of sleepiness.

Professor Neil Douglas from the audience expressed a more favourable opinion about using the multiple sleep latency test, because of the importance of excluding imitative psychosomatic causes and the therapeutic implications of imparting a confirmed diagnosis of narcolepsy to (often young) adults.

The narcolepsy syndrome is perhaps the most celebrated cause of daytime sleepiness. It was first characterised in 1880 by a French psychiatrist, Gelineau, whose case series of 14 included his wine merchant who may have fallen asleep over 200 times each day. A prevalence of approximately 0.04%[25] extrapolates to at least 20,000 sufferers in the UK, men being affected slightly more often than women, with a bimodally distributed age of onset (adolescence and 45 years).

There are both genetic and environmental influences on the development of narcolepsy syndrome, which is 41% more frequent in first-degree relatives of patients than controls. Eighteen pairs of monozygotic twins have been identified with the syndrome, although they are usually phenotypically discordant. Human leucocyte antigen (HLA) relationships are well-known: whilst 28% of the normal Caucasian population have HLA-DR2 and its DQb0602 epitope, 98% of narcoleptics have HLA DQb0602. Whilst the phenotype is identical in those with and without the epitope, the familial frequency is six times higher in DR2 negative people. A 'sleep gene' has not been identified in the HLA region of chromosome 6, but the discovery of orexin as a major sleep-modulating neurotransmitter[26] in canine and murine models is an important development. Orexin has revolutionised research into daytime sleepiness and potentially opens novel potential therapeutic approaches for narcoleptic patients, which is unsurprisingly generating considerable interest from pharmaceutical companies.

Diagnostic of the narcoleptic syndrome is unequivocal cataplexy (emotionally-triggered, sudden atonia with mutism or dysarthria, and phasic facial muscle jerking in over 70% of people). The syndrome also includes daytime sleepiness, insomnia at night with multiple arousals and pre-sleep dreaming (which is technically different from hypnagogic hallucinations). Cataplexy usually follows the initial symptom of daytime sleepiness within five years, itself often antedated by parasomnias (which are more prevalent in people with the syndrome). Sleep paralysis is not diagnostic (and occurs in most disorders that interfere with the continuity of sleep). The first-line treatment of daytime sleepiness remains amphetamine. If Modafinil is to gain wider acceptance, direct comparisons with amphetamine are needed and the 100-fold excess cost needs to be addressed. Fluoxetine in a single 20 mg morning dose is usually effective in treating cataplexy (although pronounced rebound may occur on sudden drug withdrawal), but selegiline and tricyclic antidepressants can also be used.

PARASOMNIAS AND NOCTURNAL SEIZURES

Dr Zenobia Zaiwalla, Consultant Clinical Neurophysiologist, Park Hospital for Children, Oxford, carefully disentangled the often-confused parasomnias and nocturnal seizures, illustrating the large potential for misdiagnosis.

Whilst a parasomnia is an episodic disorder in sleep, but does not produce a primary complaint of insomnia or excessive daytime sleepiness, epilepsy is an episodic disorder of brain function associated with neuronal hyper-excitability which may produce rhythmic movements or complex automatisms, that may occur in sleep. Distinguishing the two is often difficult, due to the customary paucity of clinical information, overlap of semeiology, occasional coexistence of the two disorders, familial predisposition in both, and usual lack of attacks occurring in the sleep laboratory. Features useful in distinguishing the nocturnal epilepsy syndromes (such as benign Rolandic epilepsy, juvenile myoclonic epilepsy and frontal lobe seizures) from parasomnias (night terrors, sleep walking, confusional arousals, REM behaviour disorder, and non-REM arousal disorder) are shown in Table 2.

Night terrors occur in the first third of the night because of sudden arousal from deep sleep, may be heralded by a loud scream and intense fear/panic, and are accompanied by autonomic features such as tachycardia, tachypnoea, sweating and pupillary dilatation. They tend to last less than 15 minutes, with amnesia for the episode, so any anxiety tends to be caused by parental concern. Night terrors are

TABLE 2
The differentiation of epilepsy from parasomnias.

	Frontal epilepsy	Temporal lobe epilepsy	Non-REM arousal disorder	REM behaviour disorder
Semeiology				
Time of night	Any time	Any time	First 1/3	Middle 1/3 or later
Duration	Very brief	Longer	Longer	Longer
Frequency	Very frequent	Fewer	Fewer	Fewer
Directed actions/ aggression	No	No	Possibly	Possibly
Memory of event	Absent	Absent	Absent	Present
Family history	Possibly present	Not usually present	Possibly present	Possibly present
Investigation				
Polysomnography	Non-REM stage 2 sleep	Awake	Non-REM	REM
EEG	Unhelpful	Usually abnormal	Unhelpful	Unhelpful
Video	Helpful	Helpful	May be helpful	May be helpful

common in children, there is a familial predisposition, and stress can often be a precipitant. Somnambulism usually occurs for minutes to hours in the first third of the night. Repetitive confused movements sometimes precede walking when people have a limited capacity to respond to environmental stimuli and negotiate objects. This can lead to dangerous activity and, rarely, directed violent behaviour with subsequent amnesia. Familial predisposition and stress are recognised precipitants, and the disorder may persist into adult life.

REM sleep behaviour disorder is mainly a condition of adults, starting over the age of 60 years, although it can start earlier in the context of other neurological disorders affecting the brainstem. Sufferers act out often violent dream content, with complete recall of dreams, injury in sleep and, again, there is a familial predisposition. These symptoms often respond well to clonazepam. Non-REM arousal disorder is best managed with reassurance, and by addressing any stressful precipitants.

Frontal lobe seizures mainly occur at night and are frequently misdiagnosed as parasomnias or a behavioural problem because of their abrupt onset/termination, short duration, frequent occurrence (up to 15 times per night), dystonic posturing, complicated motor/gestural automatisms, vocalisations, stereotyped movements, the lack of ictal/post-ictal confusional automatisms, sensitivity to emotional factors and often normal ictal/inter-ictal EEG. Temporal lobe epilepsy can be confused with sleep walking or night terrors but is distinguished by its aura, post-ictal confusion, complex automatisms, later timing of contralateral dystonic posturing and an often abnormal EEG.

Periodic leg movements and fragmentary sleep myoclonus are also episodic in sleep and may be confused with epilepsy and parasomnias. Periodic limb movements (repeated movements, slower and lower amplitude than epileptic jerks) in sleep are involuntary, affect 30% of adults and are strongly associated with restless legs syndrome. Fragmentary sleep myoclonus consists of clusters of brief, asynchronous, asymmetrical muscle jerks affecting the face, limbs and trunk, predominantly in non-REM sleep.

All these disorders are easily confused, but a careful history is again important in their differentiation, and the use of home video should be encouraged early in their investigation. Polysomnography and videotelemetry should be used if the episodes are frequent or unusual.

'FUNNY TURNS' AND 'BLACKOUTS'

Dr Richard Roberts, Senior Lecturer in Neurology, Ninewells Hospital, Dundee, described the diagnostic dilemmas of 'funny turns' and 'blackouts' using a series of video recordings.

The main diagnoses to distinguish are syncope, epilepsy and non-epileptic attack disorder (NEAD). Always question the accuracy of a diagnosis made elsewhere – one quarter of people referred to a specialist epilepsy clinic with a diagnosis of 'refractory' epilepsy have been found not to have epilepsy.[27] Some of these misdiagnoses arise because of confusion over the clinical features of syncope, for example 90% of people have irregular myoclonic jerks after a simple faint.[28] Prolactin does rise shortly after generalised seizures, but it can also rise after syncope (whether caused by hyperventilation or not), and may only rise slightly or not at all after partial or simple seizures. Videotelemetry is again very helpful in difficult cases.

It can be equally difficult to distinguish epilepsy from NEAD. Patients labelled with tonic-clonic, atonic or abreactive 'refractory epilepsy' may have NEAD, and those diagnosed as having NEAD or a sleep disorder may have epilepsy (most commonly frontal). NEAD should ideally be diagnosed at the outset, and if anticonvulsants are discontinued early, the prognosis is usually good. Dr Roberts stressed the importance of following up these patients once a diagnosis is made, which he does for one year in his own practice. Because of the paucity of trained personnel to provide cognitive behavioural therapy and active counselling, and the shortage of resources in clinical psychology, these therapies are not available to all patients with NEAD, making *early* diagnosis and intervention a cost-effective strategy.

ABNORMAL MOVEMENTS

Dr Nicholas Fletcher, Consultant Neurologist, Walton Centre for Neurology and Neurosurgery, Liverpool, spoke on the whole range of abnormal movements.

The most significant recent advances in the management of idiopathic Parkinson's disease (IPD) have been: the increasing trend to use first-line dopamine agonist therapy for IPD in the young; the use of amantadine (in doses of 200–300 mg) as a form of chemical pallidotomy for dopa-induced dyskinesia[29, 30] and the evaluation of stereotactic neurosurgery.

Tics (jerks of the face or upper body, which appear more deliberate than chorea, repetitive and stereotyped) may be simple or complex, and motor or vocal. Whilst Gilles de la Tourette syndrome (GTS) is the most celebrated cause of tics, transient tic disorder of childhood, Huntington's disease, neuroacanthocytosis, drugs, encephalitis, Rett's syndrome, and focal lesions should all be borne in mind. GTS is characterised by its early onset (usually <21 years) involving multiple tics, of variable severity over time, and psychological phenomena (obsessive-compulsive disorder, attention-deficit-hyperactivity disorder, self-injury and personality disorder). Remission occurs in 30–40% of people. Drug therapy is not always needed, although when it is, clonidine, neuroleptics, tetrabenazine, nicotine, selective serotonin reuptake inhibitors, tricyclic antidepressants, and methylphenidate may be helpful in specialist hands. Paediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS),[31] are of great contemporary interest in the genesis of sudden exacerbations of tics associated with streptococcal sore throats, and are creating important insights into tic pathogenesis.

Dystonias may be focal (in which case botulinum toxin is the most effective treatment), segmental, multifocal or generalised. Wilson's disease should always be considered in the differential diagnosis when seeing a young person with tremor, dystonia or dyskinetic involuntary movements. Kayser-Fleischer rings are found on slit lamp examination in almost all cases. Ninety-five per cent have a low caeruloplasmin and an increased urinary copper excretion, although a liver biopsy is needed to be certain of the diagnosis. Idiopathic torsion dystonia (with a prevalence of 330 per million) may be autosomal dominant or sporadic, and its age of onset tends to predict its severity.

Dopa-responsive dystonia is an increasingly recognised condition that should be sought due to its dramatic and sustained response to L-dopa therapy. Its onset is characteristically in childhood or adolescence usually affecting the lower limbs with diurnal fluctuation and sleep benefit. Its clinical resemblance to hereditary spastic paraparesis and occasionally cerebral palsy mean that all patients with these diagnoses should be considered for a clinical trial of L-dopa.

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