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.\(^1\)\(^2\) 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.\(^1\)\(^3\)\(^4\) Vertical, as distinct from horizontal, one and a half syndrome, has also been documented recently.\(^5\)\(^6\) 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 hypersomnia. 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.
occurring in the lower pons involves the paramedian pontine reticular formation and the medial longitudinal fasciculus. 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 left upper 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 descending 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. Vertical one and a half syndrome consists of a bilateral conjugate upgaze palsy and a unilateral downgaze palsy, or a bilateral conjugate downgaze palsy and a monocular upgaze palsy. 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. A patient was also reported with bilateral downgaze palsy and bilateral lesions of the rostral interstitial nucleus of the medial longitudinal fasciculus. Furthermore, it was reported that a unilateral lesion of the interstitial nucleus of Cajal resulted in tilting of the head towards the opposite side. 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 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 syndrome is 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.

This work was supported by the Research Grant for Longevity Sciences (11C-05) from the Ministry of Health and Welfare.


Malignant catatonia secondary to sporadic encephalitis lethargica

Catatonia is a neuropsychiatric syndrome characterised by a combination of psychosomatic withdrawal and various movement disorders. Kahlah first described this syndrome in 1868 when he noted this condition of “profound mental apathy”. Kraepelin limited catatonia to a subtype of dementia pракоец, later refined by Bleuler in 1906 as catatonic schizophrenia. Since then, it has become increasingly apparent that the catatonic syndrome is a form of encephalitis lethargica, or Von Economo encephalitis, or a subtype of dementia pракоец, later refined by Bleuler in 1906 as catatonic schizophrenia. Since then, it has become increasingly apparent that the catatonic syndrome is a form of encephalitis lethargica, or Von Economo encephalitis lethargica, or Von Economo's disease, described in 1922. It was thought to be due to two concurrent lesions of distinct nerve tracts in the left upper 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 descending on the opposite side. 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 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 eye movement still remains obscure in many respects, vertical one and a half syndrome is 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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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 various conditions, both neurological and psychiatric. Without a history of previous psychiatric impairment, aggressive investigation should be pursued for treatable medical conditions. Catatonia due to medical conditions may be treatably 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 may 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, although it is thought that the mechanism 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 39°C. He was semicomatose and was unable to follow 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 few days, the patient's serum sodium level corrected to a concentration of 2.6 mg/dl, added empirically with no evidence of hypernatremia.

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 contents. 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 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 rapid 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 oculomotor pathways, and an imbalance in the oto-occipital reflex. Experimentally, lesions of the posterior midline cerebellum can produce downbeat nystagmus. Takemori and Suzuki, for example, produced downbeat nystagmus in rhesus monkeys with bilateral foliare lesions. Experimentally, lesions of the flocculus 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 in systemic and thermal injury 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 hypomagnesaemia. 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 dystarthis.

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 normally normal neuroimaging studies.

Cerebellar Purkinje cells are known to be particularly susceptible to thermal stress, particularly hypoxic-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 function in the repair 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 hypomagnesaemia 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 hypomagnesaemia may promote or exacerbate 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 this rare syndrome is 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 hypoxic-ischaemic insult.

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Apolipoprotein E e2 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, however, have not been studied, although several groups have examined the potential association of FTD with apolipoprotein E (APOE) e4, with inconclusive results.

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 (mean 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 minimise the chance inclusion of future cases of FTD; APOE allele frequencies did not vary with age controls. Controls and patients were Caucasians from the Oxford region. Genotyping results are shown in the table.

Allele frequencies of APOE in cases of FTD versus controls, respectively, were: 0.32 versus 0.06 for APOE e2, 0.64 versus 0.78 for APOE e3, and 0.05 versus 0.16 for APOE e4. The one Pick-type case was an e2/e3 heterozygote. We did not have enough cases of FTD to distinguish between allele frequencies of predominantly frontal and mainly temporal cases. Control frequencies were similar to those widely reported for Caucasians. All control and FTD genotypes were in Hardy-Weinberg equilibrium.

In sporadic FTD, this will provide a new insight into mechanisms of risk and protection related to APOE in both diseases.

Table 1 Apolipoprotein E genotypes in sporadic frontotemporal dementia (FTD) and in elderly controls in OPTIMA

<table>
<thead>
<tr>
<th>APOE Genotypes</th>
<th>FTD (11)</th>
<th>Controls (136)</th>
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<tbody>
<tr>
<td>e2 e2</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>e2 e4</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>e4 e4</td>
<td>5</td>
<td>3</td>
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We especially thank all patients and volunteers, members of OPTIMA, the Department of Neuropathology, Radcliffe Infirmary, Dr N John, Dr S Fernandez, C Johnston, D Warden and S Litchfield. This work was supported by Bristol-Myers Squibb.

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Clinical characteristics of published cases of cerebellar syndrome from heat stroke

<table>
<thead>
<tr>
<th>Patient</th>
<th>Year</th>
<th>Age (°C)</th>
<th>Temperature</th>
<th>Cause of fever</th>
<th>Clinical syndrome</th>
<th>Initial imaging</th>
<th>Recovery</th>
<th>Follow up imaging</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>1970</td>
<td>47M</td>
<td>42.2</td>
<td>Confinement in heated cell</td>
<td>Hypotonia, intention tremor, ataxia, dysarthria</td>
<td>CT NL</td>
<td>None</td>
<td>CBLR atrophy</td>
</tr>
<tr>
<td>2</td>
<td>1987</td>
<td>50F</td>
<td>43.2</td>
<td>Exertion in heat</td>
<td>NMS, erysipelas</td>
<td>CT NL</td>
<td>None</td>
<td>CBLR atrophy</td>
</tr>
<tr>
<td>3</td>
<td>1983</td>
<td>50F</td>
<td>42.5</td>
<td>NMS</td>
<td>NMS</td>
<td>CT NL</td>
<td>None</td>
<td>CBLR atrophy</td>
</tr>
<tr>
<td>4</td>
<td>1995</td>
<td>39M</td>
<td>41.6</td>
<td>NMS</td>
<td>NMS</td>
<td>CT NL</td>
<td>None</td>
<td>CBLR atrophy</td>
</tr>
<tr>
<td>5</td>
<td>1995</td>
<td>44F</td>
<td>42.1</td>
<td>Exertion in heat</td>
<td>NMS</td>
<td>CT NL</td>
<td>None</td>
<td>CBLR atrophy</td>
</tr>
<tr>
<td>6</td>
<td>1996</td>
<td>39F</td>
<td>41.1</td>
<td>Heat stroke</td>
<td>NMS</td>
<td>CT NL</td>
<td>None</td>
<td>CBLR atrophy</td>
</tr>
<tr>
<td>7</td>
<td>1996</td>
<td>55M</td>
<td>40.9</td>
<td>Pneumonia</td>
<td>NMS</td>
<td>CT NL</td>
<td>Complete 2 weeks</td>
<td>CT at months normal</td>
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<tr>
<td>8</td>
<td>1996</td>
<td>48F</td>
<td>40.7</td>
<td>Pneumonia</td>
<td>NMS</td>
<td>CT NL</td>
<td>None</td>
<td>CBLR atrophy</td>
</tr>
<tr>
<td>9</td>
<td>1996</td>
<td>47M</td>
<td>40.7</td>
<td>Pneumonia</td>
<td>NMS</td>
<td>CT NL</td>
<td>None</td>
<td>CBLR atrophy</td>
</tr>
<tr>
<td>10</td>
<td>1996</td>
<td>60M</td>
<td>40.8</td>
<td>Erysipelas</td>
<td>NMS</td>
<td>CT NL</td>
<td>None</td>
<td>CBLR atrophy</td>
</tr>
<tr>
<td>11</td>
<td>1997</td>
<td>45M</td>
<td>42.0</td>
<td>Exertion in heat</td>
<td>NMS</td>
<td>CT NL</td>
<td>None</td>
<td>CBLR atrophy</td>
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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 characterized by increased skeletal 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, cranial 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 neurosurgical 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 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 (E 24) pseudoisochromatic plates. Pupils were equal and reactive to light, and there was a left relative afferent papillary 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 calvarial thickening, increased intracranial volume, and the cochlear and vestibular apparatus. The LPS catheter was in situ. There was no evidence of increased ICP.

Because our patient's unilateral optic canal decompression resulted in normalisation of visual field and visual acuity, 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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The London handicap scale

Jenkinson et al. show that London handicap scale scores are about the same if items are weighted equally rather than using the published scale weights. We reached much the same conclusion using the data from which the scale weights were derived. Handicap is defined as disadvantage in role performance due to impairments or disabilities, which implies valuation of the extent to which role performance is affected. Value— from the viewpoint of health services research—is quantified as the “utility” of a health state for only limited interest and the component parts of the description.

The fact that equal weighting gives roughly the same scores as the empirically derived weights is probably because the items were carefully chosen on the basis of clinical experience to be appropriately spaced across the range of possible severity. Does it matter if different weighting methods lead to much the same results? Weighting processes are inexact, be they empirically derived or equal weighting, but the second approach simply increases the level of approximation. The 95% confidence intervals around the agreement between estimated and measured scores were about ± 10 (on a 0–100 scale). This measurement imprecision arises because rating health states is difficult, leading to random measurement error, and the modelling assumed that overall valuation of a state of health could be estimated by the sum of the component parts of the description, which is almost certainly an oversimplification (although goodness of fit statistics for the model were reasonable). The London handicap scale is primarily an epidemiological tool—that is, it is intended for use in groups (such as in a clinical trial). If scores are calculated for individual patients—for example, in clinical practice—there is a further approximation, that between the values and opinions of that individual, and “average” views of the population from which the values were derived. There is some evidence that the handicap dimensions have general validity, and there is some consensus on the values assigned to states of handicap. As part of the revision process of the International Classification of Impairments, Disabilities and Handicaps1 qualitative studies established strong core transcultural agreement on six domains of participation with potential to be affected by health conditions, and these corresponded to the handicap dimensions (Martin Prince, personal communication). Furthermore, a comparison of values given to states of health by Hong Kong Chinese showed agreement with those estimated by using the London handicap scale weights (derived from Londoners).2 Neither was there convincing between population variation in scale weights assigned in the original scale development work.3 It is not safe, however, to assume that there are no between person differences.

We are pleased to see a further independent validation of the London handicap scale. If simplification of the data gathering process 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 syntax). As we have empirically derived weights have been assigned with those estimated by using the London handicap scale weights (derived from Londoners).1 Neither was there convincing between population variation in scale weights assigned in the original scale development work.3 It is not safe, however, to assume that there are no between person differences.

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 agree with the authors that the volume of intracranial lesions, and its change over time, is important in the diagnosis and management 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.

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 agree with the authors that the volume of intracranial lesions, and its change over time, is important in the diagnosis and management 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 reading of mass lesions is the choice when 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 lesions 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 use the Cavalieri’s principle have to fulfil one absolute requirement: randomness.3,4 The volume of any object may be estimated from randomised and parallel sections separated by a known distance by summing up the areas of all cross sections of the object and multiplying this sum by the known intersection distance. The total area of all cross sections may be estimated by a stereological point counting method.4 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
total area. In the study of Stocchetti et al random-ness has most probably not been accounted for, as it has not been mentioned in the text and as the grid has not randomly been placed onto the CT slices.1

(3) When applying Cavalieri’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.3 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 haematoma-mas. Spiral CT with a 3 mm section distance may overcome this problem. Another advan-tage of Cavalieri’s principle is its applicability to any mass lesion irrespective of size and formation.

(4) The average difference between the applied technique and the reference computer based value is 0.57 (SD 9.99) ml for the Cavalieri 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 derived from standard deviation limits 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 in the trauma coma data bank (TCDB) classification a volume of greater than 25 ml is defined as a mass lesion.4

(5) Although three examiners read the scans, intraobserver 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 cisterns, the degree of midline shift, and the presence of a mass lesion provides a ranking order of the severity of the intracranial injury (I=normal, II=diffuse injury, III=diffuse injury with swelling, IV=diffuse injury with shift, V=operated mass lesion, and VI=non-operated mass lesion). Intracranial mass lesion volume, although important, is but one of the measured indices in the TCDB classification. We showed recently that the TCDB CT classification system for patients with severe head injury has in fact a high interob-server and intraobserver reliability when used by clinicians without special training in neuroradiology.*

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Stocchetti and Colombo reply: We are grateful to Vos et al for their comments. Both 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 the resulting 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 prerequisite; 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 was debated, but it seems to ensure an adequate guarantee against systematic error.

(2) Our data did not obscure the beauties of the Cavalieri method. The direct estimator performed better than the Ellipsoid method, particularly for irregularly shaped lesions. We agree that the method performs even better with bigger lesions reconstructed using thin slices. As one of our goals was to describe feasibility, however, the comments of Vos et al further stress that the best can be obtained from the Cavalieri method at the price of more time and work, as we verified and further stress that the best can be obtained from the Cavalieri method at the price of more time and work, as we verified and reported in the paper. Counting more than 50 points in more than 10 slices adds to the precision, but seriously increases the burden of measurements.

(3) We did not base our comparison only on mean data. We showed the concerns of Vos et al on the analysis of mean data to the extent that we have used another method, based on that of Bland and Altman. This method com-pares every single lesion, obtained with each method, against the corresponding reference value. The results of this detailed comparison are illustrated in figs 1 and 2 of our paper.

Numerical data, summarising the analysis according to Bland and Altman, are reported in the text and table. Both in the results section and in the discussion we stated that the mean data were not able to describe the discrepancies found in single cases.

(4) Accordingly, we assessed interobserver variability by ANOVA of individual measurements, and not of the mean data. In other words, we asked whether the measurement of any specific lesion by one examiner was significantly different from the other examiners’ results. The ANOVA on the readings by the three examiners using the Ellipsoid method gave a p value of 0.86, and the same analysis applied to the Cavalieri direct estimator gave a p value of 0.81; we therefore concluded that this analysis excluded significant differences. It seems the intraob-server variability was not omitted, but was in fact logically considered, and we must apologise if the text was not clear.

(5) We agree with the final paragraph of Vos et al on the structure of the Marshall classification, in which volume is one part of the grading. That was correctly indicated in our paper. From our experience in multicentre, 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 fulfill 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 neurosurgeon. 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 fashion 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 congratulated on fulfilling their objective with such a well presented and beautifully illustrated new edition. Although clearly intended for a neurosurgical readership, there are sections that may be useful for practitioners in other disciplines, particularly 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, relevant figures, and a list for further reading. The manuscript is well proportioned, confusing experts to present their knowledge in a concise manner in often quite short chapters. This means that the busy reader can quickly assimilate the aspects of importance.

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. Enough appreciation 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 also 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 for an examination but also to those who might find themselves on the other side of the table.

RUPERT KEET-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 investigations is described (including PET). Idiopathic Parkinson’s disease is described as a diagnosis of exclusion, which will certainly alarm the neuroradiologists in my health district.

Patients are given invaluable forewarning 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 ward rounds 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 all the 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 disorders. 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 every one 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 no way of using imaging to look at the nervous system: neuroradiology, a clinical specialty practiced by organ specialised radiologists familiar with a wide range of techniques, closely related to the clinical neurosciences to which this journal is devoted—neurology, neurosurgery and psychiatry—and neuroimaging, 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 upsets 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, the 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, chaps, 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 forgiven for wondering if the author had simply downloaded his Reference Manager!!! I can only suppose the reason magnetic resonance is 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 46 of its 48 pages to technique, etc (of which two, on arch aortography, include the provocative statement that “the aortic arch angiogram should be evaluated before the vertebral arteries are cannulated”), 10 lines to indications, including the questionable statement (in the age of MRI) 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, would have been invaluable for the jobbing neurologist, paediatrician, or neuroradiologist, is given rather superficial treatment in 23 pages, with 97 references. In several chapters, too many citations are required to create an appreciable reference list rather than of authoritative source material.

The chapter on degenerative disease of the spine, written by musculoskeletal specialists who seem to deal principally with orthopaedic surgeons or rheumatologists, is out of place in a book on neuroimaging (however defined). It deals largely with plain films, and does not address the issues germane to neurological practice; furthermore, like a number of the contributions, it is a discussion of postoperative appearances and surgical instrumentation, essential knowledge for today’s clinicians. Chapter 50, on hydrocephalus and cerebrospinal fluid shunts, should carry a hazard warning that it presents views so personal as to be not only idiosyncratic but potentially misleading. Conversely, the chapter on the orbit and visual system, sensibly concentrating on the use of CT for the former, is admirable, apart from the caption to figure 77: the lesion described as a dermoid is almost certainly a dermolemma.

Some 73 North American authors, few—as yet—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 superficial, 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 overcrowded departmental bookshelf? Neuroimagers will, I imagine, identify rival texts as more suited to their specialty focused needs; trained neuroradiologists will indeed find much valuable reference material, but also some worrisome deficiencies and debatable notions.

IVAN MOSELEY


This is a multiauthour 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.

www.jnnp.com
There are chapters of practical use to physicians, 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, covering the aetiology of "young stroke" is particularly illuminating, although the account on art and neurology is not as exhaustive as it could be, given the fascinating speculations 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. and observed the monstrosity 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 historians 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 speciality 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.
Coexisting vertical and horizontal one and a half syndromes

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