LETTERS TO THE EDITOR

Acute cauda equina syndrome caused by thrombosis of the inferior vena cava

Deep venous thrombosis of the lower limbs is the most common vascular disorder in hospital. Although the clinical features are not specific, the most important symptoms are oedema, local tenderness, and pain. Well known complications of deep venous thrombosis are pulmonary embolism and chronic venous insufficiency. Neurological complications are uncommon after deep venous thrombosis.

We report on a patient who presented with an acute cauda equina syndrome, which turned out to be caused by thrombosis of the inferior vena cava.

A 58 year old previously healthy white man presented at the emergency department of our hospital with acute severe low back pain irradiating to both legs. The pain in the legs was severe and was located from the lower half of the upper legs down to the feet. He also had noted decreased strength as well as sensory disturbances of both legs. Spontaneous micturition was not possible.

Figure 1 Lumbar spine MRI. Strongly dilated epidural and foraminal veins as black tubular structures due to signal loss, consistent with increased speed of flow. (A) Axial T1 weighted cut at L4-5; Anterior epidural plexus indicated by arrows. (B) Mid-sagittal proton density weighted cut showing compression of dural sac at L5 and S1 levels. (C) Lateral sagittal T1 weighted cut showing dilated foraminal veins.

On physical examination, blood pressure was 110 over 75 mm Hg. Heart, lungs, and abdomen were normal. Peripheral arterial pulsations were present. Both legs were slightly swollen and coloured red to purple and livido reticularis was present. On catheterisation of the bladder, there was no urine retention. Neurological examination showed weakness of both legs with proximal strength Medical Research Council (MRC) grade 2-3 and distal MRC grade 1-2. There was bilateral sensory loss in the dermatomes L1 to S1. Tendon reflexes of the legs were absent. Plantar responses were both indifferent. The patient was diagnosed as having an acute cauda equina syndrome with possibly deep venous thrombosis of both legs, and an immediate MRI of the thoracic and lumbar spine was performed. This MRI disclosed a strongly dilated anterior epidural venous plexus with compression of the cauda equina and nerve roots in the foramina (fig 1 A-C). Signal intensity of the thoracic spinal cord was normal. Ultrasound examination of the lower abdomen and legs showed thrombosis of the inferior caval vein. Abdominal CT confirmed the presence of thrombosis of the inferior caval vein (just below the insertion of the renal veins) extending into the iliac veins. No other abnormalities that could have caused the inferior vena cava thrombosis were seen on CT. Routine laboratory investigations (including coagulability testing) were unremarkable, except for slight increase in erythrocyte sedimentation rate.

The patient was diagnosed as having an acute cauda equina syndrome due to dilated anterior epidural veins secondary to thrombosis of the inferior vena cava. He was treated with intravenous heparin and acenocoumarol to prevent spread of thrombosis. In the next few days, the neurological disturbances gradually diminished. Despite exhaustive testing, no cause of the thrombosis was found.

We report on a patient with an acute cauda equina syndrome due to thrombosis of the inferior vena cava. An acute cauda equina syndrome is usually caused by a prolapsed intervertebral disc and less often by a tumour, trauma, or epidural bleeding.

Well known complications of deep venous thrombosis are pulmonary embolism and chronic venous insufficiency. To our knowledge, an acute cauda equina syndrome

secondary to thrombosis of the inferior vena cava has not been reported previously.

The mechanism by which the neurological symptoms and signs were produced is probably twofold. Firstly, there is compression of cauda equina nerve roots in the spinal canal and foramen by the dilated anterior internal vertebral veins. Secondly, the symptoms and signs may be due to ischaemia of the cauda equina caused by stasis of the blood flow in the radicular veins. The mentioned anterior internal vertebral veins and radicular veins are part of the spinal venous plexus. This valveless plexus is connected by the intervertebral veins to the ascending lumbar veins which drain to the inferior caval vein (fig 2). The ascending lumbar veins, however, also communicate with the azygos system and the occipital and basilar sinuses. After occlusion of the inferior vena cava, this vertebro-lumbar collateral pathway can function as an alternative route for venous blood from the lower limbs. Due to this bypass effect running parallel to the inferior caval vein, the anterior epidural veins are dilated by increased blood flow. In our case, the dilated veins have probably compressed the cauda equina and certainly compressed spinal roots in the intervertebral foramina, as can be seen on the MRI.

Vascular spinal neurological complications are also known in spinal arteriovenous malformations (AVMs) and spinal angiomas. More than half of the patients with AVMs have bladder dysfunction, paresis, and sensory change caused by the ischaemic effect of venous hypertension. In patients with spinal AVMs, an apoplectic onset of clinical presentation, as presented in our patient, is described in 30%-50% due to thrombosis or haemorrhage.¹ Neurological signs are also known as a related phenomena to spinal angiomas. Although ischaemia of the cord in these angiomas is mostly caused by stealing blood through a significant arteriovenous shunt, spinal compression by very large draining veins is also important in some patients.² Besides cauda equina compression, dilated veins secondary to thrombosis of the inferior vena cava can also lead to destruction of pedicles of lumbar vertebral bodies and partial obstruction of the ureter.³⁻⁴ In conclusion, an acute cauda equina syndrome may be rarely caused by a dilated venous spinal plexus secondary to thrombosis of the

Figure 2 Diagram of lumbar vertebral veins.⁵ (1) Lateral anterior internal vertebral vein (AIVV); (2) medial AIVV; (3) posterior internal vertebral venous plexus; (4) basivertebral vein; (5) intervertebral vein (IVV); (6) ascending lumbar vein (ALV); (7) posterior external vertebral venous plexus; (8) anterior external vertebral venous plexus; (9) left lumbar vein; (10) inferior caval vein.

inferior vena cava. The list of causes of the cauda equina syndromes³ should therefore also include inferior vena cava thrombosis.

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Persisting rhinorrhoea and headache as the initial symptom of bilateral carotid artery dissection

Carotid artery dissection is a frequent non-atherosclerotic cause of stroke in young adults. In up to 20% of cases it is bilateral or associated with vertebral artery dissection.¹ Common clinical features include unilateral pain on the side of the dissection, signs of cerebral ischaemia, ear bruits, and Horner's syndrome,² which is usually incomplete and sometimes transient.³ Horner's syndrome is thought to result from a lesion of the periarterial sympathetic plexus caused by the dissection.² Rhinorrhoea and nasal congestion have not yet been reported as symptoms of spontaneous carotid artery dissection but have been seen in patients undergoing cranial base surgery.⁴ We here describe a patient with spontaneous bilateral carotid artery dissection in whom rhinorrhoea, nasal congestion, and headache were the first symptoms, which preceded the development of incomplete Horner's syndrome for several weeks.

A previously healthy 33 year old man was referred for evaluation of headache. He admitted to having had rhinorrhoea and nasal stuffiness for 7 weeks. Treatment with antibiotics and corticosteroids before admission had been unsuccessful. An infectious or allergic cause could not be determined. Four weeks later he developed severe periodical retro-orbital headache lasting for hours, and pulsatile tinnitus on the right side. Two weeks before admission he noted severe stabbing retro-orbital pain on the left side irradiating to the neck. This did not respond to aspirin. Pain attacks and vomiting occurred regularly during the afternoon, progressing during the night without fluctuations. Intake of alcohol and nicotine triggered the attacks. He had no history of cluster headache or migraine.

On examination he showed rhinorrhoea, increased lacrimation of the left eye without redness, left eyelid swelling, incomplete Horner's syndrome on the left side, and ear bruits on the right side that were not detected by auscultation of the skull. There were no other focal neurological deficits, in particular no anhy-

drosis. Routine laboratory blood tests, screening for cardiovascular diseases, and Doppler sonography were all normal. Cranial magnetic resonance angiography and cerebral digital subtraction angiography showed bilateral dissection of the internal carotid artery with dissecting aneurysms on both sides (figure A-D).

Anticoagulation with heparin and then dicumarole was initiated and the patient's symptoms gradually improved. On follow up examination 6 months and 14 months later, he showed marginal ptosis and a slightly smaller pupil (2 mm) in the dark on the left side, but no headaches, rhinorrhoea, or tinnitus. Cerebral magnetic resonance angiography of the left internal carotid artery was now normal but the dissecting aneurysm of the right internal carotid artery was unchanged. Therefore anticoagulation was continued.

We suggest that in our patient bilateral carotid artery dissection led to a lesion and dysfunction of the sympathetic pericarotid plexus leading to a parasympathomimetic state with nasal hypersecretion and congestion of nasal vessels. This condition was reversible after recanalisation of the left internal carotid artery. Nasal stuffiness or rhinorrhoea may be rarely reported by patients because this phenomenon may be associated only with sympa-

thetic pericarotid lesions after infrequent bilateral internal carotid artery dissections whereas unilateral dissections may cause only a mild and clinically often inapparent irritation.¹

Cusimano and Sekhar described a syndrome they termed "pseudocerebrospinal fluid rhinorrhoea" with ipsilateral nasal hypersecretion and nasal stuffiness after surgery of the cranial base.⁴ In these patients, the pericarotid sympathetic plexus, the petrous or cavernous carotid artery parts, and the greater petrosal nerve had been removed or dissected. Experimental selective parasympathetic nerve activation in the nasal mucosa of the cat leads to an increase in nasal secretion and vascular congestion.⁵ Lung found nasal congestion to be related to a withdrawal of sympathetic discharge rather than to an overactivity of the parasympathetic nerves.⁶ Thus the nasal hypersecretion and stuffiness in our patient is in agreement with the assumption of a lesion of pericarotid sympathetic nerve fibres after carotid artery dissection.

In the differential diagnosis, cluster headache and paroxysmal hemicrania have to be considered. Our patient's symptoms differed from typical cluster headache and paroxysmal hemicrania in that headache followed the beginning of autonomous symptoms after

Axial baseline images of a time of flight MR angiography at the level of the clivus (A), and at the level of the atlas (B). On (A) an older dissecting aneurysm is clearly indicated by an intimaflap (arrows), dividing the false and original lumen of the right carotid artery. On (B) a recent intramural haematoma (arrows) of the left internal carotid artery is visible surrounding the hyperintense lumen laterally. C and D: lateral views of a digital subtraction angiogram of both common carotid arteries made during the first stay in hospital. On the right side (C) a larger dissecting aneurysm of the internal carotid artery is visible just beneath the cranial base (arrows). On the left side (D) the dissecting aneurysm is smaller and only seen by an irregular vessel lumen of the internal carotid artery (arrow).

several days and pain was progressing over hours during bouts without fluctuations.⁷

We conclude that structural lesions of sympathetic nerve fibres should be considered when (1) the headache profile is not typical for cluster headache and paroxysmal hemicrania, and (2) autonomous symptoms precede and outlast headache.

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White muscle disease in humans: myopathy caused by selenium deficiency in anorexia nervosa under long term total parenteral nutrition

Selenium is an essential trace element that is known to be a component of glutathione peroxidase, a scavenger of hydroperoxides.¹ Its deficiency causes a decrease in glutathione peroxidase function, thereby resulting in oxidative damage to many organs. The two major clinical signs in patients with selenium deficiency are skeletal myopathy and cardiomyopathy. White muscle disease, named because of its characteristic acolouration of the muscle is a myopathy caused by selenium deficiency in animals in the areas where the soil is low in selenium.² In humans, it was demonstrated that Keshan disease, dilated cardiomyopathy in the Keshan area in China, was caused by selenium deficiency.³ In addition, there are reports that selenium deficiency occurs in patients who are nourished by total parenteral nutrition alone for a long time because of inflammatory bowel disease or resection of the intestine due to various intestinal diseases.^{4,5} We experienced a case of anorexia nervosa with skeletal myopathy caused by selenium deficiency under long term parenteral nutrition.

A 28 year old woman was admitted to our hospital with a 7 year history of anorexia nervosa receiving parenteral nutrition intermittently. At admission, she complained of general fatigue, but had no muscle weakness or myalgia. On physical examination, she was markedly emaciated (weight 22 kg, height 158 cm). Her skin was dry and her nail beds

appeared pale. Because her voluntary food intake was not sufficient to maintain an adequate weight, we started parenteral nutrition. A month after initiation of parenteral nutrition, her body weight had increased from 22 kg to 27 kg and her presenting complaint of general fatigue had disappeared. Instead, she had begun to complain of proximal muscle pain and weakness in all four limbs, and soon after, she had difficulty in walking or standing up.

Laboratory studies showed a rapid rise in creatine kinase to 5638 (normal 35-169) IU/l. Other myogenic enzymes such as myoglobin and aldolase were also raised. Serum electrolytes were all within the normal range. Serum thyroxine and thyroid stimulating hormone concentrations were normal, but serum triiodothyronine was slightly decreased because of impaired conversion of thyroxine caused by malnutrition. Serum selenium concentration markedly decreased to 13 (normal 107-171) µg/l, and glutathione peroxidase also decreased to 145 (normal 280-450) IU/l. Serum vitamin E decreased to 0.35 (normal 0.75-1.41) mg/dl despite being added to the parenteral nutrition. Because serum vitamin E concentration often parallels the serum selenium concentration, these antioxidants will compensate for each other. The forearm ischaemic exercise test showed a normal response. Chest radiography showed neither congestive changes nor enlargement of the heart. On an echocardiogram, the wall motion of the left cardiac ventricle was normal. Electromyography of proximal limb muscles showed myopathic patterns. Motor

Microscopic (A,B) and electron microscopic (C,D) findings of muscle biopsy from the left biceps of this patient. (A) Haematoxylin and eosin staining. There were many atrophic changes and intrafibrillar vacuoles. bar=10 µm. (B) Routine ATPase reaction. Predominance of the type II fibre as well as many vacuoles in the fibres. bar=10 µm. (C) Subperimysial and intermyofibrillar clefts composed of amorphous matrix material were found in muscle fibres. Myofibrils showed thinning and interruption. bar=4 µm. (D) There were intermyofibrillar clefts, containing numerous small granules and enlarged mitochondria with normal cristae. bar=1 µm.

and sensory nerve conduction velocities were normal.

The biopsied muscle from her left biceps seemed pale. Histological studies showed severe atrophy of all muscle fibres examined, type II fibre predominance, increased extramyofibrillar fluid without fibrosis, and many vacuoles in the myofibrils (figure A, B). The vacuoles were unstained by oil red O, periodic acid Schiff, or acid phosphatase, and were made up of subperimysial and intermyofibrillar clefts consisting of amorphous matrix material seen by electron microscopy. Myofibrillar architecture was destroyed and associated with loss and thinning of myofibrils. Some mitochondria were enlarged in size, but neither abnormal cristae nor inclusions were seen (figure C, D). These clefts and destroyed architecture of myofibrils would be caused by the intermyofibrillar and intramyofibrillar focal oedema that might be induced by unmetabolised hydroperoxides.

Within several days after a simple change from total parenteral nutrition to oral diet alone, without selenium supplementation, her muscle pain gradually improved. The serum creatine kinase concentration gradually decreased and was normal in a month. Two months later, she was able to walk alone and stand up from a chair. The concentrations of serum selenium and glutathione peroxidase tended to improve with oral diet alone.

Selenium is relatively abundant in meat, fish, and cereals, but there is very little in total parenteral nutrition or liquid formula diets. A patient nourished by total parenteral nutrition alone for a long period may risk selenium depletion, so selenium supplementation is recommended. In 1979 Van Rij *et al* reported a patient with a perforated small intestine showing skeletal myopathy during month long parenteral nutrition.⁴ Since then, there have been about 20 cases of selenium deficiency during total parenteral nutrition in the literature worldwide, but most cases received total parenteral nutrition because of the surgery for intestinal diseases or inflammatory bowel diseases. As far as we know, there is no report dealing with a patient with anorexia nervosa accompanied by selenium deficiency, although total parenteral nutrition is a popular method to ameliorate the nutritional state in severely emaciated patients with anorexia nervosa. The phenotypic difference for manifestation of either skeletal myopathy or cardiomyopathy is not understood at present. The living environment, the selenium content of the whole body, and the level of other antioxidants such as vitamin E, seem to influence one another.

Sudden death occurs occasionally in patients with anorexia nervosa because of arrhythmia and heart failure. Because selenium deficiency can cause cardiomyopathy and sudden death, we should carefully monitor for selenium deficiency in anorexia nervosa, especially in patients on long term total parenteral nutrition.

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Selective mutism, speech delay, dysmorphisms, and deletion of the short arm of chromosome 18: a distinct entity?

Elective (or selective) mutism is a rare psychiatric disorder. Diagnostic criteria in both ICD-10¹ and DSM-IV² include: (a) consistent failure to speak in specific social situations in which there is an expectation for speaking (for example, at school) despite speaking in other situations (for example, at home); (b) the disturbance interferes with educational or occupational achievement or with social communication; (c) it is not better accounted for by a communication disorder or by a lack of knowledge of the spoken language required in the social situation; (d) it has a duration of at least 1 month.³

It typically starts at preschool age, is more common in girls, and is seen in all social strata with shyness, withdrawal, sensitivity or resistance, and internalising behaviour problems as the most common personality features.

We followed up a 7.5 year old girl who was the third child from non-consanguineous parents. She was born normally at 37 weeks of an uneventful pregnancy, with a birth weight of 3.5 kg, length 47 cm, and head circumference 34.5 cm. The American pediatric gross assessment record was 9 at 5 minutes. Family history was non-contributory. There was neither family history of psychiatric illness nor of language abnormalities.

Developmental milestones were normal; she acquired head control at the 3rd month of life, sat at 7 months, and walked at 13 months. On the other hand, she presented speech delay as she used single words meaningfully as late as 24 months and was able to pronounce her first phrases at 3 years. Behavioural anomalies were first registered by her parents between 3 and 4 years, when they noted a reluctance to speak in front of other people. By the age of 4, she used to speak regularly only to one her friends, and she did not talk to nursery staff or to other children. At home, she normally spoke to her parents and her sister but would not speak to them in front of others.

She first came under our care at the age of 6 years. Physical examination showed a pattern of facial dysmorphisms involving flattened nasal bridge, short upper lip, broad philtrum, everted lower lip, and micrognathia. Short and broad fingers were also noted. Muscular tone and deep tendon reflexes were normal. No abnormal pyramidal, extrapyramidal, or cerebellar signs were present. She had no dyspraxia. Her height was below the 10th percentile, weight on the 15th percentile, and head circumference on the 10th percentile.

The autism diagnostic interview,^{4,5} administered by her mother, showed a score of 9 in

the area of communication (cut off level of 8), but she scored 6 in the areas of qualitative impairments in reciprocal social interaction (cut off of 10), and 0 in repetitive behaviours and stereotyped patterns (cut off of 3). Social and imitative play seemed inadequate, but no language abnormalities such as echolalia, neologisms, or pronominal reversal were present. Her social interactions were reciprocal although she usually only smiled at her parents, did not have easy peer relationships, and directed no language towards the hospital staff. However, she was able to engage in good eye contact. Clumsy attempts to interact with other children were made by the patient when she was not directly observed by medical staff.

The patient was also evaluated by the Wechsler intelligence scale for children which showed a performance IQ of 79, and verbal IQ of 70.

Biochemical tests for aminoacidopathies, mucopolysaccharidosis, and lysosomal disorders were normal, as was selective screening for organic acidemias. An isoelectric focusing test for sialotransferrin was normal. Molecular tests for fragile X syndrome were negative. Brain MRI examination, EEG recording, and audiometric tests were normal. Karyotype analysis of blood cells showed an abnormal chromosomal pattern with deletion of the short arm of chromosome 18, 46XX, del(18), p(11.1) in all metaphases examined. Karyotype analysis was normal in her parents.

Simons *et al* recently reported the first patient affected by elective mutism associated with deletion of the short arm of chromosome 18, del (18), p (11.1).³ Their patient had had developmental abnormalities but these could not account for her social communication disorders, and peculiar dysmorphisms were present. We also had the opportunity to study a girl affected by elective mutism in whom karyotype analysis showed an identical deletion of the chromosome 18. Speech delay, facial dysmorphisms such as flattened nasal bridge, broad philtrum, and micrognathia were the main clinical findings. Auxological indices were in the low average range; particularly, skull circumference was on the 10th percentile. No familiar trait of microcephaly was present in her family, and short stature appeared when the height of our patient was compared with the midparental height (data not shown). Psychological testing showed verbal skills and performance in the low range (table). We compared our patient with the one reported by Simons *et al* (table).³ With the exception of the round face, not seen in our patient, clinical findings of both patients overlapped. Moreover, both patients had speech delay, a similar neuropsychological profile, and the same 18 chromosome abnormality. All these findings allow us to hypothesise that the association of such signs is not by chance and it may be indicative of a distinct clinical entity.

Elective mutism is most probably a heterogeneous syndrome and several aetiological factors such as minimal brain dysfunction, somatic or psychological trauma, particularly during speech development, and a particular family structure especially the mother-child relationship, have been suggested. As a consequence clinical features are variable and speech delay and dysmorphisms can be found in a subgroup of patients only.⁶ Moreover, in most patients elective mutism is a transient disorder as it usually disappears

Comparison of clinical findings of the patients

Clinical findings	Our patient	Patient reported by Simons <i>et al</i> ¹
Head circumference	10th percentile	3rd percentile
Height	10th percentile	25th percentile
Weight	15th percentile	3rd percentile
Speech delay	Yes	Yes
Performance IQ	79	84
Verbal IQ	70	71
Round face	No	Yes
Flattened nasal bridge	Yes	Yes
Short upper lip	Yes	Yes
Broad philtrum	Yes	Yes
Everted lower lip	Yes	Yes
Micrognathia	Yes	Yes
Short broad fingers	Yes	Yes

in a few months. By contrast, in our patient as well as in the one reported by Simons *et al*, elective mutism appears as a chronic disorder and it has been affecting our patient for about 4 years. Therefore, we think that in a subgroup of patients elective mutism is related to a genetic background. This hypothesis is further corroborated by the study of Steinhausen *et al*, who pointed out that genetic factors play a part in the aetiology of selective mutism, as they found that disorders of speech, language, and psychiatric illness were more common in the relatives of affected than in the control groups.⁷

Deletion of the short arm of chromosome 18 has also been associated with several phenotypic expressions, mental retardation, and autism.^{8,9} However, in our patient diagnosis of elective mutism was firmly made as autism or connected pervasive developmental disorder were ruled out because of social disorders which were highly specific and situational.

In conclusion, we confirm that the relation between elective mutism and deletion of the short arm of the chromosome 18 is not by chance, and think that their association with developmental disorders and dysmorphisms, occurring in these patients, may delineate a specific clinical entity.

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Relation between neuropsychological and neuroimaging findings in patients with late whiplash syndrome

Radanov *et al*¹ are to be commended on their recent publication considering, in part, the issue of “brain injury” as a basis for cognitive dysfunction in the late whiplash syndrome. There are a few limitations of the study. The first is the small sample size. A second is that, unlike previous studies from Switzerland in a non-tort system, the subjects of this recent study are mostly litigants. When examining for correlation between diagnostic tests and symptoms, malingering detection efforts, as used in other studies,² may be required. This is now a confounding variable. Yet, despite these concerns, this study is an important and valid effort.

Although it can never be proved that there is no brain injury in whiplash patients, it must be realised that in both science (medicine in particular) and the law, there is an obligation to deal in probabilities. Clinicians routinely make treatment decisions based on the most likely diagnosis and current evidence, not because of absolute proof. Radanov *et al* have given clinicians and the legal community, through this and previous studies,^{3,4} an opportunity to appreciate the more highly probable sources of cognitive symptoms in whiplash patients. These alternative explanations other than brain injury sources are not only more benign (non-pathological), but are more amenable to specific interventions and prevention altogether.⁵

In whiplash patients, these symptoms are correlated with the pain experience, various causes for psychological distress, and medications (although medications are not implicated in the patients in the current study).^{3,5} The cognitive symptoms seem to also improve as the patient's pain improves.^{3,4} Furthermore, the distress of litigation as a factor is noted. In the cohort of Radanov *et al*,¹ 85% were in litigation. Lees-Haley and Brown⁶ studied 170 personal injury litigants, in whom the litigation was not related to a physical injury, but rather to issues of sex, race, or age discrimination, verbal harassment at work, wrongful termination, etc. Although the patients were not filing a claim for neuropsychological impairment, they have a similar prevalence of cognitive and other neurological complaints as those who litigate for what is commonly referred to as mild traumatic brain injury. These researchers also showed that the base rates of these complaints is actually high in the otherwise, healthy population. In many cases, claimants are likely amplifying and misattributing their symptoms to the accident, when they relate instead to pre-existing conditions, the stress of litigation, unrelated illnesses, malingering, inspiration of hysteria by prior medical-legal evaluations, or influence of third parties.⁶

Beyond this, malingering of cognitive dysfunction seems to be a particular problem in some countries. In The Netherlands, some 25% of those patients reporting such symptoms months to years after the accident may be malingering. Malingering (as detected by testing) was twice as common in litigants than non-litigants.²

Radanov *et al* are thus contributing to the effort in closing one chapter of the whiplash controversy. Clinicians can now be more confident in relating to their patients that their cognitive dysfunction is due to various reversible factors, rather than brain injury or other ominous diagnoses. Indeed, a re-education of this sort, and the biopsychosocial (non-dichotomous) approach Radanov *et al* suggest is the cornerstone of more effective approaches towards the prevention of the late whiplash syndrome.^{7,8}

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Radanov *et al* reply:

On the basis of our article,¹ which may be interpreted as indicating that there is no brain injury after whiplash, Ferrari focuses on malingering as an alternative explanation for the cognitive problems of whiplash patients. This perhaps is a biased view and is in contrast with Ferrari's statement that “the biopsychosocial (non-dichotomous) approach” to the problem may be required in these patients. The following points seem important: (1) It should be considered that there were results² outside the context of litigation which suggest that overall there was an improvement of cognitive functions (for example, attention) in whiplash patients within the first months of injury. However, there was a relapse in cognitive functioning in long term patients,² which could be explained neither by brain damage nor by litigation. Data rather suggested that this relapse may be due to symptoms (mainly pain),² adverse effects of medication,² or symptoms related to change in psychological functioning.³ Comparable results were found in additional studies^{4,5} where litigation is unlikely to have played an important role. In this research^{4,5} similar problems in cognitive

performance were found in patients who had had mild traumatic brain injury or only an injury to other parts of the body. Interestingly, in patients with more severe injuries to other parts of the body⁴ a higher impairment in cognitive functioning was found. These results may suggest that experience of symptoms (for example, pain) and the process of adjustment to the symptoms (for example, worry about achieving the pretraumatic level of functioning) may contribute to psychological changes as shown previously.³ Based on these changes, of which the prolonged experience of impaired wellbeing may be crucial, an inability for effort may follow, eventually leading to subtle problems in cognitive functioning. Assuming a dichotomous perspective with focus on malingering as the only basis for symptoms may certainly lead to an additional change in patients' illness behaviour including an exaggeration of symptoms in some cases. Considering these issues may help to develop a therapeutic approach which should allow patients to adjust better to their problems and improve recovery. Previous results generally indicate a lack of morphological brain damage after whiplash or mild traumatic brain injury.^{1,6} However, functional brain damage, whatever the cause, cannot be fully excluded⁷ and further research may provide some additional insights. For example, using SPECT, short term disturbance to prefrontal structures was found in patients with mild traumatic brain injury,⁶ which probably indicated some sort of impaired functioning. Such a functional impairment may introduce a cascade of additional problems eventually contributing to a vicious circle on which basis the previously shown symptom augmentation may follow.² This has to be prevented. Blaming patients for malingering is hardly the most appropriate approach and does not have anything to do with a non-dichotomous perspective of illness behaviour.

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Secondary prevention after cerebral ischaemia of presumed arterial origin: is aspirin still the touchstone

I agree that, for secondary prevention of ischaemic stroke, alternatives to aspirin have to be identified,¹ not only because the scope for aspirin related therapeutic benefit is limited by the fact that aspirin blocks only one of at least eight potential pathways for activation of platelet aggregation,² but also because some patients, initially responsive to the inhibitory effect of aspirin on platelet aggregation, subsequently escape from this effect,³ with consequent risk of recurrence of ischaemic stroke. Glycoprotein IIb/IIIa receptor blockers might superficially seem to be the final solution to this problem, as they block the final common pathway of platelet aggregation, but enthusiasm for their use should be tempered by the acknowledgement that acute profound thrombocytopenia (platelet count < 20 000/mm³) may be an occasional side effect,² with the consequence (at least in theory) of clinically significant intracranial haemorrhage in elderly patients who have ischaemic stroke coexisting with the type of small vessel disease predisposing to silent intracerebral microhaemorrhages,⁴ or coexisting with cerebral amyloid angiopathy, itself a risk factor for intracranial haemorrhage.⁵

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Secondary prevention after cerebral ischaemia of presumed arterial origin: is aspirin still the touchstone?

In a recent editorial, Algra *et al* summarise the current state of knowledge of drug treatment in secondary prevention after ischaemic stroke or transient ischaemic attack (TIA).¹ After a review of aspirin, ticlopidine, clopidogrel, and anticoagulation with warfarin, and a critical discussion of recent relevant clinical trials, they speculate that antagonists of the platelet fibrinogen receptor, glycoprotein IIb/IIIa, may also have a preventive role in cerebrovascular disease in the near future and they indicate that clinical trials are planned. Unfortunately, the authors fail to mention the promise of β -hydroxy- β -methylglutaryl (HMG) coen-

zyme A reductase inhibitors (statins) in preventing stroke and TIA in patients with established vascular disease. These are a novel group of compounds which lower serum cholesterol, and which have been shown to lower mortality in large randomised controlled clinical trials in secondary prevention in patients with known vascular disease, both with and without hypercholesterolaemia, and in primary prevention in those with hypercholesterolaemia without clinical vascular disease.^{2,3} In addition, these trials have demonstrated that statins reduce the risk of stroke by about 30% in patients with coronary artery disease.^{4,5} As well as reducing serum cholesterol, statins have been shown in various models to have a broad range of beneficial effects on vascular pathophysiology, including plaque stabilisation, and direct vasodilatory, antithrombotic, and antiplatelet effects.^{5,6} Some of these drugs are currently being tested in clinical trials in patients with a history of minor stroke or TIA. As statins do not exert their beneficial effects primarily through antiplatelet mechanisms, the possibility that a statin combined with aspirin (or clopidogrel or both) could provide additive therapeutic effects is exciting and needs to be tested in patients with or at risk of cerebrovascular disease. As usual the neurological community lags behind their cardiology colleagues in managing their cerebrovascular share of the systemic disease of the endothelium known as atherosclerosis.

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The authors reply:

Speculation about the results of ongoing trials was not really the purpose of our review, but we agree we might have included the use of statins in patients with cerebrovascular disease. We note that Delanty has a poor opinion of the neurovascular research community. We shall have to live with it.

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Prospective, population based studies of cavernous malformations are needed

In their welcome systematic review of supratentorial cavernous malformations and epilepsy, Moran *et al*¹ illustrate the pitfalls of regarding the prognosis of a disease in selected case series as representative of its natural history.² Studies of cavernous malformation prognosis have usually lacked clear inception cohorts with respect to mode of presentation and treatment. Referral filter bias has so often restricted ascertainment by tertiary referral centres, and further selection bias has made the prognosis seem worse than it really is, as demonstrated by the authors' own series of 33 patients in which temporal lobe lesion location and intractable seizures predominated. Conversely, by leaving community mortality unaccounted for, the prognosis can seem better than it actually is. Completeness of follow up has been variable and not always prospective. Furthermore, authors have varied in their choice of outcome, in particular their definition of haemorrhage (clinical or radiological), choice of period at risk (from birth, time of diagnosis, or start of observation) and calculation of outcomes for each patient or for each lesion. Any analyses of such heterogeneous case series should be ruthlessly systematic, but even so it is necessary to be wary about drawing firm conclusions from them.³

The only existing population based study of cavernous malformations,⁴ albeit with a denominator of merely 50 000, was retrospective. The study spanned fundamental developments in the non-invasive diagnosis of cavernous malformations during the 1980s with magnetic resonance imaging,⁵ which led to increasing detection rates with time.

There is, therefore, clearly a need for a large, population based, prospective, contemporary epidemiological survey of cavernous malformations to establish their frequency and prognosis. With a broad collaborative network, including the three other neuroscience centres in Scotland, the Scottish Intracranial Vascular Malformation Study (SIVMS) has been set up (<http://www.dcn.ed.ac.uk/ivm/>) to do just this for all types of intracranial vascular malformation (IVM). Using multiple, overlapping sources of case ascertainment we are building an inception cohort of all incident cases of any type of IVM diagnosed after 1 January 1999 in the population of Scotland (5.1 million). With prolonged follow up of this cohort we hope to settle some of the uncertainties highlighted by Moran *et al*.¹ Moreover we agree that, with such poor data available, a randomised controlled trial of surgical versus conservative treatment for cavernous malformations is overdue.

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Neurological stamp: Adam Politzer (1835-1920)

Recently, I found an interesting manuscript in your journal about Adam Politzer under the section on neurological stamps. I was mildly disappointed by the presence of some inaccuracies concerning the biography of Adam Politzer, and write to you to correct these imprecisions.

Adam Politzer published in 1878 the first volume of his textbook of otology under the original German title *Lehrbuch der Ohrenheilkunde für praktische Ärzte und Studierende*. The second volume was published in 1882 to complete his work.¹ Since the second edition, this textbook of otology was printed in one volume.

The finding that ossicles vibrate to sound stimuli was not made by Politzer but by Hermann von Helmholtz with his resonance theory published in 1863 completed by the mechanism of ossicles and tympanic membrane in 1868.² Politzer was one of his students in 1861 in Heidelberg.

Adam Politzer invented, notably, a revolutionary method to make the eustachian tube permeable in 1863,³ a method which made him famous and carries his name. He also developed an acoumeter in 1877⁴ to measure hearing, replacing the watch, which was used until this date.

In 1864 Politzer founded with Anton von Tröltzsch and Hermann Schwartz the first German and international journal of otology under the original title *Archiv für Ohrenheilkunde*.⁵ In 1879 *The American Journal of Otology*⁶ was founded and edited by Clarence J Blake and was printed for only 4 years at this time.

In addition to more than 100 publications in medical journals, and besides his textbook of otology, Adam Politzer published three other books, all translated into English. As well as one book about anatomical and histological dissection of the human ear⁷ and one about the history of otology.⁸ Politzer published an atlas of the tympanic membrane in 1865,⁹ completed and reprinted in 1896.¹⁰

Politzer was certainly the greatest otologist of the 19th century and probably one of the greatest of all time. His influence during 50 years of otology has never been equalled.

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BOOK REVIEWS

Mononeuropathies: Examination, Diagnosis and Treatment by A STAAL, J VAN GIJN, and F SPAANS (pp 243, £35.00). Published by W B Saunders, London, 1999.

The authors say that they wrote this book from a frustration at having to look at several different sources to solve a single clinical problem.

The introductory chapters contain sound clinical advice on a general approach to patients with mononeuropathy. Then each nerve is dealt with in turn using the same format: anatomy; history; examination—including the method of examination of the relevant muscles and the area of sensory loss—electrophysiological findings; differential diagnosis; causes, often tabulated; and finally treatment. The line drawings of the anatomy are clear, highlighting sites of compression. The line drawings of power testing are less satisfactory. The movement to be tested is well illustrated but the site of the muscle being tested (and hopefully observed) is not shown and for some muscles lies outside the illustration. This is followed by some chapters discussing causes of peripheral nerve injury other than focal lesions, including metabolic and physical factors and tumours. The description of the clinical syndromes is clear and succinct and well referenced throughout. The advice on treatment is sensible with a strong emphasis towards conservative management with clear statements as to when more rapid intervention is needed.

The text is interspersed with illustrative cases which appear in boxes. I thought this worked well, although was surprised to find eight doctors (including a Professor of Neurology with a partial musculocutaneous nerve lesion, and a Dean of the Faculty of Medicine with neuralgic amyotrophy), among the 40 or so cases.

While for mononeuropathies the book manages to act as a single point of reference it does not do this for some similar clinical problems whose presentations may be similar. It only briefly touches on radiculopathies as they appear in the differential diagnosis of mononeuropathies and skirts round some contentious issues such as the thoracic outlet syndrome. The anatomy of the brachial plexus (something I always have to look up) is not reproduced.

Overall I think the authors have succeeded in their objectives and there is indeed justification for this book. The book is moderately priced at less than half the price of the combined costs two of the books they aim to replace.

I would suggest that most neurology units should get a copy. I would urge you to persuade your orthopaedic colleagues to get one too.

GN FULLER

Cell Transplantation for Neurological Disorders. Edited by THOMAS B FREEMAN and HAKAN WIDNER. (Pp 350, US\$125). Published by Humana Press, New Jersey. ISBN 0-896-03449-6.

This book deals, in general, with issues pertinent to the clinical application of cell transplantation approaches, and has been written by many eminent members of both the American and European transplant communities, the editors also being well respected figures in this field. It covers neuronal cell transplantation therapies in its many forms, and although almost half relates to primary human foetal tissue transplants in Parkinson's and Huntington's disease, this does in fact reflect the balance of effort over the past decade and a half. Of particular value are the summaries of data emerging from ongoing clinical trials of transplantation in both conditions, as much of this data are to be found in the literature in a rather piecemeal fashion. Prospects for transplantation in other neurological conditions are also discussed, in particular multiple sclerosis and stroke. Alternative donor tissue to human foetal cells is discussed largely with reference to the use of xenogeneic cells, both transplanted directly and also transplanted in their encapsulated form after genetic modification, the latter having already being piloted clinically, particularly for use in chronic pain syndromes. The potential of using cell lines is mentioned in passing, but stem cell therapies (namely neuronal and embryonic stem cells) are not explicitly discussed, which is perhaps something of a hole given the likely reliance of transplantation therapy long term on the development of alternative sources of donor tissue. The book ends with a single chapter on the ethics of using human foetal tissue. This has been written very much from an American perspective and as this is such a central issue for much of the ongoing work, a more balanced account would have been use-

ful. However, that having been said, this is a clear and readable account. It is suitable as an introduction to various aspects of neural cell therapies, and is an essential handbook for anyone working in the field.

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Genetics of Focal Epilepsies. Edited by S F BERKOVIC, P GENTON, E HIRSCH, and F PICARD. (Pp 286, £59.00). Published by John Libbey and Co, London, 1999. ISBN 0 86196 569 8.

Are we on the verge of molecular Armageddon, to be ravaged by the onslaught of giant, genetically modified, giant tomatoes? Are we entering a molecular Utopia, where all the world's ills will be solved with a golden key to a nucleotide code or at the gateway of a eugenic nightmare? As far as epilepsy is concerned, a central message of this book is that clinical heterogeneity is the rule—the genes are only part of the story. Those of us with a deep suspicion (acquired not innate) of genetic models of life the universe and everything, can breathe a sigh of relief.

There are substantial methodological problems in genetic studies of epilepsy. It is a paroxysmal disorder, with age dependent expression, no diagnostic test, and frequent misdiagnosis. A tribute to workers in the field is that progress has been made despite these difficulties. Several early chapters consider benign childhood epilepsy with centrotemporal spikes. The characteristic EEG disturbance of this condition is probably inherited in autosomal dominant fashion, but only about 10% of siblings have epilepsy and they may have many different clinical varieties of epilepsy. Indeed there seems to be an association between this benign partial epilepsy and idiopathic generalised epilepsy, blurring the classic divisions of epilepsy classification.

Autosomal dominant nocturnal frontal lobe epilepsy is genetically and clinically relatively well defined and is sometimes due to

mutations of the nicotinic acetyl choline receptor. Even here the clinical expression of the same mutation may vary from a self limiting period of seizures to refractory nocturnal epilepsy with dozens of seizures each night. Other genetic epilepsy syndromes have been described recently; familial temporal lobe epilepsy and epilepsy with variable foci.

MRI has allowed the in vivo classification of subtle cortical dysplasias as well as more gross disorders such as tuberose sclerosis, whose genetic bases are becoming clear. Subcortical band heterotopia or periventricular nodular heterotopia, are seen only in females and have been shown to be X linked and fatal in males.

How do genetic abnormalities produce epilepsy and what is the cause of the clinical heterogeneity? Here there are only questions. Abnormalities of regulatory homeobox genes may reproduce some aspects of cortical dysplasia and have been identified in humans too. The nicotinic acetylcholine receptor may be involved in development, cortical excitation, or the regulation of the thalamocortical sleep wake cycle—but all is speculation at this stage. Animal models may demonstrate changes in anatomy and chemistry and transgenic animal models may be valuable in exploring pathophysiology. Genetics is providing a gateway to pathophysiology but the clinical heterogeneity even in the most genetically uniform disorders suggests that these processes will not easily be revealed by simply understanding the genes. The relevance of the rarer genetic syndromes to commoner forms of epilepsy remains to be established. Targets for novel therapies are still a long way off.

This book provides a clear account of many genetically determined, focal epilepsies, a balanced view of their genetic components, and clinical and scientific methods for their future exploration. It will be of interest primarily to epilepsy specialists and geneticists.

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