Clinical review

Recent advances

Neurology

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Most neurological problems are dealt with by general practitioners and hospital physicians, not by neurologists.[1] Neurological disorders account for 10%-20% of acute hospital admissions. Around 10% of the adult population consult their general practitioner each year with neurological symptoms, but of these less than 10% are referred to hospital clinics. Developments in the management of neurological disorders are therefore relevant to doctors without specialist neurological training.

Methods

We identified references by regular reading of general medical and neurological journals, from searching the electronic literature (Medline, BIDS), and through discussion with general practitioners and neurological colleagues with specialist interests. The final selection of papers was partly subjective.

Cerebrovascular disease

The international stroke trial and the Chinese acute stroke trial, each concerning around 20 000 patients, examined antithrombotic therapy (aspirin, heparin) given within 48 hours of acute ischaemic stroke.[2,3] Both found aspirin to be associated with about 10 fewer deaths or recurrent strokes in the first 4 weeks for each 1000 patients treated, but with slightly more haemorrhagic strokes. The international stroke trial reported no benefit from subcutaneous heparin (5000 or 12 500 IU twice daily) given with or without aspirin. Hence it was concluded that aspirin should be started as soon as possible after the onset of an acute ischaemic stroke.[2,3] Whether aspirin use is "acute treatment" or simply early secondary prevention remains debatable.

No clinical indicators reliably differentiate ischaemic from haemorrhagic stroke. The recommendation that aspirin be started only after appropriate brain imaging in patients requiring admission to hospital will place a huge burden on acute neurological services (over 100 000 people have a first stroke in England and Wales each year). The issue is still more problematic for thrombolytic therapy (tissue type plasminogen activator, streptokinase, urokinase). An overview of previous trials indicated significant excesses of early and total deaths, and of symptomatic and fatal intracranial haemorrhages, after acute thrombolytic therapy, but a significant reduction in death or dependency in patients randomised to treatment within 3 hours of stroke onset.[4] To identify the small number of patients likely to benefit from thrombolysis, early hospital admission and prompt investigation will be necessary. This may be achieved in dedicated stroke units, which have been shown to produce long term reductions in death, dependency, and need for institutional care.[5]

Carotid artery stenosis is an important predisposing factor for cerebrovascular ischaemic events, the risk increasing with the severity of stenosis and the presence of symptoms. For severe (more than 70% narrowing) symptomatic stenosis, carotid endarterectomy is recommended. For severe symptom free stenosis, optimal management has yet to be defined: a meta-analysis of trials[6] showed only a small absolute benefit from surgery in reducing the odds of ipsilateral stroke; hence the procedure cannot be routinely recommended. For mild to moderate symptomatic stenosis (less than 70% narrowing), antiplatelet therapy with aspirin or dipyridamole, or both, is recommended. Persistent symptoms may necessitate use of other treatments such as ticlopidine (named patient basis only); clopidogrel, which reduces the relative risk for further ischaemic events slightly more than aspirin[7]; or anticoagulation with warfarin.

Epilepsy

Most individuals with newly diagnosed epilepsy enter prolonged seizure remission and have an excellent prognosis, but seizures remain refractory in 20%-30%.[8] Improved evaluation of such patients with magnetic resonance imaging and telemetry may identify the structural and functional abnormalities that give rise to seizures. Up to 75% of patients with refractory partial epilepsy show evidence of abnormalities on magnetic resonance imaging,[9] some of which are amenable to surgery.

Cerebrovascular disease

- Given within 48 hours of ischaemic stroke, aspirin reduces risk of death and recurrent stroke
- Thrombolysis for acute ischaemic stroke is most effective if delivered within 3 hours of stroke onset
- Stroke units reduce death, dependency, and need for institutional care after stroke
- Carotid endarterectomy is currently recommended only for severe and symptomatic carotid stenoses

The first line drugs for epilepsy monotherapy remain carbamazepine and sodium valproate; phenytoin is now less used, and although lamotrigine has a monotherapy licence its place has still to be defined. Several new "add on agents" have been licensed in recent years including vigabatrin, gabapentin, lamotrigine, and topiramate. An overview of trials in patients with refractory partial seizures suggests no major differences between these agents in either efficacy or tolerability.[10] Severe visual field defects have recently been reported after prolonged use of vigabatrin, prompting the development of guidelines for monitoring vision.[11] Vagal stimulation remains an experimental approach to seizure control.[12]

Population based studies show that patients with epilepsy have an increased risk of death compared with age and sex matched controls.[13] Some of these deaths are related to epilepsy itself, for example, as a consequence of accidents, but others are unexplained. The category of "sudden unexpected death in epilepsy" (SUDEP) has recently been introduced to encompass all such deaths, which are more common in individuals with refractory epilepsy (about 1 per 200 patients per year).[13] Many of these deaths may be related to unwitnessed seizures, possibly associated with ventricular fibrillation, asystole, respiratory arrest, or neurologically mediated pulmonary oedema. A proportion of cases of sudden unexpected death in epilepsy may therefore be preventable with improved seizure control.

Epilepsy

- Evaluation of patients with refractory partial epilepsy with magnetic resonance imaging and telemetry may yield diagnostic information in up to 75%
- Second line, "add on," agents for refractory partial seizures show no significant differences in efficacy or tolerability
- Guidelines for monitoring of visual fields in patients receiving long term vigabatrin have been issued
- Sudden unexplained death in epilepsy (SUDEP) may be preventable with better seizure control

Multiple sclerosis

- Inteferon betas reduce relapse rate in relapsing-remitting multiple sclerosis by about one third in patients experiencing two disabling relapses every 2 years, and may have a small effect in delaying disability progression
- Magnetic resonance imaging can help predict which patients with clinically isolated syndromes will progress to multiple sclerosis
- Liaison between primary and secondary healthcare services is essential for the appropriate management of established disability in multiple sclerosis

Multiple sclerosis

Interferon betas (interferon beta-1b, Betaferon; interferon beta-1a, Avonex, Rebif) have been shown to reduce relapse rate in relapsing-remitting (non-progressive) multiple sclerosis by about one third.[14–16] The Association of British Neurologists recommends (guidelines, June 1999) interferon beta be prescribed for ambulant patients with at least two definite relapses in the previous 2 years followed by recovery (may or may not be complete). Whether reduction in relapse rate reduces or prevents later disability is not known; some evidence has been presented in favour.[15 16] The uncertainty reflects the difficulties of treatment trials for multiple sclerosis owing to the variable clinical course of the disease, the validation of disability measurements, and discrepancies between secondary outcome measures such as evidence of changes on magnetic resonance imaging, and clinical behaviour.[17] Interferon beta-1b has been reported to delay progression (for 9-12 months in a study period of 2-3 years) in secondarily progressive multiple sclerosis of moderate severity (minimum walking distance of 20 metres with assistance)[18] and has been licensed for this indication. The Association of British Neurologists has produced guidelines to aid therapeutic decision making in secondary progressive multiple sclerosis, but these may be altered in the light of a recent large study (SPECTRIMS; to date presented only in abstract), which reported no significant effect of interferon beta-1a in delaying disability in secondary progressive multiple sclerosis. Sorting out this complex area, with profound financial implications, will be a high priority for NICE.

Trials are also in progress to ascertain whether interferon betas are useful in primary progressive multiple sclerosis, or in delaying or preventing the onset of disseminated disease after clinically isolated syndromes such as optic neuritis and transverse myelitis. Defining which of these patients will progress to widespread disease may be facilitated by magnetic resonance imaging; clinically silent lesions are predictive of the long term risk of subsequent development of multiple sclerosis.[19]

Other possible treatments for multiple sclerosis include copolymer-1[20] and pulsed intravenous immunoglobulin,[21] which, like interferon betas, reduce the relapse rate. However, the place for these immunomodulatory agents remains to be defined. Intravenous methylprednisolone may hasten recovery from acute relapses but has no effect in the long term. A recent trial suggested intravenous methylprednisolone is no better than equivalent oral doses of methylprednisolone for acute relapses.[22] If so, then switching from intravenous to oral steroids for acute relapses may make considerable savings.

In advanced multiple sclerosis, management of established disability may be the primary role of the neurologist. Bladder dysfunction usually consists of combined detrusor hyperreflexia and incomplete emptying volumes of less than 100 ml of urine remaining in the bladder after micturition are managed with oxybutinin or detrusitol; volumes greater than 100 ml require clean, intermittent, self catheterisation.[23] Sexual dysfunction (erectile failure) may be helped with the phosphodiesterase inhibitor sildenafil citrate (Viagra), or more established agents such as yohimbine or other α adrenoreceptor blockers. Management of limb spasticity requires a multidisciplinary approach ensuring correct posture, prevention of skin ulceration from pressure, management of bladder and bowel dysfunction, as well as pharmacological measures. Tizanidine, an α_2 adrenoreceptor agonist, has recently been licensed in the United Kingdom as an antispastic agent.[24]

Parkinson's disease

The management of idiopathic Parkinson's disease is still centred around the use of levodopa preparations since they produce the most effective relief of

Parkinson's disease

- Accurate diagnosis of parkinsonian syndromes is important for appropriate management
- Use of levodopa sparing agents may be desirable in the treatment of early onset Parkinson's disease
- The late stages of Parkinson's disease necessitate the use of polypharmacy to manage unpredictable response fluctuations to levodopa, which are an almost invariable feature after several years' treatment
- Functional neurosurgery may improve some of the features of Parkinson's disease and treatment complications in selected patients

symptoms in most patients. Distinguishing idiopathic Parkinson's disease from other parkinsonian syndromes (for example, multiple system atrophy, Steele-Richardson-Olszewski syndrome) is crucial as the latter differ in prognosis and management. With long term treatment with levodopa, response fluctuations develop in around 10% of patients with idiopathic Parkinson's disease per year. Delaying the use of levodopa in early disease, particularly in young patients (under 50 years), is therefore desirable.

Levodopa sparing agents that may be used as monotherapy in early Parkinson's disease include amantadine, anticholinergics (particularly if tremor is predominant), selegiline, and dopamine agonists. Bromocriptine alone improves about 50% of patients during the first year of treatment but there is a gradual loss of benefit thereafter, with only 10% responding at 5 years; other dopamine agonists have similar effects. Selegiline delays the need for levodopa by a mean of 8 months. One study found increased mortality in patients taking levodopa in combination with selegilne.[25]

Once levodopa is started it may be several years before response fluctuations develop. These are usually predictable initially, such as end of dose or "wearing off" effects. Strategies to ameliorate these problems include dose fractionation, long acting levodopa preparations (particularly helpful for nocturnal immobility), and addition of dopamine agonists.[26] Three new dopamine agonists are now available: ropinirole, cabergoline, and pramipexole.[27–29] It is not yet known whether these agents confer significant therapeutic advantages over bromocriptine and pergolide as add on therapy. Add on use of catechol-O-methyltransferase inhibitors (tolcapone, entacapone) may increase total "on" time by about 20%,[30] but tolcapone has been withdrawn in the United Kingdom because of hepatotoxicity.

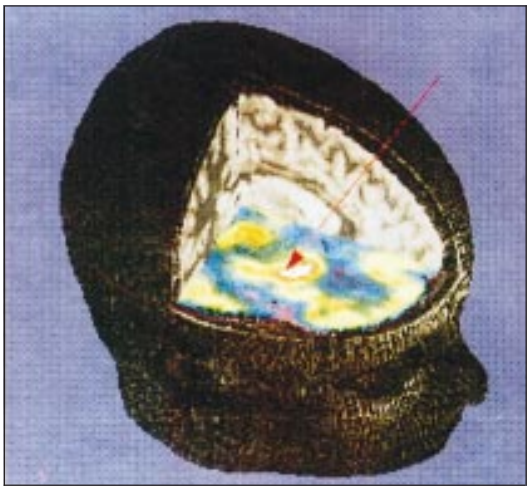
Sudden unpredictable changes between periods of mobility ("on") with severe levodopa induced involuntary movements (dyskinesias) and disabling parkinsonism ("off"), the "on-off phenomenon", present a major management problem. Various strategies may be tried to minimise the severity of dyskinesias[31]—for example, adjusting the timing of levodopa intake, optimising levodopa absorption, and addition of other antiparkinsonian agents such as dopamine agonists and amantadine thus permitting levodopa dose reduction. Increased use of the dopamine agonist apomorphine, given by subcutaneous injection or infusion, may rescue patients from severe sudden off periods, and improve overall mobility.

Renewed interest has been shown in surgery for the symptoms of Parkinson's disease, levodopa induced dyskinesias, and disorders of movement such as tremor and dystonia through the use of stereotactically placed lesions or chronic electrical stimulation with indwelling electrodes.[32] Thalamotomy or thalamic stimulation helps tremor and often rigidity but not akinesia. Unilateral pallidotomy (figure) significantly improves contralateral dyskinesias; bilateral pallidotomy may, in addition, improve parkinsonian symptoms but carries increased risks.[33] Bilateral subthalamic nucleus stimulation[34] or subthalamotomy has produced dramatic improvements in parkinsonism, sufficient to allow large reductions in the levodopa dose and thus improvement in levodopa induced dyskinesias. Appropriate patient selection is a key factor in its successful use, and it will be available only in a few specialist centres.

Dementia

The definition of a new variant of Creutzfeldt-Jakob disease[35] has attracted huge media attention, because it seems to be caused by the same strain of prion protein that causes bovine spongiform encephalopathy, and hence may have been transmitted to humans through contaminated food. However, this uniformly fatal condition remains extremely rare, with only 41 cases reported to date in the United Kingdom.

For Alzheimer's disease, the commonest cause of dementia, two cholinesterase inhibitors, donepezil (Aricept)[36] and rivastigmine (Exelon),[37] are now licensed for the symptomatic treatment of mild to moderate cognitive impairment (minimental state examination score of 10-26). Trials suggest that in some patients these agents improve cognition, global function, and behavioural function, but there are as yet no data as to whether they delay deterioration or improve outcome. Currently it is recommended that these drugs are only commenced on the advice of a specialist. Despite advances in understanding the pathological basis of Alzheimer's disease, centred around amyloid β peptides, this has not resulted in new treatments although many are in development.[38]



Superimposed 3-dimensional positron emission tomogram and magnetic resonance image of patient with idiopathic Parkinson's disease showing hypermetabolism of pallidum(white area), target for unilateral stereotaxic pallidotomy

Dementia, rare disorders

- Cholinesterase inhibitors are of symptomatic benefit in about 20% of patients with mild to moderate Alzheimer's disease
- Some peripheral neuropathies are treatable may show profound benefit with intravenous immunoglobulin treatment
- Intravenous immunglobulin may be helpful in the acute treatment of Guillain-Barré syndrome and myasthenia gravis

Migraine

Since the launch of sumatriptan, several triptans have become available for the treatment of acute migraine.[39] They differ in pharmacodynamic properties such as time of onset and duration of action. Direct comparisons have not been performed and it is not known whether the differences claimed will have significant impact on clinical practice. Preventive treatments include pizotifen and amitriptyline, but the strongest evidence of efficacy is available for β blockers and sodium valproate.[39]

Rare disorders

The glutamate antagonist riluzole (Rilutek) remains the only licensed treatment for motor neurone disease. Risk of death or tracheostomy was lower with 100 mg riluzole than placebo in limb or bulbar onset disease,[40] but it is debatable whether this translates into an improved quality of remaining life.

Intravenous immunoglobulin has been used in many neurological disorders,[21 41] but its place remains to be defined; many of these applications are empirical and the long term effects of intravenous immunoglobulin are unknown. Trials in acute idiopathic neuropathy (Guillain-Barré syndrome) suggest that intravenous immunglobulin is equivalent to plasma exchange in reducing disability at 4 weeks, but that the combination of intravenous immunoglobulin and plasma exchange offers no significant additional advantage.[42] Likewise, in myasthenia gravis, intravenous immunglobulin seems as efficacious as plasma exchange,[43] and it may also be useful in chronic inflammatory demyelinating polyneuropathy in relapse.[44]

Conclusion

In the past 5 years, new treatments have become available for neurological disorders previously considered untreatable (multiple sclerosis, Alzheimer's disease, motor neurone disease). Although the high cost of these treatments has sometimes led to antagonism between purchasers and doctors wanting to prescribe, these small, initial, therapeutic inroads have focused on the broader needs of patients with neurological disorders, engendering specialist clinics, specialist nurses, and fostering liaison with community services and patient interest groups.

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Lesson of the week

Mercury poisoning after spillage at home from a sphygmomanometer on loan from hospital

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Be aware of the potential for toxicity of mercury spilled from broken medical equipment

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When patients are managed at home, they or their carers have to operate medical equipment. This case report highlights important educational and environmental health aspects of issuing hospital equipment for home use, a practice that is likely to become more common in the future. We describe a 9 year old boy who had neurological and renal complications after mercury spillage from a sphygmomanometer three months after it had been provided by the hospital for monitoring blood pressure at home. The family were unaware of the potential risks of mercury exposure before the patient became acutely ill.

Case report

A 9 year old boy presented to his local hospital with a three week history of abdominal pain, constipation, lethargy, limb pain, and unsteadiness. Physical examination showed mild facial weakness, areflexia, ataxia, and impaired sensation and led to a provisional diagnosis of Guillaine-Barré syndrome. The boy's constant restlessness was considered strange, but his mother described him as hyperactive and regarded this behaviour as normal. It was noted, however, that his handwriting and schoolwork had deteriorated over the preceding month.

Features of encephalopathy accompanied by peripheral neuropathy led to a suspicion of heavy metal poisoning. No history of likely exposure to lead could be found; there was no lead piping or paint at home. Further inquiry revealed that the patient's sibling had undergone renal transplantation as a result of nephrotic syndrome, and the family had been provided with a mercury sphygmomanometer for home blood pressure monitoring. Three months before presentation, our patient had dismantled the sphygmomanometer in his bedroom—spilling mercury on his bed and carpet—and had played with it for a day or two before informing his mother. Attempts had been made to dispose of the mercury by vacuuming, and then by flushing it down the toilet.

The suspected diagnosis of mercury poisoning was confirmed by the finding of a serum mercury concentration of 1000 nmol/l (normal reference value <30 nmol/l). The boy was referred to a tertiary paediatric centre for further management. By now he was unable to pick up objects or to feel them in his hand. Physical examination showed that he was ataxic and areflexic and was exhibiting intermittent aggression and a fluctuating level of consciousness. He was started on sodium-(2,3)-dimercaptopropane-(1)-sulphonate (DMPS), a chelating agent which binds mercury and allows it to be excreted via the kidneys. This is given by intravenous infusion in a reducing dose over four days and is followed by oral treatment until the patient's clinical condition and results of laboratory investigations have improved. Our patient was treated for a total of 18 days; his serum mercury concentrations and urinary mercury excretion during treatment are shown in the table.

Other family members were investigated and were also found to have raised serum mercury concentrations, but in none were these high enough to necessitate treatment. Mercury was not detected in the patient's cerebrospinal fluid, but the protein concentration was very high at 1.9 g/l.

The boy developed hypertension. This was refractory to initial treatment and required an

Serum mercury concentrations and urinary mercury excretion in patient with mercury poisoning

Day	Serum mercury (nmol/l)	Urinary mercury excretion (nmol/mmol creatine)
1	500	173
4	285	650
9	256	241
21	160	223
29	83	24