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 posturgical amnesia and to predict posturgical material specific memory changes. More recently, the use of the IAP has been extended to complement EEG localisation and radiological data by lateralisating temporal lobe dysfunction.

In our series of 36 patients with refractory frontal lobe epilepsy being considered for frontobiblocotomy for intractable seizures, we have hitherto been unable to confirm a role for the IAP in predicting the risk of frontal lobe compromise, as is commonly reported in the literature. In our experience, the IAP is an unreliable predictor of the presence or extent of damage to the bilateral frontal lobes and provides no useful information about the integrity of the contralesional frontal lobe. The IAP and related procedures often have potential implications for the selection of patients for frontobiblocotomy.

We report a case of frontal lobe epilepsy secondary to a traumatic head injury. 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 road 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 fracture of the left frontal bone and he was considered likely to be post-traumatic in origin. Interictal FDG PET and HMlO 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 status 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 outcome being the remaining severely disabled individual. 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 (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 (as assessed by a separate injection of contrast medium). 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 modify his responses. The overall impression was of a pronounced fronto 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 corticotomy (as opposed to more extensive frontal lobe resection), 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 modify his responses. The overall impression was of a pronounced fronto 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.

Despite his undoubtedly valuable 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 irradiation 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 cross-flooding into the anterior communicating artery. When such crossflow is present, the ability to assess validly the integrity of contralateral frontal lobe function will be compromised 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 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 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 03 3 03 9496 5913; Fax 03 3 03 9457 2654.


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

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.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 considerable inconvenience. 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 characterised 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 after re-exposure to TBZ again ameliorated hyperkinesia, but provoked a depressive relapse. A comedication with reboxetine (6 mg/day), a new and selective noradrenaline reuptake inhibitor (SNRI) reboxetine, may thus provide a new, specific, and potent antidepressive treatment for patients suffering from TBZ induced depressive symptoms.3


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 micro-trauma due to abrupt head movements for example, by chiropractic 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 compensation 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 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.

Tibial nerve somatosensory evoked potentials (SSEPs) 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 threecervical 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 (ACA) and the vertebroarterial arteries (V4 segment) 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 atheromatous 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 V3 segments are often not detectable by MRI. In cases of unclear non-invasive findings, DSA is still the method of choice.8

In addition to consecutive brain infarctions, spinal cervical 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-

Coronal T2 weighted MRI: centrolateral paramedian right sided medulillary infarction.
American descent with a strong founder effect. Around 50% of non-Hispano-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 families 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


Spanish families with cavernous angiomas do not share the Hispano-American CCM1 haplotype

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 Hispano-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 Hispano-

(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 Hispano-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 different from those in the Hispano-American families resulting in a different size of the amplified fragment. M65B was not studied in the Hispanic-American families. Family CVE24 was not informative for D7S646. For families CVE17 and CVE29, the two haplotypes of the affected siblings are indicated. ND=not determined.
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 flow of cerebrospinal fluid (CSF) produced in the ventricles to the subarachnoid space. This typically causes an obstructive or non-communication hydrocephalus 11 days later. After 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. Although previous radiotherapy may have had some effect on the tumour, it has not precluded recurrence. In the presence of a large tumour mass, which has a first year revision rate as high as 10.1136/jnnp.67.4.550a on 1 October 1998. Downloaded from http://jnnp.bmj.com/ J Neurol Neurosurg Psychiatry: first published as 10.1136/jnnp.67.4.550a on 1 October 1998. Downloaded from
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 activation 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 (4x5 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

---

**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 metastases to cerebellum</td>
<td>Failed</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>5</td>
<td>39, F</td>
<td>Breast adenocarcinoma metastases 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.

---

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; and (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 adult subjects (mean (SD) 28.8 (4.4) years) during the cognitive tasks.3–5 We monitored concentration changes in rCBF in the left frontal lobe induced by the tasks stole 25%–30% of the increase in systemic blood pressure, which can alter tumour blood flow.4 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. Indeed, our rCBF study suggests that attention 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 normal subjects1; 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 hypothesised that a stealing of blood flow is one of the mechanisms.6 The present report supports this hypothesis.

KAORU SAKATANI
HUAONG ZOU
YENG WANG
Department of Neurosurgery, China-Japan Friendship Hospital, Beijing, China

WEMARA LICHTY
Group of Detection and Analysis of Human Body Movement, Program of BME, Department of Electrical Engineering, Yntong University, Japan

KIYOMI YABU
Department of Rehabilitation, Tokai University Hospital, Japan

Correspondence to: Dr Kaoru Sakatani, Department of Neurosurgery, China-Japan Friendship Hospital, Yntong University East Rd., Heping, Beijing 100029, People’s Republic of China. Telephone: fax: 0086 10 64203246; email sakatani@public.east.cn.net

2 Fox PT, Maldjian JA, Peltier F. Near infrared spectroscopy (NIRS)-correlation with simultaneous feline rCBF-PET measurements. Brain Res 1997;758:293–305.

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, aura is preceded by an aura.1 We describe a patient with recurrent episodes of migraine in whom headache was preceded by a constellation of visual symptoms, consisting of a triad of simultagnosia, optic ataxia, and oculomotor apraxia.1 This syndrome, consisting of a triad of simultagnosia, optic ataxia, and oculomotor apraxia, is seen with bilateral lesions of occipitoparietal cortices.2–4 The presentation of a patient with simultaneous features of Balint’s syndrome requires a high index of suspicion to make the diagnosis.3,4 We describe a patient with simultagnosia as a unique presentation of migraine aura.

The visual symptom complex in this case is suggested that a stealing of blood flow is one of the mechanisms of the decrease in rCBF. The present report supports this hypothesis.

KAORU SAKATANI
HUAONG ZOU
YENG WANG
Department of Neurosurgery, China-Japan Friendship Hospital, Beijing, China

WEMARA LICHTY
Group of Detection and Analysis of Human Body Movement, Program of BME, Department of Electrical Engineering, Yntong University, Japan

KIYOMI YABU
Department of Rehabilitation, Tokai University Hospital, Japan

Correspondence to: Dr Kaoru Sakatani, Department of Neurosurgery, China-Japan Friendship Hospital, Yntong University East Rd., Heping, Beijing 100029, People’s Republic of China. Telephone: fax: 0086 10 64203246; email sakatani@public.east.cn.net

2 Fox PT, Maldjian JA, Peltier F. Near infrared spectroscopy (NIRS)-correlation with simultaneous feline rCBF-PET measurements. Brain Res 1997;758:293–305.

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, aura is preceded by an aura.1 We describe a patient with recurrent episodes of migraine in whom headache was preceded by a constellation of visual symptoms, consisting of a triad of simultagnosia, optic ataxia, and oculomotor apraxia.1 This syndrome, consisting of a triad of simultagnosia, optic ataxia, and oculomotor apraxia, is seen with bilateral lesions of occipitoparietal cortices.2–4 The presentation of a patient with simultaneous features of Balint’s syndrome requires a high index of suspicion to make the diagnosis.3,4 We describe a patient with simultagnosia as a unique presentation of migraine aura.
involved visual association areas and their association pathways, optic ataxia, gaze apraxia, and simultagnosia seem to represent a dissociation of visual information from the frontal eye field and dorsal parietal regions.

PARVAIZ A SHAH
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, Firdousa-

“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 regimen of suckling mouse brain postrabies exposure vaccine (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 diseases 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 neurocystercerosis were negative. The CSF culture showed no evidence of bacterial growth. 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 Saharan and sub-Saharan Africa. The leaves are also chewed by members of the Yemeni and Somali communities in the United Kingdom. The psychoactive constituents of khat are cathin (an alkaloid with a structure resembling norisoeephedrine), cathidine, and cathinone (an enantiomer of both the cerebral hemispheres with marked cortical atrophy. Brain biopsy (via right frontal craniotomy) was performed 3 months after the 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 plantar reflexes are flexor but he has persistent grasp and palmo-mental reflexes. His nutrition is maintained by gastrostomy and he has a 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. An alternative for this man's presentation is a necrotising vasculitis, a well described complication of oral amphetamine misuse. The clinical features, MRI appearance, 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.

References


Necrotising vasculitis with conduction block in mononeuropathy multiplex with cold agglutinins

Cold agglutinins are cold reactive autoanti-bodies that have haemolytic effects on red blood cells mediated via complement fixation. Mononeuropathy 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 any other evidence of vasculitis. Cranial nerves and the cerebellum were not involved. There was severe weakness and atrophy of bilateral thenar, interossei, and planar 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 CSF was normal. Titre of cold agglutinins was detectable at 1:128 at 4°C, and 1:256 at 37°C. 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. Immunoelectrophoresis of the eluate confirmed IgM composition.

The initial nerve conduction study showed severe diminution or absence of compound muscle action potentials (CMAPs) with marked diminution of compound motor action potentials (CMAPs) with mildly diminished conduction velocities. F wave 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 or sensory loss in the affected muscles. 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 sloughing of red blood cells. Densities of large and myelinated fibres were markedly decreased (diameter<5 µm: 150/4 mm², diameter >5 µm/708/µm², total: 2212/µm²) (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 massive 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, duration 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 filtration plasmapheresis was performed four times. After the second plasmapheresis, dysaesthesia and muscle strength improved remarkably. The titre of cold agglutinins was reduced to 1:64. The motor nerve conduction velocity (MCV) of the right median nerve was mildly improved (pretreatment: 40.0 m/s, post-treatment: 57.0 m/s). Double filtration plasmapheresis was performed 14 times a day with 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 exacerbation of dysaesthesia that responded to intermittent steroid therapy.

Characteristic features of the present case are as follows: (1) subacute onset of mononeuropathy multiplex; (2) necrotising vasculitis with marked fibre loss; (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 were 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 determinants of red cells. Cold agglutinins (CA) are monotypic antibodies that react with sialosyl paragloboside, GT1b, GD1a, GD1b, GM3, and GD3 present in glycoproteins and glycolipids in erythrocyte membranes. Arai 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 in 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 sluggish or agglutination of red blood cells in the vasa nervorum; and (3) an 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 immune 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 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 characterization of cold agglutinin.

R OTSUKA
FUKUHARA
K ARIMURA
Y MARUYAMA
Y ARIMURA
M OSAME

The Third Department of Internal Medicine, Kagoshima University School of Medicine, Kagoshima, Japan

Correspondence to: Dr R Otsuka, The Third Department of Internal Medicine, Kagoshima University School of Medicine, Sakuragaoka 8–35–1 Kagoshima, Japan. Telephone 0081 99 275 5332; fax 0081 99 265 7164; email reika@med4.kufm.kagoshima-u.ac.jp

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. 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 presenting data from a clinical study 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. 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 32 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 blind placebo phase.

The authors reply:
We thank Professor Babic for the letter, which brings 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 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. In particular, a clear link is emerging between psychotic symptoms and cholinergic dysfunction. Thus, Bodick et al have shown that the M4 agonist, oxanthine, causes a dose dependent reduction in hallucinations, agitation, and delusions in 6 month randomised double blind placebo controlled, parallel group trial. In addition, Cummings and Kauf er have shown that the cholinesterase inhibitor tacrine is effective in reducing psychotic features than cognitive disturbances; tacrine also reduces or abolishes hallucinations in Parkinson's disease. 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 healthy controls without this feature. Finally, in animals the partial M4, agonist (5R,6R)-6-(3-propylthio-1,2,5-thiadiazol-4-yl)-1-azabicyclo[3.2.1]octane has shown that the M4 agonist, (-3-propylthio-1,2,5-thiadiazol-4-yl)-1-azabicyclo[3.2.1]octane produced a preclinical profile suggestive of antipsychotic efficacy and that the psychometic NMDA receptor antagonist ketamine (when administered at subanesthetic doses) reduced brain concentrations of acetylcholine. 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 correspondence for providing us with the opportunity to clarify these points.

The authors:

T BABIC
Department of Neurology, Medical School University of Zagreb, Klirovice 12, Zagreb, Croatia. Telephone 00385 1 217280, fax 00385 1 217280, email tomaslan.babic@zg.htz.hr


BOOK REVIEWS


The neuropathies of diabetes are common (as the chapters in this book repeatedly remind us) and can be very disappointment. Symptomless neuropathy underlies foot ulceration and sepsis as the commonest clinical consequence of diabetic neuropathy but it is not true that all unpleasant disorders range from exceptionally severe pain to the whole range of problems resulting from autonomy failure. This book comprehensively covers every aspect of the subject, systematically (and at times exhaustively) from its epidemiology and pathogenesis (exhaustively) 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. As regards 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—aspect 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 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 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 Zernor’s encephalometer more than a century ago. Just as the solution to the mariners’ problem takes its name, neuronavigation (“the surgeon’s sextant”) has relied on the advent of new technologies to provide solutions to an old puzzle.

Advances In Neuronavigation begins by tracing 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/MR 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 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 MACPHELANE


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 style 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 distil 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 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 grubs 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:


CORRECTION

K Sudo, N Fujiki, S Tsuji, M Aijki, T Higashi, M Niiho, S Kikuchi, F Moriwaka, K Tashiro.

Focal (segmental) dysthidrosis 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 normohydrosis 0.0007; hypohydrosis v normohydrosis 0.7282; normohydrosis v hypohydrosis 0.0012 should read—¶p value for each pair of items: hyperhidrosis v hypohydrosis 0.0007; hypohydrosis v normohydrosis 0.7282; normohydrosis v hypohydrosis 0.0012.