LETTERS TO THE EDITOR

Volitional and stimulation induced neuromyotonic discharges: unusual electrophysiological pattern in acquired neuromyotonia

Neuromyotonic discharges are electrophysiologically characterised as bursts of motor unit potentials firing at more than 150 Hz for 0.5 to 2 seconds. The amplitude of the response typically wanes. Discharges may occur spontaneously or be initiated by needle movement. Walsh described a case of a mediastinal tumour and neuromyotonia with very high frequency discharges that outlasted voluntary effort. We report a case of an acquired paranodamic neuromyotonia associated with thymoma, clinically manifested myotonia-like muscle stiffness, and an unusual electrophysiological pattern of neuromyotonic discharges that were evoked voluntarily or with electrical stimulation but were absent spontaneously and were not elicited by needle displacement. A 71-year-old woman presented with a 6-month history of muscle stiffness, paraesthesia provoked mostly by movement, disturbed speech, and difficulty walking. At the time of examination she could not walk independently. Clinical examination disclosed pronounced dysarthria and ataxic-like limb movement. Voluntary activation or after nerve stimulation could not interrupt the ability of shocks delivered distally to the site of the block to evoke neuromyotonic discharges.

The repetitive motor nerve stimulation study of ulnar and axillary nerves performed at a stimulation frequency of 2 Hz showed no decrement. The stimulation single fibre EMG from the extensor digitorum communis muscle on the right side showed a slightly abnormal jitter (19 recordings, mean jitter 34 μs, five recordings above 40 μs), which together with a slight incerase in fibre density (2.3) indicated the reinnervation process.

Second EMG and conduction studies performed 7 days after the end of the second IVIG treatment showed less frequent neuromyotonic discharges evoked by electrical stimulation of the motor nerves and the voluntary contraction and the ability to evoke them waned; after several contractions they disappeared. Torbergsen et al stated that, in addition to spontaneous occurrence, neuromyotonic discharges could also be registered during voluntary activation or after nerve stimulation; it was assumed that such a type of electrophysiological abnormality is caused by the slightest degree of hyperexcitability of axons when neuromyotonic discharges are triggered after a preceding impulse, simply voluntary or electrical, has passed, whereas spontaneous neuromyotonic discharges without an obvious trigger are generated in the case of more increased hyperexcitability of axons. Clinically, as well as muscle stiffness, ataxial-like voluntary movement was present in our patient; this movement was interrupted repeatedly, probably due to repeated bursts of neuromyotonic discharges. Moreover, the movement provoked corresponding sensory phenomena of dysesthesias and parasthesias. It seems likely that these sensory phenomena of dysesthesias and paraesthesias were evoked by similar types of sensory

Spa record


1 mV
Foot switch status: Hold / Run Trig: −100 μV↑

50 ms

Needle EMG from abductor pollicis brevis muscle showing high frequency (about 200 Hz) neuromyotonic discharge with waning amplitude and duration of 250 ms, provoked by voluntary contraction (arrows):
Correspondence to: J Bednarík

245 C

nucleotides 94 and 124 in exon 3. We investigated the association of Parkinson's disease, pesticide exposure, and these GSTZ1 polymorphisms. DNA was extracted from blood samples collected from patients with Parkinson's disease and matched controls as described previously. This study was approved by the Princess Alexandra Hospital ethics committee. Polymorphisms at nucleotide 94 and 124 were detected by polymerase chain reaction/RFLP analysis as described previously. To detect the nucleotide 245 polymorphism, PCR was performed with the following primers: 5′AAGAGGTGATGAGATGGTGCCCTG 3′ and 5′YAGTGCAAGTTACCAAGTGGCC3′. The PCR was carried out in a 20 µl reaction volume containing reaction buffer IV (Advanced Biotechnologies, Epsom UK), 20 mM (NH4)2SO4, 75 mM Tris/HCl pH 9.0, 0.01% Tween 20, dNTPs (0.2 mM), MgCl2, (1.5 mM), primers (0.3 µM each), thermostable DNA polymerase (Advanced Biotechnologies, 0.5 U), and DNA (25 ng). No DNA was added to control reactions. Thermal cycling was carried out using a Corbett capillary thermal cycler under the following conditions: initial denaturation at 94°C for 2 minutes; subsequently 35 cycles of 94°C for 20 seconds, 60°C for 20 seconds, 72°C for 30 seconds; and a final extension of 72°C for 2 minutes. Products of PCR were digested overnight with restriction enzyme BsaI 1236I (MBI fermentas) at 37°C and fragments were separated by 8% polyacrylamide gel electrophoresis and stained with ethidium bromide. The restriction enzyme BsaI 1236I cleaves the C245 fragment generating 12, 108, and 142 bp fragments and the T245 fragment generating 108 and 154 bp fragments.

We tested 307 Parkinson's disease and 105 control samples. The population samples were in Hardy-Weinberg equilibrium. There were no associations between the nucleotide 245, 94, or 124 polymorphisms and Parkinson's disease (table). A total of 87 patients and 53 controls reported a history of regular pesticide exposure. In this group there was a weak association between the nucleotide 245 genotype and Parkinson's disease (p=0.05) (table). Furthermore, in this group, the ZI*C genotype (G124C/T245) was less common in the patients with Parkinson's disease than in the controls (30%). In a logistic regression analysis, the 95% confidence interval (95%CI) 0.36–0.95, p=0.03, not corrected for multiple comparisons).

There was no overall association between the GSTZ1 polymorphisms and Parkinson's disease. However, we found a difference when only those who reported pesticide exposure were analysed. We also combined the data for the three polymorphic sites to determine the frequency of the four GSTZ1 alleles. The ZI*C allele is the most common variant in white control populations.

We found that this allele was less common in patients with Parkinson's disease than controls when stratified for pesticide exposure.

Studies of this nature have limitations related to selection bias, case ascertainment, recall bias, difficulty in assessing extent of exposure, and multiple comparisons. Accordingly, our conclusion that there is a potential association between GSTZ1, pesticide exposure, and Parkinson's disease must be considered preliminary. Nevertheless, it is interesting that there have now been several reports suggesting an association between the risk of Parkinson's disease, polymorphic variation in detoxification and cholinergic responses to environmental toxins. These include CYP2D6 and solvent exposure, GSTTP and pesticide exposure and CYP2P6, pesticide exposure with Parkinson's disease. Thus, it has been recognised that studies examining the association of polymorphic variation in xenobiotic metabolism genes and Parkinson's disease should take into account the effect of exposure to toxins.

This study was funded by the National Health and Medical Research Council of Australia and the Geriatric Medical Foundation of Queensland.

Correspondence to: Professor P G Board

Zeta class glutathione transferase polymorphisms and Parkinson's disease

Glutathione transferase genes (GST) are candidate genes for Parkinson's disease because they are involved with the metabolism of pesticides, dopamine, and glutathione. Recent reports have suggested an association between Parkinson's disease and polymorphisms of GSTP1 or GSTM1 and GSTT1. Recently we discovered a new polymorphic site in the zeta class G–T (GSTZ1). This consists of a G6T transition at nucleotide 245 in exon 5 that results in an amino acid change at position 82 from methionine to threonine. The T substitution occurs in 14% of white people. We have previously reported two other polymorphic sites at nucleotides 94 and 124 in exon 3. There are now thought to be four alleles of GSTZ1: Z1*A (A94G, C124), Z1*B (A94G, C124T), Z1*C (G94C, T124) and Z1*D (G94T, T124).

Association between the frequency of GSTZ1 polymorphisms and Parkinson's disease

<table>
<thead>
<tr>
<th>Polymorphism</th>
<th>Controls (n=105)</th>
<th>Patients (n=307)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TT</td>
<td>CT</td>
</tr>
<tr>
<td>245 C→T</td>
<td>0.04</td>
<td>0.33</td>
</tr>
<tr>
<td>*245 C→T</td>
<td>0.04</td>
<td>0.25</td>
</tr>
<tr>
<td>94G→A</td>
<td>0.08</td>
<td>0.40</td>
</tr>
<tr>
<td>124G→A</td>
<td>0.01</td>
<td>0.12</td>
</tr>
</tbody>
</table>

*Analysis restricted to subjects with a history of regular pesticide exposure (p<0.05).

A case of stiff limb syndrome responsive to plasma exchange

Stiff limb syndrome is a recently described, rare condition that is characterised by rigidity within the limbs that progresses in a relapsing and remitting fashion, often with involvement of the sphincters and brain stem. The axial muscles are spared in the early stages of the illness, which helps distinguish it from stiff man syndrome, although it may still represent a similar pathogenic mechanism to that
proposed in stiff man syndrome, in which anti-GAD antibodies are typically seen in about 60% of patients. However, patients with stiff limb syndrome seem to have different neuropathological abnormalities from stiff man syndrome and fewer of these patients have anti-GAD antibodies; they also typically show a poorly sustained response to baclofen and diazepam. The response to immunotherapy in stiff limb syndrome is not known, whereas patients with stiff man syndrome may respond to intravenous immunoglobulin as well as possibly plasma exchange. We now report on a patient with stiff limb syndrome who responded dramatically to plasma exchange and in whom an antibody was isolated, suggesting that this condition may have an immunological basis.

A 50 year old retired auxiliary nurse presented with a 10 year history of progressive pain, stiffness, and flexion contractures in her hands, followed by increased immobility. Her neurological problems began at 24 years of age when she developed viral meningitis based on a headache, fever, and a CSF lymphocytosis; resolved after a week. At the age of 28 she complained of back and leg pain with urinary retention but displayed no abnormal neurological signs and had a myelogram that was normal. Her leg symptoms resolved but she continued to complain of urinary retention and frequency, for which no cause was found. She went on to have a urethrotomy which did not relieve her symptoms. At the age of 40 she started to develop stiffness in the hands, which slowly clawed, after which her arms and neck became progressively stiffer and her trunk became increasingly stooled on walking, with additional difficulty raising her arms above her head. Five years after the onset of her symptoms she was incapacitated, required assistance with all activities of daily living, and was permanently catheterised. At this stage a seronegative polyarthritis was diagnosed and she was treated with hydroxychloroquine, prothiaden, and corticosteroids, all without effect. She subsequently had some spontaneous remission but at the time of her referral could only walk 10 yards with one stick and continued to complain of heaviness, pain, and stiffness in the limbs especially the left arm. In addition she had developed an intermittent tremor of the right arm and leg which sometimes affected her jaw and she had difficulty swallowing large boluses of food.

Examination at this time showed her to have flexion contractures of all fingers. She had irregular jerking movements of her right arm and leg that were accentuated by moving her shoulder. She had irregular jerking movements of the right arm and leg that were accentuated by moving the limb or walking a few steps. She had difficulty standing up from a chair without assistance and although she was not weak on strength testing, all limb movements were accompanied by pain. No reflex or sensory abnormalities were found and her plantar responses were flexor.

Investigations showed normal nerve conduction studies as well as a normal CSF examination including negative oligoclonal bands; brain and spine MRI, and routine haematological and biochemical tests were also normal. Her autoantibody screen was negative as were her anti-GAD and anti-neuronal antibodies although an anti-axonal antibody was detected in her serum which is currently being further characterised. More extensive neurophysiological testing showed her to have an abnormal hypersegmented EMG pattern during muscle spasms although no continuous motor unit activity was recorded at rest. The latency of responses to magnetic stimulation of the motor cortex was normal.

The diagnosis of stiff limb syndrome was made and she was initially treated with diazepam and baclofen, but continued to deteriorate and gradually lost all useful function of her arms. There was a similar lack of response to intravenous methylprednisolone, so she was given intravenous immunoglobulin, to which she reacted promptly and an anaphylactic reaction. Her disorder progressed and she developed prominent rigidity and spasms of the face, trunk, and limbs. Her speech developed a slurred quality and she had episodes of involuntary tachypnoea apparently due to spasms of respiratory muscles. She was bed bound and totally dependent for all activities of daily living, needing constant nursing. As a result it was decided to give her empirical treatment with two courses of plasma exchange in November and December 1996. After the first exchange, the spasms of her facial and respiratory muscles ceased and after the second there was a slow sustained improvement in limb power, so that after 6 months she had regained independence. For the next 18 months she walked and lived normally, even travelling on holiday. This improvement was punctuated by two admissions with chest infections and impaired respiratory function, which responded well to antibiotics.

Unfortunately the stiffness and tremor of her limbs returned in June 1998 and by November of that year, she was once again immobilised and dependent such that she could barely wash herself and was unable to walk at all. Any attempt to move her limbs caused disabling tremor and stiffness. Again, reflexes and plantars were normal. She had a further course of plasma exchange and again responded slowly, such that 3 months later she was able to walk on two sticks. This improvement was initially sustained although she has required a further course of plasma exchange in February 2000 and has now been started on oral cyclophosphamide with notable benefit. The patient has not had further neurophysiological investigations.

This case has all the features of stiff limb syndrome with the novel finding of antiaxonal antibodies dominating her serum. The patient failed to respond to baclofen and diazepam and could not tolerate intravenous immunoglobulin but did have a dramatic and sustained response to plasma exchange, although the need for repeated courses of this treatment has led to her being started on cyclophosphamide. This has not been reported before for this condition and whereas this case illustrates the possible therapeutic effect of this intervention it also raises the possibility that stiff limb syndrome may have an immunological basis.

We thank John Pilling for permission to present his case, Peter Brown for performing the detailed neurophysiological testing on this patient, and Angela Vincent for the serological testing and detection of the antiaxonal antibody.

A COLES
Department of Neurology, Norfolk and Norwich Health Authority, Health Park, Norwich, Norfolk NR1 3SR, UK

A COLES
R BARKER
Department of Neurology, Addenbrooke’s, NHS Trust, Hills Road, Cambridge CB2 2PY, UK

Correspondence to: Dr R Barker, Cambridge Centre for Brain Repair, Portiey Site, Robinson Way, Cambridge CB2 2PY, UK


Acute autonomic and sensory neuropathy after interferon α-2b therapy for chronic hepatitis C

Acute autonomic and sensory neuropathy (AASN) is a disorder characterised by acute autonomic and sensory nerve dysfunctions, and well preserved motor nerve function. Although the pathomechanism of AASN is not clear, autonomic and sensory ganglion neuron cell bodies may be the main target of the immune mediated process underlying AASN. On the other hand, patients treated with interferon may develop neurological complications including neuropathy. We report the first case of AASN which can be associated with interferon α-2b therapy for chronic hepatitis C.

A 57 year old Japanese man with chronic hepatitis C had been treated with interferon α-2b since June 1998. On 3 September, a skin eruption abruptly emerged on his chest and rapidly spread over his whole body. There was no history of exposure to toxins and drugs other than the interferon. The interferon therapy was stopped on 7 September; after a total dose of 390 000 000 units. The skin eruption gradually resolved, but 1 week later, numbness appeared in his limbs. Subsequently he became unable to walk and stand. Further, he developed urinary overflow incontinence and bowel distension. He was then transferred to our neurological department on 2 October.

Physical examination disclosed orthostatic hypotension without secondary tachycardia (120/60 mm Hg lying, 85/52 mm Hg sitting, fixed pulse rate 60 bpm) and paralytic ileus. He was catheterised for incontinence. He was drowsy. The pupils were anisocoric although they reacted promptly to light. Other cranial nerves were unremarkable. Muscle strength and bulk were normal. Deep tendon reflexes were generally absent. There were no pathological reflexes. Light touch, pain, and temperature sensations were impaired moderately over the trunk, more so in his limbs. Vibratory and joint sensations were impaired severely in the same distribution, and lost in...
Pathological findings in the sural nerve. (A) Histologically, most of the myelinated fibres show formation of myelin ovoids indicating active axonal degeneration, which is also present in the teased fibre preparations (B). (C) The unmyelinated fibres are also affected showing swelling of the axons (arrows). ((A) epon embedded section stained with toluidine blue; bar=20 µm; (B) teased fibre, bar=100 µm; (C) electron micrograph; bar=2 µm).
damage to the autonomic and sensory ganglion neurons leading to clinical manifestation of AASN.

T IRIOKA M YAMADA M YAMAWAKI Y SAITO H MIZUSAWA
Department of Neurology and Neurological Science, Graduate School of Medicine, Tokyo Medical and Dental U niversity, 1–5–45 Yushima Bunkyo-ku, Tokyo 113–8519, Japan
M YAMADA Department of Neurology, Kanazawa University School of Medicine, Japan
H MIURA Department of Internal Medicine, Social Insurance Chuo General Hospital, Japan

Correspondence to: Dr T Irioka
irioka@tc4.so-net.ne.jp

Radical hysterectomy. During extirpative visceral surgery such as pelvic and pudendal nerve injury can occur. Pelvic and pudendal nerve injury can occur during extirpative visceral surgery such as pelvic surgery. Neuropathic pain with vesical and rectal ganglion neurons leading to clinical manifestation of AASN. Many of these patients develop severe chronic pelvic pain and bladder symptoms, and are often referred to neurologists with suspicion of lumbosacral plexus lesions or disc disease. There are few or no signs on examination, and patients are often considered to be “hysterical”, despite having severe symptoms. Here, we describe two patients in whom severe pelvic pain and bladder dysfunction developed after hysterectomy, and who demonstrated detrusor and rectal hyperreflexia with cocontractions, features usually associated with lesions of the CNS. Whereas spinal cord sensitisation is well recognised after somatic nerve injury, our studies provide the first clear evidence for its development after visceral nerve injury in humans, and a method for its detection using ambulatory urorectodynamics.

Patient 1, a 42 year old woman, was diagnosed as having carcinoma of the cervix 5 years previously and underwent Wertheim’s hysterectomy, followed by chemotherapy and pelvic irradiation. She developed severe persistent vaginal pain and hypersensitivity, which prevented her from having sexual intercourse, and subsequently bladder dysfunctions, which required intermittent self-catheterisation. She received several analgesic drugs without benefit. Neurological and urodynamic study (after prior written informed consent) showed urethral instability, unstable vesical contractions with simultaneous abnormal rectal contractions, and falls in anal pressure.

These patients had severe symptoms but no clinical signs, and abnormalities were detected only after pudendal nerve conduction and urorectodynamic studies, which disclosed visceral hyperreflexia in both cases. Patient 1 probably had injury to the pelvic nerves, which is well recognised after extensive hysterectomy. Patient 2 had pudendal nerve damage, supported by the nerve conduction study. Our patients did not have neurological signs suggestive of CNS lesions, but demonstrated features usually associated with such lesions, namely detrusor and rectal hyperreflexia. Visceral hyperreflexia can occur after spinal cord lesions and in the absence of obvious neurogenic lesions but its occurrence after peripheral nerve damage is not well recognised. The likely explanation for visceral hyperreflexia in our patients is increased barrage originating from injured sensory nerves, leading to spinal cord sensitisation; this mechanism is well established after somatic peripheral nerve injury, but rarely considered after pelvic surgery. Persistent visceral noxious input to the spinal cord could lead to reflex activation of the intermediolateral cell column, the increased output of which may in turn increase bladder and rectal contractions. Other relevant evidence of spinal cord disinhibition in our patients is the loss of the normal inhibition...
Peripheral nerve ischaemia after internal iliac artery ligation

Ligation of the internal iliac (hypogastric) arteries has been used to control serious obstetric and pelvic bleeding. It is generally well tolerated in the young obstetric or gynaecological patient, presumably because of an extensive collateral blood supply.13 Acute limb ischaemic complications have been described, however, in older patients with vascular disease when the internal iliac arteries are interrupted.14,15 We report on a teenage patient with similar peripheral nerve ischaemia after bilateral internal iliac artery ligation for postpartum haemorrhage.

An 18 year old woman presented at 40 weeks gestation with mildly raised blood pressures, trace proteinuria, oliguria, and generalised oedema. She was diagnosed with pre-eclampsia and admitted for induction. When induction was unsuccessful, she underwent a caesarean section, which was complicated by uterine atony and a postpartum haemorrhage with an estimated blood loss of 2500 ml. After bilateral uterine artery ligation failed to control the bleeding, bilateral internal iliac artery ligation was performed with resultant haemostasis.

On the first postoperative day, she complained of left buttock pain and difficulty moving her left leg. Area of skin breakdown over the sacrum and buttocks was noted on the second postoperative day. She developed a fever and fundal tenderness on day 4. Helical CT of the abdomen and pelvis disclosed residual gas and fluid within the endometrial canal consistent with endometritis, which was treated with intravenous antibiotics. No retroperitoneal haematoma was present. Neurological evaluation on the fifth postoperative day noted pain, but disclosed normal strength, sensation, and reflexes in the arms and the right leg. Strength in the left leg was 2 to 3/5 on hip flexion and knee extension and 3 to 4/5 on ankle plantarflexion, ankle dorsiflexion, and toe extension. Sensation was diminished to all modalities in the entire left leg below the hip. The left patellar and ankle stretch reflexes were absent.

Magnetic resonance imaging of the thora-columbar spinal cord was unremarkable. An initial magnetic resonance angiogram (MRA) of the pelvis showed segmental occlusions of both internal iliac arteries with distal reconstitutions. The stenotic lesions were larger on the left. The left superior gluteal artery was not visualised. Revascularisation was considered but deferred due to the concomitant active pelvic infection. Peripheral pulses remained strong, and Doppler ultrasound of the lower extremities showed no evidence of distal thrombus.

Nerve conduction studies 1 week after ligation were extremely limited and difficult to interpret due to generalised oedema. Sural and peroneal sensory responses were absent bilaterally. Right peroneal and left tibial motor responses were normal. A small left peroneal motor response was present in the anterior tibialis muscle. Electromyography was not performed at that time. The fevers and endometritis gradually cleared, and over the next month left leg strength improved slowly, but incompletely, with greater proximal (4–5 in hip flexion and knee extension) and distal (3–4 in ankle plantarflexion, 0 in ankle dorsiflexion) recovery. The left leg continued to have diminished sensation to all modalities and remained areflexic. The superficial skin sensory loss progressed to an open non-healing ulcer 7 cm×5 cm over the sacrum and left gluteal musculature. Magnetic resonance imaging of the region disclosed additional tissue necrosis subcutaneously along the left posterolateral buttck and inflammation in the surrounding subcutaneous tissues and underlying gluteal musculature with extension into the left sacroiliac joint. There was no evidence of rectal, uterine, or bladder ischaemia.

A follow up MRA of the pelvis 6 weeks after ligation demonstrated persistent segmental occlusion of both internal iliac arteries and left external iliac artery on the left compared with the right. Again, the superior gluteal artery was not visualised on the left but appeared to fill on the right.

Electromyography of selected muscles of the left leg at 4 months (after ligation) showed 2+ to 4+ fibrillations and positive sharp waves in the vastus lateralis, tibialis anterior, and lateral gastrocnemius muscles, consistent with chronic denervation. There were no voluntary units in the tibialis anterior and low firing rates in the gastrocnemius. Low amplitude polyphasic motor units in vastus lateralis suggested early proximal recovery. Nerve conduction studies showed diminished left sural sensory amplitudes and slowed velocities (2.8 mV, 36.0 m/s). The left peroneal motor responses were attenuated, and the left posterior tibial motor velocities were slowed (32.0 m/s). The right sural sensory (13.2 µV, 42.0 m/s) and peroneal motor (2.3 mV, 46.0 m/s) responses were normal.

In general, the internal iliac artery divides into an anterior and a posterior division. The anterior division is formed by the inferior gluteal artery and its branches, which supply the pelvic viscera, the lower buttocks, and the sciatic nerve roots.7 Ligation of the internal iliac arteries has been accepted as a safe and effective means of controlling serious haemorrhaging from the uterus or lower pelvis after delivery or after gynaecological surgery.13,14 The lack of ischaemic complications from ligation of the internal iliac artery is thought to be due to the multiple sources of collateral blood flow present in the pelvis.

There are, however, reports of buttock ischaemia or lumbarосascular plexopathies as a complication of interruption of the internal iliac arteries during aortic bypass procedures or aortoiliac aneurysm resection.7,8 In a study of 11 patients (mean age 67, range 37 to 87) with aortoiliac occlusive disease or aortoiliac aneurysmal disease, seven developed ischaemic injury to the lumbarосascular plexus after bilateral internal iliac artery ligation.9 In four of those patients, buttock necrosis with extension to the bony pelvis was also seen. In another report, four women (mean age 57, range 33 to 47) with insulin dependent diabetes and end stage renal disease developed ipsilateral lumbarосascular plexopathies when the internal iliac artery was ligated during kidney transplantation.10 Electromyography showed denervation of the tibialis anterior, gastrocnemius, and vastus medialis muscles in one patient and anterior sacroiliac and gastrocnemius in another. Ischaemia of the sciatic and femoral nerves and buttocks also occurred after internal iliac artery embolisation in patients with terminal pelvic malignancies who received radiotherapy.11

Our 18 year old patient developed a combination of leg weakness, leg numbness, and buttock necrosis after internal iliac artery ligation, as described in older vasculopathic patients. In the patients described in the literature, as in our patient, the clinical and electromyographic findings do not distinguish between combined tibial and sciatic nerve lesions, a lumbarосvascular plexopathy, or a combination of the two. Our patient’s presentation, however, can be most succinctly explained by an infarction in the territory of the left superior gluteal and its branches, resulting in ischaemia to the gluteal musculature, the femoral nerve proper, and the sciatic nerve roots. This localisation is supported by serial MR angiography of the pelvis in which the left superior gluteal artery and its branches were not visualised.

It has been shown that, in experimental ligations of the internal iliac artery in rats, moderate ischaemia is associated with delayed...
Diffusion weighted magnetic resonance imaging in Neuro-Behçet’s disease

Neurological involvement is one of the most devastating manifestations of Behçet’s disease. However, the pathogenic mechanism for CNS lesions in patients with neuro-Behçet’s disease is unclear. Although vasculitis is usually considered to be the central pathological feature in Behçet’s disease, a vasculitic process was not usually demonstrated in the CNS.

Diffusion weighted imaging can detect changes in water diffusion associated with cellular dysfunction. It has been well documented that acute infarction related to cytotoxic oedema is characterised by a marked decrease in diffusion, and also that increased interstitial water related to vasogenic oedema shows increased diffusion. Conventional MRI cannot distinguish between these different types of oedema. We report on a patient with neuro-Behçet’s disease with a significantly reversible T2 signal and diffusion abnormalities in CNS lesions.

A 54 year old Asian man was admitted with dysarthria and left hemiparesis, which evolved over a period of 2 days and was associated with gradual mental deterioration. The patient had a history of frequent orogenital ulcers and acneiform nodules on his face. Physical examination showed active genital ulceration. Neurological examination disclosed drowsy consciousness and disorientation. Moderate degrees of hemiparesis and hemihypesthesia involving the face, arm, and leg were found on the left side. Deep tendon reflexes were increased and Babinski’s sign was extensor on the left side. Erythrocyte sedimentation rate (54 mm/h) and C-reactive protein concentration (3.4 mg/100 ml) were increased. Examination of CSF showed mild pleocytosis (18 white blood cells/mm³) with normal concentrations of protein and glucose. Fundus examination showed retinal vein occlusion and retinal haemorrhage on the right side. The diagnosis of Behçet’s disease was made based on the recurrent orogenital ulcerations, skin lesions, and eye involvement.

The patient was examined on a 1.5T MR unit (Signa Horizon, Echospeed; General Electric Medical Systems) with echoplanar imaging (EPI) capability. Fast spin echo, T2 weighted images (T2 weighted images; TR/TE 4200/112 ms; field of view 21×21 cm; matrix 256×192; and slice thickness 5 mm) were obtained. Diffusion weighted imaging was obtained in the transverse plane using a single shot EPI (TR/TE 6500/125 ms; field of view 24×24 cm; matrix 128×128; slice thickness 5 mm; and two b values 0 and 1000 s/mm³). The diffusion gradients were applied along the three axes (x, y, z) simultaneously. The apparent diffusion coefficient (ADC) was calculated based on the negative slope of the linear...
regression line best fitting the points for $b$ versus $a$ (SI); where $SI$ is the signal intensity from a region of interest within the images acquired at each $b$ value. Performing this calculation on a pixel by pixel basis created the ADC maps.

Brain MRI performed 3 days after symptom onset showed extensive T2 hyperintensities involving the corona radiata, internal capsule, basal ganglion, thalamus, and midbrain on the right side. Brain diffusion weighted imaging showed slight hyperintensities which were limited to the corona radiata, the medial portion of the basal ganglion, and the thalamus. Four sampled ADCs in the corresponding regions of T2 hyperintensity demonstrated increased diffusion (ranging from $1.17 \times 10^{-5}$ cm$^2$/s, compared with a matching location in the uninvolved contralateral hemisphere (ranging from 0.77 to 0.80$x10^{-5}$ cm$^2$/s, figure A and B). Magnetic resonance angiography showed no abnormalities. The patient improved rapidly after treatment with a high dose of corticosteroid. Within 2 weeks all previously noted neurological abnormalities had resolved except for a slight left hemiparesis. An MRI repeated at this time showed a partial decrease in the extent of the T2 hyperintensity. One year after he was readmitted with a slowly progressive bulbar weakness, frontal lobe dysfunction, urinary incontinence, and depressive mood changes. Follow-up MRI performed at this time, showed that the previous T2 abnormalities had improved, but the atrophy of the brain stem and basal ganglia became evident with periventricular high signal intensities. Four ADCs sampled in locations corresponding to those of the initially increased ADCs decreased to values which ranged from 0.98 to 1.07$x10^{-5}$ cm$^2$/s (figure C and D).

In our patient the ADC maps and ADC values showed high proton mobility, which suggests vasogenic oedema in acute lesions of neuro-Behçet’s disease. Vasogenic oedema develops when the blood-brain barrier is disrupted and is not primarily associated with cellular damage. Discrimination between cytotoxic and vasogenic oedema has important clinical implications because vasogenic oedema can be reversed by proper management.

According to the MRI findings for neuro-Behçet’s disease, the most prevalent abnormalities are located in the brain stem or the basal ganglia extending to the diencerebral structures during an acute attack, and brainstem atrophy in chronic cases.1 The reversibility of CT or MRI abnormalities of acute lesions in neuro-Behçet’s disease has also been documented and correlated with clinical improvement.2 The serial MRI findings in our patient were consistent with those described in previous reports. The precise pathomechanism of CNS lesions in Behçet’s disease has not been established. Studies of pathology showed that lymphocytic or neutrophilic meningoencephalitis with perivascular inflammatory cell cutting around venules and capillaries were predominant in the brain stem and basal ganglia in neuro-Behçet’s disease.3 However, most studies showed histopathological changes at a chronic stage of the disease and histopathological findings may show various lesions according to the age of lesion at the time of examination. A recent pathological report in a fulminating form of neuro-Behçet’s disease found no evidence of vasculitis but an acute destructive inflammatory process.1 It has been postulated that at an early stage of the disease, the reversibility of lesions may reflect a reversible breakdown in the blood-brain barrier rather than gliosis or infarction.1 The pattern of diffusion changes in the acute lesions in our patient strongly supports the idea that there is increased permeability in the blood-brain barrier as a result of the primary inflammatory process. We thank Byung Kee Yoo for his assistance with diffusion weighted MR data acquisition.

D-W KANG K CHU J-Y CHO J-S KOO B-W YOON J-R ROH
Department of Neurology, Seoul National University College of Medicine, 28 Yongon-dong, Chongnyu-gu, Seoul 110–744, Korea

IC SONG K H CHANG
Department of Radiology
Correspondence to: Dr J-K Roh, rohjk@snu.ac.kr


Aziathioine and interferon $\beta$-1b treatment in relapsing-remitting multiple sclerosis

Both interferon $\beta$-1b (IFN$\beta$-1b) and azathioprine (AZA) are effective in reducing relapse frequency in relapsing-remitting multiple sclerosis (RRMS).4 However, no prospective study has compared the efficacy of the two drugs. To assess their clinical efficacy and impact on the patients’ quality of life, we performed a pilot study on a small group of patients with RRMS. Patients with at least two relapses during the previous 2 years and EDSS lower than or equal to 3.5 were offered treatment with IFN$\beta$-1b or AZA after information about the efficacy, tolerability, and mode of administration of both drugs, and allocated to one of the two treatments according to the patient’s choice. Some patients refused to be treated with either drug, mainly because of the fear of side effects and the negative impact of chronic treatment on their lifestyle; they were followed up according to the same protocol (not treated [NT] group). All patients gave informed consent. Serial neurological evaluations were performed every 3 months for 1 year. At the same time a self administered disease specific questionnaire (MSQOL-54), recently validated in the Italian MS population,1 was filled in and the Hamilton depression rating scale (HD) was administered. Scores for the MSQOL-54 were analysed as previously described;1 briefly, the obtained samples were linearly transformed into 0–100 scales; the higher the transformed score, the better the patient’s quality of life. The two composite scores mental health and physical health were also evaluated. A t test for unpaired samples was used to compare the scores between groups, with adjustment for multiple comparisons. The Kruskal–Wallis test and the two sample Wilcoxon rank sum test were used to compare the change in scores between groups. The main clinical variables were compared using a t test for unpaired and paired data.

Thirty two patients were included in the study (11 IFN$\beta$-1b, 10 AZA, 11 NT). The clinical characteristics at entry were similar in the two actively treated groups, whereas in the NT group age was significantly higher than in the AZA group (but not the IFN group) and pretreatment relapse frequency (RF) was lower than in the IFN group (but not the AZA group). After 1 year, RF significantly decreased in both the

Data of patients before and after treatment

<table>
<thead>
<tr>
<th>IFN</th>
<th>AZA</th>
<th>NT</th>
</tr>
</thead>
<tbody>
<tr>
<td>No of patients</td>
<td>11</td>
<td>10</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>3/8</td>
<td>2/8</td>
</tr>
<tr>
<td>Age at entry (y)</td>
<td>33 (6.2)</td>
<td>31.2 (4.9)*</td>
</tr>
<tr>
<td>Disease duration (y)</td>
<td>8.3 (5)</td>
<td>6.95 (6.7)</td>
</tr>
<tr>
<td>EDSS at entry</td>
<td>2.32 (0.9)</td>
<td>2.35 (0.9)</td>
</tr>
<tr>
<td>&gt; At 12 months</td>
<td>2.2 (1.0)*</td>
<td>2.1 (0.9)</td>
</tr>
<tr>
<td>No of worsened patients at 12 months</td>
<td>1/1</td>
<td>0/10</td>
</tr>
<tr>
<td>RF 2 year pretreatment</td>
<td>2.2 (0.8)*</td>
<td>2 (1)</td>
</tr>
<tr>
<td>At 12 months</td>
<td>0.8 (0.7)*</td>
<td>0.9 (0.4)*</td>
</tr>
<tr>
<td>No of relapse free patients at 12 months</td>
<td>4/11</td>
<td>7/10</td>
</tr>
<tr>
<td>PCH at entry</td>
<td>68.02 (9.1)</td>
<td>61.7 (10.8)</td>
</tr>
<tr>
<td>Change at 12 months</td>
<td>26.4 (9.26)</td>
<td>+7.9 (9.8)</td>
</tr>
<tr>
<td>MHC at entry</td>
<td>74.7 (15.7)</td>
<td>61.25 (14.15)</td>
</tr>
<tr>
<td>Change at 12 months</td>
<td>−6.04 (13.9)*</td>
<td>+21.25 (11.9)*</td>
</tr>
<tr>
<td>RLE at entry</td>
<td>83.34 (32.4)</td>
<td>37.5 (33.05)</td>
</tr>
<tr>
<td>Change at 12 months</td>
<td>−10 (35.3)*</td>
<td>+49.9 (35.6)*</td>
</tr>
</tbody>
</table>

IFN=interferon$\beta$-1b treated patients; AZA=azathioprine treated patients; NT=no actively treated patients; RF=relapse frequency (No of relapses/patient/y); worsened=+increase of ≥3 EDSS point; PCH=physical composite score; MHC=mental composite score; RLE=role limitation for emotional reasons.

*One patient in NT group dropped out at 6 months.
†Significant differences between groups:
Age at entry : NT $\neq$ AZA p=0.01.
RF at entry : NT $\neq$ IFN p=0.006.
MHC change : IFN $\neq$ AZA p=0.006.
RLE change : IFN $\neq$ AZA p=0.001.
‡Significant differences within each group (12 months v entry): RF, IFN p<0.01.
AZA p=0.005.

www.jnnp.com
IFN and AZA treated groups without differences between the two treatments, whereas it was unchanged in the NT group. The EDSS remained stable in the three groups (table). Five of 11 patients treated with IFN had flu-like symptoms on one or more occasions, whereas no side effects occurred in the other two groups.

No significant differences in the HD scores and quality of life profile were found between the three groups at entry. At 6 (data not shown) and 12 months the mental health composite score significantly increased in patients treated with AZA compared with those patients treated with IFN, mainly due to the increase in role limitation for emotional reasons item; no significant differences between the NT group and actively treated groups were seen. No significant changes in HD scores in the three groups were found at 12 months. These results suggest that both AZA and IFNβ-1b are effective in reducing relapse frequency in patients with RRMS. The treatment effect on quality of life has been rarely investigated, with conflicting results: no significant change after 1 year of IFNβ-1b treatment was found by Schwartz et al, whereas an improvement on physical items after 5 years was reported by Rice et al. In our study, the impact on quality of life was better in patients treated with AZA than in those treated with IFN, mainly due to the improvement in mental score. A direct effect of the drugs on the CNS seems unlikely: no symptoms of neurotoxicity were found in either treatment group and no patients developed depression according to the HD scale. Most likely the improvement of quality of life in patients treated with AZA might be related to different tolerability or to differences in treatment schedules, resulting in a more pronounced and persistent perception of the disease in patients treated with IFN. Due to the few patients, the results of this study need to be verified by a larger randomised comparative trial.

We are indebted to Dr Alessandra Solari, Laboratory of Epidemiology, C Besta National Neurological Institute, Milan, Italy, for performing the statistical analysis of the data.

C MILANESE
L LA MANTIA
A SALMAGGI
Istituto Nazionale Neurologico C Besta, Via Celoria 11, 20133 Milan, Italy

D CAPUTO
IRCCS Fondazione Don Gnocchi, Milan, Italy

Correspondence to: Dr C Milaneses
mgroup@istituto-besta.it


Unilateral caudate head lesion simulating brain tumour in X-linked adult onset adrenoleukodystrophy

The appearance of X-linked adrenomyelo-neuropathy (AMN)/adrenoleukodystrophy (ALD) on MRI is usually specific, with bilateral symmetric areas of white matter abnormality surrounding the posterior horns of the lateral ventricles with various degrees of atrophy of the spinal cord. Our patient with AMN, however, showed a lesion in the right caudate head simulating a brain tumour, which has not been a feature in this disease.

At the age of 25 the patient started to have progressive spastic paraparesis and mild ataxia with genitourinary dysfunction (urge urinary incontinence and erectile dysfunction). On admission to our hospital at the age of 34, T2 weighted MR images showed small lesions in the bilateral internal capsule although no abnormality was seen in the spinal cord. Nerve conduction studies and the sural nerve biopsy showed evidence of peripheral nerve involvement. A low serum cortisol response to intravenous adrenocorticotropic hormone and increased concentration of plasma very long chain fatty acids were consistent with a diagnosis of AMN. Three years later he showed marked emotional liability. T2 weighted MRI showed a high signal mass lesion in the right caudate head and the ipsilateral anterior internal capsule which simulated an intracranial tumour, without marked demyelination in the surrounding deep white matter (fig 1). A year later he became wheelchair bound, apathetic, and demented. Brain MRI showed right sided dominant white matter abnormalities and atrophy of the spinal cord. Three years later he died of respiratory infection and necropsy was performed. Pathological examination showed fronto-temporal cortical atrophy with diffuse white matter demyelination including bilateral internal capsules, where astrocytes proliferated and lipid laden macrophages infiltrated around the small vessels. Neurons were moderately shrunken and the neuropil showed tissue rarefaction. Demyelination was also seen in the cerebellar white matter. The caudate head showed bilateral but right side dominant atrophy, where neuronal loss and tissue rarefaction with fibrillary gliosis (spongy state) were seen (fig 2).

Previous reports of X-ALD/AMN showed occasional unilateral basal ganglia involvement. Affi et al reported on a 4.8 year old boy whose MRI showed a right anterior white matter lesion extending into the ipsilateral putamen and the thalamus. Close et al described an 8 year old boy who had a left occipitotemporal white matter lesion extending into the ipsilateral thalamus on MRI. However, the imaging pattern in our patient is unique because of the high signal mass lesion in the right caudate head and the ipsilateral anterior internal capsule without marked demyelination in the surrounding white matter, falsely suggestive of a brain tumour. There are also other demyelinating disorders simulating brain tumour which include multiple sclerosis. The findings indicate that plasma very long chain fatty acid

Figure 1 Brain MRI of the patient at the age of 37. T2 weighted MR images showed a high signal mass lesion in the right caudate head and the ipsilateral anterior internal capsule which simulated an intracranial tumour, without marked demyelination in the surrounding deep white matter.

Figure 2 Microscopic section of the right caudate head (haematoxylin-eosin staining). This shows neuronal loss and tissue rarefaction with fibrillary gliosis, presenting as spongy with little inflammation.
Lymphadenopathy in patients with multiple sclerosis undergoing treatment with glatiramer acetate

Glatiramer acetate (GA)—formerly known as copolymer 1 or COP-1—has been shown to reduce the frequency of relapses and disease activity and burden as measured by MRI in patients with relapsing-remitting multiple sclerosis (RR-MS). The mechanism of action is thought to involve MHC-II blockade and the induction of a Th2/Th3 cytokine response. Peripherally blood mononuclear cells from patients with multiple sclerosis and healthy controls proliferate in response to GA in vitro. Therefore GA seems to have both immunostimulatory and immunomodulatory potential.

In our centre 27 patients with relapsing-remitting or relapsing-progressive multiple sclerosis were treated with 20 mg subcutaneous GA daily for 3 years as part of an open label multicentre study. Safety evaluation and expanded disability status scale (EDSS) rating were performed every 3 months and in the 3rd year every 6 months and when clinical relapses occurred. Relapses were defined according to Poser criteria and annual relapse rates were calculated for the 3 year study duration and a 2 year prestudy period. As two patients reported generalised tender swelling of lymph nodes spontaneously in temporal relation to the beginning of GA injections special attention was paid to the symptom and regular assessment of regional lymph nodes was performed in all patients. Only if patients reported symptoms such as tenderness or pain, was the diagnosis of lymphadenopathy made. All patients completed the full 3 years of the study. In one patient with generalised lymphadenopathy a lymph node biopsy was taken to rule out malignancy. As controls patients who were routinely treated with IFN-β injections at our multiple sclerosis outpatient clinic were also examined for lymphadenopathy.

In nine out of 27 patients lymphadenopathy occurred 1 to 15 months after initiating GA treatment and persisted for the study (treatment) duration. There were no significant differences between the groups with and without lymphadenopathy in their mean age, disease duration, EDSS scores, and annual relapse rates at the beginning of the study. The size of the lymph nodes ranged from 2 to 5 cm and lymphadenopathy was considered mild to moderate in eight patients and severe in one patient. In seven out of the nine patients (78%) lymphadenopathy was restricted to inguinal lymph nodes and in two patients it was generalised. Serological and haematological routine diagnostics of peripheral blood were normal. The lymph node biopsy in one patient with severe generalised lymphadenopathy showed strong immune stimulation with lymphofollicular hyperplasia but no atypical cells (thus ruling out malignancy). Lymphadenopathy did not necessitate the discontinuation of GA treatment. The examiners were reassured that all patients used a good (sterile) injection technique. In the control patients no lymphadenopathy was detected.

When analysing annual relapse rates, a significant reduction of the mean annual relapse rate was found under GA treatment. The annual relapse rate decreased from 1.8/year to 0.53/year at the beginning of the study and 1.5/year to 0.54/year in the group of patients with and without lymphadenopathy respectively. When comparing annual relapse rate for both patient groups the difference did not reach significance (Mann-Whitney U test, p=0.076) with a trend to a slightly favourable response in the group with lymphadenopathy. Although in the group with lymphadenopathy no patient showed an increase in relapse rate, the difference between both group without lymphadenopathy did. In both groups of patients no significant change in median EDSS over the 3 years of the study was noted (table 1). The frequency of lymphadenopathy found in this study (nine out of 27 patients) is significantly higher than that reported in the postmarketing surveillance of GA (55 reports of lymphadenopathy out of about 30 000 reports of other adverse events). The lymphadenopathy in our study was mild to moderate, not accompanied by changes in routine laboratory indices, and persisted as long as the GA treatment was continued. In seven out of nine patients lymphadenopathy remained localised to the draining lymph nodes. Lymph node swelling receded and reappeared depending on injection site. Lymphadenopathy did not necessitate discontinuation of GA treatment. In one patient with generalised lymphadenopathy a biopsy was performed to rule out malignancy. The patient was then continued on GA without further problems and remained relapse free; GA injections were stopped 1 year after the end of the study, due to pregnancy, and lymphadenopathy resolved completely within 4 weeks.

Lymphadenopathy, if not due to malignancy, is a clinical sign of immune activation and has not yet been reported as an adverse event of GA treatment in the literature. The effect might be due to direct stimulation of T cells in vivo as GA has been shown to induce mRNA expression of IL-2 and T cell proliferation in vitro. In previous studies immunostimulatory cytokines such as IFN-γ or viral infections worsened the clinical course of multiple sclerosis whereas immunosuppression (for example, mitoxantrone, cyclophosphamide) was beneficial. It will be interesting to study further whether lymphadenopathy related to GA is associated with alteration of the clinical outcome measures of multiple sclerosis. The cohort of patients with lymphadenopathy did not show a significant difference in annual relapse rate or EDSS compared with patients without lymphadenopathy, but the small sample size per group should be taken into account. Glatiramer acetate induces clinical signs of immune stimulation (lymphadenopathy) in a subgroup of patients with multiple sclerosis that is not associated with clinical worsening. The finding is therefore interesting with regard to the potential mechanism of action of GA in vivo. Larger numbers of patients need to be examined to determine whether lymphadenopathy in patients under GA treatment is associated with distinct immunological markers—for example, MHC-II type or cytokine secretion pattern.

Patients examined in this study were enrolled in our centre as part of the German phase IIb treatment study (protocol COP 1600) supported by TEVA and Aventis.
The remedial approach, visual rehabilitation by Kerkhoff, we think that it is prudent to communicate our experience in the management of a patient with Balint’s syndrome after traumatic brain injury. This was seen in a 41 year old right handed manual worker whose initial cranial CT showed right extradural haematoma. Subsequent scans demonstrated left posterior occipital infarct. Brain MRI 3 months after the injury showed high signal in the right occipitoparietal and left occipitotemporal regions. His physical recovery was satisfactory, in that he was fully mobilised and unaided. However, he presented with simultanagnosia, optic ataxia, and psychic paralyse of gaze. This had an adverse impact on his functional independence; he had difficulty in finding one’s way around the house and was unable to return from furniture and walls—and other activities of daily living including dressing and toileting. He failed most subtests in the Rivermead perceptual assessment battery (RPAB).

We agree with the author that effective treatment strategies are poorly developed and evaluated. We have identified three approaches for the rehabilitation of the perceptual deficits included those seen in Balint’s syndrome.

- The adaptive (functional) approach, which involves functional tasks utilising the person’s strengths and abilities, helping the person to compensate for problems or altering the environment to lessen their disabilities.
- The remedial approach, which involves restorative or compensatory measures by training in the perceptual skills, which may be generalised across all activities of daily living. This could be achieved by tabletop activities or sensorimotor exercises.
- The multicontext approach, which is based on the fact that learning is not automatically transferred from one situation to another. This involves practising a targeted strategy in a multiple environment with varied tasks and movement demands, and it incorporates self awareness tasks.

In this patient, we used the adaptive approach, practising functional tasks repeatedly with increasing complexity of the tasks as the sessions continued. This approach assumes that treatment has little effect on impairment and that generalisation to other tasks is unlikely. It also assumes that the brain has limited ability to improve and restore itself after injury. The remaining abilities are used to offset the deficits. This patient was able to develop his own compensatory strategies, learned to use his hands to acquire tactile feedback, and managed to direct his gaze to visually locate objects when required. His performance on the RPAB was improved and he was successfully discharged home with little support.

As Balint’s syndrome is likely to be seen in clinical conditions such as Alzheimer’s disease, multiple sclerosis, intracranial tumours, brain injury, and CNS complications of HIV infection, we thought it important to outline the possible options for the management of this condition. Further work is required on a larger series of patients.

I AL-KHAWAJA
Swiss Rehabilitation Centre, Brighton General Hospital, Brighton, East Sussex BN2 1EX, UK

N H HABOUBI
North Staffordshire Rehabilitation Centre, Stoke-on-Trent ST6 7AG, UK

Correspondence to: Dr I Al-Khawaja
i.khawaja@src.org.uk


Kerkhoff replies: Al-Khawaja and Haboubi have reported successful neurovisual rehabilitation in a patient with Balint’s syndrome due to a right occipitoparietal and a left occipitotemporal lesion, using adaptive practising of functional tasks with increasing complexity. This case shows, together with some of the other published cases, that individually tailored rehabilitation strategies can be adapted successfully for some severely disabled patients. Due to the various aetiologies and subsequent lesion localisations it is likely that most patients with Balint’s syndrome will have some outstanding deficits, but also some spared abilities, which can be used for compensatory purposes (for example, intact tactile feedback).

In two patients with Balint’s syndrome treated for several months in our department, significant improvements could be achieved by systematic treatment so that both patients could live independently at home with only minimal assistance. One patient, who had survived traumatic, uraeemic, and hypoxic brain damage at the age of 27 years initially was nearly blind. Two years later, when treatment started in our unit, he couldn’t perceive more than two visual stimuli simultaneously (simultanagnosia), was almost unable to read, showed optic ataxia, and had severely impaired spatial-perceptual functions in the visual and tactile modality. However, his memory, intelligence, and executive functions were largely preserved, so that he relearned reading partially, learnt to dress himself partially, and was finally able to travel by train. He managed to live alone in his flat, with only minor assistance from others.

The second patient, a 60 year old physician, had bilateral vascular parieto-occipital lesions. She was initially (falsely) considered as blind, although she could well see and describe faces and correctly identify the colour of one’s eyes. She presented with severely disturbed depth and horizontal distance perception, simultanagnosia, and optic ataxia as well as a peculiar deficit in identifying spatial directions and locating sound sources. For instance it proved difficult for her to identify the direction in which someone pointed when describing a particular route, or to decide in which direction a train would move when looking at the railway track. However, as in the first patient, she had some spared abilities—that is, excellent introspection and awareness of her disorder, preserved cognitive abilities, and she was highly motivated to relearn route finding in her town district. After intensive training for reading and route finding she could be discharged, living independently at home. She continues to use public transport to go shopping, visit friends, see her neurologist, the pharmacist, or going to a concert hall.

I think that systematic treatment in both cases helped to improve basic visual abilities and activities of daily living so that both patients could live independently at home, which was hardly expected when seeing them at the onset of treatment. To conclude, I am convinced that many patients with Balint’s syndrome can learn to compensate for at least some of their visual deficits by systematic and individualised treatment. The search for spared functions will undoubtedly disclose multiple ways for compensation and will increase our understanding of some unresolved aspects of this fascinating syndrome—for example, the tactile or auditory-spatial abilities of patients with Balint’s syndrome.

G KERKHOFF
EKN-Clinical Neuropsychology Research Group, Department of Neuropsychology, City, Hospital Bogenhausen, Dachauerstr.164,D-80992 Munich, Germany

georg.kerkhoff@extern.lrz-muenchen.de


Arnold Chiari malformation and nystagmus of skew

I enjoyed Pieh and Gottlob’s article pointing out the association of a Chiari malformation with a “unique” form of nystagmus that they call “the nystagmus of skew.” The distinctive feature of this nystagmus is a distinctive vertical oscillation in which the fast phase of one eye moves upward while, at the same time, the other eye moves downward.

The authors state that their second patient had a “rotatory component” by which I assume they mean torsional; this pattern of nystagmus is already established in the literature and is known as “jerkwaveform see-saw nystagmus.” In their first patient they point out that the amplitude of the vertical nystagmus was so small that they were unable to confidently exclude a torsional component. It would have been most interesting to obtain recordings looking for a torsional component using the modified
scleral search coil technique; they suggest that it would have shown a torsional component and that this patient also had jerk-waveform see-saw nystagmus.

Jerk-waveform see-saw nystagmus occurs with unilateral mesodiencephalic lesions, presumed due to selective unilateral inactivation of the torsional eye velocity integrator in the interstitial nucleus of Cajal; during the fast (jerk) phase, the upper poles of both eyes rotate toward the side of the lesion. With lateral medullary injury, the fast phases of the torsional component jerk away from the side of the lesion. In both situations, the torsional component is always conjugate. With mesodiencephalic lesions, the vertical component is always disjunctive, but with medullary lesions it may be either conjugate (usually upward) or disjunctive.

PATRICK LAVIN

Departments of Neurology and Ophthalmology, Vanderbilt University Medical Center, 2100 Pierce Ave. Nashville, TN 37212, USA

patrick.lavin@mcmail.vanderbilt.edu


The authors reply:

We thank Lavin for his interesting comments. We stated in our article that the possibility of a fine see-saw nystagmus could not be excluded. We did re-evaluate our patients with a torsional coil and did not record a tor- sional component. However, because of the fast improvement in both patients, all the eye movement abnormalities on re-evaluation were minimal. Clinically, even in the stage of maximal abnormalities, in one patient we did not detect any torsional component, which suggests that if there was an element of see-saw nystagmus, it was subclinical. We did not state that the type of nystagmus associated with the Arnold-Chiarl malformation was unique, precisely because we could not rule out with total certainty a see-saw nystagmus, which has been reported in one patient with the malformation. We did, how- ever, point out that this association is unusual.

Because of the lack of strong evidence of a torsional component to the dissociated verti- cal nystagmus, we preferred the term, kindly suggested by a reviewer, “nystagmus of skew”. This would represent a more inclu- sive, descriptive term, of which both the pen- dular and the jerk see-saw nystagmus forms and the dissociated vertical nystagmus with- out demonstrable torsional component would represent subvariants.

C PIEH

Kantonsspital St Gallen, Switzerland

I GOTTLUB

Department of Ophthalmology, Leicester Royal Infirmary, Leicester LE1 5SW, UK

Botulinum toxin for the treatment of sialorrhoea in ALS: serious side effects of a transducal approach

We have read with interest the article by Giess et al., which showed that botulinum toxin A (BoNT/A) might be a new treatment option for sialorrhoea in patients with bulbar palsy. We have recently conducted a similar study which was interrupted due to serious side effects.

In September 1998 we injected 25 MU Bototo into the parotid glands of a 59 year old women who had ALS with pronounced bulbar palsy. We noticed a reduction of the sialorrhoea but facial weakness on the left side worsened significantly.

After this experience we developed a protocol for the treatment of sialorrhoea in patients with ALS with bulbar palsy by retro- grade injection of BoNT/A through the salivary duct into the salivary glands. We chose the retrograde way of administration of BoNT/A for this pilot study because we thought that this technique would avoid facial weakness.

After informed consent the patients received 12.5 mouse units (MU) BoNT/A (Botox®) retrogradely into each parotid and sublingual gland from a small catheter inserted into the salivary duct. Neurological examination and quantification of saliva produc- tion were performed before the BoNT/A injection and on days 1, 3, 7, 14, and 28, as well as after 2 and 3 months. Technetium 99m scintigraphy was performed before and 7 days after the injection. Quantification of saliva production was performed with a sim- ple method: the patients were asked to expec- torate as much saliva as possible into a paper handkerchief for 10 minutes. This procedure was repeated twice. The mean of the difference in weight of the handkerchief before and after these procedures was taken as the maximum expectorated saliva produc- tion (MESP). Quality of life and the clinical effect of the treatment were evaluated by a questionnaire.

We treated a 60 year old woman (patient 1) and a 69 year old women (patient 2) with this new technique. Both had certain ALS according to the El Escorial criteria, with severe bulbar palsy with durations of 23 and 28 months respectively. Both patients had a significant reduction of MESP seven days after the injection (76% and 58% from 5420 mg to 1301 mg, and 4365 to 1829 mg) which lasted for 4 to 8 weeks. Technecium 99m scintigraphy showed a significant reduction of radiotracer uptake into the injected salivary glands in both patients (figure). Both patients estimated the injection procedure as painful. Patient 1 developed a severe swelling of the right sublingual salivary gland and base of the tongue 3 days after the injection which was treated with antibiotics and corticosteroids. Patient 2, who was able to swallow with difficulty before the injection, mentioned impairment of swallowing be- tween days 4 and 21. Both patients had a “moderate” improvement of sialorrhoea but did not want the injections to be repeated. After these experiences we decided to stop the pilot study.

The injection of BoNT/A through the sali- vary duct reduces the activity of the salivary glands significantly for several weeks but has serious side effects. Local and systemic effects of BoNT/A are probably pronounced in ALS. Subclinical EMG abnormalities distant to the injection sites have been described in therapeutic doses, but also sys- temic weakness has been found. As there are some reports that BoNT/A injections, even in low doses, may exaggerate pre-existing neuromuscular diseases, careful monitoring of neurological symptoms, which is diffi- cult in a progressive disease, is needed to exclude side effects of BoNT/A. The drug is effective in reducing drooling but we need more data about the safety of BoNT/A before it can be used safely for the treatment of sialorrhoea in ALS. The transudcal approach in particular seems to have unac- ceptable side effects.

M G M WINTERHOLLER

Department of Neurology,
Friedrich-Alexander-Universität Erlangen,
Schroedingerstrasse 8, D-91054 Erlangen, Germany

F J ERBGUTH

Department of Nuclear Medicine,
Kantonsspital St Gallen, Switzerland

S WOLF

Department of Ophthalmology

S KAT

Department of Nuclear Medicine

Correspondence to: Dr M GM Winterholler, MD
wiho.erlangen@t-online.de

www.jnnp.com
The authors reply:

We appreciate the comments by Winterholter et al on our article on botulinum toxin (BTX/A) treatment of sialorrhoea in patients with amyotrophic lateral sclerosis (ALS).

Although we did not find any serious side effects after transcutaneous injections of BTX/A into the parotid and submandibular glands Winterholter et al report on sublingual salivary gland injection in one patient and deterioration of dysphagia in another patient after a transcutaneous approach. These complications support our notion that the individually tolerated dose of BTX/A in patients with ALS may be low and also indicate that the transcutaneous approach as performed in several studies may be safer than the retrograde transdural injection. This is not unexpected as the transdural approach has possibly a higher risk of infection because of the reduced salivary gland secretion rate found in patients with ALS.

In addition, the total dose of 25 MU Botox for the sublingual glands may be rather high in view of the close anatomical relation of these glands to the pharyngeal muscles. We therefore underscore our previous suggestion to start with injections of the parotid and submandibular glands to the pharyngeal muscles. We therefore underscore our previous suggestion to start with injections of the parotid and submandibular glands to the pharyngeal muscles.

It is unfortunate that the study required a three times daily dosage regime. It seems possible that this accounts for the surprising 33% of patients on LD/DI alone who withdrew as a result of dyskinesia events, and for the occurrence of nausea in 49.4% of patients on LD/DI alone. Whether smaller, less frequent, dosage would have allowed better tolerance of and motor response to ropinirole, it seems possible that frequent dyskinesia was seen at 5 years on three times daily dosage of LD/DI. A substantial proportion of patients on LD/DI (43.8%) were also on selegiline, amplifying the effect substantially.

Whereas it may be argued that different drug preparations and methods of assessment invalidate comparison, it may be simply that less frequent higher pulsatile dosage provokes not only greater dyskinesia but also, as a mirroring effect, greater off time as postynaptic mechanisms adapt to cope with surges of dopamine and perhaps lose sensitivity to troughs. Patients seen during troughs would be liable to have their dose increased. If the interdose interval were fixed this would lead to a vicious circle.

Given reports of long term resolution of dyskinesia and on/off effects in response to various methods of dopamine stimulation at an appropriate strength, including continuous daytime jejunal infusion of LD/DI (with little or no change in LD/DI dosage requirement over 57 months), and of a neuroprotective effect of levodopa in early Parkinson's disease,

**Treatment of early onset Parkinson's disease with ropinirole**

The recent editorial supporting initial treatment of early onset Parkinson's disease with a dopamine agonist hinged in part on the demonstration in 268 patients that treatment of early onset Parkinson's disease with ropinirole alone or with supplementary levodopa/dopa decarboxylase inhibitor (benserazide) (LD/DI) resulted in substantially less dyskinesia than with LD/DI alone, with only slightly less motor benefit. Five per cent of patients on ropinirole alone developed dyskinesia after 5 years, compared with 25% with ropinirole plus LD/DI, and 45% of those on LD/DI alone.

The trial design allowed LD/DI supplementation if response was inadequate and additional trial drug could not be tolerated. Up to 24 mg ropinirole and 1200 mg LD/DI daily were allowed. Sixty six per cent of patients completing the ropinirole arm required supplementation, the average mean daily dose of ropinirole at 5 years being 16.5 mg, compared with 755 mg of LD/DI when the second was used.

This could indeed be the case although stratifying for selegeline usage in the levodopa arm did not highlight any such effect.

Secondly, he suggests that the allowed presence of selegeline may have magnified the tendency of levodopa to cause dyskinesia and so reduce the prevalence of dyskinesia.

**Brooks replies:**

Ponsford seems to focus primarily on the design and findings of the 056 trial of ropinirole versus levodopa in early Parkinson's disease recently reported in the *Neurol J Med* rather than the editorial as a whole, however, to take up his points.

Firstly, he suggests that it is unfortunate that the 056 trial required a three times daily levodopa dosage regime as use of more frequent smaller doses could have reduced the incidence of dyskinesia. This has yet to be shown. Addition of a catecho-O-methyltransferase inhibitor to smoother the plasma levodopa profile for motor fluctuations in Parkinson's disease might also prove beneficial.

Secondly, he suggests that the allowed presence of selegeline may have magnified the tendency of levodopa to cause dyskinesia. This could indeed be the case although stratifying for selegeline usage in the levodopa arm did not highlight any such effect.

Thirdly, he suggests that allowing the use of slow release levodopa preparations in early Parkinson's disease could have been beneficial. There is currently no trial data to support this viewpoint; on the contrary, early use of either slow release levodopa or enteral dopamine stimulation and so reduces the prevalence of fluctuations and dyskinesia.
Does disturbed homocysteine and folate metabolism in depression result from enhanced oxidative stress?

In their recent article, Bottiglieri et al describe increased homocysteine concomitantly with decreased folate concentrations in a subgroup of patients with depression. In addition, some relation between hyperhomocysteinemia and disturbed folate availability and disturbed monoamine metabolism was found. The close relation between increased homocysteine and reduced folate concentrations, which was described previously in other clinical conditions such as cardiovascular and cerebrovascular diseases is usually ascribed to a reduced dietary intake of folate, and dietary supplementation with folate is capable of reducing hyperhomocysteinemia.

The coincidence described of disturbed homocysteine and monoamine metabolism may shed some additional light to the possible role of folate deficiency in patients with depression as several studies have failed to confirm this. We included it in our study. We agree that simply measuring folate levels in CSF and age is not sufficient evidence that oxidative stress leads to folate deficiency in many patients with depression as several studies have failed to confirm this. We have recently reported a fall in CSF folate with aging and this may be a factor contributing to the high incidence of folate deficiency in psychogeriatric patients, including depression and dementia. We have also reported a fall in BH4 in depression which is correlated with folate deficiency, as reflected in a fall in red cell folate, and with impaired monoamine metabolism—that is, a fall in CSF monoamine metabolites.

The mechanisms of these relations between impaired folate and monoamine metabolism remain uncertain but the suggestion that oxidative stress in depression and monoamine metabolism is involved in depression and dementia is supported by several lines of evidence. First, BH4 synthesis in depression is impaired. Second, the evidence that BH4 is a key enzyme in the synthesis of serotonin and dopamine, and that these monoamines are involved in the pathogenesis and treatment of depression supports the hypothesis that BH4 is a key enzyme in the pathogenesis of depression.

We thank Widner et al for suggesting an explanation of our finding of impaired folate and monoamine metabolism in some patients with depression. The relation between homocysteine and folate is well established, which is why we included it in our study. We found a fall in BH4 in depression which is correlated with folate deficiency, as reflected in a fall in red cell folate, and with impaired monoamine metabolism—that is, a fall in CSF monoamine metabolites. The mechanisms of these relations between impaired folate and monoamine metabolism remain uncertain but the suggestion that oxidative stress in depression and monoamine metabolism is involved in depression and dementia is supported by several lines of evidence.

The coincidence described of disturbed homocysteine and folate metabolism may shed some additional light to the possible role of folate deficiency in patients with depression as several studies have failed to confirm this. We included it in our study. We agree that simply measuring folate levels in CSF and age is not sufficient evidence that oxidative stress leads to folate deficiency in many patients with depression as several studies have failed to confirm this. We have recently reported a fall in CSF folate with aging and this may be a factor contributing to the high incidence of folate deficiency in psychogeriatric patients, including depression and dementia. We have also reported a fall in BH4 in depression which is correlated with folate deficiency, as reflected in a fall in red cell folate, and with impaired monoamine metabolism—that is, a fall in CSF monoamine metabolites.

The mechanisms of these relations between impaired folate and monoamine metabolism remain uncertain but the suggestion that oxidative stress in depression and monoamine metabolism is involved in depression and dementia is supported by several lines of evidence. First, BH4 synthesis in depression is impaired. Second, the evidence that BH4 is a key enzyme in the synthesis of serotonin and dopamine, and that these monoamines are involved in the pathogenesis and treatment of depression supports the hypothesis that BH4 is a key enzyme in the pathogenesis of depression.
The authors reply.
We respond to some of the questions raised by Rinkel and Velthuis on our recent publication in this Journal. The patient of interest presented with typical clinical signs of subarachnoid haemorrhage. He complained of sudden onset of severe headaches, irradiation into the nuchal region, and nausea. Lumbar puncture was performed and blood stained CSF was found. Centrifugation of the CSF disclosed xanthochromia of the supernatant fluid and cytology demonstrated siderophages. This suggests the presence of intracranial haemorrhage as no lumbar puncture was carried out earlier.

Non-contrast enhanced CT showed blood in the ambient cisterns and these findings were interpreted as perimesencephalic subarachnoid haemorrhage in two different hospitals.

Four vessel digital subtraction cerebral angiography with multiple views was negative as was a repeated angiography 10 weeks later. A third angiography performed in the course of the second episode of haemorrhage again did not disclose any source of the bleeding, and thus the diagnosis remained unsolved. A recent publication by Canhao et al studied the prevalence of vascular risk factors in patients who had perimesencephalic subarachnoid haemorrhage. They found that hypertension is more frequent among patients with perimesencephalic haemorrhage than among two control groups and that among women, smoking was more common in perimesencephalic haemorrhage. However, the medical history of our patient was not relevant, and there was no history of previous arterial hypertension.

Rinkel and Velthuis express their concern about a high rate of persistent symptoms such as headaches, irritability, depression, and fatigability in long term follow up of our patients. They state that these findings contrast with the good quality of life found in a follow up study performed by Brilstra et al and that these differences require explanation.

In this study, which was cited by us as well, quality of life was measured by means of the sickness impact profile and outcome of perimesencephalic subarachnoid haemorrhage. It was directly on these psychosocial implications of perimesencephalic subarachnoid haemorrhage. Only 38% of our patients thought that they were fully recovered and completely well whereas 62% of the patients had residual complaints. Moreover, only 41% of the patients returned to their previous occupation whereas 53% of the patients retired from work and one man became unemployed. Thus quality of life after the haemorrhage is as poor as suggested and it becomes obvious that perimesencephalic subarachnoid haemorrhage has an enormous impact on individual patients and social life.

We do agree with Rinkel and Velthuis on the further management strategy for patients with former PMSAH. We inform the patients of the benign nature of the disease and do not impose any restrictions at all. We also reassure the patients that they can return to the same regular daily activities they undertook before the haemorrhage.

It is supposed that in 15% to 20% of the patients with subarachnoid haemorrhage the angiogram is negative and that patients with PMSAH account for about half of these patients with angiogram negative subarachnoid haemorrhage. On these premises there must be thousands of patients every year who are treated for PMSAH but not on PMSAH account. However, reviewing the literature in 1996, Schwartz and Solomon could only find 169 reported patients who had PMSAH. It seems, therefore, reasonable to compile more data to gain more information about the natural course of PMSAH in significantly larger cohorts of patients.
correspondence to: Dr O Backhouse

Correspondence to: Dr O Backhouse

Department of Ophthalmology, Leeds General Infirmary, The Leeds Teaching Hospitals NHS Trust, Leeds LS1 3EX, UK

obackhouse@hotmail.com

Progress and Interpretation

Philosophical and Ethical Problems in Mental Handicap. By Peter Byrne (Pp175, £40.00). Published by Macmillan Press, Basingstoke, 2000. ISBN 0 312 23460 0.

I cannot recommend this slim monograph highly enough to anyone working with people who have the disorders of neurodevelopment that give rise to what we term mental handicap, mental retardation, or learning disability. It is tightly argued, well written, and thought provoking and bears reading much more than once.

Psychiatrists are still the dominant medical profession working with people with learning disability, a fact of history that has been slow to change. Lothian has recently closed its large institution, one of several in Scotland that had around 1000 beds at its peak, with ward sizes to match. It is easy to condemn this partitioning of a whole section of society; it is much more difficult to reconcile and accept the fact that they do differ in a host of ways from most people and yet at the same time they have identical moral worth to any other human being. Professor Byrne’s central tenet is that these are not mutually exclusive concepts, but can be—indeed must be—integrated to make philosophical sense. The other paths lead on the one hand to the concept that the labelling process has created a fictional disability, that its use is a method of social control, of maintaining power by the creation of an underclass, and this denial of intrinsic or primary disability is inherent in some of the concepts of full inclusion and normalisation. The other position, perhaps more worrying, is held by some philosophers of bioethics who would define humanity and moral worth on the ability to reason, placing people with cognitive disability in a separate domain in which it is permissible to use eugenic policies to select against them, to justify infanticide.

Byrne argues with great care against both these paths, his arguments rest on an appreciation of a common humanity is the best protection for such people. I have usually found that the persons are not so concerned as to whether we describe their intrinsic cognitive condition as a mental handicap or a learning disability but as to whether we remember their first and second names.

Psychiatrists may think that of course we know all this, and that of course we would not follow these extreme paths that are described by Professor Byrne. The 86 men who used to be herded together in one of the old wards that I inherited might not agree.

Walter Muir

The past few years have seen a plethora of books on multiple sclerosis. Many of these books simply decorate my bookshelf and are rarely consulted by any member of the team. Some cynics have correlated a high number of recent publications with pharmaceutical interest in the condition. I am certain that many of these books are purchased by the pharmaceutical companies and are often used as marketing tools.

Each new volume, therefore, needs to justify its existence in some way. In most cases the battle is between McAlpine's *Multiple Sclerosis* and each newcomer. Most young pretenders are unable to match McAlpine in most areas. This book is no exception. In the current context of the history, epidemiology, pathology, diagnosis, and aetiology sections, Where this book is particularly strong and justly deserves its place on the multiple sclerosis bookshelf is in the clinical sections, most of which are very helpful.

The book is divided into eight sections, including most of the ones mentioned. Section 6 deals with symptom management and rehabilitation, including specific chapters on weakness, mobility, fatigue, spastic paresis, vertigo and incoordination, neuroophthalmology, paroxysmal disorders, cognitive and emotional problems, pain and dysautonomia, bladder dysfunction, bowel disturbance, sexual dysfunction, autonomic disorders, dysarthria, and dysphagia. These chapters are generally informative and well written by specialists in their field. I would particularly pick out excellent chapters on neuro-ophthalmic signs and symptoms, by Elliot Frohman and colleagues, a very useful section on clinical and rehabilitation outcome measures by Linda Coulthard-Morris, which contains analysis of most of the commonly used measures together with examples of the forms.

The later chapters are involved with “societal issues” and are more specific to the American care system than European healthcare models. The text is much weaker in the earlier sections and it is here that I would reach for my trusty McAlpine.

A volume such as this is an opportunity not only to review evidence, but also to interpret in a particular fashion. During this interpretation, authors may be tempted into controversial areas, occasionally using logic which can at best be described as woolly. Often these ideas are promulgated at commercially sponsored symposia where the promise of a free lunch and more books draws a large audience. It is much more difficult to get some of these theories into scientific peer review publication than it is to express them at such venues. For example, the concept of “asymptomatic disease” and “symptomatic disease” has been around for a while and is again exposed by Pat Coyle in this book. The logic goes something like: early inflammation causes early axonal damage, therefore we must treat early and aggressively. Jack Simon in his MRI chapter provides a good deal of common sense information, including the fact that completely expected multiple sclerosis may be detected at necropsy. At present, we have no hard information to inform us that any of the immunotherapies make a difference to secondary progression in the long term, and the implication that we should be treating MRI rather than a patient may cause dysphagia to some neurologists on this side of the Atlantic.

It is important to maintain a balanced viewpoint in life. Overall, the many good chapters in this book outweigh the mediocre ones, and the quality of the paper is wonderful!

JOHN ZAJICEK


Everything we know about structure, function, and physiology in the nervous system at the cellular level—‘‘the cellular disease’’—evolves from the concept that organisation is through the connectivity of functionally independent neurons and their processes. Santiago Ramon y Cajal distinguished neurons from glia; showed the variability of dendritic arborisations and axon terminations; established that axon cylinders end freely but form contacts; conceived that the nerve impulse is conducted between axons, dendrites, and the cell body of neighbouring neurones; had the concepts of trophism and tropism; and following Rudolph Virchow, regarded the cell as the unit of all biological systems. His most detailed studies were of the cerebellum but, in time, no part of the brain and spinal cord went unexplored. His great synthesis was to settle debate on the neuron theory. His descriptions were supplemented by beautiful drawings based on Golgi stains. He and Golgi were jointly awarded the Nobel prize for medicine in 1906. They disagreed publicly during the lectures in Stockholm.

Cajal is the most significant neuroscientist of the 20th century—Sir Charles Sherrington being his only serious competitor. They met only once when Sherrington hosted Cajal’s stay in London to deliver the 1894 Royal Society Gresham Lectures. Sherrington was inspired by Cajal: “He is the greatest anatomist the nervous system has ever known...he solved at a stroke the direction of nerve currents in their travel through the brain and spinal cord...it was a step of genius to study the embryonic nervous system.”

Between 1880 and 1933, Cajal wrote 288 scientific publications including 22 monographs. Much of his work remains untranslated from the original Spanish and hence unread. But the sustained admiration for Cajal’s writings and their contemporary relevance for neuroscience is now matched by a welcome revival in publishing his works. *Texto del sistema nervioso del hombre y de los vertebrados* was published from Madrid in three volumes (1897, 1898, and 1904). It was updated by Cajal with new text and illustrations for the translation into French as *Histologie du systeme nerveux de l’homme et des vertebres* by Dr Leon Azoulay (2 volumes: 1909-11). The complete French edition was first translated into English by Neely Swan- son and Larry Swanson as *Histology of the Nervous System of Man and Vertebrates* (Oxford University Press, 1995). Now the original Spanish text is available in English edition by Pedro Pasik and Tauba Pasik as *Texture of the Nervous System of Man and the Vertebrates*. The first of three volumes appeared in 1999; the other two are promised for 2000.

The advertising flysheet champions Cajal’s discovery of growth cones, chemoeffectant substances, dendritic spines, and cortical interneurons and claims absolute authority over both the French and English editions. It boasts illustrations based on original reproductions of drawings archived in the Cajal Institute in Madrid (the evidence is in the Muso-Cajal-Madrid stamp on many figures) with very little copied from previously published editions. Facts and citations are corrected from Cajal’s original text and authenticated against contemporary sources. In which edition should the discerning Cajal reader invest? When complete, the Springer set will cost DM850/$330/$550 compared with £150 for the two Oxford volumes. The difference is worth paying. The English-Spanish text is authentic; compare “the nervous system represents the unit of our community in the evolution of living matter, and the most complicated machinery of noblest activities that Nature has to offer” (English-Spanish) with “countless modifications during evolution have provided living matter with an instrument of unparalleled complexity and remarkable functions: the nervous system, the most highly organised structure in the animal kingdom” (English-French); or “it appears that with this [chemoautotrophic] hypothesis we have shed light into a dark cave, when in reality we have explored only the entrance, from which its imposing abyss appears even more distant and black” (English-Spanish) versus “the theory of chemotaxis we advanced...initially appeared to be pure conjecture with no hope of verification, although recently it has gained experimental support” (English-French).

The text is authoritative and the production lavish. Pedro and Tauba Pasik include, and readily identify, translation of material added by Cajal for the French edition between 1904 and 1909. Original footnotes are retained but the citations are modernised and gathered in a single section completing the English-Spanish text. The lack of an index will be put right when volume three is published. The illustrations are incomparably better in the Springer than the Oxford volume[s]. The line drawings are much more crisp; the original figures of methylene blue staining reproduce poorly as black and white (Oxford) but some of their polychromatic figures are more subtle. Volume one deals with the general principles of organisation in the nervous system and Cajal’s methods, the details of neuronal structure and the spinal cord. Volumes two and three will complete the medulla and pons, cerebellum, midbrain, diencephalon including the retina, cortex, and autonomic nervous system. The original Spanish and French editions are very expensive and virtually unobtainable. For the historian, physician, or scientist who studies neuroscience, whether or not to invest in the Springer set is simply not an issue—even if you already have the Oxford set. Both are magnificent publishing achievements...
the Psalms are on course to produce the definitive English language edition of the definitive Cajal.

ALASTAIR COMPSTON


This book comprises a selection of papers taken from a world psychiatry association symposium on preventive psychiatry. Two contributors are from the United States, one from Egypt, the remainder from Europe, particularly south eastern Europe. The preface opens with a reference to an earlier World Health Organisation (WHO) report which estimated that as many as one third to one half of all mental health problems could be averted by primary preventive measures. But it went on to note that in most spheres primary prevention had been neglected due principally to a lack of awareness of available effective methods, a deficiency that the book aimed to redress. Encouraged by this introduction the reader may then hope to become acquainted with some of the strategies and methodologies of preventive psychiatry. It is left to read of a few of its successes. If so, disappointment lies in store. Most of the writers approach their subject through a protective smoke screen of broad generalisations; few emerge from it to offer a detailed account of how any aspect of preventive psychiatry works on the ground. Some avoid the topic altogether: two of the more succinct chapters describe a process of deinstitutionalisation in Greece—a subject not without interest, but one that is only loosely connected with the book's principal purpose. Whether, and if so, how preventive psychiatry succeeds receives little attention. Surprisingly little relevant outcome data are presented. Much of the writing is stilted and lacks fluency. As with so many postsymposia offerings, thematic coherence is wanting. It is difficult to know who would benefit from reading this book. Preventive psychiatry may not be the easiest subject to write about, but if it is to reach the audience it deserves, it will need a more coherent and persuasive platform than this collection of contributions provides.

BRIAN TOONE


The libraries of Cambridge Colleges contain many treasures. Among the particular treasures to be found in Peterhouse College is a first edition of the Anatomical Engravings of Vesalius. This exquisite volume combines practical instruction with wonderful aesthetic pleasure in a manner that has long gone from our more pedestrian age. Although aesthetic pleasure is largely absorbed from our modern manuals of practical instruction, nevertheless such manuals still have a place in the training and instruction of the young surgeon. This volume will undoubtedly prove useful in that respect and indeed to some degree it follows directly in the tradition of Vesalius. It represents the distillation of a lifetime's work of Dr Segar from Freiburg and is truly a monumental volume. It is beautifully illustrated and a pleasure to handle. The labelling is clear and the diagrams are for the most part elegantly coloured, easy to follow, and stylishly executed. For a modern instruction manual it contains a significant amount of the aesthetic tradition exemplified by the Vesalius.

However, all manuals of surgical anatomy have the common characteristics that they portray the material scientists have put out as every surgeon soon learns, in the vast majority of their cases the normal appearances have been distorted or obliterated by the pathology which has caused the need for the surgery in the first place. However, surgeons must also know what things ought to look like even when they are not visible when he first starts out upon his surgery. This volume illustrates the differing anatomical appearances to be encountered in various neurosurgical approaches and this methodology is particularly likely to be helpful for the junior trainee. It is therefore an ideal book for the departmental library, but I fear may prove too costly for the average surgeon in training. The Cambridge Colleges have traditionally chosen their more valuable volumes to prevent their disappearance and I suspect this volume may require an equivalent degree of supervision to prevent it disappearing into the eager registrar's personal bookcase.

DAVID G HARDY


Hormonal changes clearly influence brain function and certain mental disorders, such as depression, are associated with, and may even result from, disorders of the endocrine system. As normal aging is associated with varying degrees of dysregulation in the endocrine system, this book addresses the hormonal basis of mental disorders in older people, which offers the possibility of new therapeutic approaches in an ever growing aged population.

The first section of the book provides a concise and comprehensive overview of the diverse sites and cellular mechanisms of action of steroid and thyroid hormones in the brain as well as their synthesis in the endocrine organs or in the brain itself. The second section identifies age related changes in the prevailing levels of cortisol, thyroid hormones, and sex steroids (estrogen, progesterone, testosterone, and dehydroepiandrosterone) and assesses the evidence for ascribing a role for these changes in the emergence of common mental disorders. For example, animal and human studies suggest that high cortisol concentrations in elderly subgroups are associated with a higher risk of developing cognitive deficits; reduced responsiveness of the hypothalamic-pituitary-thyroid axis in aging seems to be related to mood disorders; therapy with estrogen (women) or testosterone (men) may be protective against developing depressive symptoms and estrogen may have beneficial effects on cognition and dementia. Sex differences and, by implication, a role for sex steroid hormones, are also noted in schizophrenia, anxiety disorders, pain perception, immune function, and psychotropic drug metabolism. However, many contributors emphasise the inconsistencies in the scientific literature and the general lack of properly controlled hormone replacement studies in elderly people. Therefore, the view that youthful hormonal profiles will promote healthier aging must remain speculative until more controlled research is available. In its critical approach, this book should be an impetus to such potentially important research and it provides valuable information for clinicians and basic researchers alike in this complex and growing area.

GLENDA GILLIES


Psychiatry is a strange clinical subject. It has by far the smallest knowledge base of any of the major subspecialties yet the arguments over what should enter curricula and what should be in our postgraduate examinations are as fierce as in any other Royal College. There are major requirements—for example, to understand psychotherapy and psychological treatments. Yet as a treatment tool they still play a subordinate role to biological treatments in most settings for the management of the severely mentally ill. By contrast, time and time again surveys of trainee's needs persistently cry out for good information on psychopharmacology. In addition any teaching courses in psychopharmacology are always voraciously snapped up. Our own flawed Maudsley prescribing guidelines, which started life as a simple internal document, is thirstily sought after. Essential Psychopharmacology is the book I always wanted to write but have been soundly beaten to it by Stahl. The first edition was a finely crafted book with logically distinct sections on basic science, disease mechanisms, drug action, and drug classes. This third edition is now much improved again with copious colour illustrations and bang up to date scientific information about both active and new products and their associated modes of action. As the introduction states much has changed since the publication of the first edition 4 years ago. In one sense this is a slight pitfall of the book. The second edition has been prepared in the middle of a major research boom in psychopharmacology and in its attempt to be up to date it is in danger of becoming rapidly out of date. A text book format with a fair publication lag may not be the best vehicle for an attempt to cover absolutely up to date information. Nevertheless, I think the book is near perfect as a textbook of basic pharmacology. If I were to try and improve it further, I wonder whether the author and publisher might think again about the illustrations. It is superbly illustrated but sometimes the cartoon imagery is so metaphysical that it serves occasionally to be cumbersome and lacking clarity occasionally obscuring rather than clarifying the issue.

The book strangely lacks an international feel. There is a lot of Americanae (drug combos) and the contents are largely based around around a United States formulary with some unfamiliar drugs as well as missing some familiar European entities. All in all though a benchmark book for modern psychopharmacology teaching.

ROBERT KERWIN

This is the second edition of Gelb's systematic approach to the neurological problems likely to be encountered in general medical practice. The book seems to be aimed at general physicians in training, and medical students. Although it also contains much to engage the interest of specialist trainees in neurology, I suspect that most of them will use a more didactic text. Its appeal to medical students may be diminished by the relative lack of illustrations; pictorial material is mainly limited to anatomical line drawings in the early sections of the book. I did not encounter a single MR or CT brain scan; an omission giving the book questionable relevance to the starting point which is fundamental to contemporary diagnosis and understanding of neurological disease. In view of the avowed subject content, particularly in relation to the older age group, are those on diagnosis (Rodnitsky), the overview chapter on Parkinson's disease and Parkinsonism in the elderly (Meara and Bhownick), and treatment (Zesiewicz and Hauser). However, the treatment presentation of the current use of COMT inhibitors could be improved: the section meticulously describes the clinical effects of tolcapone, its half life, the appropriate dose, and the side effects, and it is not until the last paragraph that the reader is alerted to the fact that the drug is no longer used in Britain and its usage in the United States is limited.

The main failing of the book is in the selection of chapters. I have three criticisms. The chapters on ancillary areas such as nursing, physiotherapy, speech, and occupational therapy (of Parkinson's disease) and specific approaches to rehabilitation (in Parkinson's disease and parkinsonism), are brought nicely into the context of medical management. However, depending on the intended audience, too large a proportion of the book is dedicated to these areas (no fewer than five of the 14 chapters). As it stands the book will confuse and frustrate medical or para-medical readers as each group will find a large portion of the book of limited practical relevance.

Secondly, in view of the many changes that occur to the nervous system as part of the aging process (especially in relation to gait), and the controversy which still exists about the relation of Parkinson's disease to age related attrition of dopaminergic neurons, it would have been useful to include a chapter aimed at assisting the clinician to distinguish age related changes in motor function from Parkinsonian diseases. Thirdly, for the non-neurologist, or what remains of a general practitioner, there is a lack of comprehensiveness in the coverage of causes of parkinsonism other than Parkinson's disease. The various causes are mentioned briefly in the summary chapters at the beginning of the book. Subsequently, however, only three chapters are actually dedicated to other parkinsonian disorders—and the choice of these seems arbitrary—namely, gait apraxia and multifarct states; drug induced parkinsonism; and a chapter on extrapyramidal tumor. The chapter on treatment deals only with Parkinson's disease. In view of the avowed subject matter of the book I would have liked to have seen at least one chapter dealing specifically with the diagnosis and management of other parkinsonism plus disorders, such as multiple system atrophy, progressive supranuclear palsy, and corticobasal degeneration.

Michaél Donaghy


This is a multiauthor book which aims to discuss Parkinson's disease and parkinsonism in the elderly. The chapters are on the whole well written and the overall style is very much one of a practical handbook which is relatively easy to dip in and out of. There is little overlap into the context of chapters. Chapters which stand out for their useful content, particularly in relation to the older age group, are those on diagnosis (Rodnitsky), the overview chapter on Parkinson's disease and Parkinsonism in the elderly (Meara and Bhownick), and treatment (Zesiewicz and Hauser). However, the treatment presentation of the current use of COMT inhibitors could be improved: the section meticulously describes the clinical effects of tolcapone, its half life, the appropriate dose, and the side effects, and it is not until the last paragraph that the reader is alerted to the fact that the drug is no longer used in Britain and its usage in the United States is limited.

The main failing of the book is in the selection of chapters. I have three criticisms. The chapters on ancillary areas such as nursing, physiotherapy, speech, and occupational therapy (of Parkinson's disease) and specific approaches to rehabilitation (in Parkinson's disease and parkinsonism), are brought nicely into the context of medical management. However, depending on the intended audience, too large a proportion of the book is dedicated to these areas (no fewer than five of the 14 chapters). As it stands the book will confuse and frustrate medical or para-medical readers as each group will find a large portion of the book of limited practical relevance.

Secondly, in view of the many changes that occur to the nervous system as part of the aging process (especially in relation to gait), and the controversy which still exists about the relation of Parkinson's disease to age related attrition of dopaminergic neurons, it would have been useful to include a chapter aimed at assisting the clinician to distinguish age related changes in motor function from Parkinsonian diseases. Thirdly, for the non-neurologist, or what remains of a general practitioner, there is a lack of comprehensiveness in the coverage of causes of parkinsonism other than Parkinson's disease. The various causes are mentioned briefly in the summary chapters at the beginning of the book. Subsequently, however, only three chapters are actually dedicated to other parkinsonian disorders—and the choice of these seems arbitrary—namely, gait apraxia and multifarct states; drug induced parkinsonism; and a chapter on extrapyramidal tumor. The chapter on treatment deals only with Parkinson's disease. In view of the avowed subject matter of the book I would have liked to have seen at least one chapter dealing specifically with the diagnosis and management of other parkinsonism plus disorders, such as multiple system atrophy, progressive supranuclear palsy, and corticobasal degeneration.

Stavia Blunt


The first edition of this text was published 20 years ago. The growing recognition of the importance of neurotoxicology and the development of molecular and cellular pathology and toxicology have resulted in a huge increase in knowledge since the publication. As a result the second edition of this very influential publication is much increased in content. The first three chapters should be required reading by any aspiring neurotoxicologist, neuropathologist, or neurologist whether scientist, clinician, or veterinarian.

The second section, about 1000 pages in length, is a comprehensive listing of several hundred substances with neurotoxic potential. At its best, this section offers mini-reviews of many neurotoxic chemicals—for example, acrylamide, n-hexane—and therapeutic agents—for example, chlorpromazine. At times, however, the choice of compounds for inclusion seems confused, and cross referencing is particularly successful. For example, organophosphates and sarin and related organophosphate “nerve agents” are given separate sections, both dealt with in greater depth than with no cross reference at all. More problematic is the handling of natural poisons and venom and their respective toxic components (toxins). Venoms inoculated by biting and stinging animals and the poisons responsible for events such as paralytic shellfish poison and ciguatera are invariably complex.

The clinical syndrome reflects the combined activities of numerous toxins. There is, therefore, the possibility of defining the neurotoxic potential of either the entire venom or poison or only that of the neurotoxic toxins. Each approach has its strengths and weaknesses but in this publication the editors have used both approaches without either clear advantage. This has resulted in some curious choices being made. The venom of the sea snakes is given an entry, although sea snake bites are now rather rare; the venom of the taipan is not given an entry although effective bites by this snake constitute a neurological emergency. The postsynaptically active toxins of cobra venoms are discussed but not the presynaptically active toxins of krait venoms. Saxitoxin and tetrodotoxin are respectively...
paralytic shellfish poisoning, is a member of many related gonyautoxins, and interconversion is common. This is not mentioned in the entry on saxitoxins. Neither is the fact that gonyautoxins are often found in blue-green algae. These confusions could relatively easily be resolved in subsequent editions of this book by describing the neurotoxic potential of major groups of toxin, “postsynaptically active toxins of snake venoms” for example. This may seem a complaint based on the personal interests of the reviewer, but the editors clearly feel that “natural” neurotoxic agents are important.

Experimental and Clinical Neurotoxicology is an unusual book in structure, organisation, and content. But it is not easily put down. I found myself constantly moving to new sections exploring its contents much as one handles a new dictionary. It is, quite simply, a good read. This new edition will become the definitive reference for the neurotoxicologist. It is an essential component of the library of any respectable toxicology or pathology laboratory and of every neuropathologist or neurotoxicologist. I doubt we shall wait 20 years for the third edition.

J B HARRIS

---

CORRECTION

Schrag A, Jahanshahi M, Quinn N. What contributes to the quality of life in patients with Parkinson’s disease? J Neurol Neurosurg Psychiatry 2000;69:308-12. The numbers given for the PDQ-39 in depressed patients (BDI>17) and non-depressed patients (BDI<18) given in table 2 (top row of data) on page 309 should read 49.8 (21.4) and 23.6 (14.3) instead of 39 (18.3) and 16.7 (11.2).
Volitional and stimulation induced neuromyotonic discharges: unusual electrophysiological pattern in acquired neuromyotonia

J BEDNARÍK and Z KADANKA

J Neurol Neurosurg Psychiatry 2001 70: 406-407
doi: 10.1136/jnnp.70.3.406