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 right 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 aphtous 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 antimyeloperoxidase antibodies, antineutrophil cytoplasmic antibodies and antikeratin 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, prednisoln 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 of the cranial vessels showing the obstruction of (A) right and (B) left internal carotid arteries on lateral view.

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 venous-Behçet disease (secondary or non-parenchymal CNS involvement) or both. 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. 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. 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 deficits 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.

Occlusive 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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Miller-Fisher syndrome and Hodgkin’s disease

Miller-Fisher syndrome (MFS) is a rare clinical entity classically regarded as a variant of Guillain-Barré syndrome (GBS) and characterised by the clinical triad of ophthalmoplegia, ataxia and areflexia. In MFS, paralysis is restricted to extraocular and occasionally other cranial or bulbar muscles. We report on a patient with a relapsing Hodgkin’s disease who developed MFS. Conventional immunosuppressive and intravenous immunoglobulin treatments improved the neurological deficits. The patient was a white man who had an eight-year history of Hodgkin’s disease (type mixed cellularity, pathological stage IV) who had been receiving a salvage ESHAP regimen (etoposide 160 mg/m²/day, methylprednisolone 500 mg/day, and cisplatin 42.5 mg/ day for four days and cytarabine and methotrexate 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, night sweats, fatigue, malaise, and weakness. There was no history of infection. General examination was unremarkable except for a left-sided ptosis with a total bilateral external ophthalmoplegia (15%). Abnormal lymphocyte 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 384 U/l. The 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.

Stage IV Hodgkin’s disease was considered. Before starting a cycle of ESHAP chemotherapy, the patient complained of bilateral hand edema, diplopia, photophobia, dysphonia, and gait instability. Neurological function was assessed at that time, eight days after admission. Examination of the cranial nerves found a left sided ptosis with a total bilateral external ophthalmoplegia and fixed dilated pupils. The patient’s pupillary response to a 0.05% solution of pilocarpine showed increased sensitivity consistent with a postganglionic parasympathetic lesion. (Oculomotor nerves are among the few myelinated fibres of the postganglionic nervous system and this patient likely had dysfunction in these fibres similar to that observed in the other peripheral nerves. These abnormalities are encountered in about half of patients with MFS.) There was dysphonia, mild dysphagia, and peripheral seventh nerve palsy. Examination of the peripheral nervous system showed loss of sensation and reflexes. His muscle strength was normal, and pinprick, touch, position, and vibratory sensation were not impaired. There was obvious ataxia in all four limbs. He could walk with assistance and tandem gait was impossible. His cerebrospinal fluid protein concentration was 0.79 g/l with 2 lymphocytes/mm³. Cerebrospinal fluid culture and cytological studies showed normal lymphocytes. Subsequent investigations found increased IgG ganglioside antibodies to GQ1b glycolipid (titre of 4900). Standard delayed hypersensitive skin tests were performed to purified protein derivative of tuberculin (intermediate strength), Candida albicans, mumps, trichophyton, and streptokinase/streptodornase, showing failure to elicit a response to any skin test antigens. Serum immunoglobulin concentrations were increased (IgG: 19 g/l, normal 10.5 ± 2.9; IgA: 4.8 g/l, normal 1.6 ± 0.8). Gadolinium enhanced magnetic resonance imaging of the head showed no abnormalities. There was neurophysiological evidence of an axonal sensory neuropathy (sensory conduction in the right sural and median nerves was absent; if median motor compound muscle action potential was 7.1 mV with a conduction velocity of 41.5 m/s). F wave latencies from the right posterior tibial, right common peroneal, right median, and ulnar nerves were minimally prolonged two days after onset but were within normal limits by three months. The patient presented moderate reduction of facial muscle action potential amplitude to: right side 1.5 mV, left side 1.3 mV. Right latency: 3 ms, left latency: 3.2 ms. Blink reflex R1 latencies were mildly prolonged (right: 13.9 ms, left: 14.1 ms). Blink R2 response latencies were normal (right: 30 ms, left: 29 ms). Masseter reflex was normal. The amplitude of the distal sensory evoked response was greatly reduced (upper extremity somatosensory evoked potentials to median nerve stimulation at the wrist). Brainstem auditory evoked potentials were normal. Intravenous immunoglobulin was given for five days at a dosage of 0.4 g/kg/day, starting 24 hours after the onset of neurological symptoms. He gradually improved over the next two weeks. A follow up examination by the time of discharge four weeks after the onset found nearly complete clinical recovery from the ataxia and occasional diplopia but the tendon reflexes were still hyporeactive. Three months later, neurological examination and lumbar puncture results were normal, all electrophysiological parameters were normalised, and IgG antibody titres to GQ1b were not detectable.

In Hodgkin’s disease, the incidence of polyneuropathy is about the same as for the reticuloses in general—that is, approximately 1 or 2%. The major clinical picture of this patient was acute ataxia, ophthalmoplegia, and areflexia associated with increased cerebrospinal fluid protein and high titres of antineuronal antibodies. The autoimmune antibodies in the context of relapsing Hodgkin’s disease, which suggests an autoimmune mediated neurological disorder. To our knowledge this is the first report on a patient with MFS evolving during a relapse of Hodgkin’s disease. GBS and MFS occur in relation with conditions marked by autoimmune or para-neoplastic origin of the disease. Therefore, the patient sought a second opinion. Viewed this way, not only are MFS and GBS associated. Here, we report a patient with MFS evolving during a relapse of Hodgkin’s disease, who 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 voluntary admission 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 myasthenia gravis of nine years duration.

Nerve conduction studies showed evidence of a severe right-sided carpal tunnel syndrome, but otherwise they were normal. Needle electromyography revealed myokymic discharges in distal muscles of upper and lower extremities (fig 1). These discharges consisted of bursts of motor unit potentials, appearing as doublets, triplets, or multiplets with 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, and 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.

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

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

A 63-year-old woman suffered dizziness of sudden onset accompanied by nausea and vomiting. Her physician found horizontal 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 of the posterior pharyngeal wall (signe de rideau, Verney). She had ataxia in her left arm and leg and walked throwing the left leg outward. Although lesion in the left dorsal column and 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
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 presentation, a neurological examination showed ataxia 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, with negative anti-thyroglobulin and anti-tissue transglutaminase antibodies. Routine haematological and blood chemistry studies, as well as the serum levels of vita-mins B1, B12, and E, were normal. Faecal occult blood was negative. Infection by neurotrophic viruses was excluded serologically. Polymerase chain reaction analysis of the CSF for herpes simplex virus types 1 and 2 was negative. The search for gynaecological, breast, or lung cancer, as well as haematological malignancies, including whole body computed tomography, bilateral mammography, and bone and brain 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-Ab titre level determined by radioimmunoassay was highly increased at 10 400 U/ml (normal <1.5 U/ml). Evaluation of GAD-Ab from plasma frozen at her first presentation showed a titre of 9830 U/ml. Subsequently, a frequent periodic stimulating hormone was slightly increased, but thyroid hormone levels were normal, and indications of subclinical hypothyroidism were associated with 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-Ab 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 completion of the plasmapheresis course, her GAD-Ab titre decreased to 4700 U/ml, and left posterior pharyngeal wall motion and asymmetry of the posterior pharyngeal wall and asymmetric coarse nystagmus. Although she does not have diabetes mellitus, the high serum level of GAD-Ab 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-Ab 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 ambiguus receive GABA mediated inhibition. As speculated by Honnorat et al., high GAD-Ab titre would merely reflect the presence of a more complex immune reaction against the nervous system. In this context, the subacute and atypical ataxia with high GAD-Ab titre would arise in the presence of a gluten related receptor in two patients with Hodgkin's disease. At present, however, follow up examination of this patient showed no evidence for malignancy. The case of our patient suggests that progressive ataxia with high GAD-Ab 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 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 ischaemic 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 patients 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 sCAM-1 were below 13.7 ng/ml (mean (SD) 8.7 (4.7) ng/ml) and of sVCAM-1 below 35.4 ng/ml (11.5 (13.1) ng/ml) in the group of patients who survived (n = 6). However, in patients with a lethal outcome (n = 4), initial ventricular CSF concentrations of sCAM-1 were above 18.5 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 sCAM-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 two groups of 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.
The finding that the soluble adhesion molecules in the CSF of patients with ICH with ventricular tamponade. 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 healthy donors (sICAM-1: 2.8 ng/ml, range 0.9–12.7; sVCAM-1: 4.2 ng/ml, range 0–21.5) and from patients with acute ICH and ventricular drainage. Additionally, we measured increased sICAM-1, 1147 (382) ng/ml for sVCAM-1, 1422 (465) ng/ml (p < 0.01). However, the concentrations of adhesion molecules in serum did not differ significantly (non-surviving: 444 (132) ng/ml for sICAM-1, 1422 (465) ng/ml for sVCAM-1; surviving: 463 (110) ng/ml for sICAM-1, 1147 (382) ng/ml for sVCAM-1).

This is the first study to investigate soluble adhesion molecules in CSF and serum in patients with ICH with ventricular tamponade. We found a strong correlation between clinical outcome and the concentrations of soluble adhesion molecules in the CSF of patients with acute ICH and ventricular drainage. Moreover, we found more than threefold increases of sICAM-1 and of sVCAM-1 in the CSF of patients with lethal outcome as compared with CSF of healthy donors (sICAM-1: 2.8 ng/ml, range 0.9–12.7; sVCAM-1: 4.2 ng/ml, range 0–21.5) and from patients with acute ICH and ventricular drainage. Additionally, we measured increased sICAM-1, 1147 (382) ng/ml for sVCAM-1, 1422 (465) ng/ml (p < 0.01). However, the concentrations of adhesion molecules in serum did not differ significantly (non-surviving: 444 (132) ng/ml for sICAM-1, 1422 (465) ng/ml for sVCAM-1; surviving: 463 (110) ng/ml for sICAM-1, 1147 (382) ng/ml for sVCAM-1).
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 discrepancy while awake. Ondine's curse provided a further example of the broad manifestations of mitochondrial disease. Brain stem lesions have been previously described in a patient with MS-like CNS lesions and visual loss in women. Brain stem lesions have been previously described in a patient with MS-like CNS lesions and visual loss in women. Brain stem lesions have been previously described in a patient with MS-like CNS lesions and visual loss in women. Brain stem lesions have been previously described in a patient with MS-like CNS lesions and visual loss in women.

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 1141 patients (37.1%) completed the questionnaires, of whom 927 had had GBS, 179 had CIDP, and eight were excluded because they had other diseases. Of the 927 patients with GBS, 311 had received immunisations since having GBS. Eleven (3.5%, 95% confidence limits (CL) 1.8%, 6.2%) reported symptoms including increased fatigue, weakness, numbness, and paraesthesiae, but these were usually mild and no patient required hospitalisation or treatment. In the case of symptoms came on within 24 hours of immunisation and all but one developed symptoms within one week of immunisation. One patient reported symptoms rendering him unable to walk unaided for four weeks, which increased his modified Rankin scale score from grade 2 to 4.

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

Of the 311 patients with GBS who had received vaccines after having GBS, 29 had also received a vaccine in the six weeks before the onset of their initial illness. Two of these patients (6.9%, 95% CL 0.85%, 22.8%) had a relapse after immunisation. In three the symptoms occurred within one week of immunisation and all but one developed symptoms within one week of immunisation. 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 4 to 5 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 pneumococcus vaccine. Two of 63 (33%) patients, including the last mentioned, experienced relapses after pneumococcus vaccine. Fourteen patients with CIDP had no symptoms of relapse following immunisation with typhoid vaccine. Between one and seven patients with CIDP had no

| Table 1: Frequency of relapse of Guillain-Barré syndrome (GBS) and chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) following various immunisations |
|-----------------|----------|-----------|-----------------|----------|-----------|
| Vaccine         | GBS      | Relapses  | CIDP            | Relapses |
| Influenza       | 211      | 8 (3.8%)  | 46              | 2 (4.3%) |
| Tetanus         | 105      | 6 (5.7%)  | 23              | 2 (8.7%) |
| Typhoid         | 50       | 3 (6.0%)  | 14              | 0        |
| Polio           | 42       | 4 (9.5%)  | 7               | 0        |
| Hepatitis A     | 37       | 3 (8.1%)  | 7               | 0        |
| Hepatitis B     | 20       | 1 (5.0%)  | 2               | 0        |
| Rabies          | 1        | 0         | 0               | 0        |
| Pneumococcus    | 15       | 0         | 6               | 3 (33.3%)|
| BCG             | 8        | 2 (25.0%) | 4               | 0        |
| Yellow fever    | 12       | 2 (16.7%) | 2               | 0        |
| Meningococcus   | 16       | 1 (6.2%)  | 2               | 0        |
| Cholera         | 5        | 0         | 0               | 0        |
| Rubella         | 5        | 0         | 0               | 0        |
| Diphtheria      | 5        | 2 (40.0%) | 1               | 0        |
| Measles         | 2        | 0         | 0               | 0        |
| Smallpox        | 2        | 0         | 0               | 0        |
| Mumps           | 1        | 0         | 0               | 0        |

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

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

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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 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 their modified Rankin scale score. The risk of relapse severe enough to alter the modified Rankin scale score is 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%) of 21 (2.7%, 10.7%) 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 toxoid 12 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 relaxation. 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 from 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. Full term birth was uncomplicated and first psychomotor developmental milestones were normal. In the past medical history there was no sign of any metabolic disease. There were 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: general tonic seizures, which occurred a few episodes of loss of consciousness 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 activity 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 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 diffuse and fluctuating consciousness, which was preceded by prodromal symptoms, including tachycardia, sweating, light headache and irritability. On examination, there was reduction of alertness, confusion, and tachycardia with a heart rate of intermedial size, diameter and reactive to the light. No focal neurological signs were observed. EEG monitoring did not show any abnormalities. Emergency blood tests revealed severe hypoglycaemia (<20 mg/dl). Prompt correction of the hypoglycaemia was obtained by the intravenous infusion of 50 ml of 50% glucose, and a consequent recovery of consciousness occurred. Phenytoin infusion was then withdrawn and oxcarbazepine was titrated.

In the following days no further episodes of hypoglycaemia were noticed. The patient was therefore investigated with the oral glucose tolerance test, which showed normal levels of plasma glucose, immunoreactive insulin, and immunoreactive insulin/plasma glucose, and with subdermal C peptide, which 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 administered at the doses recommended for the treatment of status epilepticus. It is known that phenytoin interferes with carbohydrate metabolism. Indeed, it may inhibit the release of glucose stimulated insulin and induce a consequent hyperglycaemia. The ability of phenytoin to reduce insulin secretion or an increased sensitivity of tissues to insulin is unknown. The striking finding of our case is that the hypoglycaemia is induced by a therapeutic dose of phenytoin, and, to our knowledge, this is the first case of severe hypoglycaemia during treatment with phenytoin for status epilepticus. In this case, we have indeed excluded a different aetiology of the hypoglycaemia. In particular, a possible effect on glycaemia produced by status epilepticus has been considered not relevant, because the status epilepticus was partial and resolved nine hours before the onset of hypoglycaemia. However, what caused hypoglycaemia when a therapeutic dose of phenytoin was administrated is unclear, and further studies are needed to fully investigate the effects of phenytoin on carbohydrate metabolism.

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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. The α-synuclein/NACP gene found in three independent Japanese studies (table 1), while the frequencies of alleles 0, 1, 2, and 3 correspond to alleles 3, 2, and 1, respectively, of Krüger et al. pc = 0.21 for allele distribution and χ² = 11.4, pc = 0.00073. These results suggest a negative association of allele 1 with PD in Japanese patients. We identified five polymerase chain reaction 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 with PD in Japanese patients with sporadic Parkinson’s disease (PD) and controls in Japan.

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>0.518</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>Izumi et al.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PD (n=200)</td>
<td>0.004</td>
<td>0.003</td>
</tr>
<tr>
<td>Controls (n=250)</td>
<td>0.002</td>
<td>0.002</td>
</tr>
<tr>
<td>χ²=8.37, df=5, p=0.14</td>
<td></td>
<td></td>
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<tr>
<td>Combined</td>
<td></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>
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<tr>
<td>χ²=13.9, df=5, p=0.017, pc=0.099</td>
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</tbody>
</table>

* Nomenclature of the alleles according to Xia et al. Alleles 1, 2, and 3 correspond to alleles 3, 2, and 1, respectively, of Krüger et al. pc (corrected p value) was obtained by multiply the p value by the number of alleles. CI, confidence interval; OR, odds ratio.

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