White matter abnormalities on MRI in neuroacanthocytosis

Neuroacanthocytosis denotes a group of uncommon heterogenous neurodegenerative disorders associated with acanthocytosis in the absence of any lipid abnormality. A variety of modes of inheritance have been proposed (X linked and autosomal recessive are clearly described, but a recent report of dominantly inherited chorea acanthocytosis appears to be caused by Huntington’s disease-like type 2 expansions in the junctophilin-3 gene) and mutations in two genes have been identified, the XK gene (in the X linked McLeod phenotype) and the CHAC gene (9q21; autosomal recessive). A wide variety of clinical features including chorea, orofacial dystonia, dysphagia, dysarthria, peripheral neuropathy, myopathy, seizures, and dementia has been described in these disorders.1

Case reports

Case 1
This patient was briefly described as case 19 in the report of Danek et al. He was a 61 year old white male who had been well until 3 years previously, when he took early retirement from teaching owing to “disillusionment”. He subsequently developed a progressive dementing illness, associated with facial tics, grunting noises, dysarthria, and chorea over the subsequent 3 years. There was no family history of neurodegenerative disease. He first presented to a neurologist having had an isolated generalised tonic–clonic seizure. On examination, he had a frontal dementia (Mini Mental State Examination (MMSE) score of 27/30) with evidence of self neglect and choreiform movements in all four limbs, and a prominent facial tic. He had little insight into his current illness. All tendon reflexes were absent. Investigation demonstrated numerous acanthocytes on blood films. Creatine kinase was raised at 1125 IU/l. Kell antigens were only weakly positive, which conformed to the McLeod phenotype. DNA analysis for Huntington’s disease was negative, but a R133X mutation in exon 2 of the XK gene was found.4 All other investigations were negative (full blood count, copper studies, lipid studies, protein electrophoresis, vasculitis screen (antineuclear antibody, antineutrophil cytoplasmatic antibody, double stranded DNA antibodies) syphilis serology, CSF analysis, and urinary amino acids. An electroencephalogram showed no evidence of seizure discharge, but excess generalised slow wave activity. Nerve conduction studies were within normal limits. An MRI scan of the head (fig 1A) showed widespread areas of increased signal within the white matter of both cerebral hemispheres, especially within the lentiform nucleus bilaterally, but also within the thalamus, cerebral peduncles, and pons, and involving the corpus callosum (white arrow, fig 1B).

Case 2
This 56 year old Italian male developed chorea at the age of 42 years, and subsequently neuropsychological problems. The clinical aspects of this case have been reported previously.5 Numerous acanthocytes were seen on blood films, with weak Kell antigen. Analysis of the XK gene identified a R133X mutation. An MRI scan of the head showed mild increased signal within white matter, and contrast enhancement (fig 1D). Kell serology was normal, with exclusion of the McLeod phenotype. All other investigations including Huntington’s mutation analysis, CSF, and white cell enzyme analysis were negative. Analysis of the CHAC locus is ongoing, but no mutations were identified in the XK gene. MRI head scan (fig 1E,F) demonstrated abnormally high signal in the periventricular white matter bilaterally, with involvement of the corpus callosum and cerebellar atrophy, but without contrast enhancement.

Case 3
A 32 year old Indian male, born of consanguinoues parents, who presented with progressive disinhibition, altered personality and chorea over a 2 year period. His clinical details have not been reported previously. His family had noticed intermittent unusual head movements in which he would appear to be looking around the room into empty spaces while conversing. Although these movements were involuntary, he was able to stop them temporarily if asked to do so. His personality had become more volatile with emotional outbursts and frequent loss of temper. On examination, his MMSE was 27/30. There were continuous choreiform movements of head and neck, and of all four limbs. He was able to interrupt these temporarily if asked to do so. His speech was slightly dysarthric but there was no involuntary tongue protrusion or evidence of self mutilatory behaviour affecting the tongue or lips. The remainder of his neurological examination was normal. Numerous acanthocytes were seen on blood films (fig 1D). Kell serology was normal, with exclusion of the McLeod phenotype. All other investigations including Huntington’s mutation analysis, CSF, and white cell enzyme analysis were negative. Analysis of the CHAC locus is ongoing, but no mutations were identified in the XK gene. MRI head scan (fig 1E,F) demonstrated abnormally high signal in the periventricular white matter bilaterally, with involvement of the corpus callosum and cerebellar atrophy, but without contrast enhancement.

Discussion
Both computed tomography and MRI have been reported to show caudate and more generalised cerebral atrophy in neuroacanthocytosis.6 Although increased signal on T2 weighted MRI in the caudate and putamen has been noted previously, the increased signal throughout the cerebral hemispheres (including the corpus callosum in cases 1 and 3) reported here has not been reported previously. Extensive investigation for alternative causes of white matter abnormalities (vasculitic screen, and analysis
of CSF, very long chain fatty acids, mitochondria, white cell enzymes and plasma lysosomal enzymes) was negative and there was no history of hypertension. In view of the ages of cases 1 and 2 when these patients were initially assessed, not much weight had been given to their MRI appearances; it was in the assessment of case 3 (a normotensive young male who was being investigated for a possible leukodystrophy) that the significance of both his abnormal blood film and his MRI prompted us to review the previous two cases.

Until we have a better understanding of the functional basis of these rare neurogenetic disorders, it is difficult to speculate as to the mechanism via how such abnormalities appear. Although the appearances reported in these cases are not specific, they widen the spectrum of MRI abnormalities that have been reported in neuroacanthocytosis. Thus, clinicians need to be particularly aware of the possibility of neuroacanthocytosis in any patient presenting with unexplained chorea, as the MRI appearances are so variable.

Acknowledgements
We are grateful to the Dr J A Spillane and the late Professor S Bundey for their evaluation and referral of case 1.

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References

Disruption of facial affect processing in word deafness
Word deafness (also known as auditory agnosia for speech, or as auditory verbal agnosia) is a rare neurobehavioral syndrome characterised by an inability to understand spoken language in spite of intact hearing, speaking, reading, writing, and ability to identify non-speech sounds. The lesions associated with this condition tend to be bilateral and symmetrical in nature, and include cortical-subcortical tissue of the anterior part of the superior temporal gyrus. However, Heschl’s gyrus is not always damaged completely in the left hemisphere. Moreover, there have been documented cases of word deafness caused by unilateral left hemisphere cortical and subcortical lesions. Although these lesions are anatomically different, they represent an effective partial hemispheric disconnection.

Hemispheric disconnection has been associated with unusual disruptions of emotional processing. Bowers and Heilman reported a patient with a lesion of the deep white matter of the right occipito-temporo-parietal region. This patient could name famous faces and discriminate affectively neutral faces, but could not name facial emotions or select emotional faces reflecting a named emotion. Bowers and Heilman hypothesised a visual-verbal disconnection resulting in an anomia for affective faces. More recently, Bowers, Bauer, and Heilman further articulated this idea, suggesting that this patient’s performance resulted from a disconnection between a hypothesised non-verbal affect lexicon in the right hemisphere and the verbal lexicon in left hemisphere, which normally communicate via the deep white matter pathways damaged in their patient. The documented association between hemispheric disconnection and anomia for facial emotion raises the possibility that similar deficits in emotion processing may be observed in word deafness.

Case report
WD1 was a 45 year old man who had suffered a left posterior temporal lobe hemisphere CVA two years previously. MRI had demonstrated an acute lesion of the left temporal lobe and a chronic lesion of the right temporal lobe. His new stroke produced an initial Wernicke’s aphasia. A pre-existing high frequency sensory hearing loss was also documented. By 18 months after the stroke, the aphasia had resolved and WD1 underwent formal neuropsychological testing with the following results.

- Auditory comprehension was limited to that of Bowers’ and Heilman’s patient, and consistent with a visual-verbal disconnection. This finding

- He was able to differentiate and accurately recognise a range of environmental sounds, although he had trouble with high pitched sounds. His recognition was fast and accurate.

- He had no apraxia or other motor problems, and he was able to communicate by gestures.

Overall, the results of his neuropsychological evaluation were within normal limits. His specific deficits were consistent with those seen in word deafness.

Emotion processing
We administered a modified version of the Florida Affect Battery (FAB), including both facial and vocal prosody subtests, in an attempt to determine whether word deafness was associated with a disruption in the processing of affective prosody. The FAB consists of 10 subtests that evaluate emotion processing by different modalities: visual (facial expression), auditory (prosody), and visual/auditory cross-modal. WD1’s performance was compared with that of 20 healthy adult controls. The test was modified, in that all instructions and emotion labels were presented in written form rather than orally.

WD1 performed at chance level on the prosody tasks, regardless of their affective content. This may have been related to a premorbid occupational sensory hearing loss. The possibility that his word deafness also contributed to his poor performance cannot be ruled out. However, the relative influence of word deafness cannot be isolated in the absence of control subjects with impaired hearing.

WD1 was able to complete the visual subtests of the FAB, and his ability to discriminate facial identity and facial affect was within normal limits (table 1). His ability to match a stimulus facial expression with one from a target array was also within normal limits. However, he was moderately impaired relative to controls in his ability to match a printed affective name to facial expressions. He was also severely impaired in his ability to select the correct affective face from an array of faces when presented with a printed emotion label—that is, happy, sad, angry, frightened, neutral—despite intact reading and ability to discriminate affective facial expressions.

Discussion
WD1’s pattern of performance on the FAB was identical to that of Bowers’ and Heilman’s patient, and consistent with a visual-verbal disconnection. This finding

<table>
<thead>
<tr>
<th>Table 1 Florida Affect Battery results</th>
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<tr>
<td>FAB face subtests</td>
</tr>
<tr>
<td>-------------------</td>
</tr>
<tr>
<td>Identity</td>
</tr>
<tr>
<td>Discrimination Affect</td>
</tr>
<tr>
<td>Name the affect</td>
</tr>
<tr>
<td>Select the affect</td>
</tr>
<tr>
<td>Match the affect</td>
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</tbody>
</table>

FAB, Florida Affect Battery. z Scores are based on the distribution of the control group. WD1’s score is significantly different from controls, at alpha<0.05.
raises the possibility that a very specific disturbance of visual affect processing is a component of the word deafness syndrome. However, many neurocognitive syndromes lack a unitary functional basis and instead are artefacts of the behavioural geography of the brain. That is probably so with the affective processing disturbance observed in this case. The documentation of intact naming of affect in another word deafness case would answer this question definitively. At the same time, the functional auditory deficits and characteristic neuroanatomy of word deafness raise intriguing questions about the status of auditory emotion processing in word deafness, in view of this patient’s preserved ability to identify non-speech sounds.

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References

A case of acute urinary retention caused by periaqueductal grey lesion

Diseases of the central nervous system often cause disturbances in micturition. These diseases include lesions in the spinal cord, pons, cerebellum, hypothalamus, basal ganglia, and cerebrum. Of these regions, the dorsomedial pontine tegmentum (PAG) is considered important in micturition and urine storage in healthy humans. A case report

Case report

A 31 year old man had sudden voiding difficulty resulting in urinary retention and was referred to a neurologist. Although no particular abnormalities were observed except for an abnormal signal intensity on magnetic resonance imaging (MRI) in the right dorsal portion of the midbrain, he was suspected to have a demyelinating or inflammatory disease and 30 mg of oral prednisolone daily was prescribed. On the day he began prednisolone therapy, he was able to void but this was transient, and he was unable to void again two days later. He was referred to our department for further evaluation.

The patient’s personal and family histories were negative for neurological disorders. Physical examination was unremarkable. Neurological examination revealed nothing but the inability to void. His cranial nerve functions, motor and sensory systems, and autonomic nervous system were intact with preserved anal reflex, penile erection, and ejaculation. Nerve conduction studies on all four extremities and thermography of the upper extremities were normal.

A filling cystometrogram revealed an atonic bladder with diminished bladder sensation. There was no overflow incontinence.

Laboratory tests and analysis of the cerebrospinal fluid were all within normal reference ranges including immunological examinations. However, MRI of the brain showed a small abnormal signal in the right dorsal part of the PAG that was hypointense on T1-weighted image (WI) and hyperintense on T2-WI and fluid-attenuated inversion recovery (FLAIR) (fig 1A). The lesion was not enhanced with contrast material. No other abnormalities were found on the MRI.

Although we were unable to establish a diagnosis despite the thorough work up, we considered the PAG lesion to be responsible for his urinary symptoms and a disease originating from an immunologic abnormality such as vasculitis, was suspected based on the MRI findings and the favourable response to the steroid therapy. Therefore, 1 g methylprednisolone was given intravenously for three days (steroid pulse therapy), followed by 60 mg oral prednisolone for two weeks which was then tapered at a rate of 10 mg/week. After the steroid therapy was initiated, the patient’s symptoms and the PAG lesion on subsequent MRI of the brain improved and he was able to void (fig 1B). However, the inability to void recurred, and a second course of pulsed steroid therapy was given. Day by day his symptoms improved again and resolved completely.

Comment

The patient reported here presented with acute urinary retention and diminished bladder sensation. The only abnormality detected by imaging, laboratory, and electrophysiological studies was a small PAG lesion. Therefore, we concluded that the PAG lesion was responsible for his symptoms. Unfortunately, we could not establish a diagnosis. However, on the basis of the favourable response to steroid therapy he was suspected to have a disease caused by some immunological abnormality.

Blok et al reported that in human PET studies the right dorsomedial pontine tegmentum and the PAG were significantly activated during micturition. In addition, the results of various studies also suggest that the PAG, especially the right dorsal part, plays a critical role in the control of micturition, possibly as the relay centre from the spinal cord to the PMC. The PAG lesion in the present case was located at the site identified in PET studies to be significantly activated during micturition. Although more similar cases are needed to establish a true relation, our findings in the present case provide direct clinical evidence of the role of the PAG in integrating the micturition reflex in humans.

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Figure 1 (A) T2-weighted magnetic resonance image (T2-WI) showing hyperintensity in the periaqueductal grey (PAG) where a significant increase in blood flow has been observed on positron emission tomography during micturition and urine storage in healthy humans. (B) T2-WI showing a reduction in the intensity of the PAG lesion after steroid therapy.
proximal or truncal muscles remains obscure. This procedure for proximal tremors because of the severe tremor that exhausted because of the severe tremor that prevented him from intentional voluntary movements. It rendered his right arm useless and prevented him from upper extremity. It was severely disabling and the TRS score for his upper extremity tremor (Part A, score 5) was reduced to 6. Upon discontinuation of stimulation, the distal tremor reappeared immediately and returned to the preoperative state. The proximal tremor of his right arm was unresolved.

After discharge, he visited our outpatient department once a month. In January 2003, he complained of gradual worsening of the remaining proximal tremor; the distal tremor remained completely suppressed by thalamic Vim stimulation. We discussed Gpi pallidotomy and obtained informed consent prior to the procedure. In April 2003, left Gpi pallidotomy was performed according to the method we described previously. The optimal target for the posteroventral part of the Gpi was determined to be 2 mm anterior and 20 mm lateral to the midpoint of the AC–PC line, and 1 mm dorsal to the floor of the third ventricle. After creating a test lesion (42 °C, 60 sec), a permanent anatomical lesion was made by heating the electrode tip to 72 °C for up to 70 sec. The electrode was moved in 2 mm increments in the medial, lateral, and dorsal directions, and the lesioning process was repeated to increase the overall size of the lesion (fig 1F). Gpi pallidotomy completely abolished his proximal tremor. However, it produced only a small effect on his distal tremor and discontinuation of Vim stimulation resulted in its reappearance at almost the preoperative level. Without stimulation, the TRS score for his upper extremity tremor (Part A, score 5) was 5. The combination of Vim stimulation and Gpi pallidotomy had synergistic effects in abolishing Holmes’ tremor in our patient. The therapeutic benefits remain unchanged at the time of writing and the TRS score for his upper extremity tremor (Part A, score 5) is 0. His palatal tremor did not respond to Vim stimulation and pallidotomy and remains unresolved.

Combination of thalamic Vim stimulation and Gpi pallidotomy synergistically abolishes Holmes’ tremor

The recent report of Kim et al., who demonstrated that stereotactic surgical ablation of the thalamic nucleus ventrointermedius (Vim) markedly improved Holmes’ tremor in a patient with midbrain tumour, corroborates our earlier findings. In this patient, Vim thalamotomy alleviated tremor in both the distal and proximal segments of the upper extremity. However, controversy continues to surround the advisability of using this upper and proximal tremors because of the placement of larger lesions carries increased risks and the somatotopy of the proximal or truncal muscles remains obscure in his 53 year old right-handed man with a history of essential hypertension suddenly developed right hemiparesis and cerebellar ataxia in February 2000. He was admitted to a hospital where radiological examinations showed a left upper brainstem haemorrhage (fig 1A). His neurological state gradually improved. However, in October 2001 a coarse, slowly progressive tremor arose in his right upper extremity. It was severely disabling and he could not use his right arm. He was admitted to our hospital in December 2001.

On admission, he was alert and oriented. His speech was mildly dysarthric and slurred. There was palatal tremor. Mild hemiparesis with increased stretch reflexes and Babinski sign were noted on the right side. There were mild deficits of position, vibratory sense, and superficial sensation of light touch and pain in his right upper and lower extremities. Dysmetria was more pronounced on the right. Because of severe truncal and gait ataxia, he could not remain upright without support; he was unable to walk even with assistance. There was coarse and severe tremor in the right upper extremity. It persisted at rest and its amplitude increased during maintenance of a fixed posture and intentional voluntary movements. It rendered the right arm useless and prevented him from feeding and caring for himself. He was exhausted because of the severe tremor that persisted throughout his waking hours.

Surface electromyograms showed rhythmic grouping discharges of 3.6 Hz in the right forearm muscles. His preoperative score on the Tremor Rating Scale (TRS) for his right upper extremity (Part A, score 5) was 11. Magnetic resonance imaging (MRI) study (December 2001) showed a haemoiderin ring around the lesion in the left pontine tegmentum (fig 1B). On T2-weighted images, a high signal lesion was seen in the left inferior olive, as consistent with the hyperplastic olivary degeneration (fig 1C). As sequential pharmacotherapy using clonazepam (3 x 0.5 mg/day) and benzadine/levodopa (3 x 25/100 mg per day) was only slightly effective, he was referred for surgery. Prior informed consent was obtained from the patient and his family. In January 2002, a quadripolar DBS electrode (Model 3387; Medtronic Inc., Minneapolis, MN, USA) was implanted in the left thalamic Vim nucleus with the aid of MRI, third ventriculography, and microelectrode guidance, as previously described. The optimal target was determined to be 7 mm posterior and 14.5 mm lateral to the midpoint of the anterior to posterior commissure (AC–PC) line, and on the AC–PC line. The most ventral contact was placed precisely on the target point (fig 1D, E). As stimulation tests, performed for 5 days, confirmed the beneficial effects of DBS, a programmable pulse generator (Soletra, Model 7426; Medtronic Inc.) was implanted. His postoperative course was uneventful.

After extensive trials, stimulation was carried out using contacts 0 and 1 (fig 1D, E). The optimal stimulation parameters were determined to be 160 Hz frequency, 90 μsec pulse width, and 2.9 V and 3.4 V amplitude at the first and final session. Stimulation with amplitude exceeding 3.4 V induced unpleasant electrical paraesthesia on the right side of his face and right upper extremity. Under optimal stimulation, the tremor was markedly alleviated in the distal part of his right arm: the TRS score for his upper extremity tremor (Part A, score 5) was 0. Upon discontinuation of stimulation, the tremor of his right arm was 6. Upon discontinuation of stimulation, the tremor remained unchanged at the time of writing and the TRS score for his upper extremity tremor (Part A, score 5) is 0. His palatal tremor did not respond to Vim stimulation and pallidotomy and remains unresolved.
Stereotactic Vim surgery, either thalamotomy or thalamic stimulation, is a mainstay in the surgical treatment of Parkinson's or essential tremor. Its efficacy in tremor suppression is superior to that of pallidotomy in Parkinsonian patients. However, as evidenced by our case, it does not always produce satisfactory results in patients with Holmes' tremors, particularly with respect to their proximal tremors. The basal ganglia outflow pathway from the GPi exerts a direct influence on not only the thalamus but also the brainstem motor centres such as the pedunculopontine nucleus related to the mesencephalic tegmental field that controls the axial and proximal appendicular musculature via the descending reticulospinal tract. Therefore, unlike thalamic surgery, which interrupts the thalamocortical output that produces satisfactory results in patients with essential tremors, a 249 bp fragment spanning this mtDNA region was polymerase chain reaction (PCR)-amplified using a forward primer (5'-GATTGTAACTGTGACACACAGGG GTT 3'; nt 12164–12189) and a reverse primer (5'-GGTTAACAGGCGGTTAAGGGTT 3'; nt 12412–12390). Amplified products were purified and sequenced using BigDye terminator cycle sequencing chemistries on an ABI 377 automated DNA sequencer (Applied Biosystems, Warrington, UK).

No association of the mitochondrial DNA A12308G polymorphism with increased risk of stroke in patients with the A3243G mutation

There is a striking phenotypic variability among patients with the A3243G (rRNAe[Leu[CCU]]) mutation of mitochondrial DNA (mtDNA), the most common heteroplasmic mtDNA mutation. It is responsible for ~80% of cases of MELAS (mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes), and is also associated with several other phenotypes including maternally inherited diabetes and deafness (MIDD) and chronic progressive external ophthalmoplegia (CPEO).

Only 50% of patients carrying the A3243G mutation have stroke-like episodes1,2 and the reason for this clinical variability remains poorly understood. Although the percentage level of the A3243G mutation in clinically relevant tissues appears to be important, this relationship is far from clear.3 High percentage levels of the A3243G mutation in muscle are associated with stroke-like episodes, but approximately one in five patients harbouring >80% A3243G in muscle remain stroke free, suggesting that additional environmental and genetic factors may influence the phenotypic expression of this mutation.

One possibility is that the background mtDNA sequence variation influences phenotype. There is a well-recognised association between the mtDNA genetic background (or haplogroup) and the risk of developing vascular failure in another mtDNA disorder, Leber's hereditary optic neuropathy,4 and a similar mechanism may influence the incidence of stroke-like episodes in patients harbouring the A3243G mutation. Intrafamilial clustering of clinical phenotypes in A3243G patients would indirectly support a role for the mtDNA background, though our own clinical experience suggests that there is significant clinical variability between families.

Pulkes et al have previously reported an increased risk of stroke associated with the presence of a homoplasmic, polymorphic (A12308G) variant in 48 patients with the A3243G mutation. The A12308G polymorphism, which is the first in the second mitochondrial tRNA gene encoding leucine (tRNALeu[CCU]), occurs with a frequency of 21% in a population of European origin and defines the mtDNA super-haplogroup U/K together with two other polymorphisms (A11467G and G12372A). As haplogroup U has also been reported to be a risk factor for sporadic occipital stroke in patients with migraine,5 these observations could have profound implications for our understanding of mitochondrial genotype and its relationship to the clinical phenotype. Here we report on the investigation of the A12308G polymorphism in a larger group of well-characterised, unrelated A3243G index cases.

Methods

We carried out a large, multicentre study to investigate the A12308G polymorphism in a group of 107 unrelated family index cases harbouring the A3243G mutation. The patients (>95% Caucasian) were from England, Germany, USA, Australia, and Finland. All are presented at the neurology clinic, where stroke-like episodes were diagnosed clinically by experienced neurologists based upon a characteristic clinical history and brain imaging with computed tomography (CT) or magnetic resonance imaging (MRI); in all cases, a molecular diagnosis of the A3243G mutation was made at a centre with expertise in the investigation of patients with mtDNA disorders.

To investigate the A12308G and G12372A polymorphisms, a 249 bp fragment spanning this mtDNA region was polymerase chain reaction (PCR)-amplified using a forward primer (5'-GATTGTAACTGTGACACACAGGG GTT 3'; nt 12164–12189) and a reverse primer (5'-GGTTAACAGGCGGTTAAGGGTT 3'; nt 12412–12390). Amplified products were purified and sequenced using BigDye terminator cycle sequencing chemistries on an ABI 377 automated DNA sequencer (Applied Biosystems, Warrington, UK).

Results

The A12308G polymorphism was present in 32 of the 107 patients, while 56 had a history of stroke-like episodes. Nine of the 56 patients with a history of a stroke and 23 of 51 patients without a history of stroke harbour the A12308G polymorphism. Every patient with the A12308G polymorphism also harboured the G12372A variant, indicating that they belong to the same mtDNA super-haplogroup U/K.

As shown in fig 1, our study alone revealed an apparent negative association between stroke-like episodes and the A12308G polymorphism, an observation in direct contrast to the positive association found by Pulkes et al.1 Meta-analysis of all available data however, including the present study (n = 107) and the published study of Pulkes et al2 (n = 48), revealed that 16 of the 77 patients with a history of a stroke and 25 of 78 patients without stroke harbour the A12308G polymorphism. This did not show a statistically significant association between the A12308G polymorphism and stroke-like episodes (χ2 = 2.53, p = 0.112).

Discussion

The aim of our study was to examine whether a previously described association between the A12308G polymorphism and an increased risk of stroke in patients with the 'A3243G mutation' was reflected in a larger study group. In agreement with previous reports, 52% of our patients experienced stroke-like episodes1,2 and 30% harboured the A12308G polymorphism, confirming that our cohort of

References


A12308G polymorphism and stroke-like episodes in our group to be younger than those without. This argues against age as a risk factor for stroke-like episodes, as seen in common stroke.

The clinical diversity associated with the A12308G mutation clearly involves multiple factors. We have previously shown a correlation between clinical phenotype and mutation load in muscle. Age may well be a contributing factor, although there was a tendency for patients with stroke-like episodes in our group to be younger than those without. This argues against age as a risk factor for stroke-like episodes, as seen in common stroke.

Important findings serve to highlight the difficulty of performing association studies on small numbers of patients. This is particularly difficult for mitochondrial genetic association studies because of the high variability of the mitochondrial genome. Understanding the phenotypic differences between patients with specific, pathogenic mtDNA mutations will ultimately involve studies of large cohorts of patients, unless we are able to gain clues from experimental studies that may highlight factors involved in the altered expression or segregation of mtDNA mutations.

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Table 1: Symptoms at diagnosis of malignant cerebral glioma recorded in hospital records versus those elicited at home interviews

<table>
<thead>
<tr>
<th>Symptom or problem</th>
<th>Recorded in the hospital records (n = 92)</th>
<th>Elicited from patients and relatives at home interviews (n = 92)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weakness</td>
<td>55 (60)</td>
<td>51 (55)</td>
</tr>
<tr>
<td>Headache</td>
<td>49 (53)</td>
<td>48 (52)</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>35 (38)</td>
<td>44 (48)</td>
</tr>
<tr>
<td>Sensory loss</td>
<td>32 (35)</td>
<td>37 (40)</td>
</tr>
<tr>
<td>Cognitive loss</td>
<td>30 (33)</td>
<td>42 (46)</td>
</tr>
<tr>
<td>Dysphasia</td>
<td>29 (32)</td>
<td>23 (25)</td>
</tr>
<tr>
<td>Personality change</td>
<td>14 (15)</td>
<td>28 (30)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>13 (14)</td>
<td>44 (48)</td>
</tr>
</tbody>
</table>

Values are n (%)
experience might help further define the subacute presentation of cognitive and personality change and their relation to other complaints.

Second, the predictive power of neurological symptoms prompting to general practitioners could be explored using existing large primary care research datasets. Third, relatives of patients referred urgently should be asked to attend with them to clarify aspects of the history that the patient may be unaware of. Beginning to discuss openly the difficulty of earlier diagnosis may help families come to terms with this last stage of their concern. This might also help repair unnecessary rifts in relations with general practitioners, who are best placed to provide local support and palliative care these patients so often need.

Acknowledgements

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Five year follow up of a patient with spinal and bulbar muscular atrophy treated with leuprorelin

Spinal and bulbar muscular atrophy (SBMA; MIM 313200) is an X linked late onset motor neurone disease characterised by slowly progressive proximal and bulbar muscle weakness, muscle atrophy, postural hand tremor, gynaecomastia, and endocrine disturbances that include signs of partial androgen resistance. SBMA is caused by the expansion of a trinucleotide CAG repeat in the first exon of the androgen receptor (AR) gene encoding a polyglutamine stretch.1

Recently, Katsuno et al. reported that leuprorelin, a lutenising hormone releasing hormone (LHRH) agonist, reduces the level of testosterone release from the testes, rescued motor dysfunction and nuclear accumulation of mutant ARs in a male transgenic mouse model of SBMA. This result indicates that ligand dependent nuclear translocation of mutant ARs containing expanded polyglutamine is the main source of the pathogenesis of SBMA, and that leuprorelin suppresses this translocation. We read this report with great interest, because we followed up a patient with SBMA, who has been administered leuprorelin for 5 years to treat his coexisting prostate cancer.

Case report

A 75 year old male noticed bilateral finger tremor at age 57. At age 63, he noticed weakness in his arms. He was admitted to our hospital in December 1991, when he was 64 years old. On initial examination, he had bilateral gynaecomastia. Neurological examinations revealed facial weakness and lingual atrophy with fasciculations. Mild muscular atrophy was observed in the proximal parts of the upper extremities. Muscle strength was approximately in the range of 3/5 to 4/5 in the proximal parts, and 5/5 in the distal parts of the upper extremities. Fasciculations were observed in the distal parts of the lower extremities. Deep tendon reflexes were either lost or markedly diminished. Babinski signs were absent. Laboratory examinations revealed that the serum creatine kinase (CK) level increased to 803 IU/L (normal range 43–239 IU/L), LH (5.9 IU/L; normal range 1.8–5.2 IU/L) and follicle stimulating hormone (20.5 IU/L; normal range 2.9–8.2 IU/L) levels were elevated. After his informed consent was obtained, high molecular weight genomic DNA was extracted from peripheral leucocytes of the patient according to standard protocols. Genetic analysis of the AR gene was performed and the expansion of a CAG repeat (45 repeats) in exon 1 of the AR gene was identified, leading to a diagnosis of SBMA.

At age 67, he developed weakness in the legs, and noticed difficulty in climbing up stairs or standing up from a chair. Serum CK levels gradually increased to 1877 IU/L at age 70. In January 1998, when he was 71 years old, he was diagnosed as having prostate cancer, and was intramuscularly injected with 3.75 mg of leuprorelin every 28 days, because leuprorelin inhibits production of testosterone and dihydrotestosterone (DHT), which enhances the growth of prostate cancer cells. One month after the start of treatment, he noticed that his gait disturbance was rapidly exacerbated; however, the gait disturbance returned to the level before the start of treatment by April 1998. After the episode of transient exacerbation, his muscle weakness and atrophy exhibited no apparent progress. Deep tendon reflex was either lost or markedly diminished. Babinski signs were absent. Beginning to discuss openly aspects of the history that the patient may be unaware of. He was referred with great interest, because we followed up a patient with SBMA, who has been administered leuprorelin for 5 years to treat his coexisting prostate cancer.

Discussion

The experience of a 5 year follow up of this patient treated with leuprorelin is highly indicative of the following. Firstly, leuprorelin treatment induced a transient deterioration of the motor function in humans, as demonstrated in a transgenic mouse model of SBMA. Secondly, after the initial transient deterioration, long term stabilisation of the motor function was obtained. Finally, leuprorelin treatment was effective even when the treatment was started in the advanced stage of the disease, although the patient’s muscle weakness and atrophy have not completely disappeared. These findings provide grounds for the proposal made by Katsuno et al. that leuprorelin is a promising candidate for the treatment of SBMA.

At least nine neurodegenerative diseases are known to be caused by expanded CAG repeats. SBMA is unique among these diseases because the disease protein, AR, has a specific ligand, testosterone. It has been demonstrated that the nuclear translocation of ARs is solely dependent on testosterone. Recently, a transgenic mouse model carrying full length AR containing 97 glutamine repeats has been generated, and this model showed progressive muscular atrophy and weakness. These phenotypes were markedly enhanced in male transgenic mice, which were specifically rescued by castration. Female transgenic mice exhibited only a few manifestations that markedly deteriorated with testosterone administration. Furthermore, in the Drosophila model of SBMA, it has been demonstrated that androgen agonists induce nuclear translocation of the mutant ARs and toxicity. Taken together, this raises the possibility that blockade of nuclear translocation of the mutant ARs by hormonal intervention can provide therapeutic benefits in SBMA.

LHRH agonists including leuprorelin have been used for the treatment of prostate cancer. These drugs eventually inhibit LH production, which in turn inhibits production of testosterone and DHT, on which growth of prostate cancer cells depend. The alleviation or improvement of muscular weakness and decrease in the serum CK level in our patient may be due to the anti-androgen effects of leuprorelin. Interestingly, he noticed rapid exacerbation of gait disturbance one month after the administration of leuprorelin. It has been demonstrated that when LHRH agonists are administered continuously, the pituitary gland is initially stimulated, but after 5–12 days, the pituitary gland becomes quiescent.

Figure 1 Serum creatine kinase (CK) levels of the patient gradually decreased from 1717 IU/L to 834 IU/L after the leuprorelin treatment.
A 44 year old lady developed classic migraine at the age of 11 years. Her symptoms comprised a visual aura of flashing lights followed by severe headache (not localised to one side), photophobia, and nausea, which generally lasted for two days. There were no identifiable triggers. Her medical history consisted of sumatriptan, which she took on experiencing the visual aura. This considerably reduced the severity of her headache and usually limited the duration of her symptoms to one day. The migraines occurred frequently and randomly with the longest migraine-free period being one month.

One morning, she awoke with visual loss in her right eye. She assumed this to be the visual aura of a migraine (although it was atypical since there was no photopsia or subsequent headache), and took her normal dose of sumatriptan. The visual loss occurred before taking the medication. The visual defect fragmented into black patches followed by gradual visual improvement over the next few days. She then consulted her general practitioner who referred her to the eye department.

At presentation to the eye department one week after the initial visual loss, her visual acuity was 6/9 right and 6/4 left. There was a right relative afferent pupillary defect. Funduscopy revealed retinal haemorrhages in all four quadrants with a swollen optic disc. A diagnosis of non-ischaemic CRVO was made. She was advised to take aspirin 75 mg daily.

On follow up, her visual acuity continued to improve with resolution of the retinal haemorrhages and the disc oedema. The following investigations were normal: full blood count, erythrocyte sedimentation rate, electrolytes, fasting glucose, fasting cholesterol, and plasma protein electrophoresis. General medical examination was normal. She is a non-smoker with no family history of cardiovascular disease. At the 18 month follow up her visual acuity was 6/5 right and 6/4 left. There was no relative afferent pupillary defect. The fundal appearance returned to normal.

Follow up to date is two years and she has not experienced a single migraine since developing the CRVO. There have been no other factors to account for the cessation of her migraines during this period.

**Discussion**

There have been numerous reports of retinal vaso-occlusion and migraine in the context of “complicated migraine”. We have presented an interesting patient who instead experienced complete cessation of migraine in association with the development of a CRVO. In the natural history of migraine there is a gradual reduction in severity and frequency of attacks with age. The abrupt cessation of migraine following development of a CRVO suggests a causal relationship. She had no risk factors for a retinal vascular event.

It has been proposed that prophylactic use of platelet antagonists, such as aspirin, may reduce the occurrence of migraine. Serotonin is released locally in cerebral tissue shortly before the onset of a migraine attack. Since platelets contain all of the plasma serotonin platelet function has been implicated as a factor in migraine. The role of serotonin in migraine is complex. To the best of our knowledge there is no report of platelet antagonists causing complete cessation of migraine. It seems unlikely that aspirin was solely responsible for the cessation of migraine in our patient, however this remains a possibility.

The pathophysiology of migraine is complex but involves neuronal events linked to alterations in the calibre of intracerebral blood vessels. During a migraine aura cerebral blood flow decreases. The subsequent hyperaemia leads to headache by activation of fibres originating in the trigeminal ganglion. These trigeminovascular afferents reside primarily within the ophthalmalic division of the trigeminal nerve. The retinal vasculature is very similar to the cerebral vasculature both in structure and response to vasoactive substances. This probably accounts for cases of “complicated migraine” leading to retinal vein occlusion.

We postulate that an initial neuronal event occurred in our patient that resulted in a functional alteration in her trigeminovascular system leading to the complete cessation of migraine. This neuronal event also produced a temporary decrease in central retinal artery perfusion and the subsequent development of a CRVO. This case therefore demonstrates the potential for intracerebral events to influence the retinal vasculature.

**References**


Cessation of migraine following central retinal vein occlusion

Cases of retinal vein occlusion with migraine have been described since 1882. An interesting case of central retinal vein occlusion (CRVO) which coincided with complete cessation of longstanding, severe migraines is reported.

**Case report**

A 44 year old lady developed classic migraine at the age of 11 years. Her symptoms comprised a visual aura of flashing lights followed by severe headache (not localised to one side), photophobia, and nausea, which generally lasted for two days. There were no identifiable triggers. Her medical history consisted of sumatriptan, which she took on experiencing the visual aura. This considerably reduced the severity of her headache and usually limited the duration of her symptoms to one day. The migraines occurred frequently and randomly with the longest migraine-free period being one month.

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Follow up to date is two years and she has not experienced a single migraine since developing the CRVO. There have been no other factors to account for the cessation of her migraines during this period.

**Discussion**

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No association of the mitochondrial DNA A12308G polymorphism with increased risk of stroke in patients with the A3243G mutation

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Neurological emergencies, 4th edn

Medical SHO’s training only infrequently includes a dedicated attachment to neurology. Routine neurology then seems daunting enough, but neurological emergencies may appear a worst nightmare. This updated compilation of 13 reviews covers common neurological emergencies in surprising detail. Most practically useful are those focused on producing copy for forms, such as medical coma and acute visual loss. Stroke and status epilepticus are treated authoritatively, but first seizure, a common emergency referral, is not included. Subarachnoid haemorrhage is well presented but may have been even more useful if considered as one cause of acute headache. Brain stem death criteria are described clearly but, if emergency means cannot wait until morning, their inclusion is unexpected. The summaries concluding each chapter are disappointingly printed black on dark grey, in smaller type than the text, hard to read even in daylight. Perhaps the publishers intended it, but these summaries will not readily copy for handy laminated reference in the emergency unit.

Neurological emergencies is too large for the white coat pocket (nearly 500 pages), and too longhand for last minute reference behind the patient’s curtain. Its style is detailed prose rather than notes and bullets. Nevertheless, this book will usefully inform clinicians of all grades and increase the likelihood that neurological patients are managed safely. At £45, they may be only one departmental copy, but that must be on the registrar’s bookshelf. At risk of stating the obvious, the book should be digested, calmly, away from the coalface, before the emergency presents. Then those faced with serious neurological situations need not echo Arthur Dent in Hitchhiker’s Guide to the Galaxy, “‘‘It’s at times like this […] that I really wish I’d listened to what my mother told me when I was young.” “Why, what did she tell you?” “I don’t know, I didn’t listen.””

P E M Smith

Psychoneuroendocrinology; the scientific basis of clinical practice

In the last two decades a wealth of information has been gathered regarding the potent influences of our endocrine hormones on the brain and behaviour, giving rise to the discipline of psychoneuroendocrinology. By calling upon leading authorities in their subjects, Wolkowitz and Rothchild have produced this timely volume that explores, with great clarity and success, what might be the clinical significance of the empirical scientific findings in this emerging field and how this may underpin breakthroughs in the treatment of behavioural and affective disorders. Essentially, each contributor considers the hormonal changes observed in primary psychiatric illness, the psychiatric sequelae of hormonal dysregulation in primary endocrinological illness, and the potential for exogenously administered hormones or hormone antagonists to influence behaviour and affect.

The main text begins with a delightful account of the historical roots of psychoneuroendocrinology, dating back to the ancient philosophers, and the recent rapid development of this discipline. There is then an exhaustive coverage of central nervous system neuropeptides and hypothalamic releasing factors, which addresses the controversial question of whether alterations in their secretion contribute secondarily to or are causative of aspects of psychiatric illness. There is also a balanced view of the potential use of melatonin and its analogues as chronobiotic drugs, and a review of the psychiatric manifestations of endocrinopathies—including diabetes mellitus and those affecting secretion of prolactin, growth hormone, and parathyroid hormone. There follows a section each on glucocorticoid hormones, gonadal hormones, and thyroid hormones, considering conditions of over- and/or undersecretion, which can produce behavioural symptoms closely resembling signs of primary psychiatric illness. The penultimate section is devoted to the use and interpretation laboratory testing in clinical psychoneuroendocrinology to improve accuracy of diagnosis and treatment. The volume ends with an updating of Hans Selye’s original exposition of the general adaptation syndrome that occurs in response to stressors—both exogenous and endogenous. Although mounted to protect the host, the stress response itself may become harmful—both emotionally and physically—if allowed to proceed unchecked.

This comprehensive work clearly demonstrates the importance of crossing the traditional boundaries of endocrinology, neuroscience, and psychiatry, and represents an approachable and informative text that should be of value not only to clinicians from many disciplines, but also to basic scientists, teachers, and the educated public.

P K Newman

Behavioral medicine in primary care—a practical guide

It is well known that a large proportion of consultations in primary care have their origins in the psychological wellbeing of the patient. There is clearly a need for a reference book in this area that strikes the right balance in presentation, in usefulness, without being overbearing. With this in mind, is this book of use to a primary care physician with limited training in behavioural medicine? The early chapters go back to basics and focus on the doctor–patient relationship. The reader not so keen on this approach may be lost by the wayside in these chapters. However, for those prepared to re-value the patient interview, these chapters will continue in this edition as a firm favourite for MRCP trainees, in the GP surgery library, and to inform and stimulate the undergraduate neurology curriculum.

G Gillies

Clinical neurology, 3rd edn

Clinical neurology is now into its third edition since first appearing in 1989 under the original editors Fowler and the late David Marsden, an indication of its popularity in a congested market of similar titles. It provides excellent value as a comprehensive introduction to neurology for medical students, MRCP candidates, other junior doctors, and physicians of all specialties, but does not pretend to have the depth of detail required by more senior neurologists in training or in practice. On looking up a few topics with which medical SHO’s (and their bosses) always seem to have difficulty, I found dysphasia clearly covered, eye movement disorders well described and illustrated, and lateral medullary syndrome mentioned in the text but not in the index. Cord compression, coma, and confusion are each presented well, and there are good overviews of common (and rare) neurological conditions pitched at just the right level for the readership. Chapters on raised intracranial pressure, cerebrovascular disease, epilepsy, infection, spinal disease, and many other topics guide the neurological novice confidently through diagnosis and management. The book is substantially updated from the second (1998) edition, and although there are some hangovers and omissions, these are only minor caveats in a textbook whose uniformly British contributors have done such a good job. Clinical neurology will continue in this edition as a firm favourite for MRCP trainees, in the GP surgery library, and to inform and stimulate the undergraduate neurology curriculum.
Overall, this is a well edited and presented book, which fulfils its aims as a practical reference book adequately. It offers a different approach to vascular and intracranial problems in the primary care setting. Although the book would be of limited use to trainees in psychiatry, due to its primary care focus, it would serve as a useful text to those in primary care, other healthcare professionals, and students.

Quantitative MRI of the brain—measuring changes caused by disease


We have waited for a long time for a comprehensive book on magnetic resonance (MR) techniques that will appeal to the neurologist/neuroradiologist as well as the physicist and researcher. A book that is right up to date and is relevant across the board for all who are interested in the technique and that deals with quantification.

Paul Tofts has produced a book that is in the coffee table style, in the best sense of the concept, and in price; in the fact that the book invites you to pick a section at random and find that the information is immediately accessible and self-contained. The level of detail is impressive, as is the design of the presentation where information of different types is presented in boxes comprising summaries of opinions, and practical suggestions. The layout works well; chapters take you through theory to practical applications and mention problems and solutions along the way. It is clear that it has been written by people who have hands on experience of MR and who have had to deal with the issues associated with quantification in all forms of MR use (diffusion, magnetisation transfer, spectroscopy, contrast enhanced MRI, functional MRI, blood perfusion and volume estimation, and the various practicalities associated with analysing images, to mention just some of the topics covered).

The usual pitfalls of multiauthor books has been avoided as Paul Tofts is involved in the writing of many of the chapters and the book has the coherence of a single author book. The style of writing is occasionally poetic, for example: “the paradigm shift from qualitative picture-taking to objective measurement—making is taking place”, which elegantly summarises the theme of the book. I have to mention the introduction, which might have been written by Melvyn Bragg and at first seems a little out of place in a science textbook and more fitting to a book on the arts. It references Stravinsky, John Cleese, Bronowski, and Rachmaninov, among others, and speculates about the nature of creativity: “Sometimes I seemed to be witnessing the creation of perfection”, writes Paul Tofts. I smiled to myself when I first read this but having looked at this book in greater detail, I think he might have a point.

If you are involved with MR imaging in any way I urge you to look at this book, and once you have, you will know that you need to have it and you will want it for its sheer comprehensiveness, and the knowledge that quantification in MR imaging is truly at the cutting edge.

Neuroscience in medicine, 2nd edn


Neuroscience in medicine, second edition, is aimed primarily at medical students and seeks to explain the basic structure and function of the nervous system underlying medicine. It is arranged as a collection of essays by individual contributors, interspersed with short clinical chapters. Most of the chapters are written at a level appropriate for medical students but others (for example those on hypothalamus, muscle, and iron channels) carry detail more suited to a neuroscience undergraduate or even postgraduate student. While it is no bad thing to offer students more information than they strictly need, it does need careful management in order to avoid a fascinating subject becoming a daunting one.

In terms of coverage, it is refreshing that subjects such as sleep, cerebrospinal fluid, and neurotransmitters are well covered in several chapters while neuroanatomy are dealt with individually, as these tend to be minimised or overlooked in some textbooks. However, there are also some serious omissions. There is no chapter explaining the structure and function of the autonomic nervous system, surely one of the topics most often misunderstood by medical students. Also, parts of the motor system are described in several chapters but no attempt is made to show how it all fits together. The order in which subjects are dealt with is unusual. For example, chapters on synaptic transmission and receptors come early in the book while neurotransmitters are dealt with later. A chapter on spinal mechanisms for control of muscle is divorced from the other chapters dealing with either spinal cord or other motor functions, being placed between chapters on the thalamus and chemical messenger systems.

Perhaps the greatest disappointment is the illustrative material, which varies considerably from chapter to chapter. While some contain effective explanatory diagrams, others have figures of poor quality (apparently due to scanning at low resolution, as in the chapters on spinal cord and higher brain function). The chapter dealing with neuroanatomy relies on a few black and white photographs, the text, and historical sections—no diagrams or MRIs.

In summary, when compared to many competitors, this book is unlikely to appeal to its intended audience. Sadly the generally high quality of the individual contributions is not sufficient to compensate for the poor organisation and variable illustration of this book.

Local therapies for glioma: present status and future developments


This small book, which is a supplement of Acta Neurochirurgica, represents the proceedings of a meeting held in Milan in 2003. It is organised by the EANS Neuro-oncology Executive, which is chaired by Professor Westphal. The point of the meeting was to describe the concepts and status of local therapies for glioma. Owing to the inevitable failure of surgery, chemotherapy, and external beam radiotherapy to prolong life in gliomas, a great deal of clinical and pharmacological effort has been put into developing local therapies for gliomas.

The rationale for placing compounds or therapies in the cavity created following resection of a glioma is based on the editors’ preliminary remarks. Unfortunately, evaluating the effects of local therapies are also difficult because the therapy will induce radiological changes, which could be interpreted as reactivation of quiescent tumours. These difficulties in assessment are later discussed in a separate chapter. The first half dozen chapters cover current clinical investigation, management approaches, and assessment of gliomas with respect to state of the art technologies such as surgery incorporating image guided volumetric resection of gliomas, fluorescence guided resections, and experience with glioma surgery with intra-operative high field MRI, postoperative imaging after brain tumour resection, and the use of external beam conformal radiotherapy and interstitial stereotactic radiosurgery. These chapters are in a sense the antipaste, because they set the scene for the novel local therapeutic approaches. They provide a solid, practical background for the subsequent chapters. The article on awake craniotomy in particular has thoughtful and useful information for those interested in the technique.

A variety of local therapies are covered in subsequent chapters. Some of these are well known techniques that simply involve local administration of a chemotherapeutic drug (for example implantable drug releasing biodegradable microspheres for local treatment of brain glioma and intracavernous chemotherapy for glioblastoma, present status and further directions), which have already reached clinical practice after phase III trials. The particular difficulties with local gene therapy for gliomas are well covered in two succinct chapters, which are comprehensively referenced. Other chapters present new therapeutic approaches using specific techniques (for example non-invasive transcranial high intensity focused ultrasound (HIFU) under MRI thermometry and guidance), the treatment of brain lesions; intralesional radioimmunotherapy in the treatment of malignant glioma, clinical and experimental findings; radioimmunotherapy targeting fibrocellin; and comparing monoclonal antibodies and small peptide hormones for local targeting of malignant gliomas). The use of convection enhanced delivery techniques are described for the delivery of IL4 pseudomomas exotoksin (NBI-3001) for treatment of patients with recurrent malignant glioma, together with interim findings from ongoing phase 1 studies of IL3-PE38QQR for treatment of the same condition.

The remaining chapters reflect the editors’ particular interest in glioma cell invasion, the potential use of anti-angiogenic therapies, and stem cells in neuro-oncology. Pathophysiological advances in these areas could provide the basis for novel local therapies in the future.

What does this book offer the neuro-clinician interested in oncology? Firstly, there are some good overviews of the current state of treatments, their evidence base, and ways in which surgery and radiotherapy are likely to change in the not too distant future. The second group of chapters on true local
therapies gives the reader an idea of the spectrum of current approaches, their biological basis, the simplicities and difficulties of their applications, and innovative thought of the developers.

Overall this is a compact book that is well written. The authors represent their topics from an extremely practical viewpoint, being helpful about the difficulties confronting clinicians in malignant glioma management. All chapters are easy to read, well illustrated, and well referenced. For those interested in neuro-oncology it is a very useful reference source that covers a gamut of approaches. The overall has something for everyone interested in neuro-oncology. The editors are to be congratulated for their contributions, the selection of authors, focusing on this important and evolving area, and addressing it in a very practical, clinically orientated fashion.

I R Whittle

Neuroepidemiology—from principles to practice

Everyone, at one time or another, feels misunderstood and unappreciated. Epidemiologists are no exception. They get fed up at hearing secondhand opinions that epidemiology is a blunt instrument or that epidemiological investigations don't allow inferences to be drawn about aetiology. Their hearts sink when they encounter people who believe that its methodology amounts to little more than counting cases. Eventually, exasperation drives them to write a book explaining what their subject is really about. If this was the motive behind Neuroepidemiology—from principles to practice, I hope the authors and editors found the process of writing it therapeutic. Whether practicing neurologists, who are identified as a target readership in the preface, will find that it changes their view is another matter.

The book follows a conventional format. Introductory chapters on methods are followed by accounts of specific neurological diseases. An attractive feature is the final section with descriptions of clinical trials, evidence-based medicine, and health service research as they apply in neurology.

The trouble with epidemiological accounts of disease is that they often read like mystery stories without a dénouement. This isn't the authors' fault, of course. If the cause of a disease is still unknown, what can they do but describe investigations that are still in progress. They round up the usual suspects—things such as head injury, diet, cigarette smoking, and infections—and work them over. They tell us about the circumstantial evidence—such as global distribution, migrant studies, and time trends—that might provide a promising lead but which might equally turn out to be a red herring. In the end, the story usually peter's out and they rarely get a conviction. It's useful to have a summary of the research that has been done—although other similar accounts exist—but, on the whole, it doesn't make for gripping reading.

C N Martyn

Neurosurgical re-engineering of the damaged brain and spinal cord

Katayama, on behalf of the Neurorehabilitation Committee of the World Federation of Neurosurgical Societies, has brought together essays presented at a Neurorehabilitation Committee Meeting held in 2002.

Each chapter represents multi-author presentations largely derived from Japan. The manuscript consists of nine subsections addressing aspects of coma, restorative neurosurgery, early rehabilitation, functioning, imaging, neurological intervention, pain control, and neural transplantation. The editors have achieved a comfortable balance between scientific and clinical presentation. For example, the first section on monoaminergic and cholinergic pathologies for sleep and wakefulness in the rat model demonstrates elegant physiology, followed by clinical papers that explore median nerve stimulation effects on conscious levels in comatose patients. Both address mechanisms relevant to the reticular activating system.

Novel methods for functional imaging of brain abnormalities are well represented, with particular reference to modern MRI sequencing. Specific surgical procedures to reconstruct nerve damage and therapeutic lesioning and muscular grafting for cerebral palsy are also covered.

Finally, there are a number of papers relating to various deep brain stimulators for the control of dystonia, pain, and other movement disorders. From a surgical perspective this is an interesting area showing expansion and considerable promise.

In summary, this volume represents a collection of mostly Japanese papers exploring different aspects of surgical manoeuvres which promise to improve outcome for a variety of brain and spine injured individuals. I recommend this book to those involved in the chronic rehabilitation of central nervous injured individuals and those neurosurgeons who seek subspecialisation in this area.

P J Kirkpatrick

Biopsychosocial approaches in neurorehabilitation—assessment and management of neuropsychiatric, mood and behaviour disorders

As the title implies, this book is ambitious in its remit, encompassing the complexity of brain injury outcome for the sufferer and the wider community. The acknowledged aim is to highlight the “interaction of biological, psychological, and social influences on affect and behaviour” (p 2) by presenting a compilation of information from several research fields to provide a focus for the development of clinical practice.

The 17 papers are grouped into five sections covering assessment, mood and anxiety, behavioural health, relationships, and community services. There is no formal division between sections and, inevitably, there is some overlap. However, cross-referencing between papers is good. Perhaps not surprisingly, the overwhelming emphasis is on outcome after traumatic brain injury (TBI), but depression after stroke and psychosocial effects of aphasia are both covered.

Among the contributions, Tate presents a comprehensive overview of attempts to tease out the respective influence of pre- and post-morbid factors on outcome and draws the conclusion that personality changes are largely independent of premorbid personality. She reminds us that psychosocial factors characterising the TBI population also characterise the age group in which TBI is most prevalent. A review of literature on substance misuse (Taylor et al) identifies the importance of inter-disciplinary collaboration, noting that rehabilitation professionals may lack specific expertise in substance misuse and its treatment. Zasler and Martelli present a useful paper on the effects of mild traumatic brain injury, which are still poorly understood despite their prevalence, but which might have been strengthened by acknowledgement of recent UK work findings (for example King, 1996). In the final paper, Judd presents telling statistics to illustrate the mismatch that still exists, even in developed countries, between prevalence of traumatic brain injury and provision of adequate diagnostic and rehabilitation facilities.

Although quite expensive at £59.95, this compilation of papers serves to emphasise the multi-faceted role of modern neurorehabilitation and largely succeeds in its aim of providing a comprehensive information resource.

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Reference

CORRECTIONS

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In the Letter by Deschauer et al (J Neurol Neurosurg Psychiatry 2004;75:1204–5) the number of the nucleotide of the TREM2 gene (Q33X); this change is correctly reported in Neurol Neurosurg Psychiatry 2004;75:75 (Q33X). In the final paper, Judd presents telling statistics to illustrate the mismatch that still exists, even in developed countries, between prevalence of traumatic brain injury and provision of adequate diagnostic and rehabilitation facilities.

Soragna D, Papi L, Ratti M T, et al. An Italian family affected by Nasu-Hakola disease with a novel genetic mutation in TREM2 gene (J Neurol Neurosurg Psychiatry 2003;74:825–6). The correction in this paper regards the number of the nucleotide of the TREM2 mutation. In the paper the authors wrote that the mutation was at position 191 (191 C→T) in exon 2 of the TREM2 gene. The correct mutation is at position 97 (97 C→T) in exon 2 of the TREM2 gene. The mutation changes glutamine 33 to a stop codon (Q33X); this change is correctly reported in the paper. The authors apologise for the error.