A new antiepileptic drug

S D Shorvon, K van Rijckevorsel

Levetiracetam, a pyrrolidone recently licensed as an antiepileptic drug

Recently a new antiepileptic drug, levetiracetam (LEV), was approved for the add on treatment of partial epilepsy, both in the United States and in Europe. This is of potential importance, because this drug is from a class not previously used in epilepsy, although pira-
cetam, a compound with a structure similar to that of levetiracetam, is useful in myoclonus. Both drugs are pyrro-
lidone derivatives, a class of drugs of interest for both psychotropic and noo-
tropic applications and potentially as neuroprotectants. Levetiracetam (avail-
able under the registered trademark of UCB S.A., Keppra®) is the S-enantiomer of α-ethyl-2-oxo-1-pyrrolidine acetam-
ide (fig 1). Homologues sharing the S configuration include a range of other compounds, some of which also have antiepileptic action.1 The range and extent of the compounds’ activity in experimental models of epilepsy and other conditions varies considerably with minor changes to chemical struc-
ture, but the full extent of the range of properties of these drugs in humans has not been explored. This article reviews the experimental and clinical data relating to the antiepileptic action of levetira-
cetam.

EXPERIMENTAL STUDIES

Levetiracetam shows an unusual profile of antiepileptic activity in experimental animal models of partial and generalised epilepsy.2 Unlike other antiepileptic drugs, levetiracetam has no effect on tonic seizures induced by maximal electroschock or clonic seizures induced by pentyletreneterazol (PTZ) stimulation in the classic rodent models.2,4 It however has very marked protection against seizures in audiogenic mice, mice kind-
dled with corneal electroshock or PTZ, and amygdaloid kindled rats. It protects against spontaneous spike and wave dis-
charges in the GAERS model and in pilocarpine or kainic acid induced focal seizures in rats.2,15 The dose dependent ability of levetiracetam to inhibit the development of kindling suggests a potential antiepileptogenic effect as well.2 Levetiracetam is the most effective of any of the pyrrolidone drugs in these epilepsy models. Its R-enantiomer has no antiepileptic activity.

The dose at which toxic effects on the rotarod test are produced is much higher than the effective antiseizure dose in both the GAERS model and the cornally kindled mice. The safety margin of levetiracetam in these models is much greater than for other drugs. In acute and chronic toxicity studies in animals, levetiracetam shows generally low toxic-
ity. Oral doses up to 5000 mg/kg acutely (maximum tested dose) are not lethal in mice and rats. Levetiracetam has not dis-
played any teratogenic, mutagenic, or carcinogenic properties.

The mechanism of action of levetira-
cetam (or indeed the other -acetam drugs) is not clearly understood, and it does not seem to involve any conven-
tional modulation of the three main mechanisms relevant for the action of classic antiepileptic drugs.2 The drug does not bind to receptors associated with excitatory or inhibitory neurotrans-
mitters (for example, γ-aminobutyric acid (GABA), glutamate, glycine, adeno-
sine), has no effect on sodium or T-type calcium channel function, and does not affect GABA transaminase or glutamic acid decarboxylase (GAD) activity or second messenger systems (cyclic adenosine monophosphate, protein kinase C).2 By contrast, it has recently been reported that levetiracetam reduces high voltage activated Ca2+ currents,3 reverses inhibition of GABA and glycine gated currents induced by negative allosteric modulators,4 and effects voltage gated potassium channel conductance,5 suggest-
ing that its mechanism of action differs from other antiepileptic drugs. Leve-
tiracetam also has a specific stereoselective binding site in the CNS,1 and cannot be displaced from this site by other classic anticonvulsant drugs (car-
bamazepine, phenytoin, valproate, phe-
nobarbital), although ethosuximide does show binding affinity. The extent of the antiepileptic efficacy in the audiogenic seizure model in mice was found to be correlated with the affinity for the bind-
ing site of a series of S-homologues of levetiracetam. Levetiracetam has no binding to membranes outside of the CNS.

CLINICAL PHARMACOKINETICS

The pharmacokinetic properties of lev-
tiracetam have been studied in healthy adult volunteers, patients with epilepsy, and special populations, including paediatric and elderly patients and patients with renal or hepatic insufficiency. Levi-
tiracetam is rapidly and almost com-
pletely absorbed after oral administra-
tion of doses ranging from 250 mg to 5000 mg, with peak plasma concentra-
tions achieved in about 1 hour and steady state concentrations achieved in 48 hours. Absolute oral bioavailability is nearly 100%. When taken with food, the extent of absorption is not affected, although the rate of absorption may be slowed. Levetiracetam is not significantly bound to plasma proteins (<10%), and its volume of distribution is about 0.6 l/kg, similar to the volume of distribution of intracellular and extracellular water. In addition, levetiracetam exhibits lin-
ear, dose proportional, kinetics, with low intra- and intersubject variability, and a half life of 6 to 8 hours.11 Levetira-
cetam does not undergo hepatic metabo-
ism, nor does it induce or inhibit cytochome P-450 enzymes.12 Levetira-
cetam is to a limited extent metabolised (by hydrolysis) by a serine esterase enzyme in blood and other tissues and excreted through the kidneys un-
changed or as inactive metabolites.11

Renal clearance of levetiracetam is directly proportional to creatinine clearance. Clearance of levetiracetam is sig-
ificantly reduced in patients with se-
vere hepatic impairment and concomitant renal impairment (hepato-
renal syndrome). No differences are seen in patients with mild to moderate hepatic impairment. In studies with eld-
ery patients, the elimination half life of levetiracetam is prolonged to 10 to 11

Abbreviations: LEV, levetiracetam; PTZ, penetylsetreneterazol; GABA, γ-aminobutyric acid; 
GAD, glutamic acid decarboxylase; SUDEP, sudden and unexplained death in epilepsy.
hours and is likely attributable to the age related decline in renal function. After single oral dose administration of 20 mg/kg levetiracetam in children between 6 and 12 years old, total body clearance was about 30% to 40% higher than in adults, and the half life was roughly 6 hours.\(^7\)

Because it does not undergo hepatic metabolism and is not significantly protein bound, levetiracetam has a very low potential for pharmacokinetic interactions. Findings from studies in vitro,\(^7\) clinical trials in patients,\(^7,14,15\) and specific studies with digoxin,\(^7\) phenytoin,\(^7\) warfarin, valproic acid, and oral contraceptives\(^7\) support this assertion.

**Clinical antiepileptic effect**

**Add on therapy in partial epilepsy**

The efficacy of levetiracetam as add on therapy has been assessed in three prospective, double blind, placebo controlled trials in patients with refractory epilepsy. The studies were powered for parallel group comparison.\(^7,14,15\) Doses of levetiracetam evaluated in these trials included 1000, 2000, and 3000 mg/day given in twice daily regimens. A total of 904 patients with refractory partial seizures, with or without secondary generalisation, who were not controlled despite being on a stable dose regimen of one to a maximum of two marketed antiepileptic drugs, participated in these trials. Patients were evaluated after 12 or 14 weeks, and seizure frequency during the evaluation period was compared with a baseline period of 8 or 12 weeks. Demographic characteristics across studies were comparable for sex, age, race, and other baseline assessments. Responder rate and seizure count analyses were based on the patients who completed titration and entered the stable dose evaluation period (n=860). In addition, the responder rates were also analysed for the total randomised population during the treatment period (the intent to treat population; n=904). The data from both analyses are presented in table 1.

At all doses evaluated in these studies, levetiracetam was significantly more effective than placebo. The median percentage reduction from baseline was 32.5% for patients receiving levetiracetam compared with 7% for patients receiving placebo (p<0.001). The responder rate (the proportion of patients experiencing a 50% or greater reduction in seizure frequency compared with baseline) during the evaluation period was 27.7% (34/195), 31.6% (30/95), and 41.3% (111/269) for patients receiving 1000, 2000, and 3000 mg/day respectively, compared with 12.6% (38/301) of patients who received placebo (fig 2; p=0.001, all doses versus placebo). The percentage of patients experiencing a 75% or greater reduction in seizures was 11.8% (23/195), 16.8% (16/95), and 22.3% (60/269) of patients receiving 1000 mg, 2000 mg, and 3000 mg of levetiracetam respectively, compared with 3.3% (10/301) of placebo treated patients (p<0.001, all doses versus placebo). In addition, 5.7% (32/559) of patients treated with levetiracetam became seizure free, compared with 0.6% (2/301) in the placebo group (p<0.001). A statistically significant reduction in seizure frequency for all different subtypes of partial seizures (simple partial, complex partial, and secondarily generalised seizures) was found with levetiracetam treatment (fig 3).

**Monotherapy**

One of the efficacy trials was extended into a levetiracetam responder selected monotherapy phase.\(^7\) Forty nine of the 69 patients (71%) who were selected for the monotherapy phase were successfully down titrated, and 36 of 69 (52%) completed the monotherapy phase. The median percentage reduction compared with baseline was 73.8% (p=0.037), the 50% responder rate was 59.2% (29/49), and nine patients (18.4%) remained seizure free during monotherapy.

**Long term efficacy studies**

Long term analysis of results from the 1422 patients with epilepsy from the first day of exposure to levetiracetam or placebo in phase I, II, or III studies show estimated retention rates (Kaplan-Meier analysis) of about 60% after 1 year (number of patients at risk=826), 44% after 2 years (number of patients at risk=489), and 32% after 4 years (number of patients at risk=175), for up to 8 years (number of patients at risk=1).\(^7\) Twenty six per cent of patients withdrew due to reasons inherent to clinical trials, 16% due to adverse events and 18% due to lack of efficacy. Of the patients with a baseline evaluation (n=1321), 548 (41.5%) had≥50% and 355/1321 (26.9%) had≥75% reduction in seizure frequency compared with baseline during the last 6 months of therapy. Of the 1422 patients, 183 (12.9%) were seizure free for at least 6 months, and 109 (7.7%) were seizure free for at least 1 year. The efficacy of levetiracetam was maintained over time. Sixty six (5%) of the patients were successfully converted to monotherapy.

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### Table 1

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<thead>
<tr>
<th>Evaluation period on stable dose</th>
<th>Intent to treat population, total treatment period titration</th>
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<tr>
<td></td>
<td>Placebo (n=301)</td>
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<td>3000 mg/day (n=269)</td>
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*Seizure-free during the analysis period (evaluation period or total treatment period)
Other seizure types
The range of effectiveness of levetiracetam in human epilepsy has not yet been fully explored, but there are some indications that the drug will be useful in a wider range of seizure types and syndromes.19 Preliminary open studies of levetiracetam in patients with generalised tonic clonic, absence, and myoclonic seizures have been very encouraging, as they have in the multiple seizure types of the Lennox-Gastaut syndrome. The drug also has a dramatic effect on photosensitivity,3 and there is piloted data suggesting potential effectiveness in refractory juvenile myoclonic epilepsy.4

SIDE EFFECTS
One of the striking aspects of the clinical trial programme of levetiracetam was the low rate and mild nature of the reported side effects. The incidence of the most common adverse reactions (the FDA term) and the most common undesirable effects (the European Medicinal Evaluation Agency term) derived from three efficacy trials and one safety placebo controlled, double blind trial are shown in table 2.19 The side effects were primarily related to the CNS. Somnolence, asthenia, and dizziness were most commonly reported. In the pooled analysis, there was no evidence of a dose dependent relation within the recommended dose range of 1000 to 3000 mg/day. Patients receiving levetiracetam also reported a slightly higher incidence of symptoms of upper respiratory infection, which was not associated with leukopenia or dose reduction. The proportion of patients who discontinued treatment prematurely or required a dose reduction because of an adverse event was not significantly different between levetiracetam and placebo groups (15.0% v 11.6%). Adverse events that led to withdrawal in patients treated with levetiracetam included somnolence (4.4%), convulsion (3.0%), dizziness (1.4%), asthenia (1.3%), and headache (1.0%). A greater percentage of patients from the placebo groups discontinued because of convulsion (3.4%) and rash (1.1%). A worsening of seizure, defined as an increase in seizure frequency of ≥25%, was significantly lower in patients treated with levetiracetam compared with placebo (levetiracetam, 14.2%; placebo, 25.6%; p<0.001). During long term treatment, only 225 (16%) of the 1422 patients withdrew because of an adverse event.19

Throughout the entire clinical development programme, there were 22 deaths of patients with epilepsy receiving levetiracetam (crude mortality rate 0.91 per 100 patient-years). Eight were sudden and unexplained death in epilepsy (SUDEP) in the levetiracetam group (3.54 per 100 person years) versus one in the placebo group (6.58 per 100 person years). The difference was not significant. Safety data regarding laboratory and physical examinations have been obtained from 3347 patients exposed to levetiracetam (adults with epilepsy, n=1393; children, n=29; patients with other diseases, n=1558; healthy volunteers, n=367), for a total of 2421 patient-years. Overall, physical and neurological examinations were unremarkable in patients treated with the drug. Minor but statistically significant decreases were found in mean values of the red blood cell count, haemoglobin, and packed cell volume, but there were no significant changes in other laboratory parameters.

DOSES RECOMMENDATIONS
The recommended dosing regimen for levetiracetam as add on therapy is twice daily doses of 500 mg to 1500 mg, for a total daily dosage of between 1000 mg and 3000 mg. Higher doses have been studied, but with little evidence of added effectiveness. The initial starting dose of 1000 mg/day has been shown to be clinically effective, but if sufficient seizure control is not obtained, doses can be increased up to 3000 mg/day. In patients with renal impairment, doses should be adjusted downwards in accordance with creatinine clearance.19,20 At present, sufficient data are not available to recommend treatment with levetiracetam during pregnancy. In patients withdrawn from levetiracetam, a gradual tapering of 1000 mg every 1 to 2 weeks has been successful and has not resulted in withdrawal seizures.

The introduction of a new antiepileptic from a novel class of drug is an interesting development. The remarkable stereospecificity of levetiracetam and the diversity of properties of related compounds are intriguing.1 The fact that the different pyrrolidone derivatives have such different properties encourages our view that the full range of actions of levetiracetam has not been fully explored. Its usefulness in a wide range of seizure types has been suggested in open label studies and would indicate further clinical investigation, and studies in non-epilepsy indications such as myoclonus, migraine, neuropathic pain, bipolar disease, and other areas could be worthwhile. As an antiepileptic drug, it has a preclinical profile which is unlike any other marketed antiepileptic drug, favourable pharmacokinetics, good efficacy, and an excellent safety profile (at least at this stage of experience), and also a broad spectrum potential. For all these reasons, it is already likely to become an important addition to the range of medications which are currently available for epilepsy.
Improved antisaccade performance in schizophrenia with risperidone

S B Hutton

Atypical treatment improves cognitive function

S everal recent studies have suggested that atypical antipsychotic medications such as risperidone can ameliorate certain cognitive deficits associated with schizophrenia.1 Such findings have important implications, as cognitive impairment is a significant predictor of both social and occupational functioning in schizophrenia. In this issue, Burke and Revely (pp 449–54)2 show that patients treated with the atypical antipsychotic risperidone make fewer antisaccade errors than when they are treated with conventional antipsychotic drugs.

The antisaccade task has a number of advantages over more traditional neuropsychological indices of cognitive function in schizophrenia: it is quick to administer, the instructions are simple to comprehend, and performance can be measured objectively and accurately. Furthermore, antisaccade errors (reflexive saccades towards a sudden onset target, instead of away from it) are thought to reflect dysfunctional inhibitory control processes. Such processes are generally associated with the dorsolateral prefrontal cortex and are particularly impaired in schizophrenia. The author’s findings support suggestions that oculomotor paradigms may prove to be a particularly sensitive tool for evaluating the neurocognitive effects of antipsychotic medications.1,

Recently, increased antisaccade errors have been reported in the first degree relatives of patients with schizophrenia, leading to the suggestion that saccadic disinhibition may be a useful marker of genetic vulnerability to the disorder.3 The findings of Burke and Revely suggest that saccadic disinhibition may reflect “state” as well as “trait” factors. This has important implications for the utility of antisaccade error rate as a biological marker for schizophrenia and merits further investigation.

By using a counterbalanced crossover design, in which one group of patients switched from typical antipsychotics to risperidone and another group switched in the opposite direction, Burke and Revely were able to show that the antipsychotic agent levetiracetam does not alter digoxin pharmacokinetics and pharmacodynamics in healthy volunteers. Epilepsy Res 2001;46:93–9.

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Author’s affiliations

S B Hutton, Department of Experimental Psychology, University of Sussex, Falmer, Brighton BN1 9QG, UK

Correspondence to: Dr S B Hutton; samb@biols.susx.ac.uk

www.jnnp.com
Cervical dystonia

Respective potencies of Botox and Dysport: a double blind, randomised, crossover study in cervical dystonia

W Poewe

Clinically appropriate conversion factor may be less than three

The issue of apparently different potencies of the two available formulations of botulinum toxin type A—Dysport and Botox—has continued to perplex clinicians for more than a decade. Empirically chosen doses expressed in mouse units in different series and different indications reported in the literature seemed to differ by factors of three to six. To date only two randomised controlled studies have tried to answer the question of what the correct conversion factor yielding bioequivalence should be. One was conducted in previously untreated patients with blepharospasm or hemifacial spasm and found a bioequivalence ratio of Botox to Dysport of 1:4 with duration of effect as the primary outcome variable. The second comparative trial randomly assigned patients with cervical dystonia previously treated with Botox to receive either their clinically defined individual dose of Botox or three times that dose as Dysport units and found similar effect size, duration of effect, and rates of adverse events. In the paper by Ranoux et al (this issue pp 459–462) of this issue, results of another double blind randomised study comparing efficacy and safety of the type A preparations seem to suggest that the clinically appropriate conversion factor may be less than three.

Fifty four patients with cervical dystonia and a satisfactory response to two consecutive injections of Botox at the same dose into identical muscles received three successive treatments of either their usually effective dose of Botox or three or four times that dose of Dysport. Treatments were given in randomised order using identical volumes of injection and muscle patterns. The effect size as assessed by changes in Tsui scores and Toronto Western spasmatic torticollis rating scale (TWSTRS) pain scores was significantly greater with both Botox treatments and duration of effect was also longer. Three-fold or four-fold doses of Dysport produced similar effect sizes but duration tended to be increased with the fourfold dose. Side effects were significantly more frequent with both Botox doses than with Botox but again not significantly different between the two Botox doses (17.6% of patients treated with Botox, and 33% and 36% of patients treated with Dysport 1:3 and 1:4, respectively).

In summary, the authors suggest that even lower conversion ratios be used than 3:1 for Dysport to Botox. Should it then be 1:2.5 or even 1:2? If so, should we be using lower doses of Dysport or higher doses of Botox to achieve this? With only three randomised trials available differing in design, target population, and results, it is impossible to give a conclusive answer to this question. For the time being clinicians may be best advised to use the following landmarks for their dosing decisions when treating patients with dystonia. Firstly, the equivalence ratio of Dysport to Botox should not be greater than 3:1 according to the majority of available comparative clinical studies. Secondly, for cervical dystonia, the indication studied by Ranoux et al, a double blind dose ranging study has shown that Dysport doses needed for a satisfactory response are greater than 250 units and that doses greater than 500 units are associated with clear increases in adverse event frequency and severity.

REFERENCES


Rehabilitation

Intensity of rehabilitation: some answers and more questions?

P Langhorne

No benefits to intensive rehabilitation in the long term

For many years rehabilitation researchers have pondered whether the observed recovery of patients from stroke occurs at the optimum natural recovery rate or may be further enhanced by rehabilitation interventions, in particular by increasing the intensity of rehabilitation input. A carefully conducted randomised trial by Kwakkel et al indicated that increasing the intensity of physical training after middle cerebral artery stroke brought about improvements in the recovery during the first 6 months. When the additional training was focused on the upper limb improvements in dexterity were observed; when the lower limb was targeted walking ability and Barthel activities of daily living (ADL) scores improved. In their follow up paper (Kwakkel et al, this issue pp 473–479) they address the question of whether these benefits continue in the longer term. This follow up paper indicates that there were no significant differences between the treatment groups at one year after randomisation, an observation that appears to confirm previous similar trials.
Why did the early benefits of intensive training disappear at a later stage? The first possibility is that there were differences in treatment after the intervention period ended but this appears unlikely. None of the patient groups received much rehabilitation input after six months. The second possibility is that the treatment group suffered a decline in function after their intensive treatment was removed. This also appears unlikely, as it is not supported by the longitudinal data. A third possibility is that the control group continued to improve until their function matched that of the intervention groups. On balance, this seems the most compelling explanation.

An additional observation was that patients who were noted to have made an incomplete functional recovery at 6 months showed the largest subsequent changes (including both improvement and deterioration) in impairments and disability. This observation is probably not an artefact of the measures used and does indicate that there is potentially a subgroup of patients in whom increased therapy could be targeted at a later stage.

The main message appears to be that increasing the intensity of upper and lower limb training for selected patients after a stroke can speed up recovery but the longer term effects are uncertain. It remains to be established whether we can identify patients who are exceptions to this general rule and would benefit from later intervention to optimise their recovery.

J Neurol Neurosurg Psychiatry 2002;72:430–431

REFERENCE

D Friedman

Headache and hypertension

Headache and hypertension: refuting the myth
D Friedman

Why does the hypertension headache myth persist?

Patients often tell their physicians, “I know when my blood pressure is high because I get a headache”. The relation of headache to hypertension has been debated in the medical literature for almost a century. Janeway observed it in a large clinical study of hypertensive patients (systolic blood pressure > 160 mm Hg) in 1913. He described the “typical” hypertensive headache as non-migrainous, present upon awakening and resolving during the morning. However, his illustrative case histories are somewhat misleading because they all had malignant hypertension and systolic pressures > 230 mm Hg. Additionally, one patient was likely in analgesic rebound.

There are several reasons why the “hypertension headache” misperception persists: hypertension may be an epiphenomenon of acute pain, headache is associated with hypertensive encephalopathy as a manifestation of increased intracranial pressure, and headache is a side effect of some antihypertensive treatments. Conversely, many of the antihypertensive medications are also effective for headache prevention, so the risk of concurrent headache may be low unless the influence of treatment is considered.

The Physicians’ Health Study prospectively examined 22,701 American male physicians aged 40–84 years, who were randomly assigned to receive daily aspirin, β carotene, both agents, or placebo. Analysis of various risk factors for cerebrovascular disease found no difference in the percentage of patients with a history of hypertension between the migraine and the non-migraine groups. Additionally, no difference in risk factors was found between physicians with non-migrainous headaches and those with no headaches.

The paper by Hagen et al (this issue pp 463–466) lends definitive clarity to the issue. In their prospective study spanning 13 years of 22,685 adults in Nord-Trøndelag County, Norway, patients’ blood pressure was measured interictally and they provided information regarding headaches and the use of pain relieving medications. Patients were subdivided into those with migraine and those with non-migrainous headache based on modified International Headache Society criteria for migraine. Contrary to popular belief, high systolic blood pressure at baseline was not associated with low headache prevalence 11 years later. This was not related to antihypertensive medication treatment. A similar effect was observed in women with migraine.

Their study is relevant because it is a cross sectional study of a large unselected population. Hypertension is more common in men but women have a higher incidence of headaches. Both women (10,698) and men (11,987) participated in HUNT-1 and HUNT-2 (Nord-Trøndelag Health Survey), supporting the conclusions in both sexes. Generalisation of the results was addressed by the authors in other reports.

Race and geographic region contribute to variations in the prevalence of headache and hypertension. Participants in the HUNT studies were a homogeneous white population. Thus, the applicability of the results to other populations, such as African Americans, who have a higher prevalence of hypertension, is uncertain.

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REFERENCES

D Friedman, Department of Neurology, University Hospital, 750 E Adams Street, Syracuse, New York 13210, USA

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There are several reasons why the “hypertension headache” misperception persists: hypertension may be an epiphenomenon of acute pain, headache is associated with hypertensive encephalopathy as a manifestation of increased intracranial pressure, and headache is a side effect of some antihypertensive treatments. Conversely, many of the antihypertensive medications are also effective for headache prevention, so the risk of concurrent headache may be low unless the influence of treatment is considered.

The Physicians’ Health Study prospectively examined 22,701 American male physicians aged 40–84 years, who were randomly assigned to receive daily aspirin, β carotene, both agents, or placebo. Analysis of various risk factors for cerebrovascular disease found no difference in the percentage of patients with a history of hypertension between the migraine and the non-migraine groups. Additionally, no difference in risk factors was found between physicians with non-migrainous headaches and those with no headaches.

The paper by Hagen et al (this issue pp 463–466) lends definitive clarity to the issue. In their prospective study spanning 13 years of 22,685 adults in Nord-Trøndelag County, Norway, patients’ blood pressure was measured interictally and they provided information regarding headaches and the use of pain relieving medications. Patients were subdivided into those with migraine and those with non-migrainous headache based on modified International Headache Society criteria for migraine. Contrary to popular belief, high systolic blood pressure at baseline was not associated with low headache prevalence 11 years later. This was not related to antihypertensive medication treatment. A similar effect was observed in women with migraine.

Their study is relevant because it is a cross sectional study of a large unselected population. Hypertension is more common in men but women have a higher incidence of headaches. Both women (10,698) and men (11,987) participated in HUNT-1 and HUNT-2 (Nord-Trøndelag Health Survey), supporting the conclusions in both sexes. Generalisation of the results was addressed by the authors in other reports.

Race and geographic region contribute to variations in the prevalence of headache and hypertension. Participants in the HUNT studies were a homogeneous white population. Thus, the applicability of the results to other populations, such as African Americans, who have a higher prevalence of hypertension, is uncertain.

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D Friedman, Department of Neurology, University Hospital, 750 E Adams Street, Syracuse, New York 13210, USA

Correspondence to: Dr D Friedman; friedmad@upstate.edu
A new antiepileptic drug

S D Shorvon and K van Rijckevorsel

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Radiology of stroke
The optimum time frame for imaging embolic infarcts for stigmata of haemorrhagic transformation should have merited discussion under the heading “special clinical circumstances”; not least because of conflicting evidence about the benefits versus risks of early anticoagulation in the context of unpredictable evolution of embolic infarcts with or without anticoagulant treatment. In a study comprising 30 patients with cardio-genic cerebral embolism, three patients with an initially non-haemorrhagic cerebral infarct, visualised by computed tomography within 12 hours of stroke onset, showed asymptomatic haemorrhagic transformation in the absence of anticoagulant treatment 2–8 days later. One other patient in this subgroup did, however, develop sudden worsening of headache despite having initially presented with a small infarct.1 Among 1457 patients anticoagulated with unfractionated heparin in the presence of embolic cerebral infarct associated with atrial fibrillation, haemorrhagic transformation (within 14 days) was significantly commoner (p < 0.0001) than in their non-heparinised counterparts.1 Ischaemic stroke recurred with a 4.9% frequency in the latter subgroup (comprising 1612 patients) during that time frame, and this complication was significantly less common (p = 0.001) in their anti-coagulated counterparts. Anticoagulation in the presence of haemorrhagic transformation has been advocated as being without risk on the basis of the outcome in 12 patients so treated,2 but the caveat is that, in another study also involving patients with embolic stroke, the subsequent development of haemorrhagic transformation in 5 of 231 patients anticoagulated with heparin was associated with significant clinical deterioration.3 It is this unpredictability in the consequences and tempo of haemorrhagic transformation and in the impact of early anticoagulation on this phenomenon that causes anxiety among clinicians at all levels of experience.

O M P Jolobe
Department of Adult Medicine, Tameside General Hospital, Ashton-under-lyne OL6 9RW, UK

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Author's reply
The strongest risk factor for haemorrhagic transformation of cerebral infarction in patients not treated with any antithrombotic or thrombolytic drug is simply having an extensive large infarct. It so happens that cardio-genic cerebral embolism often results in large cerebral infarcts (because thrombi arising from the heart are often large and block a large vessel). Thus, there is an association between cardio-genic cerebral embolism and haemorrhagic transformation. This association may be exaggerated by administering antithrombotic or anticoagulant or thrombo-lytic therapy to these patients. Unfortunately, it is difficult to draw conclusions on the risks and benefits of anticoagulant treatment from non-randomised studies. The complete data from the international stroke trial (20 000 patients) clearly show that heparin started within the first 48 hours of stroke and continued for the first 14 days may reduce the risk of recurrent ischaemic stroke but at the risk of increasing haemorrhagic stroke and death, and as a result there is no net benefit.4 When to start or continue anticoagulant treatment after stroke in the small proportion of patients with a clear cardiac source of embolism is a decision that needs to be made in light of each patient’s risk factors and continues to be a thorny problem. However, the benefits of aspirin (while less effective) are still worthwhile with less risk of haemorrhagic transformation.

There is no easy answer to this problem.

J M Wardlaw
Department of Clinical Neurosciences, Western General Hospital, Crewe Road, Edinburgh EH4 2XU, UK

Thunderclap headache, reversible cerebral arterial vasoconstriction, and unruptured aneurysms
In his comprehensive review of thunderclap headache,1 Dr Dodick discusses two patients with the triad of thunderclap headache, cerebral arterial vasoconstriction, and unruptured cerebral aneurysms. We recently reported on two very similar patients, in whom the symptoms developed shortly after exposure to commonly used serotonin enhancing drugs.2 The interrelation between thunderclap headache, cerebral arterial vasoconstriction, and unruptured aneurysms is not clear, and in these four patients the aneurysms may well have been incidental findings. However, it is interesting that the association to segmental vasoconstriction, cerebral angiograms in patients with the Call-Fleming and some other vasoconstriction syndromes3 can have areas of vasodilatation beyond the normal diameter of the artery. Moreover, patients with stroke associated with the use of vasoconstrictive drugs such as cocaine and “ecstasy” are known to have an unusually high number of aneurysms.4 It is conceivable that patients who develop cerebral vasoconstriction or thunderclap headaches (without subarachnoid haemorrhage) are more likely to harbour aneurysms due to primary or drug induced abnormalities of vessel tone.

Dr Dodick reviews cases where thunderclap headache was associated with unruptured aneurysms, without cerebral arterial vasoconstriction, and where thunderclap headache was associated with vasoconstriction, without unruptured aneurysms. It should be noted that unruptured aneurysms may be exaggerated by administering anticoagulant treatment, without thunderclap headache. This point is emphasised by an additional, hitherto unpublished case (courtesy Dr C Miller Fisher) of severe cerebral vasoconstriction, stroke, and death associated with two unruptured and asymptomatic intracerebral aneurysms without thunderclap headache. The patient, a 65 year woman, was admitted in January 1998 with probable Guillain-Barré syndrome. The hospital course was notable for episodic hypertension (maximum blood pressure 200/100 mm Hg). On day 4, she developed cortical blindness, abulia, aphasia, and right hemiplegia. Computed tomography showed infarctions in both occipital lobes and a parasagittal meningioma. A selective cerebral arteriogram showed aneurysms in the anterior communicating and left middle cerebral artery, severe attenuation of proximal intracranial arteries, and “sausaging” of distal arteries. After returning from the arteriogram the patient became obtunded, then deteriorated clinically, and died on day 13. A necropsy showed cerebral oedema with bilateral temporal lobe herniations, infarctions in the inferior cerebral and both occipital and frontal lobes, a parasagittal meningioma, and two unruptured aneurysms (a 5 × 5 mm anterior communicating aneurysm and a 10 × 7 mm left middle cerebral artery aneurysm). There was no evidence for arterial inflammation. Lym- phocytic infiltration was present in the sciatric nerves, consistent with infectious polyneuritis. As stated in the review article,2 it is difficult to account for any mechanism whereby the aneurysms may have precipitated the vasoconstriction.

A B Singhal
Stroke Service, VKB-802, Massachusetts General Hospital, Boston, MA 02114, USA; asinghal@partners.org

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Author's reply
I would like to thank Dr Singhal for his inter- est and thoughtful insights concerning the review article on thunderclap headache.1 I will address his comments in order.

www.jnnp.com
Firstly, I had already read with great interest the recent article from Dr Singhal et al regarding three patients with thunderclap headache, reversible vasospasm, and ischaemic stroke possibly secondary to exposure to serotoninergic medications such as cocaine or amphetamines, as well as during hypertension—ergic metabolic states such as eclampsia and hypertensive crises. Indeed, it would have been of notable interest to explore the effects of sympathomimetic and serotoninergic medications in some patients with thunderclap headache and reversible vasospasm are possibly coincidental—a point that I made in the review article. On the basis of the association with unruptured aneurysms or exposure to sympathomimetic and serotoninergic medications in some patients with thunderclap headache and vasospasm, he raises the provocative and interesting possibility that patients who develop thunderclap headache (without subarachnoid haemorrhage) are more likely to harbour aneurysms due to primary or drug-induced abnormalities in vessel tone.

There are certainly cases of thunderclap headache with reversible vasospasm that have occurred shortly after exposure to sympathomimetic medications such as cocaine or amphetamines, as well as during hypertension—ergic metabolic states such as eclampsia and hypertensive crises. Most of the patients described in the literature, however, did not harbour intracranial aneurysms, and prospective longitudinal studies of patients with non-aneurysmal thunderclap have not found an increased risk of subarachnoid haemorrhage. Ideally, a longer prospective study of patients with thunderclap headache with cerebrovascular imaging or careful assessment of a large group of patients with unruptured aneurysms (such as the international unruptured aneurysm study) for a history of thunderclap headache would be required to address the hypothesis raised by Dr Singhal.

Dr Singhal also suggests that unruptured aneurysm present with vasospasm in the absence of a thunderclap headache. The case (courtesy of C. Miller Fisher) that he uses to illustrate this point is a very interesting one. While it is certainly possible that the unruptured aneurysm in this case may have given rise to the vasospasm, I believe the vasospasm in this 65 year old woman with Guillain-Barré syndrome was more likely related to the severe labile hypertension—ergic metabolic state. Dysautonomia is frequently seen in this disease. As alluded to earlier, vasospasm has been well described in patients with acute hypertensive crises such as pheochromocytoma, eclampsia, and hypertensive encephalopathy. Serotonergic vasospasm with posterior leucoencephalopathy syndrome (PLES) was recently described in a patient with thunderclap headache, and I have just submitted a similar case for publication in a young woman who also had reversible vasospasm in the setting of a hypertensive crisis and PLES. In fact, it is possible that in many cases of drug induced cerebral vasospasm, the effect on vascular tone and calibre may reflect the effect of these sympathomimetic drugs on arterial blood pressure in addition to a direct vasoconstrictive effect of the drugs. Indeed, it would have been of notable interest to know the arterial blood pressure in the patients he described with reversible vasospasm and stroke in patients exposed to serotoninergic medications, since the magnetic resonance imaging abnormalities in his patients are very similar to the changes seen in patients with PLES.

Cochlear implantation in a profoundly deaf patient with MELAS syndrome

In response to the article “Cochlear implantation in a profoundly deaf patient with MELAS syndrome” (mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes), we feel concerned that this patient may have a different diagnosis. This woman who received a cochlear implant is described as having the MELAS syndrome, in both the title and the article. However, she has the less severe maternally inherited diabetes mellitus with deafness (MIDD) syndrome.

She has the A3243G point mitochondrial DNA (mtDNA) mutation associated with insulin dependent diabetes mellitus, congenital cataracts, short stature, leg weakness, fatigue, and sensorineural hearing loss (SNHL), with no encephalopathy or strokes. The age of onset of SNHL was 22 years, with a slow deterioration to right profound SNHL at the age of 29 years, and bilateral profound SNHL and tinnitus at the age of 30 years. Caloric testing and computed tomography of her temporal bones were both normal. Her mother suffered from diabetes, glaucoma, and a lesser degree of SNHL, and a sister has profound SNHL and mental retardation.

MELAS is a multisystem disorder with a wide variety of gastrointestinal clinical features. Among these multiple features, the diagnostic criteria for MELAS are as follows: 1. Stroke-like episodes before age 40 years; 2. Encephalopathy (seizures, dementia, or both); 3. Mitochondrial myopathy (lactic acidosis, ragged red muscle fibres, or both); 4. Two of the following three: normal psychomotor development, recurrent headache, recurrent vomiting.

Now these clinical findings can be confirmed with a positive molecular genetic test for mtDNA mutations. The A3243G mutation in the mitochondrial tRNA{sub Gln} gene, MTTL1, causes MELAS and is responsible for MELAS in approximately 80% of patients. MIDD has a 4363G point of bilateral, progressive, symmetrical SNHL, generally preceding diabetes mellitus (ranging from abnormal glucose tolerance to insulin dependent diabetes mellitus) and occurs in adulthood, with a background of maternal inheritance. Sporadic occurrence has been noted. It is associated with short stature and can be expressed as type 1-like or type 2-like diabetes. The A3243G mutation transition has been identified as the cause of MIDD in 60% of cases.

In patients with mtDNA disease, affected cells and tissues tend to harbour mixtures of mutant and wildtype mtDNA in different proportions. This is called “heteroplasmy”, as opposed to “homoplasy”, where only one type is present. It is hypothesised that phenotypic expression of mtDNA pathology may occur when heteroplasmy within an organ reaches a certain level. This concept is known as the “threshold effect”. The severity of the phenotype is thought to correlate with the degree of heteroplasy in different tissues. Interestingly, both syndromes, MELAS and MIDD, can be found in a single pedigree with the A3243G mutation. The A3243G mutation is also associated with Kearns-Sayre syndrome. Assuming that all patients with the A3243G mutation have the MELAS syndrome leads to an incorrect diagnosis, with significant implications for patient counselling. A diagnosis of MELAS implies that the patient has developed stroke-like episodes or encephalopathy.

As more people with SNHL become genotyped and the identification of the true prevalence of mitochondrial SNHL becomes more obvious, a database of already successfully treated patients by cochlear implantation will be useful for quantitative analyses of performance of these patients. Cochlear implants. Here also, the correct label must be assigned to patients.


A R Sinnathuray, V Rout, J G Toner
Department of Otolaryngology, Belfast City Hospital, Belfast, UK
A Magee
Department of Medical Genetics, Queen’s University, Belfast at the Belfast City Hospital
Correspondence to: Mr J G Toner, Director, Regional Cochlear Implant Centre, Belfast City Hospital, Lisburn Road, Belfast BT9 7AB, Northern Ireland, UK, gtoner@itworld.com

References

Author’s reply
We are grateful to Dr Sinnathuray and colleagues for their very useful comments on the precise diagnosis of our patient’s condition. We agree entirely with the comment that the A3243G mutation also occurs in maternally inherited diabetes mellitus with deafness (MIDD). In our patient the original diagnosis was made by a clinical geneticist in 1994 and therefore, in a rapidly changing field,
greater precision in diagnosis might have been possible with a further genetics consultation at a later date. We should point out that this article was originally submitted in November 2000 and this, also, may have contributed to the diagnosis of MELAS syndrome rather than MIDD syndrome. We are most grateful to Dr Sinnathuray and colleagues for their useful comments.

J Graham
UCL Cochlear Implant Unit, Royal National Throat, Nose & Ear Hospital, 330–332 Gray’s Inn Road, London WC1X 8DA, UK

Bilateral lesions restricted to the posteroventral pallidum are unlikely to provoke corticobulbar syndrome and psychic akinesthesia

Merello et al reported a randomised study comparing bilateral simultaneous posterior-ventral pallidotomy (PVP) with a combination of unilateral PVP and contralateral pallidal stimulation.1 After having included three patients in each group, the study had to be aborted because of the severe complications encountered in the patients who had had bilateral pallidotomy.

This interesting paper raises some serious concerns.

First, the three patients who had bilateral PVP had a mean age of 67 years and those who had PVP and contralateral pallidal stimulation had a mean age of 55 years. This difference in age is said to be non-significant. As there are only three patients in each group it would perhaps have been more appropriate to have given the ages of the individual patients rather than the means.

Second, at three months after surgery, the patients who had bilateral PVP showed deterioration in parts I (mood) and II (activity of daily living) of the unified Parkinson’s disease rating scale (UPDRS). The subscores of gait and postural instability worsened significantly. The patients showed deterioration in depression and apathy scores, and it was not possible to perform neuropsychological evaluation after surgery. The patients required feeding tube, their gait freezing deteriorated, and they had no benefit from increased levodopa dose. They suffered from severe loss of initiative and motivation. In my opinion, even though bilateral pallidotomy may increase the risks of complications,2 the disastrous outcome of the three patients described in Merello’s paper poses serious questions as to the exact location of the lesions. I believe that in order to provoke the severe corticobulbar syndrome and “psychic akinesthesia” described, the pallidal lesions must have encroached on the internal capsule bilaterally, and also have included antero-dorsal-medial parts of the GPi.

The authors wrote that “brain MRI three months after surgery showed that all nine lesions and the three electrodes were located entirely within the GPi. Coordinates of the lesion/lead as well as lesion volumes were not significantly different between the groups.” The authors concluded: “Our present findings argue against the possibility that lesion inaccuracy is responsible for the unacceptable rate of side effects of bilateral procedures as targets were confirmed by microwebrcasting, lesions checked by MRI and the same criteria were followed either for lesioned or stimulated patients.”

It is indeed very fortunate that the authors did perform the postoperative MRI at three months after surgery—that is, when the surgical oedema that would disturb the interpretation of the lesion location had completely resolved. From a didactic point of view, and to allow the reader to learn more about the anatomical substrate of this rather catastrophic outcome in patients with bilateral PVP the MRI scans should have been shown in this important paper. I invite Merello et al to publish relevant axial and coronal postoperative brain MRI scans of these three patients in their answer to this letter, showing the locations of the bilateral posteroventral GPi lesions that were responsible for the reported “corticobulbar syndrome and psychic akinesthesia.”

M I Hariz
Department of Neurosurgery, University Hospital, 901 85 Umed, Sweden;
marwan.hariz@neuro.umu.se

Author’s reply

We greatly appreciate the publication of the letter from Professor Hariz, which gives us occasion to provide more information about our paper and confirm the dangerous effect of simultaneous bilateral lesions within the GPi. We all know how limited the literature is on negative results of surgical procedures and how important they are. Surgery for Parkinson’s disease is an extremely useful tool in a certain subgroup of patients, but it is not entirely risk-free and unfortunately many of the side effects seen at the bedside are poorly represented in published reports.

On the basis of unpublished descriptions by many neurosurgeons, bilateral procedures are performed by placing a normal lesion on one side, involving as much as possible of the motor portion of the GPi, followed by a smaller contralateral lesion. An excellent point arises from the concern expressed by Hariz: should both lesions be the same size? Perhaps staged asymmetric lesions could provide an alternative, but this was not the case in our report; we made simultaneous lesions which both involved as much as possible of the motor portion of the GPi, and our conclusions should not be extended to other surgical contexts.

As requested, we provide MRIs of our cases (fig 1) and fully agree that lesion placement is crucial, as Hariz is well aware, given his reported outcome of five of 13 patients (that is, almost 40%) who subsequently required seven further procedures, presumably because of initial lesion misplacement.1 Whatever the importance of descriptive photography, we believe it was more important that non-significant statistical differences were found in lesion/stimulation placement between the groups, and clinical psychic akinesthesia was only present in simultaneous bilaterally lesioned cases.

We are sure that Hariz must have already read a recent review by Laplane and Dubois,3 which clearly describes the psychic akinesthesia syndrome as a result of bilateral basal ganglia lesions, providing deep insight into the non-motor roles of the basal ganglia, such as behavioural activation, cognitive processing, affectivity, and conscious awareness, with which we fully agree.

M Merello
Movement Disorders Section, Raul Carrea Institute for Neurological Research, FLENI, Buenos Aires, Argentina;
mmmerello@fleini.org.ar

References
Ischemic cerebrovascular disease

By Harold P Adams, Vladimir Hachinski, and John W Norris

The most recent book in the very successful “black book” Contemporary neurology series from Oxford University Press is a monograph on brain ischaemia. The book is written by three experienced and well respected North American authors—Adams from the United States and Hachinski and Norris from Canada. The purpose of the monograph is to build on a previous book entitled The acute stroke by Hachinski and Norris published 16 years ago. There are now many books on stroke and on brain ischaemia. While reading this present endeavor I continued to ponder the role of this monograph among the already burgeoning library of books. Whom is it aimed at? Who will profit most by its content? When, why, and how will readers use this book?

This text has been conveniently divided into four parts. The initial portion consists of four chapters: an introductory general chapter followed by single survey chapters on epidemiology, clinical presentation of ischaemic and transient ischaemic strokes, and imaging and laboratory evaluation of these patients. The second portion of the book consists of five descriptive chapters: four concern different stroke types and in much more detail other atherosclerotic conditions and cardioembolic sources are mentioned only in brief pithy paragraphs. Non-stroke experts would derive the barest information from the text but can look up references. Unfortunately, most references are only to the previous book. References to monographs and review of topics considered scantily would also have been helpful.

This book will be most useful to non-neurologists and non-stroke specialists who have the responsibility of managing patients with acute brain ischaemia acutely in emergency rooms and in hospitals. It serves as an excellent reference source concerning a wide variety of topics related to brain ischaemia, which are considered in more detail elsewhere.

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**BOOK REVIEWS**

**Ischemic cerebrovascular disease**

By Harold P Adams, Vladimir Hachinski, and John W Norris

Edited by Christopher M Filley

**The behavioral neurology of white matter**

This is a single author review and is a small book of 279 pages. It is divided into three parts, the first covering the normal function, development, and imaging of white matter. The second and largest part is devoted to white matter dysfunction. While the range of conditions covered is comprehensive, each condition receives from a short paragraph to a couple of pages. While the material in the book is still brief. Similar comments apply to the following section on psychiatric disease. Readers consulting the book for advice on any aspect of management will be disappointed; this is scarcely mentioned at all.

Another common issue, the selection of appropriate scales and tests for the assessment of cognitive loss, is also striking by its absence. It is difficult to see where this book will fit in; the first two sections would be better covered elsewhere. The final section provides more unusual material but even so this is brief, somewhat theoretical, and devoid of information on diagnosis or management. It may be useful as a reference monograph for people in training entering the field.

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**Channelopathies of the nervous system**

Edited by M R Rose and RC Griggs

Over the past few years there has been an explosion of knowledge regarding a group of diseases that have become known as the channelopathies. Like many new chapters of medical discovery it always seems obvious in retrospect. After all, ion channels are one of the most critical structures for normal neural activity. This cascade of new knowledge has now firmly established that dysfunction of both ligand gated and voltage gated ion channels may cause human diseases. The dysfunction may cause an autoimmune attack, such as myasthenia gravis, or may be the result of mutations in ion channel genes, such as the skeletal muscle channelopathies.

In the main, channelopathies are disorders of excitable tissues and the nervous system is of course particularly affected. It is therefore timely that Channelopathies of the nervous system should be published to provide a snap shot of current knowledge in this area. The editors state that their aim is “to inform both clinicians and neuroscientists about the state of the art in channelopathies, both clinically and scientifically”. I think this has been achieved through the contributions of 34 recognized authorities in various subfields of neurological channelopathies.

The foreword is particularly informative and sets the scene very well for what is to follow. In the preface the editors acknowledge that the ultimate importance of channelopathies and of ion channel dysfunction will be important in the most common paroxysmal disorders: epilepsy and migraine. This remains unproved.

The layout of the book is logical and generally user friendly. Each chapter stands more or less alone and as expected for a multiauthored text the styles vary. The book is divided into eight main parts: basic science, assessment of channel function (in vitro and in vivo), channel gene expression, genetic and acquired channelopathies, central nervous system disorders, toxin induced channel disorders, and potential channel disorders.

Recent genetic discoveries indicate that proximal myoton myopathy and Schwartz-Jampel have in fact both bitten the dust as potential channelopathies! I found the chapters on the central nervous system disorders especially readable although already out of date in what is such a rapidly expanding area.

This is one of the first texts on this subject and I can recommend it to interested neurologists and neuroscientists.

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**Disorders of voluntary muscle**

Edited by G Karpati, D Hilton-Jones, and R C Griggs

It is estimated that at least one in 500 people will be affected by specific genetic or other lifelong neuromuscular disorders. Inevitably
Several of the dystrophies, congenital myopathies, and, of course, the inflammatory myopathies are covered in some detail, each in separate sections. These are, generally speaking, up to date and provide, in particular, a good account of the recent advances in the molecular genetics, particularly of the dystrophies. The section on mitochondrial disorders is also comprehensive and provides a useful algorithm for assessment of patients with possible mitochondrial disease. It is the section on the primary myopathies that will probably be most used by generalists, including both neurologists and rheumatologists. The section written by Dalakas and Karpati is excellent and provides a comprehensive overview of the clinical, morphological, aetiological, and therapeutic aspects of these disorders. In particular, the discussion of the involvement of muscle in other inflammatory disorders is helpful. My only suggestion might have been an algorithm to help guide clinicians in the treatment of these disorders.

Genetic counselling in muscle diseases has now become a critically important area. Therefore, the chapter by Lefebvre is very welcome. This sets out clearly the approach that clinicians should take to achieving a diagnosis and to counselling patients and relatives with the various types of inherited muscle disease. I imagine that to many myologists in particular will find its way in some easily accessible form into the clinic drawer.

Finally, the last chapter deals with practical management issues in patients with muscle disease. This is clearly a very important area for patients who sadly often progress inexorably and require an increasing degree of help from carers and the medical profession as each year passes. This section of the most important areas for managing patients with muscle disease and it is pleasing that this has been covered in some detail.

Where do the faults lie? In reality, none of my criticisms are anything but quibbles. Some of the sections seem a little superficial but inevitably this must reflect the constraint of chapter size in what must be intended to be a comprehensive review of the foundations of neuromuscular diseases. The list of contributing authors is impressive. There are several outstanding contributions. I will mention only a few of these.

Skeletal muscle biochemistry is often an area where even myologists begin to feel uncomfortable. There have been several important recent advances in this area, particularly in understanding the relation between biochemical defects and clinical manifestations. The section on skeletal muscle biochemistry by John Land is exceptional and provides a clear and succinct view of the important areas of skeletal muscle chemistry, including the effects of exercise and training. This section competes with the chapter on metabolic myopathies, which provides a detailed account of muscle biochemistry and how it may result in human disease. Inevitably some of the sections are brief but this is balanced by a good range of references. The two sections taken together should prove a significant help to those having to deal with patients who present with metabolic abnormalities of muscle.

The morphological examination of muscle disease lies at the centre of the evaluation of patients with myopathies. The section by Sewry and Dubowitz provides an excellent background review of this area, as well as a comprehensive analysis of morphological abnormalities in muscle disease. Inevitably the contribution has had to be condensed but this section should provide a rapid and easy guide to those who may not necessarily be experts in muscle morphology.

The clinical evaluation of the patient with symptoms of muscle disease is critical to achieving an accurate diagnosis. Generally, disorders of muscle have only a limited range of clinical expression and it is often the subtle features that give a guide to diagnosis or an appropriate plan of investigation. Muscle pain is probably one of the most frequent complaints described above; investigation of many of these patients is negative, although this does not, of course, exclude their having an underlying muscle disorder. A careful approach to patients with myalgia is critical. Thus, it is helpful for this topic to have been covered in some detail in this section. Moreover, the painful muscle syndromes are specifically covered by Lane, and this detailed analysis of the various causes of this symptom is also particularly helpful.

An outstanding contribution has had to be condensed but this is balanced by a good overview to anyone undertaking research in the discipline. Clinical guidelines in old age psychiatry is an invaluable resource and is likely to prove just as valuable.

James Warner

Mood and anxiety disorders in children and adolescents: a psychopharmacological approach


Anxiety disorders are among the most common psychiatric disorders of childhood, and adolescent depression is being increasingly recognised in clinical practice. In contrast with the popularity of psychotropic medication in the treatment of adults with anxiety and depressive disorders, it is comparatively rare for it to be prescribed in children. This is partly because of the efficacy of alternative psychotherapeutic techniques but is also determined by the paucity of supportive research for psychotropic drugs until recently.

This is now changing rapidly and evidence is emerging for the efficacy of selective serotonin reuptake inhibitors for both anxiety and depressive disorders of childhood.

This book is timely in outlining the current state of knowledge on these disorders from a psychopharmacological perspective and in aiming to give clinicians practical advice on the use of medication in this age group. It draws on knowledge—mainly from the adult literature—on underlying neurobiological processes. It gives an overview of neurotransmitters involved, the mechanisms of action, and side effect profiles of various drugs available in children’s disease, advice on capacity and practical advice is given on the use of medication. Families are becoming better informed about different child psychiatric treatments and they may be expected to be offering treatment choices to their child as a base. This book will be helpful to clinicians when considering the indications and contraindications of medication as part of clinical interventions.

Elena Garralda
Neurological eponyms

I enjoyed this book. It is one to delve into rather formally. It appears to have had a rather long gestation since the introduction is dated September 1999. The book is separated into five sections though at times the inclusion of a particular chapter in a particular section seems somewhat arbitrary. The editors have aimed for a uniformity of approach in which a brief historical survey is followed by a resume of the original description and then a setting of that description in a modern context. Inevitably the quality and interest of the contributions vary considerably. The chapters are well illustrated with both portraits of the person and, where relevant, illustrations from original descriptions. In general the editing has been thorough though curiously the chapter on Creutzfeldt-Jakob disease ends with a paragraph covering data that had been previously described in the middle of the text. Some authors chose not to question the appropriateness of the attribution of a particular syndrome or sign to a particular person; others do so sometimes amusingly as, for example, in the chapter by Bruyn and William Gooddy on Horner's syndrome. There is little to quibble with in terms of the attributions, though why on earth cluster headache is entitled Horton's syndrome is not entirely clear to this reviewer. Although Horton himself had the temerity to suggest that the specific type of headache he described in 1899 had not been described adequately in the literature, he clearly had not read Wilfred Harris's contributions published in Neuritis and neuralgia in 1926 and later in The facial neuralgia in 1937. Harris described virtually all the characteristic features of cluster headache including distribution, periodicity, duration, frequency, presence of conjunctival injection and lacrimation, the sometimes associated Horner's syndrome, and the response to subcutaneous ergotamine. So much for a headache that had not been described adequately in the literature.

My only concern about this book is that the publishers, who seem now to be publishing as frequently from New York as from Oxford, seem to have acquired a taste for American spelling. Perhaps they need a visit down the road at Oxford to the OED.

David Perkin

Arachnoiditis: the silent epidemic

This book provides a comprehensive analysis, and comments on a condition we hope will be significantly reduced in incidence with new imaging modalities. It provides an extensive bibliography providing reference on the views expressed, the likely multifactorial aetiological factors responsible for the development of a very disabling combination of signs and symptoms, and management strategies. The earlier chapters provide a historical perspective together with relevant anatomical, pathological, and physiological information, which will be useful to the reader while reading the later chapters. Although the book discusses predominantly the spinal arachnoid, it also covers important cranial subdivisions of the condition, in addition to associated conditions such as syringomyelia. There is an interesting section on questionable causes of arachnoiditis, which are very relevant because the previously predominating literature, injection of foreign materials into the intrathecal compartment of the spine for diagnostic and therapeutic purposes—are no longer used or are regarded with circumspection. The final sections relate to the thorny question of diagnosis, which is extremely difficult, and to the limited treatment options available. Arachnoiditis is a condition that would be better prevented than treated. Unfortunately, the prognosis remains bleak for these patients but the management strategies in dealing with multiple concerns faced by such patients are well described. The senior author is to be congratulated on producing a single volume, based on some eight thousand references, and his undoubted unique experience of dealing with hundreds of such cases, which is a unique contribution to our body of knowledge.

It is salutary reading for some of the more senior members of our profession and will provide guidance to the younger members. It is a useful book for anyone treating patients with this condition and it can provide guidance to those involved in dealing with patient complaints or litigation. The book provides both philosophical and scientific viewpoints.

J Van Dellen

Texture of the nervous system of man and the vertebrates, volume II

This is the second of three projected volumes that present for the first time in English one of the great classics of microscopical anatomy: Santiago Ramón y Cajal's Texture of the nervous system, which appeared in 1904. The Texture and Sherrington's integrative action of the nervous system, which appeared in 1906, are the two fundamental works from which modern neurological science grew. Hitherto, the Texture was available only in the original Spanish and in the somewhat enlarged French edition of 1911, reprinted in 1952.

This new edition is important, not only because it makes Ramón y Cajal's contribution widely accessible, but also because the translators have gone back to the original illustrations, which are preserved in the Museum of the Instituto Cajal in Madrid. The high quality of the paper compared with that of earlier editions means that much detail is now visible that was formerly obscure. This is well shown by comparing the section of the medulla and cerebellum in figure 238 in the present volume with figure 78 in volume II of the French edition: the beautiful cellular detail is simply not visible in the latter.

Most of the investigators are further in the debt of the editors for the assistance provided (and almost always checked) the full references cited by Cajal, correcting errors that had escaped his attention, and annotating the text sparingly but helpfully when modern research had clarified issues that remained unclear to him. The book is beautifully produced and pleasant to hold in the hand.

Ramón y Cajal's work is as central to neurological research today as it was century ago. The translators and publishers deserve our gratitude for bringing this essential work to a new generation of readers.

W I McDonald

Clinical evaluation and management of spasticity

This is a useful and interesting book. It is increasingly recognised that several treatment strategies can be beneficial in the management of spasticity, particularly using more recent drugs such as tizanidine and botulinum toxin. The book is a comprehensive review of the subject. No important topics are missed although the length and breadth of the chapters do vary to a significant degree.

The book opens with a brief chapter on the physiology and pharmacology of spasticity. Although the book is targeted towards a clinical audience, and as such is a practical textbook, it is a pity that this opening chapter is so brief with regard to the neurophysiology of spasticity. An understanding of the underlying principles is important for logical treatment. Alex Dromerick produces a good chapter covering the clinical features of spasticity and a brief resume of complications. This is followed by an excellent chapter on measurement of spasticity by David Good, which I found to be one of the most useful summaries of this field that I have read for some time. My major disappointment in the book is the brevity of the following chapter on physical and occupational approaches. The involvement of a neurological physiotherapist in the management of spasticity is vital and while this chapter is thorough it is too brief and fails to do justice to the key involvement of a physiotherapist in the spasticity team. This defect is partially overcome with an excellent subsequent chapter on orthotic management, which is very clear and usefully provides an overview of an increasingly complex subject. The standard pharmacological interventions (baclofen, tizanidine, dantrolene, and the benzodiazepines) are thoroughly covered in the ensuing chapters with an additional brief chapter on alternative pharmacological therapies. Nerve blocks, botulinum toxin, and intrathecal medications are adequately covered. The chapter by Mary Keenan and Patrick Nicholls on orthopaedic interventions for the management of limb deformities in spasticity is the best chapter on this subject I have ever read and certainly should be compulsory reading for the physician who may need to refer to surgical colleagues for the management of complex and drug resistant spasticity.

The problem with these early chapters is that they lack an overall strategic approach to the patient with spasticity. The editors have tried to correct this problem with the last four chapters in the book, which give individual views of the management of spasticity in children with cerebral palsy and in adults with multiple sclerosis, traumatic brain injury and spinal cord injury. These are useful chapters that bring the rest of the book together, although there is some rather unavoidable repetition. A few illustrative case histories might have been useful in this section.

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Overall this is a thorough, reasonably comprehensive, well referenced, and up to date textbook, which can be recommended to the multidisciplinary spasticity team and is a useful reference for any neurologist.

Michael Barnes

Autoantibodies in neurological diseases


Antineuronal antibodies were initially described 40 years ago and since then many autoantibodies have been discovered and characterised. Despite this, there is a limited number of texts devoted to the subject of autoantibodies in neurological diseases. Even less common are books that describe autoantibodies and clinical-immunological associations in a manner useful to both clinicians and investigators. This book fills the void. Although the title evokes a laundry list of antibodies this edition offers an even balance between clinical descriptions, immunological mechanisms, and therapeutic implications. The inevitable overlap of topics in a multi-authored book is kept to minimum. An introductory chapter on techniques used for measuring and evaluating the pathogenic role of autoantibodies will be useful for clinicians not directly involved in laboratory research. Subsequent chapters comprehensively cover disorders of the neuromuscular junction and peripheral nerve and less extensively disorders of the central nervous system associated either with autoantibodies or with other evidence of autoimmunity. Among the latter are chapters on autoantibodies and epilepsy and vasculitis of the central nervous system, topics rarely encountered in other texts. Two chapters on autoimmunity and pregnancy, particularly in association with myasthenia gravis, nicely discuss the effects of immunity on the embryo and newborn. With the exception of disorders associated with antibodies to gangliosides that are not discussed, descriptions of most of the recently described paraneoplastic and non-cancer related autoantibodies, as well as possible pathogenic mechanisms, are up to date and clear. A chapter on the ontogeny of skeletal muscle cells, although well written, is out of place in this text. The book is well edited and illustrated and the references are thorough. The focus of the text is weighted towards disorders of the peripheral nervous system, likely reflecting the more extensive literature on these disorders. Clinicians and basic investigators in neurology and immunology will find this book an excellent resource.

Joseph Dalmau

CORRECTIONS


Single exponential function was erroneously used for the calculation of figure 2. The correct figure 2 is reproduced below, which shows the predicted probability of recurrent TIA and stroke as calculated from the cumulative underlying hazard and the prognostic index (derived from multivariate regression coefficients, mean values of covariables, and number of embolic signals) by double exponential function.


Table 2 Adverse events (%) according to FDA and EMEA standards.

<table>
<thead>
<tr>
<th>Adverse reaction* (FDA)</th>
<th>Undesirable effects† (EMEA)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Levetiracetam (n=769)</td>
</tr>
<tr>
<td>Somnolence</td>
<td>15</td>
</tr>
<tr>
<td>Athetaisia</td>
<td>15</td>
</tr>
<tr>
<td>Dizziness</td>
<td>9</td>
</tr>
<tr>
<td>Infection</td>
<td>13</td>
</tr>
</tbody>
</table>

*Adverse reaction: any event reported during clinical trial; FDA, Food and Drug Administration; †undesirable effect: all adverse events at least possibly related to the study drug; EMEA, European Medicinal Evaluation Agency.

Note: Adverse reactions and undesirable effects are derived from three efficacy and one safety, double blind placebo controlled trials. Patient numbers differ because the FDA included the crossover part of the study in the analysis, and some of these patients were counted twice.