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

Neuromyotonic discharges are electrophysiologically characterised as bursts of motor unit potentials firing at more than 150 Hz for 0.5 to 2 seconds. The amplitude of the response typically wanes. Discharges may occur spontaneously or be initiated by needle movement. Walsh described a case of a mediastinal tumour and neuromyotonia with very high frequency discharges that outlasted voluntary effort.

We report a case of an acquired 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, paraesthesia 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 intermittently. The distal foot and hand muscles were slightly paretic and atrophic. Tendon reflexes were weak in the arms and absent in the legs. A decreased perception of vibration was present distally in all limbs.

Computed tomography disclosed a tumour of the mediastinum, which was totally removed after initial therapy and clinical improvement; the thymoma was confirmed histologically.

An examination of voltage gated K+ channel (VGKC) antibody titres was performed using immunoprecipitation of 125I-dendrotoxin labelled VGKCs extracted from human frontal cortex (Institute of Molecular Medicine, John Radcliffe Hospital, Oxford, UK). The first titre was positive (241 PM (positive titres >200 pM).

During a course of intravenous immunoglobulin (IVIg) therapy (2 g/kg) both pseudomyotonic and sensory signs and symptoms started to improve and at the end of the IVIg treatment the patient was able to walk independently. After the initial IVIg therapy (administered 1 month before surgical removal of the thymoma), clinical signs and symptoms stabilised with the ability to walk independently. After a year of stabilisation, the stiffness, dysarthria, and walking ability worsened in the course of 20 metres. After a year of stabilisation, the stiffness, dysarthria, and walking ability worsened in the course of 3 months to the point at which the patient was once more unable to walk independently. The patient then received a second course of IVIg therapy (2 g/kg) and improved to the same degree as after the first treatment.

An EMG at the beginning of clinical follow up disclosed sparse fasciculations and myokymic discharges (with a short interburst interval of about 5-10 ms) and motor unit potentials with slightly higher amplitude, longer duration, mild waveform instability, and polyphasic pattern from distal muscles in the lower limbs. Voluntary contraction evoked repetitive bursts of high frequency discharges resembling motor unit potentials with amplitude decrement and a characteristic "pinging" sound (figure); the discharges disappeared. Discharges may also be registered during voluntary contraction and the ability to evoke them waned; after several contractions they disappeared.

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 disappeared; 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 limb 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 paraesthesias were evoked by similar types of sensory phenomena.


Needle EMG from abductor pollicis brevis muscle showing high frequency (about 200 Hz) neuromyotonic discharge with waning amplitude and duration of 250 ms, provoked by voluntary contraction (arrows).
nucleotide 94 and 124 in exon 3. 14% of white people. We have previously
acid change at position 82 from methionine
This consists of a C6T transition at nucleo-
trophisms of physiological response to IVIg treatment are in
between Parkinson's disease and polymor-
Glutathione transferase genes (GST).
There are no associations between the nucleotide 245, 94, or 124 polymorphisms and Parkinson's disease (table). A total of 87 patients and 53 controls reported a history of regular pesticide exposure. In this group there was a weak association between the nucleotide 245 genotype and Parkinson's disease (p=0.05) (table). Furthermore, in this group, the Z1*C genotype (G155C) was less common in the patients with Parkinson's disease than in the controls (OR=0.49, 95% confidence interval (95% CI) 0.36–0.65, p=0.03, not corrected for multiple compari-
tions).
There was no overall association between the GSTZ1 polymorphisms and Parkinson's disease. However, we found a difference when only those who reported pesticide exposure were analysed. We also combined the data for the three polymorphic sites to determine the frequency of the four GSTZ1 alleles. The Z1* allele is the most common variant in white control populations.

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

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*Analysis restricted to subjects with a history of regular pesticide exposure (p=0.05).
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 amount of exposure, and multiple comparisons. Ac-
cordingly, our conclusion that there is a potential association between GSTZ1, pesti-
cide 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 variability in detoxification enzymes, and expo-
sure to environmental toxins. These include CYP2D6 and solvent exposure, GSTP1 and pesticide exposure, and CYP2D6, pesticide exposure, and Parkinson's disease with dementia. This, 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 toxins.

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Correspondence to: Professor P G Board

3 Blackburn AC, Tseng HF, Anders MW, et al. Activity of four allelic forms of human glutathione transferase zeta: GSTz1a-1a possess higher activity than other genotypes. Proc- eedings of the 9th North American ISSX confer-
ence 1999:209.
4 Blackburn AC, Tseng HF, Anders MW, et al. Discovery of a functional polymorphism in human glutathione transferase zeta by ex-
5 De Palma G, Mozoni P, Mutti A, et al. Case-control study of interactions between genetic and environmental factors in Parkin-
6 Hubble JP, Kurth JH, Glatt SL, et al. Gene-toxin interaction as a putative risk factor for Parkin-

A case of stiff limb syndrome responsive to plasma exchange

Stiff limb syndrome is a recently described, rare condition that is characterised by rigidity within the limbs that progresses in a relapsing and remitting fashion, often starting in the abdominal sphincters and brain stem.1 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

3 Torbergen T, Straeblas NG. Gen-
erate sites for spontaneous activity in neuro-
tibodies directed against K+ channels of peripheral nerves. Annu Neurol 1995;38:714–22.
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 neurophysiological abnormalities from stiff man syndrome and fewer of these patients have anti-GAD antibodies; they also typically show a poorly sustained response to baclofen and diazepam. The response to immunotherapy in stiff limb syndrome is not known, whereas patients with stiff man syndrome may respond to intravenous immunoglobulin as well as possibly plasma exchange. We now report on a patient with stiff limb syndrome who responded dramatically to plasma exchange and in whom an autoimmune disorder was identified, suggesting that this condition may have an immunological basis.

A 50 year old retired auxiliary nurse presented with a 10 year history of progressive pain, stiffness, and flexion contractures in her hands, followed by 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 which 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 responded 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 and weakness in the hands, which slowly clawed, after which her arms and neck became progressively stiffer and her trunk became increasingly stooped on walking, with additional difficulty raising her arms above her head. Five years after the onset of her symptoms she was incapacitated, required assistance with all activities of daily living, and was permanently catheterised. At this stage a seronegative polyarthritis was diagnosed and she was treated with hydroxychloroquine, prothiaden, and corticosteroids, all without effect. She subsequently had some spontaneous remission but at the time of her referral to us she could only walk 10 yards without a stick and continued to complain of heaviness, pain, and stiffness in the limbs especially the left arm. In addition she had developed an intermittent tremor of the right arm and leg, which sometimes affected her jaw and she had difficulty swallowing large boluses of food.

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

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

The diagnosis of stiff limb syndrome was made and she was initially treated with diazepam and baclofen, but continued to deteriorate and gradually lost all useful function of her arms. There was a similar lack of response to intravenous methylprednisolone, so she was given intravenous immunoglobulin, to which she developed an anaphylactic reaction. Her disorder progressed and she developed prominent rigidity and spasms of the face, trunk and limbs. Her speech developed a strangled quality and she had episodes of involuntary tachypnoea apparently due to spasm 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 immobile and dependent such that she could barely wash herself and was unable to walk at all. Any attempt to move her limbs caused disabling tremor and stiffness. Again, reflexes and plantars were normal. She had a further course of plasma exchange and again responded slowly, such that 3 months later she was able to walk on two sticks. This improvement was initially sustained although she has required a further course of plasma exchange in February 2000 and has now been started on oral cyclophosphamide with notable benefit. The patient has not had further neurophysiological investigations.

This case has all the features of stiff limb syndrome with the novel finding of antiaxonal antibodies detected in the serum. The patient failed to respond to baclofen and diazepam and could not tolerate intravenous immunoglobulin but did have a dramatic and sustained response to plasma exchange, although the need for repeated courses of this treatment has led to her being started on cyclophosphamide. This has not been reported before for this condition and whereas this case illustrates the possible therapeutic effect of this treatment, we raise 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 neuropsychological examination on this patient, and Angela Vincent for the serological testing and detection of the antiaxonal antibody.

ACOLESDepartment of Neurology, Norfolk and Norwich Health Authority, Queen Elizabeth Hospital, Norwich, NR2 2ER, Norfolk, NR1 3SR, UK

ACOLESR. BarkerDepartment of Neurology, Addenbrooke’s, NHS Trust, Hills Road, Cambridge CB2 2QZ, UK

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


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

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

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

Physical examination disclosed orthostatic hypotension without secondary tachycardia (120/60 mm Hg lying, 85/52 mm Hg sitting, fixed pulse rate 60 bpm) and paralytic ileus. He was catheterised for incontinence. 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. Vibration and joint positions were impaired severely in the same distribution, and lost in
his fingers, knees, ankles, and toes. Sensory ataxia and pseudopseudathetosis 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 osmolality 262 mOsmol/l, urine osmolality 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 and B) 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 paraneoplastic 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. Routine laboratory examinations were without pleocytosis but no oligoclonal bands. 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 and B) 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 paraneoplastic 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.

Pathological findings in the sural nerve. (A) Histologically, most of the myelinated fibres show formation of myelin ovoids indicating active axonal degeneration, which is also present in the teased fibre preparations (B). (C) The unmyelinated fibres are also affected showing swelling of the axons (arrows). ((A) epon embedded section stained with toluidine blue; bar=20 µm; (B) teased fibres, bar=100 µm; (C) electron micrograph; bar=2 µm).
Correspondence to: Dr T Irioka

Radical hysterectomy.

Damage to the autonomic and sensory ganglion neurons leading to clinical manifestation of AASN.

T IRIOKA
M YAMADA
Y 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 dysfunction, which required intermittent self-catheterisation. She received several analgesic drugs without benefit. Neurological and pelvic examination, were normal. An ambulatory urorectodynamics 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 urorectodynamics studies, which disclosed visceral hyperreflexia in both cases. Patient 1 probably had injury to the pelvic nerves, which is well recognised after extensive hysterectomy. Patient 2 had pudendal nerve damage, supported by the nerve conduction study. Our patients did not have neurological signs suggestive of CNS lesions, but demonstrated features usually associated with such lesions, namely detrusor and rectal hyperreflexia. Visceral hyperreflexia can occur after spinal cord lesions and in the absence of obvious neurogenic lesions but its occurrence after peripheral nerve damage is not well recognised.1

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,3 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 of pelvic...
of urinary bladder contraction induced by rectal and vaginal stimulation* and the development of bladder and rectum cocontractions, which have not been reported previ- ously.

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 mecha- nisms. Early recognition and initiation of analgesic treatment for neuropathic pain is esssential to prevent the condition becoming intractable.

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

C FOWLER 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 PAnand@ic.ac.uk


4 Zermann DH, Ishigooka M, Doggweiler R, et al. Nerve conduction studies 1 week after ligation demonstrated segmental occlusions of both internal iliac arteries with distal con- secution greater on the right side and minimal on the left. The left superior gluteal artery was not visual- ised. Revascularisation was considered deferred due to the concomitant active pelvic infection. Peripheral pulses remained strong, 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.

5 Magnetic resonance imaging of the thora- culombar spinal cord was unremarkable. An initial magnetic resonance angiogram (MRA) of the pelvis showed segmental occlusions of both internal iliac arteries with distal recon- striction greater on the right side and minimal on the left. The left superior gluteal artery was not visualised. Revascularisation was considered deferred due to the concomitant active pelvic infection. Peripheral pulses remained strong, 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.

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7 Our 18 year old patient developed a com- bination of leg weakness, leg numbness, and buttock necrosis after internal iliac artery ligation, as described in older vasculopathic patients. In the patients described in the literature, as in our patient, the clinical and electromyographic findings do not distin- guish between combinations of femoral and sciatic nerve lesions, a lumbarosacral plexopathy, or a combination of the two. Our patient’s presentation, however, can be most suc- cinctly explained by an infarction in the ter- ritory of the left superior gluteal artery and its branches, resulting in ischaemia to the lumbarosacral plexus after bilateral internal iliac artery ligation. 8 In four of those patients, buttock necrosis with extension to the bony pelvis was also seen. In another report, four women (mean age 37, range 33 to 47) with insulin dependent diabetes and end stage renal dis- ease developed ipsilateral lumbarosacral plex- opathies when the internal iliac artery was ligated during kidney transplantation. Electromyography showed denervation of the bilateral femoral and sciatic nerve roots and buttocks also occurred after internal iliac artery embolisation in patients with terminal pelvic malignancies who received radiotherapy.

8 Our 18 year old patient developed a com- bination of leg weakness, leg numbness, and buttock necrosis after internal iliac artery ligation, as described in older vasculopathic patients. In the patients described in the literature, as in our patient, the clinical and electromyographic findings do not distin- guish between combinations of femoral and sciatic nerve lesions, a lumbarosacral plexopathy, or a combination of the two. Our patient’s presentation, however, can be most suc- cinctly explained by an infarction in the ter- ritory of the left superior gluteal artery and its branches, resulting in ischaemia to the lumbarosacral plexus, the femoral nerve proper, and the sciatic nerve roots. This localisation is supported by bilateral MR angiograms of the pelvis in which the left superior gluteal artery and its branches were not visualised.

9 It has been shown that, in experimental ligations of the internal iliac artery in rats, moderate ischaemia is associated with dorsal peripheral nerve and bladder ischaemia.
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 va-

sogonic 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 asso-
ciated with gradual mental deterioration. The patient had a history of frequent orogenital ulcers and acneliform nodules on his face. Physical examination showed active genital ulceration. Neurological examination dis-
closed drowsy consciousness and disorienta-
tion. Moderate degrees of hemiparesis and hemihypaesthesia 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 hemorrhages 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 21x21 cm; matrix 256x192; 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 24x24 cm; matrix 128x128; 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.
regression line best fitting the points for β versus σ (SI), where SI is the signal intensity from a region of interest within the images acquired at each β 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 ganglia, and the thalamus. Four sampled ADCs in the corresponding regions of T2 hyperintensity demonstrated increased diffusion (ranging from 1.17 to 1.26×10-3 cm²/s), compared with a matching location in the uninvolved contralateral hemisphere (ranging from 0.77 to 0.80×10-3 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 weakness, frontal lobe dysfunction, urinary incontinence, and depressive mood changes. Follow up MRI performed at this time, showed that the previous T2 abnormalities had improved, but the atrophy of the brain stem and basal ganglia became evident with periventricular high signal intensities. Four ADCs sampled in locations corresponding to those of the initially increased ADCs decreased to values which ranged from 0.98 to 1.07×10-3 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 brain-stem atrophy in chronic cases. The reversibility of CT or MRI abnormalities of acute lesions in neuro-Behçet’s disease has also been documented and correlated with clinical improvement.6 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. 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.7 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.8 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.

Data of patients before and after treatment

<table>
<thead>
<tr>
<th></th>
<th>IFN</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 at entry (y)</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>3.25 (0.9)</td>
<td>3.25 (0.9)</td>
<td>3.18 (1.15)</td>
</tr>
<tr>
<td>At 12 months</td>
<td>2.2 (1.0)</td>
<td>2.2 (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 (0.6)</td>
<td>2.0 (0.3)</td>
<td>1.4 (0.5)</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>PCH at entry</td>
<td>60.82 (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 (9.2)</td>
<td>+7.9 (9.9)</td>
<td>+3.66 (13.7)</td>
</tr>
<tr>
<td>MHC at entry</td>
<td>74.7 (15.7)</td>
<td>61.25 (14.15)</td>
<td>58.7 (16.9)</td>
</tr>
<tr>
<td>Change at 12 months</td>
<td>-6.04 (13.9)</td>
<td>+21.25 (11.7)</td>
<td>+6.37 (21.8)</td>
</tr>
<tr>
<td>RLE at entry</td>
<td>83.34 (32.4)</td>
<td>37.5 (33.05)</td>
<td>55.55 (40.8)</td>
</tr>
<tr>
<td>Change at 12 months</td>
<td>-10.35 (33)</td>
<td>+44.9 (35.6)</td>
<td>+16.6 (53.4)</td>
</tr>
</tbody>
</table>

IFN=interferon-β1b treated patients; AZA=azathioprine treated patients; NT=no actively treated patients; RF=relapse frequency (No of relapses/patient/y); worsened=increase of 0.5 EDSS point; PCH=physical composite score; MHC=mental composite score; RLE=role limitation for emotional reasons.

*One patient in NT group dropped out at 6 months.
†Significant differences between groups: Age at entry: NT 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 vs 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 IFN–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.

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. 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 (ureginary incontinence and erectile dysfunction). On admission to our hospital at the age of 34, T2 weighted MR images showed small lesions in the bilateral internal capsule although no abnormality was seen in the spinal cord. Nerve conduction studies and the sural nerve biopsy showed evidence of peripheral nerve involvement. A low serum cortisol response to intravenous adrenocorticotropic hormone and increased concentration of plasma very long chain fatty acids were consistent with a diagnosis of AMN. Three years later he showed marked emotional liability. T2 weighted MRI showed a high signal mass lesion in the right caudate head and the ipsilateral anterior internal capsule which simulated an intracranial tumour, without marked demyelination in the surrounding deep white matter (fig 1). A year later he became wheelchair bound, apathetic, and demented. Brain MRI showed right sided dominant white matter abnormalities and atrophy of the spinal cord. Three years later he died of respiratory infection and necropsy was performed. Pathological examination showed fronto-temporal cortical atrophy with diffuse white matter demyelination including bilateral internal capsules, where astrocytes proliferated and lipid laden macrophages infiltrated around the small vessels. Neurons were moderately shrunk 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. Affifi et al reported on a 4.8 year old boy whose MRI showed a right anterior white matter lesion extending into the ipsilateral putamen and the thalamus. Close et al described an 8 year old boy who had a left occipitotemporal white matter lesion extending into the ipsilateral putamen and the thalamus on MRI. However, the imaging pattern in our patient is unique because of the high signal mass lesion in the right caudate head and the ipsilateral anterior internal capsule without marked demyelination in the surrounding white matter, falsely suggestive of a brain tumour. There are also other demyelinating disorders simulating brain tumour which include multiple sclerosis. The findings indicate that plasma very long chain fatty acid

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

We are indebted to Dr Alessandra Solaris, Laboratory of Epidemiology, C Besta National Neurological Institute, Milan, Italy, for preparing 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
mogroup@istituto-besta.it


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 Microscopical 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.
concentrations should be measured in patients with unexplained basal ganglia abnormalities on MRI.

R SAKABARAK T FUKUTAKEK K ARAIK K KATAYAMAK M MORI T HATTORIT Neurology Department Chiba University, 1-8-1 Inohana Chuo-Ku, Chiba 260-8670 Japan

R SAKABARAK T FUKUTAKEK K KATAYAMAK M MORI Neurology Department Kawasaki Rosai Hospital, 1-9108-2 Oosu-Honnachi Haachi, Kawasaki 314-03 Japan

Correspondence to: Dr R Sakakibara


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 blockade2 and the induction of a Th2/Th3 cytokine response.3 Peripher al 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-remitting or relapsing-progressive multiple sclerosis were treated with 20 mg subcutaneous GA daily for 3 years as part of an open label multicentre study. Safety evaluation and expanded disability status scale (EDSS) rating were performed every 3 months and in the 3rd year every 6 months and when clinical relapses occurred. Relapses were defined according to Poser criteria and annual relapse rates were calculated for the 3 year study duration and a 2 year prestudy period. As two patients reported generalised tender swelling of lymph nodes spontaneously in temporal relation to the beginning of GA injections special attention was paid to the symptom and regular assessment of regional lymph nodes was performed in all patients. Only if patients reported symptoms such as tenderness or pain, was the diagnosis of lymphadenopathy made. All patients completed the full 3 years of the study. In one patient with generalised lymphadenopathy a lymph node biopsy was taken to rule out malignancy. As controls patients who were routinely treated with IFN-β injections at our multiple sclerosis outpatient clinic were also examined for lymphadenopathy.

In nine out of 27 patients lymphadenopathy occurred 1 to 15 months after initiation of 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 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 lymphoholocytic hyperplasia but no atypical cells (thus ruling out malignancy). Lymphadenopathy did not necessitate the discontinuation of GA treatment. The examiners were reassured that all patients used a good (sterile) injection technique. In the control patients no lymphadenopathy was detected.

When analysing annual relapse rates, a significant reduction of the mean annual relapse rate was found under GA treatment. The annual relapse rate decreased from 1.8/year to 0.33/year at the beginning of the study. 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 reference in the group with lymphadenopathy. Although in the group with lymphadenopathy no patient showed an increase in relapse rate, three patients in the group without lymphadenopathy did. In both groups of patients no significant change in median EDSS over the 3 years of the study was noted (table 1).

The frequency of lymphadenopathy found in this study (nine out of 27 patients) is significantly higher than that reported in the postmarketing surveillance of GA (55 reports of lymphadenopathy out of about 30 000 reports of other adverse events). The lymphadenopathy in our study was mild to moderate, not accompanied by changes in routine laboratory indices, and persisted as long as the GA treatment was continued. In seven out of nine patients lymphadenopathy remained localised to the draining lymph nodes. Lymph node swelling receded and appeared depending on injection site. Lymphadenopathy did not necessitate discontinuation of GA treatment. In one patient with generalised lymphadenopathy a biopsy was performed to rule out malignancy. The patient was then continued on GA without further problems and remained relapse free; GA injections were stopped 1 year after the end of the study, due to pregnancy, and lymphadenopathy resolved completely within 4 weeks.

Lymphadenopathy, if not due to malignancy, is a clinical sign of immune activation and has not yet been reported as an adverse event of GA treatment in the literature. The effect might be due to direct stimulation of T cells in vivo as GA has been shown to induce mRNA expression of IL-2 and T cell proliferation in vitro.5 In previous studies immunostimulatory cytokines such as IFN-γ or viral infections worsened the clinical course of multiple sclerosis whereas immunosuppression (for example, mitoxantrone, cyclophosphamide) was beneficial.6 It will be interesting to study further whether lymphadenopathy related to GA is associated with alteration of the clinical outcome measures of multiple sclerosis. The cohort of patients with lymphadenopathy did not show a significant difference in annual relapse rate or EDSS compared with patients without lymphadenopathy, but the small sample size per group should be taken into account. Glatiramer acetate induces clinical signs of immune stimulation (lymphadenopathy) in a subgroup of patients with multiple sclerosis that is not associated with clinical worsening. The finding is therefore interesting with regard to the potential mechanism of action of GA in vivo. Larger numbers of patients need to be examined to determine whether lymphadenopathy in patients under GA treatment is associated with distinct immunological markers—for example, MHC-II type or cytokine secretion pattern.

Patients examined in this study were enrolled in our centre as part of the German open label phase IIIb treatment study (protocol COP 1600) supported by TEVA and Avantis.

R BLASZYCK
Abteilung für Transfusionsmedizin

Clinical data of patients with multiple sclerosis treated with glatiramer acetate

<table>
<thead>
<tr>
<th></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>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>
<tr>
<td>No lymph node swelling</td>
<td>1.5 (1–3.5)</td>
<td>0.54 (1–1.8)</td>
<td>2.5 (1–5)</td>
<td>3.0 (0–6.5)</td>
</tr>
</tbody>
</table>

Values are mean (relapse rate) or median (EDSS) (range).
Neurovisuial 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 and able to develop his own compensatory strategies. His visual recovery was more problematic. He failed most subtests in the Rivermead perceptual assessment battery (RPAB) and was almost unable to read, showed optic ataxia, and had limited ability to improve and restore itself after injury.1

The remaining abilities are used to offset the deficits. This patient was able to develop his own compensatory strategies, learned to use his hands to acquire tactile feedback, and managed to direct his gaze to visually locate objects when required. His performance on the RPAB was improved and he was successfully discharged home with little support.

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

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

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,1 that individually tailored rehabilitation strategies can be adapted successfully for patients with Balint's syndrome.


The authors state that their second patient had a “rotatory component” using the modified nystagmus of skew. This 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 complex 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.1 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.

G KERKHOF
EK-N-Clinical Neuropsychology Research Group, Department of Neuropsychology, City, Hospital Bogenhausen, Dachauerstr.164,D-80992 Munich, Germany

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

Georg.Kerkhoff@ernlkrz-muenchen.de

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

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

Arnold Chiariali malformation and nystagmus of skew

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

The authors state that their second patient had a “rotatory component” by which I assume they mean torsional; this pattern of nystagmus is already established in the literature and is known as “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
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.

PATRICK LAVIN

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


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, descriptive term, of which both the pendular and the jerk see-saw nystagmus forms and the dissociated vertical nystagmus without demonstrable torsional component would represent subvariants.

C PIEH

Kantonsspital St. Gallen, Switzerland

I GOTTLOB

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

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

We have read with interest the article by Giess et al., which showed that botulinum toxin A (BoNT/A) might be a new treatment option for sialorrhea in patients with bulbar palsy.

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

After this experience we developed a protocol for the treatment of sialorrhea 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, 3, 7, 14, and 28, as well as after 2 and 3 months. Technetium 99m scintigraphy was performed before and as after 2 and 3 months. Technetium 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 sialorrhea 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. 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 sialorrhea in ALS. The transducal approach in particular seems to have unacceptable side effects.

M G M WINTERHOLLER

F J ERGBUCH

Department of Neurology, Friedrich-Alexander-Universität Erlangen, Schnarrenbergstrasse 6, D-91054 Erlangen, Germany

S WOLF

Department of Otorhinolaryngology

S KAT

Department of Nuclear Medicine

Correspondence to: Dr M GM Winterholler, MD

www.jnnp.com

Note: This document includes a table and a figure. The table is not included in the plain text representation.
Correspondence to: M Naumann
naumann@mail.uni-wuerzburg.de

The authors reply:

We appreciate the comments by Winterhol-ler et al on our article on botulinum toxin (BTXA) treatment of saliorrhoea in patients with amyotrophic lateral sclerosis (ALS).

Although we did not find any serious side effects after subcutaneous injections of BTXA into the parotid and submandibular glands Winterholller et al report on sublin- gual 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 BTXA in patients with ALS may be low and also indic- ate that the transcutaneous approach as performed in several studies may be safer than the retrograde transducal injection. This is not unexpected as the transdudcal approach has possibly a higher risk of infec- tion 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 there- fore underscore our previous suggestion to start with injections of the parotid glands alone to cautiously escalate the dose and number of injected glands. In view of the potential risk of BTXA in deteriorating ALS symptoms injections should be re- stricted to otherwise intractable and ex- tremely disabled patients with ALS who have saliorrhoea.

M NAUMANN
G K SCHWAGER
K V TOYKA
Department of Neurology and Department of Otorhinolaryngology, Bayerische Julius-Maximilians-Universität, Josef-Schneider-Straße 11, 97080 Würzburg, Germany

Treatment of early onset Parkinson's disease with ropinirole

The recent editorial supporting initial treat- ment of early onset Parkinson's disease with a dopamine agonist hinged in part on the dem- onstration in 286 patients that treatment of early onset Parkinson's disease with ropi- inirole alone or with supplementary levodopa/dopa decarboxylase inhibitor (benserazide) (LD/DDI) resulted in substan- tially 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 response was inadequate and additional traid drug could not be tolerated. Up to 24 mg ropinirole and 1200 mg LD/DDI daily were allowed. Sixty per cent of patients completing the ropinirole arm required sup- plementation, the average mean daily dose of ropinirole at 5 years being 16.5 mg, com- pared with 753 mg of LD/DDI when the sec- ond was used.

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 the disease 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 tolerance of and motor response to ropinirole, it is not clear. The study demonstrated 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 comparison, the 5 year study of immediate release (IR) and controlled release (CR) LD/DDI (carbidopa) in 681 patients, ironically reported earlier in 1997, and later in 1999, in whom dosage could be adjusted up to five or more times a day resulted not only in a lower frequency of dys- kinesia (20.6% IR, 21.7% CR) at 5 years but also a lower mean total daily dose (426 mg IR; 510 mg CR (bioequivalent)).

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

Given reports of long term resolution of dyskinesia and on/off effects in response to varying methods of dopaminergic stimulation at an appropriate strength, including continu- ous daytime jejunal infusion of LD/DDI (with little or no change in LD/DDI dosage requirement over 57 months), and of a neu- roprotective effect of levodopa, the results of Rascol et al should not be 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, Walgrove Hospital NHS Trust, Clifford Bridge Road, Coventry CV1 2DX, UK

Brooks replies:

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

Firstly, he suggests that it is unfortunate that the 056 trial required a three times daily levodopa dosage regime as use of more frequent smaller doses could have reduced the incidence of dyskinesias. Ponsford denies the three times daily regime in part to match the three times daily regime of ropinirole and also because it was thought that this regime reflected common clinical practice in patients with early Parkinson's disease. A trial for- mally comparing use of multiple low doses of levodopa versus a three times daily medium dose regime in early Parkinson's disease would however, be of great interest. It might well be that the multiple low dose approach in early disease would spare complications but this has yet to be shown. Addition of a catechol-O-methyltransferase inhibitor to smoke out the plasma levodopa profile where it is argued that different drug preparations and methods of assessment invalidate comparison, it may be simply that less frequent higher pulsatile dosage provokes not only more frequent dyskinesia but also, as a mirroring effect, greater off time as postynaptic mechanisms adapt to cope with surges of dopamine and perhaps lose sensitivity to troughs. Patients seen during troughs would be liable to have their dose increased. If the interdose interval were fixed this would lead to a vicious circle.

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

In their recent article, Bottiglieri et al describe increased homocysteine comcomitant with decreased folate concentrations in a subgroup of patients with depression.1 In addition, some relation between reduced folate availability and disturbed monoamine metabolism was found. The close relation between increased homocysteine and reduced folate concentrations, which was described previously in other clinical conditions such as cardiovascular and cerebrovascular diseases is usually ascribed to a reduced dietary intake of folate, and dietary supplementation with folate is capable of reducing hyperhomocysteinemia.

The coincidence described of disturbed homocysteine and monoamine metabolism may shed some additional light to the possible 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 methyl-5,6,7,8-tetrahydrofolate and also 5,6,7,8-tetrahydrobiopterin deficiency. Interestingly, 5,6,7,8-tetrahydrofolate and also 5,6,7,8-tetrahydrobiopterin deficiency of which results in hyperhomocysteinaemia is associated with activation of the immune system and enhanced oxidative stress due to aging requires clarification. It is also relevant part of the cytotoxic armature of activated macrophages.

Increased oxidative stress as a consequence of disturbed homocysteine and folate metabolism in psychogeriatric patients, including depression and dementia. Revealed by glycine dehydroxymethyltransferases and S-adenosyl-methionine on catacholaminergic metabolism in dementia. J Neural Transm 2000;107:1069–74.

Reynolds and Bottiglieri reply: We thank Widner et al for suggesting an explanation of our finding that reduced 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 ageing and this may be a factor contributing to the high incidence of folate deficiency in psychiatric patients, including depression and dementia.

We have also reported a fall in 5,6,7,8-tetrahydrobiopterin (BH4) in depression which is correlated with folate deficiency, as reflected in a fall in red cell folate, and with impaired monoamine metabolism—that is, a fall in CSF homovanillic acid.

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 and that the turnover of folate 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, like folates, increase the turnover of monoamines in the brain. This and other evidence suggest that methylation mechanisms are involved in these relations and in mood and cognitive function.


2. Widner D, Fuchs Institute of Medical Chemistry and Biochemistry, Fritz Pregl Strasse 3, A-6020 Innsbruck, Austria; University of Innsbruck, Ludwig Boltzmann Institute of AIDS-Research, Innsbruck, Austria


Long term follow up after perimesencephalic subarachnoid haemorrhage

Marquardt et al describe the clinical course and long term outcome of 21 patients they diagnosed as having a perimesencephalic haemorrhage.1 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 fronto interhemispheric and Sylvian fissures.

There are several explanations for this diagnostic mystery. Firstly, the authors may have submitted an incomplete CT. In some patients with perimesencephalic haemorrhage, the prepontine cistern is the only site where CT shows blood.2 If blood was visible in the prepontine 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 prepontine cistern, the patient may have had a CT negative subarachnoid haemorrhage. In patients with unruptured aneurysms CT can be negative, even if performed within 12 hours after onset of the haemorrhage.3 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 subarachnoid 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 aneurysmal 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 fatigability. 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 study populations 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 require patients on discharge and again a couple of weeks later, at an outpatient 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 sharings of activities 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 the bleeding has not been ruled out convincingly. We do agree that the patient reported on forms a diagnostic challenge, but we do not agree that the patient has had two episodes of perimesencephalic haemorrhage. G J E RINKEL and B K VELTHUIS Department of Neurology, University Medical Centre, PO Box 85500, 5806 GA Utrecht, The Netherlands Correspondence to: Dr G J E Rinkel

The authors reply.

We respond to some of the questions raised by Rinkel and Velthuis on our recent publication in this Journal. The patient of interest presented with typical clinical signs of subarachnoid haemorrhage. He complained of sudden onset of severe headaches, irradiation of the nuchal region, and nausea. Lumbar puncture was performed and blood stained CSF was found. Centrifugation of the CSF disclosed xanthochromia of the supernatant fluid and cytology demonstrated siderophages indicating the presence of intracranial haemorrhage as no lumbar puncture was carried out earlier. Non-contrast enhanced CT showed blood in the ambient cisterns indicating these findings were interpreted as perimesencephalic subarachnoid haemorrhage in two different hospitals.

Four vessel digital subtraction cerebral angiography with multiple views was negative as was a repeated angiography 10 weeks later. A third angiography performed in the course of the second episode of haemorrhage again did not disclose any source of the bleeding, and thus the question on management strategy remains unsolved. A recent publication by Canhao et al studied the prevalence of vascular risk factors in patients who had perimesencephalic subarachnoid haemorrhage.1 They found that hypertension is a risk factor in patients with perimesencephalic haemorrhage than among control two 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 fatigability in long term follow up of our patients. They state that these findings contrast with the good quality of life found in a follow up study performed by Brilstra et al and that these differences require explanation.

In this study, which was cited by us as well, quality of life was measured by means of the sickness impact profile and outcome of these patients was compared with that of a reference population. Analysing the submitted data, however, significant differences towards less disabled patients who 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 a genuine haemorrhage leading to admission to an intensive care unit. These results imply that in the Dutch study as well persisting symptoms are frequent and 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 poor as suggested and it becomes obvious that perimesencephalic subarachnoid haemorrhage has an enormous impact on individual patients and social life.

We do agree with Rinkel and Velthuis on the further management strategy for patients with former PMSAH. We inform the patients of the benign nature of the disease and do not impose any restrictions at all. We also reassure the patients that they can return to the same regular daily activities they undertook before the haemorrhage. It is supposed that in 15% to 20% of the patients with subarachnoid haemorrhage the angiogram is negative and that patients with PMSAH account for about half of these patients with angiogram negative subarachnoid haemorrhage.2 On these premises there must be thousands of patients every year who are treated for PMSAH, and who are at risk in the world. However, reviewing the literature in 1996, Schwartz and Solomon could only find 169 reported patients who had PMSAH.3 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 NIEBUER U SCHICK R LORENZ Neurosurgical Clinic, Johann Wolfgang Goethe-University, Schleunweg 2–16, 60528 Frankfurt am Main, Germany Correspondence to: Dr G Marquardt


**Idiopathic intracranial hypertension and anticoagulant antibodies**

The study by Kesler et al concludes with the assumption that the presence of anticoagulant antibodies (aCL-Abs) indicates a unique subgroup of patients with idiopathic intracranial hypertension. Their study does not support this view. They regard as important in this respect the fact that the three patients with aCL-Abs (p<0.035) were significantly older than those without. It is surprising when it is known that the incidence of these antibodies increases with age and may be identifiable in up to 12% of healthy people.4 Their control group therefore needs to be age matched. Further speculation for
Correspondence to: Dr O Backhouse

intradural hypertension.

The authors' proposal that the patients with aCL-Ab form a subgroup of patients with

say that schizophrenia is the graveyard of

that structural alterations in the brain would

ogy of psychosis based on the assumption

was an increased interest in the neuropathol-

the middle decades of the last century there

The neuropathology of schizophrenia has

0-19-262907-7.

PAUL J HARRISON and GARETH W ROBERTS

Progress and Interpretation

The Neuropathology of Schizophrenia.

BOOK REVIEWS

The Neuropathology of Schizophrenia. Progress and Interpretation. Edited by

PAUL J HARRISON and GARETH W ROBERTS


0-19-262907-7.

The neuropathology of schizophrenia has been for a long time perhaps one of the most

controversial fields of biomedical research. In the mid to late 20th century a number of

studies were contradictory. It is thus not surprising that these studies were subsequently

rewritten with the advent of neuroimaging a new era has started. It was Johnstone and her

colleagues who showed structural alterations (enlarged ventricles) in the brain of psychotic

patients using at that time, the novel method-

ology of CT scanning. Not much later a

report of Stevens observing astrocytosis in

the brains of patients with schizophrenia,

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, macroscopical, histological,
neurochemical, and immunological changes associated with the disease. In addi-
tion there are chapters on animal models and
methodological issues, as well as on the con-
sequences of treatment. The results of struc-
tural and functional imaging are reviewed, the
second in relation to neural circuits.

There is an excellent chapter on cerebral
asymmetry, a feature important in the under-
standing of the disease. Two chapters deal
with developments 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 circuits, for
a long time inaccessible to conventional
methodology, have become the subject of
intense research, and recent developments have
been suitably summarised in two separate
chapters. The chapter on cortical
pathology reviews a new generation of quan-
titative microscopical studies in relation to
the GABA, glutamate, and dopamine
systems. The problems of gliosis 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 diagno-
sis 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 mechanisms of 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. How-
ever, less praise should be lavished on the
publishing house, which has failed to invest in
high quality reproductions. There is a single
coloured plate of neuroimaging of MRI and
PET and the black and white reproductions
of the same images have not been removed.

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. The inclusion of a free lunch and more books draws a sponsorship. Some symposiums where the promotional idea is promulgated at commercially controversial areas, occasionally using logic which pretenders are unable to match McAlpine in any of the immunotherapies make a difference. 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 of the brain and spinal cord, evolved from the concept that organisation through the connectivity of functionally independent neurons and their processes. Santiago Ramon y Cajal distinguished neurons from glia; showed the variability of dendritic arborisations and axon terminations; established that axon cylinders end freely but form contacts; conceived that the nerve impulse is conducted between axons, dendrites, and the cell body of neighbouring neurons; had the concepts of trophism and tropism; and following Rudolph Virchow, regarded the cell as the unit of all biological systems. His most detailed studies were of the cerebral cortex, 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 Croonian 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 outpour praise for 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 Swan- son and Larry Swanson as Histology of the Nervous System of Man and Vertebrates (Oxford University Press, 1995). Now the original Spanish text is updated under the direction of 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, chemotactic substances, dendritic spines, and cortical interneurons and claims absolute authority over both the French and English editions. It boasts illustrations based on original reproductions of drawings archived in the Cajal Institute in Madrid (the evidence is in the Muso-Cajal-Madrid stamp on many figures) with very little copied from previously published editions. Facts and citations are corrected from Cajal's original text and authenticated against contemporary sources. In which edition should the discerning Cajal reader invest? When considered, 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 central community in the evolution of living matter, and the most complicated machinery of noblest activities that Nature has to offer" (English-Spanish) with "countless modifications during evolution have provided living matter with an instrument of unparalleled complexity and remarkable functions: the nervous system, the most highly organised structure in the animal kingdom" (English-French); or, "it appears that with this [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 distant and black" (English-Spanish) versus "the theory of chemotaxis we advanced...initially appeared to be pure conjecture with no hope of verification, although recently it has gained experimental support" (English-French).

The text is authoritative and the production lavish. Pedro and Tauba Pasik include, and readily identify, translation of material added by Cajal for the French edition between 1904 and 1909. All the illustrations are retained but the citations are modernised and gathered in a single section completing the English-Spanish text. The lack of an index will be put right when volume three is published. The illustrations are incomparably better in the Springer than the Oxford volume[s]. The line drawings are much more crisp; the original figures of methylene blue staining reproduce poorly as black and white (Oxford) but some of their polychromatic figures are more subtle. Volume one deals with the general principles of organisation in the nervous system and Cajal's methods, the details of neuronal structure and the spinal cord. Volumes two and three will complete the medulla and pons, cerebral stem, 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. But

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 and even to read of a few of its successes. If so, disappointment lies in store. Most of the writers approach their subject through a protective smoke screen of broad generalisations; few emerge from it to offer a detailed account of how any aspect of preventive psychiatry works on the ground. Some avoid the topic altogether: two of the more succinct chapters describe a process of deinstitutionalisation in Greece—a subject not without interest, but one that is only loosely connected with the book’s principal purpose. Whether, and if so, how preventive psychiatry succeeds receives little attention. Surprisingly little relevant outcome data are presented. Much of the writing is stilted and lacks fluency. As with so many postsymposia offerings, thematic coherence is wanting. It is difficult to know who would benefit from reading this book. Preventive psychiatry may not be the easiest subject to write about, but if it is to reach the audience it deserves, it will need a more coherent and persuasive platform than this collection of contributions provides.

BRIAN TOONE


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

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

DAVID G HARDY


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

The first section of the book provides a concise and comprehensive overview of the diverse sites and cellular mechanisms of action of steroid and thyroid hormones in the brain as well as their synthesis in the endocrine organs or in the brain itself. The second section identifies age related changes in the prevailing levels of cortisol, thyroid hormones, and sex steroids (estrogen, progesterone, testosterone, and dehydroepiandros terone) 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 responsiveness of the hypothalamo-pituitary-adrenal 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 a role on cognition and dementia. Sex differences and, by implication, a role for sex steroid hormones, are also noted in schizophrenia, anxiety disorders, pain perception, immune function, and psychotropic drug metabolism. However, many contributors emphasise the inconsistencies in the scientific literature and the general lack of properly controlled hormone replacement studies in elderly people. Therefore, the view that youthful hormonal profiles will promote healthier aging must remain speculative until more conclusive evidence is available. In its critical approach, this book should be an impetus to study 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 not are as heated as in any other Royal College. There are major requirements—for example, to understand psychotherapy and psychological treatments. Yet as a treatment tool they still play a subordinate role in most treatments in most settings for the management of the severely mentally ill. By contrast, time and time again surveys of trainee’s needs persistently cry out for good information on psychopharmacology. In addition any teaching courses in psychopharmacology are always voraciously snapped up. Our own flawed Maudsley prescribing guidelines, which started life as a simple internal document, is thirstily sought after. Essential Psychopharmacology is the book I always wanted to write but have been soundly beaten to it by Stahl. The first edition was a finely crafted book with logically distinct sections on basic science, disease mechanisms, drug action, and drug classes. This third edition is now much improved again with copious colour illustrations and bang up to date scientific information about both active theories and new products and their associated modes of action. As the introduction states much has changed since the publication of the first edition 4 years ago. In one sense this is a slight pitfall of the book. The second edition has been prepared in the middle of a major research boom in psychopharmacology and in its attempt to be up to date it is in danger of becoming rapidly out of date. A text book format with a fair publication lag may not be the best vehicle for an attempt to cover absolutely up to date information. Nevertheless, I think the book is near perfect as a textbook of basic psychopharmacology. If I try and improve it further, I wonder whether the author and publisher might think again about the illustrations. It is superbly illustrated but sometimes the cartoon imagery is so metaphorical that it serves occasionally to be cumbersome and lacking clarity occasionally obscuring rather than clarifying the issue.

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

ROBERT KERWIN

www.jnnp.com

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

The main failing of the book is in the selection of chapters. I have three criticisms. The chapter book is is unlikely more from the fear of legal retribution if they miss something. At the end of the chapter on neurological examination there is a brief section on “how to modify it”. This includes a screening neurological examination. The summary range of tests which have been chosen, particularly the value of looking for pronator drift, testing finger tapping, and testing both heel-shin coordination and tandem gait. It is interesting to me that a screening neurological examination must avoid redundancy, and be rich in tests which provide unequivocal evidence of pathology. So why is fundoscopy included in the optic disc section from this recommended screening examination, given that it can reveal the crucial physical sign of papilloedema in a patient who might otherwise be thought to have non-specific headache?

Each chapter starts with a set of thought provoking case histories. Some of us are of the mental disposition that enjoys learning from such cases, although others find it more profitable to dig more formally presented textbook information. I admit that I tend to fall into the second group, finding it less easy to evaluate “paper patients” than real patients in a consulting room. My own thought process is often refined by finding that the case histories, and the discussion of them, are dislocated to separate parts of the chapter, necessitating constant thumbing backwards and forwards.

I suspect that this relatively wordy basic textbook will appeal more to students and junior doctors in North America than in the United Kingdom. In the United Kingdom many seem to want shorter books. Junior staff in general medical training often seem to use the neurology entries in general medical textbooks. Neurology trainees and consultants seem to refer to specialist textbooks. But if you like problem oriented learning, you should flick through a copy of this book to see whether it suits you.

MICHAEL DONAGHY

John Bousfield

The second edition particularly introduces details of neurological examination which are so abundant in this work as to be unavailable elsewhere. The authors’ programme for neurological examination is highly detailed and comprehensive. It is my impression that such exhaustive notes are needed as part of the contemporary 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. This is a large book which is not easy to get a handle on. The first three chapters should be required reading for any aspiring neurologist, neuropathologist, or neurologist whether scientist, clinician, or veterinarian.

The second edition, about 1000 pages in length, is a comprehensive listing of several hundred substances with neurotoxic potential. At its best, this section offers mini-reviews—many of which are informative and useful. This is now the definitive reference text on neurotoxicology, and to the major aspects of human and veterinary neurotoxicology. The chapter on human neurotoxicity describes disease processes by system rather than by class of compound; that on veterinary neurotoxic disease describes disease by class of toxic agent. I found the first a much more valuable approach. Despite this peculiarity, I suspect that these first three chapters should be required reading by any aspiring neurotoxicologist, neuropathologist, or neurologist whether scientist, clinician, or veterinarian.

The second section, about 200 pages in length, is a comprehensive listing of several hundred substances with neurotoxic potential. At its best, this section offers mini-reviews—many of which are informative and useful. This is now the definitive reference text on neurotoxicology, and to the major aspects of human and veterinary neurotoxicology. The chapter on human neurotoxicity describes disease processes by system rather than by class of compound; that on veterinary neurotoxic disease describes disease by class of toxic agent. I found the first a much more valuable approach. Despite this peculiarity, I suspect that these first three chapters should be required reading by any aspiring neurotoxicologist, neuropathologist, or neurologist whether scientist, clinician, or veterinarian.

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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).