LETTERS TO THE EDITOR

Magnetic resonance imaging and vertebral artery dissection

Since the advent of advanced radiological modalities such as MRI and magnetic resonance angiography (MRA), dissections of cervical arteries are increasingly recognised as a common cause of stroke in young adults. Auer et al. recently advocated MRA as the initial diagnostic tool for vertebral artery dissection. Conventional angiography might be avoided altogether in subjects with a suspicious history and MRA images suggestive of a dissection (double lumen or mural haematoma). The sensitivity of MRA for the diagnosis of vertebral artery dissection was only 20% in one study, but the specificity was excellent (100%). The sensitivity was considerably better in the hands of Auer et al., but in this study the specificity (true negative rate in subjects free of disease) was not considered because all patients had vertebral artery dissection. The following case report illustrates that care must be taken to avoid false positive results when using MRA for the diagnosis of vertebral artery dissection.

A 47 year old male pilot suddenly experienced clumsiness and slight loss of strength in the right arm and leg during a long distance flight, while he stooped forward. During the following hours, he developed a global headache without irradiation to the neck, but the other symptoms gradually diminished. Prior history was unremarkable, except for a 3 hour period of horizontal diplopia which suddenly developed 3 months earlier. He had never smoked. Family history was negative for cardiovascular disorders. The patient later confessed that he had recently picked up the habit of gargling his throat with toothpaste twice a day, always with his neck in extreme retroflexion.

General physical examination (8 hours after onset of symptoms) was normal. Neurological examination showed minimal paresis and impaired dexterity of the right hand, mild circumduction of the right leg, and an insecure tandem gait. An MRI (including T1 weighted spin echo images with and without fat suppression, and proton density and T2 weighted fast spin echo sequences, performed on a 1.5 Tesla whole body MRI system) performed several hours later visualised both a fresh and an old right sided cerebellar infarct (figure A). In addition, MRI showed an irregular right vertebral artery in which a patent lumen was partially surrounded by a semilunar area of high signal intensity on T1 and T2 weighted images. On fat suppressed images, this area's high signal intensity persisted, excluding the possibility that it originated from perivascular fat. This image was suggestive of mural haematoma due to vertebral dissection (figure B). Because we were reluctant to base any treatment decisions (anticoagulants) merely on MRI findings, digital subtraction angiography was performed on the day of admission. This examination was normal (figure C). Shortly after this procedure, the patient developed vertigo and nystagmus which disappeared after 3 hours. Because we were puzzled by the discrepant findings on conventional angiography and MRI, we performed an MRA 4 days later. At this examination, the semilunar area of high signal intensity was found again (figure D), despite saturation of craniofugal and craniopetal flow respectively, which was applied to exclude the possibility that the high signal originated from flow in the periarterial venous plexus. Therefore, this examination was again suggestive of right vertebral artery dissection. An extensive search for other causes of stroke showed no abnormalities. Hence, due to the continuing discrepancy between conventional angiography and MRA/MRA, and due to the absence of any other cause of stroke, no certain diagnosis could be established.

In this patient, a diagnosis of right vertebral artery dissection was initially made given the clinical course with repeated episodes of ischaemia restricted to the vertebrobasilar system, as well as the suggestive MRI findings. We speculated that habitual gargling was a potential underlying cause, as neck retroflexion can cause cervical dissections. However, we had to reject this diagnosis in view of the normal conventional angiography, which remains the gold standard for diagnosing cervical artery dissection. In one series, conventional angiography was never falsely negative in patients with clinical signs or symptoms of vertebral artery dissection. The possibility that conventional angiography had nevertheless yielded a false negative result seems highly unlikely. In dissected arteries, MRI/MRA can detect intimal flaps, mural haematomas, or aneurysmal dilatations that are sometimes missed by conventional angiography, but even in such patients, conventional angiography is never completely normal in the acute stage. Follow up examinations of patients with proven vertebral artery dissection indicate that the appearance of a dissected artery on conventional angiography can normalise in a substantial proportion of patients, but always after an interval of at least 1 to (usually) several weeks. Conventional angiography in our patient was performed on the day of admis-
Arterial dissection of the vertebral arteries is a rare cause of posterior circulation strokes. It is usually diagnosed by MRA or digital subtraction angiography. However, MRA has some specific advantages. It is non-invasive and can be performed as an outpatient procedure. Furthermore, MRA does not carry the risk of contrast allergy or renal impairment that is associated with angiography. Therefore, MRA is the preferred imaging modality for the diagnosis of vertebral artery dissection.

Our “pilot study” illustrates the specificity of MRI/MRA for the diagnosis of vertebral artery dissection. Two anatomical structures surrounding vertebral arteries contribute to these problems. The first structure is the venous plexus that surrounds vertebral arteries. This structure may have a semilunar appearance, and slow flow in its lumen may give rise to high signal intensity on T2-weighted images. The second structure is the perivascular venous plexus, which may be suppressed by saturation slabs. However, this structure cannot always be suppressed.

The second structure that may falsely present as a dissection is fat that directly surrounds vertebral arteries. This fat also gives rise to high signal intensity on T2-weighted images. However, this structure cannot always be suppressed.

Decisions based on false positive MRA results can be hazardous due to the sometimes severe side effects of anticoagulation. Therefore, the team that is recommended by some to prevent further ischaemic events. Another danger of a false positive diagnosis of vertebral artery dissection is that it may preclude the search for other causes of stroke that could be amenable to secondary prevention.

MRI/MRA remains important because it helps visualise ischaemic lesions and, in some patients, provides complementary morphological information to cerebral angiography. Furthermore, it is a non-invasive procedure, an important advantage over cerebral angiography which carries a morbidity and mortality risk. Our patient, who developed transient neurological deficits shortly after the onset of symptoms showed high intensity areas in the pons, caudate, and putamen consistent with CPEM (figure A, B). Physical and occupational therapy were instituted and she gradually recovered over the next two weeks. She was transferred to a rehabilitation hospital where she recovered completely and returned to live independently.

Cortical spinal tract signs are usually overshadowed by florid signs of brainstem and pyramidal tract dysfunction. Behavioural changes such as inappropriate affect, emotional lability, personality changes, paranoia, poor judgment, emotional incontinence, and disinhibition have been reported. Price and Mesulam described a case of pontine myelinolysis in which transient pyramidal signs were followed by confusion, restless behaviour, pressured tangential speech, and disinhibition. Our patient also had transient long tract signs but they were followed by a catatonic state.

The extensive extrapontine myelinolysis present in our patient may explain the behavioural symptoms we encountered. CPEM presents with tетraparesis and pseudobulbar palsy. Although psychiatric manifestations of CPEM have been recognised they usually manifest as an agitated delirium, or a pseudobulbar state with pathologically laughing and crying. When present, neuropsychiatric symptoms are usually overshadowed by florid signs of brainstem and pyramidal tract dysfunction.
Association between butyrylcholinesterase K variant and the Alzheimer type neuropathological changes in apolipoprotein E ε4 carriers older than 75 years

Apolipoprotein E (ApoE) ε4 has a strong influence on the development of sporadic Alzheimer’s disease in many ethnic populations. However, ApoE ε4 is neither necessary nor sufficient for the development of Alzheimer’s disease, suggesting that other genes increase the risk of Alzheimer’s disease. One such new candidate is the butyrylcholinesterase (BChE) gene (BCHE). BCHE is associated with senile plaques (SPs) and neurofibrillary tangles (NFTs) (et al 1993:559–73). Price et al (1994) reported the K variant of BCHE (BCHE-K) was associated with the development of Alzheimer’s disease, especially in ApoE ε4 carriers older than 75 years. A possible mechanism as to how BCHE-K is related to Alzheimer’s disease under the influence of ApoE ε4 is the acceleration of Alzheimer type neuropathological changes. If BCHE-K has an effect on the development of Alzheimer’s disease in ApoE ε4 carriers, the formation of Alzheimer type neuropathological changes may be accelerated by BCHE-K in the ApoE ε4 carriers.

We have examined genotypes of BCHE and ApoE, and densities of the senile plaques (SPs), with dystrophic neurites (NPs), and neurofibrillary tangles NFTs in the brains from 51 patients with Alzheimer’s disease and 90 non-demented subjects from a poor term series of Japanese. Clinical and postmortem diagnosis of Alzheimer’s disease was carried out as described previously. The densities of Alzheimer type neuropathological changes were quantified by averaging the counts of those in the hippocampus and superior temporal gyrus. Genotypes of BCHE and ApoE in all patients were determined as described elsewhere. Genotypic and allelic distributions of BCHE were analysed by χ² test. The densities of the SPs, NPs, and NFTs, and ages at onset and durations of illness were compared among BCHE genotypes with the Kruskal-Wallis test or Mann-Whitney U test in total subjects, those with Alzheimer’s disease, and non-demented subjects. We also examined these relations in the subgroups divided by the ApoE ε4 status or the age of 75 years. Statistical significance was defined as two tailed probabilities of <0.05.

There were no significant differences in the frequency of BCHE-K genotypes or alleles between patients with Alzheimer’s disease (0.16 in allele frequency) and non-demented subjects (0.18), and in the total subjects, ApoE ε4 carriers or non-ApoE ε4 carriers, although a strong association of ApoE ε4 alleles with Alzheimer’s disease was found in this population (p=0.004). Genetic association of BCHE-K genotypes with sporadic Alzheimer’s disease was non-significant in all subjects older than 75 years, the ApoE ε4 carriers older than 75 years, and non-ApoE ε4 carriers older than 75 years. There was no genetic association of BCHE-K with the densities of the SPs, NPs, or NFTs in the hippocampus and superior temporal gyrus in the total subjects, in the Alzheimer’s disease or non-demented groups, or with ages at onset or duration of illness in Alzheimer’s disease. However, when we divided total subjects into two subgroups with different ApoE ε4 status, there was significant association between BCHE-K and the density of the SPs and NPs in the superior temporal gyrus after STG in the ApoE ε4 carriers (SPs, p=0.04, NPs, p=0.03, data not shown). Further, we analysed the correlation between BCHE-K and the densities of the SPs, NPs, and NFTs in the hippocampus and superior temporal gyrus in the ApoE ε4 carriers older than 75 years and non-ApoE ε4 carriers older than 75 years. In the ApoE ε4 carriers a significant genetic association of BCHE-K with the densities of the SPs, NPs, and NFTs in the STG in the ApoE ε4 carriers older than 75 years. There was a decrease of severity of Alzheimer type neuropathological changes with BCHE-K. A similar trend was seen in the hippocampus though this did not reach significance.

Our results showed that BCHE-K might have no effect on the severity of sporadic Alzheimer’s disease even in the ApoE ε4 carriers or subjects older than 75 years. By contrast with a significant genetic association in patients confirmed at postmortem in the British population, there was no correlation in the Japanese population. Although our sample size was small, there were not even trends for a positive association in our study, suggesting that the lack of association was not due to small sample size. The frequency of BCHE-K in our Japanese control population was 0.18. This was not significantly different from that in the British population examined by Russ et al (0.20). However, the frequency of BCHE-K in the British control population reported by Lehmann et al was 0.09, which was significantly lower than our results (p=0.04). These findings indicate that the frequency of BCHE-K and its genetic linkage with the development of Alzheimer’s disease would be different among sample populations.

Our neuropathological study disclosed a significant association of BCHE-K with Alzheimer type neuropathological changes in the ApoE ε4 carriers older than 75 years, but not in the non-ApoE ε4 carriers. Lehmann et al showed that BCHE-K was strongly associated with the development of Alzheimer’s disease in the ApoE ε4 carriers older than 75 years. Analyses of the same subgroup of ApoE ε4 carriers older than 75 years increased statistical significance in both our studies and those of Lehmann et al. This suggests that BCHE-K as a genetic marker is linked with formation of Alzheimer type neuropathological changes or development of Alzheimer’s disease in the ApoE ε4 carriers older than 75 years. However, a decrease of the severity of Alzheimer type neuropathological changes with BCHE-K in our study was not expected because Lehmann et al showed an increase in frequency of the BCHE-K allele in Alzheimer’s disease. Singeton et al also reported that BCHE-K was not associated with the densities of the SPs and NFTs, even in the ApoE ε4 carriers. In addition, BCHE-K was not related to the development of Alzheimer’s disease in the ApoE ε4 carriers in our study. Russ et al and Singeton et al also showed a lack of association between BCHE-K and the development of Alzheimer’s disease. However, Hiltunen et al showed that BCHE-K had a protective effect on the development of Alzheimer’s disease in ApoE ε4 carriers younger than 75 years. The effects of BCHE-K on the Alzheimer type neuropathological changes or development of Alzheimer’s disease are different among studies, suggesting that the significant genetic association in the studies by Lehmann et al, Hiltunen et al, and ourselves might be linkage disequilibrium with relevant variability in BCHE or other alladine gene on chromosome 3, and that BCHE-K does not play a direct part in the pathogenesis of Alzheimer’s disease.

<table>
<thead>
<tr>
<th>BCHE genotype</th>
<th>ApoE ε4 carriers over 75 years (n=28)</th>
<th>non-ApoE ε4 carriers over 75 years (n=95)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>K/K (n=8)</td>
<td>K/K (n=4)</td>
</tr>
<tr>
<td>hippocampus:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SPs</td>
<td>3.0 (0.0, 17.2)</td>
<td>0.0 (0.0, 5.7)</td>
</tr>
<tr>
<td>NPs</td>
<td>0.7 (0.0, 11.9)</td>
<td>0.0 (0.0, 3.5)</td>
</tr>
<tr>
<td>NFTs</td>
<td>1.1 (0.4, 23.1)</td>
<td>3.9 (0.9, 10.0)</td>
</tr>
<tr>
<td>superior temporal gyrus:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SPs</td>
<td>0.2 (0.0, 22.8)</td>
<td>0.0 (0.0, 58.0)</td>
</tr>
<tr>
<td>NPs</td>
<td>0.2 (0.0, 8.8)</td>
<td>0.0 (0.0, 3.7)</td>
</tr>
<tr>
<td>NFTs</td>
<td>0.0 (0.0, 0.2)</td>
<td>0.0 (0.0, 0.0)</td>
</tr>
</tbody>
</table>

Values are medians (25th percentile, 75th percentile). The density represents the average counts in 2.56 mm² for the SPs and NPs, and in 0.64 mm² for the NFTs. BCHE=butyrylcholinesterase gene; ApoE=apolipoprotein E; K=the K variant allele of butyrylcholinesterase gene; N=the normal allele of butyrylcholinesterase gene; SPs=senile plaques; NPs=senile plaques with dystrophic neurites; NFTs=neurofibrillary tangles.
The patient was a 71 year old, retired physician with a 3 to 4 year history of memory impairment. Neuropsychological evaluation disclosed a high average to superior general intellectual functioning, with mild impairment in naming to confrontation and episodic memory from the verbal memory. His visuospatial ability remained relatively unimpaired and was rated as average for his age. His comprehension for verbal and written instructions were intact. At the present time he is still well oriented to time and place, and is somewhat independent in activities of daily living. He is, remarkably, not depressed, but does, repeatedly, raise concern regarding the time when he has become to his wife." Moreover, mild hypophonia in the frontotemporal lobes bilaterally was seen on SPECT investigation and no evidence of pathognomonic laboratory results were found. Taken together, the pattern of episodic memory and naming impairments and functional imaging findings was thought to be consistent with the early stages of dementia of the Alzheimer's type (DAT) in keeping with National Institute of Neurological and Communicative Disorders Association-Alzheimer's Disease and Related Disorders Association criteria. The patient was consequently referred to our department for "prospective memory book training" and follow up assessments to index progression of disease.

During our sessions his wife had stated that the patient could no longer read aloud, that he could no longer read his newspaper for "prospective memory book training" and could not produce the same acoustical quality of the phrase to the experimenter's reading of the word(s) or sentence which incorporated the appropriate prosodic elements only after he was asked to describe the affective prosodic quality of the phrase to ensure good comprehension. Five age matched normal healthy controls volunteered to read the items found in the table, and in each case, read spontaneously the word or phrase with appropriate and expected prosody.

The patient was unable to read any words or sentences with normal (appropriate and expected) prosody. Indeed, the patient had lost his ability to "act." The patient's use of prosody did, however, improve dramatically with instruction. That is, he was able to repeat eight of the 10 items in the table with appropriate and expected prosody. Interestingly, the single item that he continued to have trouble producing was item three (You know...there was a time when...). Hence, he had available the knowledge to successfully select and use appropriate prosody, but failed to produce prosodic speech to command, dysfunction of the praxis production system is implied rather than the conceptual system. The functional neurological basis of affective language in the right hemisphere is indeed dominant for organising the affective-prosodic components of language and gestural behaviour and that the functional neurological basis of affective language in the right hemisphere was analogous to the organisation of propositional language in the left (non-dominant) hemisphere. Conceptually, there is evidence of poor affective prosody to command yet normal spontaneous affective prosody, and good affective prosodic repetition and comprehension would suggest a "transcortical aprosodia." Note however, that the patient's spontaneous prosody was unaffected whereas spontaneous speech is affected by a transcortical motor aphasia. Hence, we might place the critical lesion for prosodic apraxia in the right dorsolateral frontal lobe, extending into the deep frontal
white matter, in keeping with typical dominant hemispheric lesions producing transcortical motor aphasia. This speculation is supported by the patient’s SPECT findings of mild hypoperfusion in the frontotemporal lobes bilaterally.

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Vocal cord abductor paralysis in spinocerebellar ataxia type 1

Vocal cord abductor paralysis (VCAP) is considered a sign of a poor prognosis in neurodegenerative diseases, because severe laryngeal dysfunction by VCAP may result in acute airway obstruction and require emergency tracheostomy.1 Although VCAP is a cardinal feature in multiple system atrophy (MSA), it has not been reported in several types of spinocerebellar ataxia with dominant inheritance. We evaluated the movements of the vocal cords of seven patients with SCA1 by laryngofibroscopy.

Seven unrelated patients with SCA1 who had the expanded CAG repeat of ataxin-1 were investigated. There were two men and five women ranging in age from 27 to 67 years old (mean 44.5 years). Spouses and other family members, in addition to the patients, were questioned about events of stridor, dysphagia, and dyspnoea. Vocal cord movement was examined by laryngofibroscopy and recorded during inspiration and phonation.

The rating scale used to evaluate maximal abduction of the vocal cords during laryngofibroscopy was as follows: (-)=normal; (+)=median position; (++)=paramedian position; (+++)=midline position. For the evaluation of VCAP, we tried the respiratory flow volume loop study as well as in one patient (patient 2) in whom maximal abduction of the vocal cords was slightly limited (+) on laryngofibroscopy.

The correlations between VCAP and CAG repeat length and duration of illness were analysed with the non-parametric Mann-Whitney U test.

The clinical features, including the vocal cord findings, are summarised in the table. VCAP was present in five of the seven patients with SCA1. Although it is difficult to know when the VCAP first became manifest in each patient, patient 1 showed VCAP confirmed by laryngofibroscopy only 2 years after the onset of gait disturbance. All five patients with VCAP showed mild dyspnoea requiring no tube feeding, and four patients had a history of stridor at night. Patient 1 showed VCAP accompanying dyspnoea without stridor at night even in an early stage of the disease. The VCAP was found to be severe on laryngofibroscopy in all three patients with breathing difficulty on inspiration. Patient 2, who had the severest VCAP, developed stridor during wakefulness as well. In patients 4 and 5, the breathing difficulty on inspiration was improved by tracheostomy. The respiratory flow volume loop study did not detect abnormality in patient 2.

The CAG repeat number tended to be higher in the patients with VCAP than in the patients without VCAP (p=0.05), but the duration of illness was not significantly correlated with the presence of VCAP (p=0.43).

This is the first report that VCAP often is found in patients with SCA1. As VCAP may not always be a late feature in patients with SCA1, evaluation of VCAP is necessary even in early stages of the disease. It is not surprising to find VCAP in patients with stridor, because stridor is usually caused by airway obstruction of the larynx. However, VCAP was detected by laryngofibroscopy in a patient without stridor who had dysphagia. Furthermore, all patients with VCAP exhibited dysphagia. We therefore think that laryngofibroscopy should be performed in SCA1 patients with dysphagia as well as stridor.

The mechanism of VCAP may be divided into some types, the paralytic type, the non-paralytic type, and these two combined type.1 The first is possibly caused by loss of neurons in the nucleus ambiguus.3,4 The second is considered to be due to overactivity of the intrinsic laryngeal muscles.3 Stridor due to paralysis has been found to be more prominent in sleep than during wakefulness; whereas stridor by non-paralytic dysfunction has been found both during the daytime and during sleep.5 We suspect that the VCAP in patients with SCA1 may be dominantly paralytic, because the nucleus ambiguus is sometimes pathologically involved in SCA1 and because stridor in our patients with SCA1 was more marked in sleep.

Our laryngofibroscopic findings suggested that severe VCAP caused breathing difficulty on inspiration in the patients with SCA1 by obstructing the airway. Moreover, the stridor during wakefulness as well as sleep indicated it to be very serious. The important question concerns when tracheostomy should be carried out after the diagnosis of VCAP to prevent respiratory abnormalities leading to sudden death. Although we consider tracheostomy at the stage when breathing difficulty on inspiration or stridor during wakefulness is noted, it awaits further study with a large number of patients to decide which stage is best for tracheostomy.

Furthermore, we now consider endoscopic cord lateralisation as another possible management for VCAP.

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Brief summary of the clinical features and CAG repeat numbers in the patients with SCA1

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (y)</th>
<th>Sex</th>
<th>Onset</th>
<th>Disease duration (y)</th>
<th>Stridor at night</th>
<th>Stridor during wakefulness</th>
<th>Dysphagia</th>
<th>Breathing difficulty</th>
<th>Tracheostomy</th>
<th>(CAG)n of mutant allele</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>30/M</td>
<td>28</td>
<td>2</td>
<td>(+)</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>2</td>
<td>39/F</td>
<td>39</td>
<td>3</td>
<td>(+)</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>3</td>
<td>27/F</td>
<td>20</td>
<td>7</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>4</td>
<td>34/M</td>
<td>23</td>
<td>11</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>5</td>
<td>56/F</td>
<td>46</td>
<td>9</td>
<td>+++</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>6</td>
<td>67/F</td>
<td>51</td>
<td>14</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>7</td>
<td>50/F</td>
<td>41</td>
<td>8</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
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</tr>
</tbody>
</table>

*(−)=normal; (+)=median position; (++)=paramedian position; (+++)=midline position.
Lateral gaze synkinesis on downward saccade attempts with paramedian thalamic and midbrain infarct

The symptoms of paramedian thalamic and midbrain infarct include ocular motor disturbances mainly in the vertical plane. We here describe a patient with the additional feature of an unusual horizontal eye movement synkinesis.

A 60 year old overweight man, with diabetes and mild hypertension, suddenly fell into a coma that lasted for 4 hours and was followed by slight right hemiparesis, recent memory impairment, hypersomnia, and vertical gaze impairment.

On admission to our centre, about 10 days after symptom onset, the patient still presented fluctuating drowsiness from which he could be easily aroused, normal cognitive functions with mild attention disturbance, slight right facial weakness, and mild incoordination at the finger-to-nose test with his right arm.

The most important findings involved ocular motor function. Both pupils were normal in diameter and reacted normally both to light and to convergence. The cover test did not disclose any eye misalignment. During attempted fixation, the patient showed saccade oscillations (usually square and macrosquare wave jerks)—that is, back and forth involuntary horizontal saccades with an amplitude ranging from about 2 to about 10 degrees and with an intersaccadic interval of about 200 ms, that brought the eyes away from and back to the fixation point, at an approximate rate of three every 2 seconds.

Clinical examination of eye movements in the horizontal plane and visually guided reflexive saccades recorded by the infrared reflection technique were both normal, whereas the amplitude range of vertical saccade and smooth pursuit eye movements covered only a few degrees of upward gaze. Vertical amplitude range was slightly greater for the vestibulo-ocular reflex in the pitch (yes-yes) plane. Moreover, when the patient attempted to make a downward saccade, he showed a gaze deviation to the left (figure). This synkinesis was more evident when the examiner lifted the patient’s lids, thus preventing lid synkinesis during downgaze. Attempted upward saccades did not produce any horizontal gaze deviation. Finally, the patient showed normal Bell’s phenomenon.

An EEG showed frontal, bilateral theta and theta/delta activity and sporadic horizontal oscillations during vertical saccades detectable in normal subjects. These oscillations suggest that during vertical saccades the inhibition of OPNs disinhibits both vertical and, to a lesser extent, horizontal EBNs.

In our patient, the horizontal gaze deviation was always directed to the left rather than in both directions as during oscillations. Many ocular motor structures, including those located in the midbrain, trigger a purely vertical (downward) saccade only when stimulated bilaterally, so as to nullify horizontal components with different direction depending on the stimulation side. This probably occurs for the riMLF too, as it shows ipsilateral projections to the abducens nucleus. In our patient, the projections to the left nucleus were probably spared by the fact that the lesion predominantly affected the right side.

Overall, our patient's horizontal ocular motor synkinesis is unusual, and probably derives from a strong inhibition of OPNs, which in turn frees the horizontal EBNs, and from an unbalanced activation of the left abducens neurons via riMLF projections spared from the lesion, although it is not possible to exclude the possibility that the unbalanced activation of abducens neurons originated from frontal or parietal cortical areas or from the superior colliculus rather than from riMLF projections.

This hypothesis is strengthened by the reinforcement of the leftward eye deviation when the examiner kept the patient’s lids lifted. Since this manoeuvre prevents lid synkinesis, it results in what resembles an attempted forced lid closure which, on the basis of blink induced eye oscillations, is likely to be an additional stimulus for OPN inhibition. Moreover, although they occur in various conditions, saccade oscillations during fixation are in keeping with a reduction of OPN inhibition level.

In conclusion, our patient presented an ocular motor synkinesis that should be listed among those occurring in thalamomesencephalic infarcts. This sign is unusual and it is likely to be overlooked, but it is fully explicable both by neurophysiology and
by anatomical connections of the saccade system.

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Botulinum toxin is a useful treatment in excessive drooling of saliva

Excessive drooling of saliva or hypersialorrhea is a common problem in neurodegenerative disorders such as motor neuron disease or Parkinson’s disease. It is usually caused by swallowing dysfunction and can facilitate choking, aspiration, and chest infections. Socially it is embarrassing and disabling. There are not many treatment options. Anticholinergic drugs are sometimes tried but are usually of little benefit and side effects (orthostatic hypotension, dizziness, and mental confusion, particularly in the elderly) limit their usefulness.

Occasionally, as a more drastic treatment irradiation of the parotid gland is carried out when hypersialorrhea becomes intractable. Apart from its established usefulness in dystonia and strabismus there are some data showing that botulinum toxin injections are effective in autonomic disorders—for example, gustatory sweating and hyperhidrosis of the palm.5 It has been hypothesised that botulinum toxin may help in sialorrhea.1 In a historical note Erbguth recently pointed out the potential use of botulinum toxin for hypersialorrhea, quoting a paper by the German physician and poet Justinus Kerner written in 1817.6

Botulinum toxin inhibits acetylcholine release in nerve terminals mainly at the neuro-muscular junction, but also in sympathetic and parasympathetic ganglion cells and in postganglionic parasympathetic nerves, by blocking SNAP-25, a protein involved in the fusion of acetylcholine containing vesicles with the plasma membrane.1

Against this background we evaluated the usefulness of botulinum toxin injections into the parotid gland in four patients with excessive drooling of saliva after their consent.

One patient had young onset secondary generalised dystonia with severe mouth opening spasms, one had advanced Parkinson’s disease, the third patient had progressive supranuclear palsy, and the fourth patient had motor neuron disease. Drooling in these patients was so severe that they had to wear a bib or carry a towel around their neck. With one exception 20 units of Dysport (Ipsen) were injected superficially subcutaneously above the angle of the mandible at the posterior margin of the masseter muscle, avoiding the bulk of the muscle. The shorter version (50 units) of the 25 gauge needle was used. Because worsening of dysphagia was feared only 10 U Dysport were injected into each parotid gland in the patient with motor neuron disease. Drooling did not significantly improve in the first 2 weeks due to the low dose of botulinum toxin used. He declined further treatment.

All the other patients had a beneficial response beginning by the end of the first week and lasting 6 weeks in one patient and 3 to 4 months in the others. Apart from subjective improvement reported by the patients and caregivers, reduction of drooling was demonstrated by the fact that the patients did not have to use a bib or towel. One patient had mild worsening of existing dysphagia. Two patients had mild chewing difficulties, possibly due to diffusion of the toxin into the masseter and only one patient complained of a dry mouth. None developed facial weakness. All three patients considered the response good enough and side effects sufficiently minimal to keep them continuing botulinum toxin treatment at regular intervals.

Injections of botulinum toxin into the parotid gland (and other salivary glands) may be an effective and simple treatment for excessive disabling drooling of saliva in selected patients.

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1 Naumann M, Zellner M, Toyka KV, et al. Treat-

Extensive brain calcifications in systemic sclerosis: two cases

Systemic sclerosis (scleroderma) is a multi-system connective tissue disease of unknown aetiology, characterised by progressive fibrosis of the skin and internal organs including the lungs and gastrointestinal tract.1 Pathological calcification of soft tissues (Kronenauer’s calcinosis) is a common feature in the CREST syndrome of scleroderma (calcinosis, Raynaud’s phenomenon, oesophageal dysmotility, sclerodactyly, telangiectasia). By contrast, internal organ calcification is rare, and isolated cases of spinal calcinosi and calcific constrictive pericarditis have been reported.2 We report here the cases of two patients with systemic sclerosis whose CT examination disclosed extensive brain calcifications.

Case 1, a 48 year old man was referred to hospital because of polynucleritis involving the wrists and ankles, Raynaud’s phenomenom. Mini mental state examination score was 23/30. The patient’s wife had noticed that during the previous months, he had a slowed mentation and a depressive mood. Physical examination disclosed a sclerodactyly based on lower extremities.

Routine haematological tests were normal. Antinuclear antibodies were positive at a 1:2000 dilution with nuclear fluorescence. Rheumatoid factors, antidual stranded DNA and antiphospholipid antibodies were negative. There was no cryoglobulinemia. Complement was normal. Lung function tests showed a restrictive syndrome (forced vital capacity=75% predicted). Chest radiography was normal, as were oesophageal manometry and cardiac ultrasonographic examination. A diagnosis of systemic sclerosis was made and the patient was given diltiazem (180 mg/day) and ketoprofene (150 mg/day).

Six months later the patient’s mental status had worsened. He complained of memory loss, poor concentration, and insomnia. On neurological examination he was anxious and very slow in answering questions. Mini mental state examination score was 22/30. The patient was oriented to place, but not to time. Anterograde amnesia was noted. Agnosia, apraxia, and aphasias were absent. There was no muscle weakness and muscle tone was normal, tendon reflexes were all increased. Plantar responses were both flexor. There was no sensory loss or impairment of cranial nerves. Systemic sclerosis signs were unchanged. Routine hematological tests were normal. Results of blood chemical tests were also unremarkable (serum electrolytes, urea, creatinine, iron, including phosphorus and calcium metabolism (serum parathyroid hormone concentration, blood calcium and phosphorus, 25-hydroxyvitamin D, 1,25-dihydroxyvitamin D, calcium, and phosphaturia). Serum concentrations of free triodothyronine, free thyroxine, and thyroid stimulating hormone were normal. Serological tests for syphilis, HIV-1,2, and hepatitis were negative. Brain CT showed bilateral extensive calcification in the dentate nuclei (figure 1A), basal ganglia, and subcor-

tical white matter (figure 1B). On MRI T1 weighted images and T2 weighted images, calcification was visible as a low intensity signal increasing in T1 weighted images and T2 weighted images. The lungs and gastrointestinal tract were normal. On neurological examination no other abnormalities were observed.
were noted. Telangiectasias were present on the face, hands, and palate. The patient complained of pyrosis. Oesophageal manometry showed abnormalities of oesophageal motility. Hand radiography disclosed soft tissue calcifications. Anticitromere antibodies were positive at a 1/1000 dilution. A CREST syndrome was diagnosed and the patient was given buflomedil (600 mg/day) and prednisone (25 mg/day).

One year later she was admitted for the evaluation of recent triasemic attacks (TIAs). During the previous week she had experienced three bouts of expressive aphasia and right hemiplegia, each lasting about 10 minutes. She never smoked and did not have diabetes, hypertension, or dyslipidaemia. The neurological examination was normal. Routine blood chemical tests were normal (serum electrolytes, urea, creatinine) including phosphorus and calcium metabolism (serum parathyroid hormone concentration, blood calcium and phosphorus, 25-hydroxyvitamin D, 1,25-dihydroxyvitamin D, calcitriol, and phosphaturia). Cranial CT showed bilateral calcifications of the basal ganglia, and faint calcifications of the dentate nuclei and rubrum nucleus. Moderate cerebral and cerebellar atrophy was noted. Duplex carotid ultrasound and 24-hour ECG recording were normal. Echocardiography showed a normal left ventricle with an ejection fraction of 60%. There was mild calcification and a thickening of the mitral valve leaflets. Aspirin (250 mg daily) was given at hospital discharge. No further TIA occurred during a 5 year follow up and the patient’s clinical status has remained unchanged.

Systemic sclerosis is a multisystem disease predominantly affecting the skin, lungs, vascular system, and gastrointestinal tract. Neurological involvement occurs in a few patients (ranging from 0.8 to 18.5%) including cranial nerve abnormalities, peripheral neuropathy. To our knowledge, neurological involvement in scleroderma: two autopsy cases. Stroke 1998;29:719–21.

Recently, Heron et al described two cases of cerebral involvement in systemic sclerosis. In both cases necropsy showed extensive wall calcification of the small arteries and arterioles of the brain. Our two patients have sclerodermia and extensive striopallidodentate calcifications and metabolic investigations failed to disclose any specific aetiology in either case. We think that sclerodermia should be added to the list of conditions described as occurring with basal ganglia calcification. The pathogenesis of the formation of calcium deposits in systemic diseases remains poorly understood. However, pathological calcification can be subdivided into metastatic (occurring in undamaged tissues when extracellular calcium and phosphate concentrations are increased) and dystrophic (occurring in injured tissue when extracellular calcium and phosphate concentrations are normal) calcification. In our patients, as in the patients of Heron et al, the brain calcifying process may be related to primary cerebrovascular changes induced by systemic sclerosis.

Routine brain CT examination in systemic sclerosis could help to determine the true incidence of basal ganglia calcifications and their clinical relevance.

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All tibial foot: an electrophysiological artifact

Yamashita et al claim they have proved an “all tibial foot” for the motor innervation, an anomalous dual innervation of the tibialis anterior muscle by the deep peroneal and posterior tibial nerve, and a sensory innervation of the skin between the first and second toes by the tibial and deep peroneal nerve in a patient. To support their view they quote the letters of Linden and Berlitz and of Glocker et al, ignoring our letter and that of Magistris and Truffert, both considering the conclusions of Linden and Berlitz and Glocker et al to be wrong. I point out that the mentioned letter of Linden and Berlitz and our response to it were published in the same issue.

We have recorded a compound muscle action potential (CMAP) with a negative initial deflection on tibial nerve stimulation in 83% of 50 subjects, using a surface electrode over the extensor digitorum brevis. In the same subjects no potential was recorded by means of a concentric needle electrode inserted in the extensor digitorum brevis. In our view, this proves that the CMAP recorded by surface electrode over the extensor digitorum brevis on tibial nerve stimulation is a remote potential originated in the plantar muscles (volume conducted potential). Furthermore, we consider that the CMAP recorded over the tibialis anterior muscle by surface electrode on tibial nerve stimulation in the popliteal fossa, as reported by Yamashita et al, represents a volume conduction potential originating in the foot and toe flexors. The sensory nerve action potential recorded dorsally in the space between the first and the second toes on tibial nerve stimulation could also be a volume conducted potential originating in the first common plantar digital nerve, as the distance between this nerve and the recording electrode is short. Such volume conduction phenomena are known to occur on surface recordings from the median nerve at the wrist in severe carpal tunnel syndrome, when the forth finger is stimulated. It is unclear why Yamashita et al could not record a CMAP over the extensor digitorum brevis bilaterally on deep peroneal nerve stimulation in their young patient who did not have neuropathy. A probable explanation is a bilateral aplasia of the extensor digitorum brevis, comparable with the known aplasia of the thenar. The
BOOK REVIEWS


If it moves - measure it. Such is the trend in psychiatry and this has led to a proliferation of assessment scales of variable utility; from the esoteric to the ubiquitous. This book has them all and it is, quite genuinely, one of the most useful volumes I have seen for a very long time. It covers everything from the AMT’s through to the KMW to the KEG cognitive test. Each scale is presented in full together with a short commentary, critical references and, usefully, an estimated time taken to perform the test together with an address to contact the original author.

The scales presented are divided into those covering depression, neuropsychiatric assessments, activities of daily living, global assessments, visible assessments, delirium, caregiver assessments and scales for memory function. This organisation, together with a useful and functional index, will make the task of selecting an appropriate scale much easier in the future. Some of these scales are covered by patent law and my only gripe is that it would have been useful to know which instruments can be reproduced and for what purpose without fear of being billed for the privilege. Maybe highlighting such information would give unpatented authors a competitive edge and so encourage the production of new instruments.


There are many diagnostic and therapeutic pitfalls. The author has succeeded in addressing most of these controversies in a clear and logical fashion. He occasionally blurs the distinction between the two disciplines of medicine and the only question is “Why didn’t somebody do this before”?

SIMON LOVESTONE


Professor Franco Postacchini is an orthopaedic surgeon at the University “La Sapienza” in Rome and is a well known widely respected spinal surgeon. He is to be congratulated on the publication of this book which is wide ranging, comprehensive, and beautifully illustrated. The management of lumbar disc disease is fraught with uncertainty and there are many diagnostic and therapeutic pitfalls. The author has succeeded in addressing most of these controversies in a clear and logical fashion. He occasionally blurs the distinction between the two disciplines of medicine and the only question is “Why didn’t somebody do this before”?

SIMON LOVESTONE
disappointing and somewhat introspective that they do not think that subjects such as neurobiology, microbiology, and immunology might justify equally expert contributors.

Is it an easy read? There is no easy way to write on a subject such as this, bedevilled by lack of objective facts and the writers have chosen a discursive, debating style which when not tightly controlled can slip towards verbosity. This, however, is not a standard medical text book and it would be unfair to make direct comparisons.

Is this a useful book? As a source of references, yes. As a guide to clinicians I am less convinced. The two commonest questions put to me by interested medical students are: "How long does the illness last?" and "What are my chances of recovery?" Cognitive behavioural therapy is concisely and usefully summarised. This, however, is not a standard

ANDREW LEVER}


New information about how and why migraine happens continues to break on us in a dizzying succession of waves coming from various journals in different disciplines. We need an accessible, understandable, and unitary vehicle to collect, organise, and present this information. Journals, the Internet, and the abstracting services have their place, but for this purpose nothing beats the book. How well does Lars Edvinsson’s Migraine and Headache Pathophysiology meet this need?

This book has several attractive features. Recognising that some of the world’s best science is now being done in the laboratories of industry, it has enlisted as authors several leading researchers from the major pharmaceutical manufacturing companies, in addition to “the usual suspects” from academe. Not only has this introduced some exciting writers to the “review book” audience, but it has provided a particular insight into the science of determining why drugs work, or don’t work, in migraine.

The book is up to date, containing many 1998 references. Another strong point of the book is its comprehensiveness; though only 184 pages long, it covers every major aspect of the pathophysiology of migraine. There are chapters on cranial blood vessels, receptor physiology, neurotransmitters, 5-hydroxytryptamine receptor subtypes, and computer modelling. This is achieved at the expense of some pretty terse prose at times, which can make it difficult for the non-expert to follow. It should be noted that, the title notwithstanding, this book deals almost exclusively with the pathophysiology of migraine, and the reader who buys it to get some insight into the mechanisms of tension-type headaches, or other kinds of headache, is going to be disappointed.

Who should read this book? Certainly the migraine researcher should. Though much of it will be familiar to those who have kept up with the literature, it is nevertheless an attractive and handy volume for the current research information. Moreover, the first chapter (by Lars Edvinsson and the last chapter (by Peter Goadsby) are very pretty syntheses of the field. What about clinicians? Some of it is heavy going for people who are not basic scientists. But I got through it all in about 60 hours, and found I knew more about migraine coming out than I had going in—which makes reading it a very worthwhile exercise.

JOHN EDMeadS


There is something about the anachronistic binding of the Handbook of Clinical Neurology series that is rather reassuring. Surely if classic phenomenological binding of the Handbook of Clinical Neurology series is that really is known and how the search for an instant cure (which drives many of them) is currently futile.

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This is one of a new type of medical textbook written to meet the needs of an increasingly informed patient population. Aimed very much at those with multiple sclerosis, their families, and care-workers, it is simple and clearly written with jargon and technical terms kept to a minimum but without patronising. Chronic diseases, and especially multiple sclerosis, are not always well managed by the physician. Too many of us think that there is no cure and feel helpless in a busy clinic faced with the patient with a long list of complaints. There are too few specialty multiple sclerosis clinics in which neurologists, pain specialists, uro-neurologists, physiotherapists etc liaise.

Patients often feel left in the dark, unaware which of their symptoms can be attributed to their multiple sclerosis and whether it is “worth bothering a busy doctor”. Many can cite bad experiences in their past when they have been fobbed off with well meaning reassurance but without practical help. Dysesthesia, sexual problems, and urinary incontinence are only a few of the symptoms that can bring misery to the lives of patients and their families and which are poorly addressed by doctors. This book, in a language accessible to most (and with a glossary to explain some unavoidable jargon), explains multiple sclerosis, its symptoms, and what might realistically be obtained in terms of symptom control. All aspects are covered and nothing considered too trivial; constipation or cold feet might be extremely trying for an individual patient and each is considered.

The old idea that it doesn’t help a patient to know too much about his disease (“it will only make him introspective and hypochondriac”) is outdated. Multiple sclerosis can hit anyone and patients now want, and deserve, to be informed. While doctors find it challenging to be faced with a patient equipped with the latest information down loaded from the internet or well informed having read a book such as this, this is a challenge to which we must be ready to rise. This textbook provides the information patients want and fills the gap left by busy doctors. It should be marketed appropriately and we must be ready to respond to the reaction of patients. Perhaps someone with multiple sclerosis should have been invited to write this review.

GILLIAN HALL

CORRECTION


During printing, the figure in this paper (p 164) was made darker than the original. The correct version appears below.

(A) T1 weighted MRI of the lesion. (B) Anatomical scheme of the centre of the lesion, corresponding to the leftmost image of the bottom row of the MRI. The right side of the figures corresponds to the left side of the brain. GP=globus pallidus; Caud=caudate nucleus, Acb=nucleus accumbens; CI=capsula interna; DB=diagonal band.
Association between butyrylcholinesterase K variant and the Alzheimer type neuropathological changes in apolipoprotein E ε4 carriers older than 75 years

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doi: 10.1136/jnnp.67.5.693

Updated information and services can be found at: http://jnnp.bmj.com/content/67/5/693

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