White matter abnormalities on MRI in neuroacanthocytosis

Neuroacanthocytosis denotes a group of uncommon heterogeneous 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, orofaciolingual dyskinesia, dysphagia, dysarthria, peripheral neuropathy, myopathy, seizures, and dementia has been described in these disorders.

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 debilitating 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. All other investigations were negative (full blood count, copper studies, lipid studies, protein electrophoresis, vasculitis screen (antinuclear antibody, antineutrophil cytoplasmic antibody, double stranded DNA antibodies) syphilis serology, 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, corona radiata, 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. 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 temporally (fig 1D), demonstrating "dysplastic/septum" and a decreased T1 signal on T1 turbo spin echo (TSE) images (fig 1D). T2 weighted axial and sagittal MRI were normal except for a decreased signal bilaterally in the thalamus, cerebral peduncles, and corpus callosum. A 12 month follow up MRI scan was normal except for enhancement within the white matter extending to the subcortical white matter bilaterally. The patient was commenced on clozapine, which substantially improved his psychosis and chorea. 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. 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

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of CSF, very long chain fatty acids, mitochondria, white cell enzymes and plasma lyosomal 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 which 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,\textsuperscript{3} as the MRI appearances are so variable.

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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 neurobehavioural 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.\textsuperscript{1} 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\textsuperscript{3} 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\textsuperscript{1} 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 single (maximum of two syllables) concrete nouns—for example, square or circle from the token test and adjectives such as yellow or red. The words he did understand had to be spoken slowly, loudly, and at a low pitch. He seemed to have general difficulty with rapid tonal transitions that mimic speech sounds, as in the speech sounds perception test and the seashore rhythm test.

Reading comprehension was grossly within normal limits. He did demonstrate problems with complex syntax and evidence occasional paraphasic errors. This may have been residual from his acute Wernicke’s aphasia. On the whole, his speech was functional.

- 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),\textsuperscript{4} 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 determined 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 emotional 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,\textsuperscript{3} and consistent with a visual-verbal disconnection. This finding
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 an artefact 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 (PMC), frontal lobe, and sacral spinal cord are considered important in controlling micturition. Recent studies in healthy humans using positron emission tomography (PET) have shown a significant increase in blood flow in the PMC and midbrain periaqueductal grey (PAG) during micturition and urine storage. Thus, in addition to the PMC, the PAG may play an important role in micturition control. However, to our knowledge, there is no clinical report that identifies the role of the PAG in micturition. Here we report a case of acute urinary retention caused by a small lesion in the PAG. A favourable response to steroid therapy resulted in the normalisation of micturition.

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 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 anatomic 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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References

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, corroborated our earlier findings.1 In their patient, Vim thalamotomy alleviated tremor in both the distal and proximal segments of the upper extremity.1 However, controversy continues to surround the advisability of using Vim for the treatment of proximal tremors because the placement of larger lesions carries increased risks and the somatotopy of the proximal or truncal muscles remains obscure in their patient.Vim.2 Here we present a patient with a pontine haemorrhage in whom the combination of thalamic Vim deep brain stimulation (DBS) and globus pallidus internus (GPI) pallidotomy abolished Holmes’ tremor. This 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 haemosiderin ring around the lesion in the pontine tegmentum (fig 1B). On T2-weighted images, a high signal lesion was seen in the left inferior olive, as consistent with the hypertrophic olivary degeneration (fig 1C). As sequential pharmacotherapy using clonazepam (3×0.5 mg/day) and benserazide/levodopa (3×25/100 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.1 The optimal target was determined to be 7 mm dorsal to the midline. A high signal lesion was seen in the left pontine tegmentum (fig 1B). On T2-weighted images, a signal lesion in the pontine tegmentum was seen (fig 1C). As sequential pharmacotherapy using clonazepam (3×0.5 mg/day) and benserazide/levodopa (3×25/100 mg per day) was only slightly effective, he was referred for surgery. Prior informed consent was obtained from the patient and his family.

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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: theTRS 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 pallidotomy3 and obtained informed consent prior to the procedure.

In April 2003, left GPI pallidotomy was performed according to the method we described previously.1 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.

Figure 1 (A) Computed tomography (CT) scan showing a haematomata in the pontine tegmentum. (B, C) Axial views of T2-weighted magnetic resonance images at chronic stage (22 months after onset) demonstrating a haemosiderin ring around the lesion in the pontine tegmentum (B, arrow) and a high signal intensity area in the left inferior olive nucleus indicating hypertrophic olivary degeneration (C). (D, E) Location of the electrode superimposed on the frontal (D) and lateral (E) view of a selective third ventriculography. The target point is indicated by the asterisk. (F) CT scan demonstrating the coagulative lesion made by the left GPI pallidotomy (arrow). The CT scan was carried out 10 days after pallidotomy. AC, anterior commissure; PC, posterior commissure; ML, midline.
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 (mtDNA) mutation of mitochondrial DNA (mtDNA), the most common heteroplasmic mtDNA mutation. It is responsible for ~80% of cases of MELAS (mitochondrial encephalomyopathy, 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 episodes and the reason for this clinical variability remains poorly understood. Although the percentage level of the A3243G mutation in muscle is 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 background mtDNA sequence variation influences phenotype. There is a well-recognised association between the mtDNA genetic background (or haplogroup) and the risk of developing visual failure in another mtDNA disorder, Leber’s hereditary optic neuropathy, 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 directly downstream of the second mitochondrial tRNA gene encoding leucine (tRNAleuc(CUN)) occurs with a frequency of 21% in a population of European origin and defines the mtDNA super-haplogroup UK together with two other polymorphisms (A11467G and G12372A). As haplogroup U has also been reported to be a risk factor for sporadic occlusive stroke in patients with migraine, 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 patients visited a 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 polymorphisms.

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’ GATTGTAATCCTGACCAAGGAGG CT 3’; nt 12164–12199) and a reverse primer (5’ GGTTAAACGGGTGTGAAGGTG E’; nt 12412–12390). Amplified products were purified and sequenced using BigDye terminator cycle sequencing chemistry 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 stroke of any kind harboured the A12308G polymorphism. Every patient with the A12308G polymorphism also harboured the G12372A variant, indicating that they belong to the same mtDNA super-haplogroup UK.

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. Meta-analysis of all available data however, including the present study (n = 107) and the published study of Pulkes et al (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 (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 episodes and 30% harboured the A12308G polymorphism, confirming that our cohort of
107 A3243G index cases formed a representative sample. Despite studying a larger cohort of patients, we were not able to confirm the positive association between the A12308G polymorphism and an increased risk of stroke in patients with the A3243G mutation as reported previously. Meta-analysis of all the available data failed to prove any clear association between the A12308G polymorphism and stroke-like episodes.

The clinical diversity associated with the A3243G mutation clearly involves multiple factors. We have previously shown a correlation between clinical phenotype and mutation load in muscle.1 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 with a tendency for patients with stroke-like episodes. We have previously shown a correlation between clinical phenotype and mutation load in muscle.1 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 with a tendency for patients with stroke-like episodes.

Importantly our 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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References

Early symptoms of brain tumours
Malignant cerebral glioma is the most common adult primary brain tumour but surprisingly few studies report how patients with early symptoms present in primary or secondary care. A retrospective audit in south east Scotland found considerable variation in the referral of patients with primary brain tumours: only one quarter of 439 patients were initially referred directly to specialist centres. This must relate in part to the way in which symptoms develop and the difficulty of distinguishing them from more common but less sinister problems. For example, a large case record review of initial symptoms experienced by 653 glioma patients presenting to the National Hospital for Neurology and Neurosurgery, Queen Square, London, between 1955 and 1975 found a relatively low prevalence of neurological problems such as epilepsy (38%), headache (35%), mental change (17%), and hemiparesis (10%); by the time of diagnosis the prevalences were 54%, 71%, 52%, and 43%, respectively. Few studies focus on the accounts of patients and relatives. One qualitative interview study of 28 Swedish patients suggested that relatives noticed general changes including cognitive and personality change and took the initiative in seeking help more often than the patients themselves.2

The recently published last diaries of the politician and historian the late Alan Clark provoked us to reconsider the significance of early symptoms from the perspective of patients themselves.3 Here we report data on 92 patients (table 1), suggesting a differing development of symptoms and problems from that described in their medical records, and a distinctly similar picture, in some, to that described by Alan Clark. Interviews tended to elicit histories of more subtle problems such as fatigue and cognitive and personality change almost as often as the neurological problems typically associated with brain tumours. Of the 48 patients with headache only two had developed no other symptoms by the time of diagnosis.

Our sample is limited to patients who were well enough for radiotherapy and to receive home visits after diagnosis. It therefore excludes those most disabled and confused at diagnosis and treated with steroids alone. The data only cover problems that had developed before diagnosis. We did not have access to primary care records to explore how symptoms were presented to general practitioners, but 41% (38 of 92) were referred to a neurologist. Of the 64 patients whom we questioned on the topic, 19% (12) were critical of the initial management by their general practitioner and 28% of 88 relatives thought there had been significant delay by the health care system as a whole. This issue remained salient for many, even after the patient had died. Of 56 whom we saw as part of a study after bereavement, one third (17) spontaneously mentioned concerns they continued to have about delay in diagnosis and the effect this might have had on quality of life or survival. The problems they identified ranged across primary, secondary, and tertiary care and included their perception that referrals had not been made quickly enough or that waiting for appointments and imaging had been excessive.

The lack of data on the development of symptoms means that current national criteria for urgent referral rely on data from patients presenting to specialised centres rather than on the predictive power of symptoms in the population attending primary and secondary care. The data elicited here confirm the earlier suggestion by McKeon and Thomas that the significance of headache may lie in its association with alterations in patterns of behaviour and disability.4 Although retrospective accounts cannot be used to define predictive factors for earlier diagnosis, they do suggest some implications for future research and practice. First, more detailed study of patients’ and relatives’

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 presenting 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 lasting aspect 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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References

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

Spinal and bulbar muscular atrophy (SBMA; MIM 313280) is an X linked late onset motor neurone disease characterised by slowly progressive proximal and bulbar muscle weakness, muscle atrophy, postural hand tremor, gynecomastia, 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 al2 reported that leuprorelin, a lutenising hormone releasing hormone (LHRH) agonist that reduces the level of testosterone release from the testis, 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 gynecomastia. 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 upper and 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 15–16 IU/L) levels were elevated. After his informed consent was obtained, high molecular weight genomic DNA was extracted from peripheral leucoocytes 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 1717 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 deterioration to date. On the contrary, an improved muscle strength was recorded in the neck flexor, biceps brachii, and quadriceps femoris muscles. Furthermore, serum CK levels gradually decreased from 1717 IU/l to 384 IU/l after the leuprorelin treatment (see fig 1), whereas L (0.6 IU/L) or testosterone (<0.1 IU/L; normal range 1.2–8.0 IU/L) were decreased by the leuprorelin injections.

Figure 1 Serum creatine kinase (CK) levels of the patient gradually decreased from 1717 IU/l to 834 IU/l after the leuprorelin treatment.

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.3 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.4 These phenotypes were markedly increased in male rats, on which growth of prostate cancer cells were significantly rescued by castration. Female transgenic mice exhibited only a few manifestations that markedly deteriorated with testosterone administration. Furthermore, in a Drosophila model of SBMA, it has been demonstrated that androgen agonists induce nuclear translocation of the mutant ARs and toxicity.5 Taken together, these results provide the possible knockdown of 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
cases of retinal vein occlusion (CRVO) suggested 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 ophthalmic 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.

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Medical SHOs’ 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 presenting symptoms, 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 Rothschild 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 how 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 can be very insightful. Because this is a quick reference book, if the reader is so inclined, the early chapters can be skipped, but the reader may miss out on the central message of the book, which is the understanding of the doctor–patient relationship. Further thumbing through the book will reveal comprehensive backgrounds and practical approaches to psychiatric, medical, and behavioural disorders in primary care, including pharmacological treatments for psychiatric illnesses. The book is written for the US healthcare system but most treatment options suggested are available in the UK.

The presentation of information is stylish and cohesive, with the 35 chapters following a similar format including case illustrations. These illustrations are interesting but occasionally a little too simplistic. The book’s major achievement is its diversity, which is also its weakness, as some detail is lost. However, this is a minor criticism.
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 behavioural and medical 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, 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 multi-author books have 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 ion 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 neuroimmunology 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 in a chapter on spinal mechanisms for control of muscle. Diversion 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 and histological sections—no diagrams or MRIs.

In summary, when compared to its 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

M Lowrie


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, chemotheraphy, and external beam radiotherapy to prolong life in glioma, a great deal of translational 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 given by the editors’ preliminary remarks. Unfortunately, evaluating the effects of local therapies is 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 ante pasta, 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 deposition of a chemical agent (for example implantable drug releasing biodegradable microspheres for local treatment of brain glioma and intracavity 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 cover new approaches using specific techniques (for example non-invasive transcranial high intensity focused ultrasound (HIFUS) under MRI thermometry and guidance) for the treatment of brain gliomas. The editors have dedicated a separate chapter to the technique.

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 basis, 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
Neuroepidemiology—from principles to practice

Everyone, at one time or another, feels misunderstood and unappreciated. Epidemiologists are no exception. They get fed up with 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 services 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 case here. Neuroepidemiology—from principles to practice is a gripping read. No matter how many neurological stories without a dénouement you have read, Neuroepidemiology—from principles to practice will provide a promising lead but which might equally turn out to be a red herring. In the end, the story usually pays 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.

I R Whittle

Neurosurgical re-engineering of the damaged brain and spinal cord

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

Each chapter represents multi-author presentations largely derived from papers presented at the meeting in Japan. The manuscript consists of nine subsections addressing aspects of coma, restorative neurosurgery, early rehabilitation, function imaging, neurosurgical 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 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.

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 and smoking, for example, is included. 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 multifaceted role of modern neurorehabilitation and largely succeeds in its aim of providing a comprehensive information resource.

J Cockburn


In the Letter by Deschauer et al (J Neurol Neurosurg Psychiatry 2004;75:1204–5) the order of authorship is incorrect and should be: M Deschauer, P F Chinney, S Shanske, S DiMauro, K Majamaa, E Wilichowski, D R Thorburn, S Ziert, A M Schafer, D M Turnbull, R W Taylor.

doi: 10.1136/jnp.2003.026278corr1

do: 10.1136/jnp.2003.031126corr1

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 numbering of the nucleotide of the TREM2 gene. 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.