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,1 to assess the risk of severe postsurgical amnestic adverse effects,2 to predict postsurgical material specific memory changes.3 More recently, the use of the IAP has been extended to complement EEG localisation and radiological data by lateralising temporal lobe dysfunction.4

The primary role of the IAP is a hitherto unrecognised role in patients with refractory frontal lobe epilepsy being considered for frontal lobectomy. Specifically, observation of behavioural function during the period of the ablation may provide useful information about the integrity of the contralateral frontal lobe. This is particularly relevant in those candidates with a history of cerebral trauma in whom damage to the bifrontal lobe is known or suspected. A review of the IAP studies 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 head injury in an 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 seizures types included staring spells, violent tonic-clonic seizures, and tonic drop attacks. He had complications from his epilepsy including a fracture of the 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 EEG recordings 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 seizures without any focal onset on scalp EEG. Brain MRI disclosed a well defined atrophic lesion involving the left inferior 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 cognizance and performance were normal. At a behavioural level, however, he presented as very peevish 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 evaluation including continuous monitors and 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 involvement, a left hemispheric IAP was performed. Sodium amytal (125 mg) was administered via a slow hand injection. Of relevance, no crossflow into the contralateral cerebral artery via the anterior communicating artery was evident (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 (for example, speech output), 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 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 lobectomy) was advised. Intraoperative electrocortigraphy showed active focal epileptic discharges maximal in the inferior frontal lobe of the operated hemisphere. 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.1,5 This controversy is potentially useful 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 “disable” 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 hemisphere via the anterior 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 its 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 these factors and their potential impact on issues of behavioural regulation would seem most useful.

It should be borne in mind that the degree of frontal lobe dysfunction induced by the IAP represents the “worst case scenario” as the entire frontal lobe is included in the ablation.

There are likely to be few surgical scenarios in which a comparable extensive resection of tissue is likely to be considered, and results must be interpreted in this context. This limitation notwithstanding, the IAP does seem to have a role in separating out those patients in whom more extensive frontal lobe resections could 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 Neuropsychology
SAMUEL F BERKOVIC
Department of Neurology, Austin and Repatriation Medical Centre, Melbourne, Australia; and Department of Medicine, University of Melbourne, Grattan Street, Parkville 3052, Australia.

Correspondence to: Dr Marie F O’Shea, Department of Neuropsychology, Austin and Repatriation Medical Centre (Austin Campus), Studley Road, Heidelberg, Victoria 3084, Australia. Telephone 613 3 03 9496 5913; Fax 613 3 03 9455 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. We here report on the rapid onset of depressive symptoms in a patient treated with TBZ for orofacial dystonia by administering the new and highly selective noradrenaline (norepinephrine) reuptake inhibitor (SNRI) reboxetine. On admission, the 64-year-old woman presented with perioral and lingual hyperkineties as well as intermittent and involuntary movements of her lower jaw, which had lasted for about two years, causing her considerable impairment with respect to articulation. No history of neuroleptic treatment or Parkinson's disease was evident. Her cranial CT and blood chemistry were normal. We diagnosed a segmental dystonia, which improved dramatically after a tetrabenazine medication (60 mg a day). This successful treatment response, however, was accompanied by a severe depressive syndrome, which was ameliorated by a mixed anxiolytic-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 her exposure to TBZ again ameliorated hyperkineties, but provoked a depressive relapse. A comedication with reboxetine (6 mg/day), a new and selective noradrenaline reuptake inhibitor, finally led to a stable remission of the depressive symptoms within a week, without any worsening of the dystonic syndrome. Tetrabenazine (TBZ) is known to act as a mixed-acting serotonin and dopamine receptor blocking drug. In more detail, TBZ binds to and inhibits specifically the human vesicular monoamine transporter isoform 2 (hVMAT2). Whereas the indolamine serotonin forms a similar affinity for both hVMAT1 and hVMAT2, catecholamines such as noradrenaline exhibit a threefold higher affinity for hVMAT2. As these specific transporters are responsible for packaging monoamine neurotransmitters into presynaptic secretory vesicles for release by exocytosis, the inhibition of hVMAT2 by compounds such as tetrabenazine thus results in consecutive noradrenaline depletion. Alterations of noradrenergic neurotransmission—that is, a neuronal noradrenaline depletion—can therefore be postulated to form one major origin of TBZ induced depression. In line with this assumption, brain-specific catecholaminergic activity enhancers (CAEs) such as phenylethylamine have been shown to antagonise TBZ induced depression-like behaviour in rats. Modulating this altered noradrenergic neurotransmission pattern by the administration of selective noradrenaline reuptake inhibitors such as reboxetine may thus provide a new, specific, and fast acting tool in the management of depression caused by TBZ and related (neuroleptic) compounds.

WOLFGANG SCHREIBER
JURGEN-CHRISTIAN KRIGE
Department of Psychiatry and Psychotherapy, Philipps-University, Rudolf-Bultmann-Straße 8, D-35035 Marburg/Lahn, Germany

TOBIAS EICHHORN
Department of Neurology, Philipps-University, Rudolf-Bultmann-Straße 8, D-35035 Marburg/Lahn, Germany

Correspondence to: Dr Wolfgang Schreiber, Department of Psychiatry and Psychotherapy, Philipps-University, Rudolf-Bultmann-Straße 8, D-35035 Marburg/Lahn, Germany. Telephone 0049 6421 286277; profile 0049 6421 285229; email schreibe@mailer.uni-marburg.de


Spinal sulcal artery syndrome due to spontaneous bilateral vertebral artery dissection

In young adults vertebral artery dissection (VAD) is an important cause of brain infarction. A known mechanism is microtrauma due to abrupt head movements for example, chiropractic manoeuvres. In addition a pathogenic role of connective tissue diseases, cystic media necrosis, fibromuscular dysplasia, migraine, and inflammatory diseases has been postulated. 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. Lesions of the cervical spinal cord are rare because of its good collateral supply. 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) of transcranial magnetic stimulation was prolonged to the right abductor digitii 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 thyrroeccrinal trunk (cervical ascendent artery) and the costovertebral 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 (Spinal Sulcal Artery Syndrome (VAD)) are 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.2 Magnetic resonance imaging with typical semilunar mural haematoma and in addition magnetic resonance angiography (MRA) with complementary detection of an irregularity of a vessel wall or trapping occlusion have a high sensitivity and specificity in cases of internal carotid artery dissection.2 By contrast, mural haematoma of the VA especially in the V1 and the V3 segments are often not detectable by MRI. In cases of unclear non-invasive findings, DSA is still the method of choice.1

In addition to consecutive brain infarctions, cervical spinal cord infarctions and nerve root compression syndromes may occur in cases of unilateral or bilateral VAD. Probably as a result of the pial collateral network and the dual posterior spinal artery, spi-
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 members had MRI diagnosis of cavernomas and were considered as affected. Among them, 14 experienced neurological symptoms (cerebral haemage 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

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### 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-Amercian genetic 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.

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autosomal dominant pattern of inheritance (figure A).

Eight polymorphic microsatellite markers spanning the CCM1 interval were selected for linkage analysis. Four were chosen from the Genethon linkage map (D7S2410, D7S2409, D7S2140, and D7S1850), 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 (BAC) library. The length of the genetic interval flanked by markers D7S2410 and D7S6869 is 4 centimorgans (cM). Marker distances between D7S2410/D7S2409, D7S1813/D7S1789, and D7S6869 have been estimated to be 2.2 cM, and 1.8 cM, respectively.1 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.2

Lod scores were calculated in the five families having a sufficient number of potential informative meioses—that is, CVE3 (eight), CVE4 (16), CVE10 (seven), CVE25 (five), and CVE8 (seven). Lod scores higher than 1 were obtained for three families (CVE3, 4, and 25) for at least one marker. Due to incomplete informativity of 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). In family CVE25, the patients had a lod score close to 0 to 1 for all markers. In this family, two affected and one asymptomatic sibling with normal standard MRI inherited the same haplotype from their affected father. When the data of all examined families were pooled, a maximum combined lod score of 5.92 was obtained for marker D7S2410 at θ=0.

In seven families (CVE2, 3, 4, 10, 24, 25, and 28), 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 θ=0.

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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.

Neuronal activity alters local blood flow in brain tumour adjacent to the activating cortex. 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.

**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 adenosquamous carcinoma metastasis to thalamus</td>
<td>Improved</td>
<td>17</td>
<td>4</td>
</tr>
<tr>
<td>2</td>
<td>46, F</td>
<td>Ovarian adenosquamous carcinoma 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.
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 (1300 nm) in 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, 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 92.5% 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, our NIRS activations strongly suggests that the tasks caused an increase in rCBF in the left frontal lobe of the patient.

During the task, a 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. We also 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. Therefore, the present report suggests that activity-dependent increase in rCBF can steal blood flow from the adjacent tissues including non-activated 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.

KAORU SAKATANI
HUANONG ZOU
Department of Neurosurgery, China-Japan Friendship Hospital, Beijing, China

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

KIYOMI YABU
Department of Rehabilitation, Takahashi Neurosurgical Hospital, Japan

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


Migraine aura masquerading as Balint’s syndrome

Migraine is a common neurological disorder with a prevalence of 0.5% to 2% in the general population. In one fourth of total migraineurs, headache is preceded by an aura. We describe a patient with recurrent episodes of migraine in whom headache was preceded by a constellation of visual symptomatology which constituted salient components of Balint’s syndrome.

A 29 year old female teacher presented with an 8 year history of paroxysmal alternating hemiparesis and throbbing headache. At times she was able to see the component parts of objects under direct visual guidance. However, she could not see the component parts of objects in the visual field. Occasionally these visual symptoms were not followed by headache. The patient would not lose contact with the environment during or after the visual symptoms. Her mother and two younger sisters were also having paroxysmal episodes of common migraine.

Her general physical and neurological examination in between the episodes was unremarkable. Neurological examination during the aura symptoms disclosed that she was unable to see simultaneously all the objects in the visual field (simultanagnosia). She did omit several words while reading a paragraph. However, she could comprehend and read each and every word individually. On being shown a complex picture comprising multiple subunits she was not able to comprehend and perceive the entire picture but was able to perceive the individual parts of the picture individually (seeing in piecemeal). These aforementioned features were consistent with simultanagnosia. Besides simultanagnosia, she had optic ataxia as evidenced by her inability to coordinate hand and eye movements. Optic ataxia was tested as follows: each eye was tested separately and the hand ipsilateral to the eye being tested was used. The target stimulus was a 5 mm long pin with a width of 2 mm. When the pin was touched to a preselected location the patient was asked to touch this pin with her index finger without shifting her gaze from the fixation point. The patient had difficulty in performing this test but had no problem in reaching out to her own body parts or an auditory stimulus with her eyes closed. These features were consistent with optic ataxia. Moreover, gaze apraxia was evident by her inability to look at an object on command. However, she could do it spontaneously. In addition, she had impaired smooth pursuit and voluntary saccades in all directions. Reflex eye movements were normal. Visual acuity during the episode was 6/6 bilaterally. Visual field was normal during the episode as demonstrated by the confrontation method. Ophthalmological examination, including perimetry performed during a symptom free period, was normal. There was no clinical evidence of Gerstmann syndrome, prosopagnosia, object agnosia, or colour agnosia. Her cranial CT and magnetic resonance angiography were unremarkable.

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

The visual symptom complex in this case possibly represents an aura of migraine. The pathogenesis of migraine aura has been a debatable issue. In this case it is suggested that the pathophysiological process of migraine aura results in a disconnection syndrome by...
Correspondence to: Dr Parvaiz A Shah, Firdousa-haemorrhage or mass e


easymmetric, and showed no evidence of lesions were bilateral, widely distributed, in the right hemisphere (figure A). These variably sized changes in the basal ganglion and right cerebellum were seen. The MRI also showed extensive cystic-like changes in the white matter, and cystic-like changes in the white matter, and cystic-like changes in the white matter. Bilateral subcortical and periventricular lesions are seen. (B) Brain MRI in July 1997, 12 weeks after the onset of symptoms. A 26-year-old man was admitted to hospital with a history of headache, fever, and generalized weakness. On examination, he was found to have a Glasgow coma score of 3. The patient was treated with a 7-day course of staphylococcal meningitis and a 7-day course of aminoglycoside antibiotics. The patient was discharged home in good condition. The patient was followed up for 6 months and showed no evidence of disease. The patient was admitted to hospital with a history of headache, fever, and generalized weakness. On examination, he was found to have a Glasgow coma score of 3. The patient was treated with a 7-day course of staphylococcal meningitis and a 7-day course of aminoglycoside antibiotics. The patient was discharged home in good condition. The patient was followed up for 6 months and showed no evidence of disease.

There are three types of postexposure vaccine in use worldwide. The Simple type (STV) is obtained from inactivated virus prepared on adult animal nerve tissue; it is inexpensive and relatively easy to produce. In India 3 million people receive postexposure courses of STV (phenolised sheep brain) antirabies vaccine each year. These produce neurological reactions, including postvaccination encephalomyelitis, in up to 1 in 200 courses, with a 3% mortality. Clinical forms include a reversible mononeuritis multiplex, and meningoencephalitis and encephalomyelitis reactions. Myelin basic protein and related neural proteins from the nervous tissue of the animal on which the virus was cultivated stimulate an autoimmune reaction in the human nervous system.

Paralytic rabies could not be excluded in this patient and hence steroids were not used initially. Steroids have been reported to increase mortality in experimental animals with rabies, and it has been suggested that they may abrogate the immune response to the postexposure vaccine, thus precipitating uncontrollable rabies.

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Khat misuse

The psychoactive constituents of khat are cathinone (d-norepinephrine), cathine, and cathinone (an alkaloid similar to ephedrine and amphetamine) and users report a mild euphoria similar to that of amphetamine. Khat is acknowledged as a precipitant of psychosis and has also been reported to cause cognitive impairment. We report a case in which khat chewing has been associated with a severe and disabling neurological illness.

A 56-year-old Somali living in the United Kingdom for the past 18 years was admitted to a psychiatric hospital with a 5-week history of progressive confusion and agitation. His family reported that he had been chewing khat, in their opinion to excess, every day during that time but had stopped 2 days before admission. There was one previous admission to hospital 9 months previously with khat-induced psychosis, from which he recovered without complications within 24 hours. On this occasion, shortly after admission, his conscious level deteriorated abruptly and he was referred for neurological opinion. He was apyrexial and there were no cells. His initial EEG was abnormal with marked slow waves indicative of widespread cerebral dysfunction. A chest radiograph and ultrasound examination of the abdomen were normal. Cranial MRI, although contaminated by movement artefact, showed diffuse abnormality in the deep cerebral white matter of both cerebral hemispheres. Fourteen days after admission he was witnessed to have a single brief adverse seizure with eye and head deviation to the right.

The patient was admitted to a rehabilitation unit. His mini mental state examination score and Barthel scores were zero. Feeding by percutaneous gastrostomy was started. A trial of intravenous methylprednisolone (1 g on 3 consecutive days) gave no benefit. Repeated EEGs (on four occasions) showed diffuse slow waves only. A second MRI (figure) 3 months after onset of symptoms showed the presence of a continuing diffuse extensive abnormality in the deep white matter of both cerebral hemispheres with marked cortical atrophy. Brain biopsy (via right frontotriangular 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 plantars are flexor but he has persistent use slow waves only. A second MRI, however, showed complex MRI appearances of both cerebral hemispheres. There were no new areas of abnormality. There was no evidence of acute inflammation, vasculitis, or infarction.

The clinical presentation, EEG, and MRI findings suggest a rapid progression of leukoencephalopathy. There are no previous reports of leukoencephalopathy in association with khat or amphetamine misuse; it has, however, been reported in association with other recreational drugs taken by mouth or inhalation. 1 An alternative for this man’s presentation is a necrotising vasculitis, a well-described complication of oral amphetamine misuse. 2 The clinical features, 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.

13 Swadwirudhipong W, Prayoonwiwat N, Kunsol P, et al. A high incidence of neurological complications with khat chewing: Simple and complex epilepsies, stroke, viral serology, and malaria screen all gave normal results. Tests for HIV antibody, serum angiotensin converting enzyme, white cell enzymes, and serum and urinary porphyryins were negative. Erythrocyte sedimentation rate on admission was 58 mm/h.

Examination of the CSF showed normal opening pressure; sugar 2.7 g/l, glucose 4.3 mmol/l (blood glucose 6.1 mmol/l), and no cells. His initial EEG was abnormal with diffuse slow waves indicative of widespread cerebral dysfunction. A chest radiograph and ultrasound examination of the abdomen were normal. Cranial MRI, although contaminated by movement artefact, showed diffuse abnormality in the deep cerebral white matter of both cerebral hemispheres. Fourteen days after admission he was witnessed to have a single brief adverse seizure with eye and head deviation to the right.

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

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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 detected at 1:1024 at 4°C (normal <1:256). The patient’s serum agglutinated adult group O-red blood cells, but not O-red blood cells or human cord red blood cells, signifying cold agglutinins with 1 specificity. Immunelectrophoresis of the eluate confirmed IgM composition.

The initial nerve conduction study showed severe diminution or absence of compound motor 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 confirmed mild neurogenic changes, but there were no fibrillating potentials except in the left anterior tibialis muscle. Sural nerve biopsy was performed. Epineurial vessels were surrounded by mononuclear cell infiltrates (figure A). Some vessels had focal necrosis of endoneurium. (bar=30 µm). (A) Sural nerve (toluidine blue staining) showing epineurial vessel surrounded by mononuclear cell infiltrates. Note fibrin deposition (arrow) and necrosis (50 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 macrophages and eosinophils; (3) probable conduction block in the median nerve; (4) increased concentrations of serum titres of cold agglutinin; and (5) marked response to plasmapheresis. Extensive investigation for other causes of neuropathy was negative except for an increased serum concentration of cold agglutinins, which strongly suggests that cold agglutinins may play an important part in the induction of neuropathy in this case.

Six patients with neuropathy associated with cold agglutinins have been reported including our patient. Cold agglutinins are cold reactive autoantibodies that react with the antigenic determinant termed Pr present on glycoproteins and glycolipids in erythrocyte membranes. Ari et al reported a case of polyneuropathy and IgM M proteinemia with anti-Pr2 IgM cold agglutinin reacting 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 neuronal 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 slugging 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 immunemediated 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, F UMEHARA, 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

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 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 36 week randomised double blind study, as mentioned in the review. The authors are probably referring to the randomised 24 week double blind placebo controlled trial with an additional 6 week single blinded placebo phase.

T BABIC
Department of Neurology, Medical School University of Zagreb, Klišina cesta 12, 10000 Zagreb, Croatia.
Telephone 00385 1 217280, fax 00385 1 217280, email tommabes.babic@crg.hr


The authors reply:
We thank Professor Babic for the letter, which raises several interesting points. We agree that it may be more helpful to put the results attributed to treatment with donepezil in the context of the placebo response. In general, looking at this as a class effect in relation to several compounds, the picture emerging is that about twice as many people obtain a response to active treatment as to that with placebo. The high placebo response is a common factor in most studies in this field and is worthy of some exploration 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 in support of clinical trials to suggest that cholinomimetic drugs act 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 M1/M2 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 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 with hallucinations than in patients without this feature. Finally, in animals the partial M1/M2 agonist (3R,6R)-6-(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 psychomimetic NMDA receptor antagonist ketamine (when administered at subanaesthetic doses) reduced brain concentrations of acetylcholine and pyridine from postmortem data showing that the activity of choline acetyltransferase in the temporal cortex of patients with Lewy body dementia was lower in those patients with hallucinations than in patients without this feature.

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 blinded treatment phase.

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

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

ALAN M PALMER
MICHAEL SNAPI
Cerebrus Pharmaceuticals Ltd, Wimersh, Wiltshire, RG41 3SU, UK

GORDON K WILCOCK
Department of Care of the Elderly, Frimley Hospital, Bracknell, RG14 2EW, UK

BOOK REVIEWS


The neuropathies of diabetes are common (as the chapters in this book repeatedly remind us) and can be very disagreeable. Symptomless neuropathy underlies foot ulceration and sepsis as the commonest clinical consequence of diabetic neuropathy but other extremely 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 (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, in part, I would suggest, 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—for 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.


Letters, Correspondence, Book reviews, Correction

Downloaded from http://jnnp.bmj.com/ on November 9, 2017 - Published by group.bmj.com
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 title and back cover of the latest addition to Neurology later 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 131. Similarly, the absence of diagrams and tables is an unexpected omission as I would imagine that this would have complemented the overall style of the book. These are minor gripes of what in print largely matches the sleeve 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 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: hyperhydrosis v normohydrosis 0.0007; hypohydrosis v normohydrosis 0.7282; normohydrosis v hypohydrosis 0.0012 should read—p value for each pair of items: hyperhydrosis v hyperhydrosis 0.0007; hypohydrosis v hypohydrosis 0.0007; normohydrosis v normohydrosis 0.7282; normohydrosis v hypohydrosis 0.0012.
Migraine aura masquerading as Balint’s syndrome

PARVAIZ A SHAH and A NAFEE

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