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. These behaviours are probably the reflection of early plastic changes of brain maps after an acute lesion and an active process induced by disinhibition to establish new compensatory pathways. 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 postcentral 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. The 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 hypersensitive behaviours 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. Touch, pain and temperature were intact in the upper limb, but there was no improvement in position and vibration in the entire left hemibody. 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 all 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. 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 hyperesthesia in 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. 

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 (unaffected) 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 hypersensations 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.

Grotta et al. reported the subjective experiences of 24 patients with nonlacunar ischaemic stroke who dramatically recovered. They speculated that their unawareness of deficit was a form of anosognosia rather than a deficit of knowledge of their own capacities. However, as most patients (19 of 24) could remember important events during the first 3 months of their problem and did not complete “functional” transection of the spinal cord. Buschker-Ratmann et al. suggested that the disinhibition or hyperexcitability to facilitate functional reorganisation may have been the main cause of hyperesthesia in stroke.

Various 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. 

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 movements and abnormal position of her paralysed lower limbs. These findings suggest that the disinhibition 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 an 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 of micturition, 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 had been 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 thyroidec- tomy 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. The rectal examination and general physical examination was unremarkable. A full blood count, urea and electrolytes, and liver and thyroid function tests were within normal limits. An MRI scan of the cervical spine confirmed the presence of mild degenerative changes in the cervical spine at the level of C5–C7. There was no radiological evidence of an intrinsic or extrinsic cord 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 clear demarcation 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 calf 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 bacteriological 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 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 characteristics1 or in a distorted form.2,3 Patients often report normal functions associated with the absent organ—for example, penile erection, ejaculation, and orgasm after removal of the genitalia.4–6 These sensations may occur after limb amputations7 and have also been reported in about 15% of patients after a mastectomy.8–10 Sometimes they may follow spinal cord injury.11 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 these patients.12 Another hypothesis is that damaged peripheral somatosensory receptors fire spontaneously and give rise to the painful or abnormal experiences.13 However, phantom sensations have been reported by patients after spinal anaesthesia in the absence of damage to the peripheral nervous system.14 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 at the neuromatrix level.
triggered 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.\(^1\)

Ramachandran and Hirstein\(^2\) 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, the presence of "diffuse neural matrix".\(^3\)

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\(^4\) 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.

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**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.\(^2,4\) Click sensitivity of primary vestibular neurons arise from the saccular macula in the guinea pig and electrical stimulation of these neurons in the cat evokes inhibitory postsynaptic potentials in ipsilateral SCM motor neurons which are abolished by transection of the vestibulospinal tract.\(^3\) These clinical and neurophysiological data suggest that VEMPs are mediated by a pathway consisting of the saccular macula, its primary neurons, vestibulospinal neurons from the lateral vestibular nucleus, the medial vestibulospinal tract, and finally motor neurons 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\(^3\) 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 in the supine patient from symmetric 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. Rarefaction 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.\(^1\) 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 (SD) 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=25.4 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 (9.14 ms, left=4.30 ms, figure B).

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

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**References**

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 cer
cbral 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,6,14 the VEMP delay could be attributed to demyeli
nation either of primaryafferent axons at the root entry zone or secondary vestibulospinal tract axons rather than to lesions involving vestibular nucleus neurons. The MRI find
ings in these patients were not inconsistent with this proposition. Measurement of VEMPs could be a useful clinical test to evaluate function of the vestibulospinal path-
way 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 neuropathy (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 in the early stages.15 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.16 An involvement of facial and bulbar musculature with fasciculations and atrophy of these muscles and, therefore, often dysarthria and dysphagia, are common symp
toms of an advanced stage.16 Nevertheless, life expectancy does not seem to be consider
ably reduced. With respect to survival, no improvement was reported to be minimal or non-existent.1,17

Pathoanatomical studies showed that a degeneration of both the lower motor and primary sensory neurons represent the un
derlying pathological process for the clinical symptoms.18 The pathogenic 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 anterior horn cells and the primary sensory neurons with consequent axonal degeneration of the dorsal root fibres has not been established yet.19 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 abnormality.20 We report 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. After the subsequent years the distally accentuated and symmetric loss of sensitivity 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 fam
ily; 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, as well as in the tongue. Deep tendon reflexes could generally not be detected and there were no pathological reflexes. A proxi
mally accentuated weakness and atrophi
of the legs and arms was evident as a distally accen
tuated hypeaesthesia 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 conduction velocities were within the normal range, whereas sensory action potentials were ab
sent. Electromyography showed the typical features of chronic denervation in the proxi
mal muscles of the lower and upper limbs as well as in the tongue. Motor evoked poten
tials showed normal central conduction times but partially prolonged latencies with stimu
lation of the cervical and lumbal roots. With tibial and median nerve stimulation no soma
towernucleus efferent activity was 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, 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 al
though 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 process as to why a specific neuronal degeneration can lead to a les 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 afebrile but had all the other features of the neuroleptic malignant syndrome. This paper high
lights the need to suspect neuroleptic malign
ant syndrome and immediately initiate investigation and appropriate management in any patient who develops rigidity and clouding of consciousness while receiving antipsy
chotic medication, thus averting potentially lethal sequelae?

The neuroleptic malignant syndrome (NMS) is an uncommon but potentially fatal idiosyncratic reaction characterised by the development of altered consciousness, autonomic dysfunction, and muscular rigidity on exposure to neuroleptic (and probably other psychotropic) medications.2

According to the DSM IV criteria,2 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 possibly a 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.3 However, on reviewing the literature since 1965, we found three pre
vious case reports highly suggestive of NMS occurring without fever.4 We report three patients who had all the major features of NMS but were afebrile during the entire course of their illness. These case reports are 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
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 tachycardia. 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 semi-consciousness. 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 30%, 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 trifluperazine twice a day for schizoaffective disorder with catatonic features and discharged after being given a depot injection of 40 mg haloperidol intramuscularly. Fifty 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 somnolent. By the 5th day of treatment his heart rate had increased to 100 beats per minute, respiratory rate 28 per minute, and his blood pressure showed marked fluctuations. The creatine phosphokinase assay done on the 2nd day gave 2109 IU/l and the white blood cell count was 12 400/mm³ (neutrophils 93%). Other investigations including analysis of his CSF was normal. We made a tentative diagnosis of NMS, even though the patient did not have fever, as we had treated a patient with NMS presenting without fever previously. The neuroleptic medication was stopped and he was started on 2.5 mg bromocriptine three times a day. As the response was poor the dose was gradually increased to 10 mg three times a day. He made a relatively slow recovery and came out of the comatose state after 1 week of treatment and autonomic disturbances and rigidity disappeared after 10 days of treatment. On discharge from hospital on the 14th day after starting bromocriptine his creatine phosphokinase was 230 IU/l.

An 18 year old boy with schizophrenia was on long term antipsychotic drugs. He was admitted with increasing stiffness of the body, drowsiness, and urinary incontinence. On examination he was rigid, had a tachycardia (pulse rate 130 beats per minute) alternating with a bradycardia (pulse rate 50 beats per minute) and his blood pressure showed wide fluctuations. There was no increase in body temperature at admission or during the course of his illness. The creatine phosphokinase concentration was 1450 IU/l on the 2nd day of his illness and the white cell count was 15 000/mm³ (neutrophils 85%). Antipsychotic medication was stopped and he was started on 2.5 mg bromocriptine three times a day. He made a complete recovery, with the autonomic disturbances and rigidity subsiding within 5 days of treatment. One week later his creatine phosphokinase was 100 IU/l.

The neuroleptic malignant syndrome usually occurs with the use of therapeutic doses of neuroleptic drugs and commonly develops during the initial phases of treatment, when the drug dose is being stepped up, or when a second drug is introduced. However, it can occur at any time during long term neuroleptic treatment with factors such as exhaustion, agitation, and dehydration acting as triggers.

The above point is noteworthy especially given the possibility of the occurrence of a variant and uncommon clinical picture such as that described in our paper. There are no specific laboratory findings, but new-onset leucocytosis and raised creatine phosphokinase concentrations lend weight to the diagnosis.4 These three cases illustrate the point that NMS can occur without fever. Our patients had all the features of NMS apart from fever and the response to bromocriptine can be taken as strong evidence that the diagnosis was accurate. Being familiar with this fact and other differential diagnoses, this syndrome can present plus a high degree of suspicion are important in making an early and accurate diagnosis of NMS. In fact, the appearance of muscle rigidity and clouding of consciousness in a patient receiving antipsychotic medication should prompt clinicians to suspect NMS and immediately initiate appropriate investigation and management. A failure to do so may lead to delay or failure to withdraw neuroleptic medication, and thus lead to potentially irreversible sequelae and even death. The first case also illustrates that at times of doubt about the diagnosis of an uncommon or surprising finding, a well described illness, reference to the literature including an immediate Medline search could help in making decisions about appropriate patient management.
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 icctal 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 psychotic 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 related. 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 psychosis 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 psychotict-like reactions in epileptic patients have been proposed by many authors. In our patient seizure cessation had a temporal sequence as detected by immunoblotting on nerve polypeptides or the induction of the neuropsychopathological process through the transfer of the anti-MAG IgM in animal models. The low rate (30%) of clinical improvement with chlorambucil (CLB) or plasma exchange in 12 months; (2) show the presence of a serum monoclonal IgM as well as the titre of -interferon produced a significant improvement of sensory symptoms compared to treat basis. Comparisons used a statistical analysis method on an intention to treat basis. Comparisons used a Kruskal and Wallis test for continuous variables, Fisher’s exact test for binary variables. Relations between continuous variables were studied by the Spearman coefficient. All tests were two sided. The SAS (SAS Institute, Cary, NC) software package was used.

After the inclusion of 24 patients, Roche laboratory decided not to proceed any more because of trade difficulties. The promoter of the study (AP-HP) decided to carry out the interim analysis which led to stopping the accrual of patients because of the absence of benefit of -IFN versus placebo.

Twenty four patients were enrolled from five hospitals, 12 being assigned to -IFN and 12 to placebo. Eleven patients (five in the -IFN group, six in the placebo group) had been previously treated with CLB without improvement of the neuropathy. In 10 of them, plasma exchanges had also been unsuccessful. The mean duration (SD) of the peripheral neuropathy was 3.6 (3.9) years.

A randomised double blind trial versus placebo does not confirm the benefit of -IFN in polyneuropathy 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 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 anti-MAG IgM in animal models. The low rate (30%) of clinical improvement with chlorambucil (CLB) or plasma exchange in 12 months; (2) show the presence of a serum monoclonal IgM as well as the titre of -IFN produced a significant improvement of sensory symptoms without benefit of -IFN versus placebo.

The study was designed to be a multicentre, prospective, randomised double blind clinical trial comparing -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 -IFN or placebo. -Interferon (Roferon, Roche) was given at 4.5 MU three times a week for 6 months. Placebo consisted of sodium chloride, benzyl alcohol, polysorbate 80, and glacial acetic acid diluted in sterile water. The reconstituted vials of -IFN or placebo were delivered by the pharmacy of each centre and appeared identical.

The clinical neuropathy disability score (CNDs) was the same as that used in our preliminary study. The score in a normal subject was 0. It could range from 0 to 93, summing 0 to 28 points for the motor component, 0 to 12 for the reflexes component, and 0 to 53 points for the sensory component. In addition, the patient was asked to appreciate the change in five symptoms: paresthesia, dysaesthesia, ground perception, ataxia, and walking mood (< −2), slight improvement (−1), stability (0), slight worsening (+1), major worsening (+2). This score termed “subjective assessment” ranged from −10 to +10 and was added to the previous one except for the walking mood. Follow up examinations were performed by the same physician for each patient every 3 months.

The main end point was defined by the absolute difference in the CNDs from baseline to the 6th month (or to the time of withdrawal of treatment if the treatment was stopped before the 6th month). The number of patients in each group who experienced an improvement of the CNDs of more than 20% defined a secondary end point.

Estimation of sample size was based on the main criterion, using a two sample t test. We were expecting a difference of CNDs between treatment groups of 10 with SD 10, using the estimates derived from a previous trial. Specifying a type I error of 0.05, a power of 0.90, a two sided test required 22 patients per group. Given the low incidence of peripheral neuropathy, the protocol was designed to minimise the sample size, using repeated significance tests with a nominal significance level of 0.029.

Our case may differentiate the proposals for the underlying mechanism of psychosis and EEG normalisation in epileptic patients. We suggest that seizure cessation in an epileptic brain seems to play a major part in the development of psychotic symptoms, independent of antiepileptic medication.

As far as we know, this is the first report of a psychotic reaction with a forced normalisation induced by vagus nerve stimulation. Recent studies show that -fos expression is increased during vagus nerve action in the posterior thalamus, cingulate cortex, and other areas. Extensive brain areas seem to be involved and thereby possibly influence on behavioural mechanisms could not be excluded.
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 only because of worsening of the neuropathy. No patients had to stop treatment because of haematological toxicity.

The mean CNDS did not change significantly in either group or 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 references were close in the two randomised groups: in the α-IFN group and placebo, we did not confirm the effect of cytokine in patients with monoclonal IgM associated polyneuropathy. No patients had to stop treatment because of worsening of the CNDS of more than 20%.

In conclusion, these disappointing results of a 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 trial. 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 signs, the number of patients previously treated and anti-B cell monoclonal antibodies, should be tested in further studies.

Reversable posterior leukencephalopathy syndrome induced by granulocyte stimulating factor filgrastim

Posterior leukencephalopathy syndrome is characterized by visual disturbances, altered mental status, drowsiness, seizures, headache, and occasionally focal neurological signs. It is usually associated with severe hypertension and has most often been seen in patients treated with immunosuppressive drugs such as cyclosporin A, tacrolimus, and interferon-α.2 3 4

The granulocyte and granulocytic macrophage stimulating factor filgrastim (Neupogen) is used in chemotherapy induced bone marrow suppression. By contrast with molgramostim (Leukomax®) filgrastim is supposed to have fewer CNS side effects. Intracranial hypertension and convulsions have been reported after molgramostim therapy. Only one case of reversible encephalopathy and focal status epilepticus due to filgrastim is published.5 In that case the contrast enhanced CT was normal.

We report a case of reversible posterior leukencephalopathy syndrome with transient bilateral changes in the occipital and parietal regions involving white matter on MRI induced by filgrastim. This is to our knowledge the first documented case of reversible posterior leukencephalopathy syndrome induced by filgrastim.

A 45 year old previously healthy woman was diagnosed with late stage III-B non-Hodgkin’s lymphoma with intermediate to high malignancy in August 1999. The first cycle of chemotherapy with vincristine, ifosfamide, and etoposide was well tolerated. Two days after termination of chemotherapy she received subcutaneously 300 μg filgrastim (Neupogen) daily because of bone marrow suppression with leukopenia for 9 days. After 3 days the dose was increased to 600 μg/day. One day after termination of filgrastim and almost 2 weeks after chemotherapy, she developed acute cortical blindness within 30 minutes. On the next day simple partial and complex partial seizures, non-convulsive status, agitation, and desorientation followed. Brain MRI obtained 1 day later showed bilateral hyperintensities in the parietal and occipital regions involving white matter with some involvement of the overlaying grey matter on proton density images (figure). Non-convulsive status with somnolence and disorientation were documented by EEG, which showed a bilateral parieto-occipital focus with continuous rhythmic delta waves.
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 (0.05 mg) 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 hypoxia or hypoglycaemia were found. Pre-existing medication consisted of 20 mg amitryptiline and 1000 mg metformin a day. On initial examination, the most obvious symptoms 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 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.

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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. 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.

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 benzodiazepines. The mechanisms responsible for these adverse effects are not exactly known, but opioidergic, serotonergic, dopaminergic, and other mechanisms are considered.

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. This publication caused controversy on the dissociation between autonomic dysfunction and pain during cluster headache. 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 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 of the affected side. 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 anticholinergic receptor antibodies were negative. Low rate repetitive nerve stimulation did not result in pathologic decremental responses. Thyroid hormones and antibodies were in the normal range and absent, respectively. In the symptom free interval, pupillary responses to various 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 ophalmoplegia. Distinctive clinical features of this rare syndrome are the intermittent evolution of external ophalmoplegias, 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 characteristic, anhidrosis, is lacking or even replaced by hyperhidrosis. 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...
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 quixotic 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 extrapolation 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 acrimony,” 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 it?” Fothergill asked. Yes, the Earl replied. “Does it agree with your Lordship?” Yes. “Why then it is wholesome.” Compston essays the anatomical illustrations of 18th and 19th century neurological texts to illustrate the emerging clinical pathological 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