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 vasmorum 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 vertical nystagmus of the neck with 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 epididymis 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 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 antinuclear, antineutrophil cytoplasmic and anticardiolipin antibodies were negative. ECG, 2D echo, chest radiograph, abdominal ultrasonography, and colour Doppler ultrasound 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 voids in both ICAs 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 aetiologic factor in patients with bilateral ICA occlusion, whereas essential thrombocytopenia, giant cell arteritis, and BD are among the very rare causes.1,2

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.3

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 (parenchymal CNS involvement) or vascular-Behçet disease (secondary or non-parenchymal CNS involvement) or both.2 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.4 On the other hand, vascular-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.5-7 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 vascular-Behçet.

Diffuse cerebral atrophy and survival with minimal or no neurological signs 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.8

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 aetiologic 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 characterized 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 immunosuppressive and intravenous immunoglobulin treatments improved the neurological deficits. 

A 58-year-old man of Portuguese descent started nine years before and had been attributed to cervical radiculopathy. 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 with the retinaculum in the fingers of the right hand. Symptoms had started nine years before and had been attributed to cervical radiculopathy. 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 with......

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. 'Acquired neuromyotonia' is defined as neuromyotonia in the absence of autoimmune or paraneoplastic origin reported. Here, we report a patient with neuromyotonia, associated with myasthenia gravis and anti-voltage-gated potassium channel (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 hypesthesia in the first three fingers of the right hand. Symptoms had started nine years before and had been attributed to cervical radiculopathy. 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 with...
computer. Frequent cramps occurred in the fingers and toes. There was painful tension in the calves, the feet, and the hands. The patient also complained of excessive sweating. These 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 migrainae, arterial hypertension, and hypercholesterolaemia. Treatment consisted of fenofibrate and metoprolol. The family history was non-contributory.

On clinical examination, continuous undulating movements were noted in the small muscles of hands and feet and in the orbicularis 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 nystagmus 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 constrictor muscles of the left side. A few days later, her posterior pharyngeal wall (signe de rideau, Verneil). 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 positive oligoclonal IgG bands and a

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 and train found horizontal, gaze 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 constrictor muscles of the left side (signe de rideau, Verneil). 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

References


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

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Conflicts of interest: The University of Oxford on behalf of AV receives consulting fees from RSR Ltd who market AChR antibody assays
and GAD-Abs.

patients with progressive cerebellar ataxia and presence of organ specific autoantibodies GAD-Abs titre, intrathecal GAD-Ab synthesis, have type I diabetes mellitus, the high serum cal coarse nystagmus. Although she does not the posterior pharyngeal wall and asymmetry of brain stem involvement as hemiparesis of acute onset, exacerbations, and such signs of subarachnoid hydrocephalus and bone and gallium scintigrams produced negative results; anti-Hu and Yo antibodies were negative. Genetic analysis for spinocerebellar ataxia type 6 was negative. Glucose tolerance was impaired, but insulin secretion preserved. The serum GAD-Abs level determined by radioimmunoassay was highly increased at 10 400 U/ml (normal <1.5 U/ml). Evaluation of GAD-Abs from plasma frozen at her first presentation showed a titre of 980 U/ml. Serum autoantibodies to thyroid peroxidase and thyroglobulin. Low titre positivities were found for antinuclear, anti-double stranded DNA, anti-parietal cells, and anti-insulin antibodies. CSF GAD-Abs titre was 496 U/ml. Intrathecal GAD-Ab synthesis, calculated by Schüller’s formula, titre was 4700 U/ml, and left posterior flocxor on both sides. There was neither sensory nor bladder disturbance. Repeat CSF analysis and brain MRI results were normal, and a microneuropathy and nerve conduction studies gave normal results.

Routine haematological and blood chemistry studies, as well as the serum levels of vita- 

mins B1, B12, and E, were normal. Fecal occult blood was negative. Infection by neuro-

trophic viruses was excluded serologically. Polymerase chain reaction analysis of the CSF for herpes simplex virus types 1 and 2 was negative. In a search for gynaecological, breast, or lung cancer, as well as haematologi-

cal malignancies, including whole body com-
puted tomography, bilateral mammography, and bone and lung scintigrams produced poor results; anti-Hu and Yo antibodies were negative. Genetic analysis for spinocerebellar ataxia type 6 was negative. Glucose tolerance was impaired, but insulin secretion preserved. The serum GAD-Abs level determined by radioimmunoassay was highly increased at 10 400 U/ml (normal <1.5 U/ml). Evaluation of GAD-Abs from plasma frozen at her first presentation showed a titre of 980 U/ml. Serum autoantibodies to thyroid peroxidase and thyroglobulin. Low titre positivities were found for antinuclear, anti-double stranded DNA, anti-parietal cells, and anti-insulin antibodies. CSF GAD-Abs titre was 496 U/ml. Intrathecal GAD-Ab synthesis, calculated by Schüller’s formula, gave a ratio of 10.7 for intrathecal GAD-Ab specific activity (ASA)/serum ASA, consistent with positive intrathecal synthesis.

Her limb and gait ataxia progressed and were overtaken by truncal ataxia within a month. She underwent a five time course of double filtration plasmapheresis that filtered 15 litres of plasma. Immediately after comple-
tion of the plasmapheresis course, her GAD-Abs titre decreased to 4700 U/ml, and left pos-
terior pharyngeal wall motion and independent gait returned. Ataxia, however, returned three weeks later and then pro-
gressed, accompanied by a gradual rise in GAD-Abs titre. A five day course of intravenous immunoglobulin 0.4 g/kg/day pro-
gressed, accompanied by a gradual rise in GAD-Abs titre. A five day course of intra-

vascular immunoglobulins 0.4 g/kg/day pro-

duced no improvement.

The overall clinical picture for this patient, subacute cerebellar ataxia, was complicated by acute onset, exacerbations, and such signs of brain stem involvement as hemiparesis of the posterior pharyngeal wall and asymmetrical coarse nystagmus. Although she does not have hypothyroidism following treatment, the high serum GAD-Abs titre, intrathecal GAD-Ab synthesis, and presence of organ specific autoantibodies are comparable to previous findings for patients with progressive cerebellar ataxia and GAD-Abs. Selective suppression of GABA-ergic transmission by GAD-Abs is a possible cause of SMS, cerebellar ataxia, focal epilepsy, and palatal myoclonus. This mech-

anism, however, does not explain our patient’s paralytic facies because motoneurons in the nucleus ambiguous receive GABA mediated inhibition. As speculated by Honnorat et al., high GAD-

A Medullor 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 raises the possibility that the GAD-Abs might have been a paraneoplastic phenomenon. Sillevi Smit et al reported reversible cerebellar ataxia attributable to a GABA-ergic receptor in two patients with Hodgkin’s disease. At present, however, follow up exami-

inations of this patient showed no evidence for malignancy. The case of our patient suggests that progressive ataxia with high GAD-Abs titre may present with episodes that resemble multiple sclerosis or recurrent brain stem encephalitis.

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References

High concentrations of sVCAM-1 and sICAM-1 in the cerebrospinal fluid of patients with intracerebral haemorrhage are associated with poor outcome

Intracerebral haemorrhage (ICH) accounts for approximately 10% of strokes and is a life threatening condition with a 30 day mortality of around 45%. The adhesion molecules intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) are proinflammatory parameters for the activation of the immune system. They have been correlated with acute inflammation in several systemic and neurological inflammatory diseases. Recently, it was sug-

Figure 1 Ventricular cerebrospinal fluid concentrations of [A] soluble intercellular adhesion molecule-1 (sICAM-1) and [B] soluble vascular cell adhesion molecule-1 (sVCAM-1) in two groups of patients who had intracerebral haemorrhage with ventricular tapamode. The patients are 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 (152) 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 of patients with acute ICH and ventricular drainage. However, based on our results, it can be speculated that these cells are already inside the central nervous system.


Ondine’s curse in a woman with Leber’s hereditary optic neuropathy

Leber’s hereditary optic neuropathy (LHON) is a maternally inherited disease of mitochondrial DNA. Several mutation sites have been described. All have been associated with visual loss, but mutations at nucleotide position 11778, 3460, and recently 14484, have also been associated with a multiple sclerosis (MS)-like disease.14

We report a woman with undiagnosed LHON who presented with life threatening ventilatory failure.

A 39 year old woman who had had bilateral synchronous severe visual loss to perception of light some two years earlier (see below), was admitted after a two week illness with a purulent cough. She was confined to bed and had received oral antibiotics from her general practitioner. She had a history of chronic headaches but reported no change in their frequency before presentation. On admission she was obtunded with a Glasgow Coma Scale (GCS) score of 3/5. She was hyperventilating, with a severe respiratory acidosis. Arterial blood gas (ABG) showed pH 7.04, Po, 40.9 kPa, PCO, 16.2 kPa, and bicarbonate 22 mmol/l. She was admitted to an intensive care unit and ventilated with later tracheostomy. She was weaned from the ventilator after 31 days and transferred to a ward. Five days later she had a second respiratory arrest requiring further ventilation. She was transferred to another unit 73 days after admission for consideration of long term non-invasive ventilation.

This patient had consumed alcohol to excess and had been admitted previously for benzodiazepine overdose and complications of alcoholic liver disease. Two years earlier she had presented to an ophthalmologist complaining of two months of painless visual loss. Visual acuity was counting fingers bilaterally with central scotomata and absent pupil reactions. Fundoscopy showed bilateral disc oedema, dilated capillaries around the disc margins, and venous pulsations. A CT brain scan was normal, but the patient declined further investigation and a diagnosis of possible toxic amblyopia was made. Her family history of visual loss. She had three siblings in their 30s, and three children aged 9–12 years who were well.

On examination after transfer (two months after her first respiratory arrest), she was alert, oriented, and breathing room air spontaneously. She was unable to stand and had globally worsened limbs consistent with prolonged illness. She could just perceive a light with both eyes but could not visually orient in any direction. A jaw jerk was present and she had a mild facial diplegia with intact sensation. She could speak and swallow adequately and was able to cough and hold her breath to command. She had a spastic quadriparesis with grade 4/5 power in the arms but weaker legs and a flicker of movement only at the toes. Anterior abdominal motion during breathing while lying on her back was reduced. Reflexes were brisk throughout and plantar responses were extensor. There was a subjective sensory abnormality to light touch to the mid-thighs and joint position sense was severely impaired in the forearms and fingers. Breath sounds were quiet and chest excursion limited. She had a distended abdomen with a four finger breadth liver edge palpable and shifting dullness consistent with ascites. ABG on air showed pH 7.31, Po, 6.8 kPa, PCO, 10.5 kPa, and bicarbonate 34.8 mmol/l. Four hours later she became drowsy with a GCS of 8/15. Further ABG revealed pH 7.19, Pao, 5.5 kPa, Pco, 12.8 kPa, and bicarbonate 28.3 mmol/l. After four hours of non-invasive intermittent positive pressure ventilation (NIPPV); ABG on two litres of entrained oxygen showed pH 7.44, Pao, 16.4 kPa, Pco, 5.2 kPa, HCO3- 34.8 mmol/l. She was subsequently transferred to a ward and treated with NIPPV, on room air, at a pressure of 14 cm H2O overnight and during daytime naps.

An MRI scan of her brain showed symmetrical high signal lesions in the brainstem in the floor of the fourth ventricle at the level of the obex and in the medulla and upper cervical cord (fig 1). The remainder of the brain was spared and in particular there were no lesions suggestive of central pontine myelinolysis or alcoholic damage. CF examination was unremarkable except for a marginally increased protein at 0.48 g/l. CSF and
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.

Our patient had the mutation most often associated with MS-like CNS lesions and visual loss in women. 1 Brain stem lesions have been previously described in a patient with visual loss, complete ophthalmoplegia, and bilateral tinnitus. 2 However, to our knowledge, this is the first description of LHON in association with brain stem lesions presenting with respiratory arrest and loss of involuntary ventilation (Ondine’s curse). The high signal lesions in the pons and medulla involved the nucleus ambiguus and nucleus of the solitary tract, which are part of the ventral and dorsal respiratory groups respectively, and would seem well placed to account for loss of respiratory control during sleep with well preserved capacity for volitional respiratory manoeuvres while awake. Ondine’s curse produced by lesions of these structures and their tracts through a variety of causes has been well described. 3,4 However, the exact nature of CNS lesions in patients with mitochondrial cytopathy remains obscure.

Our patient tolerated NIPPV. She improved on this regimen such that 123 days after admission she was able to take a 45 minute daytime nap and maintain an oxygen saturation of >97% throughout, while breathing room air unassisted. Eight months after her respiratory arrest, she was able to take a few steps with a Zimmer frame and had successfully weaned off NIPPV support. This patient provides a further example of the broad manifestations of mitochondrial disease.

Acknowledgement

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The Guillain–Barré Syndrome Support Group, a British patient organisation, posted 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. 5 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 these cases 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 unaided in five to six 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 reported 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% CL 0.8%, 22.8%) had reported a relapse of 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 these cases 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 unaided in five to six weeks, which increased his modified Rankin scale score from grade 2 to 4.

The 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 6 and occurrence of symptoms following subsequent immunisation 7 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, 8 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.

Table 1: Frequency of relapse of Guillain-Barré syndrome (GBS) and chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) following various immunisations

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>GBS Patients</th>
<th>GBS Relapses</th>
<th>CIDP Patients</th>
<th>CIDP Relapses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Influenza</td>
<td>211</td>
<td>8 (3.8%)</td>
<td>46</td>
<td>2 (4.3%)</td>
</tr>
<tr>
<td>Tetanus</td>
<td>105</td>
<td>6 (5.7%)</td>
<td>23</td>
<td>2 (8.7%)</td>
</tr>
<tr>
<td>Typhoid</td>
<td>50</td>
<td>3 (6.0%)</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td>Polio</td>
<td>9</td>
<td>4 (9.5%)</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>Hepatitis A</td>
<td>37</td>
<td>3 (8.1%)</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>20</td>
<td>1 (5.0%)</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Rabies</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Pneumococcus</td>
<td>15</td>
<td>0</td>
<td>6</td>
<td>(33.3%)</td>
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<tr>
<td>BCG</td>
<td>8</td>
<td>2 (25.0%)</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Yellow fever</td>
<td>12</td>
<td>2 (16.7%)</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Meningococcus</td>
<td>16</td>
<td>1 (6.2%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Cholera</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Rubella</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Diphtheria</td>
<td>5</td>
<td>2 (40.0%)</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Measles</td>
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<td>Smallpox</td>
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<td>Mumps</td>
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</table>

Some patients had received more than one vaccine.
symptoms after yellow fever, diphtheria, meningococcus, oral polio, BCG, 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 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% CI 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 symptoms were tetanus toxoid and influenza vaccine. The risk of relapse severe enough to alter the modified Rankin scale score was 0.3% (95% CI 0.01%, 1.78%) while the risk of a relapse requiring treatment or hospitalisation is at most 1.18% (95% CI).

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%, 95% CI 2.5%, 17.0%) of 68 patients noted a return of symptoms following immunisation. The reports of minor symptoms or acceleration of deterioration following influenza and pneumococcus vaccines merit caution in recommending 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% CI 1.7%, 28.0%) in our patient sample. In view of these figures and previous reports of relapse of CIDP following tetanus toxoid17 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 own classification and relapse. 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.

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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 con
c fusional 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 de
velopmental milestones were normal. In the past medical history there was no sign of any metabolic disorder and 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 during episodes of loss of contact without any other manifesta
tions, 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 4 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 symp
oms 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 ob
servation was still ongoing, the patient developed a period of unconsciousness, which was preceded by prodromal symp
toms, including tachycardia, sweating, light headness, and irritability. On examination, there was reduction of alertness, confusion, and tachycardia. There were no signs of intermediate diameter and reactive to the light. No focal neurological signs were observed. EEG mon
itoring 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.

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 a 75 g glucose load, which also did not show evidence of pancreatic insulinaemia.

Comment

We have described a patient who experienced a severe episode of hypoglycaemia induced by intravenous phenytoin, which was adminis
trated at the doses recommended for the treatment of status epilepticus. It is known that phenytoin interferes with glucose metabolism.1 Indeed, it may inhibit the release of glucose stimulated insulin and induce a consequent hyperglycaemia. The ability of phenytoin to induce hyperglycaemia is controversial. One 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 inhibitory effects of phenytoin on insulin secretion or an increased sensitivity of the tissues to insulin. 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, we cannot rule out hypoglycaemia when a therapeutic dose of phenytoin was administrated is unclear, and further studies are needed to fully investigate the effects of phenytoin on carbohydrate metabolism.

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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>
</thead>
<tbody>
<tr>
<td></td>
<td>-2</td>
<td>-1</td>
</tr>
<tr>
<td>Present study</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PD (n=165)</td>
<td>0.009</td>
<td>0.158</td>
</tr>
<tr>
<td>Controls (n=155)</td>
<td>0.013</td>
<td>0.406</td>
</tr>
<tr>
<td>χ²=9.93, df=4, p=0.042, pc=0.21</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Izuimi et al</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PD (n=200)</td>
<td>0.004</td>
<td>0.002</td>
</tr>
<tr>
<td>Controls (n=250)</td>
<td>0.004</td>
<td>0.002</td>
</tr>
<tr>
<td>χ²=8.37, df=5, p=0.14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Combined</td>
<td></td>
<td></td>
</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>
</tr>
<tr>
<td>χ²=13.9, df=5, p=0.017, pc=0.099</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Nomenclature of the alleles according to Xia et al 1. Alles 1, 2, and 3 correspond to alleles 3, 2, and 1, respectively, of Krüger et al 4. pc (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). 1 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. 2 The previous Japanese study by Izuimi et al 3 found a tendency of a low expression of α-synuclein in late-onset PD patients than in controls. 2 To examine the trend of association, we performed a similar analysis in 165 PD patients and 155 healthy controls in Japan. The patients with sporadic PD (97 women and 68 men, mean (SD) age 64 (9.6) years, mean age at onset 56 (11) years) had been under treatment at the neurological clinic of Utano National Hospital. The control group was matched for age (mean 63.0 (8.6) years), sex ratio (97 women and 58 men), and birthplace (Kyoto and Osaka prefectures) with the PD patients. The controls were selected from the annual health examination at a city clinic. All participants were Japanese. The institutional ethics committees approved the study protocol and informed consent was obtained from each participant. The dinucleotide repeat polymorphism was analysed as reported. 4 We identified five polymerase chain reaction products with different lengths and termed them according to Xia et al 1 as follows: 257 bp, allele 0; 259 bp, allele 1, 261 bp, allele 2; and 263 bp, allele 3. Statistical analysis was performed by χ² test. The corrected p value (pc) was obtained by multiplying the p value by the number of alleles.

As table 1 shows, in our study allele 1 tended 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. 2 To increase the power of the Japanese PD control analysis, we combined our data with those of Izuimi 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 in PD in Japanese.

As reviewed by Farrer et al, 4 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 those in 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 those in white populations.

The relation between dinucleotide repeat polymorphism and the functional aspects of α synuclein remains unknown. Lee et al 5 recently reported that overexpression of α synuclein in human neuroblastoma cell line retards cell death induced by serum withdrawal or hydrogen peroxide. This suggests that the dose of α synuclein may influence neuronal viability. Thus, in Japanese, allele 1 may be associated with high expression or low degradation of α synuclein.

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

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