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 nuchal rigidity 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 and urine antineutrophil cytoplasmic and anticardiolipin 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 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 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 thrombocytaemia, 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 (papenychal CNS involve ment) or vasculo-Behçet disease (secondary or non-papenychal 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 symptoms 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.7

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.1 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 immuno- suppressive and intravenous immunoglobulin treatments improved the neurological deficits.

A white man who had an eight year history of Hodgkin’s disease (type mixed cellularity, pathological stage IVB) had been receiving a salvage ESHAP regimen (etoposide 160 mg/day, methylprednisolone 500 mg/day, and cisplatin 42.5 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, 39°C fever, recurrent night sweats, fatigue, malaise, and weakness. There was no history of infection. General examination was unremarkable except for bilateral inguinal adenopathy (1.5 cm × 1.5 cm). Haemoglobin concentration was 63 g/l, packed cell volume 17.8%, platelet count 89 × 10^9/l, white cell count 3.34 × 10^9/l (neutrophils 2.42 × 10^9/l), and lactate dehydrogenase 425.4 U/l. Results of the following investigations were normal: glucose, cholesterol, triglycerides, and ions; renal, liver, and thyroid function tests; vitamin B12 and folate 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.

Neuromyotonia is a syndrome characterised by the clinical triad of ophthalmoplegia, ataxia, and areflexia.1 Myasthenia gravis and anti-voltage-gated potassium channel antibodies (AChR) antibodies without thymoma. 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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Competing interests: none declared

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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, autoimmunemediated or paraneoplastic in origin. Myasthenia gravis and anti-voltage-gated potassium channel antibodies (VGKC) and anti-acetylcholine receptor (AChR) antibodies without thymoma is common.” Myasthenia gravis, thyrotoxicosis, systemic sclerosis, inflammatory demyelinat- ing neuropathies, thymoma, bronchial carcinomma, 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 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 for a chronic condition. 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

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and plantar responses were flexor. Upward gaze was noted. Horizontal diplopia and there was right hand grip weakness. Right nystagmus movements with his fingers. Tactile and patients had difficulty performing rapid alternating movements of fingers and toes were considered oculi muscles. Small amplitude, involuntary movements were noted in the small muscles of hands and feet and in the orbicularrays. 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 hypercholesterolemia. 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 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 anti-nuclear 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 nmol/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 rightsided 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, myasthenia gravis 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.

200 µV 200 ms

200 µV 50 ms

Figure 1 Myokymic discharges recorded at rest with a concentric needle electrode from the right dorsal interosseus muscle, shown at two different sweep speeds.
patients with progressive cerebellar ataxia and presence of organ specific autoantibodies GAD-Abs titre, intrathecal GAD-Ab synthesis, coarse nystagmus. Although she does not of brain stem involvement as hemiparesis of posterior pharyngeal wall and asymmetrixion. She underwent a five time course of double filtration plasmapheresis that filtered 15 litres of plasma. Immediately after completion of the plasmapheresis course, her GAD-Abs titre was normal, indicative of subclinical hypothyroidism associated with autoantibodies against thyroperoxidase 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 she was overtook by truncal ataxia within a month. She underwent a five time course of double filtration plasmapheresis that filtered 15 litres of plasma. Immediately after completion of the plasmapheresis course, her GAD-Abs titre decreased to 4700 U/ml, and left post-terial pharyngeal wall motion and independent gait returned. Ataxia, however, returned three weeks later and then progressed, accompanied by a gradual rise in GAD-Abs titre. A five day course of intravenous immunoglobulins 0.4 g/kg/day produced no improvement.

The overall clinical picture for this patient, subacute ataxia, is 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 signs of cerebellar ataxia, her GAD-Abs titre was normal, indicative of subclinical hypothyroidism associated with autoantibodies against a glutamate receptor in two patients with Hodgkin's disease. At present, however, follow up examinations 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.

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 rate of about 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 suggested that an inflammatory reaction is responsible for reperfusion damage leading to brain damage and tissue destruction after acute ischaemia and subarachnoid haemorrhage. In this study, we investigated whether ventricular cerebrospinal fluid (CSF) and serum concentrations of adhesion molecules can be used as prognostic markers for the clinical outcome in path with ICH. For this purpose, we studied prospectively 10 patients with acute ICH and ventricular tamponade. Estimated blood volume of the ICH was between 40 and 60 ml in all patients. Initial intubation and mechanical ventilation due to coma were required in all patients. All of them were being treated at the neurological intensive care unit after neurological application of a ventricular drainage to treat acute hydrocephalus. Paired serum and CSF samples from the ventricular drainage were obtained within eight hours after the first 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 33.7 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 18.5 ng/ml (25.9 (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

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 patients who had intracerebral haemorrhage with ventricular tamponade. 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.
Acknowledgements

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References


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.1

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 3/15. She was hypoxaemic, 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 after 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. There was a 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 wasted limbs consistent with prolonged illness. She could just perceive bilaterally and both optic discs looked pale and the pupils were mid-dilated and unreactive. She had a divergent gaze in the primary position with coarse gaze evoked nystagmus in all directions. 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 supine relaxed, Reflexes were brisk throughout and plantar responses were extensor. There was a subjective sensory abnorality to light touch to the mid-thighs and joint position sense was severely impaired in the four limbs, with no two fingers. Breath sounds were quiet and chest excursions limited. She had a distended abdomen with a four finger breadthead 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, Po, 16.4 kPa, Pco, 5.2 kPa, HCO3 27.4 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. CSF 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 intensities of the pons and medulla involved the nucleus ambiguous 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 occurs through a variety of causes has been well described.3 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
We thank Dr M Hebden for permission to report a patient under his care.

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

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<th>GBS Patients</th>
<th>Relapses</th>
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Some patients had received more than one vaccine.

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

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.7 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 for 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 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 a recurrence of symptoms within 24 hours of immunisation and all but one 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 infection. 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

References

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. 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 for 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 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 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 score increased from 1 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 infection. 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% 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 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 after immunisation. The risk of relapse severe enough to alter the modified Rankin scale score. The risk of relapse is high enough to alter the modified Rankin scale score. Therefore, after 30 minutes, intravenous phenytoin 1000 mg was given by slow infusion. There was a reduction of alertness, confusion, and tachycardia. Pupils were intermediate to light on reflex testing. There was loss of contact without any other abnormalities. The authors suggested that the hypoglycaemia induced by an abdominal CT scan, 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 interfere with the hypoglycaemia. The ability of phenytoin to reduce carboxylic acidosis and insulin resistance has been suggested to be related to the blockage of the calcium channel. The authors suggested that the hypoglycaemic effect might be attributable either to 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 hypoglycaemia. In particular, a possible effect on glycaemia produced by status epilepticus.

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 confusion of 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 is uncomplicated and no psychomotor developmental milestones were normal. In the past medical history there was no sign of any metabolic disease. No report of a 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 discharges localised over both fronto-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 fronto-central regions with right predominance. Emergency drug treatment to control the seizure was made. 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 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 confusion, which was preceded by prodromal symptoms, including tachycardia, sweating, light headedness, and irritability. On examination, there was reduction of alertness, confusion, and tachycardia. There was no intermediate to light on reflex testing. The 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 a 75 g oral glucose tolerance test, which did not show evidence of pancreatic insufficiency.

References

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 in Japan. 

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 neurologological 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. We identified five polymerase chain reaction products with different lengths and termed them according to Xia et al.2 as follows: 253 bp, allele –2; 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. 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 Parkinson’s disease patients.

As reviewed by Farrer et al.,5 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 range from 22–32%, 58–72%, and 3–9%, respectively, in white studies.4 The relation between dinucleotide repeat polymorphism and the functional aspects of α-synuclein remains unknown. Lee et al.4 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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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>
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<tbody>
<tr>
<td></td>
<td>–2</td>
<td>–1</td>
</tr>
<tr>
<td>Present study</td>
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<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>χ²=9.93, df=4, p=0.042, pc=0.21</td>
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<tr>
<td>Izumi et al.6</td>
<td></td>
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<tr>
<td>PD (n=200)</td>
<td>0.004</td>
<td>0.002</td>
</tr>
<tr>
<td>Controls (n=250)</td>
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<td>0.001</td>
</tr>
<tr>
<td>χ²=8.37, df=5, p=0.14</td>
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<tr>
<td>Combined</td>
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<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>
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Acute attacks and brain stem signs in a patient with glutamic acid decarboxylase autoantibodies

S Matsumoto, T Kusuhara, M Nakajima, S Ouma, M Takahashi and T Yamada

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