LETTERS TO THE EDITOR

Coexisting vertical and horizontal one and a half syndromes

Supranuclear ocular movements comprise chiefly vertical and horizontal movements; horizontal movements are controlled by the subcortical centres located mainly at the pontine level and vertical movements at the level of the rostral midbrain. The classic one and a half syndrome is produced by a unilateral pontine tegmental lesion that includes the paramedian pontine reticular formation and medial longitudinal fasciculus on the same side, and has been considered an important ocular sign in neurological diagnosis. Vertical, as distinct from horizontal, one and a half syndrome, has also been documented recently. We report on a patient with concurrent vertical and horizontal one and a half syndromes.

A 57 year old man was admitted to hospital with a sudden onset of dysarthria and loss of consciousness while playing golf. He had a history of aortic regurgitation and heart failure 8 years previously, and underwent aortic valve replacement 5 years previously, when he started to take oral antiplatelet and anticoagulant drugs. On admission, he was comatose, and his blood pressure was 140/76 mm Hg. He also had atrial fibrillation, Cheyne-Stokes respiration, bilateral miosis, and a positive Babinski's sign. Brain CT showed lesions suspected of being infarcts in the right medial thalamus and the left upper cerebellum. According to neurological findings on day 4 after onset of disease, he was in a state of hyperomnia. While awake, his head tilted slightly to the left, the right eye was slightly deviated upward, the left eye slightly downward, and there was bilateral miosis. For horizontal ocular movements, only the right eye could abduct with monocular horizontal nystagmus. Also, there was bilateral conjugated leftward palsy, indicating horizontal left one and a half syndrome. On the other hand, for vertical ocular movement, only the left eye could gaze downward. Also, difficulty in downward gaze of the right eye and bilateral conjugated upward palsy, indicating vertical one and a half syndrome, were noted (figure A). Doll's eye test (oculoccephalic reflex) was weak but positive, and the eyes were unable to converge. There was also ataxic dysarthria, cerebellar ataxia of the left limbs and trunk, right sided hemisensory disturbance, and bilaterally positive Babinski's sign. Brain MRI showed infarcts in the right medial thalamus, left dorsal portion of the upper midbrain, and left upper cerebellum (figure B). On magnetic resonance angiography performed at the same time, partial obstruction of the left posterior cerebral artery was noted at its origin. Cardiogenic cerebral embolism was suspected in the pathogenesis of the serial episode in this patient.

At 7 days the patient still tended to become unconscious, accompanied by Cheyne-Stokes respiration, when talking to a familiar person. About 1 month later he talked about occurrences at the onset and began to show an interest in his surroundings. At 2 months, adduction of the left eye, bilateral leftward gaze, downward gaze of the right eye, and bilateral upward gaze showed moderate improvement. The gait disturbance persisted and he is still in a wheelchair.

Classic horizontal one and a half syndrome is commonly caused by a vascular accident.

(A) Ocular movements of the patient. The right eye was slightly deviated upward, the left eye slightly downward in the primary position (P). For vertical movement, only the downward gaze of the left eye is possible. Downward palsy of the right eye and bilateral conjugated upward palsy were seen. For horizontal movements, the rightward gaze of only the right eye is present. The rightward palsy of the left eye and bilateral conjugated leftward palsy are shown. The eyes are unable to converge (C) and Doll's eye test (D) is weak but positive. (B) Brain MRI. a, b axial FLAIR imaging. c, d coronal T2 weighted imaging. High signal intensity areas are noted in the right medial thalamus, the left dorsal part of the rostral midbrain, and the left upper cerebellum.
occurring in the lower pons involving the paramedian pontine reticular formation and the medial longitudinal fasciculus. 1-3 In the present patient one and a half syndrome, however, was thought to be due to two concurrent lesions of distinct nerve tracts in the upper left midbrain—that is, descending fibres from the frontal eye fields of the cerebral cortex after decussation at the midbrain level and medial longitudinal fasciculus fibres ascending on the opposite side. Attention has recently focused on the rostral interstitial nucleus of the medial longitudinal fasciculus, interstitial nucleus of Cajal, and posterior commissure, all located in the tegmentum of the mesencephalon, as the brain stem centres for vertical eye movement. 1-3 Vertical one and a half syndrome consists of a bilateral conjugate upgaze palsy and a unilateral downward palsy, 1 or a bilateral conjugate downward palsy and a monocular upgaze palsy. 1 It has been reported that the fibres involved in upward gaze from the posterior commissure may explain bilateral upgaze palsy, and the fibres involved in downward gaze may be affected on one side before their decussation in contralateral lesion, or after their decussation in ipsilateral lesion. 1 A patient was also reported with bilateral downgaze palsy and bilateral lesions of the rostral interstitial nucleus of the medial longitudinal fasciculus. 1 Furthermore, it was reported that a unilateral lesion of the interstitial nucleus of Cajal resulted in tilting of the head towards the opposite side. 1 Therefore, it can be assumed that the leftward tilting of the head seen in the patient under study was caused by a lesion of the right interstitial nucleus of Cajal. The present patient thus seems to be a rare case of the coexistence of two distinct syndromes, vertical and horizontal one and a half syndromes, although the lesions responsible for these syndromes are different. Even though the exact anatomical and physiological mechanism underlying vertical gaze still remains obscure in many respects, vertical one and a half syndromes are considered to be one of the important neurological signs suggestive of a lesion affecting the rostral midbrain. The particular pathogenetic mechanism of this interesting syndrome will be elucidated through future elaborate comparative studies of clinical manifestations and diagnostic imaging.

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Malignant catatonia secondary to sporadic encephalitis lethargica

Catatonia is a neuropsychiatric syndrome characterised by a combination of psychosocial withdrawal and various movement disorders. Kahlbaum first described this syndrome in 1868 when he noted this condition of “profound mental and neurological depression.” Kraepelin limited catatonia to a subtype of dementia pракox, later redefined by Bleuler in 1906 as catatonic schizophrenia. Since then, it has become increasingly apparent that the catatonic syndrome can be found in various psychiatric conditions, including schizophrenia and other psychoses, in which patients have a range of movement disorders from the extreme immobility and waxy flexibility to dramatic aberrations of movements and postures. 4

Case description

The patient was a 22 year old previously healthy woman who was transferred to the Barrow Neurological Institute after a 4 week stay in hospital for progressive immobility, mutism, posturing, and tremor. Initial evaluation had shown a CSF pleocytosis with increased liver transaminases, and an EEG with bifrontal slowing. Further investigation as to etiology of her meningoencephalitis was negative including brain biopsy, vasculitis, and comprehensive infectious disease evaluation for both endemic and as well as viral infection. An FDG-PET showed bilateral cortical hypometabolism and asymmetric thalamic hypometabolism. Over the course of her initial stay in hospital, she was intermittently agitated and chanting with dramatic improvement in her symptoms. She was discharged to a rehabilitation facility and at 6 month follow up, she had made a full recovery and returned to full employment.

The diagnosis of catatonia has not been standardised but instead relies on a range of typical clinical features that combine an alteration of behaviour with stereotypic movement disorders. Cataplexy, although considered by Bleuler to be intrinsic to the condition, is currently not considered mandatory for the diagnosis. Cardinal signs are felt to be immobility, mutism, and withdrawal with secondary features including posturing, rigidity, posturing or grimacing, negativism, waxly flexibility, echophenomenon, stereotypy, and verbalisation. Criteria have been proposed which include many of the above signs in an effort to standardise diagnosis and treatment. 6 Lethal (or malignant) catatonia has additional features of hyperthermia, autonomic instability, rigidity often severe enough to lead to death through rhabdomyolysis, renal failure, and cardiovascular collapse.

Aetiologies of catatonia are varied and although its association with schizophrenia is accepted, it is most often seen with affective disorders. Medical conditions are increasingly being recognised as causes of a catatonic syndrome. When first described, encephalitis lethargica produced three relatively distinct, although often overlapping syndromes. The first, and most common, began with the acute onset of mental changes, which progressed with increasing sleepiness, ocular motility problems (including oculogyric crisis), and pupillary abnormalities and is known as the somnolent-ophthalmoplegic form. The parkinsonian form is presented with bradykinesia, cataplexy, and mutism and most closely resembles catatonia. The final variety, recognised as the hyperkinetic form, had a more psychiatric presentation with agitation, motor restlessness, obsessional behaviour, psychosis, and dyskinesia. There are no contemporary criteria for diagnosis of encephalitis lethargica, however based on historical data, we think that our patient represents a hyperkinetic form into a more parkinsonian picture punctuated by occasional dyskinesias.

The pathological substrate for catatonia is largely unknown. When it is produced by an anatomical derangement, abnormalities of neuronal network are most often seen in the thalamus, subthalamic nucleus, and substantia nigra. In patients dying from encephalitis lethargica, severe destruc
tive changes were seen in the substantia nigra and, to a lesser extent, in the subthalamic nuclei and other basal ganglia structures. Our patient had a normal brain MRI and FDG-PET suggesting asymmetric thalamic hypometabolism which resolved with ECT, suggesting at least functional impairment in these anatomical areas.

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Evaluation for the aetiology of catatonia is outlined in our report. Treatment is aimed at addressing any underlying medical conditions that may be producing the syndrome and once this is done, directly treating the catatonia itself. Historically, this has been varied, but recent studies suggest excellent efficacy for both high dose intravenous benzodiazepines and ECT.

Our patient began responding within 24 hours of her first ECT and although spontaneous recovery remains a possibility, we think that her improvement is due to ECT. Data regarding outcome in epidemic encephalitis lethargica reports a mortality up to 35% with an additional 50% experiencing neurological and psychiatric sequelae. Post-encephalitic parkinsonism could be seen as far out as 20 years in patients who seemed to have recovered from the acute infection. Recovery in our patient has been complete without evidence for a progressive or relapsing neurological or psychiatric disorder, although follow up has been limited to 1 year.

In conclusion, catatonia may be produced by a variety of both neurological and psychiatric conditions. Without a history of previous psychiatric impairment, aggressive investigation should be pursued for treatable medical conditions. Catatonia due to medical conditions may be successfully treated with therapies typically reserved for psychiatric indications. The clinical syndrome of encephalitis lethargica, although no longer epidemic in nature, is still sporadically seen and the underlying inflammatory cause is, as yet, unknown.

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Downbeat nystagmus from heat stroke

Downbeat nystagmus is an ocular motility disturbance that can be seen in various pathological conditions. Although classically associated with structural lesions of the cervicomedullary junction or cerebellum, it can also occur in the setting of toxic insults and metabolic abnormalities. Heat stroke is the most severe form of heat related illness, and is associated with multisystem organ failure. Heat stroke is infrequently associated with a cerebellar syndrome. We describe a patient in which downbeat nystagmus was associated with a midline cerebellar syndrome in a patient with heat stroke, suggesting that the vermal cerebellum and vestibulocerebellum may be particularly susceptible to thermal injury.

A previously healthy 22 year old man with no relevant medical history collapsed while on a 4 mile run during military basic training. Initial core body temperature was 39°C. He was incoherent and combative. Laboratory data showed increased creatine kinase, increased liver function tests, and prolonged coagulation variables. Measures to lower body temperature were initiated and he was transferred to our institution.

On arrival, core body temperature was 37°C. He began responding to commands. His sodium concentration was 135, potassium 3.2, calcium 7.5, magnesium 1.6, alanine transaminase (ALT) 2739, aspartate transaminase (AST) 2112, white blood count 4.2, haemoglobin 12.5, platelet count 43 000, international normalised ratio (INR) 2.9, and ammonia 33. Serological tests for HIV and RPR were negative. An ECG and chest radiograph were unremarkable.

Over the next 24 hours the patient’s liver enzyme activity improved. He received several transfusions to correct his thrombocytopenia and hypocoagulability. Three days after admission, the patient’s family noted that his speech was slurred. The patient complained of blurred vision when reading or looking down.

Neuro-ophthalmological examination 5 days after the onset of his visual symptoms showed near visual acuity of J16 in primary gaze (secondes), J1 and J1 in upgaze. Kinetic perimetry was full in both eyes. Pupils, external examination, anterior segments, and fundi were within normal limits. Motility examination showed full ductions and versions. Vertical and horizontal saccades were hypometric. Vertical and horizontal smooth pursuit were normal (vertical more than horizontal), showing low pursuit gain. There was impaired suppression of the vestibulo-ocular reflex. Downbeat nystagmus was present in primary gaze, worsening in down-gaze, and gaze down and laterally. This was poorly suppressed by fixation. His neurological examination showed cerebellar ataxia (truncal more than appendicular), and dysarthria. A high quality MRI of the brain with and without contrast and with diffusion weighted imaging was performed 6 days after the onset of visual symptoms and was normal. A lumbar puncture showed normal opening pressure and normal CSF profile. Thiamine was added empirically with no effect. Magnesium was corrected to a concentration of 2.6 mg/dL with no change in the patient’s downbeat nystagmus. The patient was discharged to a rehabilitation facility. He was lost to follow up.

Slow upward drifts and downward rapid phases characterise downbeat nystagmus. The velocity and amplitude of the upward phases are often maximal when looking downward and laterally. Upward gaze typically dampens or eliminates downbeat nystagmus. Several mechanisms responsible for the syndrome have been proposed, including dysfunction of a neural integrator located in the brainstem, tonic imbalance in the vertical semicircular canal and ocular motor pathways, and an imbalance in the otolith-ocular reflex. Experimental studies have shown that lesions in the posterior midline cerebellum can produce downbeat nystagmus. Takemori and Suzuki, for example, produced downbeat nystagmus in rhesus monkeys with bilateral floccular lesions. Experimental evidence suggests that the flocculus, presumably through Purkinje cell activity, exerts an inhibitory influence on the mechanisms responsible for producing pathological nystagmus. Downbeat nystagmus also can be seen with lesions of the cervicomedullary region such as Chiari malformation or basilar invagination. It may be a manifestation of ischaemic or demyelinating disease in this region or in the cerebellum. It has also been associated with lithium toxicity, B12 and thiamine deficiencies, and hypogammaglobulinaemia.

Heat stroke is the most severe form of heat related illness. It results from a failure of thermoregulatory mechanisms, causing increase of core body temperature to extreme levels. Predisposing factors for heat stroke include lack of acclimatization, fatigue, obesity, sleep deprivation, and deconditioning. It is characterised clinically by signs and symptoms of CNS injury, core temperature greater than 39°C (102°F), and multisystem organ failure. Involvement of the CNS in heat stroke may infrequently include cerebellar dysfunction. The cerebellar syndrome associated with heat stroke classically consists of both truncal and appendicular ataxia, horizontal nystagmus, and scanning dysarthria. The clinical characteristics, neuroimaging findings, and neurologic outcomes of cases published since the advent of neuroimaging are summarised in the table. All of the patients had some degree of midline cerebellar dysfunction, and all had initially normal neuroimaging studies.

Cerebellar Purkinje cells are known to be particularly susceptible to metabolic stress, particularly hyposodic-ischaemic injury. There is evidence that the cerebellum in general, and Purkinje cells in particular, are selectively vulnerable to thermal injury. Heat shock proteins are a family of proteins that act as heat stressors and protective processes essential for cellular survival. Thermal injury has been shown to induce the transcription of heat shock protein in the rabbit cerebellum. This may reflect an increased demand for thermal injury repair by Purkinje cells.

Our case is unique in that our patient had a midline cerebellar syndrome with downbeat nystagmus in the setting of heat stroke. Although hypogammaglobulinaemia has been implicated as a cause of downbeat nystagmus, our patient’s magnesium concentration was only slightly below normal for our laboratory. Furthermore, the syndrome persisted even after correction of his serum magnesium into the normal range. It may be that in the setting of an already compromised cerebellum, even borderline hypogammaglobulinaemia may promote or accentuate downbeat nystagmus.

Our case provides clinical findings which are compatible with experimental data supporting localisation of downbeat nystagmus to the vestibulocerebellar region. It provides further evidence that the cerebellum can be particularly susceptible to thermal injury. The normal diffusion weighted MRI also supports the theory that cerebellar damage in heat stroke is caused by direct thermal injury, rather than a hyposodic-ischaemic insult.

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Clinical characteristics of published cases of cerebellar syndrome from heat stroke

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<th>Year</th>
<th>Age (°C)</th>
<th>Temperature</th>
<th>Cause of fever</th>
<th>Clinical syndrome</th>
<th>Initial imaging</th>
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<th>Follow up imaging</th>
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<tr>
<td>1</td>
<td>1970</td>
<td>Mehta and Baker</td>
<td>47M</td>
<td>42.2</td>
<td>Confinement in heated cell</td>
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<td>Yaquib et al</td>
<td>50F</td>
<td>43.2</td>
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<td>NMS, dystonia, dysarthria, ataxia</td>
<td>CT NL</td>
<td>Nearly complete 5 months</td>
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<td>42.5</td>
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<tr>
<td>4</td>
<td>1995</td>
<td>Manto et al</td>
<td>39M</td>
<td>41.8</td>
<td>NMS</td>
<td>Gait ataxia</td>
<td>CT NL</td>
<td>None 1 year</td>
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<td>Manto</td>
<td>44F</td>
<td>42.1</td>
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<td>Dysarthria</td>
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<td>MRI NL</td>
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NMS = neuroleptic malignant syndrome; CBLR = cerebellar; NL = normal.


Apolipoprotein E ε2 may be a risk factor for sporadic frontotemporal dementia

Frontotemporal dementia (FTD) is the second most common form of presenile dementia, after early onset Alzheimer’s disease. Up to half of cases of FTD are thought to be familial, probably with an autosomal dominant mode of inheritance, some with mutations on chromosome 17. The genetics of sporadic FTD have been less studied, although several groups have examined the potential association of FTD with apolipoprotein E (APOE) ε4, with inconclusive results.1

We studied 11 patients with sporadic FTD (excluding patients with first degree relatives with dementia) in the cohort of the Oxford project to investigate memory and aging (OPTIMA). Nine of the 11 were histopathologically confirmed and the remaining two fulfilled the consensus criteria of Neary et al (three of the first nine had also been clinically diagnosed by these criteria and all three were confirmed at necropsy); only one of the nine confirmed cases was Pick-type. Apolipoprotein E genotyping was performed, blind to diagnosis, by polymerase chain reaction methods for the 11 patients with FTD (move age at death or last examination: 65.7 years; six women) and for 136 elderly controls (mean age: 77.5 years; 77 women), without cognitive impairment and with CAMCOG scores greater than 80, from the OPTIMA cohort. An older control group was used to mimic the inclusion of only patients fulfilling the consensus criteria of FTD; APOE allele frequencies did not vary with age at death or last examination. Controls and patients were Caucasians from the Oxford region. Genotyping results are shown in the table.

| Frequency in sporadic FTD and related disorders. Since submitting this letter, we have read an important and relevant report by the Manchester group, easily the largest and most comprehensive study to date on APOE frequencies in FTD and related disorders. The group examined 35 controls and 163 patients, including 58 with FTD without family history, and found no association of any APOE allele with FTD. Their APOE ε2 allele frequencies were 0.06 in controls, similar to ours, and 0.09 in non-familial cases of FTD. When pooling their data with ours, however, we obtained APOE ε2 frequencies of 0.12 in sporadic FTD (n=69) and 0.06 in controls (n=171). This gave an odds ratio of sporadic FTD for that allele of 2.15 (95% CI 1.1–4.2, p=0.04).

We especially thank all patients and volunteers, members of OPTIMA, the Department of Neuro-ophthalmology, Radcliffe Infirmary, Dr N John, Dr S Fernando, C Johnston, D Warden and S Litchfield. This work was supported by Bristol-Myers Squibb.

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Bilateral visual improvement after unilateral optic canal decompression and cranial vault expansion in a patient with osteopetrosis, narrowed optic canals, and increased intracranial pressure

Osteopetrosis (Albers-Schonberg disease, marble bones) is a relatively rare disease that is characterised by increased skeleton mass and bone density. It results from a defect in the development or function of osteoclasts with consequent impairment of bone resorption. The defect may be intrinsic to the osteoclast lineage or the mesenchymal cells that support the development and activation of the osteoclasts. Osteopetrosis is inheritable, and four clinical forms have been distinguished: autosomal-recessive malignant, autosomal-dominant benign, mild autosomal-recessive, and autosomal-recessive osteopetrosis with renal tubular acidosis. Of the four, the first two are the most prevalent. The disease is characterised clinically by multiple fractures, abnormally shaped bone, and anaemia. Its neurological manifestations include cerebrovascular complications, optic nerve palsies, papilloedema, and blindness from optic nerve atrophy. Optic nerve atrophy is common and can result from the chronic effects of papilloedema or compression by a narrowed optic canal. Optic neuropathy associated with papilloedema can be prevented by aggressive management of intracranial pressure (ICP), whereas that associated with narrowing of the optic canal is usually treated by surgical decompression.

A 19 year old man, diagnosed with autosomal recessive osteopetrosis at about 5 months of age, presented in March 1997 with a dramatic decline in vision. He previously had had a visual acuity of 20/30 in his right eye, 20/50 in his left eye, and full visual fields for most of his life. A brain CT in 1986 showed no optic canal narrowing. In 1994, he developed increased ICP and underwent a left optic nerve sheath fenestration and placement of a lumbarperitoneal shunt (LPS). His vision remained normal until August of 1996 when he began to experience declining vision. He was referred to the Johns Hopkins Hospital in March of 1997.

Visual acuity with correction was 20/200 in each eye. Near vision was 20/400 in each eye. Visual fields were limited in each eye to a tiny paracentral area of about 5 degrees. Colour vision was markedly impaired, with the patient being unable to identify any of the figures on the Hardy-Rand-Rittler (HRR) pseudosochromatic plates. Pupils were equal and reactive to light, and there was a left relative afferent pupillary defect of 0.3 log units when measured using a neutral density filter. Extraocular movements were normal. Ophthalmoscopy disclosed bilaterally pale optic discs.

Non-contrast CT of the head showed marked diffuse thickening of the calvarium with a ground glass appearance. The bony dysplasia involved the skull base, and there was narrowing of both optic canals, the petrous carotid canals, the internal auditory canals, and the cochlear and vestibular apparatus (figure A). There was also ossification of the mastoid and frontal sinuses. The CT also showed evidence of increased ICP, including an effaced third ventricle. An iodinated radio-opaque study showed that the LPS catheter was patent, but ultrasonography demonstrated bilateral enlargement of the retrobulbar optic nerves and a positive 30 degree test, consistent with increased ICP, and a lumbar puncture disclosed an opening pressure of 450 mm Hg, with normal CSF contents.

Consideration was given to treating the patient with acetazolamide, but because of the severity of visual loss associated with pale optic discs, and because it was unclear if his decreased visual function was caused by compression of the optic nerves by the narrowed optic canals or increased ICP, it was decided to perform bilateral non-simultaneous optic canal decompressions combined with a cranial vault expansion. A bicornal incision was made, a full thickness scalp flap was turned down to the level of the superior orbital rims bilaterally, and a large bifrontal bone flap was removed. The roof of the right optic canal was then removed along with the right optic canal and cranial vault expansion. (A) Preoperative scan shows marked thickening of the calvarium. The optic canals are narrowed by the diffusely thickened bone. (B) Postoperative scan shows that the right optic canal has been completely unroofed. Note that the decompression extends well into the orbital apex. Anterior cranial vault expansion can also be appreciated.

Four days after surgery, the patient’s visual acuity had improved to 20/30 bilaterally, he could correctly identify figures on seven of 10 HRR plates with the right eye and six of 10 colour plates with the left eye, and his visual fields were markedly expanded, almost to normal. A postoperative CT confirmed complete unroofing of the right optic canal (figure B). Osteopetrosis related visual loss is often ascribed to optic nerve compression secondary to the narrowing of the optic foramina. However, optic nerve dysfunction can also result from the effects of increased ICP. Because our patient’s unilateral optic canal decompression resulted in bilateral improvement in visual acuity and visual fields, it is reasonable to conclude that increased ICP and not narrowing of the optic canals was the cause of his visual deterioration. Thus, the cranial vault expansion that was performed in addition to the unilateral optic canal decompression was responsible for the rapid and dramatic improvement in the patient’s visual function.

This case provides an important lesson on the evaluation of any patient with optic neuropathy that is presumed to be secondary to narrowing of optic canals in the setting of one of the craniosenoses. Although direct compression may indeed be primarily responsible for visual deterioration in patients with osteopetrosis and related conditions, increased ICP, related to either thickening of the skull or secondary occlusion of one of the cerebral venous sinuses, should always be considered a potential aetiology, and aggressively treated when identified or suspected.
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4 further approximation, that between the handicap dimensions (Martin Prince, personal com-

4 munication). Furthermore, a comparison of values given to states of health by Hong Kong Chinese showed a good agreement with those esti-

4 mated by using the London handicap scale weights (derived from Londoners). Neither was there convincing between popu-

4 lation variation in scale weights assigned in the original scale development work. It is not safe, however, to assume that there are no between person differences.

5 We are pleased to see a further independ-

5 ent validation of the London handicap scale. If simplification of the scale is more useful then we welcome it. The additional burden in applying the weights, however, is no more than that of adding six lines of commands in a statistical computer program (for instance, using SPSS). On the other hand, researchers who empirically derived estimates of valuations of handicap states, we see no reason why the further approximation of equal weighting is neces-

5 sary.

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2 World Health Organisation. International classi-


2 index.html (1st April 2000).)

4 Lo R, Harwood R, Woo J, et al. Cross-validation of London handicap scale in Hong Kong Chi-


Mant et al reply:

Whether one decides to use the original weighing scoring system of the London handicap scale or the simpler unweighted scoring system as we proposed is essentially a trade off between the advantages of each approach. As argued by Harwood and Ebra-

him, the weighting system will provide what at least seems to be a more accurate estimate of the value of a health state for only limited additional analysis. However, it should be noted that weighted systems more often than not give the impression of greater accuracy when in fact all they produce is different results.1 Further, even if the weights are regarded as the “gold standard” the increase in accuracy is small, and there is scope for confusion concerning the weightings that have been published,1 and the derivation of the score is more complex, which might lead to computational errors. However, perhaps the greatest advantage of the unweighted scoring system is that there is a simpler relation

between the questionnaire responses and the final score, which makes interpretation more straightforward. There is a role for both methods of analysing the London handicap scale. Use of the simpler unweighted scoring would be likely to increase uptake and use of the instrument, with an allowance for accuracy. On the other hand, researchers who are already familiar with the weighting system have little to gain from switching to the unweighted system.

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Mass volume measurement in severe head injury

We read with interest the article by Stocchetti et al on the accuracy and feasibility of the ellipsoid and the Cavalieri method in assessment of the volume of intracranial mass lesions in patients with severe head injury.1 We consulted with the authors on the use of intracranial lesions, and its change over time, is important in the diagnosis and manage-

ment of patients with head injury and in the evaluation of clinical trials.

However, the methodology used in the study raised our concern. We have several comments on their statements, because they are potentially misleading.

(1) The statement that computer based readings of mass lesions when the choice with accurate volume estimation is necessary, is insufficiently founded. Tracing CT lesions on a digitised screen automatically calculating area and hence volume, is a hazardous task: delineating hyperdense and hypodense le-

sions from normal surrounding intracranial structures cannot always be performed reliably, due to isodensity of normal brain tissue at some edges and due to partial volume effects. Moreover, lesion tracing is the same as area estimation using a simple device such as a point counting grid with sufficient grid points, and is in fact not superior at all.2

(2) Volume estimations that on the Cava-

leri’s principle have to fullfill one absolute requirement: randomness.3,4 The volume of any object may be estimated from ran-

domised and parallel sections separated by a known distance by summing up the areas of all cross sections of the object and multiply-

ing this sum by the known intersection distance. The total area of all cross sections may be estimated by a stereological point counting method.5 A systematic array of grid intersection points is superimposed on each section. Giving random positioning of the test array on each section, the total number of grid intersection points hitting the object of interest affords an unbiased estimate of the

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total area. In the study of Stocchetti et al random- 
ness has most probably not been ac- 
counted for, as it has not been mentioned in 
the text and as the grid has not randomly 
been placed onto the CT slices.

(3) When applying Cavaleri’s principle it becomes mathematically possible to calculate the coefficient of error of the individual lesion mass volume. It declines in direct proportion to the total number of CT planes and to the total number of grid intersection points. Generally, a coefficient of error of less than 0.05 is obtained if the number of CT planes used is 10 or more, and the number of grid intersection points is 50 or more. From our own practical experience we and others know that CT at standard settings (5 or 8 mm slice thickness) almost never renders sufficient sections through the lesion mass, except for very huge subdural or extradural haemato- 
mas. Spinal CT with a 3 mm section distance may overcome this problem. Another advan- 
tage of Cavaleri’s principle is its applicability to any mass lesion irrespective of size and for- 
type.

(4) The average difference between the applied technique and the reference compu- 
ter based value is 0.57 SD (9.99) ml for the Cavaleri method and 0.20 (SD 15.48) ml for the ellipsoid method, suggesting on average acceptable agreement. However, what really matters is the accuracy, validity and reliability of the individual volume measure- 
ments. That these are not very high can be deduced from the huge standard deviations of the average differences and from the consid- 
erable limits of agreement in the graphical depiction of the results.

Accuracy of the individual measurements has to be high as in the trauma coma data 
bank (TCDB) classification a volume of greater than 25 ml is defined as a mass 
lesion.

(5) Although three examiners read the same CT scans, interobserver variability was calculated with analysis of variance (ANOVA) on 
the mean volumes. No intraobserver variabil- 
ity studies were conducted which can be con- 
sidered as an omission.

(6) The TCDB CT classification being the resultant of the status of the mesencephalic cistern, the degree of midline shift, and the presence of a mass lesion provides a ranking 
cisterns, the degree of midline shift, and the 
resultant of the status of the mesencephalic 


Stocchetti and Colombo reply: 
We are grateful to Vos et al for their comments. Briefly the main reason for our research was the fact that intracranial mass lesions are rarely measured, it is reassuring that some centres have documented expertise on such measurement.

We do not think, however, that our data, and the conclusions drawn from them, are potentially misleading, and we will try to clarify our arguments.

As indicated in the paper, we compared two pragmatic methods and a computer based method. There are, of course, limitations to each method, and tracing on the computer screen can be tricky; however, a careful tracing is feasible in expert hands and we think that this rendering calculation still gives a very acceptable reference point. If this reference method is to be questioned, an appropriate, preferably superior, method should be identified. We cannot think of any pragmatic method that would be the best choice.

Regarding the other points that aroused the concern of Vos et al, we agree on many and will try to clarify them.

(1) Randomness is an important prerequi- site; it was not mentioned in the paper but the grid was placed on the CT slices at each reader’s convenience and choice. Whether this was random enough as in the trauma coma data bank classification, in which volume is one part of the grading. That was correctly indicated in our paper. From our experience in multicen- tre, international clinical trials, we are less optimistic about the proper application of the TCDB CT classification, but that is another point in favour of improving the methods for CT readings. 

In conclusion we have applied a methodology that seems solid enough to substantiate our conclusion and, we hope, to fulfil the requirements of careful and competent readers.

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BOOK REVIEWS

This two volume book is unique in providing a comprehensive overview of all the aspects of basic neuroscience relevant to the neurosurge- on. As such it can be regarded as an essen- tial source of information for neurosurgical trainees around the world. The authors state in the foreword to this edition that their ambition was to “reflect in as up to date fash- ion as possible the expanding knowledge so essential both to trainees and established neurosurgeons alike if they are to base their clinical practice on a proper scientific basis.” They can be gratified on fulfilling their objective with such a well presented and beautifully illustrated new edition. Although clearly intended for a neurological reader- ship, there are sections that can be valuable for practitioners in other disciplines, particu- larly neurologists, oncologists, and orthopaedic surgeons involved in spinal surgery.

The third edition has expanded with the increased range of knowledge required by the
clinical neurosurgeon. There are new and increased sections covering genetics, embryology, biomechanics, and measurement, bringing the total of chapters to 83 in 11 sections. An additional feature distinguishing it from the blue second edition is the handsome red cover, perhaps unconsciously reflecting changes in the political climate! Each chapter is very clearly laid out with an introductory outline, well-structured headings, a summary, references, and a list for further reading. The manuscript is well proportioned, confining experts to present their knowledge in a concise manner in often quite short chapters. This means that the busy reader can quickly find mention of the points of interest.

The devotion of a section to biomechanics appears justified. The field has expanded rapidly and is a field that contains concepts with which the neurosurgeon should, at the very least, be familiar. Knowledge of how the spine responds to forces after injury and following fixation is a prerequisite to planning treatment. This has been well described, with plenty of good illustrations and radiographic images.

The chapters in the new section “Measurement and the Neurosurgeon” are welcome. They have been written in a fresh, understandable style that is kind to the reader and have been specifically targeted to the neurosurgeon. Such a comprehensive outline of assessment scales, outcome scores, statistical analysis, and study design is essential for those aiming to improve their management of patients by estimating the likelihood of success. Familiarity with outcome assessment is now expected not only by examiners, but is increasingly necessary for clinical practice as doctors must justify treatments to patients and the institutions that fund healthcare.

In summary, this book is an authoritative, relevant, and comprehensive account of the scientific basis for the clinical practice of neurosurgery. It can be highly recommended not only to those preparing for an examination but also to those who might find themselves on the other side of the table.

RUPERT KETT-WHITE


Information is a vital tool for patients wishing to gain more control over their lives. Different sources of information will suit different patients, and this book is a useful addition to the range of available resources. Its strength comes from the authors immense clinical experience. Its weakness is that it is too hospital centred. A formidable fist of potential deficiencies and debatable notions. Parkinson’s disease is described as a diagnosis of exclusion, which will certainly alarm the neurologists in my health district.

Patients are given invaluable warning of conditions in a late 20th century British hospital: “Don’t expect to be seen at the time specified on the appointment letter...” “You may see a different doctor each time”; “The neurologist may know very little about the individual’s circumstances and about him or her as a person”. Some advice about how to complain would have been invaluable. Readers are advised that “You may be presented to a large number of doctors in the course of a clinical ‘presentation’”, but there is no mention of multidisciplinary case conferences, hospital with a therapist, or hospital discharge planning.

The limited information about community care arrangements is dated, making no mention of care management, or of the statutory right of carers to have their own needs separately assessed. There is an invaluable and fairly comprehensive list of non-statutory resources, although much more could have been said about management of difficulties in car mobility. Oddly, wheelchairs are not in the index and get scant attention in the text. There are two unusually helpful sections on sexual dysfunction, but not enough on the management of sleep. Levodopa does increase alertness in some patients, but not in others, and in my experience improved night time mobility can sometimes improve sleep. Books of this type can never suit everyone and can never be comprehensive, but there is plenty of useful and accessible information in this one. I commend it to patients and families and especially to neurologists.

CHRISTOPHER WARD


The express aim of the editor of this book was to create “a master reference file on the field of neuroimaging”. This may sound somewhat enigmatic, particularly as, in Europe at least, we recognise two ways of doing imaging: one to look at the nervous system: neuroradiology, a clinical specialty practised by organ-specialised radiologists familiar with a wide range of techniques, closely related to the clinical needs to which this journal is devoted—neurology, neurosurgery and psychiatry—and neuromaging, usually the domain of physicists, psychologists, or neuroscientists expert in the application of a single technique, the impact of which on routine clinical practice has, it can be argued, often been negligible. A failure to distinguish clearly between the two markedly upset the balance of this book.

The text is divided into four sections: history and technology (16 chapters); brain (11); head, neck, and spine (13, of which only four deal with the spine); and paediatrics (10). In each space devoted to some subjects seems inversely proportional to their clinical impact. Thus, in section I, the physical basis of CT and MRI merits 24 pages, with 15 references, whereas functional MRI occupies 22 pages, supported by no fewer than 154 references. Functional MRI is in vogue but, come on, what about a sense of proportion? If that were not enough, two chapters on radionuclide studies (PET and SPECT respectively) have 60 pages of text between them, with 1011 references; one could be forgotten for wondering if the author had simply downloaded his Reference Manager!!! I can only suppose the reason magnetic resonance imaging is still taking up 22 pages, with 117 references, must be that it is one of the editor’s hobby horses.

To put things in perspective, a chapter of about 50 pages on cerebral angiography devotes 40% of its weight to technique, etc (of which two, on arch aortography, include the provocative statement that “the aortic arch angiogram should be evaluated before a vertebro arterial series are cannulated”); 10 lines to indications, including the questionable statement (in the age of MRA) that intra-arterial injection should be used to detect arterial dissection. I failed to find a description of spinal angiography or its indications. Spinal arteriovenous malformations or fistulae do not appear in the index. It would be tedious to go through the rest of the two volumes in the same way, but certain things stand out. Children’s brain tumours, admittedly photogenic but usually not a source of significant problems, occupy 80 pages (plus 651 references), while that most difficult and complex field, paediatric metabolic and endocrine disease, in which a source of definitive information, helpfully presented, should be really valuable for the jobbing neurologist, paediatrician, or neuroradiologist, is given rather superficial treatment in 23 pages, with 97 references. In several chapters, too many cita—major international figures, contributed to the 52 chapters, more than a dozen of which are the result of collaboration between at least three people. As this might lead one to expect, the literary and intellectual level, including the critical evaluation of the literature central to review-type chapters, is very variable. However, the illustrations are almost uniformly excellent and the 75 page index, included in both volumes, if also somewhat idiosyncratic, is generous. Much useful information is to be found between these hard covers, although for me the book fails to live up to the promise of the rather facetious foreword. Does it deserve a place on that already perilously overburdened departmental bookshelf? Neuroimagers will, I imagine, identify rival texts as more suited to their specially focused needs; trained neuroradiologists will indeed find much valuable reference material, but also some worrisome deficiencies and debatable notions.

IVAN MOSELEY


This is a multiauthor reference book with contributions from epidemiologists, neuroradiologists, neurologists, and cardiologists. It succeeds in being both comprehensive and concise, making it a valuable book to have available to “dip into”. However, it is quite a long haul to read from start to finish.
There are chapters of practical use to physicians in both community and hospital based, who are involved in vascular risk factor management and specifically the primary and secondary prevention of stroke. For example, the chapter on "when to anticoagulate and at what dose" is particularly useful. Topics such as lipid lowering, antiplatelet strategies, and the management of carotid disease are covered well with pragmatic advice based on the available evidence. Where there are gaps in the evidence is also clearly stated.

There is a helpful section on haematological disorders and stroke risk with detailed information on the congenital and acquired thrombophilias and advice on routine screening for these problems. A chapter devoted to the aetiology of "young stroke" is particularly fascinating for these problems. A chapter devoted to the aetiology of "young stroke" is particularly welcome. At the cellular level there is a fascinating review chapter of the molecular mechanisms affecting the development of symptomatic carotid plaques—obviously fertile ground for further research.

Contained within each chapter are helpful tables usually summarising results from available randomised controlled trials and there are some clear schematic diagrams to illustrate relevant pathophysiological and biochemical pathways. In summary this book would be an excellent addition to any hospital or community service involved in this very important subject. It will be of value to general practitioners, physicians, cardiologists, neurologists, and trainees.

LIZ WARBURTON


This is an incredibly enjoyable book, which provides a fascinating insight into the history of neuroscience. It was devised by the late A Earl Barker and has been put together as a tribute to his industrious efforts to trace the history of neuroscience from ancient to modern times, and it serves as a fine tribute to him. The book builds through 11 chapters from prehistoric times through Galen and Vesalius to the founders of modern day neurology from the later part of the 19th century. The book contains endless fascinating insights into multiple aspects of neuroscience and although the illustrations are a little disappointing in parts there are some rare pictures, such as one of James Parkinson himself.

The book opens with a series of chapters which lay out the historical perspective of neuroscience, following which chapters detailing specific conditions are presented. Thus in the chapter on peripheral nerves we discover that Rollo in 1797 first described diabetic neuropathy, whereas Bonnini in 1642 first described heri-heritable. Those chapters on regional neurology then pass on to the final chapters of the book that deal with the evolution of neurosurgery, which details in particular the first descriptions of various brain tumours. The book concludes with a chapter on the modern age of neuroscience and a magnificent list of references. If this were not enough, we are then treated to three appendices on art and neurology, medical fees, and a glossary of neurological syndromes. All most illuminating, although the account on art and neurology is not as exhaustive as it could be, given the fascinating speculation that are rife in this area. For example, what was the problem with Monet giving rise to his visual failure in later life and what, if anything, is the neurological abnormality shown in Dürer’s drawing of praying hands. This book is, though, a treasure trove of fascinating facts—for example, it was news to me that Galen was the first to describe the corpus callosum while the quadrigeminal bodies had to wait until Willis before they were acknowledged. This attention to detail and the ingenuity of these earlier investigators is inspiring, although many of these early investigators may have run into problems with local ethics committees or the Home Office inspector—for example, Galen cut the spinal cord at 4 a.m., an observed the mortality state of the animal. Indeed the industry of some of these early investigators is to be greatly admired. For example, Raymond de Vieussens de Montpellier dissected 500 fixed brains in his bid to clarify some of the finer points of neuroanatomy.

A book such as this is always going to struggle to define its audience, not least because chapters are irrelevant to the high tech age of molecular genetics and functional imaging. If we can see the acetylcholine receptor at the resolution of a few Angstroms, why bother with the gross techniques of years gone by. However, there is much to admire and learn about through a knowledge of the pioneering days of neuroscience, and the elucidation of anatomical structures along with clinical conditions. It teaches much about diligence and thoughtful investigation as well as ingenuity in the face of seemingly intractable problems and scientific dogma. It is a book that is, therefore, not solely relegated to that of source material for quiz questions but reminds us of how our specialty took shape. It documents the influences that have made neurology and neurosurgery what it is today and the inspiration that has fallen on individuals over the ages and through whom we have made giant leaps in our understanding of how the brain works in health and disease. As you might have guessed by now, I loved this book and strongly recommend it to others.

ROGER BARKER


This book undertakes an extensive review of the fast moving field of cell death, an area of neurobiology that is currently the centre of intensive investigation both at the level of mechanisms and disease pathogenesis. The book divides into four sections that move from cellular and molecular mechanisms to animal models and human disease with possible therapeutic interventions bringing up the rear. It is thus a book that will interest both neuroscientists and neurologists alike, albeit a rather select group in each case.

The chapters are generally well written although a little sparse on illustrations, which can make some of the chapters quite daunting and intimidating. For example, the chapter on Parkinson’s disease has only one figure in 12 pages of text, which tends to put all but the most dedicated reader off. In this chapter there is also evidence of some delay from the time of writing to publication as there is no real mention of the recent genetic advances in familial Parkinson’s disease which should be in there given that the book was published in 1999. This is a pity given that this is currently a burgeoning field and the possible contribution of these genetic defects (for example, α-synuclein and parkin) in understanding the pathogenesis of idiopathic Parkinson’s disease is a major research interest at the present time. However other chapters are more up to date; for example, the chapter on Huntington’s disease discusses intranuclear inclusions even though their significance is still currently not known—do they represent a precursor to cell death or a marker of cellular neuroprotection?

Overall though the book is well presented both in terms of the topics selected and their discussion with a generally high quality of figures, including a series of rather beautiful colour plates in the middle of the book. It is therefore a book that will be a useful addition to the libraries of neurologists with an interest in neurodegenerative disorders, although other neurological conditions associated with neuronal death are touched on (for example, viral encephalitis, HIV-1 infection, trauma, and schizophrenia) which may widen its appeal. However this book will probably only ultimately interest those seeking greater neuroscientific understanding of neuronal cell loss and as such will bypass most neurologists.

ROGER BARKER