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

We report a case of frontal lobe epilepsy in our comprehensive epilepsy programme (1991–8) that suggests 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 a car 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 atonic drop attacks. He had comorbid psychiatric illness including a history of postictal confusion and probable postictal seizures, and atonic drop attacks. He had comorbid staring spells, violent tonic-clonic seizures, and atonic drop attacks. He had comorbid staring spells, violent tonic-clonic seizures, and atonic drop attacks.

He-2.5 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 hemisphere that was considered likely to be post-traumatic in origin. Interictal FDG PET and HMPO SPECT disclosed hyperfusion in the left anterior frontal region commensurate with the abnormality shown on MRI. Although his electroclinical pattern was suggestive of symptomatic generalised epilepsy, because of the left frontal lesion, seizure onset from that region was considered likely. On neuropsychological examination, his general cognitive functioning 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 one of mild left frontal 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 consent proceeding against the advice of treatment. However, as surgical management would involve resection of the left frontal lobe against a background of traumatic head injury and the possibility of more generalised frontal lobe impairment, 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 (goal directed movements), together with marked behavioural disinhibition (agitation, swearing, verbosity, childishness). Although seemingly aware of some aspects of his behaviour (apologising for swearing), he seemed unable to control these 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 recommended to the region of damage was advised. Intraoperative electrocorticography showed active focal epileptiform discharges maximal in the inferior frontal lobe in the electrodes closest to the lesion. A cortical resection was performed with frameless stereotaxy guidance excision of the frontal lobe. Histopathology on the resected tissue showed an old post-traumatic cyst involving the cortex and white matter. His postoperative course was unremarkable. When reviewed 3 months after surgery he was seizure free. His performance on neuropsychological evaluation remained commensurate with presurgical status. There were no novel subjective complaints. Mood, behaviour, and temperament remained stable.

Despite its undoubted value in many individual cases of temporal lobe epilepsy, the IAP has remained a controversial assessment instrument.1 Amid this controversy its potential usefulness in other patient groups seems to have been overlooked. A primary criticism of its use in temporal lobe epilepsy has been the question of irrigation and whether the medial temporal lobe is adequately “disabled” during the procedure. This particular limitation is not applicable to the patient with frontal lobe epilepsy, as the region of interest is clearly ablated via supply from the carotid arterial system. Caution must, however, be exercised with respect to possible crossflow into the 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 in any patient with frontal lobe epilepsy, as the region of interest is clearly ablated via supply from the carotid arterial system. 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. Assessment focussing 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.

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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 primarily characterised by the triad of drowsiness/ fatigue, parkinsonism, and depression; depression is found in about 15% of patients treated with TBZ. We here report on the rapid reversal of depressive symptoms in a patient treated with TBZ for orofacial dystoria by administering the new and highly selective noradrenaline (norepinephrine) reuptake inhibitor (SNRI) reboxetine.

On admission, the 64 year old woman presented with perioral and lingual hyperkinesias as well as intermittent and involuntary movements of her lower jaw, which had lasted for about 2 years, causing her a considerable interference with her articulation. No history of neuroleptic treatment or Parkinson’s disease was evident. Her cranial CT and blood chemistry were normal. We diagnosed a segmental dystonia, which improved dramatically after a tetrabenazine medication (60 mg a day). This successful treatment response, however, was accompanied by a severe depressive syndrome, which was characterized by a mixed anxious-depressive mood, low self esteem, a complete loss of drive, and intermittent suicidal ideations. After switching from TBZ to tiapride, the patient recovered from depression, but her neurological status worsened significantly with re-exposure to TBZ again ameliorated hyperkinesia, but provoked a significantly. The re-exposure to TBZ again worsened the patient’s depressive symptoms. After switching from TBZ to reboxetine (6 mg/day), a new and selective noradrenaline (norepinephrine) reuptake inhibitor (SNRI) reboxetine may thus provide a new, specific, rapid reversal of depressive symptoms in a depressed patient.


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 pathogenetic 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 side 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 vertebral 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 thymoceletral 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 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. Magnetic resonance imaging with typical semilunar mural haematoma and in addition magnetic resonance angiography (MRA) with complementary documentation of an irregularity or tapering occlusion have a high sensitivity and specificity in cases of internal carotid artery dissection.

By contrast, mural haematomas of the VA especially in the V1 and the V3 segments are often not detectable by MRI. In cases of unclear non-invasive findings, DSA is still the method of choice.

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-
nal cord infarction is often located in the anterior spinal artery territory with the grey matter of the anterior horns exhibiting the highest vulnerability to ischaemia.\textsuperscript{2} This mechanism may lead to a typical “snake eye” configuration of medullary infarction.\textsuperscript{1} Besides the supply via VA spinal branches, which is found in 19% only unilaterally,\textsuperscript{3} there are branches originating from the ascendant cervical artery (thyrocervical trunk) and the costocervical trunk supplying the spinal cord.\textsuperscript{4}

DSA findings in the present case suggest that spinal branches originating from the right V2 segment were dominant feeders of the anterior spinal artery whereas there was no evidence of direct communication between vertebral and spinal arteries from the V4 segment. The dissection involved the V2 segment from which these spinal branches originate. A transient occlusion of these spinal branches is a likely consequence. This unusual type of arterial medullary supply may explain why VAD causes spinal cord infarction. Contrary to Pullicino,\textsuperscript{5} who described upper limb atrophies due to cervical spinal cord infarction involving the anterior horns, the present case shows a unilateral involvement of commissural, spinohalamic, pyramidal, and vasoconstrictor tracts. To our knowledge, such a spinal artery syndrome caused by bilateral spontaneous VAD has not yet been described. In conclusion, differential diagnosis of acute spinal symptoms in young adults should include spontaneous unilateral or bilateral VAD with cervical spinal cord ischaemia.

\textbf{Letters, Correspondence, Book reviews, Correction

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\textbf{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.\textsuperscript{1} Cerebral cavernous malformations occur as a sporadic or hereditary condition. From the Hispano-American population, familial forms were reported with a high frequency.\textsuperscript{2} CCM1, a hitherto unidentified gene mapping on chromosome 7 was shown to be involved in all families with cerebral cavernous malformations of Hispano-American descent with a strong founder effect.\textsuperscript{3} Around 50% of non-Hispano-American families showed linkage to \textit{CCM1} but no common haplotype was found.\textsuperscript{4} A recent study showed linkage of cerebral cavernous malformations to two additional loci.\textsuperscript{5} No Spanish family with cerebral cavernous malformations has been analysed so far.

We report herein a genetic linkage analysis conducted on nine Spanish families with cerebral cavernous malformations. All procedures were approved by an ethics committee. The families were unrelated and originated from different regions of Spain (south west (CVE2, 3, 4, 10, 17, 25), central (CVE24), south east (CVE28), and north east (CVE29). Seventy seven subjects including 55 potentially informative meioses and 12 spouses gave their informed consent. They were examined by a board certified neurologist, underwent cerebral MRI, and blood samples were taken. Magnetic resonance imaging was used to establish status for linkage analysis. Thirty four members had MRI diagnosis of cavernomas and were considered as affected. Among them, 14 experienced neurological symptoms (cerebral haemorrhage n=6, seizures n=8). Nineteen members with normal cerebral MRI were considered as healthy. Twelve members without MRI investigation had an unknown status. Analysis of pedigrees was consistent with an...
for all markers. In this family, two 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, D7S758, and D7S689), and three from the Cooperative Human Linkage Center (D7S1813, D7S1789, D7S558). The last one (M65B) was identified by SL based on sequencing data of a bacterial artificial chromosome (Genbank HSAC0000665; BAC RG085C05). The length of the genetic interval flanked by markers D7S2410 and D7S689 is 4 centimorgans (cM). Marker distances between D7S2410/D7S2409, D7S1813/D7S1789, D7S646/D7S558, and D7S689 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 were performed as previously described.2 Lod scores were calculated in the five families having a sufficient number of potential informative meioses—that is, CVE1 (eight), CVE4 (16), CVE10 (seven), CVE25 (five), and CVE28 (seven). Lod scores higher than 1 were obtained for four families (CVE3, 4, and 28) for at least one marker. Due to the 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, and D7S689). Family CVE8 total score was always less than 0.0 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 \( \theta = 0.0 \).

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 \( \theta = 0.0 \).

Of the five families, none of the shared a common haplotype (figure B). In addition, the extended Hispano-American haplotype was not segregating with the disease phenotype in any of the nine families including the four families with suggested linkage to CCM1. However, two out of nine families (CVE2 and 3), the D7S646 (185bp) and D7S558 (107bp) alleles segregating with the disease phenotype were identical to the ones observed in the Hispano-American haplotype. Consequently, we analysed the frequency of this combination of alleles within a panel of 80 haplotypes of 40 healthy white subjects. Frequency was 17% compared with 2% in our Spanish sample. Therefore, this finding might be attributed to a random distribution of these alleles.

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

Hydrocephalus caused by metastatic brain lesions: treatment by third ventriculostomy

Metastasis to the brain occurs in 20%–40% of cancer patients.1 About 20% of these metastases are located in the posterior fossa, cerebellum, and brainstem. Metastatic disease to pterional brain tissue can obstruct the flow of cerebrospinal fluid (CSF) produced in the ventricles to the subarachnoid space where it is normally absorbed by arachnoid granulations. This typically causes an obstructive or non-communication hydrocephalus. A temporary or custom-made catheter is placed to drain CSF from a lateral ventricle through a pressure regulating valve and into the atrium or peritoneal or pleural cavity. Even though this technique has been successful in relieving the hydrocephalus, it has about a 50% chance of infection or failure from blockage.2

Another option for the treatment of obstructive hydrocephalus is third ventriculostomy, a minimal invasive endoscopic neu-rosurgical procedure. In performing third ventriculostomy, a hole is created in the floor of the third ventricle, allowing CSF inside the ventricle to drain out to the CSF space surrounding the brain. Although third ventriculostomy has a low operative morbidity and a high probability of success,2 it is frequently used to treat hydrocephalus, it is only commonly used on patients with aqueductal stenosis and the pediatric population. To avoid placing shunts in patients with inoperable metastatic brain tumours who typically have only a few months to live, we have offered the patients third ventriculostomy as a palliative procedure.

In all cases, we performed third ventriculostomy on selected patients with inoperable metastatic brain tumours. This technique was preferred to other treatment options, such as radiation therapy. In selected cases, this technique might provide palliative relief for a few weeks to a few months.

We performed third ventriculostomy on selected patients with hydrocephalus due to metastatic tumours of the posterior fossa or thalamus. These patients had a median hospital stay of 5–6 days and median survival of 6 weeks after the operation. The hospital stay was prolonged by care of their primary disease. However, most of our patients who underwent this operation for hydrocephalus caused by other diseases were discharged from the hospital in less than 48 hours.

None of the patients had any evidence of relief of hydrocephalus up to the last clinic visit. The shunt was successful in relieving the hydrocephalus in all cases. Although the follow-up period was short, the patients and their families were satisfied with the results obtained with third ventriculostomy.

Hydrocephalus caused by metastatic brain lesions: treatment by third ventriculostomy

Letters, Correspondence, Book reviews, Correction

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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 related to 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 for obstructive hydrocephalus from unresectable tumours.

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

<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 (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>70, M</td>
<td>Lung mixed adenocarcinoma and squamous cancer metastasis to thalamus</td>
<td>Improved</td>
<td>17</td>
<td>4</td>
</tr>
<tr>
<td>2</td>
<td>46, F</td>
<td>Ovarian adenocarcinoma metastases to cerebrum and medulla</td>
<td>Improved</td>
<td>9</td>
<td>13</td>
</tr>
<tr>
<td>3</td>
<td>38, F</td>
<td>Breast ductal carcinoma metastases to brainstem and cerebellum</td>
<td>Improved</td>
<td>3</td>
<td>8</td>
</tr>
<tr>
<td>4</td>
<td>75, M</td>
<td>Rectal adenocarcinoma metastasis to cerebellum</td>
<td>Failed</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>5</td>
<td>39, F</td>
<td>Breast adenocarcinoma metastasis to cerebellum</td>
<td>Improved</td>
<td>4</td>
<td>11</td>
</tr>
<tr>
<td>6</td>
<td>60, M</td>
<td>Lung adenocarcinoma metastasis to thalamus</td>
<td>Failed</td>
<td>6</td>
<td>6†</td>
</tr>
<tr>
<td>7</td>
<td>64, M</td>
<td>Osteophageal 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.

Such an interaction between cortical blood flow and tumour blood flow may be of value for evaluating mechanisms of neurological symptoms associated with brain tumours.

Neuronal activation causes an increase of regional cerebral blood flow (rCBF) in the activating cortical area. Near infrared spectroscopy (NIRS) demonstrates the increase in rCBF during neuronal activity as increases in oxygenated haemoglobin (oxy-Hb) and total haemoglobin (total-Hb) with a decrease in deoxyhaemoglobin (deoxy-Hb). NIRS is an optical method to measure concentration changes of oxy-Hb, deoxy-Hb, and total-Hb (oxy-Hb+deoxy-Hb) in cerebral vessels by means of the characteristic absorption spectra of haemoglobin in the near-infrared range. In the present study, we measured changes of oxygenation and haemodynamics in the brain tumour adjacent to the activating cortex by means of NIRS. We found transient decreases in oxy-Hb and total-Hb in the tumour during neuronal activation, suggesting that the local blood flow of the tumour was decreased by a transient increase of rCBF induced by neuronal activation.

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

We measured haemodynamic changes in the brain tumour during neuronal activation in the left frontal lobe induced by cognitive function.
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 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) confrontation naming, which involves naming ordinary items presented by the tester; (3) backward digit span, a working memory task which involves reporting of digits (2 to 8) in the reverse order; and (4) her index finger without shifting her gaze to the pin. The patient was asked to touch this pin with her index finger without shifting her gaze to the pin. 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 most normal adults—for example, increases in oxy-Hb and total-Hb—were found in 92.3% of young adult subjects (mean SD) 28.8 (4.4) years during the word fluency task (unpublished data). Therefore, although we could not measure the changes in rCBF in the left frontal lobe of the present patient from our previous studies, it strongly suggests that the tasks caused an increase in rCBF in the left frontal lobe of the patient. During the task, the decrease in oxy-Hb and total-Hb recorded from the brain tumour indicates a decrease of local blood flow in the tumour because the NIRS measurement area was restricted to the brain tumour. The decreases in oxy-Hb and total-Hb were found only during the tasks; consequently, these changes were probably not due to changes in systemic blood pressure, which can alter tumour blood flow. Based on these assumptions, one hypothesis is 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 propose that this support suggests that activity-dependent increase in rCBF can steal blood flow from the adjacent tissues including non-activating cortex. Recent NIRS activation studies have shown that cognitive tasks cause decreases in oxy-Hb and total-Hb in the left frontal lobe in some normal subjects; these decreases indicate a decrease in rCBF. Although the physiological mechanisms of the decrease in rCBF during neuronal activity have not yet been elucidated, we hypothesise that a stealing of blood flow is one of the mechanisms. The present report supports this hypothesis.

Because the NIRS measurement area was recorded from the brain tumour indicates a patient. The decrease in oxy-Hb and total-Hb 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. The visual symptoms and headache decreased considerably after the patient was started on flunarizine at a daily dosage of 10 mg at bedtime. The visual symptoms, after being recognised by the primary visual cortex (Brodmann area 17), are interpreted and integrated in visual association areas 18 and 19. 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 bedtime. The visual symptoms, after being recognised by the primary visual cortex (Brodmann area 17), are interpreted and integrated in visual association areas 18 and 19. Broadmann area 19, in turn, is connected with the angular gyrus and frontal eye field via 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
invoking 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.

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

A healthy 39 year old man was bitten on the ankle by his own apparently normal dog. After the incident the dog disappeared into the forest and was not seen again. Three days later the patient was seen at a provincial hospital in Vietnam and started on an alternate day regi-
men of suckling mouse brain postrabies expo-
sure vaccination (SMBV). After the second dose, he felt unusually lethargic although he
was still able to work. After the third dose, he
became unresponsive, and was transferred to the Centre for Tropical Diseases, Ho Chi Minh
City, the referral hospital for infectious dis-
eses in southern Vietnam. On admission, he
was afebrile, confused, had slurred speech, and
his Glasgow coma score was 13. He had mild
spastic weakness of his left face, left arm, and
both legs. Full blood count and results from
routine biochemistry and chest radiography
were all normal. The CSF: blood glucose ratio
was 0.47 (63/140 mg%), the protein content
was raised (78 mg/dl), and there was one
lymphocyte/ml in the CSF. Screen for malaria
toxoplasmosis, cryptococcus, and neurocyst-
cercosis were negative, as was a CSF gram
stain. The CSF was sterile after 2 weeks of
culture. Brain MRI (Access Toshiba LPT
6.01p, 0.064 Tesla) showed areas of high signal
throughout the white matter, and cystic-like
areas in the bilateral hemisphere (figure A). These variably sized lesions were ab-
normalities in the basal ganglion, and gen-
eralised increase in ventricular size, consist-
ent with residual cerebral atrophy.

Rabies is caused by an RNA virus, a mem-
ber of the Rhabdoviridae family, it infects
mammals and can be transmitted to humans
by contact, generally from an animal excret-
ing the virus in the saliva. Rabies manifests
as an acute encephalomyelitis, the development of which is almost invariably fatal. The
distinction between rabies and postrabies encephalitis is difficult and may be helped by
antigen detection via a skin biopsy; however,
this technique is not available in Vietnam.

Paralytic rabies could not be excluded in this
patient and hence steroids were not used ini-
tially. Steroids have been reported to increase
mortality in experimental animals with ra-
bies, and it has been suggested that they may
abrogate the immune response to the postex-
posure vaccine, thus precipitating uncon-
trolled rashes.1

There are three types of postexposure vac-

cine in use worldwide. The Semple type
(STV) is obtained from inactivated virus pre-
pared on baby hamster kidney cell tissue
(SMBV). The attenuated virus is cultured on
the tissue of the animal on which the virus was
inoculated, and it has been suggested that they may
produce neurological reactions, including postvacci-
nation encephalomyelitis, in up to 1 in 1000
courses, with a 3% mortality.1 Clinical forms
include a reversible mononeuritis multiplex,
and meningoencephalitic and encephalomy-
elitic reactions. Myelin basic protein and
related neural proteins from the nervous
tissue of the animal on which the virus
cultivated stimulates an autoimmune reaction
in the human nervous system.

Tolerance has been improved by the devel-
opment of the suckling mouse brain vaccine (SMBV).4 The attenuated virus is cultured on
immature mouse brain tissue, which contains
little myelin, thus reducing the risk of compli-
cations. SMBV is inexpensive (US$1.5 per
treatment course) and easily manufactured
locally; it is the most widely used postrabies
vaccine in Vietnam. Rare neurological reac-
tions do occur with SMBV, Complications of the
cNS have been reported to occur after vacci-
nation with an incidence of 1:27000
treated people, with a 22% mortality.4 The
mortality was particularly high (80%) if there
was extensive CNS involvement. The third
type of vaccine available is the human diploid
cell tissue culture vaccine (HDCV), which
is both safe and efficacious. However, the recom-
ended regimen is not affordable in most
developing countries.

When we approached the Rabies Labora-
tory, Ministry of Agriculture and Fisheries,
United Kingdom for advice in this case their
response was “why do you use the SMBV,
can’t you use another vaccine”. Worldwide
about 10 million people each year receive
rabies vaccine after exposure; at the Centre
for Tropical Diseases we treat 3000 people
annually. The cost of an
dose of dog bites annually. The cost of an
rabies vaccine after exposure; at the Centre
for Tropical Diseases we treat 3000 people
annually. The cost of an

This is the first report to show the demyeli-
nating CNS lesions on MRI, and their
resolution after steroid therapy. It is relatively
rare for patients to survive if they develop
severe CNS effects after postexposure rabies
vaccination. Although the incidence of reac-
tions to SMBV is very much lower than
STV, this report confirms that it does still occur.
Both SMBV and STV are widely used
throughout the developing world, and would
be the vaccine administered to travellers
exposed to animal bites in such countries.

This case stresses the need for high dose ster-
oids in postexposure vaccine encephalitis and
the urgent need for the development and
deployment of a safe, and critically, afford-
able postrabies exposure vaccine regimen.

The economic low dose multisite intradermal
regimen using the HDCV provides an example
of how this goal may be achieved although it
is not yet widely accepted. Such a vaccine
regimen (0.1 ml HDCV given at multisite
injections on days 0, 3, 7, 14, and 28 with an optional booster on
day 90) is US$ 125, making the use of this
vaccine unaffordable.

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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 inhabitants of the United Kingdom. The psychoactive constituents of khat are cathin (d-norcathinone), cathine, and cathinone (an analgesic, with a pharmacologic action resembling ephedrine and amphetamine) and users report a mild euphoria similar to that of amphetamine. Khat is acknowledged as a recreational drug taken by mouth or inhalation. Other recreational drugs taken by mouth or inhalation, however, have not been reported in association with khat misuse.

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 progressing dysaesthesia 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 neurologic opinion. He was apyrexic and general medical examination was normal. He opened his eyes spontaneously but there was no verbal response and he did not obey commands. He withdrew all four limbs to pain. Upper and lower limbs were flexor with markedly increased tone. Reflexes were brisk but equal. The right plantar was extensor. There were bilateral palmar and plantar reflexes.

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

Examination of the CSF showed normal opening pressure; protein was 0.27 g/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 contracted by movement artefact, showed diffuse slow waves only. A second MRI (figure 3) 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 frontotemporal craniotomy) was performed 3 months after onset of his illness. There was no evidence of acute inflammation, vasculitis, or infarction.

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

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

The likely precipitant of this man's illness seems to be his 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 patient 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.
M-protein, direct and indirect Coombs tests, cryoglobulin, antibodies to mycoplasm, 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 (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 A specificity. Immunelectrophoresis of the eluate confirmed IgM composition.

The initial nerve conduction study showed severe diminution or absence 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. Electrophysiological studies of the affected muscles showed moderate neurogenic changes, but there were no fibrillation potentials except in the left anterior deltoid muscle. (bar=20 µm). (B) Most of myelinated fibres are undergoing axonal degeneration. Many macrophages containing myelin debris infiltrate the endoneurium. (bar=30 µm).

In the present case, we have confirmed the existence of vasculitis and 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 mediate 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 Harata for their technical assistance, Dr S Kusunoki (Department of Neurology, Institute for Brain research, University of Tokyo) for analyses of antibodies to gangliosides, and Mr H Moug (Division of Blood Transfusion Medicine, University of Kagoshima) for characterization of cold agglutinins.

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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’s 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. 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. Th

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 from non-pharmacological clinical trials to suggest that cholinomimetics as a whole may have a beneficial effect on some non-cognitive behavioural symptoms. This has now been reported for at least two cholinesterase inhibitors, and two muscarinic agonists. In particular, a clear link is emerging between psychotic symptoms and cholinergic dysfunction. Thus, Bodick et al have shown that the M/M agonist xanomeline causes a dose-dependent reduction in hallucinations, agitation, and delusions in a 6 month randomised double blind placebo controlled, parallel group trial. In addition, Cummings and Kaufer have shown that the cholinesterase inhibitor metrifonate was also shown to reduce the number of hallucinations in a 26 week randomised, double blind, placebo controlled safety and efficacy study in patients with Alzheimer’s disease. Further support for a link between cholinergic 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 M/M agonist (S)-6R(-)-(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. Thus, on the basis of both clinical and preclinical data, a clear rationale is emerging for prescribing cholinomimetic agents for treating the non-cognitive behavioural symptoms associated with dementia, particularly psychosis.

Professor Babic is also correct in identifying two of the studies referred to as the 30 week randomised multicentre placebo controlled parallel group studies, which included a 24 week double blind treatment phase. We are grateful to your correspondent for providing us with the opportunity to clarify these points.

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 unpleasant disorders range from exceptionally severe pain to the whole range of problems resulting from autonomic failure. This book comprehensively covers every aspect of the subject, systematically (and at times exhaustively) from its epidemiology and pathogenesis (exhaustingly) to structural, functional, and clinical problems and their treatment. Most of the authors are well known in the field and their accounts are up to date and authoritative.

Unfortunately, struggle as they might, all authorities have difficulty in defining what they mean by diabetic neuropathy. In regard, understanding of this complication both in clinical and pathological terms, as well as with regard to treatment, lags far behind that of the other classic diabetic complications, nephropathy and retinopathy. Even its classification presents problems and attempts to do so are found in four different chapters, describing four classifications. Replication is an unfortunate feature of this book and—quite apart from the confusion over classification—aspects of pathogenesis, structural changes, epidemiology, diagrams, and some reference to treatment (for example, that of pain) appear repeatedly in different chapters in greater or lesser detail.
This is certainly a book for the specialist and not at all (as the preface suggests) for the family practitioner. There are good reviews of nerve structure, causation, and treatment of painful neuropathies and focal neuropathies. The comprehensive survey of the Diabetes Control and Complications Trial (DCCT) shows in detail the only treatment which is truly effective (diabetic control); and the lengthy description of aldose reductase inhibitor trials establishes that, even after more than two decades of investigation, further trials are still needed.

Clinical evaluation of somatic and autonomic neuropathies are useful and also, to 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 Zermon's encephalometer more than a century ago. Just as the solution to the mariners' problem of determining longitude from which it partly takes its name, neuronavigation ("the surgeon's sextant") has relied on the advent of new technologies to provide solutions to an old puzzle.

*Advances In Neurosurgical Navigation 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 had in surgery of the spine. This aside it is an excellent book although, like the technology it chronicles, one which is likely to date quite rapidly.

ROBERT MACFARLANE


The title and back cover of the latest addition to *Neurology Lite* texts contains the usual proclamations. "Concise, key topics, revision aid, essential, review..." the well trailed soundbites demanded by the consumer in the increasingly competitive market of "read less - learn more" books. This book, however, is unusual and distinct. Unlike many rivals it is not an A5 facsimile of a superior parent A3 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

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