Focal (segmental) dyshidrosis in syringomyelia

Kazumasa Sudo, Naoto Fujiki, Sachiko Tsuji, Minoru Ajiki, Takuya Higashi, Masaaki Niino, Seiji Kikuchi, Fumio Moriwaka, Kunio Tashiro

Abstract
The features or mechanisms of dyshidrosis have not been sufficiently clarified. Neither has the difference between hyperhidrosis and hypohidrosis. To clarify the features and mechanisms of dyshidrosis (hyperhidrosis and hypohidrosis) in syringomyelia, the clinical features focusing on hidrosis of 30 patients with syringomyelia and Chiari malformation located from a syringomyelia database were prospectively analysed. The patients were classified into three groups: eight patients (26.7%) had segmental hypohidrosis, 10 (33.3%) had segmental hyperhidrosis, and 12 (40.0%) had normohidrosis. We found that the Karnofsky functional status for the hyperhidrosis and normohidrosis groups were significantly higher than for the hypohidrosis group (p=0.0012), with no significant differences between the hyperhidrosis and normohidrosis groups.

The duration from the onset of syringomyelia to the current dyshidrosis was significantly longer in the hypohidrosis group than in the hyperhidrosis group (p=0.0027). A significant correlation was identified between the duration from the onset of syringomyelia to the time at study and the performance score (r=−0.599, p=0.0003). The results substantiate previous hypotheses that in its early stage syringomyelia causes segmental hyperactivity of the sympathetic preganglionic neurons, and hyperactivity of these gradually subsides as tissue damage progresses. Focal hyperhidrosis may be regarded as a hallmark of a relatively intact spinal cord, as well as normohidrosis.

Methods

Patients and Methods

We have stored clinical data of a consecutive 34 patients (0.28%) with MRI confirmed syringomyelia and Chiari malformation among the 11 967 outpatients who visited our neurology clinic from April 1989 to November 1996. Three quarters of the patients came without referral, and a quarter came with referral. Our outpatient clinic is not only a primary but also a secondary and tertiary centre for diagnosis and treatment of all neurological disorders. The case records of each patient showed that there had been no referral bias to our clinic as a consequence of our interest in dyshidrosis in syringomyelia. The protocol includes items for the autonomic nervous system as well as other systems. The data were obtained prospectively, with the intention of avoiding any predetermination bias, according to a protocol for examining patients with syringomyelia, which we ourselves designed. At the time of registration for this study, we obtained informed consent from patients to enter their information into our study database. Four of the 34 patients were dropped from the study because they refused to give us permission to employ clinical information about themselves for any clinical study; this left 30 patients. Twelve of these patients were operated on for syringomyelia, and we completed entering their information at the time of the operation.

Protocol for Examining Dyshidrosis

We obtained detailed clinical information for each patient, including their previous experience of hidrosis. A structured protocol was used to examine the state of hidrosis: step 1 asking about the nature and distribution of the hidrosis and the effects of room temperature, exercise, clothing, psychological burdens, food, etc; step 2 examining the state of hidrosis by observation, manual examination, and drawing a metal spoon across the surface of the skin (spoon test) either after adequate physical exercise or when lying in a bed warmed in advance by electric blankets. When further investigation was necessary to clarify the nature and distribution of dyshidrosis, the following steps were performed; step 3 taking a thermometer in a room at a temperature of 21–28°C; step 4 a hidrosis examination (the iodine-starch method) at a room temperature of 45–50°C, or in a bed warmed in advance. Consequently we
performed thermography in 16 patients, and the iodine-starch method in nine patients. We assessed the performance status by Karnofsky performance score (K score); this ranges from 0 to 100, and the higher the score, the better the performance.13

CASE RECORDS
(See also our previous case records for three patients with hyperhidrosis14).

Patient 18 (hyperhidrosis; 37 year old woman) had a 7 month history of persistent hyperhidrosis and pain in the left upper quadrant of the body. There was no muscle weakness or atrophy. Thermography showed low temperature in the left upper quadrant, which was consistent with hyperhidrosis of the area (figure A). She underwent an operation (a syringosubarachnoid shunt) 7 months after onset, after which hyperhidrosis and pain subsided within a week, as indicated by thermography (figure B).

STATISTICAL ANALYSIS
We performed a statistical analysis of five factors (age at time of study, age of onset of symptoms, duration from onset of symptoms to time of study, K score, and duration of follow up period) for the three groups of patients (hyperhidrosis, normohidrosis, and hypohidrosis) by one way factorial analysis of variance (ANOVA) (Fisher's PLSD method as a post hoc test), and for two factors (age of onset of current dyshidrosis and duration from onset of symptoms to current dyshidrosis) between the two groups of patients (hyperhidrosis and hypohidrosis) by non-paired t test. We then obtained the Pearson's correlation coefficient for duration from onset of symptoms to time of study, and K score for all 30 patients.

Results
Of the 30 patients, eight (26.7%) had hypohidrosis, 10 (33.3%) had segmental hyperhidrosis, and 12 (40%) had normohidrosis. In all patients, the distribution of dyshidrosis corresponded with the location of the syrinx and other neurological manifestations; the syrinx was located roughly in the region from the central canal to the unilateral (or sometimes bilateral with asymmetry) posterior angle of the spinal cord.

We have summarised the results of the statistical analyses in the table. Although we

Table 1  Summary of evaluation of each item

<table>
<thead>
<tr>
<th>Item</th>
<th>Hypohidrosis</th>
<th>Hyperhidrosis</th>
<th>Normohidrosis</th>
<th>p Value</th>
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<tr>
<td>Number of patients</td>
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<td>10</td>
<td>12</td>
<td></td>
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<tr>
<td>Age at time of study:</td>
<td></td>
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<tr>
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<tr>
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<tr>
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<td>10-69</td>
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<tr>
<td>Mean (SD)</td>
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<td>1-32</td>
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<tr>
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<td>15.5 (10.1)</td>
<td>9.67 (9.61)</td>
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<td>Mean (SD)</td>
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<td>Mean (SD)</td>
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<tr>
<td>Mean (SD)</td>
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<td>29.2 (13.5)</td>
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<td>0.1287†</td>
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<tr>
<td>Duration of onset from symptoms to current</td>
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<td>—</td>
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<tr>
<td>Mean (SD)</td>
<td>12.6 (4.5)</td>
<td>5.50 (4.70)</td>
<td>—</td>
<td>0.0027†</td>
</tr>
</tbody>
</table>

*p Value for each pair of items: hyperhidrosis v hypohidrosis 0.1148; hyperhidrosis v normohidrosis 0.0078; normohidrosis v hyperhidrosis 0.2194.
†p Value for each pair of items: hyperhidrosis v hyperhidrosis 0.0007; hypohidrosis v normohidrosis 0.7282; normohidrosis v hypohidrosis 0.0012.
ourselves were not able to confirm any change in the features of hidrosis during the follow up period, the clinical histories of five patients indicate that hidrosis decreased segmentally and diffusely over a long period. Duration from onset of symptoms to study was significantly longer in the hypohidrosis group than in the hypohidrosis group (ANOVA, F(2, 27)=4.127, p=0.0273) (table). The K scores were significantly higher in the hypohidrosis and normohidrosis groups than in the hypohidrosis group (ANOVA; F(2, 27)=8.765, p=0.0012), with no significant difference between the hypohidrosis and normohidrosis groups (p=0.7282).

Duration from onset of symptoms to current dyshidrosis was significantly longer in the hypohidrosis than in the hyperhidrosis group (p=0.0027). There were no significant differences between hidrosis groups in the other factors. A significant correlation between the two items (duration from onset of symptoms to study, and K score) was recognised (r=-0.599, n=30, p=0.0003).

Discussion

We performed a MEDLINE search for publications dealing with dyshidrosis in syringomyelia between January 1966 and June 1997, with a language limitation of English, German, and French. This search confirmed the scant accumulation of information regarding dyshidrosis in syringomyelia; we were able to locate only four cases accompanied by Chiari malformation (three of which we have already reported and are currently included in this study).

We previously speculated that hypohidrosis is caused by stimulation of sympathetic preganglionic neurons (SPGNs) rather than interference to the inhibitory tract. This is equivalent to the hypothesis regarding body hyperhidrosis which we recently presented. Later, disinhibition of the inhibitory local interneurons (ILINs), which are located in the vicinity of SPGNs, was supposed to be the cause of segmental hyperactivity of the SPGNs. When, in the clinical course of syringomyelia, slowly progressive tissue damage around the syrinx reaches the lateral horn, it will segmentally affect the SPGNs or adjacent structures. This time our results have shown, from the viewpoint of sweating, that there evidently is a hyperactivity of the SPGNs as long as the disability is mild; however, as the disability progresses, the hyperactivity gradually decreases and is replaced by hypoactivity (table).

We have a choice of two possibilities for the mechanism responsible for the hyperactivity of the SPGNs so far; the first is that the SPGNs are stimulated directly by a minimal tissue damage; the second is damage to the ILINs (preceding the damage to the SPGNs) — we have recently acquired some knowledge of these ILINs. In either case, as the disease progresses, hyperactivity will shift to normoactivity and finally to hypoactivity because of progressive and irreversible damage to the SPGNs, consistent with the clinical history of five of our eight patients with hypohidrosis. By contrast, immediate resolution of hyperhidrosis after decompression of the syrinx in patients, whose disability was minimal, showed that the damage to the SPGNs was mild and tends to be reversible in patients with mild disability (figure). Before we reached the above hypothesis for the mechanism of hyperhidrosis, we had ruled out the possibility of interference to the inhibitory tract that connects the upper centre and the SPGNs as before because of the segmental distribution of hyperhidrosis and because of the locational relation among the syrinx, inhibitory tracts, and SPGNs.

Current results substantiate previous speculation about the mechanism of and relation between hyperhidrosis and hypohidrosis in syringomyelia. We now think that, in syringomyelia, focal hyperhidrosis can be regarded as a hallmark of a relatively intact - even though slightly damaged — spinal cord. We also think that, in syringomyelia, some part of normohidrosis is associated with a considerable amount of spinal cord damage. We propose that in diagnosing focal dyshidrosis, more attention should be given to the possibility of syringomyelia.

We are indebted to Drs Kazutoshi Hida, Yoshinobu Iwasaki, and Hiroshi Abe (Department of Neurosurgery, Hokkaido University School of Medicine) for their help in providing us with clinical information regarding surgical treatment. This study was supported by Research Grant (3B-3) for Nervous and Mental Disorders, from the Japanese Ministry of Health and Welfare.

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Letters to the Editor

Behavioural status during the intracarotid amobarbital procedure (Wada test): relevance for surgical management (J Neurol Neurosurg Psychiatry 1999;67:549–559)

Presurgical evaluation in many epilepsy programmes often includes the intracarotid amobarbital procedure (IAP). Succinyl 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 post-surgical amnesia,2 and to predict post-surgical material specific memory changes.3 More recently, the use of the IAP has been extended to complement EEG localisation and radiological data by lateralisating temporal lobe dysfunction.4

In this report, we describe a hitherto unrecognized 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 helpful 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 lobes 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 arise 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 posted a traffic accident at the age of 12 years when he sustained a head injury with an ill defined period of loss of consciousness. Seizures commenced within months of that injury and, although initially well controlled, became refractory within a few years. The seizure types included staring spells, violent tonic-clonic seizures, and tonic drop attacks. He had complications from his epilepsy including a fractured jaw, two episodes of severe burning due to seizures while showering, multiple episodes of postictal confusion and possible 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 hemisphere which 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 level was 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 danger of life remaining unequivocal. 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 compromise, 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 generation (sensorimotor testing), together with marked behavioural disinhibition (agitation, swearing, verbosity, childishness). Although seemingly aware of some aspects of his behaviour (apologising for swearing), he seemed unable to control his responses. The overall impression was of a pronounced frontal lobe syndrome, suggesting that the right frontal lobe had incurred some damage secondary to the documented head trauma and that he must have been reliant on some left frontal contribution.

On the basis of the IAP findings, a selective cortical resection (as opposed to more extensive frontal lobectomy) seemed likely on the basis of the 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 “disabused” during the procedure. This particular limitation is not applicable for 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 ipsilateral 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 crossflow 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 assessment focusing 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 since the entire frontal lobe is included in the ablation. There are likely to be few surgical scenarios in which a comparable extensive resection of tissue is likely to be considered, and results must be interpreted in this context. This limitation notwithstanding, the IAP does seem to have a role in separating out those patients in whom more extensive frontal lobe resections could be considered opposed to those in whom a more conservative approach is warranted.

This case report forms only the basis for a novel hypothesis that clearly requires more rigorous scientific research before its clinical utility can be reliably established. Nonetheless, we think that it is worth drawing the attention of the epil-psychological 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 mainly characterised by the triad of drowsiness-fatigue, parkinsonism, and depression; depression is found in about 15% of patients treated with TBZ. We here report on the rapid reversal of depressive symptoms in a patient treated with TBZ for orofacial dystonia by administering the new and highly selective noradrenaline (norepinephrine) reuptake inhibitor (SNRI) reboxetine.  

On admission, the 64 year old woman presented with perioral and lingual hyperkinesias as well as intermittent and involuntary movements of her lower jaw, which had lasted for about 2 years, causing her a considerable increase in medication. 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 tapering of tetrabenazine medication (60 mg a day). This successful treatment response, however, was accompanied by a severe depressive syndrome, which was characterised by a mixed anxious-depressive mood, low self esteem, a complete loss of drive, and intermittent suicidal ideation. 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 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 monoamine oxidase type 2 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 phenylephrine 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.

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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. The cervical spinal cord is incompletely 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. Further 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 digiti minimi (9.2 ms) and tibialis anterior (23.1 ms). The CMCT to the left target muscles was normal. Duplex sonography showed increased flow velocity on the level of the cervical vertebrae 3 to 5 with a maximum of 214 cm/s in the right and 197 cm/s in the left vertebral artery. Colour mode showed irregular narrowings of the lumen indicating dissections.

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

The intradural origins of the anterior spinal artery (ASPA) are rare because of its embryological development.  

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 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 irreversible 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, spinocerebellar pathways, and possibly further collaterals are preserved.
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. This mechanism may lead to a typical “snake eye” configuration of medullary infarction. Besides the supply via VA spinal branches, which is found in 19% only unilaterally, there are branches originating from the ascending cervical artery (thyrrocervical trunk) and the costocervical trunk supplying the spinal cord.

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, 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 vasocostrictor 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.

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Spanish families with cavernous angiomas do not share the Hispanic-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 Hispanic-American population, familial forms were reported with a high frequency. CCM1, a hitherto unidentified gene mapping on chromosome 7 was shown to be involved in all families with cerebral cavernous malformations of Hispanic-American descent with a strong founder effect. Around 50% of non-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 haemorrhages n=6, seizures n=8). Nineteen members with normal cerebral MRI were considered as healthy. Twelve members without MRI investigation had an unknown status. Analysis of pedigrees was consistent with an American descent with cavernous angiomas on MRI; half filled symbols=asymptomatic members with cavernous angiomas on MRI; empty symbols=at risk members with normal MRI; question mark=members with unknown status. (B) Comparison of the Hispanic-American CCM1 haplotype and the haplotypes segregating with the disease phenotype within Spanish families. Polymorphic markers are shown on the left. Numbers indicate the sizes in base pairs. Primers used to amplify D7S2409 were not informative for D7S646. For families CVE17 and CVE29, the two haplotypes of the affected siblings are indicated. ND=not determined.
for all markers. In this family, two a
Due to incomplete informativity of three
more than 1 were obtained for three families
(five), and CVE28 (seven). Lod scores higher
families having a su
D7S689 have been estimated to be 2.2 cM,
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, Balti-
more). Genotyping and linkage analysis (LINKAGE package version 5.1) were per-
formed as previously described.4 Lod scores were calculated in the five families having a sufficient number of poten-
tial informative meioses—that is, CVE1 (eight), CVE4 (16), CVE10 (seven), CVE25 (five), and CVE28 (seven). Lod scores higher than 1 were obtained for three families (CVE3, 4, and 26) for at least one marker. 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). For family CVE25, two patients had unsuccessful results from their third ventriculostomy. One patient (case 4) showed no change from his initial scan obtained on the day of admission. The patient's family requested comfort care only and the patient died 2 days later. In the second case (case 6) the patient had improve-
ment in his neurological examination and ventricle size by CT scan immediately after the operation, but had recurrent symptoms of hydrocephalus 11 days later. After placement of a ventriculoperitoneal shunt, his examina-
tion returned to baseline. Every patient except the person described in case 4 received brain radiation therapy after the palliative procedure. One patient (case 3) underwent a course of radiation treatment prior to the operation. Another (case 5) had radiation to her orbit in the dis-
tant past after enucleation for retinoblast-
amia. Even though previous radiotherapy may be considered a contraindication for third ventriculostomy by some authors, it did not seem to affect the success of third ventricu-
lostomy in our patients. Carcinomatous menin-
giomas which could have caused a contri-
tant communicating hydrocephalus was not grossly evident on examination, on any of the brain imagnings, or during endoscopy. How-
ever, tumours in contact with CSF space can also cause a communicating hydrocephalus by raising CSF protein which can obstruct the CSF pathway. However, two out of
three families having a su
eight patients with hydrocephalus caused by metastatic tumours of the posterior fossa or thalamus. They typically presented with symptoms of acute hydrocephalus in addition to any local mass effect of the tumour. Postoperatively, five patients were relieved of hydrocephalic symptoms and follow up brain imaging studies disclosed decreased ventricu-
lar size. These five patients had a median hospital time of 6.5 days and median survival of 95 weeks after the operation. One patient's 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 3 to 6 days and had their third ventriculostomy as a palliative proce-
dure.
We performed third ventriculostomy on seven patients with hydrocephalus caused by metastatic tumours of the posterior fossa or thalamus. They typically presented with symptoms of acute hydrocephalus in addition to any local mass effect of the tumour. Postoperatively, five patients were relieved of hydrocephalic symptoms and follow up brain imaging studies disclosed decreased ventricu-
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dure.

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 dis-
ease to pereiventricular brain tissue can obstruct the fourth ventricle, CSF is produced in the ventricles to the subarach-
noid space where it is normally absorbed by arachnoid granulations. This typically causes an obstructive or non-communication hydro-
cephalus. Thus, a drain is customarily 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 success-
ful in relieving the hydrocephalus, it has about a 50% chance of infection or failure from blockage.1
Another option for the treatment of obstructive hydrocephalus is third ventricu-
lostomy, 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 ven-
triculostomy has a low operative morbidity and a high probability of success, it is only commonly used on patients with aqueductal stenosis and the pediatric population. To avoid placing shunts in patients with inoperable metastatic brain tumours who typically have only a few months to live, we have offered the patients third ventriculostomy as a palliative proce-
dure.
Neuronal activity alters local blood flow in brain tumour adjacent to the activating cortex

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

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

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

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

We measured haemodynamic changes in the brain tumour during neuronal activation in the left frontal lobe induced by cognitive

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

<table>
<thead>
<tr>
<th>Case No</th>
<th>Age (y)</th>
<th>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></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></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></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></td>
<td>Rectal adenocarcinoma metastasis to cerebellum</td>
<td>Improved</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>5</td>
<td>39,F</td>
<td></td>
<td>Breast adenocarcinoma metastasis to cerebellum</td>
<td>Failed</td>
<td>4</td>
<td>11</td>
</tr>
<tr>
<td>6</td>
<td>60,M</td>
<td></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></td>
<td>Osteopagial carcinoma metastatic to cerebellum</td>
<td>Improved</td>
<td>7+</td>
<td>1+†</td>
</tr>
</tbody>
</table>

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

To activate the left frontal lobe, we used the following four tasks: (1) semantic verbal fluency, which entails naming as many items in a semantic category (for example, animals) as possible; (2) confrontational naming, which involves naming ordinary items presented by the tester; (3) backward digit span, a working memory task which involves reporting of digits (2 to 8) in the reverse order; and (4) naming, 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.1 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 case, the discrepancy from our previous studies strongly suggests that the tasks caused an increase in rCBF in the left frontal lobe of the patient.

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.1 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.1 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.

The decrease 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.1 Although the physiological mechanisms of the decrease in rCBF during neuronal activity have not yet been elucidated, we hypothesis that a stealing of blood flow is one of the mechanisms.2 The present report supports this hypothesis.

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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.1 In one fourth of total migraineurs, visual aura was preceded by an aura.2 We describe a patient with recurrent episodes of migraine in whom headache was preceded by a constellation of visual symptoms which constituted salient components of Balint’s syndrome. This syndrome, consisting of a triad of simultanopsia, optic ataxia, and oculomotor apraxia, is seen with bilateral lesions of occipitoparietal cortices affecting connections between visual cortical regions and the frontal eye field.3

A 29 year old female teacher presented with an 8 year history of paroxysmal alternating hemianopia and throbbing headache which was often associated with nausea, phonophobia, and occasionally vomiting. Headache used to last for about 4 to 8 hours and would respond to either ergot drugs or sumatriptan, especially if taken during the waning of the episode. 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. Neurologically, the patient was fully oriented and had no visual field defects. 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. The visual impulses, after being recorded from 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 that controls visual attention fibres. Any lesion in the visual association areas or their connections would result in impaired integration of visual impulses despite normal visual acuity.

The visual symptom complex in this case possibly represents an aura of migraine. The pathogenesis of migraine aura has been a debatable issue.3 In this case it is suggested that the pathophysiological process of migraine aura results in a disconnection syndrome by
involved visual association areas and their association pathways. Optic ataxia, gaze apraxia, and simultagnosia seem to represent a dissociation of visual information from the frontal eye field and dorsal parietal regions.

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Correspondence to: Dr Parvaiz A Shah, Firdousa, asymmetric, and showed no evidence of change in the basal ganglion and right cerebellum throughout the white matter, and cystic-like areas in the left cerebral hemisphere. Brain MRI (Access Toshiba LPT 6.01p, 0.064 Tesla) showed areas of high signal intensity indicating postrabies encephalomyelitis, the development of which is almost invariably fatal. Antiparalytic actions and postvaccinal 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 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.

There are three types of postexposure vaccine in use worldwide. The Simple type (STV) is obtained from inactivated virus prepared on adult mouse brains; 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 220 courses, with a 3% mortality. Clinical forms include a reversible mononeuropathy multiplex, and meningoencephalitic 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.

Tolerance has been improved by the development of the suckling mouse brain vaccine (SMBV). The attenuated virus is cultured on immature mouse brain tissue, which contains little myelin, thus reducing the risk of complications. SMBV is inexpensive (US$1.5 per treatment course) and easily manufactured locally; it is the most widely used postexposure vaccine in Vietnam. Rare neurological reactions do occur with SMBV. Complications of the CNS have been reported to occur after vaccination with an incidence of 1:2700 treated people, with a 22% mortality.

The mortality was particularly high (60%) if the vaccine was extensive CNS involvement. The third type of vaccine available is the human diploid cell culture vaccine (HDCV), which is both safe and efficacious. However, the recommended regimen is not affordable in most developing countries.

When we approached the Rabies Laboratory, Ministry of Agriculture and Fisheries, United Kingdom for advice in this case their comment was “why do you use the SMBV, can’t you use another vaccine”. Worldwide about 10 million people each year receive rabies vaccine after exposure; at the Centre for Tropical Diseases we treat 3000 people exposed to animal bites in such countries.

This is the first report to show the demyelinating 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 reactions to SMBV is very much lower than with 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 steroids in postexposure vaccine encephalitis and the urgent need for the development and deployment of a safe, and critically, affordable 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 multiple injections on days 0, 7, 14, and 28) could be made affordable, and offers excellent protection without the risks of postexposure immune mediated encephalitis.

Brain MRI in July 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 May 1997. T2 weighted image shows resolution of the white matter lesions.

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Leukoencephalopathy associated with khat misuse

The leaves of the tree Catha edulis, or khat (also qat and kat) are chewed by a large proportion of the adult population of the Yemen, and throughout Saharan and sub-Saharan Africa. The leaves are also chewed by members of the Yemeni and Somali community in the United Kingdom. The psychoactive constituents of khat are cathin (d-norpseudoephedrine), cathine, and cathinone (a hallucinogenic alkaloid). Folks chew in small bundles resembling ephedrine and amphetamine) and users report a mild euphoria similar to that of amphetamine.

Khat is acknowledged as a przez khat or amphetamine misuse; it has, reports of leukoencephalopathy in association with khat misuse. The leaves of the tree Catha edulis, or khat (also qat and kat) are chewed by a large proportion of the adult population of the Yemen, and throughout Saharan and sub-Saharan Africa. The leaves are also chewed by members of the Yemeni and Somali community in the United Kingdom. The psychoactive constituents of khat are cathin (d-norpseudoephedrine), cathine, and cathinone (a hallucinogenic alkaloid). Folks chew in small bundles resembling ephedrine and amphetamine) and users report a mild euphoria similar to that of amphetamine. Khat is acknowledged as a psychoactive substance that has 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 Yemeni 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 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 held in flexion with markedly increased tone. Reflexes were brisk but equal. The right plantar was extensor. There were bilateral palmar and grasp reflexes.

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

Examination of the CSF showed normal opening pressure and protein 0.27 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 nerves and the cerebellum were intact. He had weakness of the limbs. He had no anaemia, and atrophy of bilateral thenar, interossei, and vibratory sensation in both hands and feet.

We report the clinical, electrophysiological, and pathological findings of a case of leukoencephalopathy in association with khat misuse. The leaves of the tree Catha edulis, or khat (also qat and kat) are chewed by a large proportion of the adult population of the Yemen, and throughout Saharan and sub-Saharan Africa. The leaves are also chewed by members of the Yemeni and Somali community in the United Kingdom. The psychoactive constituents of khat are cathin (d-norpseudoephedrine), cathine, and cathinone (an hallucinogenic alkaloid). Folks chew in small bundles resembling ephedrine and amphetamine) and users report a mild euphoria similar to that of amphetamine.

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

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

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Examination of the CSF showed normal opening pressure and protein 0.27 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 nerves and the cerebellum were intact. He had weakness of the limbs. He had no anaemia, and atrophy of bilateral thenar, interossei, and vibratory sensation in both hands and feet. Deep tendon reflexes were hypoactive. Babinski’s sign was negative.

Laboratory investigation showed a raised erythrocyte sedimentation rate: 52 mm/hour (normal <10) and serum C reactive protein: 1.8 mg/dl (normal <0.5). Blood cell counts were within normal limits. The following were normal or negative: IgG, IgA, IgE, IgM,
M-protein, direct and indirect Coombs tests, cryoglobulin, antibodies to mycoplasma, myelin associated glycoprotein, gangliosides (GM1, GD1b, asialo-GM1, GT1b, GQ1b, Gal-C), P-ANCA, and C-ANCA. The CSP was normal. Titre of cold agglutinins was detectable at 1:256 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. Immunoelectrophoresis of the eluate confirmed IgM composition.

The initial nerve conduction study showed severe diminution or absence of compound nerve action potentials (CNAPs) with mildly diminished conduction velocities. 

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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 tibialis muscle. Sural nerve biopsy was performed. Epineurial vessels were surrounded by mononuclear cell infiltrates (figure A). Some vessels had focal necrosis of vessel walls. The small vessels in the endoneurium and epineurium showed sloughing of red blood cells. The densities of large and small myelinated fibres were markedly decreased (diameter<5 µm: 1504/mm²; diameter >5 µm: 708/mm²; total: 2212/mm²)(figure B). 

Teased fibre analysis showed that 90% of the fibres were undergoing axonal degeneration. Oral prednisolone (30–50 mg/day) for 4 weeks reduced the erythrocyte sedimentation rate and C reactive protein, but not the serum titre of cold agglutinins; neither was there any improvement of symptoms. He received massive dose intravenous corticosteroid therapy. This moderately improved the muscle strength and sensory disturbance. Follow up nerve conduction studies (71 days after the initial study) suggested conduction block of the right median nerve on the forearm (CMAP, duration at the wrist: 2.76 ms, 8.4 µm; CMAP, duration at the elbow: 1.87 ms, 8.8 µm), whereas CMAP could not be elicited in the initial study. We adapted the following criteria to define conduction block: <15% change in duration and >20% fall in negative peak amplitude between proximal and distal sites by percutaneous supermaximal stimulation of motor nerves. As the conduction block might delay smooth recovery of symptoms, Double filtration plasmapheresis was performed four times. After the second plasmapheresis, dysesthesia and muscle strength improved remarkably. The titre of cold agglutinins was reduced to 1:64. The motor nerve conduction velocity (MCV) of the right median nerve likewise improved (pretreatment: 40.0 m/s, post-treatment: 57.0 m/s). Double filtration plasmapheresis was followed by oral azathioprine (50 mg/day) with tapering of steroid. He was discharged on prednisolone (20 mg/day). In the subsequent 4 years, he has had mild 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 containing myelin debris; (3) probable conduction block in the median nerve; (4) increased concentrations of serum titres of cold agglutinin; and (5) marked response to plasmapheresis. Extensive investigations for other causes of neuropathy was negative except for an increased serum concentration of cold agglutinins, which strongly suggests that cold agglutinins may play an important part in the induction of neuropathy in this case.

Six patients with neuropathy associated with cold agglutinins have been reported including our patient. Cold agglutinins are cold reactive autoantibodies that react with the antigenic determinant termed I/i or Pr present on glycoproteins and glycolipids in erythrocyte membranes. Ari et al reported a case of polyneuropathy and IgM M proteinemia with anti-Pr2 CA activity. IgM M protein cross reacted with sialosyl paragloboside, GT1b, GD1a, GD1b, GM3, and GD3 present in myelin and in endothelial cells of the peripheral nervous system. It has been speculated that anti-Pr2 IgM protein induced immune mediated damage to vascular endothelium and peripheral nervous system myelin. A similar pathomechanism has been postulated in the other cases. However, necrotising vasculitis has never been reported in neuropathy with cold agglutinins. This is the first demonstration of vasculitic neuropathy with cold agglutinins.

The mechanism for neuropathy with cold agglutinins is unknown, mechanisms similar to those in cryoglobulinaemic neuropathy have been postulated. The hypotheses are (1) immunologically mediated demyelination; (2) ischaemic injury secondary to sluggish or agglutination of red blood cells in the vasa nervorum; and (3) an associated vasculitis. In the present case, we have confirmed the necrotising vasculitis and probable conduction block. Pathophysiological explanations for association of vasculitis and conduction block may be as follows. Firstly, conduction block may occur as a consequence of nerve ischaemia due to small vessel occlusion. There have been reports of conduction block occurring in vasculitic neuropathy which support this possibility. Secondly, humoral factors including cold agglutinins may induce 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.

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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 representatives presenting data from a clinical study also commonly use this statement. However, this only partially reveals the truth. In fact, the same study produced improvement or no deterioration in 59% patients on placebo. I think that the beneficial effect of donepezil in particular clinical trials should always be critically reviewed in comparison with placebo. In addition, as both 24 week placebo controlled donepezil trials performed so far excluded patients with behavioural disturbances, my impression is that the positive effect of donepezil on the symptoms of behavioural disturbances still remains controversial. In fact there are reports that donepezil might induce behavioural disturbances in patients with Alzheimer’s disease.

Therefore, I would be extremely cautious about prescribing donepezil to patients with Alzheimer’s disease accompanied by behavioural disturbances.

Finally, donepezil was never investigated in a 36 week randomised double blind study as was mentioned in the review. The authors are probably referring to the randomised 24 week double blind placebo controlled trial with an additional 6 week single blinded placebo phase.

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BOOK REVIEWS


The neuropathies of diabetes are common (as the chapters in this book repeatedly remind us) and can be very disagreeable. Symptoms are foot ulceration and sepsis as the commonest clinical consequence of diabetic neuropathy but also 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 and, in regard, understanding of this complication both in clinical and pathological terms, as well as with regard to treatment, lags far behind that of the other classic diabetic complications, nephropathy and retinopathy. Even its classification presents problems and attempts to do so are found in four different chapters, describing four classifications. Repetition is an unfortunate feature of this book and—quite apart from the confusion over classification—aspects of pathogenesis, structural changes, epidemiology, diagrams, and some reference to treatment (for example, that of pain) appear repeatedly in different chapters in greater or lesser detail.
Some extent, comprehensive but lacking 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 or 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 taxied the minds of clinicians from early in the history of the specialty, starting with Zernov’s encephalometer more than a century ago. Just as the solution to the mariners’ problem of determining longitude from which it partly takes its name, neuronavigation (“the surgeon’s sextant”) has relied on the advent of new technologies to provide solutions to an age old puzzle.

Advances in Neuronavigation begins by 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/MRI frame based stereotaxis. The final part of the first section discusses the roots of image guided frameless stereotaxis through the integration of high speed graphics computers, informatics, biotechnology, and robotics.

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

The incorporation of new technology is likely to alter surgical practice radically over the coming decade and equipment that seemed at the cutting edge of technology only a few years ago, such as the mechanical arm, has already passed into near obscurity 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 contains the usual proclamations. “Concise, key topics, revision aid, essential, review…” the well trampled soundbites demanded by the consumer in the increasingly competitive market of “read them, 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 that this would have complemented the overall style of the book. These are minor gripes that this would have complemented the overall style of the book.

R. P. Santosh


CORRECTION

K Sudo, N Fujiki, S Tsuji, M Aijki, 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: hyperhidrosis v normohydrosis 0.0007; hypohydrosis v normohydrosis 0.7282; normohydrosis v hypohydrosis 0.0012 should read—p value for each pair of items: hyperhidrosis v hyperhidrosis 0.0007; hypohydrosis v hypohydrosis 0.0012; normohydrosis v hypohydrosis 0.0012.