The association between venous outflow obstruction and the development of pseudotumour syndrome is well known, although the mechanism by which the rise in CSF pressure is brought about is less certain. Although there is much evidence that alterations in CSF formation, and to a lesser extent absorption, are responsible for the development of the syndrome.

At 2 years of age, as part of investigating a febrile history of abnormal growth, a female child underwent cerebral CT. This showed an unexpected arteriovenous malformation involving the vein of Galen. Although there was no evidence of cardiac failure or hydrocephalus associated with this, assessment by angiography was advised. This, initially declined by the parents, was not undertaken until the age of 5 years when vertigo and intermittent numbness of the left arm and leg had been present for about 12 months.

Angiography showed a deep right temporal lobe arteriovenous malformation consisting of three separate fistulae supplied by the right posterior cerebral and posterior communicating arteries drained into a large venous varix which subsequently drained into the Galenic venous system. A cerebral blood flow study showed a steal syndrome affecting the right frontoparietal area, and a decision was made to attempt embolisation. Complete occlusion of the fistulae was achieved by transarterial platinum coil embolisation.

The patient complained of right sided headache for 24 hours after the procedure, resolving with minor analgesia. Brain CT the next day was reported as normal. A full ophthalmological examination was performed on CSF samples in tuberculous meningitis established by culture.

The polymerase chain reaction (PCR) has been reported to be of diagnostic value when performed on CSF samples in tuberculous meningitis.1-4 Rapid amplification of Mycobacterium tuberculosis specific DNA enables results to be available within 48 hours and can influence treatment decisions.

Recently two patients presented to our hospital with symptoms and signs suggestive of tuberculous meningitis. Examination of CSF disclosed a lymphocytic exudate. Repeated samples were sent to a British referral laboratory where CSF PCR for M tuberculosis was reported negative. Despite this, antituberculous treatment was continued for 12 months and both patients responded clinically. Several weeks after the negative PCR result, M tuberculosis was cultured on Lowenstein-Jensen slopes from CSF taken from both patients. False negative CSF PCR in tuberculous meningitis established by culture has rarely been reported. The two patients are described to emphasise the dangers of overreliance on PCR in cases of suspected tuberculous meningitis. Premature cessation of treatment would have had tragic consequences for the two patients concerned.

The first patient was a 28 year old Asian man, last in India 8 years previously. He was sent from a clinic to hospital for incision and drainage of two deep seated Staphylococcus
examination she had mild neck stiffness. She had peritoneal tuberculosis diagnosed at the age of 6 years during laparotomy for an appendiceal abscess and had received antituberculosis medication for 1 month only. On examination she had mild neck stiffness and a partial left third cranial nerve palsy. Brain CT was normal. Lumbar puncture results showed a high opening pressure (15 cm CSF), 90 white blood cells/µl, predominantly lymphocytes, a raised protein concentration (1.62 g/l), and a low CSF/blood glucose ratio (1.7/6.1). A sample of 0.5 ml CSF was sent to a British referral laboratory and PCR for M tuberculosis was negative. Twenty four hours later, because of increasing confusion and agitation, treatment with intravenous acyclovir, antituberculous chemotherapy (600 mg rifampicin, 300 mg isoniazid, 2 g pyrazinamide, and 10 mg pyridoxine daily), and dexamethasone was commenced. Clinically he showed signs of improvement and was discharged home 2 weeks later on the above treatment. A repeat lumbar puncture 4 weeks later showed similar results. A PCR CSF for M tuberculosis was again negative although a fully sensitive M tuberculosis grew 12 weeks later from the first sample on Lowenstein-Jensen slopes.

The second patient was a 21 year old Kenyan woman living in the United Kingdom for 3 years. She had been infected with 3 month history of photophobia and occipital headaches. She had no other systemic symptoms. She had peritoneal tuberculosis diagnosed at the age of 6 years during laparotomy for an appendiceal abscess and had received antituberculosis medication for 1 month only. On examination she had mild neck stiffness and a partial left third cranial nerve palsy. Brain CT was normal. Lumbar puncture results showed a high opening pressure (15 cm CSF), 90 white blood cells/µl, predominantly lymphocytes, a raised protein concentration (1.62 g/l), and a low CSF/blood glucose ratio (1.7/6.1). At the same referral laboratory CSF PCR for M tuberculosis was negative but culture after 8 weeks was again negative although a fully sensitive M tuberculosis grew 12 weeks later from the first sample on Lowenstein-Jensen slopes.

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J T BROWN
Department of Microbiology, St Thomas' Hospital, Lambeth Palace Road, London SE1 7EH, UK

S LACEY
L R BAGG
King George Hospital, Barley Lane, Goodmayes, Essex IG1 6YB, UK

Correspondence to: Dr M Melzer, Department of Microbiology, St Thomas' Hospital, Lambeth Palace Road, London SE1 7EH, UK.


False negative polymerase chain reaction on cerebrospinal fluid samples in tuberculous meningitis

There have been few studies in the literature concerned solely with the use of the polymerase chain reaction (PCR) to identify Mycobacterium tuberculosis DNA directly from the CSF. These studies suggest that in some cases, PCR may be more sensitive than culture; however, in the largest study, performed by Nguyen et al, specimens from seven patients, who were culture positive for M tuberculosis were not positive by PCR. The study did report on 22 culture negative, PCR positive patients, suggesting that PCR can be more sensitive than culture. Studies comparing PCR with culture of M tuberculosis using other clinical specimens, particularly respira-

ory diseases are used. Claims that PCR can detect 1–10 M tuberculosis organisms “in vitro” seems not to be the case in clinical samples such as CSF.

In the two patients presented above adequate volumes and repeated samples of CSF were assayed using suitable primers and with appropriate controls at a British referral laboratory. Results for these two patients show the dangers of over reliance on PCR CSF when tuberculous meningitis is clinically suspected.

A novel mutation of the myelin P gene segregating Charcot-Marie-Tooth disease type 1B manifesting as trigeminal nerve thickening

Charcot-Marie-Tooth disease (CMT) is the most common type of hereditary peripheral neuropathy. It is classified into two types based on pathological and electrophysiological findings: type 1 and type 2. CMT type 1 has been mapped to chromosome 17 (CMT1A), chromosome 1 (CMT1B), another unknown chromosome, (CMT1C) and the X chromosome (CMTX). CMT1B is a rare form of CMT1 associated with mutations of the myelin protein zero (P) gene. Mutations in the P gene have recently been identified and are the most common cause of CMT1B. A recent study has identified a mutation in the P gene that is associated with a rare form of CMT1B, Charcot-Marie-Tooth disease type 1B manifesting as trigeminal nerve thickening.
been recognised in Dejerine-Sottas disease, peripheral neuropathy with an early onset in childhood, and a more severe phenotype than CMT1. CMT1 and Dejerine-Sottas disease are characterised by thickening of peripheral nerves, and thickening of the cauda equina, nerve roots, and ganglia have often been found. Although cranial nerves are generally spared in CMT, thickening of the acoustic or optic nerve has been reported in some cases. We report here on a Japanese woman who exhibited severe polyneuropathy, bilateral trigeminal thickening on MRI, and an abnormality of the auditory brain stem response. Gene analysis disclosed a novel mutation (His81Arg) of P0. The cranial nerve involvement in this patient may be associated with the novel missense mutation of P0 (His81Arg).

A 15 year old Japanese girl presented with CMT disease. She showed delayed motor development. Although she became ambulant at 1 year and 8 months of age, she was never able to run. She was referred to our hospital due to progression of her gait abnormality. Her mentality and higher brain function were normal. Neurological examination disclosed weakness in both proximal and distal muscles of the legs, decreased grasping power, sensory disturbance of distal limbs, and sensory deafferentation. Facial sensation, mastication power, and hearing acuity were normal. She also had atrophy of the lower limbs, drop foot, a steppage gait, claw hands and clawed toes. Her facial sensation, mastication power, and hearing acuity were normal, the thickness of bilateral trigeminal nerves on MRI and prolongation of the I-III interpeak intervals in auditory brain stem response were found. The I-III interpeak interval represents the conduction time from the eighth nerve to the pontocerebellar portions of the auditory pathway. Prolongation of the auditory brain stem response suggested peripheral conduction delay of the auditory nerve.

Trigeminal neuralgia with CMT has been reported. In these rare cases, trigeminal neuralgia was inherited, suggesting a partial symptom of CMT. Although some patients were surgically treated, it was not clear whether a thickened trigeminal nerve was present. Moreover, on electrophysiological studies of facial and trigeminal nerves in CMT, Kimura reported that the sensory component of the trigeminal nerve was relatively spared, despite extremely delayed conduction of the motor component. However, the MRI study of our patient suggested that the fifth cranial nerves were subjected to the same pathological process that affects other peripheral nerves.

Our patient showed no DNA duplication on chromosome 17p11.2 and we found a novel mutation (A to C) representing an Arg to His substitution in the P0 gene. Histidine 81 is conserved among many other species, including cows, rats, chickens, and sharks. This mutant allele was absent in the DNA from 100 controls. Therefore we identified this mutation as pathogenic. Arg81His was located in exon 3, which codes for the extracellular domain of P0. The extracellular domain plays a part in myelin compaction by homophilic interaction and many mutations in this area have been reported. Although the phenotypic variability is related to the position and nature of the P0 mutation, patients with cranial nerve involvement are rare in CMT with a P0 mutation. Therefore, the unique thickening of trigeminal nerves and the clinical severity in this patient may be related to this novel missense mutation.

The six exons of the P0 gene were amplified by the polymerase chain reaction using primers, and analysed by single strand conforma-
tional polymorphism (SSCP) and sequencing analyses. DNA sequencing of exon 3 showed a novel point mutation (A to C at codon 81) resulting in a substitution of arginine for histidine only in the patient. A DNA duplication in chromosome 17p11.2-p12, including the peripheral myelin protein-22 (PMP-22) gene, was not present. The patient’s mother did not show any mutations in the P0 gene.

CMT1 type 1 is caused by abnormalities in myelin protein of Schwann cells. Repeated demyelinating and remyelinating responses in the peripheral nerve produce differentially enlarged diameters of nerves in CMT type 1, and thickening of the cauda equina, nerve roots, and ganglia has also been found. Although blepharophytosis, ophthalmoplegia, facial weakness, deafness, dysphagia, and dysphonia in CMT have been previously reported, clinical involvement in the cranial nerves is rare and thickening of cranial nerves has not been reported except for the acoustic or optic nerves in some cases.

In the present study, we observed severe clinical manifestations of early onset and undetectable conduction velocities. Therefore, this patient was considered to have a severe variant of CMT1 or Dejerine-Sottas disease. Although her facial sensation, mastication power, and hearing acuity were normal, the thickness of bilateral trigeminal nerves on MRI and prolongation of the I-III interpeak intervals in auditory brain stem response were found. The I-III interpeak interval represents the conduction time from the eighth nerve to the pontocerebellar portions of the auditory pathway. Prolongation of the auditory brain stem response suggested peripheral conduction delay of the auditory nerve.

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MASAMI SHIZUKA
YOSHIKO IKEDA
MITSUNORI WATANABE
KOICHI KAMOTO
MIKIO SHOJI
Department of Neurology, Gunma University School of Medicine, 5–39–22 Showa-machi, Maebashi, Gunma 371–8511, Japan

TORU UEGAMI
KIYOSHI HAYASAKA
Department of Pediatrics, Yamagata University School of Medicine, Yonezawa, Yamagata, Japan

Correspondence to: Dr Masami Shizuka, Department of Neurology, Gunma University School of Medicine, 3–39–22 Showa-machi, Maebashi, Gunma 371–8511, Japan. Telephone 0081 27 220 8061; fax 0081 27 220 8068; email mshizuka@news.sb.gunma-u.ac.jp


Intracranial extracerebral follicular lymphoma mimicking a sphenoid wing meningioma

Primary lymphoma in the brain is uncommon, accounting for only 2% of primary intracranial neoplasms. Although its incidence seems to be dramatically increasing, leptomeningeal lymphomas are even rarer but have been described. However, no leptomeningeal lymphoma of the follicular type has previously been reported. We present a case of a primary meningeal follicular lymphoma which mimicked a sphenoid wing meningioma, both radiologically and intraoperatively.

A 57 year old Ghanaian woman was referred with a 3 year history of worsening bitemporal headache, followed by a 6 month history of daily right frontal headache lasting for 2–3 hours associated with mild photophobia. There were no reports of seizures, nausea, or other visual disturbances. Her medical history was 3 years of treated hypertension, sickle cell carrier trait, and a cataract extraction. The patient was obese but physical examination was otherwise normal. Neurological examination showed no papilloedema and there were no cranial nerve or long tract signs.

Brain CT showed an enhancing mass consistent with a right sided sphenoid wing

Axial T1 weighted (TR 600/TE 15) brain MRI at 1.5 Tesla of our patient with CMT. Note the thickness of the bilateral trigeminal nerves.
Non-Hodgkin’s lymphoma, although primary intracranial lymphoma is the most common diagnosis of a focal intracranial lesion in patients with AIDS. Malignant primary lymphoma can occur throughout the CNS and they often have a periventricular distribution. Multifocality seems to be more common in patients with AIDS. The CT scan usually shows hypodense masses with peritumoral oedema and 92% enhance after administration of contrast medium.

Leptomeningeal lymphoma is usually encountered as a late complication of systemic non-Hodgkin’s lymphoma, although primary leptomeningeal lymphoma is occasionally seen. The prognosis for these tumours is poor. Diffuse primary central lymphomas have been mistaken for more common lesions: solitary primary B cell lymphoma of the cerebellopontine angle mimicking acoustic neuroma or meningioma has been reported; Vigusin et al described a case with a calcified temporaloperiorbital lymphoplasmacytic lymphoma which resembled a meningioma; however, this tumour was entirely extradural. There is only one previous report of a follicular rather than diffuse primary central lymphoma: Rubinstein described a case of follicular lymphoma metastasis found in the dura of a 61 year old man at necropsy.

We found no report of a primary follicular extracerebral lymphoma. Similar radiological and intraoperative appearances of the tumour in our case to sphenoid wing meningioma suggest that this entity should be considered as a rare differential diagnosis.

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Dominic J Hodgson
Karoly M David
Michael Powell
Department of Surgical Neurology

Jan L Holton
Department of Neurology, The National Hospital for Neurology and Neurosurgery

Francesco Pezzella
Department of Pathology, University College Hospital, London, UK

Correspondence to: Mr Michael Powell, Department of Surgical Neurology, The National Hospital for Neurology and Neurosurgery, Queen Square, London, WC1N 3BG, United Kingdom. Telephone 0044 171 837 3611; fax 0044 171 209 3875.


Determinants of the copper concentration in cerebrospinal fluid

The measurement of CSF copper concentration can serve as an indicator of brain copper concentration. However, the complex mechanisms by which copper crosses into the CSF, and the factors determining the CSF copper concentration in humans are largely obscure. Copper can pass into and out of the CSF by various mechanisms. For example, active transport through the blood-brain barrier or the blood-CSF barrier, or passive diffusion of the free or the bound fraction (bound to albumin or coeuloplasmin) through the blood-CSF barrier. We studied the factors influencing CSF copper concentration using a stepwise multiple linear regression model. The independent variables were age, plasma coeuloplasmin, CSF/serum albumin ratio, total serum copper concentration, and calculated serum free copper concentration (based on serum coeuloplasmin and total serum copper concentration). The CSF copper concentration was treated as a dependent variable of the continuous type. We investigated lumbar CSF samples from 113 patients. These patients had dementia, extrapyramidal, or tremor symptoms; lumbar puncture was performed to exclude Wilson's disease, and none of the patients had the disease. Copper was measured by flame atomic absorption (Perkin Elmer, HGA 500, Uerberlingen, Germany). Coeuloplasmin was determined nephelometrically (Beckman Instruments, Brea, CA, USA). The age of the patients was 50.0 (SD15.5) years; 50 were women and 65 were men. Mean serum coeuloplasmin concentrations were 394.3 (SE 1.7) mg/l. Mean serum copper concentrations were 1194 (SD 335) μg/l. Mean calculated free copper concentrations in serum were 78.5 (SD 1285) μg/l. Mean CSF copper concentrations were 14.16 (SD 6.00) μg/l. The mean albumin ratio (AR) was 6.63×10⁻³. The mean ratio of calculated free copper concentration to total serum copper was 6.6%, the ratio of CSF copper to serum copper was 1.2%, and the ratio of free serum copper to CSF copper was 18%. In the
The formula for the CSF copper concentration (on logarithmic axes; simple linear regression between CSF/serum no statistically significant relation with CSF dependent variables mentioned above showed that patients report feeling better when the CSF copper concentration is below this value. This analysis also shows that the raised copper concentration in the CSF can only originate from the brain. In particular, it is not associated with free serum copper, but evidently only via storage in the brain. The investigation here also shows that, after determining the CSF copper concentration, the coeruleoplasmin-bound fraction originating from the plasma should be subtracted according to the formula we have given, or better, all measured copper concentrations in the CSF should be adjusted using the CSF/serum albumin ratio and serum coeruleoplasmin concentration. A statistical relation with a low correlation (p<0.05) between CSF protein content and CSF copper was already shown in various neurological diseases; our study shows a much higher significance and, in addition, the effect of serum coeruleoplasmin (therefore of bound serum copper). Furthermore, we have been able to determine quantitatively the fraction of CSF copper which enters the CSF across the blood-CSF-barrier.

HANS JOERGSTUERENBURG
MATTHIAS OECHSNER
SVEN SCHROEDER
KLASS KUNZIE
Neurological Department, University Hospital Hamburg-Eppendorf, Hamburg, Germany. Telephone 0049 40 4717 4832; fax 0049 40 4717 5086.

Correlation of blood-CSF barrier (albumin ratio, (AR)) with total CSF copper concentration (on logarithmic axes), R²=0.46, p=0.0001; 95% confidence bands for the true mean of the total CSF copper concentration are shown.

stepwise linear regression model (F to enter 4.0, F to remove: 3.996), significant positive predictive power of the CSF copper concentration were found to be AR (p=0.0001) and serum coeruleoplasmin (p=0.0057). The other independent variables mentioned above showed no statistically significant relation with CSF copper concentration. The figure shows the simple linear regression between CSF/serum albumin ratio and CSF copper concentration (on logarithmic axes; AR=0.46, p=0.0001). The formula for the CSF copper concentration, derived from the multiple linear regression model, is: copper concentration (mg/l) = 3.32 X 10⁻² X albumin ratio (mg/l) + 0.012 X coeruleoplasmin (mg/l).

According to this analysis, CSF/serum albumin ratio and serum coeruleoplasmin together determine 25.3% of the variation in CSF copper concentration (adjusted R²=0.253), implying that other (unknown) factors determine the remaining 74.7% of the variation. We have been able to demonstrate here that the CSF copper concentration is determined in a highly significant manner by disturbances in the blood-CSF barrier and by the serum coeruleoplasmin concentration. It can be assumed that in the case of normal blood-CSF barrier function and the serum coeruleoplasmin concentration, 25.3% of the measured CSF copper originated from the brain; the CSF by passive diffusion bound to coeruleoplasmin, and only around 0.9% by passive diffusion bound to albumin. In the case of a markedly raised CSF/serum albumin ratio of 20:1, this would mean that 60.6% of the measured CSF copper originated from the blood (bound to coeruleoplasmin). A variable fraction of the CSF copper concentration, depending on the degree of damage to the blood-CSF barrier, therefore crosses from the blood into the CSF and can be measured there. Our formula would therefore predict, in patients with Wilson’s disease with an intact blood-CSF barrier (assuming a CSF/serum albumin ratio of 6.5:1.0), that the CSF copper concentration is actually reduced by 27.4%, when the serum coeruleoplasmin concentration falls from its normal value of 394 µg/ml to 68 µg/ml. In consequence, CSF copper in patients with Wilson’s disease is evidently substantially free, implying that a larger fraction than previously assumed of the raised CSF copper in patients with untreated Wilson’s disease originates from the brain; the fraction entering the CSF by passive diffusion (bound to coeruleoplasmin) tends towards zero. It can be concluded from this that, when the aim of therapy is considered in terms of the total CSF copper concentration, a region around 30% lower than the upper limit of the normal range should be aimed for. This is supported by the clinical findings that patients report feeling better when the CSF copper concentration is below this value. This analysis also shows that the raised copper concentration in the CSF can only originate from the brain. In particular, it is not associated with free serum copper, but evidently only via storage in the brain. The investigation here also shows that, after determining the CSF copper concentration, the coeruleoplasmin-bound fraction originating from the plasma should be subtracted according to the formula we have given, or better, all measured copper concentrations in the CSF should be adjusted using the CSF/serum albumin ratio and serum coeruleoplasmin concentration. A statistical relation with a low correlation (p<0.05) between CSF protein content and CSF copper was already shown in various neurological diseases; our study shows a much higher significance and, in addition, the effect of serum coeruleoplasmin (therefore of bound serum copper). Furthermore, we have been able to determine quantitatively the fraction of CSF copper which enters the CSF across the blood-CSF-barrier.

Solitary intracranial myofibroma in a child

A rare case of solitary interhemispheric myofibroma with excellent outcome in a 20 month old boy is described. The clinico-pathological features of this unusual condition are reviewed with emphasis on the CNS manifestations. A case of congenital fibrosarcoma was first diagnosed by William and Schrum and was subsequently renamed congenital generalised fibromatosis by Stout in 1954 as a distinct form of juvenile fibromatosis characterised by tumour-like nodules involving the skin, soft tissues, bones, and viscera. Based on the ultrastructural and immunohistochemical features of the cell of origin and the occurrence of this condition in infants, as well as congenitally, it was renamed infantile myofibromatosis by Chung and Enzinger in 1981. This disorder is considered to represent a hamartomatous myofibroblastic prolif-
myoglobin. Ultrastructural examination showed elongated cells with surrounding collagen fibrils, some showing intracytoplasmic myofilaments.

Solitary lesions of infantile myofibromatosis are more common than multiple lesions, with twice as many males as females being afflicted, and generally involve the skin and soft tissues, especially of the head and neck. Solitary lesions are less commonly found in viscera or bones.1 Involvement of the CNS is exceedingly rare and only one other case of a solitary mass is reported2 along with few cases of CNS involvement in the generalised form of infantile myofibromatosis.3–5 The prognosis is best for cases with solitary masses and less favourable for multicentric cases, particularly where visceral lesions are present, in which morbidity and mortality derive predominantly from pulmonary involvement or mass effect.

The differential diagnosis for this lesion included meningeoma, schwannoma, and haemangiopericytoma. Regionally, the histology was reminiscent of the rare microcystic variant of meningeoma. Meningiomas are extremely rare in this age group, this lesion was not meningeal based and such lesions are usually reactive for epithelial membrane antigen unlike this tumour. This lesion, unlike schwannomas showed no immunoreactivity for S-100 protein. Haemangiopericytoma is a diagnosis of exclusion and shows no reactivity for actin, unlike this tumour.

Prior intracranial involvement by myofibromatosis includes patients with widespread systemic involvement and multiple leptomeningeal nodules in one patient and extradural masses in another, both of which were fatal at the age of 10 days, a non-fatal extradural mass in one patient, and a patient with systemic involvement, in which there was recurrence of orbital and temporal lesions 2 years after operation. A single previous case of solitary intracranial myofibroma has been reported6 in which the patient died within 24 hours of surgery, secondary to cardiorespiratory arrest.

We present a patient with a solitary intracranial myofibroma with an excellent postoperative outcome. Although rare, infantile myofibroma should be included in the differential diagnosis of intracranial neoplasms in children.

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C B O’SULLEBACH
C J MARKS
Department of Neurosurgery

D RYDER
Department of Radiology

C KEOHANE
M J O’SULLIVAN
Department of Pathology, University College Cork, Cork University Hospital, Cork, Ireland

Correspondence to: Dr. M.J. O’Sullivan, Lauren V Ackerman Laboratory of Surgical Pathology, Washington University Medical Center, PO Box 8118, 660, South Euclid Avenue, St Louis, MO 63110, USA. Telephone 011 314 362 0101; fax 011 314 362 8950.


Axonal polyneuropathy and encephalopathy in a patient with verotoxin producing Escherichia coli (VTEC) infection

Escherichia coli serotype O157:H7 causes serious food poisoning worldwide, especially in children and elderly people.1 It is also called verotoxin producing E coli (VTEC), which produces a cytotoxic Shiga-like toxin.2 Gastrointestinal, haemorrhagic, and uroaemic effects are well known in VTEC infection,3 and neurological problems are likely to be more frequent than is generally recognised.4 Here we describe axonal polyneuropathy and encephalopathy in a young female patient associated with haemolytic-uraemic syndrome caused by VTEC infection.

A 26 year old woman began to have abdominal pain and haemorrhagic diarrhoea. She was admitted to an emergency hospital and diagnosed as having haemorrhagic colitis due to probable food poisoning. Then her urinary volume gradually decreased and serum creatinine increased, and she was transferred to our hospital. On the 9th day she had a high fever of 39.7°C with increased C reactive protein of 7.6 µg/ml and a leucocytosis of 17 800/µl. She was in a state of anuria and her blood analysis showed severe kidney dysfunction (increased serum creatinine of 6.76 µg/ml). She had severe anaemia (haemoglobin 0.6 g/dl), fragmentation, and tear drop deformation of red blood cells in the blood smear and increased lactate dehydrogenase concentration of 4095 IU (normal range 230–460 IU), suggestive of haemolytic anaemia. Her platelet count was decreased to 23 000/mm3, suggestive of haemolytic-uraemic syndrome and haemolysis. Her blood gas analysis showed metabolic acidosis, and uraemia, following diarrhoea, which is the main complication of VTEC infection. Experimentally, vero cells, an immortalised primate kidney cell line, is killed by low doses of verotoxin through the process of apoptosis.5 Verox is the main virulence factor of VTEC, leading to a microvascular thrombosis.6 The patient was treated with antibiotics, plasma exchange, and continuous haemodialysis, with benefit.

During the course of the disease, our patient was in a delirious state with visual hallucinations and tonic convolution. She showed mild brain swelling on CT and diffuse slow waves in the frontal area on EEG, evidence of encephalopathy. Previous reports have shown that the incidence of encephalopathy in haemolytic-uraemic syndrome (mortality of 25%) in cases of VTEC infection, including seizures in 17%–44%, altered consciousness in 7%–40%, and paralysis in 1%–16%. Many of the patients, including ours, seemed to have metabolic encephalopathy but some developed encephalopathy without metabolic abnormalities.7 There is experimental evidence that verotoxins have direct virulence to both endothelial cells and neurons in the nervous system, and its initial lesion is in the hypothalamic areas, then

given 250 mg/day dihydropyridinoiditanton. During the next two weeks her kidney function, haemolytic anaemia, and encephalopathy gradually improved.

After recovery of consciousness she began to complain of numbness of the limbs, manifesting in the legs. She sometimes felt walking like frost bite when she was lying on the bed, and this gradually exacerbated to a burning pain. On examination she was alert and cooperative. Her cranial nerves were normal. Muscle strength was normal and coordination was intact. Deep tendon reflexes were decreased in the four limbs. Sensation for vibration was impaired in the lower legs, but preserved for pin prick, light touch, and joint sensation. Routine laboratory data including haematological studies, serum chemistry, urinalysis, and CSE analysis were normal. Serum concentrations of vitamin B1, B6, and B12 were normal. Nerve conduction studies were carried out on her right limbs, and showed normal findings in the distal latencies, motor conduction velocities, and F wave latencies of the median, ulnar, and tibial nerves, and no evidence of conduction block. However, there were markedly decreased amplitudes of the sensory nerve action potential (SNAP) (20 µV) and sural (0.98 µV) nerves. These findings and the clinical features confirmed the diagnosis of sensory dominant, axonal polyneuropathy. She was given 300 mg/day sulindac (an anti-inflammatory agent) and 1500 µg/day mechocholin (vitamin B12) without effect. Two weeks after administration of 300 mg/day oral metexit, her numbness and pain gradually disappeared.

The patient was diagnosed as having VTEC infection, because of a typical history of an acute haemorrhagic colitis, the cultured growth of enterohaemorrhagic E coli O157:H7, and the detection of verotoxin in her stool. She had haemolytic-uraemic syndrome (haemolytic anaemia, thrombocytopenia, and uraemia, following diarrhoea), which is the main complication of VTEC infection. Experimentally, vero cells, an immortalised primate kidney cell line, is killed by low doses of verotoxin through the process of apoptosis.4 Verotoxin is the main virulence factor of VTEC, leading to a microvascular thrombosis.6 Our patient was treated with antibiotics, plasma exchange, and continuous haemodialysis, with benefit.
Crying spells as symptoms of a transient ischaemic attack

In the absence of depression, crying spells associated with neurologic disease usually result from pseudobulbar palsy or, more rarely, from crying seizures. To our knowledge, there are no prior reports of crying spells heralding or signifying a transient ischaemic attack. We report on a patient with prominent cerebrovascular risk factors who had a transient episode of intractable crying and focal neurologic findings.

The patient was a 55 year old right handed man who presented with acute, uncontrolled crying spells followed by left sided paraesthesia. Around 6:00 am he awoke with a diffuse pressure headache and suddenly started crying for no apparent reason. There was no accompanying feeling of sadness. This crying, which involved lacrimation and "sobbing," abruptly ceased after 5 minutes. Within 30 minutes of his initial crying spell, his headache had resolved but he became aware of numbness over his left face and numbness and pain in his left neck and arm. The numbness was not progressive, and the patient did not complain of paraesthesia in his trunk or left upper extremity. He also had photophobia, nausea or vomiting, blurred vision, visual obscurations, difficulty swallowing, dysarthria, or focal weakness. Over the next 2 to 3 hours, he had five more crying spells, each lasting 5 to 10 minutes, occurring out of context, without precipitating factors or sadness, with an acute onset and offset, and without alteration of consciousness. The patient's left face and arm numbness persisted during and between the spells, but abruptly resolved shortly after his last crying spell. This patient had hypertension, diabetes mellitus, coronary artery disease, an old myocardial infarction, raised cholesterol concentrations, and a history of heavy smoking.

On examination between recurrent crying spells, his blood pressure was 143/92 with a regular pulse of 62, and there were no carotid bruits. His mental state was normal. Cranial nerve examination disclosed bilateral, symmetrically flattened, right normal infratemporal and left nasolabial fold and decreased pinprick sensation over his left face, with a sensory level to pinprick at the level of the root of his nose. There was a right VI cranial nerve palsy. The rest of the neurologic examination showed mild weakness in his left upper arm, and decreased pinprick and temperature sensation over the left half of his body. Reflexes were +2 and symmetric with downgoing toes.

The patient lacked prior depression, new depressive symptoms, or prior crying spells as an adult except for a single episode during dental anaesthesia. At the time of his admission, he had not had any recent adverse events in his life, and was totally surprised by his reaction.

The patient's crying spells, paraesthesia, and neurologic findings entirely resolved within about 3 hours. Routine laboratory tests, ECG, and CT were normal. Two days after admission, MRI disclosed a mild degree of white matter vacuolation over the right frontal horn and an ECG showed diffuse frontal intermit- tent rhythmic delta activity but no epileptiform changes. Carotid Doppler studies showed atherosclerotic changes without haemodynamically relevant obstruction. He was discharged on antipileptoid therapy with aspirin.

These results suggest that crying spells can be a manifestation of a transient ischaemic attack. He presented with paroxysmal crying spells followed by a left sided hypoaesthesia and a mild left sided weakness, all of which resolved. His crying was non-emotional, inappropriate to the context, and did not correspond to his underlying mood. Moreover, the patient had multiple vascular risk factors supportive of a cerebrovascular aetiology for his episode.

The most common cause of pathological crying is pseudobulbar palsy, a complication of strokes and other diffuse or bihemispheric brain damage.1 Pseudobulbar palsy results from bilateral interruption of upper motor neuron innervation of bulbar motor nuclei and brainstem centres. In addition to crying, pseudobulbar palsy may include dysarthria, dysphagia, bifacial weakness, increased facial and mandibular reflexes, and weak tongue movements. There were no signs or symp- toms of pseudobulbar palsy at this patient in his physical examination.

Crying or dacrystic seizures also occur but are rare. These seizures are part of the range of complex partial seizures and usually emanate from the right temporolimbic system.2 Crying seizures may result from prior cerebral infarctions.3 Although our patient had mild mismatching of his left face, he did not have other evidence suggesting definite seizure activity.

It is likely that this patient had a single transient ischaemic attack with multiple crying spells. The localisation of his attack is unclear; involvement of the right thalamus or neighbouring internal capsule is a possibility. Similar to spells of laughter, spells of crying may occur in relation to unilateral cerebrovascular events. Although most reports of crying after unilateral strokes have reported left hemispheric lesions,4 crying also may result from right hemispheric strokes.5 Even more similar to our patient, sudden laughing spells, "le fou rire prodromique," rarely precede strokes involving the left capsular-thalamic, lenticular-caudate, or pontine regions.6 Our patient may have had a comparable phenomenon from the right hemisphere. The mechanism for this phenomenon may have been temporary activation or stimulation of ischaemic motor pathways.

Continuous drop type of orthostatic hypotension

Orthostatic hypotension has usually been evaluated for 2–10 minutes after standing.7,8 Multiple system atrophy (MSA: Shy-Drager syndrome) is one of the neurodegenerative diseases which show marked orthostatic hypotension. We studied changes of blood pressure for more than 20 minutes after standing in 30 patients with MSA.

The patients lay on a tilted table, and an intravenous cannula was introduced into the cubital vein more than 30 minutes before the 25 minute test of 60° head up tilt. Blood pressure and heart rate were recorded every minute with an automatic sphygmomanometer. Patients could clearly be classified into two groups in terms of the time taken to reach the minimum blood pressure. In 12 patients systolic blood pressure fell rapidly, reached a minimum within 5 minutes, and then remained stable or partially recovered (early drop type); whereas, in 13 patients blood pressure fell immediately after tilting but kept decreasing by more than 8 mm Hg from that at 5 minutes (mean 12.9 mm Hg;
with orthostatic hypotension of the continuous drop type. To prevent the concentration of plasma, saline of calculated volume was infused during tilting. During the continuous decrease in blood pressure, cardiac output proportionally decreased but systemic vascular resistance did not change (figure).

Our results suggest that in many patients with MSA the blood pressure drops continuously on standing. The continuous blood pressure drop is caused by continuous reduction of cardiac output. A part of the mechanism for continuous reduction of cardiac output should be lack of reflex tachycardia and no significant release of noradrenaline (norepinephrine) level (+0.05% mean=1.4%).

Most patients with continuous drop type orthostatic hypotension reported reduced endurance for more than 10 minutes of exercise (easy fatiguability). Two experienced patients could not remain standing for more than 5 minutes because of symptoms of orthostatic hypotension. No patient showed the sudden drop type (figure). The other five patients could not remain standing for more than 5 minutes because of symptoms of orthostatic hypotension.

Continuous drop type of orthostatic hypotension during 25 minute tilt up in a patient with MSA.

SBP = systolic blood pressure; HR = heart rate; CO = cardiac output; SVR = systemic vascular resistance; NA = plasma noradrenaline concentration.

maximum 74 mm Hg, taking more than 10 minutes to reach the minimum (continuous drop type) (figure). The other five patients could not remain standing for more than 5 minutes because of symptoms of orthostatic hypotension. No patient showed the sudden drop in blood pressure and heart rate seen in vasovagal syncope. In the continuous drop type, there were no decreases between 5 and 20 minutes in heart rate (+2.3 bpm) and the noradrenaline (norepinephrine) level (+0.05 ng/ml) during the decrease in blood pressure. A slight increase in packed cell volume between 5 and 20 minutes was noted (mean=1.4%).

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Idiopathic cerebellar ataxia associated with celiac disease: lack of distinctive neurological features

Although applauding the contribution of Pel- lechia et al to a more widespread recogni-
tion of the association between gluten sen-
sitivity and ataxia, we disagree that ataxia associated with gluten sensitivity lacks “dis-
tinctive neurological features”. Both their data and ours indicate that this group of patients can be distinguished by the late (non-childhood) onset of gait ataxia with relatively mild upper limb signs, analogous to Harding’s group.1 Again, coexistent neu-
ropathy is common in these patients, found in two out of three of the patients of Pellechia et al and 21 of our 28.3 We agree that gastrointestinal symptoms are rare: rather than entitling their paper “lack of distinctive gastrointestinal features”, perhaps “lack of distinctive gastroenterological features” might have been more appropriate.

We were surprised at the high specificity and sensitivity of increased antigliadin anti-
bodies at titres in their hands. Although we found both IgA and IgG antigliadin antibodies to be invaluable screening tools in patients with ataxia, only 11 of our 28 patients had evidence of cerebellar atrophy on MRI, whereas all of our patients had cer-
neurophysiological and pathological charac-


Pellechia et al reply:
We thank Hadjivassiliou et al for their interesting comments on our paper. They suggest that patients with gluten ataxia can be distinguished by the late onset of gait ataxia and the relatively mild upper limb signs. Our results support the finding of a late onset in these patients, but this feature cannot be con-
sidered a distinctive one. In fact, in our popu-
lation 11 out of 24 patients with idiopathic cerebellar ataxia had a late onset, but only three of them were affected by celiac disease. Furthermore, we do not think that celiac patients may be distinguished by mild upper limb signs and coexistent neuropathy; in our study 20 out of 24 patients with idiopathic cerebellar ataxia, including the three patients with celiac disease, had ataxic gait as the pre-
senting and prominent clinical feature. Simi-
larly, nerve conduction studies, performed in 17 out of 24 patients, showed a peripheral neuropathy in nine, including two out of the three patients with celiac disease. We understand that some discrepancies arise comparing our study with that of Hadji-
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Flail arm syndrome or Vulpian-Bernhardt’s form of amyotrophic lateral sclerosis

We read with interest the article by Hu et al concerning flail arm syndrome, a distinctive variant of amyotrophic lateral sclerosis. The authors presented a subgroup of patients affected by amyotrophic lateral sclerosis that presented signs and symptoms of lower motor neuron disease in the upper limbs without significant functional involvement of other regions upon clinical presentation. This subgroup of patients is clinically characterised by the display of progressive atrophy and weakness in the arms with little evidence of corticospinal involvement. The reason for the prevalence in the proximal muscles of the upper limbs is unknown. We can furnish little more information in this respect. However, in the 1960s, in the differential diagnosis of this syndrome, it was proposed that the muscles predominantly affected in Vulpian-Bernhardt’s form were the deltoideus, the infraespinaus, the supraspinatus, the sternocleidomastoideus, and the teres minor. The predominant involvement of these muscles permitted its distinction from that previously called Erb’s dystrophy.

As a consequence of the atrophy of these muscles, the upper limbs adopt a characteristic position, with the shoulders slumped, and the arms, forearms, and hands in pronation. As the illness progresses, the hand muscles are affected, with atrophy of the following muscles: opponens pollicis, flexor brevis, abductor pollicis brevis, adductor pollicis brevis, adductor pollicis, interossei, and lumbricales, which leads to the formation of the characteristic Aran-Duchenne hand.

Obviously, signs of corticospinal involvement with hyperreflexia in the lower limbs and Babinski’s sign both appear. In the initial stages of the illness, there is no effect on the diaphragm. The presence of signs of involvement of the upper motor neuron, its different clinical evolution, and the data supplied by genetic molecular investigation allow us to distinguish the syndrome previously known as Vulpian-Bernhardt’s from the diagnosis of lower motor neuron disease such as of the spinal muscular atrophies, Kennedy’s disease, multifocal motor neuropathy, and monomelic amyotrophy.

JOSÉ GÁMEZ
CARLOS CERVERA
AGUSTÍN CODINA
Servicio de Neurología, Hospital Universitari Vall d’Hebron, Passeig Vall d’ Hebron 119-135, 08035 Barcelona, Spain
Correspondence to: Dr Josep Gámez, Servicio de Neurología, Hospital Universitari Vall d’Hebron, Passeig Vall d’ Hebron 119-135, 08035 Barcelona, Spain, email: 12784jgc@comb.es


Pain after whiplash

This latest study from Lithuania1 is an answer to many questions—namely, that the previous difficulties that these researchers had in replicating the latency window syndrome in Lithuania is that they were not looking “in the right place”. As it turns out, the problem is that Lithuanians simply are not behaving the way many in western countries (underlies whiplash associated disorders) do. How do we conduct a study in a country where people have not been preselected by their attendance at emergency departments, or contaminated by therapists or lawyers, can be studied to appreciate the natural evolution of the injury which, underlies whiplash associated disorders grades 1 and 2. This is the study’s greatest strength. The study has, however, its limitations.

The first consideration is that there were 98 accident victims who reported acute symptoms, and thus were at risk for the late whiplash syndrome. How does this compare with other studies documenting the natural evolution of the late whiplash syndrome in other countries? How do we conduct a study in a country where people have not been preselected by their attendance at emergency departments, or contaminated by therapists or lawyers, can be studied to appreciate the natural evolution of the injury which, underlies whiplash associated disorders.

The Swiss study may be useful for comparison because it too has only 117 subjects, yet is much quoted. Setting aside for the moment that the Swiss study is hampered by the selection atrocity of advertising for subjects, and has a host of other reportedly fatal faults, and giving some benefit of the doubt, the study is said to be an accurate representation of the state of affairs in Switzerland at that time, in Switzerland, not even 60% manage to recover fully by 3 months and many of these were reporting total disability during that time, whereas the Lithuanians fully recover in 4 weeks or less, with little or no therapy.1,2 Studies in other western countries disclose an even greater contrast, with 50%–70% of patients reporting pain even after 3–6 months, despite the fact that all these studies are examining the same grades (1 and 2) of whiplash associated disorders.3,4 Thus, while the sample size is small in this Lithuanian study, it is comparable with others reporting the prognosis of whiplash, and yet gives a different picture of outcome.

A second consideration is that perhaps these Lithuanians are in very minor collisions. True, some of their vehicles were completely wrecked, but perhaps the vehicles were not very good quality and so were easily damaged. Perhaps that is why this cohort had such a good outcome and only minor injuries. This is an unhelpful consideration however, as studies in Canada have shown that with absolutely no vehicle damage, in very low velocity collisions, are just as likely to result in chronic pain as those in more severe collisions. Lithuanians seem to behave appropriately then for minor collisions (if that is what they indeed had), but Canadians seem unable to behave appropriately. Again, another culture's in the rate of recovery from whiplash injury is demonstrated.

Thirdly, there are sex differences and even differences in seat belt usage between this population and some others, but even then, it does not seem to matter what sex, age, and use of seat belts there is in other western countries, none of these preclude chronic pain. In Lithuania, those who were female, and who did not wear seat belts, still insisted on behaving as the rest of the cohort.

Finally, perhaps the Lithuanians simply refuse to report their chronic pain, and chronic pain cannot be studied in other cultures in this way. The Lithuanians have no difficulty identifying whiplash in their people, and who did not wear seat belts, still insisted on behaving as the rest of the cohort.

If there were trials of foreign barriers to identifying symptons, the control population would have grossly underreported their symptoms. Indeed, chronic pain can and is reported by studies in many different cultures and languages, including Japan, France, Italy, and others. If researchers in these non-English speaking populations can use simple questionnaires to document the late whiplash syndrome so effectively there, then the same should be possible in Lithuania.

And so, despite the potential limitations of this study as outlined, there is no way to get around the stark realisation that the natural history of acute whiplash injury in Lithuania is a benign syndrome with 4 weeks or less of pain. Equally compelling is the fact that Lithuania is not the only place where researchers are having difficulty identifying epidemics of chronic pain. Recovery from acute whiplash injury without neurological injury or fracture routinely occurs within 4–6 weeks in Germany\(^4\) and Greece.\(^5\) The time has not been missed for a reconciliation of these epidemiological observations with our own experience of late whiplash syndrome in western populations. The truth has been laid bare and it is our responsibility to utilise this truth to help prevent the chronic pain and the suffering we otherwise encounter.\(^6\)

R FERRARI


BOOK REVIEWS


This book purports itself to be a comprehensive reference. Certainly the title would suggest so. However, it is clear that this is not a comprehensive text, but a book that is an update on particular timely topics in the field of pain medicine. There are sections on pain mechanisms, a chapter on the pharmacology of acute and chronic pain, and other chapters on postoperative pain, obstetric pain, and acute paediatric pain. There are three further chapters specifically on the management of chronic low back pain, cancer pain, and an overview of interventional pain techniques.

Many of the authors are internationally known and this is perhaps the book’s strongest point—one does get a state of the art review and to this end I warmly welcome this book as an addition to the bookshelf to update a busy anaesthetist or pain specialist, though the chapter on chronic low back pain and cancer pain will also be of interest to those in other fields.

The chapter on the anatomy and physiology of pain is excellent in that it has clear explanations and a number of very helpful diagrams. Unfortunately it fails to mention increasing understanding of the role of GABA in mediating analgesia within the spinal cord and furthermore does not mention some of the other neurochemical changes which are well known to occur in chronic pain states such as central sprouting and phenotypic switching.

The chapter on pharmacology of acute and chronic pain is well written, but unfortunately a lot of time is spent on non-steroidal drugs. There is a review of the adjuvant drugs such as antidepressants and anticonvulsants that are used in chronic pain, however one is left at the end with a sense of knowing about the drugs but not quite to use them. There is no mention of the increasing use of gabapentin or nor of other drugs that are sometimes used in chronic pain states such as clonidine and other sympatholytic agents or calcium channel blockers.

The chapter on acute postoperative pain management is well written and informative as are the chapters on obstetric and paediatric pain. The chapter on chronic low back pain by Rauck is one of the best I have seen for some time. It is a comprehensive review of both acute and chronic low back pain. It is excellent as it also mentions treatments that are often performed outside the medical specialist arena. I was pleased to see in it the mention of some of the newly evolving techniques such as facet denervation, spinal cord stimulation, and disc denervation. It was a pity that the randomised control trials which have shown facet denervation to be an outstandingly useful technique for chronic low back pain were not mentioned. It was also a pity that the reference to the disc denervation procedure was to another text book rather than any original papers.

The chapter on cancer pain management has been written by internationally known authors and is an excellent summary of the subject. In the section on interventional pain techniques the emphasis was on spinal cord stimulation, radiofrequency, and cryosurgery. Again this chapter has been written by an internationally well known author who concentrated on general overview of the techniques rather than a how to do it approach, which I think one would have to go to a bigger text for. In summary I think that this volume would make an excellent addition to the bookshelf of those involved in the treatment and management of pain.

RAJESH MUNGALANI


This is a really excellent book which is both comprehensive and amazingly up to date, with the inclusion of many references from as late as 1997. As a clinical neurologist and neuropathologist with a long standing interest in the dementias, I found it extremely valuable. The editor has done a very good job in posing a coherence, format, and style, which is often lacking from multicontributor textbooks. The title of the book is perhaps a little misleading in that the book includes, as well as traditional neuropathology, a very comprehensive overview of the molecular biology and genetics of the dementias. As would be expected, a considerable proportion of the book is dedicated to Alzheimer’s disease with chapters on both the clinical features, genetics, and the neuropathology. The frontotemporal dementias are also well covered and the book includes a chapter on the many frontotemporal dementias and their associations with other neurodegenerative diseases. There are also sections on progressive supranuclear palsy, Huntington’s disease, corticobasal degeneration, dementia with Lewy bodies, and prion diseases and vascular dementia.

The editor has managed to persuade many of the world’s experts to contribute. For instance, the chapter on prion diseases is by D’Almond and the recent Nobel laureate Prusiner, and the frontotemporal dementias are reviewed by Brun and Gustafson. Genetics of Alzheimer’s disease are dealt with by St George-Hyslop and the neuropathology of Alzheimer’s disease by Price and coworkers.
The standard of illustrations is excellent and the style generally very readable. I shall certainly find it extremely useful as a work of reference and for teaching purposes. The editor is to be complimented on producing such a delightful work.

JOHN HODGES


I very much enjoyed reviewing this textbook of instrumented spinal surgery written by Giuseppe Tabasso under the auspices of Jürgen Harms. Dr Harms is well known to all spinal surgeons and has made a very important contribution to the development of spinal surgery over the past 20 years, based on strong personal convictions. Many surgeons who manage spinal disorders would not choose to implement all of Professor Harms' solutions but all who have a serious interest in the surgical treatment of the spine admire and are grateful for his contribution. Within this book spinal surgeons will find a rational and practical approach which will allow them to treat a wide range of spinal disorders according to well thought out principles.

The opening chapter describes spinal biomechanics under normal and pathological circumstances mainly by using easily understood drawings and diagrams. Some of these drawings reminded me of images that I have recently seen on an interactive CD ROM that I bought for my 4 year old son. This is not a criticism and I fully support any attempt to simplify the science of biomechanics which is often cloaked in seemingly contradictory jargon. Most spinal surgeons will be able to assimilate the two basic principles which underpin much of instrumented spinal surgery—namely, that the anterior column resists load compression forces and that the posterior column acts as a tension band which when disrupted should be reconstructed in compression. The remaining chapters cover fracture management, late kyphosis, metastatic tumours, spondylolisthesis, degenerative spinal disease, and infection. Each chapter sets out the principles of management which are illustrated schematically. There then follow case studies illustrated by radiological images including CT and MRI. These have reproduced well and surgeons will admire the technical precision and excellent anatomical reductions illustrated by these clinical cases. It is, however, a source of constant annoyance to spinal surgeons that perfect postoperative films do not always correlate with good clinical results and this discrepancy remains a source of fascination and mystery.

It is in the degenerative spine that this discrepancy between radiological and clinical findings is most apparent and it is partly for this reason that the management of these conditions is often controversial. It is difficult to disagree with much of the logic presented by the authors in planning their interventions but there is a danger that inexperienced surgeons may be misled into adopting complex solutions when often more simple operations will suffice. The authors' description of their approach to failed back surgery syndrome illustrates this problem and the inadequacies of attempting to treat a complex clinical problem by focusing on one aspect of it.

This book will be a useful addition to the shelves of spinal surgery textbooks and many orthopaedic and neurosurgical departmental libraries will wish to buy a copy.

RODNEY LAING


I wondered, when I received this book, how I could possibly say anything adverse about a book written by three such world renowned experts. I have heard them all lecture often and have seen them all at work. They have a vast knowledge and experience of treating disorders of peripheral nerves. In clinic and the operating theatre, they have shown myself and many trainees a clarity in their planning of management of complex problems that humbles one's own thoughts. That clarity has continued in this text book of over 500 pages. The field of peripheral nerve surgery is covered comprehensively, commencing with descriptions of anatomy, physiology, and pathological reaction to injury. This is followed in subsequent chapters with descriptions of approaches to virtually all the main peripheral nerves, and the operative management of brachial plexus injury and outcomes is covered in three detailed chapters. These are followed by chapters on nerve entrapment, neuropathy, iatropathic injury, and neoplasm within the peripheral nerve. The final section covers electrodiagnosis, pain, nerve recovery, reconstruction techniques, and rehabilitation.

The text is well written, easy to read, and supplemented by some excellent line drawings similar to those used in Lundborg's text. There are detailed plates showing histology and various imaging techniques. Each chapter is comprehensive, containing important historical aspects as well as up to date techniques, and there is an extensive reference section. I would recommend that trainees of all specialties dealing with peripheral nerve injuries should read much of this text and it would be extremely useful as a regular reference. It would also make an important and necessary addition to most medical libraries. All clinicians would be well advised to read the chapters on iatropathic injuries, not only for the extensive causes of such injuries encompassing all medical and surgical departments, but also for the precis of the changes occurring in medical negligence claims. This text represents good value for money.

IAN WHITWORTH