Acute Optic Neuritis in Australia: a 13 year prospective study

The frequency with which multiple sclerosis develops after an attack of acute optic neuritis varies widely in different series and has been reported to range from 11.5% to 85%. The variability in the findings may relate to different methods of patient selection, diagnostic criteria, geographical factors, duration of follow up, and study design.

A cohort of 82 patients (59 females, 23 males) with uncomplicated ON aged 10 to 50 years (mean 29.2) who were examined neurologically and had visual evoked responses (VERs) performed in our department during the period 1973-83 were re-examined in 1983-85. Twenty six of the patients (32%) had progressed to probable or clinically definite multiple sclerosis during the follow up period of 7-114 (mean 57) months. Female sex, young adult age, and the presence of HLA-B7 or DR2 seemed to increase the risk of developing the disease. Seventy one of the 82 (87%) (52 females, 19 males) were reviewed in 1991-2; 11 patients could not be traced. Neurological examination was performed on 49; two patients had died with multiple sclerosis and a telephone questionnaire was completed on the remainder. Thirty three (46%, or 40% of the original 82) had developed probable or clinically definite multiple sclerosis after a mean duration of 13.25 years (range 8-29.6 years). Eight cases had developed multiple sclerosis since the previous review. Kaplan-Meier and actuarial methods of assessment, predicted that 52% would develop the disease after 15 years (figure). There was a significantly greater risk of developing multiple sclerosis for patients in the 21–30 year age group than those outside this range but there was no significant difference in the rate of progression to the disease for males and females. There was no significant difference in the probability of developing multiple sclerosis in patients with single or recurrent attacks of optic neuritis or bilateral optic neuritis, nor in those who were DR-2 positive (table 1).

The finding in the Australian cohort that 52% of patients with optic neuritis were at risk of developing probable or clinically definite multiple sclerosis in 15 years compares with that of 57% in 11.6 years in the United Kingdom, 26-33% in the United States, and 45% in 15 years in Sweden.

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Clinical features of patients with optic neuritis (ON)

<table>
<thead>
<tr>
<th>Age (y)</th>
<th>ON-patients</th>
<th>ON-multiple sclerosis</th>
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<tbody>
<tr>
<td>&lt;20</td>
<td>10, 4</td>
<td>9, 4</td>
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<td>21-30</td>
<td>8, 17</td>
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<td>31-40</td>
<td>11, 9</td>
<td>11, 9</td>
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<tr>
<td>41-50</td>
<td>9, 3</td>
<td>9, 3</td>
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Sex:
- Males: 13, 6
- Females: 25, 27

ON Type:
- Single: 23, 17
- Recurrent: 11, 13
- Bilateral: 4, 3

HLA Type:
- DR-2+ 15, 22
- DR-2- 19, 11

*Four patients not typed.

multiple sclerosis in 15 years is comparable to the normal range for the pressure-volume index, calculated from the constant (an inverse of elastance coefficient) is different from the values obtained by the bolus injection. Values below 13 ml indicate a tight brain, from 13 ml to 23 ml normal compliance, and above 23 ml hyperventilatory brain. A slow constant rate infusion tests global compliance of the craniospinal axis whereas a fast bolus volume load probably tests compartmental compliance of the container into which the extra volume is added.

This pattern of CSF circulation with low or normal resistance to CSF outflow, increased brain compliance, and very few vasogenic waves is characteristic of cerebral atrophy.

Cranioplasty was carried out as his deterioration was attributed to the "syndrome of trephined" where the brain sinks in, particularly with erect posture and dehydration producing deterioration in conscious level and focal signs. However, 1 month later, there had been no progress in the patient’s condition and repeat CT again suggested progressive ventriculomegaly. The infusion study was repeated. The opening ICP was now dramatically different (10 mm Hg) to the previous study. However, the pulse amplitude (1.5 mm Hg) was increased, and the calculated resistance to CSF outflow was greatly increased to 20 mm Hg/ml/min, with a slow cerebral perfusion pressure index of 15 ml. Such a pattern is specific for hydrocephalus. After this test the patient was shunted with a Codman Medos programmable valve (setting 120 mm H2O) ventriculoperitoneal shunt with remarkable clinical improvement, the GCS rose to 14, he began to talk and his spasticity in his arms and legs decreased dramatically. It is obvious why the pressure-volume compensatory reserve (PVR) decreases after cranioplasty, but the interpretation of an increase in the resistance to CSF is not immediately apparent. Two explanations are possible:

- The patient had developed an acute hydrocephalus, possibly as a result of traumatic subarachnoid haemorrhage. Cranioplasty was a factor allowing compensation of CSF circulation in the early stages. It is difficult to explain what is the nature of such compensation. Shapiro et al attempted to offer an interesting but conceptually difficult hypothesis that the time constant (resistance to CSF outflow/compensation of cerebrospinal space) of cerebrospinal system hydrodynamics has a tendency to remain constant. Therefore, a
mechanistic increase in compliance after craniectomy tends to be followed by a decrease in the resistance to CSF outflow. This process may be reversed after cranioplasty—that is, a decrease in PVI may be followed by an increase in the resistance to CSF outflow.

The second possible scenario is more important for clinical management. A large craniectomy may facilitate irreversible ventricular enlargement over weeks or months. Thus, after cranioplasty, the expanded ventricles may, via the cerebral mantle, obstruct the lumen of the cortical subarachnoid space and increase the resistance to CSF outflow.

This case demonstrates that when the CSF circulation is studied in patients with a large craniectomy the CSF outflow resistance cannot be taken reliably as a guide for shunting. Overnight ICP monitoring or CSF infusion study should be performed after cranioplasty, when CSF circulatory reserve decreases dramatically. Moreover, a prolonged period without a bone flap may encourage ventricular dilatation.

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CT and infusion studies. (A) Scan performed on admission. (B) After right frontal lobectomy and bone flap removal. (C) Four months after injury, before cranioplasty. (F) Infusion test demonstrated low resistance to CSF outflow and increased brain compliance. ICP=mean intracranial pressure; AMP= pulse amplitude of ICP waveform. Constant infusion rate of 1.5 ml/min is indicated by a thick horizontal line. X axis=time. (D) Five months after injury, after cranioplasty. (G) Infusion test demonstrated grossly increased resistance to CSF outflow and normal brain compliance. (E) One month after shunting: normalisation of ventricles. Bicaudate index decreased from 33% to 21% with a decrease in the 3rd ventricle diameter (from 13 mm to 8 mm).
Diencephalic amnesia and apraxia after left thalamic infarction

Amnesia and apraxia are unusual manifestations of unilateral thalamic lesions. A patient in whom severe amnesia and apraxia were the presenting features of a left thalamic infarct is presented. The findings support the concept that memory and praxis both utilise circuits which include the dominant thalamus. 

A 78 year old right handed Hungarian woman presented with memory loss and disorientation. She had been well and conversed normally with her daughter on the evening before presentation. The next morning, her daughter was alarmed to find her mother’s house in a state of disarray. Dishes were unwashed, lights left on, and doors open. The patient seemed baffled by eating utensils, attempting to scoop food with her knife. Later that morning, she failed to recognise longstanding Hungarian friends. She was unable to recall her address, the name of the city in which she lived, or the names of her grandchildren. She subsequently failed to recognise her family doctor of 7 years. History included non-insulin dependent diabetes, hypertension, hyperlipidaemia, and atrial fibrillation. Medications were digoxin, glibenclamide, and metoprolol. Captopril had been prescribed 4 weeks previously but was ceased 2 days before presentation due to presyncope symptoms. The patient consumed no alcohol. There was no history of cerebrovascular events.

Cognitive functions were examined at the bedside with the assistance of an interpreter, as the patient spoke no English, although she conversed freely in her native Hungarian. She had no recollection of events since emigrating to Australia 50 years previously, gave her correct maiden name, and could not recognise or name her grandchildren, although she recognised her daughter. She acknowledged she was in a hospital, but maintained it was in Budapest and the year was 1947. Although her recollections regarding her early life and wartime Hungary seemed accurate, she confabulated when asked for details of recent events. Short term recall of verbal material and people was poor. The patient was able to name objects such as a pencil and a watch, and obey two and three stage commands. She wrote her name and copied simple designs correctly, and could imitate gestures such as waving goodbye or blowing a kiss. However, she was unable to use eating utensils or a toothbrush, either in pantomime or when provided with the object itself. Movements of the face and limbs were normal, and there were no sensory abnormailities. Knee and ankle jerks were absent bilaterally and both plantar responses were extensor. General examination revealed atrial fibrillation and mild cardiomegaly.

The patient continued to display severe impairment of anterograde memory. She was reluctant to leave her bed, and quickly became lost unless supervised. She did not recognise familiar staff members and was unable to use ward landmarks to reorientate herself. She required assistance to feed herself, brush her teeth, and shower. When reviewed 3 months later, her memory disturbance, and apraxia for simple actional and daily life (such as brushing her teeth) persisted, necessitating care in a supervised environment.

Brain MRI (figure) showed a left anterior thalamic lesion consistent with lacunar infarction and periventricular white matter ischaemic changes.

Deficits of anterograde and retrograde memory after thalamic lesions are well recognised.7 The syndrome of diencephalic amnesia after bilateral medial thalamic lesions typically involves striking disorientation for time, loss of autobiographical information (often extending back for many years), confabulation, and severe anterograde amnesia for verbal and visual material, including recognition of familiar faces.7 These features were well illustrated by our patient, who became “marooned” in an earlier place and time. Amnesia after unilateral thalamic lesions is rare.8 There is increasing evidence that thalamic lesions interrupt the multiple brain networks which form the anatomical substrate of memory,9 encompassing the hippocampus, medial temporal lobes, and cingulate cortices, and overlapping with the language areas of the left hemisphere.9 The thalamus is activated in retrieval of episodic ( autobiographical) and semantic (encyclopaedic) information from long term storage and execution of learned motor tasks,9 which may reflect its widespread connections with other subcortical and cortical structures.

The patient’s ability to name or identify objects was not tested systematically. On the evidence available, it seems likely that her difficulty in utilising common objects was a manifestation of apraxia for daily tasks rather than, for example, agnosia for the objects involved. Apraxia is a rare manifestation of isolated thalamic lesions.5 The ability to access stored motor representations is thought to be crucial for normal execution of learned actions.6 These motor representations are thought to be analogous to motor memories. Although praxis is generally regarded as a function of distributed cortical regions in the left hemisphere, apraxia in association with thalamic amnesia has not been emphasised in previous reviews of the amnesic syndrome.6,14 involvement of deep hemispheric white matter in association with basal ganglia pathology is thought to be critical for the development of apraxia after lesions of subcortical structures.6 The conjunction of diencephalic amnesia and apraxia after thalamic infarction in the present case may be interpreted as further evidence that retrieval of episodic, semantic, and motor memories is mediated by overlapping functional networks in the dominant hemisphere.6,14

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Transverse myelopathy in the antiphospholipid antibody syndrome: pinworm infestation as a trigger?

The antiphospholipid antibody syndrome is a disorder characterised by the production of autoantibodies directed against negatively charged cell membrane phospholipids. Antiphospholipid antibodies have been described in various neurological disorders. It has been generally accepted that viral, bacterial, and parasitic infections can serve as a trigger or autoimmune reactions. Despite the growing knowledge that has accumulated, the relation between parasites and autoimmunity has not been clarified.

Enterobius vermicularis (pinworm) is a nematode rarely found outside the gastrointestinal tract, but allergic reaction due to enterobiasis has been reported.1 We describe the case of transverse myelopathy preceded by intestinal pinworm infestation in the primary antiphospholipid antibody syndrome. To our knowledge, such an association has not been reported previously. Pinworm therapy was complicated by the Jarisch-Herrheimer reaction manifested by temporary exacerbation of primary antiphospholipid syndromes.

In March 1998, a 40-year-old woman who complained of perianal itching noticed the presence of worms migrating from the anus. Three days later itching and numbness involved both legs, and the patient had weakness in the legs. These symptoms progressed over the next 3 days to severe paraparesis and urinary urgency. Her medical history was relevant for three unexplained miscarriages which all occurred in midpregnancies. In the local hospital, she underwent brain and lumbar-sacral spine MRI and findings were relevant for three unexplained miscarriages. At that time she was asymptomatic with only mild spasticity left. Mebendazole was given in a single dose of 100 mg and the next day the Jarisch-Herrheimer reaction occurred, with deterioration of leg spasticity, inability to walk, and development of urinary retention. At that time, low positive IgG ACA was detected. The dose of pinworms was raised to 50 mg/day and slowly tapered off within the next 2 months. Sphincter disturbances resolved in 1 day and motor dysfunction gradually improved with only mild spasticity left.

Diagnosis of antiphospholipid antibody syndrome in our patient was based on the presence of recurrence from tarsal eye, transverse myelopathy, and raised ACA. The ACA titre was probably lowered by previously administered corticosteroid therapy. There are several reports of transverse myelopathy as a manifestation of antiphospholipid antibody syndrome in the past decade.2 A potential pathogenic role of antiphospholipid antibodies in transverse myelopathy might be based either on vascopathy or on interaction with spinal cord phospholipids.

Infection by helminths is universally associated with activation of T helper 2 (Th2)-type cells. Recent mechanisms and protective value of antihelminthic Th2 responses, such responses may also be detrimental to the host. The presence of ACA, anti-GM1, and antifilatide antibodies in our patient suggested a cross response to Enterobius vermicularis, as it has been shown that nematodes contain cardiolipin, ganglioside GM1, and sulfatides within their complex lipid composition.3 When parasites share epitopes with host tissue, cellular mimicry may exploit host immune tolerance against a self-determinant. Autoimmunity may occur if immune tolerance is overridden in genetically susceptible hosts. It has been proposed that the presence of pathogenic cross-reactive autoantibodies could be the basis for the regression between nematodes and autoimmunity. It may be also postulated that Enterobius vermicularis stimulated Th2 response which enhanced polyclonal autoantibody production resulting in the presence of ACA, anti-GM1, and antifilatide antibodies. The association of transverse myelopathy, ACA, and enterobiasis might be purely coincidental, which we assume to be unlikely. The finding of different autoantibodies, as well as the isotype switch of ACA, strongly suggests that pinworm infestation in our patient was the “triggering event for anti-GM1 and anti-filatide antibodies. The appearance of the spinal cord damage caused by ACA in our patient might have been facilitated by the simultaneous effect of anti-GM1 and anti-filatide antibodies. A significant subset of the human anti-GM1 antibodies that reacts with the Gal(b1–3)GalNAc determinant also bound to oligodendrocyte-myelin glycoprotein which is a constituent of the myelin of the CNS. As for anti-filatide antibodies, their presence has been already shown in some diseases affecting the CNS.

It is clear that parasitic infections can serve as a trigger factor of autoimmune reacties, but the presence of autoantibodies or self-reactive T cells is rarely associated with clinical manifestations. They develop only in patients with adequate immunogenetic and hormonal background for autoimmune diseases. In several studies, increased frequencies of HLA-DR4, DR7, and DR3, and DQ2 were found in patients with antiphospholipid antibody syndrome,1 and in our patient HLA-DR4 and DR53 were present. Additional studies are necessary to further elucidate the complex mechanisms of involvement of intestinal helminths in the processes of autoimmune activity.

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Radiologically selective visual pathway involvement in adult onset cerebral adrenoleukodystrophy

A case of adult onset cerebral adrenoleukodystrophy is presented with serial MRI showing selective involvement of the visual system with spread of disease along the fibre tracts of this system.

Adult onset cerebral adrenoleukodystrophy is the rarest presentation of adrenoleukodystrophy.1 It may present with various symptoms often including visual impairment.1 Brain MRI may show multiple areas of symmetric high signal intensity within cerebral white matter, usually affecting the occipital lobes.2,3 We present a case of adrenoleukodystrophy, in whom serial MRI demonstrated selective progression of demyelination through the visual pathways.

A thirty year old man presented in May 1996 with a 7 month history of deteriorating vision, slurred speech, incoordination, poor balance, generalised weakness, sleep disturbance, and headaches. His symptoms were worse on the right. He had no symptoms of postural hypotension.

His mother had been shown to be a carrier of X linked adrenoleukodystrophy (X-LALD). His two elder brothers had died of X-LALD at the ages of 6 and 7 years. In 1993 our patient had been shown to have abnormal serum concentrations of very long chain fatty acids (VLCFAs) and to be a carrier of the X-LALD gene. At that time he was asymptomatic and had no abnormal clinical signs. Crohn’s disease had been diagnosed in 1987 after an ileal resection although this had remained in remission.

On examination, visual acuities were 6/12 (right), 6/9 (left). Fields were full to confron-
tation using a finger but there was a left homonymous field defect to a red pin and he had a left afferent pupillary defect. Fundoscopy showed bilateral optic atrophy. The remainder of the cranial nerve examination was normal. In the arms tone and power were normal, but coordination was mildly impaired on the right. The reflexes were exaggerated and Hoffman’s sign was present bilaterally. A palmometric reflex was present on the right. In the legs power was normal, but tone was increased and there were several beats of ankle clonus; reflexes were exaggerated and plantar responses were upgoing. Coordination was impaired in both legs, his gait was ataxic, and Romberg’s test was positive. He had a minor reduction in vibration sensation at the right ankle; otherwise sensation was normal. He appeared moderately tanned, but there was no other hyperpigmentation. Supine blood pressure was 114/78, falling to 108/80 on standing. The remainder of the examination was normal.

Routine biochemistry was normal. A morning cortisol was 469 nmol/l (normal >160 nmol/l), but a short synacthen test showed an abnormally flat response (serum
coronary rise from 338 to 449 nmol/l over 1 hour. His plasma VLCFA profile was abnor-
mal consistent with XL-ALD. Humphrey visual field testing demonstrated a left
homonymous field defect. Brain MRI was abnormal (figure A and B). He was placed on
a very low fat diet with supplements of glycerol trioleate oil.

By October 1996 his headaches had settled but his eyesight, memory, coordination, and
walking were worse. Visual acuity was below 6/60 in both eyes. Brain MRI was repeated
(figure C-E). By August 1997 there had been no new clinical developments (MRI figure
F-G). In May 1998 he complained of naviga-
tional difficulties in familiar surroundings,
further memory loss, and cognitive decline
(MRI figure H-I).

In May 1996 (figure A) T2 weighted axial imaging showed high signal intensity areas in
the region of the right lateral geniculate
nucleus and left optic tract. The occipital
white matter was normal. T1 weighted
images with gadolinium contrast enhance-
ment (figure B) showed bilateral enhance-
ment of these structures and right optic tracts.

By October 1996 (figure C) T2 weighted axial imaging showed spread of the areas of
high signal intensity continuously from the
lateral geniculate nuclei posteriorly along the
optic radiations into the white matter of both
occipital lobes, more prominent on the right.
T1 weighted images showed contrast en-
hancement in the optic chiasm and optic tracts
(figure D), lateral geniculate nuclei, origins of the optic radiations, and right
occipital white matter (figure E).

By August 1997 (figure F) there had been
further progression in the white matter
changes in both occipital lobes, with spread
to the splenium of the corpus callosum. Con-
trast enhancement (figure G) was seen in the
optic radiations and right occipital white
matter. The cerebellar white matter was of
low signal intensity with a small area of con-
trast enhancement above the fourth ventricle
to the right of the midline.

In May 1998 (figure H and I) the changes in
white matter were yet more extensive with the
appearance of ring enhancement.

Our case illustrates MRI appearances typi-
cal of adrenoleukodystrophy and demon-
strates in particular the evolution of these
changes with time. The tendency of this con-
dition to affect the visual pathways selectively
is well illustrated as is the spread of disease
along the fibre tracts of that system.

The allowed visualisation of parts of the visual
system, the anatomy of which is usually
hidden—for example, the intracerebral por-
tion of the optic tracts. The characteristic
MRI appearances are thought to result from an
advancing front of active demyelination,
followed by an area of inflammatory cellular
response demonstrating contrast enhance-
ment, surrounded by areas of established
damage, gliosis, and neuronal loss.'

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Golf ball epilepsy
Blunt head injuries may cause epilepsy. We
present the cases of four young people whose
heads were all subject to contact with golf
balls travelling at speed. Each had post-
traumatic seizures, three early and one late,
despite the apparent absence of post-
traumatic amnesia. Although many patients
who develop epilepsy recall some type of head
injury preceding their first seizure, post-
traumatic epilepsy probably accounts for less
than 5% of all the epilepsies. There is good
evidence that the risk of post-traumatic
epilepsy increases with the severity of the injury. Thus, Jennett identified the presence
of intracranial haemorrhage, dural laceration,
and early post-traumatic seizures as the chief
risk factors for late post-traumatic epilepsy.
Annegers et al. also emphasised that in the
absence of a post-traumatic amnesia of 30
minutes or greater, there was no significant
increased risk for the development of post-
traumatic epilepsy.

From a practical point of view and for
medicolegal purposes, it is necessary to
decide if a seizure is post-traumatic. As a
general rule it may be stated that if the person
concerned does not give a history of a post-
traumatic amnesia lasting for a signifi-
cant period of time (an hour or more), and
there is no history of a compound or
depressed fracture with dural tear, it is
reasonable to exclude the possibility that the
epilepsy is post-traumatic. However, it is
worth noting that this view is based on
Jennett’s work and precedes CT. There is no
good evidence from a large series to indicate
whether findings on acute imaging add
anything to the prediction of post-traumatic
epilepsy.
Four examples of acute symptomatic seizures and epilepsy developing after head injuries with golf balls are described, which seem to be an exception to these clinical rules.

An 11 year old boy was struck on the right temple by a golf ball resulting in right frontal skull fracture. His consciousness was not impaired until about 3 hours later when he became drowsy and had two focal motor seizures affecting the left arm. He was intubated and ventilated. A head CT showed a right frontal extradural haematoma with no skull fracture (figure A). The haematoma was evacuated (figure B). He was woken and extubated the next day and was discharged without sequelae two days later on phenytoin. No further follow up is yet available.

A 16 year old boy, who was a keen golfer with a single figure handicap, was struck on the head by a golf ball which rebounded several yards after striking him on the forehead. He experienced local pain, bruising, and swelling. Although he was never unconscious, some 4–5 hours later he developed repetitive jerking of the right face and arm. He was taken to his local casualty department where the diagnosis of serial focal seizures was made. His consciousness was then somewhat obtunded. A brain CT was performed which showed a small, discrete, spherical intracerebral haematoma in the left frontal lobe. This was slightly beneath the scalp at the point where he had been struck (similar in shape, but more hypointense than the appearance in the figure B). The haematoma gave the distinct impression of a golf ball embedded in the surface of the cerebral hemisphere!

He was treated with parenteral anti-epileptic drugs and subsequently with thio- pentone requiring ventilation for 48 hours with no other sequelae. He has remained seizure free.

He was maintained on phenytoin for 12 months but subsequently this was withdrawn and he has remained seizure free.

A 5 year old girl was struck on the forehead above the right eye by a golf ball struck 10 metres away. On arrival in the accident and emergency department she was fully alert, orientated, and neurologically intact. A lacrimation was present but there had been no apparent loss of consciousness or vomiting. However, 90 minutes after the injury she had a generalised tonic clonic seizure lasting 25 minutes. She was intubated and a head CT scan showed a small depressed fracture with minimal haemorrhagic contusion in the cortex of the right frontal lobe (figure C). She was woken and extubated later that day. She has had no further seizures.

A 12 year old boy was practising golf with a friend. He was struck on the front of the head by a golf ball which rebounded a considerable distance after striking him. He did not lose consciousness and had no more than localised pain, tenderness, and bruising at the site of impact. He did not seek any medical advice about the injury. Over the next 4 years he had three well documented tonic-clonic seizures that started after the golf stroke sleep.

A CT scan 3 years after the original injury showed a small, wedge shaped area of low density affecting the cortex close to the point at which he recalls being struck (figure D).

The heads of these young people were all subject to contact with golf balls which at club level travel at speeds of up to 130 miles/ hour. Each had post-traumatic seizures, three episodes, of whom one had apparent absence of post-traumatic amnesia. Patients 1 and 2 would indicate that this kind of injury is capable of transferring energy across the skull, independent of a skull fracture, to cause an acute extradural or cortical haematoma.

In patient 4 the lesion identified at a later date by CT is consistent with the late onset of giving rise to the intracranial haematoma. It therefore seems reasonable to assume that the late epilepsy in patient 4 was also related to the initial golf ball injury. In the third patient, a minor depressed fracture and contusion were again associated with an early seizure without evidence of intervening impairment of consciousness. It does therefore seem that golf ball injuries are capable of giving rise to both acute symptomatic seizures and late epilepsy without causing post-traumatic amnesia, skull fracture or dural tear. CT evidence, however, would predict the possibility of seizures in these examples in whom the development of post-traumatic epilepsy probably results from the physical properties of golf balls and their ability to transmit considerable mechanical energy at a small site of impact. The problem is one of which classifiers on golf courses (and their doctors) should be aware.

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Sensory predominant neuropathy with GM1 antibodies, conduction blocks, and orbital pseudotumour

Two male patients developed multifocal sensory neuropathy with high titre IgM anti-GM1 antibodies (Mann et al 1990) and infiltrative orbitopathy. Nerve conduction studies showed multiple motor conduction blocks and evidence of a similar phenomenon in sensory nerves. Both patients deteriorated after corticosteroid administration but benefited substantially from intravenous immunoglobulin therapy. Our findings suggest the existence of a predominantly sensory subtype of multifocal motor neuropathy (MMN) and challenge the concept of motor specificity of anti-GM1 antibodies.

Anti-GM1 antibodies have been implicated in the aetiology of multifocal motor neuropathy (MMN) and are assumed to be specific for this disease when occurring at high titres.1,2 We report on two patients with high titre IgM anti-GM1 antibodies and electrophysiological features typical of MMN presenting with severe sensory neuropathy.

Patient 1 was a woman who developed asymmetric numbness of limbs and difficulty in performing fine motor movements around the age of 55. Sensory deficits showed a multifocal pattern (multiple mononeuropathy) and involved proximal limb regions, trunk, and face. The course of illness was steadily deteriorating with some episodes of prominent disease progression usually preceded by minor infections. After 10 years he was unable to write, needed assistance for dressing and walking, and complained of diplia. Neuropsychological examination showed profound sensory and cognitive impairments in sensory modalities in the arms and legs and pseudoanesthesia of the fingers and wrist. Deep tendon reflexes were preserved and muscle strength was normal. The patient showed marked protrusion and downward deviation of the left eye with a complex impairment of all eye movements.

Patient 2, a 68 year old man, reported an insidious onset and gradual worsening of asymmetric sensory loss and sensory neuropathy (MMN) and are assumed to be specific for this disease when occurring at high titres.1,2 We report on two patients with high titre IgM anti-GM1 antibodies and electrophysiological features typical of MMN presenting with severe sensory neuropathy.

Patient 1 was a woman who developed asymmetric numbness of limbs and difficulty in performing fine motor movements around the age of 55. Sensory deficits showed a multifocal pattern (multiple mononeuropathy) and involved proximal limb regions, trunk, and face. The course of illness was steadily deteriorating with some episodes of prominent disease progression usually preceded by minor infections. After 10 years he was unable to write, needed assistance for dressing and walking, and complained of diplia. Neuropsychological examination showed profound sensory and cognitive impairments in sensory modalities in the arms and legs and pseudoanesthesia of the fingers and wrist. Deep tendon reflexes were preserved and muscle strength was normal. The patient showed marked protrusion and downward deviation of the left eye with a complex impairment of all eye movements.

Patient 2, a 68 year old man, reported an insidious onset and gradual worsening of asymmetric sensory loss and sensory neuropathy (MMN) and are assumed to be specific for this disease when occurring at high titres.1,2 We report on two patients with high titre IgM anti-GM1 antibodies and electrophysiological features typical of MMN presenting with severe sensory neuropathy.

Patient 1 was a woman who developed asymmetric numbness of limbs and difficulty in performing fine motor movements around the age of 55. Sensory deficits showed a multifocal pattern (multiple mononeuropathy) and involved proximal limb regions, trunk, and face. The course of illness was steadily deteriorating with some episodes of prominent disease progression usually preceded by minor infections. After 10 years he was unable to write, needed assistance for dressing and walking, and complained of diplia. Neuropsychological examination showed profound sensory and cognitive impairments in sensory modalities in the arms and legs and pseudoanesthesia of the fingers and wrist. Deep tendon reflexes were preserved and muscle strength was normal. The patient showed marked protrusion and downward deviation of the left eye with a complex impairment of all eye movements.
Antibody titres presented were those before treatment (baseline).

SNAP=sensory nerve action potential; DL=distal latency; NCV=motor nerve conduction velocity in the following segments: median nerve: wrist–elbow (NCV1, normal >50 m/s), elbow–axilla (NCV2, normal >56 m/s); ulnar nerve: wrist–elbow (NCV1, normal >50 m/s), elbow–axilla (NCV2, normal >56 m/s); peroneal nerve: ankle–fibula neck (NCV1, normal >42 m/s), fibula neck–popliteal fossa (NCV2, normal >41 m/s).

We report on a predominantly sensory variant of MM(S)N and accurate diagnosis in such patients. Voluntary motor strength both of our patients had multiple motor conduction blocks. Rapid clinical improvement after IVIg therapy despite a more than 10 year history of illness tempts us to speculate on a similar phenomenon in sensory nerves (sensory conduction block).

Good response to therapy argues against a pathogenic significance of high titre GD2 antibodies in patient 2, because the rare GD2 associated sensory axonal neuropathy (sensory ganglionopathy) is mostly irreversible. In addition, this patient showed multiple conduction blocks and slowing of nerve conduction velocities rather than predominantly axonal damage and had no monoclonal gamopathy, which is usually present in cases with the GD2 associated neuropathy.

We propose that multifocal neuropathies with conduction blocks and high titre anti-GM antibodies have a clinical range from predominantly sensory to predominantly motor variants and suggest that all these variants be subsumed under the term “multifocal motor-sensory neuropathy (MMSN)”.

This concept is of clinical relevance in that all phenotypes share the same therapeutic peculiarities including good response to IVlg and indefiniteness (most cases) or even unfavorable effects of corticosteroids, which are first line drugs in the treatment of other immune neuropathies. Our report aims to increase awareness for sometimes prominent sensory involvement in MM(S)N and to facilitate early and accurate diagnosis in such patients.

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ALTERATIONS OF MUSCARINIC ACETYLCHOLINE RECEPTOR SUBTYPES IN DIFFUSE LEWY BODY DISEASE: RELATION TO ALZHEIMER’S DISEASE

The article by Shiozaki et al demonstrating significantly less muscarinic acetylcholine receptor binding sites in the temporal cortex in dementia with Lewy bodies than in Alzheimer’s disease and different upregulation of the m1 and m2 receptor subtypes suggests differences in the manner of degeneration of the cholinergic system between both dementing disorders that may be of basic and practical therapeutic relevance. The more severe reduction of ChAT activity in the neocortex in dementia with Lewy bodies than in Alzheimer’s disease, the higher upregulation of the postsynaptic m1 receptor in dementia with Lewy bodies, and the higher level of the presynaptic m2 receptor subtype in Alzheimer’s disease suggest a severe depletion of presynaptic projection neurons in dementia with Lewy bodies but their relative preservation or upregulation in Alzheimer’s disease.

These data are in line with previous—including personal—findings on cell loss and shrinkage in the cholinergic magnocellular posterior part of the nucleus basalis of Meynert in dementing neurodegenerative disorders. In Parkinson’s disease (brain stem type of dementia with Lewy bodies), cell depletion in the nucleus basalis of Meynert averages 30% to 40% without correlation with age or duration of the illness. It is much higher in demented patients and Parkinson’s disease (similar to Alzheimer’s disease range 50% to 70%) than in non-demented patients (0% to 40%), who show neuronal loss similar to or only slightly higher than age matched controls. Cell loss in the nucleus basalis of Meynert in non-demented patients with Parkinson’s disease is usually associated with little or no cortical Alzheimer’s disease pathology, whereas in severely demented patients with Parkinson’s disease, heavy cell depletion in the nucleus basalis of Meynert is often, but inconsistently, accompanied by severe cortical neuritic Alzheimer’s disease pathology suggesting threshold levels of cholinergic forebrain impairment and deficit for the development of dementia. Even more severe depletion of the nucleus basalis of Meynert with 75% to 80% loss of large cholinergic neurons was found in dementia with Lewy bodies (figure).

There were no major differences in cell loss in the nucleus basalis of Meynert between dementia with Lewy bodies with “plaque only” Alzheimer’s disease (two cases) and with “true” Alzheimer’s disease (eight cases with Braak stages V or VI). Lewy bodies and neurofibrillary tangles in the nucleus basalis of MeNeyert neurons were seen in eight brains of patients with Lewy body disease.
These changes are associated with a decrease in cholinergic innervation of the cortex and hippocampus that may or may not correlate with the severity of cell loss in the nucleus basalis of Meynert and mental status. Neocortical cholinergic activity (choline acetyltransferase) is far more severely depleted in dementia with Lewy bodies than in Alzheimer’s disease and Parkinson’s disease, and correlates well with dementia and nucleus basalis of Meynert pathology (neuron loss, tangles, and Lewy bodies), but not with local cortical pathology. The heterogeneity of degeneration of cholinergic neurons in the basal forebrain and its relative independence from cortical pathology suggests primary involvement of the basal forebrain in Alzheimer’s disease, by contrast with probable retrograde damage in Alzheimer’s disease and dementia with Lewy bodies confirmed by defective retrograde transport of nerve growth factor to the nucleus basalis of Meynert in Alzheimer’s disease.1

These morphological differences in the degeneration of the cholinergic forebrain system between various dementing neurodegenerating disorders are, at least in part, supported by the data presented by Shiozaki et al. indicating differences between Alzheimer’s disease and Parkinson’s disease. These and other genetic, morphological, and biochemical differences between the three disorders may strengthen the hypothesis that they represent different nosological entities. This, however, needs further confirmation.

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Mortality from Parkinson’s disease

The publication of the 10 year mortality data from the Sydney multicentre study of Parkinson’s disease serves as a timely reminder that patients with this condition still die at a rate in excess of their peers despite advances in therapeutics and surgery.1

This fact has been lost on many of our colleagues working in this area, both on the clinical and the research fronts. On many occasions at local and national meetings, I have been forced to remind people that levodopa is also to be suggested between Alzheimer’s disease and dementia with Lewy bodies as are also to be suggested between Parkinson’s disease, by contrast with prob-able retrograde damage in Alzheimer’s disease and dementia with Lewy bodies: choline acetyltransferase parallels nucleus basalis pathology. J Neurol Neurosurg Psychiatry 1999; 61:525–35.2

Mufson EJ, Conner JM, Kordower JH. Nerve growth factor to the nucleus basalis of Meynert serves as a timely reminder that Parkinson’s disease must consider not only quality of life and health economics issues, but also mortality in the hope of establishing reduced death rates.

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7 Diamond SG, Markham CH. Present mortality in Parkinson’s disease: the ratio of observed to expected deaths with a method to calculate expected deaths. J Neurol Neurosurg Psychiatry 1978; 41:259–69.
Anaphylactoid reaction to methylprednisolone. Is it surprising when pharmacological and immune effects of a drug differ?

Clear reports a case of anaphylactoid reaction to methylprednisolone which developed after starting treatment with interferon β-1b. She states that “allergic reaction to steroids is rare and anaphylactoid reaction to methylprednisolone rarer still with only three reports in the literature.” Her report surprised us as on the week of publication of her case we had a patient with multiple sclerosis who developed an urticarial rash within 15 minutes of commencing treatment with intravenous methylprednisolone. Although we thought this to be an unusual response to methylprednisolone, we were not overly perplexed by the drug’s capacity to induce a presumably IgE mediated immune response. Surely for almost all drugs the pharmacological and immune properties are quite distinct.

I undertook a brief literature search. The database was interrogated using Medline Pubmed and the words “anaphylaxis” and “methylprednisolone”. At least 29 cases of anaphylactoid reaction to methylprednisolone are documented in this simple search. Kamm and Haghmeyer systematically review allergic reactions to corticosteroids in the April 1999 publication of Annals of Pharmacotherapy. Their primary data source is a Medline search from January 1966 to December 1997. They report 56 allergic-type reactions to intravenous corticosteroids, including death in 12 patients suspected to be related to corticosteroid anaphylaxis. Methylprednisolone and hydrocortisone were the most commonly implicated corticosteroids. Is it surprising that the frequency of reporting of anaphylactoid reactions to corticosteroids is low? I can see no inherent paradox between the ability of methylprednisolone to bind IgE and its pharmacological anti-inflammatory action. Clear’s speculations about mechanisms by which interferon β may predispose to anaphylaxis may be interesting. However, it is unreasonable to ascribe the anaphylactoid response to methylprednisolone to therapy with interferon β.

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Clear replies:
Mea culpa! The disparity in yield of our literature searches reflects different search strategies. These are often problems in electronic search systems. It is still reasonable to state, though, as Van den Berg and Van Eikema Hommes do in their report,1 that anaphylactoid reaction to methylprednisolone is rare. Few clinicians have come across it.

I agree that it is unreasonable to ascribe the anaphylactoid response to methylprednisolone therapy with interferon β. Nevertheless, it remains the case that a man who had had numerous courses of methylprednisolone without adverse effect had...
anaphylactoid reactions to the drug soon after the introduction of interferon \(\beta\), and that such an unusual event should alert us to the possibility that interferon \(\beta\) may have paradoxic effects. If we see only what we expect to see we run the risk of missing the truth.

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What I liked most reading through the Shiloh, Nutt, and Weizmann’s Atlas of Psychiatric Pharmacotherapy is its completeness. It is indeed a marriage of basic and clinical psychopharmacology, divided into four main sections: basic principles of psychiatric pharmacotherapy, abused substances, drug interactions, and treatment strategies.

As a basic reference for the science researcher, I like the fact that these authors succeed, in the first section, in the very difficult task of translating complex biochemical mechanisms into concise pictures and legends. I particularly like those on second messenger pathways, in action pathways, as these are rare to find and difficult to understand in other books. Switching to more specific psychopharmacology topics, the tables explaining the mechanisms of action of the various drugs are also very well made and updated. For example, the tables illustrating the mechanisms of action of antidepressant drugs go beyond the “catecholamine hypothesis” into explaining the effects, at the genomic level, on the synthesis of growth factors. There is also a great deal of information on the side effects of psychotropic medications, including the pharmacological mechanisms involved. In this regard, the tables describing sexual dysfunctions are particularly useful, as they describe the physiology and the pharmacology of sexual functions in both males and females.

The second section deals with well established as well as novel findings in the field of substance abuse. For each substance, the book explains the receptor mediated effects, the acute effects, the long-term psycho-somatic effects, and the biological mechanisms responsible for dependence, adverse effects, and treatments. The book also gives up to date information on drugs for which biological pathways are less well known, such as non-phenylcyle and LSD.

The third section is on drug interactions. For each class of medication—and, if relevant, for each single drug—the book lists different drugs in the same class of medication on the lateralisation of line bisection judgements of children with attention deficit hyperactivity disorder. J Neurol Neurosurg Psychiatry 1999;66:57–63.

Sheppard DM, Bradshaw JL, Mattingley JB, Lee P. Effects of stimulant medication on the lateralisation of line bisection judgements of children with attention deficit hyperactivity disorder. J Neurol Neurosurg Psychiatry 1999;66:57–63. In this paragraph, figs 2 and 3 were wrongly ascribed the legends for figs 4 and 5 and figs 4 and 5 were given the legends for figs 2 and 3.
Post-traumatic hydrocephalus: influence of craniectomy on the CSF circulation

MAREK CZOSNYKA, JO COPEMAN, ZOFIA CZOSNYKA, ROY S MCCONNELL, CATHERINE DICKINSON and JOHN D PICKARD

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