LETTERS TO
THE EDITOR

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

(Mark Waddington, Richard D. Wyper, Marie F. O'Shea, Michael M. Saling, Michael G. S. Wood, Department of Neurology, Austin and Repatriation Medical Centre (Austin Campus), Studley Road, Department of Neuropsychology, Austin and Repatriation Medical Centre, Melbourne, Australia; and Department of Medicine, University of Melbourne, Grattan Street, Parkville 3052, Australia)

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 frontal lobe epilepsy being considered for anterior temporal lobectomy. In these cases it is used to determine cerebral dominance for language, to review the possible impact of postsurgical material specific memory changes. More recently, the use of the IAP has been extended to compliment EEG localisation and radiological data by lateralisering temporal lobe dysfunction.

This letter describes a Wada test, performed on patients with temporal lobe epilepsy in our comprehensive epilepsy programme (1991–8) suggests that the emergence of frontal lobe behavioural features is common in patients in whom the anatomy leads to the suspicion of bifrontal compromise (for example, a history of traumatic head injury). By contrast, these features rarely occur in cases of non-traumatic aetiology, in which the integrity of frontal lobe systems is presumed. Although it remains an incidental finding in the context of determining the suitability of a candidate for anterior temporal lobectomy, this outcome may have potential implications for the selection of patients for frontal lobectomy.

We report a case of frontal lobe epilepsy secondary to a traumatic head injury. Out of concern for untoward postoperative behavioural change, we employed the IAP in an attempt to predict the risk of a frontal lobe syndrome. A 39 year old man had a 23 year history of severe refractory epilepsy. The seizures postdated a traffic accident at the age of 12 years when he sustained a head injury with an ill defined period of loss of consciousness. Seizures commenced within months of that injury and, although initially well controlled, became refractory within a few years. The seizure types included staring spells, violent tonic-clonic seizures, and tonic drop attacks. He had complications from his epilepsy including a fractured jaw, two episodes of severe burning due to seizures while showering, multiple episodes of postictal confusion and probable postictal psychosis, a lung abscess secondary to aspiration, and episodes of status epilepticus. Interictal EEGs showed bilateral generalised spike and wave discharges at around 2 Hz–5 Hz with some mild increase in bilateral slow activity and no convincing evidence of electrographic focalisation. Video EEG monitoring showed apparent generalised seizure without any focal onset on scalp EEG. Brain MRI disclosed a well defined atrophic lesion involving the left frontal lobe, considered likely to be post-traumatic in origin. Interictal FDG PET and HMPO SPECT disclosed hyperfusion in the left anterior frontal region commensurate with the abnormality shown on MRI. Although his electroclinical pattern was suggestive of symptomatic generalised epilepsy, because of the left frontal lesion, seizure onset from that region was considered likely.

On neuropsychological examination, his general cognitive function was normal. At a behavioural level, however, he presented as very peurile in manner with a very rigid, inflexible cognitive style. The neuropsychological opinion was of a mild frontal lobe syndrome consistent with the history of traumatic head injury. There was no current evidence of psychiatric disorder. Although having successfully passed his final year of secondary school (together with several courses of advanced education), he had remained unemployed due to his seizures. He was socially isolated and his interpersonal relationships were limited.

He had severe life threatening epilepsy with the surgical emphasis being on the remaining aseptic 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 which could not be influenced by the examiner. Despite normal comprehension, he showed severely impaired capacity for motor regulation (go-no go paradigm), together with marked behavioural disinhibition (agitation, swearing, verbosity, childishness). Although seemingly aware of some aspects of his behaviour (apologising for swearing), he seemed unable to control his responses. The overall impression was of a pronounced frontal lobe syndrome, suggesting that the right frontal lobe had incurred some damage secondary to the documented head trauma and that he must have been reliant on some left frontal contribution.

On the basis of the IAP findings, a selective cortical resection (as opposed to more extensive frontal lobe resection) was recommended. At the time of resection, the area of damage was controlled. Intraoperative electrocorticography showed active focal epileptiform 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 performance on neuropsychological evaluation remained commensurate with presurgical status. There were no novel subjective complaints. Mood, behaviour, and temperament remained stable.

Despite its undoubted value in many individual cases of temporal lobe epilepsy, the IAP has remained a controversial assessment instrument.1 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 the 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 superior or inferior frontal or cerebral artery via the anterior communicating artery. When such crossflow is present, the ability to assess validly the integrity of contralateral frontal lobe function will be compromised by virtue of bilateral 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 the potential implications for the selection of patients for frontal lobectomy 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” since 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 not withstanding, the IAP does seem to have a role in separating out those patients in whom more extensive frontal lobe resections could be considered, as 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 the attention of 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 Neurology

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 9496 5913; Fax 613 3 03 9455 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 predominantly characterised by the triad of drowsiness/fatigue, parkinsonism, and depression; depression is found in about 15% of patients treated with TBZ.1 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.2

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 significant impairment of mastication. 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 terfenadine medication (60 mg a day). This successful treatment response, however, was accompanied by a severe depressive syndrome, which was characterized by a mixed major depressive mood, low self esteem, a complete loss of drive, and intermittent suicidal ideations. After switching from TBZ to triadipride, the patient recovered from depression, but her neurological status worsened significantly. After re-exposure to TBZ again ameliorated hyperkinesia, but provoked a depressive relapse. A comedication with tiapride, the patient recovered from depressive ideations. After switching from TBZ to reboxetine, the patient recovered from depression.

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.2


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, ophthalmoscopic manoeuvres. In addition a pathogenetic 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 cervical spinal cord are rare because of its good collateral supply.4 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 hypalgesia and nearly a loss of temperature sense. 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.

Table: Vascular risk factors

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>Present</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Present</td>
</tr>
<tr>
<td>Smoking</td>
<td>Non-smoker</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>Present</td>
</tr>
</tbody>
</table>

Vascular risk factors were present in the patient. In view of the rapid onset of the symptoms, VAD is an important cause of brain infarction. In most cases microtrauma precedes the dissection which can be recalled by the patient. 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.1 Magnetic resonance imaging with typical semilunar mural hematoma and in addition magnetic resonance angiography (MRA) with complementary documentation of an impaired collateral flow or tapering occlusion have a high sensitivity and specificity in cases of internal carotid artery dissection.5 By contrast, mural haematomas of the VA especially in the V1 and the V3 segments are often not detectable by MRA. In cases of unclear non-invasive findings, DSA is still the method of choice.6

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. Cerebral cavernous malformations occur as a sporadic or hereditary condition. From the Hispanic-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

(3) Hundtsberger T, Thömek F, Hopf HC, et al. Symmetrical infarction of the spinal cord due to spontaneous bilateral vertebral artery dissec-

(A) Pedigrees of the nine families with cerebral cavernous malformations. Black symbols= symptomatic patients with cavernous angiomas on MRI; half filled symbols= asymptomatic members with cavernous angiomas on MRI; empty symbols= asymptomatic members with normal MRI; question mark= members with unknown status. (B) Comparison of the Hispanic-American CCM1 haplotype and the haplotypes segregating with the disease phenotype within Spanish families. Polymorphic markers are shown on the left. Numbers indicate the sizes in base pairs. Primers used to amplify D7S2409 were di

(B) Marker Hispanic American CVE2 CVE3 CVE4 CVE10 CVE12 CVE25 CVE28 CVE17 CVE29

- D7S2410 279 273 265 269 265 265 267 263 265 269
- D7S2409 ND 221 219 215 221 219 223 219 223 219
- D7S1813 137 123 127 127 127 127 131 126 127 127
- D7S1789 137 139 133 133 129 131 133 129 129 133
- M65B ND 135 133 133 133 133 139 129 129 133
- D7S564 ND 135 133 133 133 133 133 129 ND 137 133
- D7S566 185 185 185 187 197 193 185 181 187 197 201 197 185
- D7S558 107 107 107 103 107 103 103 103 103 103 103
- D7S568 129 127 126 129 127 127 139 127 125 127 127

autosomal dominant pattern of inheritance (figure A).

Eight paramorphic microsatellite markers spanning the CCM1 interval were selected for linkage analysis. Four were chosen from the Genethon linkage map (D7S2410, D7S2409, D7S546, D7S590), and three from the Cooperative Human Linkage Center (D7S1813, D7S1789, D7S558). The last one (M65B) was identified by SL based on sequencing data of a bacterial artificial chromosome (Genbank HSAC000065; BAC RG085C05). The length of the genetic interval flanked by markers D7S2410 and D7S6869 is 4 centimorgans (cM). Marker distances between D7S2410/D7S2409, D7S1813/D7S558, and D7S6869 have been estimated to be 2.2 cM, and 1.8 cM, respectively.

Oligonucleotide sequences are available through the Genome Data Bank (John Hopkins University, Baltimore). Genotyping and linkage analysis (LINKAGE package version 5.1) were performed as previously described.

Lod scores were calculated in the five families having a sufficient number of potentially informative meioses—that is, CVE1 (eight), CVE4 (16), CVE10 (seven), CVE25 (five), and CVE28 (seven). Lod scores higher than 1 were obtained for three families (CVE3, 4, and 26) for at least one marker. Delta lod score information was available for three markers within family CVE4, lod scores did not reach the level of 3. In family CVE10, lod scores were close to 1 for four markers (D7S2410, D7S1789, D7S558, D7S689). Furthermore, the patients had one asymptomatic sibling with normal MRI inherited the same haplotype from their asymptomatic father. When the data of all examined families were pooled, a maximum combined lod score of 5.92 was obtained for marker D7S2410 at ø=0.

In seven families (CVE2, 3, 4, 10, 24, 25, and 26), all affected members inherited an haplotype that was not shared by their healthy relatives (figure B). In family CVE17, both affected siblings inherited a distinct haplotype from their affected mother. When the data of all examined families were pooled, a maximum combined lod score of 5.92 was obtained for marker D7S2410 at ø=0.

In seven families (CVE2, 3, 4, 10, 24, 25, and 26), all affected members inherited an haplotype that was not shared by their healthy relatives (figure B). In family CVE17, both affected siblings inherited a distinct haplotype from their affected mother. Although the limited size of this family does not allow to formally test for allelic heterogeneity, in family CVE29, the two affected siblings inherited the same haplotypes from their mother and father whose statuses were unknown.

None of the families shared a common haplotype (figure B). In addition, the extended Hispano-American haplotype was not segregating with the disease phenotype in any of the nine families including the four families with suggested linkage to CCM1. However, two out of nine families (CVE2 and 3), the D7S646 (185bp) and D7S558 (107bp) alleles segregating with the disease phenotype were identical to the ones observed in the Hispano-American haplotype. Consequently, we analysed the frequency of this combination of alleles within a panel of 80 haplotypes of 40 healthy white subjects. Frequency was 17% compared with 25% in our Spanish sample. Therefore, this finding might be attributed to a random distribution of these alleles.

In conclusion, linkage analysis of Spanish families with cerebral cavernous malformations did not show any evidence for Hispano-American haplotype sharing or a founder effect. Although our sample was limited in size and does therefore not formally exclude the possibility of a Spanish-Hispanic American haplotype in additional Spanish families with cerebral cavernous malformations, this haplotype is more likely not predominant in Spain, and the strong founder effect seen in all published Hispanic-American families with cerebral cavernous malformations might be specific for this population.

Hydrocephalus caused by metastatic brain lesions: treatment by third ventriculostomy

Metastasis to the brain occurs in 20%-40% of cancer patients. About 20% of these metastases are located in the posterior fossa, cerebellum, and brainstem. Metastatic disease to periventricular brain tissue can obstruct the CSF flow and cause obstructive hydrocephalus. However, the presence of the Hispano-American haplotype sharing or a founder effect could have caused a concomitant communicating hydrocephalus was not grossly evident on examination, of any of the brain images, or during endoscopy. However, tumours in contact with CSF space can also cause a communicating hydrocephalus by raising CSF protein which can obstruct the hydrocephalus, it is only commonly used on the pediatric population. To avoid placing shunts in patients with inoperable metastatic brain tumours, who typically have only a few months to live, we have offered the patients third ventriculostomy as a palliative procedure.

We performed third ventriculostomy on seven patients with hydrocephalus due to metastatic tumours of the posterior fossa or thalamus. They typically presented with symptoms of acute hydrocephalus in addition to any local mass effect of the tumour. Postoperatively, five patients were relieved of hydrocephalic symptoms and follow up brain imaging studies disclosed decreased ventricular size. In these five patients, we had a median hospital time of 6.5 days and median survival of 9 weeks after the operation. The hospital stay was prolonged by care of their primary disease. However, most of our patients who underwent this operation for hydrocephalus caused by other diseases were discharged from the hospital within 48 hours from the procedure. There were no operative complications. All five patients had no evidence of redevelopment of hydrocephalus up to the last clinic visit.

In conclusion, our success rate of about 70% (five of seven) for third ventriculostomy in patients with inoperable metastatic disease was comparable with the ones observed in the Hispano-American population. The third ventriculostomy, a hole is created in the floor of the third ventricle, allowing CSF inside the ventricle to drain out to the CSF space surrounding the brain. Although third ventriculostomy has a low operative morbidity and a high probability of success, it is only commonly used on patients with aqueductal stenosis and the pediatric population. To avoid placing shunts in patients with inoperable metastatic brain tumours who typically have only a few months to live, we have offered the patients third ventriculostomy as a palliative procedure.


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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 treatment of hydrocephalus for patients with an expected shortened life span. We propose that third ventriculostomy should be offered as a first treatment to patients suffering from obstructive hydrocephalus from unresectable tumours.

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

<table>
<thead>
<tr>
<th>Case No</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>Oesophageal 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.

Neuronal 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. Such an interaction between cortical blood flow and tumour blood flow may be of value 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 deoxyhaemoglobin (deoxy-Hb). NIRS is an optical method to measure concentration changes of oxy-Hb, deoxy-Hb, and total-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
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 on the centre of the tumour. With an interoptode distance of 4 cm, correlations of oxy-Hb and total-Hb by NIRS and rCBF by PET suggested that the reliable penetration depth of near infrared light 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) confrontation 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, which entails reading a short descriptive passage aloud. The speech responses of the patient to the tasks were normal.

Figure 2 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. Furthermore, our NIRS activation study using the cognitive tasks showed increases in oxy-Hb and total-Hb in the left frontal lobe in most normal adults—for example, increases in oxy-Hb and total-Hb—were found in 92.3% of young adult subjects (mean SD) 28.8 (4.4) years during the word fluency task (unpublished data). Therefore, although we could not measure the changes in rCBF in the left frontal lobe of the present patient from our previous studies, it strongly suggests that the tasks caused an increase in rCBF in the left frontal lobe of the patient. The decrease in oxy-Hb and total-Hb recorded from the brain tumour indicates a decrease of local blood flow in the tumour because the NIRS measurement area was restricted to the brain tumour. The decreases in oxy-Hb and total-Hb were found only during the tasks; consequently, these changes were probably not due to changes in systemic blood pressure, which can alter tumour blood flow. Based on these assumptions, we suggest that the increase of rCBF in the left frontal lobe induced by the tasks stole the local blood flow of the brain tumour through the cortical branches, leading to the decrease of local blood flow in the tumour. Gay et al. also suggested that activity dependent increase in rCBF can steal blood flow from the adjacent tissues including non-activating cortex. Recent NIRS activation studies have shown that cognitive tasks cause decreases in oxy-Hb and total-Hb in the left frontal lobe in some normal subjects; these decreases indicate a decrease in rCBF. Although the physiological mechanisms of the decrease in rCBF during neuronal activity have not yet been elucidated, we hypothesise that a stealing of blood flow is one of the mechanisms. The present report supports this hypothesis.
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.
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 Sabahan and sub-Sabahan Africa. The leaves are also chewed by members of the Yemeni and Somali community in the United Kingdom. 1 The psychoactive constituents of khat are cathin (d-norisoephedrine), cathine, and cathinone (an alkaloid with a structure resembling norisoephedrine), cathidine, and cathinone. 2

Khat misuse. The leaves are also chewed by a large proportion of the adult population of the Yemen, and throughout Sabahan and sub-Sabahan Africa. The leaves are also chewed by members of the Yemeni and Somali community in the United Kingdom. 1 The psychoactive constituents of khat are cathin (d-norisoephedrine), cathine, and cathinone (an alkaloid with a structure resembling norisoephedrine), cathidine, and cathinone. 2

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blood cells. The densities of large and small endoneurium and epineurium showed slugging of red rounded by mononuclear cell infiltrates were performed. Epineurial vessels were sur-
tibialis muscle. Sural nerve biopsy was neugenic changes, but there were no fibril-
euromyelitis (50 mg/day) with tapering of steroid. He was discharged on prednisolone (20 mg/day). In the subsequent 4 years, he has had mild exac-
taneous avascular neuropathy. Taken together, neuropathy with cold agglutinins may involve immunologically me-
diarized demyelination, microcirculation occlu-
sion, and vasa nervorum vasculitis. The diver-
sity of pathomechanisms may come from the difference target antigens recognised by cold agglutinins. Plasmapheresis proved effective in all 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 re-
command plasmapheresis as first choice treat-
ment for neuropathy associated with cold agglutinins.

We thank Dr Gerard Salazar for critical reading of the manuscript, Ms M Teshima and N Harata 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 Mosgl (Division of Blood Transfusion Medicine, University of Kagoshima) for characterization of cold agglutinin.

R OTSUKA
K ARIMURA
Y MARUYAMA
Y ARIMURA
M OSAME

The Third Department of Internal Medicine,
Kagoshima University School of Medicine,
Sakuragaoka 8–35–1 Kagoshima, Japan
Correspondence to: Dr R Otsuka, The Third
Department of Internal Medicine, Kagoshima
University School of Medicine, Sakuragaoka 8–35–1 Kagoshima, Japan

1 Arai M, Yoshino H, Kusano Y, et al. Ataxic polyneuropathy and anti-Pr2 IgM M pro-
2 Wilisson HJ, Paterson G, Veitch J, et al. Periph-
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clonal IgM cold agglutinins with anti-Pr1d specificity in a patient with peripheral neu-
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(A) Sural nerve (toluidine blue staining) showing epineural vessel surrounded by mononuclear cell infiltrates. Note fibrin deposition (arrows) and necrosis in media. (bar=20 µm). (D) Most of myelinated fibres are undergoing axonal degeneration. Many macrophages containing myelin debris infiltrate the endoneurium. (bar=50 µm).

M-protein, direct and indirect Coombs tests, cryoglobulin, antibodies to mycoplasma, my-
elin associated glycoprotein, gangliosides (GM1, GD1b, asialo-GM1, GT1b, GQ1b, Gal-C), P-ANCA, and C-ANCA. The Csf was normal. Titre of cold agglutinins was detectable at 1:128 at 37°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 agglutinins with 1 specificity. Immunelectrophoresis of the eluate confirmed IgM composition.

The initial nerve conduction study showed severe diminution or absence of compound nerve action potentials (CMAPs) with mildly diminished conduction velocities. F wave latencies were mildly prolonged. There were no evoked sensory nerve action poten-
tials (SNAPs) in median, ulnar, and sural nerves bilaterally. Electromyographic studies of the affected muscles showed moderate neurogenic changes, but there were no fibril-
latory potentials except in the left anterior tibialis muscle. Sural nerve biopsy was per-
formed. Epineurial vessels were sur-
rounded by mononuclear cell infiltrates (figure A). Some vessels had focal necrosis of their wall. The small vessels in the endoneu-
rium and epineurium showed slugging of red blood cells, and densities of large and small myelinated fibres were markedly decreased (diameter<5 µm: 150±8/mm2, diameter >5 µm: 708/mm2, total: 2212/mm2) (figure B). Teased fibre analysis showed that 90% of the 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 titre of cold agglutinins; neither was there any improvement of symptoms. He received mas-
vive dose intravenous corticosteroid therapy. This moderately improved the muscle strength and sensory disturbance. Follow up nerve conduction studies (71 days after the initial study) suggested conduction block of the right median nerve on the forearm (CMAP, dura-
tion at the wrist: 2.76 mV, 8.4 ms; CMAP, duration at the elbow: 1.87 mV, 8.8 ms), whereas CMAP could not be elicited in the initial study. We adapted the following criteria to define conduction block: <15% change in duration and >20% fall in negative peak amplitude between proximal and distal sites by percutaneous supramaximal stimulation of motor nerves. As the conduction block might delay smooth recovery of symptoms, Double filtra-
tion plasmapheresis was performed four times. After the second plasmapheresis, dys-
eaesthesia and muscle strength improved remark-
ably. The titre of cold agglutinins was reduced to 1:64. The motor nerve conduction velocity (MCV) of the right median nerve like-
wise improved (pretreatment; 40.0 m/s, post-
treatment; 57.0 m/s). Double filtration plas-
mapheresis was followed by oral azathioprine (50 mg/day) with tapering of steroid. He was discharged on prednisolone (20 mg/day). In the subsequent 4 years, he has had mild exac-
taneous avascular neuropathy. Taken together, neuropathy with cold agglutinins may involve immunologically me-
diarized demyelination, microcirculation occlu-
sion, and vasa nervorum vasculitis. The diver-
sity of pathomechanisms may come from the difference target antigens recognised by cold agglutinins. Plasmapheresis proved effective in all 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 re-
commend plasmapheresis as first choice treat-
ment for neuropathy associated with cold agglutinins.
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 representatives presenting 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

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 36 week randomised double blind study. I recall mentioning 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, Kisačeva 12, 10000 Zagreb, Croatia.
Telephone 00385 1 217280, fax 00385 1 217280, email tomaslasc.babic@zg.rr.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 contributed 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 consideration 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 emerging from clinical trials to suggest that cholinomimetic drugs 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.4 In particular, a clear link is emerging between psychotic symptoms and cholinergic dysfunction. Thus, Bodick et al have shown that the M2/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 Kauffer have shown that the cholinesterase inhibitor tacrine may be effective in reducing psychotic features than cognitive disturbances; tacrine also reduces or abolishes hallucinations in Parkinson’s disease.5 Another 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 than in patients without this feature. Finally, in animals the partial M2/M4 agonist (3R,6R)-6-(3-propylthio-1,2,5-thiazidol-4-yl)-1-azabicyclo[3.2.1]octane reduces psychotic-like activity with the muscarinic receptor ligand (5R,6R)-(3-propylthio-1,2,5-thiazidol-4-yl)-1-azabicyclo[3.2.1]octane.6

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


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 inappropriately 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 part, 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.


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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 some extent, comprehensive but lack specificity—that is, normal values for simple tests are difficult to find. The huge subject of the diabetic foot is covered in these chapters and “the impact of micro and macrovascular disease” is compressed into the last nine pages of the book. 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 comprehensive reviews and their assembly of the appropriate literature.

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 reference tome. 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 skilfully 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 disorientating in that, for example, History taking in Neurology is to be found at p 151. 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 hype and with a price tag of just £27-50 the book will be welcomed by undergraduates through to specialist registrars.

SIDDHARTHAN CHANDRAN

Readers may be interested in:


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

Focal (segmental) dyshidrosis 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: hypoaldosteronism 0.0007; hypohydrosis v normohydrosis 0.7282; normohydrosis v hypoaldosteronism 0.0012 should read —|p value for each pair of items: hyperaldosteronism v hyperaldosteronism 0.0007; hypoaldosteronism v normohydrosis 0.7282; normohydrosis v hypoaldosteronism 0.0012.
Hydrocephalus caused by metastatic brain lesions: treatment by third ventriculostomy

TIEN T NGUYEN, MARK V SMITH, GERARD S RODZIEWICZ and SHEILA M LEMKE

J Neurol Neurosurg Psychiatry 1999 67: 552-553
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