LETTERS TO THE EDITOR

Behavioural status during the intracarotid amobarbital procedure (Wada test): relevance for surgical management

Presurgical evaluation in many epilepsy programmes often includes the intracarotid amobarbital procedure (IAP). Sodium amytal is injected into the internal carotid artery to produce a temporary “pharmacological paralysis” of hemispheric function. Traditionally, the IAP has been employed in patients with refractory temporal lobe epilepsy being considered for anterior temporal lobectomy. In these cases it is used to determine cerebral dominance for language, to assess the risk of severe postsurgical amnestic syndrome and to predict postsurgical material specific memory changes. More recently, the use of the IAP has been extended to complement EEG localisation and radiological data by lateralisering temporal lobe dysfunction.

We report a case of frontal lobe epilepsy undergoing surgery and present an unusual aspect of treatment. However, as surgical management would involve resection of the left frontal lobe against a background of traumatic head injury and the possibility of more generalised frontal lobe dysfunction, a left hemispheric IAP was performed. Sodium amytal (125 mg) was administered via a slow hand injection. Of relevance, no crossflow into the contralateral anterior cerebral artery via the anterior communicating artery was present (as assessed by a separate injection of contrast medium). The injection was accompanied by a dense right hemiplegia and global aphasic arrest. Resolution of language was characterised by a dense perseveration of counting (go-no go paradigm), together with marked behavioural disinhibition (agitation, swearing, verbosity, childishness). Although seemingly aware of some aspects of his environment, he showed severely impaired capacity for motor regulation (as well as for advanced education), he had unremitted employment due to his seizures. He was socially isolated and his interpersonal relationships were limited.

He had severe life threatening epilepsy with the surgical diagnosis being frontal lobe dyscortical resection (as opposed to more extensive frontal lobectomy) restricted to the region of damage was advised. Intraoperative electrocorticography showed acute focal epileptic discharges maximal in the inferior frontal lobe in the electrodes closest to the lesion. A cortical resection was performed with frameless stereotaxy guidance excision of the frontal lesion. Histopathology on the resected tissue showed an old post-traumatic cyst involving the cortex and white matter. His postoperative course was unremarkable. When reviewed 3 months after surgery he was seizure free. His mood, behaviour, and temperament were normal. Despite his unoubted value in many individual cases of temporal lobe epilepsy, the IAP has remained a controversial assessment instrument. Amid this controversy its potential usefulness in other patient groups seems to have been overlooked. A primary criticism of its use in temporal lobe epilepsy has been the question of irritation and whether the medial temporal lobe is adequately “disabled” during the procedure. This particular limitation is not applicable to this patient with frontal lobe epilepsy, as the region of interest is clearly ablated via supply from the carotid arterial system. Caution must, however, be exercised with respect to possible crossflow into the anterior cerebral artery via the anterior communicating artery. When such crossflow is present, the ability to assess validity the integrity of the contralateral frontal lobe function will be confounded by virtue of a pharmacologically induced bilateral frontal lobe syndrome. As with the use in cases of temporal lobe epilepsy, only a restricted form of assessment is possible with the frontal lobe patient during the period of ablation. An awareness of issues of behavioural regulation would seem most useful.

It should be borne in mind that the degree of frontal lobe dysfunction induced by the IAP represents the “worst case” scenario, as the entire frontal lobe is included in the ablation. There are likely to be few surgical scenarios in which a comparable extensive resection of tissue is likely to be considered, and results must be interpreted in this context. This limitation notwithstanding, the IAP does seem to have a role in separating out those patients in whom more extensive frontal lobe resections could not be considered opposed to those in whom a more conservative approach is warranted.

This case report forms only the basis for a novel hypothesis that clearly requires more rigorous scientific research before its clinical utility can be reliably established. Nonetheless, we think that it is worth drawing attention the epileptological community to the potential application of the IAP in the surgical management of extratemporal cases.

MARIE F O’SHEA
MICHAEL M SALING
Department of Neuropsychology
SAMUEL F BERKOVIC
Department of Neurology, Austin and Repatriation Medical Centre, Melbourne, Australia; and
Department of Medicine, University of Melbourne, Grattan Street, Parkville 3052, Australia.

Correspondence to: Dr Marie F O’Shea, Department of Neuropsychology, Austin and Repatriation Medical Centre (Austin Campus), Studley Road, Heidelberg, Victoria 3084, Australia. Telephone 613 3 03 4946 5913; Fax 613 3 03 4954 2654

Reversal of tetrabenazine induced depression by selective noradrenaline (norepinephrine) reuptake inhibitor

Tetrabenazine (TBZ), a synthetic benzoquinolizine, was first introduced as a neuroleptic agent in 1960, and is now widely used in the treatment of hyperkinetic movement disorders such as chorea, tics, or tardive dyskinesia. The side effect profile is mainly characterised by the triad of drowsiness/fatigue, parkinsonism, and depression; depression is found in about 15% of patients treated with TBZ. We here report on the rapid reversal of depressive symptoms in a patient treated with TBZ for orofacial dystonia by administering the new and highly selective noradrenaline (norepinephrine) reuptake inhibitor (SNRI) reboxetine.

On admission, the 64 year old woman presented with perioral and lingual hyperkinesias as well as intermittent and involuntary movements of her lower jaw, which had lasted for about 2 years, causing her a considerable inconvenience in articulation. No history of neuroleptic treatment or Parkinson's disease was evident. Her cranial CT and blood chemistry were normal. We diagnosed a segmental dystonia, which improved dramatically after a tetrabenazine medication (60 mg a day). This successful treatment response, however, was accompanied by a severe depressive syndrome, which was characterized by a mixed anxious-depressive mood, low self esteem, a complete loss of drive, and intermittent suicidal ideations. After switching from TBZ to tiapride, the patient recovered from depression, but her neurological status worsened significantly upon re-exposure to TBZ again ameliorated hyperkinesia, but provoked a depressive relapse. A comedication with reboxetine (6 mg/day), a new and selective monoamine depleting and dopamine receptor blocking drug,1 led to a stable remission of the depressive symptoms within a week, without any worsening of the dystonic syndrome.

Tetrabenazine (TBZ) is known to act as a noradrenaline (norepinephrine) and dopamine receptor blocking drug.1 In more detail, TBZ binds to and inhibits specifically the human vesicular monoamine transporter isoform 2 (hVMAT2). Whereas the indolamine serotonin forms a similar affinity for both hVMAT1 and hVMAT2, catecholamines such as noradrenaline exhibit a threefold higher affinity for hVMAT2. As these specific transporters are responsible for packaging monoamine neurotransmitters into presynaptic secretory vesicles for release by exocytosis, the inhibition of hVMAT2 by compounds such as tetrabenazine thus results in consecutive noradrenaline depletion.2

Alterations of noradrenergic neurotransmission—that is, a neuronal noradrenaline depletion—can therefore be postulated to form one major origin of TBZ induced depression. At this assumption, brain-specific catecholaminergic activity enhancers (CAEs) such as phenylethylamine have been shown to antagonise TBZ induced depression-like behaviour in rats.3 Modulating this altered noradrenergic neurotransmission pattern by the administration of selective noradrenaline reuptake inhibitors such as reboxetine may thus provide a new, specific, and fast acting tool in the management of depression caused by TBZ and related (neuroleptic) compounds.

WOLFGANG SCHREIBER
JÜRGEN-CHRISTIAN KRIEG
Department of Psychiatry and Psychotherapy, Philipps-University, Rudolf-Bultmann-Straße 8, D-35033 Marburg/Lahn, Germany

TOBIAS EICHHORN
Department of Neurology, Philipps-University, Rudolf-Bultmann-Straße 8, D-35033 Marburg/Lahn, Germany

Correspondence to: Dr Wolfgang Schreiber, Department of Psychiatry and Psychotherapy, Philipps-University, Rudolf-Bultmann-Straße 8, D-35033 Marburg/Lahn, Germany. Telephone 0049 6421 285329; fax 0049 6421 285329; email schreibe@mail.uni-marburg.de


Spinal sulcal artery syndrome due to spontaneous bilateral vertebral artery dissection

In young adults vertebral artery dissection (VAD) is an important cause of brain infarction.1,2 A known mechanism is microtrauma due to abrupt head movements: for example, carotid sinus manoeuvres. In addition a pathogenic role of connective tissue diseases, cystic media necrosis, fibromuscular dysplasia, migraine, and inflammatory diseases has been postulated.3 In VAD initial neck pain is often reported, which may be slight. Lesions caused by VAD are cerebellar or brainstem infarcts, unilateral or bilateral thalamic infarcts (top of the basilar syndrome), or infarctions in the posterior cerebral artery territory due to intra-arterial embolism or haemodynamic decompensation when collaterals are insufficient.4 Lesions of the spinal cord are rare because of its good collateral supply.5 We report on a patient with a syndrome of the spinal sulcal artery (incomplete Brown-Séquard syndrome) caused by spontaneous bilateral VAD.

A 43 year old man with a history of arterial hypertension presented with left sided numbness sparing the face, which had evolved suddenly while he was walking. In addition, he reported on dull right sided neck pain irradiating into the occiput, which had been initiated by a head rotation while he was working at a computer 2 weeks before. The neck pain had spontaneously ceased 6 days later. Neurological examination disclosed dissociated sensation defect on the left with an indistinct level around C4 to C6. Below this level on the left he had a marked hypalgnesia and nearly a loss of temperature sensation. The right limbs were warmer than the left ones. In addition, we found mild right sided motor system deficits. Cranial nerve function was intact, despite a right sided Horner's syndrome. According to chest radiography phrenic nerve function was preserved. Routine laboratory findings including CSF analysis were normal. The hemiparesis and the different temperature sensation in the limbs resolved completely within 3 weeks.

Tibial nerve somatosensory evoked potentials (SEEPs) had regular N22 and P40 latencies and amplitudes. Central motor conduction time (CMCT) and transcranial magnetic stimulation was prolonged to the right abductor digiti minimi (9.2 ms) and tibialis anterior (23.1 ms). The CMCT to the left target muscles was normal. Duplex sonography showed increased flow velocity on the level of the cervical vertebrae 3 to 5 with a maximum of 214 cm/s in the right and 197 cm/s in the left vertebral artery. Colour mode showed irregular narrowings of the lumen indicating dissections.

Cervical MRI showed a spinal cord infarction at the level C2 (figure). The circumference and dorsal part of the cord were not affected. In digital subtraction angiography (DSA) both vertebral arteries had string signs in the V1 and V2 segments with collateral flow to the distal V2–4 segments via the thyrocervical trunk (cervical ascendent artery) and the costocervical trunk also. The anterior spinal artery was incompletely contrasted by unilateral spinal branches of the right vertebral artery. They originated at the level of dissection. The intradural origins of the anterior spinal artery from the VA especially in the V1 and V3 segments were not visible.

Bilateral spontaneous VAD is not rare, but often missed. In most cases, microtrauma preceding the dissection can be recalled by the patients. Due to the mild mechanical impact, the action of predisposing factors might be postulated. Among these may be changing in type III collagen, migraine, fibromuscular dysplasia, infections in the near past, and inflammatory vasculopathy.6 Magnetic resonance imaging with typical semilunar mural haematoma and in addition magnetic resonance angiography (MRA) with complementary documentation of an aneurysm or tapering occlusion have a high sensitivity and specificity in cases of internal carotid artery dissection.7 By contrast, mural haematomas of the VA especially in the V1 and the V3 segments are often not detectable by MRI. In cases of unclear non-invasive findings, DSA is still the method of choice.1

In addition to consecutive brain infarctions, cervical spinal cord infarctions and nerve root compression syndromes may occur in cases of unilateral or bilateral VAD. Probably as a result of the pial collateral network and the dual posterior spinal artery, spi-
Cerebral cavernous malformations are vascular malformations mostly located in the CNS. Their frequency is estimated close to 0.5% in the general population. 1 Cerebral cavernous malformations occur as a sporadic or hereditary condition. From the Hispanic-American population, familial forms were reported with a high frequency. 2 CCM1, a hitherto unidentified gene mapping on chromosome 7 was shown to be involved in all families with cerebral cavernous malformations of Hispanic-American descent with a strong founder effect. 3 Around 50% of non-Hispanic-American families showed linkage to CCM1 but no common haplotype was found. 4 A recent study showed linkage of cerebral cavernous malformations to two additional loci. 5 No Spanish family with cerebral cavernous malformations has been analysed so far.

We report herein a genetic linkage analysis conducted on nine Spanish families with cerebral cavernous malformations. All procedures were approved by an ethics committee. The families were unrelated and originated from different regions of Spain (south west (CVE2, 3, 4, 10, 17, 25), central (CVE24), south east (CVE28), and north east (CVE29). Seventy seven subjects including 55 potentially informative meioses and 12 spouses gave their informed consent. They were examined by a board certified neurologist, underwent cerebral MRI, and blood samples were taken. Magnetic resonance imaging was used to establish status for linkage analysis. Thirty four members had MRI diagnosis of cavernomas and were considered as affected. Among them, 14 experienced neurological symptoms (cerebral haemorrhage n=6, seizures n=8). Nineteen members with normal cerebral MRI were considered as healthy. Twelve members without MRI investigation had an unknown status.

Analysis of pedigrees was consistent with an American population, familial forms were reported with a high frequency. CCM1, a hitherto unidentified gene mapping on chromosome 7 was shown to be involved in all families with cerebral cavernous malformations of Hispanic-American descent with a strong founder effect. Around 50% of non-Hispanic-American families showed linkage to CCM1 but no common haplotype was found. A recent study showed linkage of cerebral cavernous malformations to two additional loci. No Spanish family with cerebral cavernous malformations has been analysed so far.

We report herein a genetic linkage analysis conducted on nine Spanish families with cerebral cavernous malformations. All procedures were approved by an ethics committee. The families were unrelated and originated from different regions of Spain (south west (CVE2, 3, 4, 10, 17, 25), central (CVE24), south east (CVE28), and north east (CVE29). Seventy seven subjects including 55 potentially informative meioses and 12 spouses gave their informed consent. They were examined by a board certified neurologist, underwent cerebral MRI, and blood samples were taken. Magnetic resonance imaging was used to establish status for linkage analysis. Thirty four members had MRI diagnosis of cavernomas and were considered as affected. Among them, 14 experienced neurological symptoms (cerebral haemorrhage n=6, seizures n=8). Nineteen members with normal cerebral MRI were considered as healthy. Twelve members without MRI investigation had an unknown status.

Analysis of pedigrees was consistent with an American population, familial forms were reported with a high frequency. CCM1, a hitherto unidentified gene mapping on chromosome 7 was shown to be involved in all families with cerebral cavernous malformations of Hispanic-American descent with a strong founder effect. Around 50% of non-Hispanic-American families showed linkage to CCM1 but no common haplotype was found. A recent study showed linkage of cerebral cavernous malformations to two additional loci. No Spanish family with cerebral cavernous malformations has been analysed so far.

We report herein a genetic linkage analysis conducted on nine Spanish families with cerebral cavernous malformations. All procedures were approved by an ethics committee. The families were unrelated and originated from different regions of Spain (south west (CVE2, 3, 4, 10, 17, 25), central (CVE24), south east (CVE28), and north east (CVE29). Seventy seven subjects including 55 potentially informative meioses and 12 spouses gave their informed consent. They were examined by a board certified neurologist, underwent cerebral MRI, and blood samples were taken. Magnetic resonance imaging was used to establish status for linkage analysis. Thirty four members had MRI diagnosis of cavernomas and were considered as affected. Among them, 14 experienced neurological symptoms (cerebral haemorrhage n=6, seizures n=8). Nineteen members with normal cerebral MRI were considered as healthy. Twelve members without MRI investigation had an unknown status.

Analysis of pedigrees was consistent with an American population, familial forms were reported with a high frequency. CCM1, a hitherto unidentified gene mapping on chromosome 7 was shown to be involved in all families with cerebral cavernous malformations of Hispanic-American descent with a strong founder effect. Around 50% of non-Hispanic-American families showed linkage to CCM1 but no common haplotype was found. A recent study showed linkage of cerebral cavernous malformations to two additional loci. No Spanish family with cerebral cavernous malformations has been analysed so far.
cerebral cavernous malformations, this hap- lotype is more likely not predominant in Spain, and the strong founder effect seen in all published Hispano-American families with cerebral cavernous malformations might be specific for this population.

HJ is supported by the Schweizerische Stiftung für medizinisch-biologische Stipendien (Switzerland), SL, by the Fonds de Recherche en Sante (Canada), PL, by the Collège des Enseignants Cédex de Neurologie and ZENNECA pharmacautical group. The work was founded by INSERM, Ministère de l’Enseignement Supérieur et de la Recherche, CSIC, and the Fondo de Investigacion de la Seguridad Social (Fiss: 990407).

Letters, Correspondence, Book reviews, Correction

Hydrocephalus caused by metastatic brain lesions: treatment by third ventriculostomy

Metastasis to the brain occurs in 20%–40% of cancer patients.1 About 20% of these metastases are located in the posterior fossa, cerebellum, and brainstem. Metastatic disease to periventricular brain tissue can obstruct the flow of cerebrospinal fluid (CSF) produced in the ventricles to the subarachnoid space. This typically causes an obstructive or non-communication hydrocephalus. As a potential therapy, a temporary placement of a ventriculoperitoneal shunt, his examination returned to baseline.

Every patient except the person described in case 4 received brain radiation therapy after the palliative procedure. The patient described in case 3 underwent a course of radiation treatment prior to the operation. Another (case 5) had radiation to her orbit in the distant past after enucleation for retinoblastoma. Even though previous radiotherapy may be considered a contraindication for third ventriculostomy by some authors, it did not seem to affect the success of third ventriculostomy in our patients. Carcinomatous meningitis, which could cause a communicating hydrocephalus, was not grossly evident on examination, on any of the brain imagings, or during endoscopy. However, tumours in contact with CSF space can also cause a communicating CSF obstruction by raising CSF protein which can obstruct distal CSF space and arachnoid granulations.

Our success rate of about 70% (five of seven) for third ventriculostomy in periventricular metastatic disease is consistent with the results observed with third ventriculostomy for adult patients with secondary hydrocephalus.2 This is comparable with the alternative shunting with an implanted shunt which has a first year revision rate as high...
as 50%, with the highest failure rate in the first few months after shunt placement. The complication rates for both procedures are low. Third ventriculostomy and shunting can potentially cause a stroke, bleeding, ventriculitis, meningitis, a subdural haematoma, CSF leak, diabetes insipidus, and SIADH. However, shunting has additional risks of mechanical malfunction, complications associated with implanting a foreign body, and overdrainage syndrome.

Because third ventriculostomy restores near normal CSF dynamics, overdrainage is prevented. The procedure is also minimally invasive and safe. The procedure’s low morbidity, high efficacy, and potentially short hospital stay are well suited as a palliative therapy monitoring. Our study is well suited as a palliative treatment for evaluating mechanisms of neurological symptoms associated with brain tumours.

Neuronal activation causes an increase of regional cerebral blood flow (rCBF) in the activating cortical area. Near infrared spectroscopy (NIRS) demonstrates the increase in rCBF during neuronal activity as increases in oxygenated haemoglobin (oxy-Hb) and total haemoglobin (total-Hb) with a decrease in deoxygenated haemoglobin (deoxy-Hb). NIRS is an optical method to measure concentration changes of oxy-Hb, deoxy-Hb, and total-Hb (oxy-Hb+deoxy-Hb) in cerebral vessels by means of the characteristic absorption spectra of haemoglobin in the near infrared range.

In the present study, we measured changes of oxygenation and haemodynamics in the brain tumour adjacent to the activating cortex by means of NIRS. We found transient decreases in oxy-Hb and total-Hb in the tumour during neuronal activation, suggesting that the local blood flow of the tumour was decreased by a transient increase of rCBF induced by neuronal activation.

The patient was a 35 year old right handed man who presented with complaints of headache and dizziness. A neurological examination showed no abnormalities and a decline in language functions. A postcontrast CT showed a well defined large enhancing tumour (4×5 cm) compressing the left frontal lobe. Computed tomographic angiography showed that the branches of the left middle cerebral artery supplied the tumour (figure A). The patient underwent a left frontal craniotomy for removal of the tumour; the pathological diagnosis was meningioma. The NIRS measurement was performed before the operation.

We measured haemodynamic changes in the brain tumour during neuronal activation in the left frontal lobe induced by cognitive activity alters local blood flow in brain tumour adjacent to the activating cortex.

Characteristics of blood flow in brain tumours have been studied extensively; these studies are important for diagnosis of malignancy and therapy monitoring. Our study is the first to consider how activity dependent changes of regional cerebral blood flow (rCBF) alter tumour blood flow in the brain tumour adjacent to the activating cortex.

Table 1 Clinical characteristics of patients who underwent third ventriculostomy for obstructive hydrocephalus

<table>
<thead>
<tr>
<th>Case</th>
<th>Age (y), Sex</th>
<th>Diagnosis</th>
<th>Result*</th>
<th>Postoperative stay in hospital(days)</th>
<th>Survival time (weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>70, M</td>
<td>Lung mixed adenocarcinoma and squamous cancer metastasis to thalamus</td>
<td>Improved</td>
<td>17</td>
<td>4</td>
</tr>
<tr>
<td>2</td>
<td>46, F</td>
<td>Ovarian adenocarcinoma metastases to cerebrum and medulla</td>
<td>Improved</td>
<td>9</td>
<td>13</td>
</tr>
<tr>
<td>3</td>
<td>38, F</td>
<td>Breast ductal carcinoma metastases to brainstem and cerebellum</td>
<td>Improved</td>
<td>3</td>
<td>8</td>
</tr>
<tr>
<td>4</td>
<td>75, M</td>
<td>Rectal adenocarcinoma metastasis to cerebellum</td>
<td>Failed</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>5</td>
<td>39, F</td>
<td>Breast adenocarcinoma metastasis to cerebellum</td>
<td>Improved</td>
<td>4</td>
<td>11</td>
</tr>
<tr>
<td>6</td>
<td>60, M</td>
<td>Lung adenocarcinoma metastasis to thalamus</td>
<td>Failed</td>
<td>6</td>
<td>6+</td>
</tr>
<tr>
<td>7</td>
<td>64, M</td>
<td>Osteopaggeal carcinoma metastatic to cerebellum</td>
<td>Improved</td>
<td>7+</td>
<td>1+</td>
</tr>
</tbody>
</table>

*Results are considered improved if the patient had resolution of symptoms and follow up imaging showed hydrocephalus improved or resolved.

†Patient is currently alive.

tasks. We monitored concentration changes of oxy-Hb, deoxy-Hb, and total-Hb, using an NIRO-500 instrument (Hamamatsu Photonics KK, Japan). The optodes were placed at an interoptode distance of 3.5 cm on the left forehead so that the centre of the two optodes was placed at the centre of the tumour. With an interoptode distance of 4 cm, correlations of oxy-Hb and total-Hb measured by NIRS and rCBF measured by PET suggested that the reliable penetration depth of near infrared light into brain tissue is about 1.3 cm; thus the present NIRS measurement area was restricted in the tumour. The patient was seated and had his eyes open during the NIRS measurement. Informed consent was obtained from the patient.

To activate the left frontal lobe, we used the following four tasks: (1) semantic verbal fluency, which entails naming as many items in a semantic category (for example, animals) as possible; (2) confrontational naming, which involves naming ordinary items presented by the tester; (3) backward digit span, a working memory task which involves reporting of digits (2 to 8) in the reverse order; (4) short descriptive passage aloud. The speech responses of the patient to the tasks were normal.

Figure B shows an example of changes in NIRS during the naming task. After the beginning of the task, oxy-Hb and total-Hb decreased to negative values during the task, and deoxy-Hb also decreased. These changes returned to the control level gradually after the end of the task. The other tasks also caused similar changes of oxy-Hb, total-Hb, and deoxy-Hb.

The rCBF in the left frontal lobe is generally increased by all the tasks used in the present study. Indeed, our NIRS activation study using the cognitive tasks showed increases in oxy-Hb and total-Hb in the left frontal lobe in normal adults—for example, increases in oxy-Hb and total-Hb—were found in 92.3% of young adult subjects in most normal adults—for example, increases in oxy-Hb, total-Hb, and deoxy-Hb.


Migraine aura masquerading as Balint’s syndrome

Migraine is a common neurological disorder with a prevalence of 0.5% to 2% in the general population. In one fourth of total migraineurs, headache is preceded by an aura.1,2 We describe a patient with recurrent episodes of migraine in whom headache was preceded by a constellation of visual symptoms and headache decreased considerably after the patient was started on flunarizine at a daily dosage of 10 mg at bedtime.

Electroencephalography was also non-contributory. The frequency of visual aura symptoms and headache decreased considerably after the patient was started on flunarizine at a daily dosage of 10 mg at bedtime. The visual impulses, after being received by the primary visual cortex (Brodmann area 17), are interpreted and integrated in visual association areas 18 and 19. Brodmann area 19, in turn, is connected with the angular gyrus and frontal eye field through association fibres. Any lesion in the visual association areas or their connections would result in impaired integration of visual impulses despite normal visual acuity.

The visual symptom complex in this case possibly represents an aura of migraine. The pathogenesis of migraine aura has been a debatable issue.3 In this case it is suggested that the pathophysiological process of migraine aura results in a disconnection syndrome by


Letters, Correspondence, Book reviews, Correction
involving visual association areas and their associated pathways. Optic ataxia, gaze apraxia, and simultanagnosia seem to represent a dissociation of visual information from the fronto eye field and dorsal parietal regions.

PARVAIZ A SHAH
A NAFEEPI
Division of Neurology, Department of Medicine, Government Medical College and Associated SMHS Hospital, Srinagar, Kashmir, J and K 190001, India

Correspondence to: Dr Parvaiz A Shah, Firdousah-
haemorrhage or mass e

lar hemisphere (figure A). These variably sized
change in the basal ganglion and right cerebel-
lar hemisphere, and cystic-like

stain. The CSF was sterile after 2 weeks of
routine biochemistry and chest radiography
was still able to work. After the third dose, he
pent rabies could not be excluded in this
patient and hence steroids were not used ini-
tially. Steroids have been reported to increase
mortality; however, this technique is not available in Vietnam. Paralytic rabies could not be excluded in this patient and hence steroids were not used initially. Steroids have been reported to increase mortality in experimental animals with rabies, and it has been suggested that they may abrogate the immune response to the postexposure vaccine, thus precipitating uncontroled rabies. There are three types of postexposure vac-

cine in use world wide. The Semple type (STV) is obtained from inactivated virus pre-

an antigen detection via a skin biopsy; however,

mortality was particularly high (90%) if there
was extensive CNS involvement. The third
type of vaccine available is the human diploid
cell tissue culture vaccine (HDCV), which is
both safe and efficacious. However, the recom-
mented regimen is not affordable in most
developing countries.

When we approached the Rabies Labora-
tory, Ministry of Agriculture and Fisheries,
United Kingdom for advice in this case their
comment was “why do you use the SMBV, can’t you use another vaccine”. Worldwide about 10 million people each year receive
rabies vaccine after exposure; at the Centre
for Tropical Diseases we treat 3000 people
with dog bites annually. The cost of an
HDCV in Vietnam, administered in its
present regimen (1ml given for 5 days on days
0, 3, 7, 14, and 28 with an optional booster on
day 90) is US$ 125, making the use of this
case stresses the need for high dose ster-
oids in postexposure vaccine encephalitis and
the urgent need for the development and
deployment of a safe, and critically, afford-
able postrabies exposure vaccine regimen.

The economic low dose multisite intradermal
regimen using the HDCV provides an exa-
ple of how this goal may be achieved although
it is not yet widely accepted. Such a vaccine
regimen (0.1 ml HDCV given at multisite
injections on days 0, 7, 28, and 90) could be
made affordable, and offers excellent protec-
tion without the risks of postexposure immu-
noc ones per year. In India 3 million people receive postexposure
courses of STV (phenolised sheep brain) antirabies vaccine each year. These produce
neurological reactions, including postvaccina-
tion encephalomyelitis, in up to 1 in 200


Letters, Correspondence, Book reviews, Correction

“Can’t you use another vaccine”? postrabies vaccination encephalitis

A healthy 39 year old man was bitten on the
ankle by his own apparently normal dog. After
the incident the dog disappeared into the
forest and was not seen again. Three days later
the patient was seen at a provincial hospital in
Vietnam and started on an alternate day regi-
men of suckling mouse brain postrabies expo-
sure vaccination (SMBV). After the second
dose, he felt unusually lethargic although he
was still able to work. After the third dose, he
became unresponsive, and was transferred to the Centre for Tropical Diseases, Ho Chi Minh
City, the referral hospital for infectious dis-
eses in southern Vietnam. On admission, he
was afebrile, confused, had slurred speech, and
his Glasgow coma score was 13. He had mild
spastic weakness of his left face, left arm, and
both legs. Full blood count and results from
routine biochemistry and chest radiography
were all normal. The CSF: blood glucose ratio
was 0.47 (63/140 mg%), the protein content was
raised (78 mg/dl), and there was one lymphocyte/ml in the CSF. Screens for malaria
toxoplasmosis, cryptococcus, and neurocysticercosis were negative, as was a CSF gram
stain. The CSF was sterile after 2 weeks of
culture. Brain MRI (Access Toshiba LPT
6.01p, 0.064 Tesla) showed areas of high signal in the
cerebral white matter. Bilateral subcortical and
periventricular lesions are seen (figure B). After 6 weeks he was discharged talking, eat-
ing, walking, and continent but with some
persistent emotional liability and mild
memory impairment. A follow up MRI examination performed 4 weeks later showed
further improvement, apart from minor
abnormalities in the basal ganglion, and
generalised increase in ventricular size, consist-
ent with residual cerebral atrophy.

Rabies is caused by an RNA virus, a mem-
it in the saliva. Rabies manifests as
an acute encephalomyelitis, the development
of which is almost invariably fatal. The
distinction between rabies and postvaccine
encephalitis is difficult and may be helped by
antigen detection via a skin biopsy; however,

A healthy 39 year old man was bitten on the
ankle by his own apparently normal dog. After
the incident the dog disappeared into the
forest and was not seen again. Three days later
the patient was seen at a provincial hospital in
Vietnam and started on an alternate day regi-
mencases of migraine.

1 Ziegler DK. Headache: public health problem.
2 Campbell JK. Manifestations of migraine. Neu-
3 Damasio AR, Tranel D. Disorders of higher
brain function. In: Rosenberg RN, ed. Compre-
4 Headache classification Committee or Inter-
national Headache Society. Classification and
diagnostic criteria for headache disorders, cra-
nic neuropathies, and facial pain. Cephalalgia
5 Blau JN. Migraine: theories of pathogenesis.

Brain MRI in May 1997. (A) T2 weighted
image showing multiple areas of high signal in the
cerebral white matter. Bilateral subcortical
and periventricular lesions are seen. (B) Brain
MRI in July 1997, T2 weighted image shows
resolution of the white matter lesions.
Khat is acknowledged as a recreational drug taken by mouth or inhalation with markedly increased tone. Reflexes were brisk but equal. The right plantar was extensor. There were bilateral palmar and grasp reflexes.

Full blood count, urea and electrolytes, glucose, liver function test, thyroid function test, viral serology, and malaria screen all gave normal results. Tests for HIV antibody, serum angiotensin converting enzyme, white cell enzymes, and serum and urinary porphyrins were negative. Erythrocyte sedimentation rate on admission was 58 mm/h.

Examination of the CSF showed normal opening pressure, 46 cm H2O, 2.7 g/l glucose, 4.3 mmol/l (blood glucose 6.1 mmol/l), and no cells. His initial EEG was abnormal with diffuse slow waves indicative of widespread cerebral dysfunction.

A chest radiograph and ultrasound examination of the abdomen were normal. Cranial MRI, although complicated by movement artefact, showed diffuse abnormality in the deep cerebral white matter of both cerebral hemispheres. Fourteen days after admission he was witnessed to have a single brief adrenergic seizure with eye and head deviation to the right.

The patient was admitted to a rehabilitation unit. His mini mental state examination score and Barthel scores were zero. Feeding by percutaneous gastrostomy was started. A trial of intravenous methylprednisolone (1 g on 3 consecutive days) gave no benefit. Repeated EEGs (on four occasions) showed diffuse slow waves only. A second MRI (3 months after onset of symptom showed the presence of a continuing diffuse extensive abnormality in the deep white matter of both cerebral hemispheres with marked cortical atrophy. Brain biopsy (via right frontotemporal craniotomy) was performed 3 months after onset of his illness. There was no evidence of acute inflammation, vasculitis, or infarction.

While undergoing rehabilitation there has been slow improvement in his cognitive and locomotor function. After 1 year he is able to open and close his eyes, occasionally verbalise, localise pain, and obey simple commands. His plantars are flexor but he has persistent grasp and palmar reflexes. His nutrition is maintained by gastrostomy and he has an indwelling catheter.

The clinical presentation, EEG, and MRI findings suggest a rapidly progressive leukoencephalopathy. There are no previous reports of leukoencephalopathy in association with khat or amphetamine misuse; it has, however, been reported in association with other recreational drugs taken by mouth or inhalation.1 An alternative for this man's presentation is a necrotising vasculitis, a well described complication of oral amphetamine misuse.2 The clinical features, brain biopsy, absence of haemorrhage, and lack of response to steroids make this unlikely.

The likely precipitant of this man's illness seems to be the use of khat. A drug screen on admission was negative, and his family denied misuse of other drugs. It remains possible that the sample of khat chewed by this man was contaminated. We are unaware of any previous reports of khat misuse with severe neurological deterioration; previous cases may not have been investigated or reported. In reporting this case our intention is to alert others to a possible complication of the misuse of this drug. Evidence of other cases would provide a powerful argument for the restriction of import and sale of khat.


Leukoencephalopathy associated with khat misuse

The leaves of the tree Catha edulis, or khat (also qat and kat) are chewed by a large proportion of the adult population of the Yemen, and throughout Saharan and sub-Saharan Africa. The leaves are also chewed by members of the Yemeni and Somali community in the United Kingdom.3 The psychoactive constituents of khat are cathin (d-norfephedrine), cathidine, and cathinone (an alkaloid structure resembling ephedrine and amphetamine) and users report a mild euphoria similar to that of amphetamines.3 Khat is acknowledged as a recreational drug taken by mouth or inhalation with markedly increased tone. Reflexes were brisk but equal. The right plantar was extensor. There were bilateral palmar and grasp reflexes.

Full blood count, urea and electrolytes, glucose, liver function tests, thyroid function test, viral serology, and malaria screen all gave normal results. Tests for HIV antibody, serum angiotensin converting enzyme, white cell enzymes, and serum and urinary porphyrins were negative. Erythrocyte sedimentation rate on admission was 58 mm/h.

Examination of the CSF showed normal opening pressure of 46 cm H2O, 2.7 g/l glucose, 4.3 mmol/l (blood glucose 6.1 mmol/l), and no cells. His initial EEG was abnormal with diffuse slow waves indicative of widespread cerebral dysfunction.

A chest radiograph and ultrasound examination of the abdomen were normal. Cranial MRI, although complicated by movement artefact, showed diffuse abnormality in the deep cerebral white matter of both cerebral hemispheres. Fourteen days after admission he was witnessed to have a single brief adrenergic seizure with eye and head deviation to the right.

The patient was admitted to a rehabilitation unit. His mini mental state examination score and Barthel scores were zero. Feeding by percutaneous gastrostomy was started. A trial of intravenous methylprednisolone (1 g on 3 consecutive days) gave no benefit. Repeated EEGs (on four occasions) showed diffuse slow waves only. A second MRI (3 months after onset of symptom showed the presence of a continuing diffuse extensive abnormality in the deep white matter of both cerebral hemispheres with marked cortical atrophy. Brain biopsy (via right frontotemporal craniotomy) was performed 3 months after onset of his illness. There was no evidence of acute inflammation, vasculitis, or infarction.

While undergoing rehabilitation there has been slow improvement in his cognitive and locomotor function. After 1 year he is able to open and close his eyes, occasionally verbalise, localise pain, and obey simple commands. His plantars are flexor but he has persistent grasp and palmar reflexes. His nutrition is maintained by gastrostomy and he has an indwelling catheter.

The clinical presentation, EEG, and MRI findings suggest a rapidly progressive leukoencephalopathy. There are no previous reports of leukoencephalopathy in association with khat or amphetamine misuse; it has, however, been reported in association with other recreational drugs taken by mouth or inhalation.1 An alternative for this man's presentation is a necrotising vasculitis, a well described complication of oral amphetamine misuse.2 The clinical features, brain biopsy, absence of haemorrhage, and lack of response to steroids make this unlikely.

The likely precipitant of this man's illness seems to be the use of khat. A drug screen on admission was negative, and his family denied misuse of other drugs. It remains possible that the sample of khat chewed by this man was contaminated. We are unaware of any previous reports of khat misuse with severe neurological deterioration; previous cases may not have been investigated or reported. In reporting this case our intention is to alert others to a possible complication of the misuse of this drug. Evidence of other cases would provide a powerful argument for the restriction of import and sale of khat.


Necrotising vasculitis with conduction block in mononeuropathy multiplex with cold agglutinins

Cold agglutinins are cold reactive autoantibodies that have haemolytic effects on red blood cells mediated via complement fixation. Mononeuropathy multiplex associated with cold agglutinins has been described, however details of its pathomechanism are unclear. Here, we report the clinical, electrophysiological, and pathological findings of a mononeuropathy multiplex in a patient with cold agglutinins, who responded very well to plasmapheresis.

A 72 year old man was admitted with a 1 month history of progressing dysaesthesia and weakness of the limbs. He had no anaemia, jaundice, hepatosplenomegaly, or signs of vasculitis. Cranial nerves and the cerebellum were not involved. There was severe weakness and atrophy of bilateral thenar, interossei, and plantar muscles with severe dysaesthesia of both palms and plantaris. Pin prick and light touch were reduced as well as position and vibratory sensation in both hands and feet. Deep tendon reflexes were hypoactive. Babinski's sign was negative.

Laboratory investigation showed a raised erythrocyte sedimentation rate: 52 mm/hour (normal <10) and serum C reactive protein: 1.8 mg/dl (normal <0.5). Blood cell counts were within normal limits. The following were normal or negative: IgG, IgA, IgE, IgM,
M-protein, direct and indirect Coombs tests, cryoglobulin, antibodies to mycoplasma, myelin associated glycoprotein, gangliosides (GM1, GD1b, asialo-GM1, GT1b, GQ1b, Gal-C), P-ANCA, and C-ANCA. The CSP was normal. Titre of cold agglutinins was detectable at 1:320 at 4°C (normal <1:256). The patient's serum agglutinated adult group O red blood cells, but not O red blood cells or human cord red blood cells, signifying cold antibodies with 1 specificity. Immunelectrophoresis of the eluate confirmed IgM composition.

The initial nerve conduction study showed severe diminution or absence of compound muscle action potentials (CMAPs) with mildly diminished conduction velocities. W ave latencies were mildly prolonged. There were no evoked sensory nerve action potentials (SNAPs) in median, ulnar, and sural nerves bilaterally. Electromyographic studies of the affected muscles showed moderate neurogenic changes, but there were no fibrillation potentials except in the left anterior tibial muscle. Sural nerve biopsy was performed. Epineurial vessels were surrounded by mononuclear cell infiltrates (figure A). Some vessels had focal necrosis of their wall. The small vessels in the endoneurium and epineurium showed sludging of red blood cells. The densities of large and small blood vessels were markedly decreased (figure B).

Teased fibre analysis showed that 90% of the myelinated fibres were undergoing axonal degeneration. Fibrils and axons measured 5 µm and 1504/mm, respectively, at 1°C. The myelinated fibres were markedly decreased (diameter<5 µm: 1504/mm2, diameter>5 µm:708/mm2, total: 2212/mm2). The small vessels in the endoneurium and epineurium showed sludging of red blood cells. The densities of large and small myelinated fibres were markedly decreased (diameter<5 µm: 1504/mm2, diameter>5 µm:708/mm2, total: 2212/mm2). The small vessels in the endoneurium and epineurium showed sludging of red blood cells. The densities of large and small myelinated fibres were markedly decreased (diameter<5 µm: 1504/mm2, diameter>5 µm:708/mm2, total: 2212/mm2). The small vessels in the endoneurium and epineurium showed sludging of red blood cells. The densities of large and small myelinated fibres were markedly decreased (diameter<5 µm: 1504/mm2, diameter>5 µm:708/mm2, total: 2212/mm2). The small vessels in the endoneurium and epineurium showed sludging of red blood cells. The densities of large and small myelinated fibres were markedly decreased (diameter<5 µm: 1504/mm2, diameter>5 µm:708/mm2, total: 2212/mm2). The small vessels in the endoneurium and epineurium showed sludging of red blood cells. The densities of large and small myelinated fibres were markedly decreased (diameter<5 µm: 1504/mm2, diameter>5 µm:708/mm2, total: 2212/mm2).

F wave velocities were mildly prolonged. There were no evoked sensory nerve action potentials (SNAPs) in median, ulnar, and sural nerves bilaterally. Electromyographic studies of the affected muscles showed moderate neurogenic changes, but there were no fibrillation potentials except in the left anterior tibialis muscle. Sural nerve biopsy was performed. Epineurial vessels were surrounded by mononuclear cell infiltrates (figure A). Some vessels had focal necrosis of their wall. The small vessels in the endoneurium and epineurium showed sludging of red blood cells. The densities of large and small myelinated fibres were markedly decreased (diameter<5 µm: 1504/mm2, diameter>5 µm:708/mm2, total: 2212/mm2). The small vessels in the endoneurium and epineurium showed sludging of red blood cells. The densities of large and small myelinated fibres were markedly decreased (diameter<5 µm: 1504/mm2, diameter>5 µm:708/mm2, total: 2212/mm2).

Teased fibre analysis showed that 90% of the myelinated fibres were undergoing axonal degeneration. Oral prednisolone (30–50 mg/day) for 4 weeks reduced the erythrocyte sedimentation rate and C reactive protein, but not the serum M proteinemia, direct and indirect Coombs tests, characteristic features of the present case are as follows: (1) subacute onset of mononeuropathy multiplex; (2) necrotising vasculitis with macrophage infiltration of large and small blood vessels; (3) probable conduction block in the median nerve; (4) increased concentrations of serum titres of cold agglutinin; and (5) marked response to plasmapheresis. Extensive investigations for other causes of neuropathy with cold agglutinins was negative except for an increased serum concentration of cold agglutinins, which strongly suggests that cold agglutinins may play an important part in the induction of neuropathy in this case.

Six patients with neuropathy associated with cold agglutinins have been reported including our patient. Cold agglutinins are cold reactive autoantibodies that react with the antigenic determinant termed I/i or Pr present on erythrocyte glycoproteins and glycolipids in erythrocyte membranes. Arrow et al reported a case of polyneuropathy and IgM M proteinemia with anti-Pr2 CA activity. IgM M protein cross reacted with sialosyl paragloboside, GT1b, GD1a, GD1b, GM3, and GD3 present in myelin and endothelial cells of the peripheral nervous system. It has been speculated that anti-Pr2 IgM protein induced immune mediated damage to vascular endothelium and peripheral nervous system myelin. A similar pathomechanism has been postulated in the other cases. However, necrotising vasculitis has never been reported in neuropathy with cold agglutinins. This is the first demonstration of vasculitic neuropathy with cold agglutinins. Although the mechanism for neuropathy with cold agglutinins is unknown, mechanisms similar to those in cryoglobulinaemic neuropathy have been postulated. The hypotheses are (1) immunologically mediated demyelination; (2) ischaemic injury secondary to sludging or agglutination of red blood cells in the vasa nervorum; and (3) associated vasculitis. In the present case, we have confirmed the necrotising vasculitis and probable conduction block. Pathophysiological explanations for association of vasculitis and conduction block may be as follows. Firstly, conduction block may occur as a consequence of nerve ischaemia due to small vessel occlusion. There have been reports of conduction block occurring in vasculitic neuropathy which support this possibility. Secondly, humoral factors including cold agglutinins may induce immunologically mediated demyelination in the peripheral nervous system. Taken together, neuropathy with cold agglutinins may involve immunologically mediated demyelination, microcirculation occlusion, and vasa nervorum vasculitis. The diversity of pathomechanisms may come from the difference target antigens recognised by cold agglutinins. Plasmapheresis proved effective in all these cases. These findings strongly suggest that humoral factors including cold agglutinins may play an important part in the induction of neuropathy with cold agglutinins. We recommend plasmapheresis as first choice treatment for neuropathy associated with cold agglutinins.

We thank Dr Gerard Salazar for critical reading of the manuscript, Ms M Teshima and N Hirata for their technical assistance, Dr S Kusunoki (Department of Neurology, Institute for Brain research, University of Tokyo) for analyses of antibodies to gangliosides, and Mr H Moug (Division of Blood Transfusion Medicine, University of Kagoshima) for characterisation of cold agglutinin.
CORRESPONDENCE

The cholinergic hypothesis of Alzheimer’s disease: a review of progress

I read with interest the review of Francis et al regarding the progress of the cholinergic hypothesis of Alzheimer’s disease.1 They mentioned that donepezil produced improvement or no deterioration in more than 80% of patients, and that such responses should be viewed positively considering the progressive, degenerative nature of the disease. Various donepezil manufacturer’s medical representative presentations data from a clinical study2 also commonly use this statement. However, this only partially reveals the truth. In fact, the same study produced improvement or no deterioration in 59% patients on placebo. I think that the beneficial effect of donepezil in particular clinical trials should always be critically reviewed in comparison with placebo. In addition, as both 24 week placebo controlled donepezil trials performed so far excluded patients with behavioural disturbances, my impression is that the positive effect of donepezil on the symptoms of behavioural disturbances still remains controversial. In fact there are reports that donepezil might induce behavioural disturbances in patients with Alzheimer’s disease.3–5 Therefore I would be extremely cautious about prescribing donepezil to patients with Alzheimer’s disease accompanied by behavioural disturbances.

Finally, donepezil was never investigated in a 3 week randomised double blind study as was mentioned in the review. The authors are probably referring to the randomised 24 week double blind placebo controlled trial with an additional 6 week single blinded placebo phase.

T BABIC
Department of Neurology, Medical School University of Zagreb, Kistcarsica 12, 10000 Zagreb, Croatia.
Telephone 00385 1 217280, fax 00385 1 217280, email tomoslas.babic@zg.et.hr

The authors reply: We thank Professor Babic for the letter, which raises several interesting points. We agree that it may be more helpful to put the results attributed to treatment with donepezil in the context of the placebo response. In general, looking at this as a class effect in relation to several compounds, the picture emerging is that about twice as many people obtain a response to active treatment as to that with placebo. The high placebo response is a common factor in most studies in this field and is worthy of some explanation in its own right. Although it seems that these studies compare drug treatment with that of a placebo (one treatment against no treatment), the reality is that it is a comparison of patients receiving two treatments against other patients who are receiving one form of treatment. The additional treatment regime is, of course, the care and attention that they receive by being part of the clinical study, which often seems to have an impact, not just on the patient but also on their main carer or carers.

As far as behavioural disturbances are concerned, however, our review was making the point that evidence is still lacking from clinical trials to suggest that cholinomimetics as a whole may have a beneficial effect on some non-cognitive behavioural symptoms. This has now been reported for at least two cholinesterase inhibitors and two muscarinic agonists.6,7 In particular, a clear link is emerging between psychotic symptoms and cholinergic dysfunction. Thus, Bodick et al have shown that the M1/M4 agonist xanomeline causes a dose-dependent reduction in hallucinations, agitation, and delusions in a 6 month randomised double blind placebo controlled, parallel group trial. In addition, Cummings and Kaufer have shown that the cholinesterase inhibitor, metrifonate, was also shown to reduce the number of hallucinations in a 26 week randomised, double blind, placebo controlled safety and efficacy study in patients with Alzheimer’s disease. Further support for a link between acetylcholine and psychosis derives from postmortem data showing that the activity of choline acetyltransferase in the temporal cortex of patients with Lewy body dementia was lower in those patients with hallucinations than in patients without this feature. Finally, in animals the partial M1/M4 agonist (5R,6R)-6-(3-propylthio-1,2,5-thiadiazol-4-yl)-1-azabicyclo[3.2.1]octane produced a preclinical profile suggestive of antipsychotic efficacy8 and that the psychomimetic NMDA receptor antagonist ketamine (when administered at subanesthetic doses) reduced brain concentrations of acetylcholine.9 Thus, on the basis of both clinical and preclinical data, a clear rationale is emerging for prescribing cholinomimetic agents for treating the non-cognitive behavioural symptoms associated with dementia, particularly psychosis.

Professor Babic is also correct in identifying two of the studies referred to as the 30 week randomised multicentre placebo controlled parallel group studies, which included a 24 week double blind treatment phase.

We are grateful to your correspondent for providing us with the opportunity to clarify these points.

PAUL T FRANCIS
Neuroscience Research Centre, GKT School of Biomedical Science, King’s College London, London SE1 9RT, UK

ALAN M PALMER
MICHAEL SNAPE
Cerebrus Pharmaceuticals Ltd, Wimersh, Woborough, RG41 5UA, UK

GORDON K WILCOCK
Department of Care of the Elderly, Frongoch Hospital, Bala, Gwynedd, LL41 1EX, UK

BOOK REVIEWS


The neuropathies of diabetes are common (as the chapters in this book repeatedly remind us) and can be very disagreeable. Symptomless neuropathy underlies foot ulceration and sepsis as the commonest clinical consequence of diabetic neuropathy but the unpleasant disorders range from exceptionally severe pain to the whole range of problems resulting from autonomic failure. This book comprehensively covers every aspect of the subject, systematically (and at times exhaustively) from its epidemiology and pathogenesis (exhaustingly) to structural, functional, and clinical problems and their treatment. Most of the authors are well known in the field and their accounts are up to date and authoritative.

Unfortunately, struggle as they might, all authorities have difficulty in defining what they mean by diabetic neuropathy, in regard, understanding of this complication both in clinical and pathological terms, as well as with regard to treatment, lags far behind that of the other classic diabetic complications — nephropathy and retinopathy. Even its classification presents problems and attempts to do so are found in four different chapters, describing four classifications. Repetition is an unfortunate feature of this book and—quite apart from the confusion over classification—aspects of pathogenesis, structural changes, epidemiology, diagrams, and some reference to treatment (for example, that of pain) appear repeatedly in different chapters in greater or lesser detail.

This is certainly a book for the specialist and not at all (as the preface suggests) for the family practitioner. There are good reviews of nerve structure, causation, and treatment of painful neuropathies and focal neuropathies. The comprehensive survey of the Diabetes Control and Complications Trial (DCCT) shows in detail the only treatment which is truly effective (diabetic control); and the lengthy description of aldose reductase inhibitor trials establishes that, even after more than two decades of investigation, further trials are still needed.

Clinical evaluation of somatic and autonomic neuropathies are useful and also, to than two decades of investigation, further shows in detail the only treatment which is effective (diabetic control); and the truly e shows in detail the only treatment which is

The bibliography is important and often very up to date with references ranging from 33 to 283 per chapter. If this book is at times confusing, this reflects the confusion regarding the nature and treatment of the diabetic neuropathies as much as the overlap and repetition found in its different chapters. It is a book of reference for the specialist who will be well served by the comprehensiveness of some of its reviews and their assembly of the appropriate literature.

PETER WATKINS


The quest for a means of accurate localisation of structures during neurosurgery has taxed the minds of clinicians from early in the history of the specialty, starting with Zornov’s encephalometer more than a century ago. Just as the solution to the mariners’ problem of determining longitude from which it partly takes its name, neuronavigation (“the surgeon’s sextant”) has relied on the advent of new technologies to provide solutions to an age old puzzle.

Advances In Neuronavigation begins by trac ing the history of stereotaxis from a Cartesian coordinate system devised by Clarke and Horsley at the beginning of this century, through ventriculography, stereotactic brain atlases, and CT/MRI frame based stereotaxis. The final part of the first section discusses the roots of image guided frameless stereotaxis through the integration of high speed graphics computers, informatics, biotechnology, and robotics.

The remainder of the text is divided into four sections. The first concerns the creation of maps from CT, MRI, MRA, PET, and various types of functional imaging. The following section discusses clinical applications of stereotaxis, beginning with different authors’ experiences of their own favoured frames, the biopsy of difficult lesions such as those in the brainstem or posterior fossa, and finally experience with different image guidance systems, and their integration with the operating microscope and endoscope. There then follows a series of chapters devoted to radiosurgery, and to image guidance in epilepsy and functional surgery. The final section is entitled Frontiers in Neurosurgical Navigation and considers, among other topics, intraoperative MRI, telepresence in neurosurgery, and robotics.

The incorporation of new technology is likely to alter surgical practice radically over the coming decade and equipment that seemed at the cutting edge of technology only a few years ago, such as the mechanical arm, has already passed into near obsolescence at a bewildering rate. This volume provides an excellent account of the developments which have occurred in neuronavigation, and a thought provoking insight into the wider applications of equipment of which many of us use only a fraction of the potential capability. The title of the book should perhaps have included the word cranial, as there is almost no discussion of the impact that this technology has had in surgery of the spine. This aside it is an excellent book although, like the technology it chronicles, one which is likely to date quite rapidly.

ROBERT MACFARLANE


The title and back cover of the latest addition to Neurology Lite texts contains the usual proclamations. “Concise, key topics, revision aid, essential, review...” the well trailed soundbites demanded by the consumer in the increasingly competitive market of “read less - learn more” books. This book, however, is unusual and distinct. Unlike many rivals it is not an A5 facsimile of a superior parent A3 text. Brevity, so essential to the success of an overview work, has sacrificed neither clarity nor clinical relevance. The strength of Key Topics in Neurology owes much to the author’s ability to negotiate skillfully the compromises necessary for a successful distillation of a large and complex field. He has not shied from wholesale culling of neurological ballast. The allied ability to distinguish and highlight the salient and relevant from the obscure and historical allows this small book to be surprisingly thorough in its coverage and topicality. There is sufficient up to date information on most areas of neurology such that this book would be useful for specialist registrars albeit without the detail or embellishment they seek. In terms of the aims of this book such observations must be regarded as complimentary.

My limited criticisms relate to details of layout and presentation. I found the exclusive alphabetical arrangement of chapters mildly disorienting in that, for example, History taking in Neurology is to be found at p 131. Similarly, the absence of diagrams and tables is an unexpected omission as I would imagine that this would have complemented the overall style of the book. These are minor gripes of what in print largely matches the sleeve of what in print largely matches the sleeve. I found the exclusive alphabetical arrangement of chapters mildly disorienting in that, for example, History taking in Neurology is to be found at p 131. Similarly, the absence of diagrams and tables is an unexpected omission as I would imagine that this would have complemented the overall style of the book. These are minor gripes of what in print largely matches the sleeve. This book, however, is unusual and distinct. Unlike many rivals it is not an A5 facsimile of a superior parent A3 text. Brevity, so essential to the success of an overview work, has sacrificed neither clarity nor clinical relevance. The strength of Key Topics in Neurology owes much to the author’s ability to negotiate skillfully the compromises necessary for a successful distillation of a large and complex field. He has not shied from wholesale culling of neurological ballast. The allied ability to distinguish and highlight the salient and relevant from the obscure and historical allows this small book to be surprisingly thorough in its coverage and topicality. There is sufficient up to date information on most areas of neurology such that this book would be useful for specialist registrars albeit without the detail or embellishment they seek. In terms of the aims of this book such observations must be regarded as complimentary.

My limited criticisms relate to details of layout and presentation. I found the exclusive alphabetical arrangement of chapters mildly disorienting in that, for example, History taking in Neurology is to be found at p 131. Similarly, the absence of diagrams and tables is an unexpected omission as I would imagine that this would have complemented the overall style of the book. These are minor gripes of what in print largely matches the sleeve. This book, however, is unusual and distinct. Unlike many rivals it is not an A5 facsimile of a superior parent A3 text. Brevity, so essential to the success of an overview work, has sacrificed neither clarity nor clinical relevance. The strength of Key Topics in Neurology owes much to the author’s ability to negotiate skillfully the compromises necessary for a successful distillation of a large and complex field. He has not shied from wholesale culling of neurological ballast. The allied ability to distinguish and highlight the salient and relevant from the obscure and historical allows this small book to be surprisingly thorough in its coverage and topicality. There is sufficient up to date information on most areas of neurology such that this book would be useful for specialist registrars albeit without the detail or embellishment they seek. In terms of the aims of this book such observations must be regarded as complimentary.

SIDDHARTHAN CHANDRAN

Readers may be interested in:


CORRECTION

K Sudo, N Fujiki, S Tsuji, M Ajiki, T Higashi, M Ninomi, S Kikuchi, F Moriwaka, K Tashiro.

Focal (segmental) dyshydrosis in syringomyelia. J Neurol Neurosurg Psychiatry 1999;67:106-8. During the editorial process the footnote to table 1 (p 107) was wrongly transcribed. The last line—p value for each pair of items: hyperhidrosis v norhydrosis 0.0007; hypohydrosis v norhydrosis 0.7282; normohydrosis v hypohydrosis 0.0012 should read—p value for each pair of items: hyperhidrosis v norhydrosis 0.0007; hypohydrosis v norhydrosis 0.7282; normohydrosis v hypohydrosis 0.0012.