LETTERS TO THE EDITOR

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

Neuromyotonic discharges are electrophysio-
logically 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 a high frequency discharges that outlasted voluntary effort. We report a case of an acquired paraneoplastic 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 women presented with a 6 month history of muscle stiffness, paraesthesias provoked mostly by movement, disturbed speech, and difficult walking. At the time of examination she could not walk independently.

Clinical examination disclosed pronounced dysarthria and ataxic-like limb movement interrupted by superimposed tonic involuntary contractions. The muscle decontraction was prolonged and percussion myotonia was absent. Fasciculations and myokymia-like movements were seen in her arms, but occurred only sparsely and inter-

mittently. The distal foot and hand muscles were borderline. Decreased; sensory conduction velocities were present uniformly in all examined muscles. The amplitudes of the sensory nerve CMAPs, or conduction dispersion of CMAPs, or conduction slowing. The amplitudes of the sensory nerve action potentials were either unrecordable or decreased; sensory conduction velocities were borderline.

The supramaximal stimulation of upper and lower limb motor nerves (median, ulnar, peroneal, and tibial nerves bilaterally) evoked CMAPs followed immediately or after a short period—up to 30 ms—by repetitive “neuromyotonic” discharges of high frequency (about 230 Hz), waning amplitude, and duration of hundreds of milliseconds that could be recorded with the surface recording electrodes.

The complete blockade of ulnar and median nerves at the elbow by lidocaine did 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 increase 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, ataxic-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 dysaesthesias and paraesthesias. It seems likely that these sensory phenomena of dysaesthesias and paraesthesia-
sias were evoked by similar types of sensory

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1 mV</td>
<td>Foot switch status:</td>
<td>Run ↑</td>
</tr>
<tr>
<td></td>
<td>Trig: 100 μV↑</td>
<td>50 ms</td>
</tr>
</tbody>
</table>

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 contractions (arrows):
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 GSTT1.1 Recently we discovered a new polymorphic site in the zeta class G–T (GSTZ1) polymorphism. This consists of a C6T transition at nucleotide 94 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 5.3 There are now thought to be four alleles of GSTZ1: Z1*1 (A, A, A, C), Z1*2 (A, G, A, C), Z1*3 (G, G, G, C) and Z1*4 (G, G, T, C). Here 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.4 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.5 To detect the nucleotide 245 polymorphism, PCR was performed with the following primers: 5′AAGAGGTGTAGTGATGTTGTCATGGTGCAAGTTGTCAC 3′; AGTGCC3′. The PCR was carried out in a 20 μl reaction volume containing reaction buffer IV (Advanced Biotechnologies, Epsom UK), 20 μM (NH4)2SO4, 75 mM Tris/HCl pH 9.0, 0.1% 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 Bsh1236II (MBI fermentas) at 37°C and fragments were separated by 8% polyacrylamide gel electrophoresis and stained with ethidium bromide. The restriction enzyme Bsh1236II cleaves the 245 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).6) (Table). Furthermore, in this group, the Z1*C genotype (G, G, G, C) was less common in the patients with Parkinson's disease than in the controls (30%). A 95% confidence interval (95% CI) 0.36–0.95, p=0.03, was 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 from the three polymorphic sites to determine the frequency of the four GSTZ1 allelic. The Z1*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 variants in detoxification genes, and exposure to environmental toxins. These include CYP2D6 and solvent exposure,7 GSTP1 and pesticide exposure8 and CYP2D6, pesticide exposure with Parkinson's disease with dementia.9 Thus, it has been recognised that studies examining the association of polymorphic variation in xenobiotic metabo- lism genes and Parkinson's disease should take into account the effect of exposure to toxicants.

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


A case of stiff limb syndrome responsive to plasma exchange

Stiff limb syndrome is a recently described, rare condition that is characterized by rigidity within the limbs that progresses in a relapsing and remitting fashion, often involving the muscles of the spondiers and brain stem.10 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 neurophysiologic abnormalities from stiff man syndrome and fewer of these patients have anti-GAD antibodies; they also typically show a poorly sustained response to bcaoan 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 autoantibody 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 contractions in her hands, followed by increasing immobility. Her neurological problems began at 24 years of age when she developed viral meningitis based on a headache, fever, and a CSF lymphocytosis that 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 and 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 her hands, which slowly progressed to the arms, and became progressively stiffer and her trunk became increasingly stooped 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 contractions of all fingers. She had irregular jerking movements of her right arm and leg that were accentuated by moving her hands and legs, which sometimes affected her jaw and she had difficulty swallowing large boluses of food. 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 showed 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 incapacitated 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 antitaxonal antibodies directed against GABA-ergic neurons. The patient had 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 treatment 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 neurophysiology on this patient, and Angela Vincent for the serological testing and detection of the antiauxonal antibody.

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

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

Correspondence to: Dr R Barker, Cambridge Centre for Brain Repair, Forvie Site, Robinson Way, Cambridge CB2 2YQ, 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 abruptly disappeared within 1 week. 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
his axia and pseudoathetosis in his fingers were noted.

Routine laboratory examinations were normal except for hyponatraemia due to the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) (plasma sodium 124 mEq/l, urinary sodium 182 mEq/l, plasma osmolarity 262 mOsmol/l, urine osmolarity 775 mOsmol/l, vasopressin 1.86 pg/ml; and normal renal, thyroid, and adrenal function). Liver function was normal, and blood hepatitis C virus RNA was negative. Immunoglobulins and complements were normal. Cryoglobulin, M-protein, antinuclear antibody, and anti-SS-A/-B antibodies were negative. We examined various antiviral antibodies (coxsackie viruses, herpes simplex virus, varicella zoster virus, cytomegalovirus, Epstein-Barr virus, measles, rubella, mumps, adenovirus, and influenza A) in the serum or CSF, but they showed no remarkable change. Several tumour markers in the serum also showed no particular change. Serum IgG class anti-GQ1b antibody was present with low titre as demonstrated by enzyme linked immunosorbent assay (ELISA).

Immunohistochemistry using frozen sections of rat cerebral cortex, cerebellum, spinal cord, and dorsal root ganglion showed no antineuronal antibody in the serum from the patient, although the serum from a patient with anti-Hu antibody positive para-neoplastic syndrome showed positive reactions with these neurons (data not shown). ELISA for anti-Hu antibody was negative in the serum and CSF. His CSF showed an increased protein concentration (159 mg/dl) without pleocytosis but no oligoclonal bands.

Brain and spinal MRI were normal. Whole body CT examination; colon fibroscopy and gastric biopsies were normal. Cryoglobulin, M-protein, antinuclear antibody, and anti-SS-A/-B antibodies were negative. We examined various antiviral antibodies (coxsackie viruses, herpes simplex virus, varicella zoster virus, cytomegalovirus, Epstein-Barr virus, measles, rubella, mumps, adenovirus, and influenza A) in the serum or CSF, but they showed no remarkable change. Several tumour markers in the serum also showed no particular change. Serum IgG class anti-GQ1b antibody was present with low titre as demonstrated by enzyme linked immunosorbent assay (ELISA).

Immunohistochemistry using frozen sections of rat cerebral cortex, cerebellum, spinal cord, and dorsal root ganglion showed no antineuronal antibody in the serum from the patient, although the serum from a patient with anti-Hu antibody positive para-neoplastic syndrome showed positive reactions with these neurons (data not shown). ELISA for anti-Hu antibody was negative in the serum and CSF. His CSF showed an increased protein concentration (159 mg/dl) without pleocytosis but no oligoclonal bands.

Brain and spinal MRI were normal. Whole body CT examination; colon fibroscopy and a "Ga-citrate scintigram showed no malignancy.

On neurophysiological studies, an EEG showed delta bursts in all leads. Motor conduction velocity and amplitude of compound muscle action potentials in the right median, ulnar, and posterior tibial nerves were within the normal range. By contrast, sensory nerve action potentials (SNAPs) could not be elicited in right median and sural nerves. In the right ulnar nerve, amplitude of SNAPs was markedly decreased (5 µV) with preservation of sensory conduction velocity (53.3 m/s). A needle EMG gave normal results. Sympathetic skin response could not be elicited in the upper and lower limbs. The coefficient of variation of R-R intervals on ECG was decreased (1.17% at rest; mean value and lower limit in the 50s age group 2.80, 1.41).

The sural nerve biopsy disclosed marked axonal degeneration with a significant decrease of both myelinated (1359/mm²) and unmyelinated fibres (13 791/mm²) (figure). There was no inflammatory cell infiltration or vasculitis.

The patient was treated with plasmapheresis (3000 ml×3) beginning on 6 October. Soon after the plasmapheresis, joint sensation in his fingers was slightly improved and anisocoria disappeared. Plasma sodium concentration, the patient's level of consciousness, and the EEG were subsequently normalised. After the plasmapheresis, he was treated with steroids (methylprednisolone (1000 mg intravenously), for the first 3 days, and then prednisone (60 mg orally), followed by a gradual taper). This did not further improve his symptoms; severe sensory impairment, orthostatic hypotension, and constipation persisted 3 months after the onset of the disorder.

Our patient presented with acute onset of sensory impairment, autonomic dysfunctions, selective impairment of sensory and autonomic nerves in electrophysiological studies, and a raised CSF protein concentration. These clinical features are compatible with a diagnosis of AASN. In addition, our patient showed SIADH and consciousness disturbance suggestive of involvement of the CNS.

In AASN, episodes of infection before the onset are often seen, suggesting that preceding infection may initiate the immunemediated process leading to AASN. Pavesi et al described a patient with Coxsackie B virus infection complicated by an acute autonomic and sensory neuropathy. In their patient, diffuse mucosal and cutaneous erythema preceded neurological complications. Our patient also presented a cutaneous lesion followed by an autonomic and sensory neuropathy. However, serum and CSF studies for antiviral antibodies showed no evidence for any viral infection.

Peripheral neuropathy is a rare neurological side effect of interferon. There have been reports of multiple mononeuropathy, acute motor or sensorimotor axonal polyneuropathy, and cranial nerve palsies. Although the pathomechanism underlying peripheral neuropathy associated with interferon is unknown, immunomodulatory effects of interferon may cause disorders of the peripheral nervous system.

In our patient, AASN developed after the interferon therapy with an increased protein concentration in the CSF, and plasmapheresis seemed to result in slight improvement and prevention of the disease progression. This is the first report suggesting association of interferon and AASN. We suggest that interferon may induce an immune mediated pathomechanism underlying peripheral neuropathy associated with interferon.
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 University, 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

Neuropathic pain with vesical and rectal hyperreflexia and cocontraction after pelvic surgery

Pelvic and pudendal nerve injury can occur during extirpative visceral surgery such as radical hysterectomy. 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 studies, which showed vesical instability associated with unstable urethral function; simultaneous vesical and rectal hyperreflexia in both cases. This patient 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 without discomfort. She developed progressive urinary and rectal urgency. Neurological examination and anal tone were normal. Vaginal examination showed exquisite tenderness on the left. Nerve conduction study showed prolonged pudendal nerve latency (left 2.7 ms, right 2.4 ms; normal range 2.0 ± 0.2 ms).

Magnetic resonance imaging of the spine and pelvis were normal, as was flexible cystoscopy. An ambulatory urorectodynamic 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. Both patients probably had injury to the pelvic nerves, which is well recognised after extensive hysterectomy.

Figure 1. Eight minute trace from first ambulatory study on patient 1, showing uninhibited vesical contraction, urethral instability, and abnormal rectal contraction associated with a fall in anal pressure. Note simultaneous vesical and rectal contractions (cocontractions).

www.jnnp.com
of urinary bladder contraction induced by rectal and vaginal stimulation and the development of bladder and rectum cocontractions, which have not been reported previously.

Our cases show how pelvic surgery could be complicated by persistent neuropathic pain and bladder and bowel hypersensitivity, and further studies of spinal cord excitability are needed to clarify underlying mechanisms. Early recognition and initiation of analgesic treatment for neuropathic pain is essential to prevent the condition becoming intractable.

P SHEMBALKAR P ANAND
Periperal Neuropathy Unit, Department of Neurology, Imperial College School of Medicine, Area A, Ground Floor, Hammersmith Hospital, Du Cane Road, London, W12 6NB, UK

I JRtextarea
Department of Urology, The Royal London Hospital, Whitechapel, London E1 1BB, UK

N S WILLIAMS
Academic Department of Surgery, The Royal London Hospital, Whitechapel, London E1 1BB, UK

Correspondence to: Professor P Anand P:Anand@ic.ac.uk


82


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.1 Acute lumbo-sacral plexopathies have been described, however, in older patients with vascular disease when the internal iliac arteries are interrupted.2,3 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 markedly raised blood pressures, trace proteinuria, oliguria, and generalised oedema. She was diagnosed with preeclampsia 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. A 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 demonstrated loss of 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- cocolumbar spinal cord was unremarkable. An initial magnetic resonance angiogram (MRA) of the pelvis showed segmental occlusions of both internal iliac arteries with distal reconstitutio n greater on the left than on the right. 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 left leg 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, 3 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 necrosis progressed to an open non-healing ulcer 7 cm5 cm over the sacrum and left gluteal musculature. Magnetic resonance imaging of the region disclosed additional tissue necrosis subcutaneously along the left posterior lateral buttock and inflammation in the surrounding subcutaneous tissues and under 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 superior gluteal arteries 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 8 weeks (after ligation) showed 2+ to 4+ fibrillations and positive sharp waves in the vastus lateralis, tibialis anterior, and lateral gastrocnemius muscles, consistent with acute 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 mV, 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 part of the thigh, and the skin of the buttocks. The sciatic nerve roots are interrupted.

We report on a teenage patient with similar peripheral nerve ischaemia after bilateral internal iliac artery ligation for postpartum haemorrhage.
clination, whereas severe ischaemia produces Wallerian degeneration. In our patient, the reduction in the left sural sensory amplitude and slowing of the left sural sensory and posterior tibial motor conduction velocities were more consistent with axonal degeneration than demyelination, implying a significant degree of injury.

Our patient had no pre-existing vascular risk factors that would have predisposed her to ischaemic complications, but possible contributing factors in her case include pre-eclampsia, prior bilateral uterine artery ligation, and postpartum endometritis. Pre-eclampsia is associated with changes in the renin-angiotensin-aldosterone axis, an increased thromboxane to prostacyclin ratio, and an increase in plasma endothelin. These factors result in vasoconstriction and platelet aggregation, which could interfere with pelvic collateralisation. The ligation of both uterine arteries before the internal iliac artery ligation may have reduced pelvic collateral flow. Postpartum pelvic infections can also alter vascular tone or extend to involve ovarian and pelvic vessels, potentially interfering with collateralisation.

In summary, although internal iliac artery ligation is generally well tolerated because of multiple collateral sources of blood supply, complications such as peripheral nerve injury and necrosis of the gluteal musculature can occur. Although this occurs most commonly in patients with severe aortoiliac vascular disease or vascular risk factors such as insulin-dependent diabetes mellitus or radiotherapy treatment, it can occur even in their absence.

R K SHIN
M M STECKER
Department of Neurology, Hospital of the University of Pennsylvania, 3400 Spruce Street, Philadelphia, PA 19104–4283, USA

S G IMBESI
Department of Radiology

Correspondence to: Dr R K Shin
shirobk@mail.med.upenn.edu

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 vascular 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 aceneiform nodules on his face. Physical examination showed active genital ulceration. Neurological examination disclosed drowsy consciousness and disorientation. Moderate degrees of hemiparesis and hemihypoesthesia 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 (Sigma 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/mm²). 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

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 aceneiform nodules on his face. Physical examination showed active genital ulceration. Neurological examination disclosed drowsy consciousness and disorientation. Moderate degrees of hemiparesis and hemihypoesthesia 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 (Sigma 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/mm²). 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

T2 weighted image (A) and apparent diffusion coefficient map (B) obtained 3 days after onset show T2 hyperintensity and increased diffusion involving a basal ganglion on the right side. Follow up images (C and D) obtained 1 year later show considerable resolution of previous T2 and diffusion abnormalities but basal ganglia atrophy.

www.jnnp.com

Downloaded from http://jnnp.bmj.com/ on June 25, 2017 - Published by group.bmj.com
regression line best fitting the points for k versus s (SI); where SI is the signal intensity from a region of interest within the images acquired at each k 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 to 1.26 × 10^-10 cm²/s), compared with a matching location in the uninvolved contralateral hemisphere (ranging from 0.77 to 0.80 × 10^-10 cm²/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 later he was readmitted with a slowly progressive bulbar syndrome, 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 × 10^-10 cm²/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 diencephalic 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 types of lesions according to the age of lesion at the time of examination. A recent pathological report in a fulminant 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-J KOO
B-W YOON
J-K ROH
Department of Neurology, Seoul National University College of Medicine, 28 Yongong-dong, Chongno-gu, Seoul 110–744, Korea

I C SONG
K H CHANG
Department of Radiology

Correspondence to: Dr J K Roh,
rohjk@snu.ac.kr

Aziathioine and interferon β-1b treatment in relapsing-remitting multiple sclerosis

Both interferon β-1b (IFNβ-1b) and aziathioine (AZA) are effective in reducing relapse frequency in relapsing-remitting multiple sclerosis (RRMS).† 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 IFNβ-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 times 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; briefly, the scores 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 IFNβ-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 (but not the IFNβ-1b) group and pretreatment relapse frequency (RF) was lower than in the IFNβ-1b 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></th>
<th>IFNβ-1b</th>
<th>AZA</th>
<th>NT</th>
</tr>
</thead>
<tbody>
<tr>
<td>No of patients</td>
<td>11</td>
<td>10</td>
<td>11*</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>3/8</td>
<td>2/8</td>
<td>3/8</td>
</tr>
<tr>
<td>Age (entry)</td>
<td>33 (6.2)</td>
<td>31.2 (4.9)†</td>
<td>38 (6.3)†</td>
</tr>
<tr>
<td>Disease duration (y)</td>
<td>8.3 (5)</td>
<td>6.95 (6.7)</td>
<td>8.4 (6.8)*</td>
</tr>
<tr>
<td>EDSS at entry</td>
<td>2.32 (0.9)</td>
<td>2.35 (0.9)</td>
<td>1.83 (1.15)</td>
</tr>
<tr>
<td>At 12 months</td>
<td>2.2 (1.0)</td>
<td>2.1 (0.9)</td>
<td>1.9 (1.3)</td>
</tr>
<tr>
<td>No of worsened patients at 12 months</td>
<td>1/11</td>
<td>0/10</td>
<td>2/10</td>
</tr>
<tr>
<td>RF 2 year pretreatment</td>
<td>2.2 (0.8)†</td>
<td>2 (1)</td>
<td>1.4 (0.3)†</td>
</tr>
<tr>
<td>At 12 months</td>
<td>0.8 (0.7)‡</td>
<td>0.9 (0.4)‡</td>
<td>1.0 (0.9)</td>
</tr>
<tr>
<td>No of relapse free patients at 12 months</td>
<td>4/11</td>
<td>7/10</td>
<td>4/10</td>
</tr>
<tr>
<td>PUC at entry</td>
<td>68.02 (9.1)</td>
<td>61.7 (10.8)</td>
<td>61.7 (11.7)</td>
</tr>
<tr>
<td>Change at 12 months</td>
<td>+2.64 (9.26)</td>
<td>+7.9 (9.8)</td>
<td>+3.86 (13.7)</td>
</tr>
<tr>
<td>MHC at entry</td>
<td>74.7 (15.7)</td>
<td>61.25 (14.5)</td>
<td>58.7 (16.9)</td>
</tr>
<tr>
<td>Change at 12 months</td>
<td>-6.04 (13.9)†</td>
<td>+21.25 (11.9)‡</td>
<td>+6.37 (21.8)</td>
</tr>
<tr>
<td>RLE at entry</td>
<td>38.34 (32.4)</td>
<td>37.5 (33.0)</td>
<td>55.55 (40.8)</td>
</tr>
<tr>
<td>Change at 12 months</td>
<td>+19.5 (29.5)</td>
<td>+16.7 (24.5)</td>
<td>+5.56 (8.2)</td>
</tr>
</tbody>
</table>

IFN=Interferonβ-1b treated patients; AZA=aziathioine treated patients; NT=no actively treated patients; RF=relapse frequency (No of relapses/patient/y); worsened= Increase of ≥1 EDSS point; PUC=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 vs AZA p=0.01.
‡RF at entry : NT vs IFN p=0.006.
‡MHC change : IFN vs AZA p=0.006.
‡RLE change : IFN vs AZA p=0.001.
§Significant differences within each group (12 months v entry):
§RF, IFN p<0.001.
§AZA p=0.005.
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 the 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 relapse frequency in patients with RRMS. The occurrence in the other two groups.

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, originally×50). This shows neuronal loss and tissue rarefaction with fibrillary gliosis, presenting as spongy with little inflammation.

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 Milanese
mrgroup@istituto-besta.it


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

The appearance of X-linked adrenomyeloneuropathy (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.1 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).2 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.3 Close et al described an 8 year old boy who had a left occipitotemporal white matter lesion extending into the ipsilateral thalamus on MRI.4 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.5 The findings indicate that plasma very long chain fatty acid
concentrations should be measured in patients with unexplained basal ganglia abnormalities on MRI.

R SAKIKARIB
T FUKUTAKE
K ARAY
K KATAYAMA
M MORI
T HATTORI
Neurology Department Chiba University, 1-8-1 Inohana Chuo-Ku, Chiba 260-8670 Japan

R SAKIKARIB
T FUKUTAKE
K KATAYAMA
M MORI
Neurology Department Kashima Rosai Hospital, 1-9108-2 Ootsu-Honnachi Hasashii, Kashima 314-03 Japan

Correspondence to: Dr R Sakikarib
sakiki@med.m.chiba-u.ac.jp

turisnal disturbance in a patient with adreno-
3 Afifi AK, Menezes AH, Reed LA, et al. Atypical
presentation of X linked childhood adrenoleu-
k dystrophy with an unusual magnetic reso-

4 Close PJ, Sinnett SJ, Nolan KT. Adrenoleukodystrophy: a case report demon-

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).1 The mechanism of action is thought to involve MHC-II block-
ade2 and the induction of a Th2/Th3 cytokine response.3 Peripheral blood mononuclear cells from patients with multiple sclerosis and healthy controls proliferate in response to GA in vitro.4 Therefore GA seems to have both immunostimulatory and immunomodulatory potential.

In our centre 27 patients with relapsing-
remiting 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. Re-
lapsing-relapsing according to Poser crite-
ria 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 lymphadenopa-
yth 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 (patient 1) 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 lymphaden-
opathy 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 0.33/year at the beginning of the study and from 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 lymphopa-


Patients examined in this study were enrolled in our centre as part of the German phase IIb study (protocol COP 1600) supported by TEVA and Aventis.

A WINDHAGEN
S MANIAT
S MARCKMANN
A WILKENING
R B LINDERT
F HEIDENREICH
Neurologische Klinik, Medizinische Hochschule Hannover, Carl-Neuburg-Straße 1, 30623 Hannover, Germany

R BLASZCZYK
Abteilung für Transfusionsmedizin

www.jnnp.com

Clinical data of patients with multiple sclerosis treated with glatiramer acetate

<table>
<thead>
<tr>
<th>Lymph node swelling</th>
<th>Annual relapse rate at start</th>
<th>Annual relapse rate in study</th>
<th>EDSS at start of study</th>
<th>EDSS at end of study</th>
</tr>
</thead>
<tbody>
<tr>
<td>No lymph node swelling</td>
<td>1.5 (1–3.5)</td>
<td>0.54 (1–1.8)</td>
<td>2.5 (0–3.5)</td>
<td>3 (0–6.5)</td>
</tr>
<tr>
<td>Lymph node swelling</td>
<td>1.8 (1–3.5)</td>
<td>0.33 (0–1)</td>
<td>2.5 (0–3.5)</td>
<td>2.5 (0–3.5)</td>
</tr>
</tbody>
</table>

Values are mean (relapse rate) or median (EDSS) (range).

Correspondence to: Dr A Windhagen
Windhagen.Anja@mh-hannover.de

CORRESPONDENCE

Neurovisual rehabilitation in Balint’s syndrome

Further to the excellent review of neurovisual 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 mobile unaided. However, he presented with simultanagnosia, optic ataxia, and psychic paralysis of gaze. This had an adverse impact on his functional independence; he had difficulty reading or finding things in furniture and walls—and other activities of daily living including dressing and toiletting. 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 them to compensate for problems and altering the environment to lessen their disabilities.
- The remedial approach, which involves restoration of the damaged CNS 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 of 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 3EX, 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 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 people with Balint’s syndrome. It is contingent on a multidisciplinary approach for optimal outcome. This case helped to improve basic visual abilities as well as the patient’s ability to live independently.

In two patients with Balint’s syndrome treated for several months in our unit, severe visual deficits 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,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 disorders, 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. However, there is a need to find appropriate methods 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 severe traumatic, uraemic, 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 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 “jerk-waveform see-saw nystagmus”.[1] 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 platform.


Neurology Immunogenic potential of copolymer 1 in nor-...
scleral search coil technique. I suspect 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) phases 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.

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 torsional 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-Chiari 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, however, point out that this association is unusual.

Because of the lack of strong evidence of a torsional component to the dissociated vertical nystagmus, we preferred the term, kindly suggested by a reviewer, “nystagmus of skew.” This would represent a more inclusive disjunctive jerk away from the side of the lesion.

Jacobson et al described in therapeutic doses, but also 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 systemic 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 difficult 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 salivorrhoea in ALS. The transducat approach in particular seems to have unacceptable side effects.

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 salivorrhoea 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 Bottox into the parotid glands of a 59 year old women who had ALS with pronounced bulbar palsy. We noticed a reduction of the salivorrhoea but facial weakness on the left side worsened significantly.

After this experience we developed a protocol for the treatment of salivorrhoea in patients with ALS with bulbar palsy by retrograde 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 production were performed before the BoNT/A injection and on days 1, 5, 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 simple method: the patients were asked to expectorate 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 production (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 between days 4 and 21. Both patients had a “moderate” improvement of salivorrhoea 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 salivary 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. After these experiences we decided to stop the pilot study. The injection of BoNT/A through the salivary 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. After these experiences we decided to stop the pilot study.

We have recently conducted a similar study which was interrupted due to serious side effects.

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

After this experience we developed a protocol for the treatment of salivorrhoea in patients with ALS with bulbar palsy by retrograde 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 production were performed before the BoNT/A injection and on days 1, 5, 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 simple method: the patients were asked to expectorate 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 production (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 between days 4 and 21. Both patients had a “moderate” improvement of salivorrhoea 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 salivary 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. After these experiences we decided to stop the pilot study.

The injection of BoNT/A through the salivary 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. After these experiences we decided to stop the pilot study.

We have recently conducted a similar study which was interrupted due to serious side effects.

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

After this experience we developed a protocol for the treatment of salivorrhoea in patients with ALS with bulbar palsy by retrograde 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 production were performed before the BoNT/A injection and on days 1, 5, 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 simple method: the patients were asked to expectorate 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 production (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 between days 4 and 21. Both patients had a “moderate” improvement of salivorrhoea but did not want the injections to be repeated. After these experiences we decided to stop the pilot study.
Treatment of early onset Parkinson’s disease with ropinirole

The recent editor’s supporting initial treatment of early onset Parkinson’s disease with a dopamine agonist hinged in part on the demonstration in 266 patients that treatment of early onset Parkinson’s disease with ropinirole alone or with an additional levodopa dopa decarboxylase inhibitor (benserazide) (LD/DDI) resulted in substantially less dyskinesia than with LD/DDI 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/DDI, and 45% of those on LD/DDI alone. The trial design allowed LD/DDI supplementation if required was unadministered. 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/DDI alone who withdrew as a result of dyskinesia events, and for the occurrence of nausea in 49.4% of patients on LD/DDI alone. Whether smaller, more frequent, dosage would have allowed better toleration of and motor response to ropinirole, it is possible that frequent dyskinesia was seen at 5 years on three times daily dosage of LD/DDI. A substantial proportion of patients on LD/DDI (43.8%) were also on selegiline, amplifying the effect substantially. By 5 years, 25% of patients on LD/DDI alone.

Whereas it may be argued that different drug preparations and methods of assessment invalidate comparison, it may be simple that less frequent high pulsatile dosage provokes not only greater dyskinesia but also, as a mirroring effect, greater off time as postsynaptic 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 was 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/DDI (with little or no change in LD/DDI dosage requirement over 57 months), and of a neuroprotective effect of levodopa, the results of Rascol et al. should not dissuade others from pursuing oral treatment with LD/DDI in a more frequent, lower dose regime. With gradual (allowing for the long duration action of levodopa) titration of slow release LD/DDI dosage and interdose interval (if necessary using a timer), against response and compliance of patient (or carer), it may in theory, and with sufficient observation and titration, in practice be possible to approximate to such a steady state stimulation and response. This would have potentially less risk for developing hallucinations, and would cost less.

J R PONSFORD

Department of Neurology, Walsgrave Hospital NHS Trust, Clifford Bridge Road, Coventry CV2 2DX, UK


The authors reply:

We appreciate the comments by Winterholer et al on our article1 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 Winterholer et al report on sublingual salivary gland infection 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 lower and also indicate that the transcutaneous approach as performed in several studies1 may be safer than the retrograde transducal injection. This is not unexpected as the transducal 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 and later in 1999,3 patients, ironically reported earlier in 1997, and later in 1999,4 in whom dosage could be adjusted up to five or more times a day resulted not only in a lower frequency of dyskinesia (20.6% IR, 21.7% CR) at 5 years but also a lower mean total daily dose (426 mg IR; 510 mg CR (biocoequivalent)).

Whereas it may be argued that different drug preparations and methods of assessment invalidate comparison, it may be simple that less frequent high pulsatile dosage provokes not only greater dyskinesia but also, as a mirroring effect, greater off time as postsynaptic 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 was 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/DDI (with little or no change in LD/DDI dosage requirement over 57 months), and of a neuroprotective effect of levodopa, the results of Rascol et al. should not dissuade others from pursuing oral treatment with LD/DDI in a more frequent, lower dose regime. With gradual (allowing for the long duration action of levodopa) titration of slow release LD/DDI dosage and interdose interval (if necessary using a timer), against response and compliance of patient (or carer), it may in theory, and with sufficient observation and titration, in practice be possible to approximate to such a steady state stimulation and response. This would have potentially less risk for developing hallucinations, and would cost less.

J R PONSFORD

Department of Neurology, Walsgrave Hospital NHS Trust, Clifford Bridge Road, Coventry CV2 2DX, UK


J Neurol Neurosurg Psychiatry 2001;70:406–425

The authors reply:

We appreciate the comments by Winterholer et al on our article1 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 Winterholer et al report on sublingual salivary gland infection 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 lower and also indicate that the transcutaneous approach as performed in several studies1 may be safer than the retrograde transducal injection. This is not unexpected as the transducal 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 and later in 1999,3 patients, ironically reported earlier in 1997, and later in 1999,4 in whom dosage could be adjusted up to five or more times a day resulted not only in a lower frequency of dyskinesia (20.6% IR, 21.7% CR) at 5 years but also a lower mean total daily dose (426 mg IR; 510 mg CR (biocoequivalent)).

Whereas it may be argued that different drug preparations and methods of assessment invalidate comparison, it may be simple that less frequent high pulsatile dosage provokes not only greater dyskinesia but also, as a mirroring effect, greater off time as postsynaptic 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 was 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/DDI (with little or no change in LD/DDI dosage requirement over 57 months), and of a neuroprotective effect of levodopa, the results of Rascol et al. should not dissuade others from pursuing oral treatment with LD/DDI in a more frequent, lower dose regime. With gradual (allowing for the long duration action of levodopa) titration of slow release LD/DDI dosage and interdose interval (if necessary using a timer), against response and compliance of patient (or carer), it may in theory, and with sufficient observation and titration, in practice be possible to approximate to such a steady state stimulation and response. This would have potentially less risk for developing hallucinations, and would cost less.

J R PONSFORD

Department of Neurology, Walsgrave Hospital NHS Trust, Clifford Bridge Road, Coventry CV2 2DX, UK


Does disturbed homocysteine and folate metabolism in depression result from enhanced oxidative stress?

In their recent article, Bottiglieri et al described increased homocysteine concomitant with decreased folate concentrations in a subgroup of patients with depression. In addition, some relation between folate deficiency 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 mechanism underlying this metabolic abnormality. Both metabolic pathways depend on the presence of reduced pteridine species: (1) the biosynthesis of methionine requires supply of methyl groups from 5,6,7,8-tetrahydrofolic acid, deficiency of which results in hyperhomocysteinemia; (2) biosynthesis of serotonin, dopamine, and noradrenaline (norepinephrine) depends on the presence of 5,6,7,8-tetrahydrobiopterin, deficiency of which thus results in monoamine deficiency. Both tetrahydropteridines are recycled by dihydropyridine reductases; both compounds have strong reducing capacities and are thus rapidly oxidised by oxidising chemicals. Interestingly, recent studies show that depression is associated with activation of the immune system, and it is even speculated that an infectious agent might be involved. Immune-system activation is accompanied by an increased production of reactive species by cytotoxic cells such as activated monocytes and macrophages to achieve antimicrobial and antiviral activities. Activated human monocytes/macrophages also release increased amounts of neopterin — another pteridine derivative — which is a sensitive index for the mediation of cell mediated immune reactions in patients. Recent data also point to a new functional aspect of neopterin—namely, to enhance oxidative processes. Increased concentrations of neopterin have been described in patients with depression. The question arises whether oxidative stress rather than insufficient dietary intake of folate is the basis of 5,6,7,8-tetrahydrofolic acid and also 5,6,7,8-tetrahydrobiopterin deficiency. Interestingly, in patients with Alzheimer’s dementia a similar relation has already been demonstrated: hyperhomocysteinemia was associated with reduced folate concentrations, but also an increased degree of impaired activation could be detected in the same patients. There is good reason to think that the scenario might be similar in patients with depression, and enhanced oxidative stress due to chronic immune system activation is a major cause of the loss of reductants such as 5,6,7,8-tetrahydrofolic acid and 5,6,7,8-tetrahydrobiopterin.

B. WIDNER
D. FUCHS
Institute of Medical Chemistry and Biochemistry, Fritz Probst Strasse 3, A-6020 Innsbruck, Austria; University of Innsbruck, Ludwig Boltzmann Institute of AIDS-Research, Innsbruck, Austria

F. LEBL HUBER
Department of Gerontology, Landesenzervenlinik Wagner-Jauregg, Linz, Austria

B. SPERNER-UNTERWEGER
Department of Psychiatry, University of Innsbruck, Innsbruck, Austria

Correspondence to: Dr D Fuchs
Dietmar. Fuchs@uibk.ac.at


Reynolds and Bottiglieri reply:

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 agree that simply dietary deficiency is an inadequate explanation for 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 described a fall in BH4 in depressed patients 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 plays a part is speculative. We are unaware of any clinical or experimental evidence that oxidative stress leads to folate deficiency. It has been suggested that folates play a part in maintaining BH4 synthesis in patients with folate deficiency and BH4 to aging requires clarification. It is also relevant that S-adenosyl-methionine, the major methyl donor in the brain which derives its methyl group from methyl folate, can be lost, increased turnover of monomethyls in the brain. This and other evidence suggests that methylation mechanisms are involved in these relations and in mood and cognitive function.

E H REYNOLDS
Institute of Epileptology, Weston Education Centre, King’s College, Denmark Hill Campus, Cuncombe Road, London SES 9P7, UK

T BOTTIGLIERI
Metabolic Disease Center, Baylor Research Institute, 8181 Elms Street, Dallas, Texas 75235, USA

Correspondence to: Dr E H Reynolds
reynolds@buckes.t.net.com


Long term follow up after perimesencephalic subarachnoid haemorrhage

Marquardt et al describe the clinical course and long term outcome of 21 patients who were diagnosed as having a perimesencephalic haemorrhage. The paper raises two questions.

The first is an impression of an “emperor’s new clothes syndrome” given by the first figure of the publication. This figure shows a slice of the CT made shortly after the initial episode of headache in the patient reported to have a recurrent episode of perimesencephalic haemorrhage. The legend of the figure states that the CT shows extravasated blood in the perimesencephalic subarachnoid space, but we fail to see any blood at all. Thanks to the electronic availability of the Journal we were able to review not only the paper version of the figure, but also an enlarged version on screen. Even after enlargement no blood was seen; the slice nicely shows the tentorium adjacent to the ambient cisterns, the proximal parts of the posterior cerebral arteries, and perfectly clear CSF in the perimesencephalic (chiasmatic and partly the ambient and quadrigeminal) cisterns and in the frontotemporalis and Sylvian fissures.

There are several explanations for this diagnostic mystery. Firstly, the authors may have submitted an inappropriate slice of the CT. In some patients with perimesencephalic haemorrhage, the precommunicant cistern is the only site where CT shows blood. If blood was visible in the precommunicant cistern in this particular patient, the authors have indeed found a patient with a perimesencephalic, non-aneurysmal haemorrhage with a recurrent haemorrhage. Given the unique character of this sequence of events, it would be fair to provide the appropriate slice to convince readers of the Journal.

Secondly, if no evidence of blood is found even in the precommunicant cistern, the patient may have had a CT negative subarachnoidal haemorrhage. In patients with aneurysms CT can be negative, even if performed within 12 hours after onset of the haemorrhage. But a negative CT plus a negative angiography does not add up to a diagnosis of perimesencephalic haemorrhage.

Thirdly, the patient may not have had a subarachnoidal haemorrhage at all. The case report tells us that lumbar puncture was positive, but does not give details. Because
lumbar puncture was performed before the CT, and CT was performed on the day of the headache, lumbar puncture may have been performed too early to detect blood degradation products in the CSF and therefore too early to distinguish a traumatic tap from a genuine haemorrhage. In the absence of degradation products the patient may have had a non-haemorrhagic cause of the headache.

With regard to figure 2, a slice of the CT made after the second episode of headache, it would be interesting to know the interval between the onset of symptoms and the CT. Perimesencephalic haemorrhage can be diagnosed reliably only if the initial CT is performed within 3 days after onset of the symptoms. After this interval distinction between aeurysmal and perimesencephalic patterns becomes unreliable.

The second issue is that of long term outcome. On long term follow up the authors found a high rate of persisting symptoms such as headaches, irritability, depression, and fatigue. This contrasts with the good quality of life (as measured by the sickness impact profile) of a validated questionnaire on quality of life found in a follow up study performed in The Netherlands.1 If the methods used by Marquardt et al are valid, the difference in outcome between these two studies population requires an explanation. This is where the question on management strategy for patients with perimesencephalic haemorrhage comes in. Do the authors include any restriction in counselling their patients who have had a perimesencephalic haemorrhage, or are such restrictions imposed on these former patients by physicians who assess people before employment or by medical advisors of insurance companies? We reassure patients on discharge and again a couple of weeks later, at an outpatients, consultation, that a perimesencephalic haemorrhage is not a warning for a major neurological event, we do not impose any restrictions, and we stimulate patients to take up all activities they undertook before the haemorrhage. We hypothesise that imposing restrictions or sharing worries or worries with patients can lead to subjective symptoms as described above. Given this possibility we are reluctant to start informing patients that perimesencephalic haemorrhages can reoccur, as long as no evidence has not been reported convincingly. We do agree that the patient reported on forms a diagnostic challenge, but convincingly. We do agree that the patient as recurrences have not been reported.

A third angiography performed in the course of treatment in the second episode of haemorrhage again did not disclose any source of the bleeding, and thus the diagnosis of PMSAH remains 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 persisting symptoms such as headaches, irritability, depression, and fatigue 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 explana-

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 patients with PMSAH, which was compared with that of a reference population. Analysing the submitted data, however, significant differences towards less dysfunction and less disability between patients were proved only for the categories body care, movement, and household management. Six of the 25 patients (24%) had more dysfunction in the category work than the reference population, and 11 patients (44%) reported a change in their headache pattern as non-specific headaches occurred more often than before the haemorrhage in 10 patients and less often than before in one patient. Two patients reported fear of rebleeding. Brilstra et al concluded that patients with a perimesencephalic haemorrhage have no reduction in quality of life but had to admit “that most consequences of the perimesencephalic subarachnoid haemorrhage are found in the psychosocial domains.” They relate the problems with short term memory, sleeping, fears, irritability, and nervousness with the haemorrhage itself and with the experience of being admitted leading to admission to an intensive care unit. This does not contrast with our findings at all. However, the focus of our follow up study 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 was described and that is surprising 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 previous 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 on PMSAH account for about half of these patients with angiogram negative subarachnoid haemorrhage.1 On these premises there must be thousands of patients every year who are treated for PMSAH without any account of the patient world. However, reviewing the literature in 1996, Schwartz and Solomon could only find 169 reported patients who had PMSAH.1 It seems, therefore, reasonable to compile more data to gain more information about the natural course of PMSAH in significantly larger cohorts of patients.

G MARQUARDT
T NIEBAUER
U SCHICK
Neurological Clinic, Johann Wolfgang
Goethe-University, Schleusenweg 2-16, 60528
Frankfurt am Main, Germany

Correspondence to: G J Rinkel


Idiopathic intracranial hypertension and antiparticle antibodies

The study by Kesler et al concludes with the assumption that the presence of antiparticle antibodies (aCL- Abs) indicates a unique subgroup of patients with idiopathic intracranial hypertension. Their study does not sup-

this conclusion is in their statement that there may have been an occult thrombosis of the cerebral venous sinuses, a fact that I agree with as CT and MRI cannot exclude a thrombosis for certain—hence intracranial hypertension would not be the diagnosis. It is not stated how soon cerebral sinus imaging was performed after the onset of symptoms. Thirdly, the concentration of raised aCL-Ab in these patients is not very high apart from one patient with less than 40 units are generally not thought to be pathological but this is quite an arbitrary figure as test systems are variable and not standardised. Fourthly, with a prevalence of aCL-Ab at 5% in Israel, the presence of these antibodies in three of 37 patients is not a significant finding ($\chi^2 p>0.45$). Finally, it is an accepted view that the presence of aCL-Ab may represent an epiphenomenon due to a non-specified injury. This is supported by the incidental findings of aCL-Ab in symptom-free patients. Hence the findings cannot support the authors' proposal that the patients with aCL-Ab form a subgroup of patients with intracranial hypertension.

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

Correspondence to: Dr O Backhouse obackhouse@hotmail.com

BOOK REVIEWS


The neuropathology of schizophrenia has been for a long time perhaps one of the most controversial fields of biomedical research. In the mid decades of the last century there was an increased interest in the neuropathology of psychosis based on the assumption that structural alterations in the brain would provide insight into the understanding of this complex and devastating disease. However, the results of these investigations have been contradictory and it has become a cliché to say that schizophrenia is the graveyard of neuropathologists. Indeed, the results of neuropathological investigations were confusing, and resulted from both clinical and pathological problems. The clinical definition of schizophrenia has been controversial and for a long time internationally accepted diagnostic criteria did not exist. Patients' cohorts were extremely variable and clinical histories far from complete. Most patients had treatment which again varied from centre to centre. The neuropathological methodology was also somewhat primitive and inappropriate to detect subtle changes. Moreover, the material examined varied considerably from centre to centre and sometimes the pathological changes described were the result of another disease process, including epilepsy or minor traumas. It was thus not surprising that these studies were both contradictory and arbitrary.

With the advent of neuroimaging a new era has started. It was Johnstone and her colleagues who showed structural alterations (enlarged ventricles) in the brains of psychotic patients, rekindled interest in the neuropathology of schizophrenia. This book is a comprehensive review of cerebral changes associated with psychosis. The 15 chapters cover a wide range of structural, functional, macroscopic, histological, neurochemical, and other pathological and methodological changes associated with the disease. In addition there are chapters on animal models and methodological issues, as well as on the consequences of treatment. The results of structural and functional imaging are reviewed, the second in relation to neural circuitries. There is an excellent chapter on cerebral asymmetry, a feature important in the understanding of the disease. Two chapters deal with development, one more specifically with cortical development, giving a concise review of the molecular basis for the organisation of the forebrain and pattern formation in relation to pathogenesis. Synaptic pathology and the organisation of cortical circuitries, for a long time inaccessible to conventional methodology, have become the subject of intense research, and recent developments have been suitably covered in two separate chapters. The chapter on cortical pathology reviews a new generation of quantitative microscopical studies in relation to the GABA, glutamate, and dopamine systems. The problems of the disorders are revisited in a separate chapter with the conclusion that it is unlikely to be a core feature of the neuropathology of schizophrenia. A chapter examines schizophrenia from the perspective of other neurodegenerative, diseases and lesions, including those which may cause schizophrenia-like symptoms—for example, metabolic diseases, epilepsy, and psychosis in neurodegenerative disorders. These provide useful information in the differential diagnosis of schizophrenia and other diseases of the nervous system with similar symptomatology. This is a timely book, reviewing recent developments in our understanding of the disease schizophrenia. The editors have brought together international experts in the field to produce a book with a true multidisciplinary approach. Their achievement should be congratulated. However, less praise should be lavished on the editors in the organisation of the book. The chapters on cortical pathology and the organisation of cortical circuitries are not as quantitative and specific as the respective chapters. The book is a comprehensive review of the diseases of the nervous system with similar symptomatology. It is a must for anyone working with people and should be purchased by those interested in schizophrenia, both neuropathologists and psychiatrists.

None the less, this is a book which should be purchased by those who are interested in schizophrenia, both neuropathologists and psychiatrists.

P L LANTOS

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 as it covers the advantages and disadvantages of eugenic policies to select against them, to justify infanticide. The other approaches 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 disabilities 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 grounded on the commonality of humanity and what it is to be human, carefully dissecting and dismissing the accusation that this opens the way to the charge of speciesism. He progresses from the definitions of mental handicap, the moral status of the disabled, through the difficult terrain of euthanasia, abortion, genocide, and oppression, finally ending with theological interpretations that offer alternatives to humanism.

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 any of those 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 these areas, occasionally using logic which is almost completely unsuspected 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—Sir Charles Sherrington fell over themselves to outpraise Cajal’s writings and their contemporary illustrations based on Golgi stains. He and Golgi went unexplored. His great synthesis was to evolve from the concept that organisation is a function 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 neurons; had the concepts of tropism 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 Crompton Lecture. During the visit, Cajal was arrested as a vagrant at Cambridge railway station when visiting the provinces to receive an honorary doctorate. Cajal and Sherrington fell over themselves to outpraise each other. Sherrington on 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. Textura 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 Swanson 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 translation by Pedro Pasik and Tauba Pasik as Texture of the Nervous System of Man and the Vertebrates. The first of these three volumes appeared in 1999; the other two are promised for 2000.

The advertising flysheet champions Cajal’s discovery of growth cones, chemoattractant 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 Musée-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 ultimate boundary 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 beings 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 [chemotactic] 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 deterrent 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. Facts and citations 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 deal with 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. 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 before being left to ponder over 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 post-symposia 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


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 corticosteroid concentrations in elderly subgroups are associated with a higher risk of developing cognitive deficits; reduced responsivity of the hypothalamo-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 steroids, 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 and 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 omitted keep: A discerning reader may often become frustrated due to the polysyllabic nature of many of the words that are used. The average surgical trainee would be hard put to manage the plethora of medical acronyms. The book aims to bridge the gap between the rapidly changing research literature and the practical and it provides valuable information for clinicians and basic researchers alike in this complex and growing area.

ROBERT KERWIN

This is the second edition of Gelb's systematic approach to the neurologic 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 these 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 management. One could take issue with the frequent use of case histories around which the authors build discussion of differential diagnosis.

This second edition particularly introduces details of neurological examination which are so ably presented elsewhere. The authors' programme for neurological examination is highly detailed and comprehensive. It is my impression that such exhaustiverote neurological examination is falling out of fashion now that systematic neurological practice in Britain. Yet it seems popular still with North American neurologists who may benefit from the luxury of more time for patient consultation. Students may be intriguéd by the frequency of case histories around which the authors build discussion of differential diagnosis.

This second edition particularly introduces details of neurological examination which are so ably presented elsewhere. The authors' programme for neurological examination is highly detailed and comprehensive. It is my impression that such exhaustive rote neurological examination is falling out of fashion now that systematic neurological practice in Britain. Yet it seems popular still with North American neurologists who may benefit from the luxury of more time for patient consultation. Students may be intriguéd by the frequency of case histories around which the authors build discussion of differential diagnosis.

This second edition particularly introduces details of neurological examination which are so ably presented elsewhere. The authors' programme for neurological examination is highly detailed and comprehensive. It is my impression that such exhaustive rote neurological examination is falling out of fashion now that systematic neurological practice in Britain. Yet it seems popular still with North American neurologists who may benefit from the luxury of more time for patient consultation. Students may be intriguéd by the frequency of case histories around which the authors build discussion of differential diagnosis.

This second edition particularly introduces details of neurological examination which are so ably presented elsewhere. The authors' programme for neurological examination is highly detailed and comprehensive. It is my impression that such exhaustive rote neurological examination is falling out of fashion now that systematic neurological practice in Britain. Yet it seems popular still with North American neurologists who may benefit from the luxury of more time for patient consultation. Students may be intriguéd by the frequency of case histories around which the authors build discussion of differential diagnosis.

This second edition particularly introduces details of neurological examination which are so ably presented elsewhere. The authors' programme for neurological examination is highly detailed and comprehensive. It is my impression that such exhaustive rote neurological examination is falling out of fashion now that systematic neurological practice in Britain. Yet it seems popular still with North American neurologists who may benefit from the luxury of more time for patient consultation. Students may be intriguéd by the frequency of case histories around which the authors build discussion of differential diagnosis.

This second edition particularly introduces details of neurological examination which are so ably presented elsewhere. The authors' programme for neurological examination is highly detailed and comprehensive. It is my impression that such exhaustive rote neurological examination is falling out of fashion now that systematic neurological practice in Britain. Yet it seems popular still with North American neurologists who may benefit from the luxury of more time for patient consultation. Students may be intriguéd by the frequency of case histories around which the authors build discussion of differential diagnosis.

This second edition particularly introduces details of neurological examination which are so ably presented elsewhere. The authors' programme for neurological examination is highly detailed and comprehensive. It is my impression that such exhaustive rote neurological examination is falling out of fashion now that systematic neurological practice in Britain. Yet it seems popular still with North American neurologists who may benefit from the luxury of more time for patient consultation. Students may be intriguéd by the frequency of case histories around which the authors build discussion of differential diagnosis.

This second edition particularly introduces details of neurological examination which are so ably presented elsewhere. The authors' programme for neurological examination is highly detailed and comprehensive. It is my impression that such exhaustive rote neurological examination is falling out of fashion now that systematic neurological practice in Britain. Yet it seems popular still with North American neurologists who may benefit from the luxury of more time for patient consultation. Students may be intriguéd by the frequency of case histories around which the authors build discussion of differential diagnosis.

This second edition particularly introduces details of neurological examination which are so ably presented elsewhere. The authors' programme for neurological examination is highly detailed and comprehensive. It is my impression that such exhaustive rote neurological examination is falling out of fashion now that systematic neurological practice in Britain. Yet it seems popular still with North American neurologists who may benefit from the luxury of more time for patient consultation. Students may be intriguéd by the frequency of case histories around which the authors build discussion of differential diagnosis.

This second edition particularly introduces details of neurological examination which are so ably presented elsewhere. The authors' programme for neurological examination is highly detailed and comprehensive. It is my impression that such exhaustive rote neurological examination is falling out of fashion now that systematic neurological practice in Britain. Yet it seems popular still with North American neurologists who may benefit from the luxury of more time for patient consultation. Students may be intriguéd by the frequency of case histories around which the authors build discussion of differential diagnosis.

This second edition particularly introduces details of neurological examination which are so ably presented elsewhere. The authors' programme for neurological examination is highly detailed and comprehensive. It is my impression that such exhaustive rote neurological examination is falling out of fashion now that systematic neurological practice in Britain. Yet it seems popular still with North American neurologists who may benefit from the luxury of more time for patient consultation. Students may be intriguéd by the frequency of case histories around which the authors build discussion of differential diagnosis.

This second edition particularly introduces details of neurological examination which are so ably presented elsewhere. The authors' programme for neurological examination is highly detailed and comprehensive. It is my impression that such exhaustive rote neurological examination is falling out of fashion now that systematic neurological practice in Britain. Yet it seems popular still with North American neurologists who may benefit from the luxury of more time for patient consultation. Students may be intriguéd by the frequency of case histories around which the authors build discussion of differential diagnosis.

This second edition particularly introduces details of neurological examination which are so ably presented elsewhere. The authors' programme for neurological examination is highly detailed and comprehensive. It is my impression that such exhaustive rote neurological examination is falling out of fashion now that systematic neurological practice in Britain. Yet it seems popular still with North American neurologists who may benefit from the luxury of more time for patient consultation. Students may be intriguéd by the frequency of case histories around which the authors build discussion of differential diagnosis.

This second edition particularly introduces details of neurological examination which are so ably presented elsewhere. The authors' programme for neurological examination is highly detailed and comprehensive. It is my impression that such exhaustive rote neurological examination is falling out of fashion now that systematic neurological practice in Britain. Yet it seems popular still with North American neurologists who may benefit from the luxury of more time for patient consultation. Students may be intriguéd by the frequency of case histories around which the authors build discussion of differential diagnosis.

This second edition particularly introduces details of neurological examination which are so ably presented elsewhere. The authors' programme for neurological examination is highly detailed and comprehensive. It is my impression that such exhaustive rote neurological examination is falling out of fashion now that systematic neurological practice in Britain. Yet it seems popular still with North American neurologists who may benefit from the luxury of more time for patient consultation. Students may be intriguéd by the frequency of case histories around which the authors build discussion of differential diagnosis.

This second edition particularly introduces details of neurological examination which are so ably presented elsewhere. The authors' programme for neurological examination is highly detailed and comprehensive. It is my impression that such exhaustive rote neurological examination is falling out of fashion now that systematic neurological practice in Britain. Yet it seems popular still with North American neurologists who may benefit from the luxury of more time for patient consultation. Students may be intriguéd by the frequency of case histories around which the authors build discussion of differential diagnosis.

This second edition particularly introduces details of neurological examination which are so ably presented elsewhere. The authors' programme for neurological examination is highly detailed and comprehensive. It is my impression that such exhaustive rote neurological examination is falling out of fashion now that systematic neurological practice in Britain. Yet it seems popular still with North American neurologists who may benefit from the luxury of more time for patient consultation. Students may be intriguéd by the frequency of case histories around which the authors build discussion of differential diagnosis.

This second edition particularly introduces details of neurological examination which are so ably presented elsewhere. The authors' programme for neurological examination is highly detailed and comprehensive. It is my impression that such exhaustive rote neurological examination is falling out of fashion now that systematic neurological practice in Britain. Yet it seems popular still with North American neurologists who may benefit from the luxury of more time for patient consultation. Students may be intriguéd by the frequency of case histories around which the authors build discussion of differential diagnosis.

This second edition particularly introduces details of neurological examination which are so ably presented elsewhere. The authors' programme for neurological examination is highly detailed and comprehensive. It is my impression that such exhaustive rote neurological examination is falling out of fashion now that systematic neurological practice in Britain. Yet it seems popular still with North American neurologists who may benefit from the luxury of more time for patient consultation. Students may be intriguéd by the frequency of case histories around which the authors build discussion of differential diagnosis.

This second edition particularly introduces details of neurological examination which are so ably presented elsewhere. The authors' programme for neurological examination is highly detailed and comprehensive. It is my impression that such exhaustive rote neurological examination is falling out of fashion now that systematic neurological practice in Britain. Yet it seems popular still with North American neurologists who may benefit from the luxury of more time for patient consultation. Students may be intriguéd by the frequency of case histories around which the authors build discussion of differential diagnosis.

This second edition particularly introduces details of neurological examination which are so ably presented elsewhere. The authors' programme for neurological examination is highly detailed and comprehensive. It is my impression that such exhaustive rote neurological examination is falling out of fashion now that systematic neurological practice in Britain. Yet it seems popular still with North American neurologists who may benefit from the luxury of more time for patient consultation. Students may be intriguéd by the frequency of case histories around which the authors build discussion of differential diagnosis.

This second edition particularly introduces details of neurological examination which are so ably presented elsewhere. The authors' programme for neurological examination is highly detailed and comprehensive. It is my impression that such exhaustive rote neurological examination is falling out of fashion now that systematic neurological practice in Britain. Yet it seems popular still with North American neurologists who may benefit from the luxury of more time for patient consultation. Students may be intriguéd by the frequency of case histories around which the authors build discussion of differential diagnosis.

This second edition particularly introduces details of neurological examination which are so ably presented elsewhere. The authors' programme for neurological examination is highly detailed and comprehensive. It is my impression that such exhaustive rote neurological examination is falling out of fashion now that systematic neurological practice in Britain. Yet it seems popular still with North American neurologists who may benefit from the luxury of more time for patient consultation. Students may be intriguéd by the frequency of case histories around which the authors build discussion of differential diagnosis.

This second edition particularly introduces details of neurological examination which are so ably presented elsewhere. The authors' programme for neurological examination is highly detailed and comprehensive. It is my impression that such exhaustive rote neurological examination is falling out of fashion now that systematic neurological practice in Britain. Yet it seems popular still with North American neurologists who may benefit from the luxury of more time for patient consultation. Students may be intriguéd by the frequency of case histories around which the authors build discussion of differential diagnosis.
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