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. 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 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 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 normal. Cranial magnetic resonance imaging showed diffuse cerebral atrophy and typical cranial MRI findings of the epididymitis. 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.

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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 thrombocythaemia, giant cell arteritis, and BD are among the very rare causes.1 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 urological 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 (pachymeningeal CNS involvement) or vasculo-Behçet disease (secondary or non-pachymeningeal 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 as in our patient is not infrequent in patients with bilateral ICA occlusion. This is explained by the adequate collateral flow provided by verteobasilar 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 characterized by the clinical triad of ophthalmoplegia, ataxia and areflexia. It is often regarded as a variant of Hodgkin's disease. The syndrome is rare and occurs in association with lymphoma.

Case Presentation:
A 27-year-old white man was admitted to the hospital with a one-year history of Hodgkin's disease (mixed cellularity, pathological stage IVB) and a relapse of Hodgkin's disease. He was treated with chemotherapy, including ESHAP regimen (etoposide, cisplatin, dexamethasone, and cytarabine). His cerebrospinal fluid protein was increased, and his muscle strength was normal. He had a history of deep tendon reflexes and were not impaired. His muscle power was normal, but his muscle tone was slightly decreased. His muscle atrophy was observed in the upper and lower extremities.

Neurological Examination:
On admission, the patient had a mild dysphonia, mild dysphagia, and peripheral seventh nerve palsy. His muscle power was normal, but his muscle tone was slightly decreased. His muscle atrophy was observed in the upper and lower extremities. His brainstem auditory evoked potentials were normal. His magnetic resonance imaging showed no abnormalities in the brain. There was no history of infection. General physical examination was unremarkable except for a 39°C fever, recurrent night sweats, fatigue, malaise, and weakness.

Investigations:
Serum and cerebrospinal fluid samples were obtained. Serum tests for Epstein-Barr virus, herpes simplex virus, and varicella-zoster virus were negative. The patient's pupillary response to a 0.05% solution of pilocarpine showed increased sensitivity (IgG: 19 g/l, normal 10.51 ± 2.9), IgA: 4.8 g/l, normal 1.65 ± 0.8). A gadolinium-enhanced T1-weighted magnetic resonance imaging of the head showed no abnormalities. There was no evidence of partial immunosuppression, and the presence of IgG anti-GQ1b is possible pathogenic mechanisms.

References:

Neuromyotonia and myasthenia gravis without thymoma

Neuromyotonia and myasthenia gravis are syndromes characterized 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.

Myasthenia gravis, thyrotoxicosis, 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 autoimmune delayed cutaneous hypersensitivity. 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.
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 ophthalmaline migraine, 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, involuntarily 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. Improvement was rapid and after a few weeks treatment was stopped. Two weeks before presenting to us, he developed ptosis of the right upper eyelid, 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 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 in-traburst 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 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 interosseus muscle, shown at two different sweep speeds.
normal IgG index of 0.45. Her condition remained unchanged for six months, after which gait unsteadiness progressed gradually for one month. Thereafter, she had difficulty in speaking and swallowing on waking in the morning. In addition to the signs seen at the first examination, a neurological examination showed ataxic dysarthria and limb ataxia on both sides. She became dependent on walking aids. The muscular tone of her limbs was decreased, but the strength was normal. Tendon reflexes were normal, and plantar responses flexor on both sides. There was neither sensory nor bladder disturbance. Repeat CSF analysis and brain MRI results were normal, as were the electrolyte and serum creatinine levels. Maglevence was also normal.

Routine haematological and blood chemistry studies, as well as the serum levels of vitamin B1, B12, and E, were normal. Facial and general blood chemistry was negative. Infection by neurotropic viruses was excluded serologically. Polymerase chain reaction analysis of the CSF for herpes simplex virus type 1 and 2 was negative. Immunohistochemical search for gynaecological, breast, or lung cancer, as well as haematological malignancies, including body cell computed tomography, bilateral mammography, and bone and joint 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 persisted. 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 9800 U/ml. Serum thyroid-stimulating hormone was slightly increased, but thyroid hormone levels were normal, indicative of subclinical hypothyroidism associated with autoimmune thyroiditis, hyperprolactinemia, and thyroglobulin. Low titre positivities were found for antinuclear, anti-double stranded DNA, anti-patellar cells, and anti-insulin antibodies. CSF GAD-Abs titre was 496 U/ml. Intrathalcal GAD-Abs synthesis, calculated by Schüller’s formula, gave a ratio of 10.7 for intrathalcal GAD-Abs specific activity (ASA)/serum ASA, consistent with positive intrathalcal 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 completion of the plasmapheresis course, her GAD-Abs titre decreased to 4700 U/ml, and left posterior 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 immunoglobulin 0.4 g/kg/day produced no improvement.

The overall clinical picture for this patient, subacute ataxia, is comprised 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 nystagmus, the high titre of GAD-Abs titre, intrathalcal GAD-Abs 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 mechanism, however, does not explain our patient’s paralysis of the pharyngeal constrictor muscles because motoneurons in the nucleus ambiguous receive GABA mediated inhibition. As speculated by Honnorat et al., 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 in our patient raises the possibility that the GAD-Abs might have been a paraneoplastic phenomenon. Sillevis Smitt et al. reported reversable cerebellar ataxia attributable to autoantibodies against a glutamate receptor in two patients with Hodgkin’s disease. At present, however, follow up examination of these patients 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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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 lethal outcome 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 and have type I diabetes mellitus, the high serum GAD-Abs titre. A five day course of intrathecal GAD-Ab synthesis, calculated by Schüller’s formula, was slightly increased, but thyroid hormone levels were normal, indicative of subclinical hypothyroidism associated with autoimmune thyroiditis, hyperprolactinemia, and thyroglobulin. Low titre positivities were found for antinuclear, anti-double stranded DNA, anti-patellar cells, and anti-insulin antibodies. CSF GAD-Abs titre was 496 U/ml. Intrathalcal GAD-Ab synthesis, calculated by Schüller’s formula, gave a ratio of 10.7 for intrathalcal GAD-Abs specific activity (ASA)/serum ASA, consistent with positive intrathalcal synthesis.

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References

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 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 (survival 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 3.7 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 < 0.01). 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, 1422 (465) 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. Our CSF concentrations from patients with multiple sclerosis (s-ICAM-1: 2.8 ng/ml, range 0.9–12.7; sVCAM-1: 4.2 ng/ml, range 0–21.3) and from healthy donors (sICAM-1: 5.2 (2.2) ng/ml) as determined in our laboratory by identical test systems.4 5 The finding that the soluble adhesion molecules were increased in CSF but not in serum may indicate that the process leading to poor outcome occurs predominantly in the brain. There are two possible explanations for the origin of increased CSF concentrations of soluble adhesion molecules. Firstly, brain tissue destruction may lead primarily to the release of adhesion molecules due to necrotic destruction. Secondly, ICH may initiate an inflammatory process leading to secondary brain damage, as has been suggested in human ischaemic stroke,6 7 as well as for experimental ICH and subarachnoid haemorrhage in animal models.8 9 With regard to the second hypothesis, it would be interesting to investigate the effects of early anti-inflammatory treatment in patients with ICH and an initially high 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.10 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 inflamma- tory cells into the central nervous system,11 however, based on our results, it can be speculated that these cells are already inside the central nervous system and thus out of reach of these antibodies.

With these data of only 10 patients, it cannot finally be concluded whether the increased soluble adhesion molecules in CSF are indicators of the fatal process or are responsible for the initiation of secondary brain damage.

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.12 13

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 hypotensive, with a severe respiratory acidosis. Arterial blood gas (ABG) showed pH 7.04, Po2 40.9 kPa, Pco2 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 maternal family history of visual loss. She has 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 shied just perceptible 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 palsy on rightward and leftward deviation. 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 was limited. 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 toes, without sensory impairment of the 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, Po2 6.8 kPa, Pco2 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, Pao2 5.5 kPa, Pco2 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 oxygen showed pH 7.44, Pao2 16.4 kPa, Pco2 5.2 kPa, HCO3 37.7 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 right cerebellum 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 reference values were within normal limits. Bilateral tinnitus had been previously described in a patient with mitochondrial DNA mutation.

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 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 four 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, and four others were unable to walk unaided but could walk unaided with support. Eight months after her admission she was able to take an 45 minute walk unassisted. Eight months after her admission she was able to take a 45 minute walk unassisted.

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 (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 0.85%, 22.8%) had a relapse after immunisation. In three the symptoms worsened after a relapse after 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 grade 2 to 4 and they became dependent on a walking stick and unable to drive.

The patient 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 meningitis. 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 of relapse following immunisation with tetanus vaccine.
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 the modified Rankin scale score. 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 0.85%). 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 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 toxoid 17 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.

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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.

Once the patient recovered from the state of hypoglycaemia, hypoglycaemia was noticed. The patient was admitted because of hypoglycaemic unawareness. The patient was started on routine treatment of status epilepticus.

The patient was referred to the epilepsy department after 30 minutes, but there was no change in the patient’s clinical status. Therefore, after 30 minutes, intravenous phenytoin was administered is unclear, 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, any possible effect on glucose production by status epilepticus has been considered not relevant, because the status epilepticus was partial and resolved nine hours before the onset of hypoglycaemia. However, 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.

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 (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 lower frequency of allele 1 in Japanese PD patients than in controls. 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 birth place (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 dinucleotide repeat products with different lengths and termed them according to Xia et al. 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 in 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 (table 1), while the frequencies of alleles 0, 1, and 2 range from 22–32%, 58–72%, and 3–9%, respectively, in white studies.

The relation between dinucleotide repeat polymorphism and the functional aspects of α synuclein remains unknown. Lee et al. 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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