An unusual case of Behçet’s disease presenting with bilateral internal carotid artery occlusion

Behçet’s disease (BD) is a multisystemic recurrent inflammatory disorder, which is originally described as a triad of oral and genital ulcerations with uveitis. As vasculitis of the vasa vasorum is the main pathological hallmark of BD, it is generally seen in the form of superficial thrombophlebitis or occlusion of major veins; however arterial obstruction and aneurysms may also be seen to a lesser extent.1 We present a patient with BD who developed bilateral internal carotid artery (ICA) occlusions.

**Case report**
A 43 year old, right handed male patient was referred to Ege University Neurology Department for evaluation of an acute onset right sided weakness, fever, headache, and difficulty with gait and speech in August 2001.

On admission, he was alert and fully oriented. His temperature was 38°C, pulse was regular (90/min), blood pressure was 150/80 mm Hg. His speech was severely dysarthric but he could name, repeat, read, and follow instructions. His cranial nerves and fundoscopic examination were normal. His gait was wide based and unsteady. He had four sided mild weakness, which was prominent on the right. Muscle stretch reflexes were normal but plantar reflexes were extensor bilaterally. His coordination was impaired in proportion to weakness in all four extremities. He had mild neck stiffness and positive Brudzinski’s sign. On physical examination, erythema nodosum like dark red, painful lesions were noticed on both anterior aspects of the legs. His ophthalmological examination did not reveal any signs of uveitis. He also complained of pain and fever in his scrotum, and urological examination showed swelling, induration, and marked tenderness of epididymia on both sides as the clinical findings of epididymitis. His medical history showed that he had complained about recurrent oral aphthous lesions and aforementioned skin lesions for about 8 to 10 years without medical consultation. He had no other medical history associated with BD. He was a moderate cigarette smoker for 20 years.

Laboratory tests were consistent with an inflammatory condition with a high erythrocyte sedimentation rate (100 mm 1st h) and C reactive protein (12.27 mg/dl; normal range 0–5 mg/dl) levels. CSF examination, serum immunoglobulin levels, platelet count, protein C, protein S, antithrombin III, C3 and C4 complement, rheumatoid factor, and lipid levels were within the normal range. Serum anti-neutrophil cytoplasmic and antineutrophil antibodies were negative. ECG, 2D echo, chest radiograph, abdominal ultrasonography, and colour Doppler ultrasonography of the lower extremity vessels were normal. Cranial magnetic resonance imaging showed diffuse cerebral atrophy and chronic ischaemic lesions in both cerebral hemispheres as well as the absence of the flow void in both ICA on T2 weighted axial images. Digital subtraction angiography (DSA) showed complete occlusion of the bilateral internal carotid arteries just rostral to the bifurcation (fig 1).

After consultation with the rheumatology clinic, a pathergy test was performed to confirm the diagnosis of BD and found to be positive. The patient was then transferred to the rheumatology clinic. He was treated with aspirin 300 mg/day, prednisolon 1 mg/kg/day, pentoxifylline 1200 mg/ day, 750 mg pulse cyclophosphamide monthly for BD. He was also treated with oral antibiotics and analgesics for the epididymitis. Two months later, he had almost completely recovered.

**Comment**
Our patient had presented with unusual neurological findings for a classic stroke syndrome. DSA and MRI showed bihemispheric ischaemic lesions and bilateral ICA occlusion, which was also shown by DSA. It is known that cardiovascular risk factors, smoking, fibromuscular dysplasia, or moyamoya disease are frequently found as an aetiological factor in patients with bilateral ICA occlusion, whereas essential thrombocytosis, giant cell arteritis, and BD are among the very rare causes.2,3

Although our patient did not have cardiovascular risk factors except for smoking, he had been suffering from BD for about 10 years, which was not diagnosed before neurological presentation. His medical history, skin lesions, and urogenital findings supported with a positive pathergy test verified the diagnosis of BD according to latest diagnostic criteria for BD.4

Neurological involvement in BD has been reported to occur in 2.2% to 43% of cases in large series, either in the form of neuro-Behçet disease (papillopathy CNS involvement) or vasculo-Behçet disease (secondary or non-papillopathy CNS involvement) or both.5 Neuro-Behçet’s disease has a characteristic clinical picture with male predominance and typical cranial MRI findings of reversible inflammatory parenchymal lesions, attributable to small vessel disease, which may rarely be confused with those of MS.6 On the other hand, vasculo-Behçet’s disease is attributable to large vessel disease generally in the form of cerebral venous thrombosis and has limited symptoms with a better prognosis.7 Our patient’s neurological signs and symptoms were highly suggestive of neuro-Behçet; however CSF findings with acellularity and normal protein level and neuro-imaging studies showing ischaemic lesions and bilateral ICA occlusions supported a very unusual type of vasculo-Behçet. Diffuse cerebral atrophy and survival with minimal or no neurological deficit in our patient is not infrequent in patients with bilateral ICA occlusion. This is explained by the adequate collateral flow provided by vertebrobasilar system and slow, gradual occlusion.6

Oclusive lesions in the bilateral ICAs, as seen in our patient, are extremely rare in BD and we suggest that this is a very unusual case of vasculo-neuro-Behçet’s disease. We also conclude that BD should always be remembered as an aetiological factor for bilateral ICA occlusions, especially in countries where the disease is highly prevalent.

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**References**
Miller-Fisher syndrome and Hodgkin's disease

Miller-Fisher syndrome (MFS) is a rare clinical entity classically regarded as a variant of Guillain-Barré syndrome (GBS) and characterised by the clinical triad of ophthalmoplegia, ataxia and areflexia. In MFS, paralysis is restricted to extraocular and occasionally other cranial or bulbar muscles. We report on a patient with a relapsing Hodgkin's disease who developed MFS. Conventional immunomodulatory and intravenous immunoglobulin treatments improved the neurological deficits. The patient was a 26 year old white man who had an eight year history of Hodgkin's disease (type mixed cellularity, pathological stage IVB) who had been receiving a salvage ESHAP regimen (etoposide VP-16, 68 mg/day, methylprednisolone 500 mg/day, and cisplatin 4.25 mg/day for four days and cytosine arabinoside 3.4 g/day on the fifth day) since the first disease relapse four months before admission. He was admitted to the hospital for constitutional symptoms (39ºC fever, recurrent night sweats, fatigue, malaise, and weakness). There was no history of infection. General examination was unremarkable except for bilateral hilar adenopathy (1.5 X 2.0 cm). Haemoglobin concentration was 63 g/L, packed cell volume 17.8%, platelet count 89 X 10³/mm³, white cell count 3.34 X 10³/mm³ (neutrophils 2.42 X 10³/mm³), and lactate dehydrogenase (LDH) 144 U/L. Results of the following investigations were normal: glucose, cholesterol, triglycerides, and ions; renal, liver, and thyroid function tests; vitamin B12 and folic acid; and tests for Campylobacter jejuni, herpes simplex virus, herpes zoster virus, cytomegalovirus, Epstein-Barr virus, Streptococcus pyogenes, Borrelia sp, syphilis, and cerebrospinal fluid parameters.

Staging evaluation included negative computed tomography of the thorax. Computed tomography of the abdomen showed paraaortic nodal enlargement and normal sized spleen. Bone marrow examination found histological evidence of Hodgkin's disease. Therefore, a diagnosis of relapsing Hodgkin's disease was considered. Before starting a cycle of ESHAP chemotherapy, the patient complained of bilateral headache, dysarthria, photophobia, dysphagia, and gait instability. Neurological function was assessed at that time, eight days after admission. Examination of the cranial nerves found a left sided ptosis with a total bilateral external ophthalmoplegia and fixed dilated pupils. The patient's pupillary response to a 0.05% solution of pilocarpine showed increased sensitivity consistent with a postganglionic parasympathetic lesion. (Oculomotor nerves are among the few myelinated fibres of the postganglionic nervous system and this patient likely had dysfunction in these fibres similar to that observed in the other peripheral nerves.) Several abnormalities were encountered in about half of patients with MFS.1 There was dysphonia, mild dysphagia, and peripheral seventh nerve palsy. Examination of the peripheral nervous system showed loss of coordinated movements. His muscle strength was normal, and pinprick, touch, position, and vibratory sensation were not impaired. There was obvious ataxia in all four limbs. He could walk with assistance and tandem gait was impossible. His cerebrospinal fluid protein concentration was 0.79 g/l with 2 lymphocytes/mm³. Cerebrospinal fluid culture and cytological studies showed normal lymphocytes. Subsequent investigations found increased IgG ganglioside antibodies to GQ1b glycolipids (titre of 4900). Standard delayed hypersensitive skin tests were performed to purified protein derivative of tuberculosis (intermediate strength), Candida albicans, mumps, trichophyton, and streptokinase/streptodornase, showing failure to elicit a response to these antigens. Serum IgG anti-streptolysin concentrations were increased (IgG: 19 g/l, normal 10.3 ± 2.9, IgA: 4.8 g/l, normal 1.6 ± 0.8). Gadolinium enhanced magnetic resonance imaging of the head showed no abnormalities. There was neurophysiological evidence of an axonal sensory neuropathy (sensory conduction in the right sural and median nerves was absent; normal by median compound motor conduction action potential was 7.1 ms with a conduction velocity of 41.5 m/s). F wave latencies from the right posterior tibial, right common peroneal, right median, and ulnar nerves were minimally prolonged two days after onset but were within normal limits by three months. The patient presented moderate reduction of facial muscle action potentials (right: 1.3 mV, left: 1.4 mV). Blink R2 response latencies were normal (right: 30 ms, left: 29 ms). Masseter reflex was normal. The amplitude of the distal sensory evoked response was greatly reduced (upper extremity somatosensory evoked responses to median nerve stimulation at the wrist). Brainstem auditory evoked potentials were normal. Intravenous immunoglobulin was given for five days at a dosage of 0.4 g/kg/day, starting 24 hours after any skin test of neurologic symptoms. He gradually improved over the next two weeks. A follow up examination by the time of discharge four weeks after the onset found that clinical recovery from the ataxia and occasional diplopia but the tendon reflexes were still hypotonic. Three months later, neurological examination and lumbar puncture results were normal, all electrophysiological parameters were normalised, and IgG antibody titres to GQ1b were not detectable.

In Hodgkin's disease, the incidence of polyneuropathy is about the same as for the reticuloses in general—that is, approximately 1% or 2%. The major clinical picture of this patient was acute ataxia, ophthalmoplegia, and areflexia associated with increased cerebrospinal fluid protein and high titres of antibodies to the GQ1b ganglioside in the context of relapsing Hodgkin's disease, which suggests an autoimmune mediated neurological disorder. To our knowledge this is the first report on a patient with MFS evolving during a relapse of Hodgkin's disease. GBS and MFS occur in relation with conditions marked by immunosuppression, such as systemic lupus erythematosus, pregnancy, postoperative states, and specific infections. Such situations are commonplace, and yet only a tiny proportion is complicated by GBS or MFS. This suggests that a special set of circumstances must prevail for MFS and GBS to occur. VIetnam was the way, not only are MFS and GBS disorders that can occur in the presence of partial immunosuppression, but also the immunosuppression may be involved in the pathogenesis of the syndromes. One must ask how an autoimmune, possibly cell mediated reaction can occur in an immunosuppressed patient.

Animal models such as the NZB mouse show that depression of cell mediated immunity and those of autoimmune diseases, even though this increase is more often humorally mediated.8–9 Lisak et al described three patients with GBS and Hodgkin's disease, postulating that selective depression of cell mediated immunity from whatever cause may allow the development of an immune reaction, either humoral, cellular, or both, directed against peripheral nervous system antigens.

The development of MFS in the context of relapsing Hodgkin's disease, together with the improvement of this syndrome after tumour treatment and intravenous immunoglobulins, supports the theory that partial immunosuppression and the presence of IgG anti-GQ1b are possible pathogenic mechanisms.

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References


Neuromyotonia and myasthenia gravis without thymoma

Neuromyotonia is a syndrome characterised by motor unit hyperactivity leading to muscle cramps, fasciculations, muscle stiffness, and persistent muscle contraction. In most neuromyotonia patients, the disorder is acquired. An autoimmune or paraneoplastic origin is common.4 Myasthenia gravis, thyrotocosis, systemic sclerosis, inflammatory demyelinating neuropathies, thymoma, bronchial carcinoma, and small cell lung cancer may be associated. Here, we report a patient with neuromyotonia, associated with myasthenia gravis and anti-voltage-gated potassium channels (VGKC) and anti-acetylcholine receptor (AChR) antibodies without thymoma.

A 58 year old man of Portuguese descent presented at our neuromuscular clinic with dysesthesia and hyperesthesia in the first three fingers of the right hand. Symptoms had started nine years before and had been attributed to cervical radioculopathy. Over the years, the symptoms had been fluctuating but for the past two months they had become debilitating. Therefore, the patient sought a second opinion. The patient volunteered that, although right hand pain was his main complaint, for many years his hands and feet were swollen and red. There was stiffness and loss of dexterity of all fingers. He had difficulty writing, using scissors, and using a handheld...
Blood urea nitrogen, liver function tests, and plantar responses were flexor. Occurred in right lateral and vertical gaze upward. Diplopia was noted. Horizontal diplopia, upper eyelid ptosis, rapidly increasing on right hand grip weakness. Right palpebral ptosis and diplopia. The symptoms had progressively worsened. One year before presenting to us, he developed ptosis of the right upper eyelid, rapidly followed by vertical and horizontal diplopia. These symptoms were fluctuating with worsening in the evening. Repetitive stimulation of the facial nerve showed a decremental response, symptoms and signs disappeared after injection of prostigmine, and anti-AChR antibodies were found. It was concluded that the patient had ocular myasthenia and the patient was treated with oral methylprednisolone. Improvement was rapid and after a few weeks treatment was stopped. Two weeks before presentation, the patient again complained of right palpebral ptosis and diplopia. The symptoms were responsive to pyridostigmine bromide. The medical history was remarkable for ophthalmal migraine, arterial hypertension, and hypercholesterolaemia. Treatment consisted of fenofibrate and metoprolol. The family history was non-contributory.

On clinical examination, continuous undulations of the oracularis oculi muscles. Small amplitude, involuntary movements of fingers and toes were conspicuous at rest. The fingers were stiff and the patient had difficulty performing rapid alternating movements with his fingers. Tactile and pain sensation was diminished only in the first three fingers of the right hand. Tinel’s and Phalen’s signs were present at the right wrist and there was right hand grip weakness. Right upper eyelid ptosis, rapidly increasing on upward gaze was noted. Horizontal diplopia occurred in right lateral and vertical gaze directions. Deep tendon reflexes were normal and plantar responses were flexor.

Complete blood count, serum creatinine, blood urea nitrogen, liver function tests, serum electrolytes, thyroid function tests, and serum creatine kinase were normal. Rheumatoid factor was negative and there were no antibodies against striated muscle, but antinuclear antibodies were positive at a titre of 1/80. Prostate specific and carcinoembryonic antigens were negative. Both ACHR antibodies (26 nmol/ml, normal values less than 0.5 mmol/ml) and VGKC antibodies (1091 pmol/l, normal values less than 100 pmol/l) were detected. Computed tomography of the chest was normal.

Nerve conduction studies showed evidence of a severe right-sided carpal tunnel syndrome, but otherwise they were normal. Needle electromyography revealed myokymic discharges in distal muscles of upper and lower extremities (fig 1). These discharges consisted of bursts of motor unit potentials, appearing as doublets, triplets, or multiplets with intraburst frequencies of 40 to 100 Hz. Burst recurrence was irregular with an interburst frequency of 5–8 Hz. There was evidence of mild chronic denervation with slightly reduced recruitment in distal muscles. Anti-VGKC antibodies are found in approximately 40% of patients with acquired neuromyotonia. They are also found in patients with other neuromuscular hyperexcitability syndromes, such as cramp fasciculation syndrome, acquired rippling muscle syndrome, facial myokymia. In a significant proportion of these patients, coexistence of myasthenia gravis and neoplastic disorders, thymoma in particular, is observed. About 20% of all reported neuromyotonia patients had thymoma; 70% thereof also had myasthenia gravis and anti-AChR antibodies and 20% had anti-AChR antibodies without overt myasthenia gravis. The absence of anti-striated muscle antibodies and of radiological evidence of mediastinal tumour in a patient with neuromyotonia of nine years duration illustrates that the association of autoimmune neuromyotonia and myasthenia gravis can occur without thymoma.

**Figure 1** Myokymic discharges recorded at rest with a concentric needle electrode from the right dorsal intersosseus muscle, shown at two different sweep speeds.

**References**


**Acute attacks and brain stem signs in a patient with glutamic acid decarboxylase autoantibodies**

Glutamic acid decarboxylase (GAD) is a major autoantigen in type 1 diabetes mellitus and stiff-man syndrome. Patients with progressive cerebellar ataxia and GAD autoantibodies (GAD-Abs) have been reported, and the pathogenetic role for GAD-Abs in suppressing cerebellar γ-aminobutyric-acid (GABA)ergic transmission has been discussed. We present a woman who eventually developed progressive cerebellar ataxia, but had stroke-like episodes and brain stem involvement during her clinical course.

A 63 year old woman suffered dizziness of sudden onset accompanied by nausea and vomiting. Her physician found horizontal, gazed evoked nystagmus. A few days later, she noticed transient horizontal diplopia, after which spontaneously all her symptoms gradually subsided. Two months later, she experienced intermittent vertigo when she turned her head and then unsteadiness of gait. Her past medical and family histories were unremarkable. On examination, she was fully conscious and had no general physical abnormalities. There was coarse horizontal nystagmus, coarser on the left side. On phonation, her posterior pharyngeal wall shifted rightward, indicating paralysis of the left side of the posterior pharyngeal wall (signe de radeau, Verney). She had ataxia in her left arm and leg and walked throwing the left leg outward. Although lesion in the left dorsolateral lower brain stem was suspected, MRI and MR arteri and venous images were unremarkable. A routine blood examination, as well as glucose tolerance and thyroid function tests, detected no abnormalities. CSF analysis was normal with negative oligoclonal IgG bands and a
Selective suppression of GABA-ergic transmission by GAD-Abs is a possible cause of SMS, cerebellar ataxia, focal dystonia, facial palsy, palatal myoclonus. This mechanism, however, does not explain our patient’s paralysis of the pharyngeal constrictor muscles because motoneurons in the nucleus ambiguus receive GABA mediated inhibition.1 As speculated by Honnorat et al,2 high GAD-Abs titre would merely reflect the presence of a more complex immune reaction against the nervous system. In this context, the subacute and atypical presentation of this patient raised the possibility that the GAD-Abs might have been a paraneoplastic phenomenon. Sillevis Smitt et al reported reversible cerebellar ataxia attributable to autoantibodies against a glutamate receptor in two patients with Hodgkin’s disease.3 At present, however, few reports of patients with SMS showed no evidence for malignancy. For this purpose, we studied prospectively the clinical outcome of patients with ICH. Patients with prior cerebrovascular diseases and patients who subsequently died of non-cerebral causes were excluded from this pilot study. Data were analysed using the SPSS statistical program (SPSS, Chicago, Illinois, USA). The Wilcoxon test was applied to compare the two patient groups. This two patient groups (surviving versus non-surviving) did not differ statistically with regard to age, sex, location and size of ICH, and initial Glasgow coma scale and Scandinavian stroke scale scores. As fig 1 shows, the CSF concentrations of sICAM-1 were below 13.7 ng/ml (mean (SD) 8.7 (4.7) ng/ml) and of sVCAM-1 below 35.4 ng/ml (11.5 (13.1) ng/ml) in the group of patients who survived (n = 6). However, in patients with a lethal outcome (n = 4), initial ventricular CSF concentrations of sICAM-1 were above 18.3 ng/ml (25.5 (9.3) ng/ml) and of sVCAM-1 were above 44.5 ng/ml (76.8 (45.0) ng/ml). These differences were significant for the CSF concentrations of sICAM-1 (p < 0.01) and of sVCAM-1 (p < 0.001). Patients who had intracerebral haemorrhage with ventricular drainage were obtained within eight hours after the initial symptoms attributed to ICH and within three hours after operation. Concentrations of soluble ICAM-1 (sICAM-1) and sVCAM-1 were determined by enzyme linked immunosorbent assay (ELISA). In corresponding clinical examinations, the Scandinavian stroke scale and Glasgow coma scale scores were determined. The patients were categorised into two groups: patients who survived (n = 6) and patients who died (n = 4) from cerebral causes within eight weeks after the onset of ICH. Patients with prior cerebrovascular diseases and patients who subsequently died of non-cerebral causes were excluded from this pilot study. Data were analysed using the SPSS statistical program (SPSS, Chicago, Illinois, USA). The Wilcoxon test was applied to compare the two patient groups. The two patient groups (surviving versus non-surviving) did not differ statistically with regard to age, sex, location and size of ICH, and initial Glasgow coma scale and Scandinavian stroke scale scores. As fig 1 shows, the CSF concentrations of sICAM-1 were below 13.7 ng/ml (mean (SD) 8.7 (4.7) ng/ml) and of sVCAM-1 below 35.4 ng/ml (11.5 (13.1) ng/ml) in the group of patients who survived (n = 6). However, in patients with a lethal outcome (n = 4), initial ventricular CSF concentrations of sICAM-1 were above 18.3 ng/ml (25.5 (9.3) ng/ml) and of sVCAM-1 were above 44.5 ng/ml (76.8 (45.0) ng/ml). These differences were significant for the CSF concentrations of sICAM-1 (p < 0.01) and of sVCAM-1 (p < 0.001). Patients who had intracerebral haemorrhage with ventricular drainage were obtained within eight hours after the initial symptoms attributed to ICH and within three hours after operation. Concentrations of soluble ICAM-1 (sICAM-1) and sVCAM-1 were determined by enzyme linked immunosorbent assay (ELISA). In corresponding clinical examinations, the Scandinavian stroke scale and Glasgow coma scale scores were determined. The patients were categorised into two groups: patients who survived (n = 6) and patients who died (n = 4) from cerebral causes within eight weeks after the onset of intracerebral haemorrhage.
sVCAM-1 (p < 0.01). However, the concentrations of adhesion molecules in serum did not differ significantly (non-surviving: 444 (132) ng/ml for sICAM-1, 1422 (465) ng/ml for sVCAM-1; surviving: 463 (110) ng/ml for sICAM-1, 1147 (382) ng/ml for sVCAM-1).

This is the first study to investigate soluble adhesion molecules in CSF and serum in patients with ICH with ventricular tamponade. We found a strong correlation between clinical outcome and the concentrations of soluble adhesion molecules in the CSF of patients with acute ICH and ventricular drainage. Moreover, we found more than threefold increases of sICAM-1 and of sVCAM-1 in the CSF of patients with lethal outcome as compared with CSF samples. In patients with multiple sclerosis (s-ICAM-1: 2.8 ng/ml, range 0.9–12.7; sVCAM-1: 4.2 ng/ml, range 0.2–3.5) and from healthy donors (sICAM-1: 5.2 (2.2) ng/ml) as well as from patients with acute ICH and ventricular drainage. Moreover, we found more than threefold increases of sICAM-1 and of sVCAM-1 in the CSF of patients with lethal outcome as compared with CSF samples. In patients with multiple sclerosis (s-ICAM-1: 2.8 ng/ml, range 0.9–12.7; sVCAM-1: 4.2 ng/ml, range 0.2–3.5) and from healthy donors (sICAM-1: 5.2 (2.2) ng/ml) as well as from patients with acute ICH and ventricular drainage.

With regard to the hypothesis, it would be interesting to investigate the effects of early anti-inflammatory treatment in patients with ICH and an initial highly increased concentration of adhesion molecules in their ventricular CSF samples. In this condition, early application of corticosteroids may be useful to suppress the deviating inflammatory reaction. The blockage of ICAM-1 and VCAM-1 by systemic treatment with monoclonal antibodies would probably not be helpful, as the pathogenetic concept is to block the migration of inflammatory cells into the central nervous system, as well as for experimental ICH and subarachnoid haemorrhage in animal models. With regard to the hypothesis, it would be interesting to investigate the effects of early anti-inflammatory treatment in patients with ICH and an initial highly increased concentration of adhesion molecules in their ventricular CSF samples. In this condition, early application of corticosteroids may be useful to suppress the deviating inflammatory reaction. The blockage of ICAM-1 and VCAM-1 by systemic treatment with monoclonal antibodies would probably not be helpful, as the pathogenetic concept is to block the migration of inflammatory cells into the central nervous system, as well as for experimental ICH and subarachnoid haemorrhage in animal models.

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plasma lactate were both 2.1 mmol/l and oligoclonal bands were not found. DNA was extracted from a blood sample and analysed for mtDNA mutations using standard procedures and was negative at positions 3243, 8344, 8993, 3460, and 14484, but with a homoplasmic mutation at position 11778.

**Table 1**

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<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Measles</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Smallpox</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Mumps</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Some patients had received more than one vaccine.

**Risk of relapse of Guillain-Barré syndrome or chronic inflammatory demyelinating polyradiculoneuropathy following immunisation**

Reports of the rare occurrence of Guillain-Barré syndrome (GBS) or chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) following immunisation and recurrence of symptoms following subsequent immunisation have given rise to concern over the safety of vaccine administration in this patient group. Similar concerns have been addressed and dismissed in patients with multiple sclerosis, but no such information exists for inflammatory neuropathy. To provide more information about vaccine safety in GBS and CIDP we audited the recurrence of neurological symptoms following immunisation.

The Guillain-Barré Syndrome Support Group, a British patient organisation, provided 3000 questionnaires to its members, asking them to identify their illness, record all immunisations administered after their illness, and describe any symptoms within six weeks of immunisation suggestive of recurrence of GBS or worsening of CIDP.

All but one of the patients who reported neurological symptoms after immunisation were contacted by telephone to confirm their history and to grade their symptoms using the modified Rankin scale. For the patient who could not be contacted by telephone, the patient’s consultant neurologist provided the information. Questionnaires were sent to the general practitioner for each patient who reported a “relapse” to confirm which vaccine had been administered.

A total of 1114 patients (37.1%) completed the questionnaires, of whom 927 had had GBS, 179 had CIDP, and eight were excluded because they had other diseases. Of the 927 patients with GBS, 311 had received immunisations since having GBS. Eleven (3.5%, 95% confidence limits (CL) 1.8%, 6.2%) reported symptoms including increased fatigue, weakness, numbness, and paraesthesiae, but these were usually mild and no patient required hospitalisation or treatment. In the case of symptoms came on within 24 hours of immunisation and all but one developed symptoms within one week of immunisation. One patient reported symptoms rendering him unable to walk until three weeks, which increased his modified Rankin scale score from grade 2 to 4.

Influenza, tetanus, and typhoid were the most common immunisations associated with a relapse after GBS but the number of patients who reported symptoms was small compared with the total numbers receiving each of these vaccines (table 1). Although the results suggest that some vaccines that are administered less frequently (such as diphtheria) may be associated with a higher relapse risk, the numbers were small and most of these vaccines were administered at the same time as other vaccines.

Of the 311 patients with GBS who had received vaccines after having GBS, 29 had also received a vaccine in the six weeks before the onset of their initial illness. Two of these patients (6.9%, 95% CI 0.85%, 22.8%) had reported a recurrence of symptoms after a second, different, vaccine was subsequently administered.

Of the 179 patients with CIDP, 65 had been immunised after disease onset. Five reported worsening of neurological symptoms following immunisation. In three the symptoms were similar to a typical relapse of their CIDP but only one of these patients required treatment within two months of immunisation. The other two patients with CIDP were immunised when already experiencing mild neurological symptoms, which then worsened, so that their modified Rankin scale scores changed from 3 to 4 and they became dependent on a walking stick and unable to drive.

Of the patients with CIDP who experienced a relapse after immunisation, two relapses occurred among 23 patients who received the tetanus vaccine, giving a risk of relapse of 8.7%. Two of 46 (4.3%) patients with CIDP had relapses after influenza vaccine, of whom one had simultaneous pneumococcal vaccine. Two of six (33%) patients, including the last mentioned, experienced relapses after pneumococcal vaccine. Fourteen patients with CIDP had no symptoms of relapse following immunisation with typhoid vaccine. Between one and seven patients with CIDP had no
symptoms after yellow fever, diphtheria, meningococcus, oral polio, HCG, hepatitis A, hepatitis B, cholera, or rubella vaccine.

This audit of patients with GBS and CIDP who have received vaccines suggests that the risk of relapse following immunisation is low. The response rate to the questionnaire was small as a proportion of the membership of the GBS Support Group. This is partly because an unknown but large proportion of members are relatives or friends and not former GBS or CIDP patients.

Only 11 of 311 patients with GBS (3.5%, 95% CL 1.8%, 6.2%) who had been immunised after having the disease reported a recurrence of symptoms. All of the vaccines that were associated with neurological symptom recurrence had also been received by many more patients who remained well. Some of the patients who reported symptoms after receiving vaccines had also received the same or other vaccines on other occasions without experiencing any problems. Only one respondent experienced symptoms that increased the modified Rankin scale score. The risk of relapse severe enough to alter the modified Rankin scale score is 0.3% (95% CL 0.01%, 1.78%) while the risk of a relapse requiring treatment or hospitalisation is at most 1.18% (95% CL).

It is more difficult to draw conclusions about the risk of immunisation for relapse in CIDP because our sample size was smaller. Five (7.7%) of the 66 patients who had been vaccinated noted a return of symptoms following immunisation. The reports of minor symptoms or acceleration of deterioration following influenza and pneumococcus vaccines merit caution in recomending these immunisations in patients with CIDP; although the risk of infection in immunosuppressed patients may outweigh any potential risk. Of greatest concern is the risk of relapse following tetanus toxoid, which was 8.7% (95% CL 1.7%, 28.0%) in our patient sample. In view of these figures and previous reports of relapse of CIDP following tetanus toxoid, patients may wish to avoid routine tetanus toxoid immunisation.

Finally, it is important to acknowledge the difficulties in drawing conclusions from a questionnaire in which the patients reported their classification and relapses. It is intuitively likely that more patients who experienced symptoms following immunisation responded to the questionnaire, which would overestimate the frequency of relapses. Consequently the true risks of relapse following immunisations after GBS or in CIDP may be less than those discovered in this audit.

Acknowledgements

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Competing interests: none declared

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References


Hypoglycaemia induced by phenytoin treatment for partial status epilepticus

A 22 year old woman was admitted at our epilepsy unit in status epilepticus. On examination, seizures were characterised by a confusional state with little response to external stimuli, and recurrent, brief, tonic motor manifestations lateralised to the left side. Family history was negative for epilepsy and metabolic disorders. Full term birth was uncomplicated and first psychomotor developmental milestones were normal. In the past medical history there was no sign of any metabolic disease. Routine biochemical tests revealed no reports of cognitive dysfunction or personality disturbances. At the age of 16, the patient presented with epilepsy, which was characterised by two types of seizures: global tonic seizures, which occurred mainly during episodes of loss of contact without any other manifestations, which were rare. The patient was treated for many years with 20 mg of clobazam twice daily. The awake EEGs that were performed routinely during the years of treatment with clobazam showed normal background rhythm with rare epileptiform discharges, characterised by irregular 2–3 Hz spike and wave complexes localised over both frontal-central regions. Magnetic resonance imaging of the brain, which was performed at the age of 18 years, showed no abnormalities.

On the day of admission at the epilepsy unit, the patient had an urgent EEG that revealed continuous, rhythmic spikes or spike and wave complexes over both frontal-central regions with right predominance. Emergency drug treatment with intravenous lorazepam 2 mg was performed twice with a 15 minute interval, but there was no change in the clinical status. Therefore, after 30 minutes, intravenous phenytoin 1000 mg was given by infusion over a period of 20 minutes, and then an infusion of 750 mg of phenytoin was set up for a period of 24 hours. Clinical symptoms and EEG abnormalities rapidly improved and completely resolved after 40 minutes from the start of the administration of phenytoin.

Nine hours later, while the medical observation was still ongoing, the patient developed an episode of somnolence and consciousness, which was preceded by prodromal symptoms, including tachycardia, sweating, light headness, and irritability. On examination, there was reduction of alertness, confusion, and tachycardia. Pupils were of intermediate diameter and reactive to the light. No focal neurological signs were observed. EEG monitoring did not show any abnormalities. Emergency blood tests revealed severe hypoglycaemia (<20 mg/dl). Prompt correction of the hypoglycaemia was obtained by the intravenous infusion of 50 ml of 50% glucose, and a consequent recovery of consciousness occurred. Phenytoin infusion was then withdrawn and oxcarbazepine was titrated. In the following days no further episodes of hypoglycaemia were noticed. The patient was therefore investigated with the oral glucose tolerance test, which showed normal levels of plasma glucose, immunoreactive insulin, and immunoreactive insulin/plasma glucose, and with dexamethasone suppression test, which did not show evidence of pancreatic insufficiency.

Comment

We have described a patient who experienced a severe episode of hypoglycaemia induced by intravenous phenytoin, which was administered at the doses recommended for the treatment of status epilepticus. It is known that phenytoin interferes with carbohydrate metabolism. Indeed, it may inhibit the release of glucose stimulated insulin and induce a consequent hyperglycaemia. The ability of phenytoin to inhibit insulin release has been suggested to be related to the blockade of Ca2+ uptake via voltage dependent Ca2+ channels. For this hyperglycaemic property, phenytoin has been often used in the treatment of hypoglycaemia induced by inoperable insulinomas.2

Beside the well known hyperglycaemic effect of phenytoin, it has been reported that high doses of the drug can induce hypoglycaemia in particular, a recent case report studied a case of hypoglycaemia secondary to an acute voluntary intoxication with 20 g of phenytoin. The authors suggested that the hypoglycaemic episode might be attributable either to an escape from the inhibitors effects of phenytoin on insulin secretion or an increased sensitivity of the tissues to insulin.3 The striking finding of our case is that the hypoglycaemia is induced by a therapeutic dose of phenytoin, and, to our knowledge, this is the first case of severe hypoglycaemia during treatment with phenytoin for status epilepticus. In this case we have indeed excluded a different aetiology of the hypoglycaemia. In particular, a possible effect on glycaemia produced by status epilepticus, has been considered not relevant, because the status epilepticus was partial and resolved nine hours before the onset of hypoglycaemia. However, what caused hypoglycaemia when a therapeutic dose of phenytoin was administered is unclear, and further studies are needed to fully investigate the effects of phenytoin on carbohydrate metabolism.

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References


Table 1  Meta-analysis of α synuclein/non-amyloid β component precursor allele and genotype distributions in patients with sporadic Parkinson’s disease (PD) and controls in Japan

<table>
<thead>
<tr>
<th>Study</th>
<th>Allele* frequency</th>
<th>Genotype frequency</th>
</tr>
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<tr>
<td></td>
<td>-2</td>
<td>-1</td>
</tr>
<tr>
<td>Present study</td>
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</tr>
<tr>
<td>PD (n=165)</td>
<td>0.009</td>
<td>0.518</td>
</tr>
<tr>
<td>Controls (n=155)</td>
<td>0.013</td>
<td>0.406</td>
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<tr>
<td>Izumi et al. b</td>
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<td>PD (n=200)</td>
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</tr>
<tr>
<td>Controls (n=250)</td>
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<td>0.001</td>
</tr>
<tr>
<td>Combined</td>
<td></td>
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</tr>
<tr>
<td>PD (n=365)</td>
<td>0.004</td>
<td>0.001</td>
</tr>
<tr>
<td>Controls (n=405)</td>
<td>0.007</td>
<td>0.001</td>
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</tbody>
</table>
| **C**n (corrected p value) was obtained by multiply the p value by the number of alleles. CI, confidence interval; OR, odds ratio.


Meta-analysis of α synuclein/ NACP polymorphism in Parkinson’s disease in Japan

α Synuclein is a presynaptic protein highly and broadly expressed in the brain but its normal function is unknown. The protein is also termed non-amyloid β component precursor (NACP) because of its localisation in amyloid plaques of Alzheimer’s disease. However, subsequent studies failed to confirm α synuclein as a component of the amyloid plaque. α Synuclein/NACP is now known to be a major component of Lewy bodies in Parkinson’s disease (PD). Point mutations of the α synuclein gene found in three independent PD families suggest that α synuclein may participate in the aetiology of sporadic PD. To address this possibility, several groups reported case-control studies using a dinucleotide repeat polymorphism in the promoter region of the gene. The previous Japanese study by Izumi et al found a tendency of a difference in allele distribution between PD patients and controls and others did not. We did not combine Japanese data with data from white populations because of the difference in allele distribution between PD patients and controls. A recent study by Xia et al showed a significant lower frequency of the allele 1 positive genotype in patients with PD than in controls after correction (pc = 0.0044, odds ratio 0.61, 95%CI 0.45 to 0.81). These results suggest a negative association of allele 1 with PD in Japanese. As reviewed by Farrer et al, results of studies of white populations have varied—some suggested a significant difference between patients with PD and controls and others did not. We did not combine Japanese data with data from white populations because of the difference in allele distribution between them: the frequencies of alleles 0, 1, and 2 in Japanese are 40%, 33%, and 25%, respectively, of Krüger et al. The previous Japanese study by Izumi et al found a tendency to be less frequent in patients with PD than in controls (p = 0.042 for allele distribution and p = 0.012 for genotype distribution), although the difference was insignificant after correction by the number of alleles (pc = 0.21 for allele distribution and pc = 0.072 for genotype distribution). This result was similar to the previous Japanese work. To increase the power of the Japanese PD control analysis, we combined our data with those of Izumi et al (table 1). The meta-analysis showed a significantly lower frequency of the allele 1 positive genotype in patients with PD than in controls even after correction (pc = 0.0044, odds ratio 0.61, 95%CI 0.45 to 0.81). These results suggest a negative association of allele 1 with PD in Japanese.

References

Neuronal viability. Thus, in Japanese, allele 1 may be associated with high expression or low degradation of α synuclein.