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 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 antibodies against neutrophil cytoplasmic and anti-cardiolipin antibodies were negative. ECG, 2D echo, chest radiograph, abdominal ultrasonography, and colour Doppler ultrasoundography of the lower extremity vessels were normal. Cranial magnetic resonance imaging showed diffuse cerebral atrophy and chronic ischaemic lesions in both cerebral hemispheres as well as the absence of the flow voids in both ICAs on T2 weighted axial images. Digital subtraction angiography (DSA) showed complete occlusion of the bilateral internal carotid arteries just rostral to the bifurcation (fig 1).

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

Comment

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

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.

Neurological involvement in BD has been reported to occur in 2.2% to 43% of cases in large series, either in the form of neuro-Behçet disease (parenchymal CNS involvement) or vascular-Behçet disease (secondary or non-parenchymal CNS involvement) or both. 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 vascular-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.

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 vascular-neuro-Behçet’s disease. We also conclude that BD should always be remembered as an aetiologic factor for bilateral ICA occlusions, especially in countries where the disease is highly prevalent.

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References
Miller-Fisher syndrome and Hodgkin’s disease

Miller-Fisher syndrome (MFS) is a rare clinical entity classically regarded as a variant of Guillain-Barré syndrome (GBS) and 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 (type mixed cellularity, pathological stage IVB) who developed MFS. Conventional immunosuppressive and intravenous immunoglobulin treatments improved the neurological deficits. This 27 year old 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, night sweats, recurrent fever and areflexia. There was obvious ataxia in all four limbs. He could walk with assistance and tandem gait was normal, and pinprick, touch, position, and vibratory sensations were impaired. He also complained of bilateral dysphonia, mild dysphagia, and difficulty in swallowing liquids. Three months later, neurological examination was unremarkable except for the asymmetric increase in dexterity of all fingers. He had difficulty with buttoning and tying. No other cranial or bulbar muscles were involved. We report on a patient with MFS evolving during a relapse of 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. Neuromyotonia without an inflammatory or paraneoplastic origin is uncommon.1 Myasthenia gravis, thyrotoxicosis, systemic sclerosis, inflammatory demyelinating neuropathies, thyromegaly, bronchial carcinoma, and small cell lung cancer may be associated. Here, we report a patient with neuromyotonia, associated with myasthenia gravis and anti-voltage-gated potassium channel (VGKC) and anti-acetylcholine receptor (AChR) antibodies without thymoma.

A 58 year old man of Portuguese descent presented at our neuromuscular clinic with dysesthesia and hypotension in the first three fingers of the right hand. Symptoms had started nine years before and had been attributed to cervical radiculopathy. Over the years, the symptoms had been fluctuating but for the past two months they had become debilitating. Therefore, the patient sought a second opinion. The patient volunteered that, although right hand pain was his main complaint, for many years his hands and feet were swollen and red. There was stiffness and loss of dexterity of all fingers. He had difficulty 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 ophthalmalmic 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, involuntary movements of fingers and toes were conspicuous at rest. The fingers were stiff and the patient had difficulty performing rapid alternation movements of fingers and toes were conscious at rest. The patient had thymoma in particular, is observed. 4

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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. Vnystagmus 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
patients with progressive cerebellar ataxia and presence of organ specific autoantibodies have type I diabetes mellitus, the high serum calcium and coarse nystagmus. Although she does not have posterior pharyngeal wall and asymmetry of brain stem involvement as hemiparesis of the pharyngeal constrictor muscles because motoneurons in the nucleus ambiguous 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 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 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 of 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 neurosurgical 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 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 18.5 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 sICAM-1 (p < 0.01) and of sVCAM-1 (p < 0.01), which are shown in fig 1.
Dr B Engelhardt is gratefully acknowledged for the initiation of secondary brain damage. The concentrations of adhesion molecules in serum did not differ significantly (non-surviving: 444 (152) ng/ml for sICAM-1, 1422 (465) ng/ml for sVCAM-1; surviving: 463 (110) ng/ml for sICAM-1, 1147 (382) ng/ml for sVCAM-1). This is the first study to investigate soluble adhesion molecules in CSF and serum in patients with ICH with ventricular tap. 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 ICH. Our data on 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 0.2–21.3) and from healthy donors (sICAM-1: 5.2 (2.2) ng/ml) as determined in our laboratory by identical test systems. 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 predominately 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 to increased 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, as well as for experimental ICH and subarachnoid haemorrhage in animal models. 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. The blockade of ICAM-1 and VCAM-1 by systemic treatment with monoclonal antibodies would probably not be helpful, as the pathogenetic concept is to block the migration of inflammatory cells into the central nervous system. 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 be 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
Dr B Engelhardt is gratefully acknowledged for critically discussing the manuscript.

Figure 1 Left: T2 weighted axial MRI through the medulla. Right: diagram showing relevant medullary components.
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. 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 (Onidne's curse). The high signal lesions in the pons and medulla involved the nucleus ambiguus and nucleus of the solitary tract, which are part of the ventral and dorsal respiratory groups respectively, and would seem well placed to account for loss of respiratory control during sleep with well preserved capacity for volitional respiratory manoeuvres while awake. Ondine's curse produced by lesions of these structures and their tracts through a variety of causes has been well described.1 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 Hehen for permission to report a patient under his care.

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References

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. 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 two 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 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 4 to 4 and they became dependent on a walking stick and unable to drive.

Of the patients with CIDP who experienced a relapse after immunisation, two relapses occurred among 23 patients who received the tetanus vaccine, giving a risk of relapse of 8.7%. Two of 46 (4.3%) patients with CIDP had relapses after influenza vaccine, of whom one had simultaneous pneumococcal vaccine. Two of six (33%) patients, including the last mentioned, experienced relapses after pneumococcal vaccine. Fourteen patients with CIDP had no symptoms of relapse following immunisation with typhoid vaccine. Between one and seven patients with CIDP had no

<table>
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<th>Vaccine</th>
<th>GBS Patients</th>
<th>GBS Relapses</th>
<th>CIDP Patients</th>
<th>CIDP Relapses</th>
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<td>46</td>
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<tr>
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<tr>
<td>Mumps</td>
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Some patients had received more than one vaccine.

Table 1 Frequency of relapse of Guillain-Barré syndrome (GBS) and chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) following various immunisations.
symptoms after yellow fever, diphtheria, meningococcus, oral polio, RCG, 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 least 1.18% (95% CI).

It is more difficult to draw conclusions about the risk of immunisation for relapse in CIDP because our sample size was smaller. Five (7.7%, 95% CI 2.7%, 17.0%) of 65 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, patients may wish to avoid routine toxoid 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 in GBS or in CIDP may be less than those discovered in this audit.

Acknowledgements

We thank Mr Roland Price and members of the GBS Support Group for facilitating this audit and Dr A V Swan for statistical advice.

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Competing interests: none declared

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References


Hypoglycaemia induced by phenytoin treatment for partial status epilepticus

A 22 year old woman was admitted at our epilepsy unit in status epilepticus. On examination, seizures were characterised by a focal convulsional 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 disorder and no reports of cognitive dysfunction or personality disturbances. At the age of 16, the patient presented with epilepsy, which was characterised by two types of seizures; global tonic seizures, which occurred at a frequency of 20 episodes of loss of contact without any other manifestations, which were rare. The patient was treated for many years with 20 mg of clobazam twice daily. The awake EEGs that were performed routinely during the years of treatment with clobazam showed normal background rhythm with rare epileptiform discharges, characterised by irregular 2–3 Hz spike and wave discharges and 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 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 clouding of consciousness, which was preceded by prodromal symptoms, including tachycardia, sweating, light headedness, and irritability. On examination, there was reduction of alertness, confusion, and tachycardia. There were no episodes of intermediate dia-meter 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 noted. 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 20 mg/dl. CTG which also failed to 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 hypoglycaemia to inhibit an insulin release has been suggested to be related to the blockage of Ca2+ uptake via voltage dependent Ca2+ channels. For this hyperglycaemic property, phenytoin has been often used in the treatment of hypoglycaemia induced by inoperable insulinomas.

Despite the well known hyperglycaemic effect of phenytoin, it has been reported that high doses of the drug can induce hyperglycaemia in particular, a recent case report described a case of hypoglycaemia secondary to an acute voluntary intoxication with 20 g of phenytoin. The authors suggested that the hyperglycaemic episode might be attributable either to the inability to escape from the inhibitory effects of phenytoin on insulin secretion or an increased sensitivity of the tissues to insulin. Indeed, 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 this 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 causes hypoglycaemia when a therapeutic dose of phenytoin was administered is unclear, and further studies are needed to fully investigate the effects of phenytoin on carbohydrate metabolism.

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References


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 synuclein as a component of the amyloid plaque. 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 polymerase chain reaction products with different lengths and termed them according to Xia et al. as follows: 253 bp, allele –2; 256 bp, allele 0; 259 bp, allele 1, 261 bp, allele 2; and 263 bp, allele 3. Statistical analysis was performed by Pearson 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 = 0.072 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.

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.

Acknowledgements

This work was supported in part by grants in aid from the Ministry of Health and Welfare of Japan (Health Science Research Grants, Research on Brain Science, and a grant in aid for Neurodegenerative Disorders).

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References

Neuromyotonia and myasthenia gravis without thymoma

V Van Parijs, P Y K Van den Bergh and A Vincent

*J Neurol Neurosurg Psychiatry* 2002 73: 344-345
doi: 10.1136/jnnp.73.3.344-a

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