An unusual case of Behçet’s disease presenting with bilateral internal carotid artery occlusion

Behçet’s disease (BD) is a multysystemic recurrent inflammatory disorder, which is originally described as a triad of oral and genital ulcerations with uveitis. As vasculitis of the vasa vasmorum is the main pathological hallmark of BD, it is generally seen in the form of superficial thrombophlebitis or occlusion of major veins; however arterial obstruction and aneurysms may also be seen to a lesser extent. 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 patchy 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 within the normal range. Serum anti-neutrophil cytoplasmic and anticanidiolipin antibodies were negative. ECG, 2D echo, chest radiograph, abdominal ultrasonography, and colour Doppler ultrasonography of the lower extremity vessels were normal. Cranial magnetic resonance imaging showed diffuse cerebral atrophy and chronic ischaemic lesions in both cerebral hemispheres as well as the absence of the flow void in both ICAs on T2 weighted axial images. Digital subtraction angiography (DSA) showed complete occlusion of the bilateral internal carotid arteries just rostral to the bifurcation (fig 1).

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

Comment

Our patient had presented with unusual neurological findings for a classic stroke syndrome. DSA and MRI showed bithemispheric 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 aetiologial factor in patients with bilateral ICA occlusion, whereas essential thrombocytocemia, 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 vasculo-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, 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. Our patient’s neurological signs and symptoms were highly suggestive of neuro-Behçet; however CSF findings with acellularity and normal protein level and neuro-imaging studies showing ischaemic lesions and bilateral ICA occlusions supported a very unusual type of vasculo-Behçet.

Diffuse cerebral atrophy and survival with minimal or no neurological symptoms in our patient is not infrequent in patients with bilateral ICA occlusion. This is explained by the adequate collateral flow provided by vertebrobasilar system and slow, gradual occlusion.

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 aetiologial factor for bilateral ICA occlusions, especially in countries where the disease is highly prevalent.

References

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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 is characterised by the clinical triad of ophthalmoplegia, ataxia and areflexia. In MFS, paralysis is restricted to extraocular and occasionally other cranial or peripheral 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 27-year-old white man who had an eight year history of Hodgkin's disease (type mixed cellularity, pathological stage IVB) who had been receiving a salvage ESHAP regimen (etoposide 1000 mg/m²/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 constitutively increased C-reactive protein, fever, recurrent night sweats, fatigue, malaise, and weakness.

There was no history of infection. General examination was unremarkable except for bilateral inguinal adenopathy (1.5 × 1.5 cm).

Haemoglobin concentration was 63 g/l, packed cell volume 17.8%, platelet count 89 × 10⁹/l, white cell count 3.34 × 10⁹/l (neutrophils 2.42 × 10⁹/l), and lactate dehydrogenase increased to 1952 l/m (normal 240–300 l/m). Neutropenia and hypogammaglobulinaemia were noted. The patient's past medical history was significant for ankylosing spondylitis, Crohn's disease, and GBS.

In view of the possibility of a relapse of MFS, the patient was admitted to the hospital for a relapse of MFS. Conventional immunosuppressive and intravenous immunoglobulin treatments improved the neurological deficits. Serum immunoglobulin concentrations were increased (IgG: 19 g/l, normal 10.51 ± 2.9 g; IgA: 4.8 g/l, normal 1.65 ± 0.8 g). 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; the 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 potentials (right: 1.39 mV, left: 1.42 mV). 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: 0.08 mV, right hand: 0.1 mV, right ankle: 0.1 mV). Bladder reactivity was normal. Cerebrospinal fluid protein and high titres of IgG anti-GQ1b supported the theory that partial immunosuppression may be involved in the pathogenesis of the syndromes. One must ask how an autoimmune, possibly cell mediated reaction can occur in an immunosuppressed patient. Animal models such as the NZB-BB mouse show that depression of cell mediated immunity from whatever cause may allow the development of an immune reaction, either humoral, cellular, or both, directed against peripheral nervous system antigens.

The development of MFS in the context of relapsing Hodgkin's disease, together with the improvement of this syndrome after tumour treatment and intravenous immunoglobulins, supports the theory that partial immunosuppression and the presence of IgG anti-GQ1b are possible pathogenic mechanisms.

J Neurol Neurosurg Psychiatry 2002;73:343–350

Competing interests: none declared

Correspondence to: E Rubio-Nazabal, Servicio de Neurología, Hospital Juan Canalejo, A Xubias sn, 15006 La Coruña, Spain; jnarey@telefonica.net

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 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 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 hyperesthesia 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 was thin, although right hand pain was his main complaint, for many years his hands and feet were swollen and red. There was stiffness and loss of dexterity of all fingers. He had difficulty writing, using scissors, and using a handheld

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and plantar responses were flexor. 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 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. Both AChR antibodies (26 nmol/ml, normal values less than 0.5 nmol/ml) and VGKC antibodies (1091 pmol/l (normal values less than 100 pmol/l)) were detected. Computed tomography of the chest was normal.

Nerve conduction studies showed evidence of a severe rightsided carpal tunnel syndrome, but otherwise they were normal. Needle electromyography revealed myokymic discharges in distal muscles of upper and lower extremities (fig 1). These discharges consisted of bursts of motor unit potentials, appearing as doublets, triplets, or multiplets with intraburst frequencies of 40 to 100 Hz. Burst recurrence was irregular with an interburst frequency of 5–8 Hz. There was evidence of mild chronic denervation with slightly reduced recruitment in distal muscles. Anti-VGKC antibodies are found in approximately 40% of patients with acquired neuromyotonia, they are also found in patients with other neuromuscular hyperexcitability syndromes, such as cramp fasciculation syndrome, acquired rippling muscle syndrome, facial myokymia. In a significant proportion of these patients, coexistence of myasthenia gravis and neoplastic disorders, thymoma 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 Rados, Verne). She had ataxia in her left arm and leg and walked throwing the left leg outward. Although lesion in the left dorsolateral lower brain stem was suspected, MRI and MRA arterial and venous images were unremarkable. A routine blood examination, as well as glucose tolerance and thyroid function tests, detected no abnormalities. CSF analysis was normal with negative oligoclonal IgG bands and a positive anti-GAD antibody (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.

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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, with normal cerebrospinal fluid (CSF) analysis and serum concentrations of adhesion molecules (sICAM-1 and sVCAM-1). 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 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 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). 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 (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 concentrations from patients with multiple sclerosis (+ICAM-1: 2.8 ng/ml, range 0.9–12.7; sVCAM-1: 4.2 ng/ml, range 0.2–21.5) and from healthy donors (+ICAM-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 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, 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 concentration of adhesion molecules in their ventricular CSF samples. In this condition, early application of corticosteroids may be useful to suppress the developing inflammatory reaction. 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 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 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.

### 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.

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 hypoxaemic, with a severe respiratory acidosis. Arterial blood gas (ABG) showed pH 7.04, Pco2 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 acute amblyopia was made. She had no family history of visual loss. She had three siblings in their 30s, and three children aged 9–12 years who were well.

On examination after transfer (two months after her first respiratory arrest), she was alert, oriented, and breathing room air spontaneously. She was unable to stand and had globally wasted limbs consistent with prolonged illness. She could just perceive light and could recognize 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 movements in all directions. A jaw jerk was present and she had a mild facial diplegia with intact sensation. She could speak and swallow adequately and was able to cough and hold her breath to command. She had a spastic quadriparepsis 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 was limited by her posture. Breath sounds were quiet and chest excursion limited. She had a distended abdomen, with a GCS of 8/15. Further ABG revealed pH 7.31, Pco2 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, Pco2 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 entrained oxygen showed pH 7.44, Pco2 16.4 kPa, Pco2 5.2 kPa, HCO3 27.4 mmol/l. She was subsequently transferred to a ward and treated with NIPPV on room air, at a pressure of 14 cm H2O overnight and during daytime naps.

An MRI scan of her brain showed symmetrical high signal lesions in the brainstem in the floor of the fourth ventricle at the level of the obex and in the medulla and upper cervical cord (fig 1). The remainder of the brain was spared and in particular there were no lesions suggestive of central pontine myelinolysis or alcoholic damage. CSF examination was unremarkable except for a marginally increased protein at 0.48 g/l. CSF and
plasma lactate were both 2.1 mmol/l and oligoclonal bands were not found. DNA was extracted from a blood sample and analysed for mtDNA mutations using standard procedures and was negative at positions 3243, 8344, 8993, 3460, and 14484, but with a homoplasmic mutation at position 11778.

We have previously described in a patient with mitochondrial optic neuropathy defined by the presence of a pathogenic mitochondrial DNA mutation. Brain 1992;115:979-99.

However, to our knowledge, this is the first description of LHON in association with brain stem lesions presenting with respiratory arrest and loss of involuntary ventilation (Ondine's curse). The high signal lesions in the pons and medulla involved the nucleus ambiguus and nucleus of the solitary tract, which are part of the ventral and dorsal respiratory groups respectively, and would seem well placed to account for loss of respiratory control during sleep with well documented respiratory groups respectively, and would seem well placed to account for loss of respiratory control during sleep with well documented.

However, the exact nature of CNS lesions in patients with mitochondrial cytopathy remains obscure.

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

Acknowledgement

We thank Dr M Hebden for permission to report a patient under his care.

M Sadler, C M Wiles
Department of Neurology, University Hospital of Wales, Cardiff, UK

N Stoolday
Department of Radiology, University Hospital of Wales

Table 1

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Some patients had received more than one vaccine.

S J Linnane, A P Smith
Department of Respiratory Medicine, Llandough Hospital, Llandough, UK
Correspondence to: Dr M Sadler, Department of Neurology, University Hospital of Wales, Heath Park, Cardiff CF4 4XN, UK msadler@spirochete.net

References


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 1 and occurrence of symptoms following subsequent immunisation 2 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, 3 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.

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. 4 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 intervals (CI) 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 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 within 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% CI 0.85%, 22.8%) had 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. Fourteen patients with CIDP had no symptoms of relapse following immunisation with typhoid vaccine. Between one and seven patients with CIDP had no
Hypoglycaemia induced by phenoxytin 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 developments 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: global tonic seizures, which occurred occasionally, and 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 complexes located on both fronto-central regions. Magnetic resonance imaging of the brain, which was performed at the age of 18 years, showed no abnormalities.

On the day of admission at the epilepsy unit, the patient had an urgent EEG that revealed continuous, rhythmic spikes or spike and wave complexes over both 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 profound consciousness which was preceded by prodromal symptoms, including tachycardia, sweating, light headiness, and irritability. On examination, there was reduction of alertness, confusion, and tachycardia. The CTC was of intermediate 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.

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 an oral glucose tolerance test, which did not show evidence of pancreatic insufficiency.

Comment

We have described a patient who experienced a severe episode of hypoglycaemia induced by intravenous phenoxytin, which was administered at the doses recommended for the treatment of status epilepticus. It is known that phenytoin interferes with carbohydrate metabolism.1 Indeed, it may inhibit the release of glucose stimulated insulin and induce a consequent hyperglycaemia. The ability of phenoxytin to induce severe hypoglycaemia was demonstrated by a the blockage of the transport 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.1

Beside the well known hyperglycaemic effect of phenoxytin, it has been reported that high doses of the drug can induce hypoglycaemia.1 In particular, a recent paper reported a case of hypoglycaemia secondary to an acute voluntary intoxication with 20 g of phenoxytin. The authors suggested that the hypoglycaemic episode might be attributable either to an escape from the inhibitory effects of phenoxytin on insulin secretion or an increased sensitivity of the tissues to insulin.2 The striking finding of our case is that the hypoglycaemia is induced by a therapeutic dose of phenoxytin, and, to our knowledge, this is the first case of severe hypoglycaemia during treatment with phenoxytin for status epilepticus. In this case we have indeed excluded a different aetiology of the hypoglycaemia. In particular, a possible effect on glycemia produced by status epilepticus,3 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 phenoxytin was administered is unclear, and further studies are needed to fully investigate the effects of phenoxytin 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 localization in amyloid plaques of Alzheimer’s disease. However, studies of Japanese have not identified five polymerase chain reaction products with different lengths and termed them as polymorphism of the α-synuclein gene found in three independent PD families. 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 birthplace (Kyoto and Osaka prefectures) with the PD patients. The controls were selected from each 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; 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 population.

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, 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 Neurogenetic Disorders).

I Mizuta, *M Nishimura, E Mizuta, S Yamasaki, **M Ohta, S Kuno
Clinical Research Centre, Utano National Hospital, Kyoto 616-8255, Japan
*Also the Department of Clinical Neuroscience, Tokushima University Hospital, Tokushima 770–8503, Japan
**Also the Department of Clinical Chemistry, Kobe Pharmaceutical University, Kobe 658–8585, Japan
Competing interests: none declared
Correspondence to: Dr S Kuno, Clinical Research Centre, Utano National Hospital, Kyoto 616-8255, Japan; yakuri@alles.or.jp

References

Table 1 Meta-analysis of α-synuclein/non-amyloid β component precursor allele and genotype distributions in patients with sporadic Parkinson’s disease (PD) and controls in Japan

<table>
<thead>
<tr>
<th>Study</th>
<th>Allele* frequency</th>
<th>Genotype frequency</th>
</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>0.02</td>
</tr>
<tr>
<td>χ²=8.37, df=5, p=0.14</td>
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<td></td>
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<tr>
<td>Combined</td>
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<tr>
<td>PD (n=365)</td>
<td>0.004</td>
<td>0.001</td>
</tr>
<tr>
<td>Controls (n=405)</td>
<td>0.007</td>
<td>0.001</td>
</tr>
<tr>
<td>χ²=13.9, df=5, p=0.017, pc=0.099</td>
<td></td>
<td></td>
</tr>
</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.
High concentrations of sVCAM-1 and sICAM-1 in the cerebrospinal fluid of patients with intracerebral haemorrhage are associated with poor outcome

J Kraus, P Oschmann, S Leis, B Neundörfer and J G Heckmann

*J Neurol Neurosurg Psychiatry* 2002 73: 346-347
doi: 10.1136/jnnp.73.3.346

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