LETTERS TO THE EDITOR

Right ipsilateral hypersensation in a case of anosognosia for hemiplegia and personal neglect with the patient's subjective experience

Recently, there have been some reports regarding hyperkinetic motor behaviours contralateral to hemiplegia in acute stroke.1,2 These behaviours are probably the reflection of early plastic changes of brain maps and circuits after an acute lesion and an active process induced by disinhibition to establish new compensatory pathways.3 I encountered a peculiar case of a patient with right ipsilateral “hypersensation” after a right hemispheric infarction in the acute period who also presented severe left sensorimotor disturbance, hyperkinetic motor behaviours in the right upper limb, anosognosia for hemiplegia, and personal neglect. It was possible to record the patient's subjective experience of the acute phase, which was helpful for understanding the mechanism of anosognosia.

A 76 year old right handed woman was admitted to hospital soon after the onset of left hemiparesis and hemisensory disturbance. She had undergone implantation of a cardiac pacemaker because of sick sinus syndrome. On neurological examination, she was awake and oriented to time and place, but showed inattention and motor impersistence. There was no aphasia or apraxia, but mild left hemispatial neglect was detected. Left hemiparesis was noticed (upper limb 0/5, lower limb 2/5, and face 3/5). Sensory loss was complete in all modalities in the upper limb and severe in the face and lower limb, being slightly preserved for pain and coldness. She denied the existence of left hemiparesis and had completely lost the sensation of ownership of her left hemibody. When I asked her the owner of her left hand and leg while showing them to her, she remarked that these belonged to her grandmother. Brain CT (figure) showed a fresh infarction in the right precentral and post-central gyrus, extensively extending to the right medial aspect of the frontal lobe (supplementary motor area).

From the second hospital day she complained that she felt very cold in the right half of her body and even sometimes felt pain because the wind from the air conditioner was too strong. I told her that the air conditioning system worked but it was not set at a low temperature because it was winter. She understood my explanation but she continued to complain of spontaneous, abnormal sensation in her right hemibody. This sensation was most severe in the upper limb followed by the face and lower limb, whereas it was not triggered or worsened by any sensory stimulation, and objective sensory deficits were not present in the right hemibody. She usually wrapped herself tightly in a blanket to avoid coldness. She did not complain of any other delusional or illusional feelings. There were also hyperkinetic movements in the right upper limb such as patting the head with the right arm, manipulations of sheets and blanket, and rhythmic finger movements.

The result of a mini mental state examination performed on the fourth hospital day was 25/30.

The abnormal sensation persisted for almost 1 month and gradually subsided, whereas the left hemiparesis and sensory disturbance improved. In the meantime, she began to recognise the left hemiparesis and regained the sensation of ownership of her left hemibody. The following are her recollections from the time of onset on the 60th hospital day:

“One morning, I woke up and found that there was a strange hand and foot close to the left side of my body, as though my dead grandmother lay aside me. I tried to throw them off but they were too heavy to move. I glanced at them and felt that they looked flabby and wrinkled, so I was convinced that they belonged to my grandmother. I had no idea that the left side of my body was disabled or even ill.

After hospitalisation, I felt very cold in the right half of my body and sometimes felt pain because of the powerful wind from the air conditioner. I understood that the hospital did not use cold air conditioning in winter, but that powerful, cold wind could not have come from anything other than an air conditioner. Anyway, this unpleasant feeling gradually subsided, and at the same time, I realised that the disabled left side of my body belonged to me and that I had suffered a brain disorder.”

Ghika et al. described 20 patients with hyperkinetic motor behaviours contralateral to hemiplegia in acute stroke who were found only with large infarcts in the territory of the internal carotid artery, middle cerebral artery, or the anterior cerebral artery and which correlated significantly with the severity of motor deficit and the presence of aphasia, neglect, or sensory loss. These characteristics are similar to those in the present patient. However, “hypersensation” as found in this case was not described. Regarding the mechanism of these behaviours, Ghika et al. speculated that they represent the clinical expression of early plastic changes of brain maps and circuits after an acute lesion and probably an active process induced by disinhibition to establish new compensatory pathways.3 Such ipsilateral symptoms might occur not only in the motor system, but in the sensory system as well. In the present patient, the degree of right hypersensation...
was parallel with the degree of the disturbance of sensory deficits of the homologous left side, and hypersensations subsided as the sensory disturbance of the left side improved. This suggests that the disinhibition or hyperexcitability to facilitate functional reorganisation may have been the main cause of hypersensation after stroke.

Lesional extent must also be considered. Studies in animals and patients with stroke with sensorimotor cortical lesion provided several insights into the basis for recovery. In the cortical region, there are three areas where increased activation has been suggested: the sensorimotor cortex of the unaffected hemisphere, the supplementary motor area (probably bilateral, ipsilateral much greater than contralateral to the lesion), and peri-infarct lesion of affected hemisphere.19

In the present case, the right supplementary motor area belonged to the lesion and the right sensorimotor cortex was extensively involved. Acute onset of severe motor and sensory disturbance caused rapid disinhibition and increased activation which had to depend exclusively on the left (affected) sensorimotor cortex as the right supplementary motor area and right peri-infarct area could not be involved in the reorganisation process. I speculate that this provoked hyperkinetic motor behaviour as well as hypersensation in the right hemibody.

In the case of patients who recovered, there have been few reports of subjective perceptions in the acute stage of stroke.6 Grotta et al.2 reported the subjective experiences of 24 patients with nonlacunar ischaemic stroke who dramatically recovered. They clearly recall the exact circumstances involved. Acute onset of severe motor and sensory disturbance caused rapid disinhibition and increased activation which had to depend exclusively on the left (affected) sensorimotor cortex as the right supplementary motor area and right peri-infarct area could not be involved in the reorganisation process. I speculate that this provoked hyperkinetic motor behaviour as well as hypersensation in the right hemibody.

Phantom limb sensations after complete thoracic transverse myelitis

Phantom phenomena are common complications of limb amputations and may occasionally follow traumatic paraplegia and severe injuries of peripheral nerves. However, they have not been previously reported in patients with non-traumatic paraplegia. The following case history describes a patient with transverse myelitis resulting in complete paraplegia who experienced persistent motor movements of an abnormal portion of her paralysed lower limbs. These findings suggest that disruption of the anatomical and functional integrity of the spinal cord may be the most important factor in the pathogenesis of phantom sensations.

A 61 year old woman presented with severe weakness of both legs, skin sensory loss and paraesthesia of the lower limbs, and bowel and bladder symptoms. She was well until 3 months earlier when she started to develop a tingling sensation and numbness over the outer side of her left leg. These symptoms gradually progressed and by the time she was admitted to hospital she had anaesthesia and sensory impairment of the whole of the left leg and in the distal half of the right leg. A month before admission she had become unsteady on her feet and developed urinary frequency, urgency, incontinence, and constipation. There was also a rapidly progressive weakness of both legs, but no other symptoms.

Four years earlier the patient had had paraparesis in both feet. This was thought to be due to peripheral neuropathy, but the diagnosis was not confirmed with neurophysiological tests. The symptoms resolved in a few weeks. The patient had a partial thyroideaomy for a nodular goitre 15 years ago. There was no other medical or family history of note. She was not taking any medication.

Physical examination confirmed the presence of complete flaccid paraplegia with skin sensory loss of all sensory modalities to the waist. The knee and ankle jerks were absent and both plantar responses were extensor. She had retention of urine and symptoms, signs, and radiological features of a paralytic ileus. There was no evidence of organomegaly and general physical examination was unremarkable. A full blood count, urea and electrolytes, and liver and thyroid function tests were within normal limits. An urgent magnetic resonance imaging confirmed the presence of mild degenerative changes in the cervical spine at the level of C5–C7. There was no radiological evidence of an intracranial or extracranial compression or demyelination. However, the five distal segments of the thoracic cord appeared swollen and there was loss of the normal CSF rim ventral and dorsal to the cord on T1 weighted images. The T2 signal was prolonged and there was no contrast enhancement of the lesion. The appearances were considered consistent with oedema of the thoracic spinal cord. Brain MRI was normal. Visual evoked responses and brain stem auditory evoked potentials were within normal limits. Somatosensory evoked potentials of the posterior tibial nerve could not be obtained because the patient developed severe myoclonic jerks of the extremities at very low stimulus intensities. Her CFS protein concentration was 0.88 g/dl. No oligoclonal bands were detected on CSF protein electrophoresis. There were 2 lymphocytes/mm³ and four polymorphs/mm³. There was no bacterial growth on CFS culture.

Shortly after admission the patient started to experience phantom sensations in her lower limbs. At times she thought that her legs were crossed and on other occasions she felt that that she was standing on tiptoes. These symptoms were persistent and appeared to be spontaneous. The patient did not disclose any specific stimuli. Their intensity remained unchanged until the patient was started on 200 mg carbamazepine three times a day. With this treatment the phantom sensations became less frequent and the images were less intense but they did not resolve completely. The paralytic ileus resolved with conservative treatment. However, the patient's neurological impairments remained unchanged until she was discharged from hospital 6 months later.

Non-painful phantom phenomena are continuous or intermittent sensations emanating from an amputated or deafferented part of the body. The missing or denervated part may be perceived in its premorbid shape, size, and other physical characteristics or in a distorted form. Patients often report normal functions associated with the absent organ—for example, penile erection, ejaculation, and orgasm after removal of the genitalia or voluntary or involuntary movements of an amputated limb. Often, sensations such as touch, pressure, and cold are experienced in the phantom organ. Phantom sensations often occur after limb amputations and have also been reported in about 15% of patients after a mastectomy. Sometimes they may follow spinal cord injury. However, their occurrence after transverse myelitis has not been previously reported.

Understanding the pathogenesis of phantom sensations is important for developing the appropriate treatment strategies. However, the mechanisms that underlie these phenomena are not fully understood at present. It has been suggested that they may be a manifestation of a psychological disorder or due to organic neurophysiological abnormalities.

Psychological factors such as denial or grief for the lost body part have been suggested as the cause of the postamputation phantom phenomena. However, this explanation is not supported by the current evidence. For example, the occurrence of phantom phenomena does not correlate with poor psychological adjustment or with the incidence of depressive symptoms in patients. Another hypothesis is that damaged peripheral somatosensory receptors fire spontaneously and give rise to the painful or abnormal experiences. However, phantom sensations have been reported by patients after spinal anaesthesia in the absence of damage to the peripheral nervous system. At present the neuromatrix theory offers the most plausible explanation for phantom sensations and pain.

According to this theory the symptoms associated with the phantom phenomena originate from genetically predetermined sensory images (or sensory engrams) that are stored in the cerebral cortex. It was postulated that the sensory images are triggered when neural impulses from the periphery are blocked. The patient reported here had complete “functional” transection of the spinal cord. The occurrence of phantom sensations in this patient was therefore independent of the neural input from the peripheral nervous system. This case provides further evidence that phantom phenomena are due to a central neurophysiological mechanism, probably...
triggers by impulses arising spontaneously from damaged spinal cord neurons. This is in accord with a previous report of structural and functional changes in the spinal cord in the acute stage after deafferentation.

Ramachandran and Hirstein reviewed the studies of the topographical reorganisation of the cerebral cortex after limb amputations and concluded that the mechanism of phantom experiences is “remapping” of specific brain areas. The present study did not consider this question. However, the diversity of the illusory experiences of movement reported by our patient suggests a more diffuse cortical reorganisation. This is more in keeping with the neuromatrix theory and the presence of “diffuse neural matrix”.

The occurrence of phantom limb phenomena in patients with non-traumatic CNS lesions had also been previously described in a few patients with stroke. Halligan et al carried out a detailed study of a 65 year old man with severe left sided weakness, sensory loss, and hemianopia who, for several weeks, consistently reported a phantom (or supernumerary) third limb. Like our patient, he had good insight into his neurological deficits and his behaviour was completely rational, suggesting that the phantom experience was not a delusional belief but a direct result of organic brain damage. A M O BAKHEIT Beausachmp Centre, Mount Gould Hospital, Plymouth PL4 7QD, UK


**Vestibular evoked myogenic potentials in multiple sclerosis**

Myogenic potentials generated by a click evoked vestibulospinal reflex can be easily recorded from the tonically contracting ipsilateral sternocleidomastoid muscle (SCM). These “vestibular evoked myogenic potentials” (VEMPs) are abolished by selective vestibular nerve section as well as by certain peripheral vestibular diseases.

Click sensitivity primary vestibular neurones arise from the saccular macula in the guinea pig and electrical stimulation of these neurones in the cat evokes inhibitory postsynaptic potentials in ipsilateral SCM motor neurones which are abolished by stimulation of the ipsilateral vestibulospinal tract. These clinical and neurophysiological data suggest that VEMPs are mediated by a pathway consisting of the sacular macula, its primary neurones, vestibulospinal neurones from the lateral vestibular nucleus, the medial vestibulospinal tract, and finally motor neurones of the ipsilateral SCM. Therefore a lesion anywhere in this pathway could result in abnormal VEMPs. We studied VEMPs in three patients with definite multiple sclerosis to search for lesions in the vestibulospinal pathways.

Patient 1, a woman aged 30, and patient 2, a man aged 32, both showed dysarthria, cerebellar ataxia, bilateral internuclear ophthalmoplegia, and a spastic tetraparesis. Patient 3, a woman aged 36, showed cerebellar ataxia and a spastic tetraparesis only. Apart from VEMPs, all patients underwent auditory evoked potential (AEP) testing as well as MRI.

Our recording methods have been described previously. Briefly, surface EMG activity was recorded by the supine patients from symmetrical sites over the upper half of each SCM with a reference electrode on the lateral end of the upper sternum. During the recording, the patients were instructed to rotate their heads to the opposite side to the stimulated ear to activate the SCM. Rarefraction clicks (0.1 ms, 95 dB normal hearing level) were presented through a headphone. The responses to 100 stimuli were averaged twice. Our normal control values have been reported previously.

Briefly, all normal subjects show a biphasic response (p13-n23) from the ipsilateral SCM. The mean (SD) of the positive peak (p13)=11.4 (0.8) ms, the mean of the negative peak (n23)=20.8 (2.3) ms. We defined the mean±2 SD as the upper limit of the normal range—that is, p13=13 ms and n23=26.4 ms.

All of the six sides in three patients showed biphasic responses (p13-n23) with significantly prolonged latencies. Patient 1 showed prolonged p13 and n23 on both sides (right p13=16.7, n23=26.9 ms; left p13=19.8, n23=29.2 ms, figure A). Patients 2 and 3 showed bilaterally prolonged p13 (right p13=15.3, left p13=16.5 ms (patient 2), and right p13=15.0, left p13=18.5 ms (patient 3). In patient 1 the latency of the left p13 (19.8 ms) was longer than that of the right p13 (16.7 ms); in this patient the interpeak latency between waves I and V of the AEP was significantly prolonged only on the right (right 5.14 ms, left 4.30 ms, figure B).

T2 weighted MRI of patient 1 showed high intensity areas in the tegmentum of the pons.

(A) VEMPs, (B) AEPs, and (C) MRI from patient 1. VEMPs are significantly bilaterally, asymmetrically prolonged on both sides. On the left: p13=19.8 ms, n23=29.2 ms; on the right: p13=16.7 ms, n23=26.9 ms. L−responses from the left SCM to the left ear stimulation; R−responses from the right SCM to the right ear stimulation. AEPs on the left were normal, while on the right wave V was delayed to 6.5 ms (normal < 5.9 ms) and the I−V interpeak latency was prolonged to 5.1 ms (normal < 4.4 ms). T2 weighted MRI shows high intensity lesions in the pontine tegmentum involving the vestibular nuclei and vestibulospinal tracts bilaterally.
on both sides involving the vestibulospinal tracts bilaterally (figure C). Patients 2 and 3 also had high intensity areas in the same areas. Apart from lesions in this area, all showed high signal intensity areas in the cerebral white matter.

This preliminary study shows that latencies of a vestibulospinal reflex can be prolonged in multiple sclerosis. As in these three patients the VEMPs were remarkably delayed rather than simply abolished as occurs in patients with peripheral vestibular lesions,4 5 the VEMP delay could be attributed to demyelination either of primary afferent axons at the root entry zone or secondary vestibulospinal tract axons rather than to lesions involving vestibular nucleus neurons. The MRI findings in these patients were not inconsistent with this proposition. Measurement of VEMPs could be a useful clinical test to evaluate function of the vestibulospinal pathway and for detecting subclinical vestibulospinal lesions in suspected multiple sclerosis.

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Sensory ataxia as the initial clinical symptom in X-linked recessive bulbospinal neuropathy

X-Linked recessive bulbospinal neuropinopathy (X-BSNP) has previously been described as a disease in which the first clinical symptoms which occur concern the motor system. A weakness of the shoulder and pelvic girdle muscles as well as cramps and muscle pain in the proximal limbs are normally found early in the course.1 11 The onset of X-BSNP generally ranges between the ages of 25 and 50 years; the disorder then shows a slow but continuous progression of symptoms.1 11 An involvement of facial and bulbar musculature with fasciculations and atrophy of these muscles and, therefore, often dysthria and dysphagia, are common symptoms of an advanced stage.1 11 Nevertheless, life expectancy does not seem to be consider- ably reduced.1 11 A recent report was reported to be minimal or non-existent.1 11

Pathoanatomical studies showed that a degeneration of both the lower motor and primary sensory neurons represent the under- lying pathological process for the clinical symptoms.1 The pathogenetic link between the abnormally expanded CAG trinucleotide repeat in the first exon of the androgen receptor gene which is found in affected patients and the development of the anterior horn cells and the primary sensory neurons with consecutive axonal degeneration of the dorsal root fibres has not been established yet.1 11 Although central and peripheral sen- sory conduction has been shown to be highly abnormal with absent or markedly prolonged sensory action potentials, most of the time the clinical findings of only a little sensory impairment do not correspond well to this electrophysiological finding.1 11 We re- port sensory ataxia as the initial clinical symptom in a patient with X-BSNP.

A 63 year old retired journalist felt like “walking on pillows” for the first time when he was 45 years old and had afterwards for the subsequent years the distally accentuated and symmetric loss of sensibility for touch, temperature, pain, position, and vibration was progressive in the legs—and later—also in the arms. At the age of 48 he noticed fasciculations of the facial muscles and a slow development of a painless, bilateral weakness of the proximal muscles of the lower and upper limbs. No related disease was found in his father’s family; nothing is known about the maternal side of his family history.

The clinical examination of the patient showed a severe sensory gait ataxia as well as a dyspraxia of his hands. Other symptoms were a tremor of the hands and occasional spasms of the oral and pharyngeal musculature. The functions of other cranial nerves were normal. Spontaneous fasciculations of the buccal mus- cles and less often of the proximal and distal limb musculature persisted. Deep tendon reflexes could generally not be detected and there were no pathological reflexes. A proximal- ly accentuated weakness and atrophy of the legs and arms, and the distally accentuated hyperreflexia for all qualities was found. There were no cognitive deficits, cerebellar ataxia, or gynecomastia.

Laboratory results were not abnormal (including plasma testosterone, follicle stimu- lating hormone, luteinising hormone, and glucose tolerance) except for a raised creatine kinase (354 U/l). The CSF examination also showed no abnormalities. Motor nerve con-duction velocities were only slightly reduced whereas sensory action potentials were absent. Electromyography showed the typical features of chronic denervation in the proximal muscles of the lower and upper limbs as well as in the tongue. Motor-evoked potentials showed normal central conduction times but partially prolonged latencies with stimu- lation of the cervical and lumbar roots. With tibial and median nerve stimulation no soma- totoncoding responses were obtained as well as compound action potentials were found neither at the cervical or lumbal nor at the cortical recording sites. Brain MRI was normal. The genetic analysis showed 42 CAG trinucleotide repeats in the androgen receptor gene (normal length 11–34 repeats), which is a valuable criterion in the diagnosis of X-BSNP.

The example of our patient shows that the electrophysiological findings of the sensory system may correspond well to the clinical syndrome in X-BSNP. It is not clear why patients with X-BSNP in most cases do not show significant sensory impairment although substantial loss of the primary sensory neuron has been proved. We hope that findings as in this case report may be an incentive for us to work for a better understanding of the problem as to why a specific neuronal degeneration can lead to a less specific pattern of clinical symptoms.

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Neuroleptic malignant syndrome without fever: a report of three cases

Although fever is considered to be a cardinal feature of neuroleptic malignant syndrome, we report on three patients who were afibrile but had all the other features of the neuroleptic malignant syndrome. This paper highlights the need to suspect neuroleptic malig- nant syndrome and immediately initiate investigation and appropriate management in any patient who develops rigidity and cloud- ing of consciousness while receiving antipsy- chotic medication, thus averting potentially lethal sequelae such as death.

The neuroleptic malignant syndrome (NMS) is an uncommon but potentially fatal idiosyncratic reaction characterised by the development of altered consciousness, autonomic hyper- thermia, autonomic dysfunction, and muscu- lar rigidity on exposure to neuroleptic (and probably other psychotropic) medications.1 2 According to the DSM IV criteria, ‘promi- nence has been given to signs of increase in temperature (>39 °C) and muscular rigidity. These must be accompanied by two or more of: diaphoresis, dysphagia, tremor, inconti- nence, altered consciousness, tachycardia, blood pressure changes, and altered mental status, or raised creatine kinase concentrations. Some researchers have also advocated that a pyrexia in excess of 38°C or 39°C is necessary for the diagnosis of NMS.1 2 However, on reviewing the literature since 1965, we have found no case reports highly suggestive of NMS occurring without fever.1 2 We report three patients who had all the major features of NMS but were afibrile during the entire course of their illness. These case reports of NMS occurring within a 1 year period from July 1998 to July 1999.

A 52 year old man who was on treatment for postpsychotic depression presented after an act of deliberate self poisoning with a

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rodenticide. As he became acutely disturbed and violent in the ward he was given several injections of intramuscular haloperidol, and he received no further antipsychotic medication. On the next day he developed severe rigidity associated with profuse sweating and marked agitation. His heart rate was 120 beats per minute and was irregular. His blood pressure showed wide fluctuations and there was urinary incontinence. He then became confused and went into a state of semiconsciousness. There was no increase in body temperature. The creatine phosphokinase concentration was 1575 IU on the 2nd day and 6771 IU on the 4th day of his illness, and the white cell count was 17 000/mm³ (neutrophils 30%, lymphocytes 18%, monocytes 9%, eosinophils 6%, macrophages 4%). As the patient did not have any increase in body temperature there was doubt as to the diagnosis. In standard medical texts fever was recorded as a necessary finding in NMS. However, a medline search contained reports of three patients with NMS in the absence of fever. The patient was immediately started on bromocriptine at a dose of 2.5 mg three times a day. By the 5th day of treatment his condition improved with the autonomic disturbances disappearing and the rigidity subsiding. His creatine phosphokinase concentration became normal after 5 days of treatment.

A 20 year old man was started on 10 mg flupenthixol intramuscularly. Five days later he was readmitted due to progressively increasing stiffness of his body, difficulty in swallowing, drowsiness, and incontinence of urine. On examination he was very rigid and semicomatose. By the 5th day of treatment his condition improved with the autonomic disturbances disappearing and the rigidity subsiding. His creatine phosphokinase concentration became normal after 5 days of treatment. After that the number of seizures gradually increased and secondary generalised seizures appeared. Phenytoin, carbamazepine, valproic acid, phenobarbital, vigabatrin, lamotrigine, and clonazepam were used in different combinations without an acceptable seizure control. Repeat EEG recordings during the past few years were abnormal with prominent slow activity, long intervals of voltage attenuation, and common bursts of high voltage spike wave complexes recorded mainly at the left frontotemporal area. A high resolution MRI was normal.

In October 1997, a vagus nerve stimulator was implanted because of poor seizure control. During a 12 week baseline preceding the implantation, more than 40 complex partial and one to two secondary generalised seizures every 4 weeks were noted. The patient also experienced bursts of uncontrolled short lasting complex partial seizures on a few days every month. At the time of implantation medical treatment consisted of 500 mg topiramate and 475 mg lamotrigine daily. The patient had been on this daily dose for 6 months before implantation.

The stimulator output was progressively increased over 1 month from implantation. The final parameters were: pulse rate 30 Hz, 5 minutes off, 30 seconds on, 1.5 mA intensity, and 500 ms pulse width. During the subsequent 2 months the intensity of matically reduced even though medication remained unchanged. For the last 2 weeks of the second month he had noted only one short lasting complex partial seizure; at the same time the family had noted a change in the patient's behaviour. Psychiatric evaluation disclosed a schizophrenia-like syndrome with auditory hallucinations, delusions of persecution, thought insertion, choreoathetoid motor agitation, and complete lack of insight.
An EEG recording showed a low voltage normal background activity coexisting with low voltage fast rhythms without any paroxysmal activity. The patient was admitted to hospital and antipsychotic medication with 15 mg/day haloperidol was added to his antiepileptic drug treatment. Biperiden (4 mg/day) was added to reduce extrapyramidal side effects. After 4 weeks of treatment the patient’s symptomatology was reduced to a degree of 50% from the initiation of the treatment and the patient left the hospital. In the follow up, the haloperidol dose was reduced gradually within 4 months to a dose of 5 mg/day (maintenance therapy).

The psychotic reaction in our patient was not an ictal symptom because it occurred in a state of clear consciousness with a normal EEG in a period that was seizure free. Regarding the involvement of drugs as a causative factor for psychosis, all established antiepileptic drugs have been shown to precipitate psychiatric symptoms. Treatment of the patient consisted of lamotrigine and topiramate, drugs that have been implicated in the provocation of psychiatric symptoms but as he had been already under the same medication for the past 10 months before the vagus nerve stimulator was implanted, the precipitation of psychosis does not seem to be pharmacologically relevant. Further support to the above hypothesis is provided by the fact that the psychotic symptoms appeared just when seizure control was achieved by vagus nerve stimulation.

The comorbidity of psychosis and epilepsy in our patient could not be excluded. However, the absence of a history of psychiatric illness as well as the lack of a positive family history for any major psychiatric disorder does not render support to the above possibility. The reduction of seizure frequency and EEG normalisation as a cause of psychoticle reactions in epileptic patients have been proposed by many authors. In our patient seizure cessation had a temporal sequence with development of psychosis and EEG normalisation.

The term “forced or paradoxical normalisation” is more or less a theoretical concept with unknown biochemical mechanisms. Neurotransmitter hypotheses, kindling the mesial temporal lobe, and the induction of the neuropathological process through the transfer of the monoclonal IgM in animal models. The low rate (30%) of clinical improvement with chlorambucil (CLB) or plasma exchange in such patients justifies the search for new therapeutic strategies.

In a previous phase II open clinical trial randomly comparing intravenous immunoglobulins (IVIg) and interferon-α (IFN) we concluded that IVIg was inefficient but that α-IFN produced a significant clinical improvement in eight out of 10 patients at 6 months and in seven of them at 12 months. The mechanism of action of α-IFN was unclear as the concentration of the monoclonal IgM as well as the titre of anti-MAG antibody were unchanged. As the concentration of IgM to nerve polypeptides or glycolipids, the detection of IgM deposits on the myelin sheaths of patients’ nerve biopsies, and the induction of the neuropathological process through the transfer of the monoclonal IgM in animal models. The low rate (30%) of clinical improvement with chlorambucil (CLB) or plasma exchange in such patients justifies the search for new therapeutic strategies.

In a previous phase II open clinical trial randomly comparing intravenous immunoglobulins (IVIg) and α-interferon (α-IFN), we concluded that IVIg was inefficient but that α-IFN produced a significant clinical improvement in eight out of 10 patients at 6 months and in seven of them at 12 months. The mechanism of action of α-IFN was unclear as the concentration of the monoclonal IgM as well as the titre of anti-MAG antibody were unchanged. As the improvement with α-IFN was mainly related to an improvement of sensory symptoms, most of them being subjective, we designed a multicentre, prospective, randomised double blind study of α-IFN versus placebo. Patients included in this study had to fulfill all the following criteria: (1) have had stable laboratory abnormalities for at least 3 months; (2) show the presence of a serum monoclonal IgM with anti-MAG antibody activity and the induction of the neuropsychiatric symptoms; (3) have a clinical neuropathology disability score (CNDs) of 10 (see below); (4) have no other causes of peripheral neuropathy, especially diabetes, alcohol, cryoglobulinaemia, and amyloidosis; (5) have not had treatment in the past 3 months. The study was designed to be a multicentre, prospective, randomised, double blind clinical trial comparing α-IFN and placebo. The protocol was approved by the Hôpital Pitié-Salpêtrière ethics committee. After providing written informed consent, patients underwent stratified randomisation according to the existence of a previous treatment, through a blind telephone assignment procedure. The patients were randomized to receive either α-IFN or placebo. The clinical features are a specific entity. The peripheral neuropathy associated with a monoclonal anti-MAG IgM is considered as a specific entity. The clinical features are different from those seen with monoclonal IgG or IgA, with sensory loss and ataxia more often present than in those seen with monoclonal IgM or IgG, with sensory loss and ataxia more often found. A causal link between the monoclonal IgM and the development of the neuropathy is suggested by the antibody activity of the IgM to nerve polypeptides or glycolipids, the detection of IgM deposits on the myelin sheaths of patients’ nerve biopsies, and the induction of the neuropathological process through the transfer of the monoclonal IgM in animal models. The low rate (30%) of clinical improvement with chlorambucil (CLB) or plasma exchange in such patients justifies the search for new therapeutic strategies. A randomised double blind trial versus placebo does not confirm the benefit of α-interferon in polynuropathy associated with monoclonal IgM.

The peripheral neuropathy associated with a monoclonal anti-MAG IgM is considered as a specific entity. The clinical features are different from those seen with monoclonal IgG or IgA, with sensory loss and ataxia more often found. A causal link between the monoclonal IgM and the development of the neuropathy is suggested by the antibody activity of the IgM to nerve polypeptides or glycolipids, the detection of IgM deposits on the myelin sheaths of patients’ nerve biopsies, and the induction of the neuropathological process through the transfer of the monoclonal IgM in animal models. The low rate (30%) of clinical improvement with chlorambucil (CLB) or plasma exchange in such patients justifies the search for new therapeutic strategies.

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The randomisation procedure resulted in balanced treatment groups for patient characteristics and neurological abnormalities (table). Three patients in the α-IFN group withdrew from treatment, two because of side effects (one at day 30 for diarrhoea and one at day 60 for influenza symptoms) and one because of day to day worsening of the neuropathy. No patients had to stop treatment because of haematological toxicity.

The mean CNDS did not change significantly in either group in the α-IFN group, it moved from 31.4 at baseline to 28.5 at 6 months, in the placebo group from 30.3 at baseline to 27.8 at 6 months. The absolute differences were close in the two randomised groups—namely, 1.8 in the α-IFN group and 2.5 in the placebo group (p=0.84) and the relative differences were also close (~6% vs 6.5% respectively, p=0.79). In both groups, three out of 12 patients (25%) had improvement in CNDS of more than 30% (p=1.00). Electrophysiological data were available in nine patients treated with α-IFN and in 11 patients treated with placebo and did not detect significant improvement (data not shown).

In this double blind study of α-IFN versus placebo, we did not confirm the efficacy of α-IFN in peripheral neuropathy associated with a monoclonal anti-MAG IgM as suggested in a preliminary phase II open study.11 This discrepancy is not easy to explain. The mean baseline neurological scores, the number of patients previously treated, and the disease duration were the same in the two studies. However, both studies dealt with small cohorts. We think that the effect found in our preliminary study could have been amplified by the enthusiasm of physicians and patients in favour of interferon, a new therapeutic strategy at that time in neurological diseases, given that the trial was not blind. Both physicians and patients knew that it was not a placebo group. Interestingly, in our preliminary study, the decrease of the CNDS was mainly due to improvement in sensory symptoms (most of them subjective) and to subjective assessment by the patient. Moreover, we could not elucidate the potential mechanism of action of α-IFN as neither the level if monoclonal IgM, nor the anti-MAG antibody activity was modified.

In conclusion, these disappointing results of α-IFN in monoclonal IgM associated neuropathy point out to the need of double blind randomised studies versus placebo in neurological diseases where sensory symptoms are predominant. In monoclonal IgM associated neuropathy, new strategies leading to eradication of the B cell clone secreting monoclonal IgM, such as the use of fludarabine12 or anti-B cell monoclonal antibodies,13 should be tested in further studies.
activity, sharp waves, and spike wave complexes; status could be terminated with 1 mg intravenous clonazepam.

Lumbar puncture and ultrasonography of the vertebral and basilar arteries did not show any abnormalities. Transoesophageal echocardiography showed normal left ventricular function. Routine biochemistry including electrolytes, creatinine, and blood urea nitrogen were normal throughout except increased C reactive protein (due to tumour). Haematological values showed pancytopenia. There was no evidence for viral and bacterial infection. A pleural effusion on the left side had developed before chemotherapy. A chest radiograph was now normal. Blood pressure was normal throughout.

As no other diagnosis could be ascertained, a causal relation with filgrastim, her sole new medication, was discussed. The patient was treated with a diuretic (furosemid), a neuroleptic (haloperidol), and anticonvulsants (phenytoin and clonazepam intravenously). Administration of a morphine antagonist, naloxone (0.8 mg intravenously). As the effect of the naloxone wore off, there was a dramatic improvement of the patient's condition. The symptoms of disturbance of consciousness, hemiparesis, generalised myoclonus, and pinpoint pupils pointed to brainstem injury. To rule out basilar artery thrombosis, CT angiography was performed. There were no pathological findings in the brainstem or the basilar artery.

Transcranial Doppler ultrasound and sensory evoked potentials were normal. The EEG under sedation with midazolam and fentanyl showed intermittent bilateral synchronised frontal delta rhythms. Systolic blood pressure was slightly increased, between 140 and 180 mm Hg. Due to the patient's development of pneumonia, artificial ventilation was continued, and further sedation was given with fentanyl/midazolam. Sedation was continued for 72 hours, with an infusion of fentanyl (0.157 mg/h) and midazolam (3.3 mg/h) for ventilation therapy. After sedation was stopped, the distinctive neurological symptoms abruptly improved. Within a few hours the patient was extubated. He then seemed normal, except for slight disorientation and agitation. Twelve hours after cessation of sedation, the patient was normal. To clarify and confirm the diagnosis of an adverse reaction to fentanyl, we carried out a provocation test after obtaining full informed consent. A dose of 0.1 mg fentanyl intravenously was enough to induce agitation, generalised myoclonus, and paroxysmal dystonic movements and rigor that particularly affected the legs. No cognitive disturbances were apparent. The fentanyl dose was then increased to a total of 0.2 mg. At this point, a 6 mg dose of diazepam was given but did not improve the patient. In fact the patient reported increased agitation. Administration of a morphine antagonist, naloxone (0.8 mg intravenously) dramatically improved his condition, completely normalising the myoclonus, rigor, and paroxysmal movements. No further improvement occurred on administration of the benzodiazepine antagonist flumazenil (0.25 mg intravenously). As the effect of the naloxone wore off, there was a

Acute adverse reaction to fentanyl in a 55 year old man

We report an acute drug induced adverse reaction to fentanyl that was not immediately recognised as such. A 55 year old police officer was given a small dose of diazepam (5 mg) and fentanyl (0.03 mg) for the treatment of left chest pain. Immediately after receiving the medication, the patient developed acute confusion, intermittent somnolence, and stupor, and fluctuating tetraparesis. Before the onset of symptoms, no relevant hypertension or hypoglycaemia were found. Pre-existing medication consisted of 20 mg amitryptiline and 1000 mg metformin a day. On initial examination, the most obvious symptom included profuse sweating, bilateral miosis (pinpoint pupils), and severe generalised myoclonus predominantly affecting the face. Babinski's sign was negative on both sides. The patient showed severe fluctuating tetraparesis. Investigation of the cranial nerves showed no abnormalities. On admission in our institution, the patient immediately underwent intubation and artificial ventilation for suspected pulmonary aspiration. Thiamin was started at 100 mg thrice daily. Myocardial infarction and dissection of the aorta were ruled out. The previously given dosage of fentanyl and diazepam did not seem to explain the current neurological condition of the patient. The symptoms of disturbance of consciousness, hemiparesis, generalised myoclonus, and pinpoint pupils pointed to brainstem injury. To rule out basilar artery thrombosis, CT angiography was performed. There were no pathological findings in the brainstem or the basilar artery.

Transcranial Doppler ultrasound and sensory evoked potentials were normal. The EEG under sedation with midazolam and fentanyl showed intermittent bilateral synchronised frontal delta rhythms. Systolic blood pressure was slightly increased, between 140 and 180 mm Hg. Due to the patient's development of pneumonia, artificial ventilation was continued, and further sedation was given with fentanyl/midazolam. Sedation was continued for 72 hours, with an infusion of fentanyl (0.157 mg/h) and midazolam (3.3 mg/h) for ventilation therapy. After sedation was stopped, the distinctive neurological symptoms abruptly improved. Within a few hours the patient was extubated. He then seemed normal, except for slight disorientation and agitation. Twelve hours after cessation of sedation, the patient was normal. To clarify and confirm the diagnosis of an adverse reaction to fentanyl, we carried out a provocation test after obtaining full informed consent. A dose of 0.1 mg fentanyl intravenously was enough to induce agitation, generalised myoclonus, and paroxysmal dystonic movements and rigor that particularly affected the legs. No cognitive disturbances were apparent. The fentanyl dose was then increased to a total of 0.2 mg. At this point, a 6 mg dose of diazepam was given but did not improve the patient. In fact the patient reported increased agitation. Administration of a morphine antagonist, naloxone (0.8 mg intravenously) dramatically improved his condition, completely normalising the myoclonus, rigor, and paroxysmal movements. No further improvement occurred on administration of the benzodiazepine antagonist flumazenil (0.25 mg intravenously). As the effect of the naloxone wore off, there was a
reappearance of the dystonic movements. Under these conditions, the patient presented with distinct bilateral miosis, but no other disturbances.

Through this provocation test, the diagnosis was confirmed. As a result of an adverse reaction to fentanyl, the patient experienced an acute and unusual neurological syndrome. The clinical symptoms were agitation, generalised myoclonus, intermittent disturbances of consciousness, fluctuating bilateral hemiparesis, and pinpoint pupils. The diagnosis remained obscure for 72 hours due to the continuing ventilation, sedation, and analgesic treatment with fentanyl; indeed, it was the continuing administration of fentanyl that was maintaining the symptoms. Both the improvement after cessation of fentanyl, and the controlled provocation test confirmed the diagnosis.

In recent years, various central side effects of opioids have been described. These include generalised myoclonus, hyperalgesia, grand mal seizures, and agitation. 2–4 Although some reports have shown unexpected central side effects after low doses of fentanyl, in most cases this type of effect developed in patients receiving high doses of opiates for prolonged periods. 5–7 Opiate induced myoclonus is often generalised and is either periodic or associated with rigidity, often occurs in the context of underlying medical conditions, and usually responds to either naloxone or benzodi- azepines. 8 The mechanisms responsible for these adverse effects are not exactly known, but opioidergic, serotonergic, dopaminergic, and other mechanisms are considered. 6 The interesting feature of this particular case was the possibility of confusion of an acute fentanyl induced adverse syndrome with basilar artery thrombosis.

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Relapsing alternating ptosis in two siblings

In this Journal, Peatfield described the recurrence of cluster headaches presenting with a virtually painless Horner's syndrome in a 56 year old man. 9 This publication caused controversy on the dissociation between autonomic dysfunction and pain during cluster headache. 1 We add to this discussion our report on relapsing alternating ptosis in two siblings:

A 46 year old woman had intermittent episodes of alternating ptosis for more than 8 years. Her 47 year old sister was affected similarly. As shown in figure 1, attacks occurred more often than once a month with a mean duration of the episodes of 8 days (range 3–14 days). Intrinsic oculomotor muscles and the bulbar muscles were spared (fig 2). She never complained about double vision. Elevating and maintaining the ptotic eyelid in a fixed position during sustained upward gaze did not result in a drop of the opposite eyelid. Signs of autonomic dysfunction and miosis were absent. The ptosis was never accompanied by miosis. There was no history of migraine or cluster headache. However, during the episodes they experienced some mild aching at the frontal region. On the serotonin antagonist pizotifen, the younger sister felt improved due to slightly prolonged symptom free intervals. However, 60 mg prednisone every day for 6 weeks did not change the occurrence of ptosis.

On repeated neurological examination, there was no abnormality apart from the fluctuating ptosis. Magnetic resonance imaging of the brain, the orbital region, and the cervicothoracic spinal cord segments were normal. Laboratory studies showed no abnormality. Westergren sedimentation rate and serum creatine kinase activity were normal. Repeated tests for anticholinesterase receptor antibodies were negative. Low rate repetitive nerve stimulation did not result in pathologi- cal decremental responses. Thyroid hor- mones and antibodies were in the normal range and absent, respectively. In the symp- tom free interval, pupillary responses to var- ious pharmacological agents did not indicate a sympathetic dysfunction.

Relapsing alternating ptosis in two sisters is unique. In some aspects, our observation resembles Bielschowsky's relapsing alternating ophthalmoplegia. 10 Distinctive clinical features of this rare syndrome are the intermittent evolution of external ophthal- moplegias, the alternate involvement of one eye after the other, the constant sparing of the intrinsic oculomotor muscles, and the absence of pain.

We think that our finding of relapsing alternating ptosis is related to intermittent sympathetic dysfunction. Interestingly, in a subgroup of patients with cluster headache a “partial” Horner's syndrome may develop during each attack and disappear as the attack subsides. The term “partial” Horner's syndrome indicates that in patients with cluster headache one or two components of the typical Horner's syndrome are present—that is, miosis or ptosis, whereas a third character- istic, anhidrosis, is lacking or even replaced by hyperhidrosis. 11 Some of the patients with cluster headache even show a permanent Horner-like syndrome on the symptomatic side. Several studies on the pupil responsiveness in patients with cluster headache...

Figure 1 Occurrence of ptosis over a period of 21 months (protocol of the 46 year old patient). One eye after the other was affected intermittently (filled bars=presence of ptosis).

Figure 2 Alternating ptosis representative findings between November 1998 (11/98) and December 1999 (12/99). Note the absence of miosis. The ptosis resolved completely each time.
indicate that dysfunction of the sympathetic nervous system, whether peripheral or central, is involved in the pathophysiology of the cluster headache. Additionally, alternating Horner’s syndrome has been reported in patients with lesions of the lower cervical and upper thoracic spinal cord segments. In those cases, Horner’s syndrome may alternate sides at intervals ranging from 2 hours to 2 weeks. Horner’s syndrome alternating on a daily basis can occur rarely in multisystem atrophy with dysautonomia. Unfortunately, we cannot offer any proof for a sympathetic dysfunction in our patients.

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BOOK REVIEW


Some books deserve their title and others, like this one, definitely do not. For this is not a comprehensive survey of the British contribution to neurology through 250 years. Thank goodness; because such an account could so easily be familiar and self important. Instead, Clifford Rose has assembled a delightful and quirky collection of essays from an international panel of authors; only six of the 20 contributors are British. He has eschewed the predictable; the chapter on Gowers, for instance, is devoted solely to his promotion of the use of shorthand in medicine. Of the three chapters on Hughlings-Jackson, one is an extrapoloation of his ideas on neurophysiology to the archaeological record of human mental evolution. Humour abounds from even the most unpromising subjects. “There is something especially delicious about controversy and ceremony,” writes Robert Gordon on the Bell Magendie debate in his impish chapter on collecting antiquarian neurological books. The diplomatic skills of John Fothergill, who described trigeminal neuralgia in the 18th century, are carefully recorded. A patient, the Earl of Macclesfield, asked him over the dinner table whether the food they were eating was wholesome: “Does your Lordship like the food?” Fothergill asked. Yes, the Earl replied. “Does it agree with your Lordship?” Yes. “Why then it is wholesome.” Compston describes the anatomical illustrations of 18th and 19th century neurological texts to illustrate the emerging clinicopathological technique. CU Smith makes an excellent case for stressing the importance of the young JZ Young’s visit to Naples in 1928, where he rediscovered the squid giant axon that was to become such a fruitful experimental model in the hands of Hodgkin and Huxley and Curtis and Cole. In 1940 Young was to write “unfortunately work was terminated by the outbreak of war which rendered the capture of squids impossible”.

Purists may be upset that familiar neurological icons are not given the usual plaudits; in particular, in 274 pages, there are only four passing references to the National Hospital, Queen Square. But the familiar can be boring and this compulsive little book most certainly is not.

ALASDAIR COLES