“Sporadic” familial amyloidotic polyneuropathy in a German patient with B cell lymphocytic leukaemia

We report a 70-year-old German man presenting with a three-year history of progressive numbness and painful tingling and burning paresthesiae in his hands, feet, and lower legs, which had worsened during recent months. He also reported unsteadiness of gait, fatigue, night sweats, loss of appetite, and a weight loss of 12 kg within one year. He denied bowel or bladder problems and alcohol ingestion, but admitted smoking (110 pack-years). His family history was negative for neurological diseases.

The family was originally from Gdansk (now Northern Poland). The patient’s father and his four siblings all reached their 80s without developing neurological symptoms. The patient’s mother died at the age of 64 of blood cancer, and her half brother died at the age of 78. Three of the patient’s siblings died at the ages of 1, 17, and 33 (starvation, killed in the war, stomach cancer). Two further sisters, aged 64 and 69, their descendants, and the patient’s own five sons and their children were healthy. Both of the patient’s grandmothers died in their 80s, whereas the paternal grandfather died early of unknown cause, and the maternal grandfather drowned in his 30s.

Neurological examination revealed severe ataxia of gait and stance, atrophy of the small hand and foot muscles, and bilateral distal pareses (3–4/5 on the MRC scale), diminished tendon jerks, a glove and stocking distribution of hypoesthesia for all sensory qualities up to the mid-thighs and elbows, and severe trophic skin disturbances of the lower legs and hands with oedema and ulcers, suggestive of autonomic neuropathy. No orthostatic hypotension was observed.

Quantitative sensory testing showed markedly increased or undetectable thermal thresholds for heat and cold sensation in both hands and feet. Dynamic (brush) and static (von Frey hair) mechanical stimuli were not detected. Electrodiagnostic studies revealed absent sensory nerve potentials in the right sural nerve, absent compound muscle action potentials (CMAP) of the right tibial nerve, and markedly reduced CMAP, moderately slowed conduction velocity, and no F waves in the right median nerve. An ECG showed atrial fibrillation. On transthoracic echocardiography there was concentric hypertrophy of the left ventricle, dilatation (51 mm) of the left atrium, no stenoses of the cardiac valves, and normal left ventricular function. The patient had no history of hypertension. Abdominal and thoracic computed tomography detected no tumour mass or lymph node enlargement.

Isoelectric focusing of the serum showed oligoclonal bands identified as IgG λ and κ on immunofixation. In the urine, no Bence-Jones proteinuria was detected, and creatinine clearance was within normal limits. The blood leucocyte count was 7.1 × 10^9/µl, 40% of which were lymphocytes. Flow cytometric analysis of the peripheral blood showed that 38% of the lymphocytes were positive for CD19, CD5, CD23, and CD27. These cells showed normal CD20 expression and slight surface expression of λ light chains. A bone marrow biopsy showed multifocal 40% infiltration with

Figure 1 [A] Semithin section of sural nerve stained with methylene blue azure-two, showing massive loss of myelinated fibres and an amyloid plaque (arrow). [B] Paraffin section with Congo red staining showing birefringence in polarised light. [C] Cryosection reacted with antibodies to transthyretin (prealbumin Dako, 1:20 000), showing dense immunoreactivity of the plaque for transthyretin. [D] Cryosection reacted with polyclonal antibodies to human IgG (Dako, 1:1000) showing no immunoreaction on the amyloid plaque (arrows). [E] Protein analysis by hybrid isoelectric focusing under half denaturing conditions (left), and restriction fragment analysis after amplification of exon 2 of the transthyretin (TTR) gene and digestion with NsiI for the identification of the ATTR(Val30Met) mutation (right). Lane 1 represents the patterns of the patient, lane 2 the patterns of a normal control individual, and lane 3 the patterns of a known FAP patient with normal TTR and the ATTR(Val30Met) mutation.
lymphoid B cells of low proliferative activity and no clear birefringence in Congo red staining. A diagnosis of smouldering B cell lymphocytic leukaemia (B-CLL) was made.

Sural nerve biopsy disclosed a dramatic loss of both myelinated and unmyelinated fibres without signs of regeneration (fig 1A). Surprisingly, several amyloid plaques were seen on Congo red staining (fig 1B). Immunohistochemistry showed unequivocal immunoreactivity for transthyretin (TTR) (fig 1C), while polyclonal antibodies to human IgG (fig 1D) stained negative. On skin biopsy of the left lower leg, there was total loss of epidermal nerve fibres. Protein and DNA analysis showed heterozygosity for normal TTR and active for TTR were found in the sural nerve biopsy and the ATTR(Val30Met) mutation in the propositus is essential for identifying the major amyloidogenic protein. Finally, the diagnosis of FAP must be based on molecular protein/DNA analysis.

Although FAP is a disease of autosomal dominant inheritance, a negative family history of polyneuropathy or amyloidosis does not rule out the disease, owing to incomplete penetrance or a new mutation. FAP should be considered in all cases of sporadic neuropathy with prominent autonomic symptoms, trophic ulcers, or weight loss, even in countries with a low incidence like Germany. Possibly the prevalence of FAP is underestimated in such countries because of incomplete diagnostic workup.

The recognition of FAP is important for two main reasons. First, treatment is possible by liver transplantation when performed early in the course of disease. Second, diagnosis of FAP in the propositus is essential for identifying relatives at risk for the disease and for providing adequate genetic counselling.

### References


### Aneurysm of the extracranial internal carotid artery presenting as the syndrome of glossopharyngeal pain and syncope

The syndrome of glossopharyngeal pain and/syncope mimicking idiopathic glossopharyngeal neuralgia has been reported to be associated with a variety of intracranial or extracranial conditions including mass lesions in the parapharyngeal space,\(^1\) the elongated styloid process,\(^2\) and multiple sclerosis.\(^3\) However, aneurysm of the cervical part of the internal carotid artery (ICA) presenting as episodic glossopharyngeal pain and syncope has not been reported previously to the best of our knowledge. We report here the first such case that was successfully treated by surgical resection of the aneurysm.

A 66 year old woman with a two year history of paroxysmal attacks of pharyngeal pain with occasional syncopal episodes was admitted to our hospital. She had been in good health until two years previously, when she first noticed pain in the region of the left
pharynx, sometimes with radiation to the ipsilateral ear and submandibular area. The pain was neither stabbing nor triggered by swallowing and eating. The attacks recurred about 10 times a day and lasted from several seconds to five minutes. During the year before admission, the attacks had become more frequent, and the duration of pain increased to 30 minutes. She had also felt foreign body sensations in her throat regardless of food. During the four months before admission, the painful episodes were occasionally accompanied by abdominal pain, diarrhea, and syncope. The episodes of syncope recurred about twice a month. She had a positive gag reflex; there was no palpable mass or bruit after examination. Welling et al. reported that 41 of 118 aneurysms of the peripheral arteries arose from the extracranial carotid system. Only four of them were saccular aneurysms. The aneurysms of the extracranial ICA do not usually produce neurological symptoms, they may result in potentially serious problems, such as cerebrovascular events, as a consequence of thromboembolic phenomena or impairment of flow in the proximal carotid artery. Isolated cranial neuropathies can also occur as the result of direct nerve compression. In this case, the aneurysmal parapharyngeal mass produced episodic glossopharyngeal pain and syncope.

Y-M Lim, S-A Lee
Department of Neurology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea

D-K Kim, G-E Kim
Division of Vascular Surgery, Asan Medical Center

Correspondence to: Dr Lee, Department of Neurology, Asan Medical Center, 388-1, Pungnap-dong, Songpa-gu, Seoul, 138-736, Korea; solteme@www.amc.seoul.kr

References


Acute hyperperfusion syndrome complicating EC-IC bypass

The extracranial-intracranial (EC-IC) arterial bypass study has been criticised for failing to select for patients with chronic haemodynamic insufficiency and for revascularisation with low flow grafts, which may augment perfusion inadequately. We report a case of EC-IC bypass in a patient with severe intracranial carotid stenosis and compromised cerebrovascular reserve, which was complicated by intraoperative hyperperfusion syndrome. Hyperperfusion syndrome following surgery of EC-IC bypass is not well documented and its occurrence directly after bypass has not been reported before. We discuss the pathophysiology and prophylactic measures of this complication, with special attention to the nature of the bypass performed.

A 48 year old handed woman presented with a four month history of recurrent transient ischaemic attacks characterised by left sided symptoms of perioral paraesthesia, hand numbness, and upper extremity weakness (grade 4/5). The attacks were refractory to treatment with ticlid, a platelet aggregation inhibitor, and at the time of admission to hospital she was having several episodes daily, each lasting up to 15 minutes. She was therapeutically heparinised, her blood pressure was augmented to 150–180 mm Hg with intra-venous vasopressors, and florinef treatment was begun to expand her vascular volume. The transient ischaemic attacks persisted unabated during the time of this regimen in the intensive care unit.

Preoperative T2 weighted and magnetic resonance imaging revealed a few scattered subcortical signal changes, but no evidence of a previous cerebrovascular event. Cerebral angiography showed severe right supraculpid internal carotid artery and proximal right M1 stenosis with contributory narrowing of the middle cerebral artery from pial collaterals. The carotid arteries were normal. Transcranial Doppler studies with carbon dioxide vasodilation challenge showed flow limiting stenoses with compromised cerebrovascular reserve.

On the basis of these data and the refractory nature of the symptoms, we decided to proceed with a high flow revascularisation procedure. An autologous saphenous vein graft was inserted into a proximal M2 branch and the external carotid carotid artery in end to side fashion. During this time the patient’s systolic and diastolic blood pressure were maintained between 160 and 180 mm Hg, and she had been cooled to %34°C and treated with 20% mannitol (100 g). An intraoperative angiogram, performed immediately after connection of the anastomoses, confirmed patency of the bypass graft and normal filling of the middle cerebral tree.

As we were preparing to close the craniotomy, approximately 45 minutes after flow was established through the bypass graft, the brain became massively swollen. A temporary clip was placed across the graft, and the brain relaxed, becoming soft with return of pulsatility. A second intraoperative angiogram showed evidence of hyperperfusion syndrome with the presence of a dense vascular blush throughout the middle cerebral tree (fig 1). Attempts to limit flow through the graft failed and a permanent clip was placed across the graft. Postoperative computed tomography showed intracranial haemorrhage and cerebral oedema with progressive mass effect, commensurate with a worsening neurological state. After discussions with the family, aggressive supportive measures were withdrawn and the patient died.

Symptoms of intracranial stenotic lesions are usually haemodynamic in etiology and develop after the collateral blood supply fails
to support metabolic demands despite maximum oxygen extraction. Management of patients refractory to treatment with antiplatelet or anticoagulant agents, blood pressure augmentation, and blood volume expansion is difficult. There is a high risk of stroke, and several studies have argued strongly in favour of EC-IC bypass in these patients. Consequently, a decision was made in this case to carry out a high flow bypass from the external carotid artery to an M2 branch of the middle cerebral artery. The long nature of the lesion in the supracarotid carotid, ext budding into the proximal M1 segment, was judged not amenable to angioplasty. We failed to consider seriously the use of a low flow bypass graft.

Hyperperfusion following cerebral revascularisation is well recognised, particularly in the context of carotid endarterectomy. Its occurrence secondary to EC-IC bypass is not surprising. Intraarteral haemorrhages can complicate both supraclival temporal artery to middle cerebral artery (STA-MCA) and saphenous vein EC-IC bypasses for carotid occlusive disease, but evidence for hyperperfusion as the underlying cause of these haemorrhages is not established. A dense perfusion blush on the intraoperative angiogram documented hyperperfusion following connection of the EC-IC bypass in this case (fig 1). In chronic ischaemic brain, hyperperfusion syndrome is thought to arise as a result of disturbed cerebral autoregulation.1 The vasculature is maximally dilated and following restoration of flow vascular reactivity is impaired and unable to vasoconstrict appropriately, to protect the capillary bed against the increased perfusion pressure. Low signal oedematous changes and cerebral haemorrhage result, as was evidenced on postoperative computed tomography in this case.

Several factors led to the development of hyperperfusion syndrome in our case. Preoperatively we failed to recognise that altered microvascular permeability of the chronically hyperperfused brain may lower the safe threshold for ischaemia and hypertension.2 Despite neuroprotective measures, temporary occlusion of the M2 branch for the bypass may have resulted in a serious degree of ischaemia, and our routine practice of modestly raising the patient's blood pressure during temporary clipping may have been detrimental in this setting. Given the increased susceptibility of the chronically ischaemic brain—barrier to injury, the choice of a high flow bypass was in retrospect an error. Depending on the diameter of the graft, saphenous vein bypass grafts provide flows to 110 ml/min.3 By comparison, STA-MCA bypasses generate flows through the graft in the range of 10 to 15 ml/100 g/min.4 Revascularisation is instituted to rescue tissue with blood flows of 20–25 ml/100 g/min from dropping to 10–15 ml/100 g/min leading to cell death. This incremental augmentation of blood flow can be achieved by a low flow STA-MCA bypass with a lower risk of complications. Over time, adaptation will occur, allowing increased flow through the bypass graft to be tolerated with safety. As long as an ischaemic brain is subjected acutely to these high flows.

Patients with intracranial stenosis and compromised cerebrovascular reserve—highlighted as a group most likely to benefit from EC-IC bypass—are at high risk for hyperperfusion syndrome. Strict attention to judicious choice of bypass conduit, minimising ischaemic time for the anastomosis, optimal neuroprotection, and meticulous control of blood pressure and intravenous fluids is mandatory to minimise complications of hyperperfusion syndrome and optimise the potential benefit of EC-IC bypass in these patients.

References


A Japanese case of steroid responsive myopathy with deficient chondroitin sulphate

In 1998, Al-Lozi et al described a case of steroid responsive myopathy with deficient chondroitin sulphate C that had not been reported before. The patient developed diffuse bulbar and systemic weakness with respiratory failure. While muscle biopsy showed only a moderate degree of type 2 atrophy with one small perimysial, perivascular mononuclear cell infiltration, immunocytochemistry showed an absence of chondroitin sulphate C in the endomysium. Prednisone treatment resulted in a marked increase in muscle strength. Here we report another case of this interesting and treatable muscle disorder.

Case history

A Japanese woman first developed neck muscle weakness, dysphagia, and weight loss at the age of 42 years. She was diagnosed as having anorexia nervosa at age 20, but later developed symptoms of an antidepressive drug treatment. Her symptoms worsened and after a few months she developed weakness in all of her limbs, sluggish speech, and diplopia, and began having difficulty with breathing. She was admitted to our outpatient clinic in 1993 at the age of 43. Her personal and family histories were negative for neuromuscular disorders. On physical examination, she was very thin (height 162 cm; weight 32 kg), and her temperature was 38.1°C. Coarse crackles were heard in the right lower lung. Neurological examination revealed dysarthria, dysphagia, ptosis, limlimb weakness, and autonomic system were normal, as was her cognitive function.

Laboratory tests showed signs of inflammation (white blood count 9000/µL, C reactive protein 3.2 mg/dl), considered to be the result of mild aspiration pneumonia in the right lower lung on chest x-ray and left hypoproteinaemia. Blood gas analysis revealed hypoxia, with a PaO2 of 8.05 kPa, a PaCO2 of 9.27 kPa, and a blood pH of 7.392. Other blood constituents were normal, including creatine kinase, aldolase, lactate dehydrogenase, receptor antibody, antinuclear antibody, lactic acid, and pyruvic acid. Urinalysis, ECG, and cerebrospinal fluid examination were also normal, as was brain magnetic resonance imaging.

Electromyography (EMG) showed myogenic discharges in both biceps brachii, the left rectus femoris, and in both sternocleidomastoid muscles. Motor and sensory nerve velocities were normal in the median, ulnar, tibial, peroneal, and sural nerves. Repetitive stimulation tests of the facial and deltoid muscles gave normal results. A tension test was negative.

Because she was clinically diagnosed as having atypical oculopharyngeal myopathy with respiratory failure, a biopsy was performed on the right rectus femoris muscle. On histochemical examination, a moderate degree of type 2 atrophy was identified (fig 1A). Immunohistochemical investigation using antibodies to CD3, CD4, CD8, CD68, and CD22 failed to show the presence of infiltrating inflammatory cells (data not shown).7 At this time, the origin of the patient’s disorder remained undetermined.

The patient was given prednisone orally in a dose of 60 mg/day and her symptoms markedly improved. By day 7, the diplopia, dysphagia, and dysnea had resolved. After four months, she was discharged with no remaining neurological deficit. Her prednisone dosage was gradually reduced and eight years later, at the time of writing, she was taking a maintenance dose of 20 mg every other day and showed no neurological deterioration.

Because the clinical features of steroid responsive myopathy with deficient chondroitin sulphate C—first reported in 1998—were similar to those in our case, we carried out an immunohistochemical study using a monoclonal antibody to chondroitin sulphate C.
The other patient with steroid responsive myopathy was similarly reported to have been malnourished, for a period of 18 months. Thus it is likely that the type 2 fibre atrophy shown in both these patients was caused by malnutrition.

Chondroitin sulphates are major constituents of the extracellular matrix of skeletal muscle and play an important role in binding cytokines as well as in cellular adhesion, differentiation, and signal transduction.1 Thus their disruption in muscle is thought to be involved in the pathogenesis of disease. Al-Lozi et al suggested that myopathy might be caused by a deficit in chondroitin sulphate C as developing as a result of immune mediated mechanisms.1 In our case, there was dramatic improvement with steroid treatment, further supporting a role of the immune system in the disease pathogenesis.

In conclusion, we presented a case of steroid responsive myopathy with deficient chondroitin sulphate. This condition should be considered in cases of atypical oculopharyngeal myopathy of unknown origin.

**References**

consequence of ureterosigmoidostomy: alone, ammonia concentrations as high as these have never been observed in patients with hyperammonaemia following ureterosigmoidostomy. The patient had been treated a few weeks before for urosepsis following cystostomy. The patient had been treated a few weeks before for urosepsis following cystostomy.


On admission, ammonia was elevated to 250 µmol/l and the patient was comatose and showed clinical features such as retinal pigmentary changes, familial hyperammonaemia and retinal dystrophies. The patient had been treated a few weeks before for urosepsis following cystostomy. The patient had been treated a few weeks before for urosepsis following cystostomy.


Palatal tremor and cognitive decline in neuroferritinopathy

Neuroferritinopathy is a recently described autosomal dominant neurodegenerative disorder associated with iron accumulation, particularly in the basal ganglia. All patients found to date have a single adenine insertion between nucleotides 466 and 467 of the ferritin light chain gene. This results in a frame shift and is predicted to cause structural alteration of the polypeptide carboxy terminus. Magnetic resonance imaging of the brain shows iron accumulation in the basal ganglia, which has been confirmed pathologically with the detection of numerous iron positive inclusions particularly in the globus pallidus. In spite of this, serum ferritin levels are found to be abnormally low or at the low end of the normal range. Patients tend to present in mid-life with a movement disorder, characterised by chorea, dystonia, and rigidity. In contrast with Hallervorden-Spatz syndrome, which is also associated with accumulation of brain iron, visual and cognitive function is preserved.

Here, we report a patient with genetically proven neuroferritinopathy in which both palatal tremor and cognitive decline are associated with iron accumulation in the globus pallidus.

The differential diagnosis in this case initially included HD, neuroacanthocytosis, and Wilson's disease, but these conditions were excluded by appropriate investigations. Atypical Hallervorden-Spatz syndrome was also considered, particularly in the light of the appearances on brain imaging, but this condition is recessively inherited and associated with a defective pantothenate kinase gene.

### References


### Figure 1

Magnetic resonance imaging of the brain showing hyperintensity with surrounding hypointensity on T2 weighting affecting the putamen, pallidum, and thalamus.
(PANK2). Interestingly, our patient had significant cognitive impairment and palatal tremor in addition to the movement disorders so far described in patients with neuroferritinopathy. In other neurodegenerative disorders, particularly HD, the causative proteins may be involved in iron metabolism. Thus, cognitive impairment may be predicted to occur in neuroferritinopathy, especially in the presence of a pre-existing hyperkinetic movement disorder.

The development of palatal tremor in our patient deserves further explanation. Palatal tremor (previously known as palatal myoclonus) may be classified as essential or symptomatic. It is thought that the palatal tremor arises because of functional disruption in “Mollaret’s triangle”, which consists of the inferior olivary nucleus, red and dentate nuclei. The symptomatic form is usually associated with hypertrophy of the inferior olivary nucleus and may arise from vascular lesions, particularly in the cerebellum. Further evidence for this hypothesis comes from a positron emission tomography study, which showed hypermetabolism in the inferior olivary nucleus. Most patients also have cerebellar ataxia. However, palatal tremor may also occur in other conditions including multiple system atrophy, progressive supranuclear palsy, and Alexander’s disease. As in our case, symptomatic palatal tremor is not usually associated with ear clicking. Presumably, in our patient, iron deposition in the dentate nuclei was responsible for disruption of rubral and olivary pathways.

Ferritin is an iron storage protein and alteration in structure of the carboxy terminus could lead to the release of free iron and excessive oxidative stress. In other conditions, such as haemosiderosis, the use of iron chelators has been advocated as a potentially useful treatment. Results, in the main, have been disappointing. Whether free radical scavengers, such as idebenone, have useful therapeutic value in neuroferritinopathy remains to be seen.

Neuroferritinopathy should be considered in all patients with a hyperkinetic movement disorder, imaging evidence of iron deposition within the brain, and an autosomal dominant family history.

Cocaine induced hypokalemic periodic paralysis

The use of cocaine has been associated with a number of pathophysiologic and neurologic complications. This is the second reported case of a patient who suffered three distinct episodes of paralysis after engaging in a cocaine binge.

Case report

A 33 year old male horse breeder with no significant medical history was evaluated at the Texas Tech Health Sciences Center after the abrupt onset of ascending generalized weakness. He reported not being able to walk or lift his arms or legs, much less climb up or get down the stairs of his home. He reported no bowel or bladder symptoms, loss of sensation, headache, nausea, or vomiting. The patient did report mild chest pain at the time. Ten days before his initial evaluation he had suffered a very similar episode but had not sought medical attention. At the time of his evaluation the patient stated that he would be better in 24–48 hours. A very similar event had occurred five years earlier, for which he was seen in an urgent care facility and discharged home; symptoms resolved after 2–3 days. Records of this first episode were not available, although he reported that potassium supplements were provided at that time. Physical examination found an uncomfortable appearing, slightly dishevelled, unshaven man with no spontaneous motor activity. Vital signs were a pulse of 88 beats/min, respiration 16 breaths/min, and blood pressure 132/94 mm Hg. Neurological evaluation found an awake, alert, and oriented person. Speech and language were normal. Cranial nerves were intact. Motor examination found normal bulk with a reduction in tone. Strength was 2/5 in the upper extremities and 0/5 in the lower extremities. Babinski signs were absent.

The patient was admitted to the acute care unit for close observation. Potassium concentration was 1.9 mmol/l and the CK concentration declined 4.5 mmol/l and the CK concentration declined to 133 IU/l.

It is not clear why the use of cocaine led to such severe generalized weakness and hypokalemia in this patient. Nalluri et al reported a similar case and suggested that the hypokalemia was caused by an intracellular shift of potassium secondary to the adrenergic effects of cocaine; a hyperkalemic form of periodic paralysis in patients suffering from thyrotoxicosis has also been postulated. In their report, as in this case, the patient responded quickly to potassium supplementation. An alternative mechanism may have been cocaine’s potential effects on potassium channels. The increased CK and serum glucose concentrations were felt to be the result of cocaine’s effects.

A J Wills, G V Sawle
Department of Neurology, Queen’s Medical Hospital, Nottingham, UK

P R Guilbert
Department of Clinical Genetics, Nottingham City Hospital

A R J Curtis
Institute of Human Genetics, The International Centre for Life, Central Parkway, Newcastle upon Tyne, UK

Correspondence to: Dr Wills; ade@wills99.swinternet.co.uk

References


Sulcal abnormalities on brain magnetic resonance imaging in the Guillain–Barré syndrome

The Guillain–Barré syndrome is an immunologically mediated condition affecting the peripheral nervous system. There is evidence that Guillain–Barré syndrome, Miller–Fisher syndrome, and Bickerstaff brain stem encephalitis form a closely related spectrum of disorders. Magnetic resonance imaging (MRI) abnormalities were not ascertained in these conditions have been well described,

but intracranial findings are infrequent. We report resolution of sulcal changes on serial MRI of the brain concomitant with clinical recovery in a typical case of Guillain–Barré syndrome.
An 81 year old man had a one week history of progressive lower limb weakness and numbness associated with pain radiating down his right leg. There was no preceding history of infection or trauma. He had no significant past medical history.

On examination, he was alert and rational. There was no slurring of speech or paresis of the extraocular muscles. Cranial nerve and visual field examination was unremarkable and the neck was supple. He had mild proximal symmetrical upper limb weakness (MRC grade 4/5) and bilateral lower limb weakness (MRC grade 3/5). He had difficulty in walking unaided and in tandem walking. Sensory loss to touch was elicited in the distal lower extremities in stocking distribution. Reflexes in all four limbs were absent. The clinical features were consistent with the Guillain–Barre syndrome.

The patient was initially referred to an orthopaedic surgeon for possible lumbosacral spondylitic disease. Unenhanced MRI scans of the lumbar and thoracic spine showed mild degenerative changes and excluded intrinsic cord abnormalities or external compression. Subsequent enhanced cervical spine MRI scans were also negative. He was then referred for a neuroclinical opinion.

Nerve conduction studies revealed significantly prolonged distal motor latency (median motor distal latency 6.7 to 9.8 ms; posterior tibial distal latency 7.7 to 9.4 ms) and reduced conduction velocities in the median (40.3 m/s), ulnar (39.6 m/s), and tibial nerves (35.7 m/s). F responses were prolonged (> 37 ms) or absent in all four limbs. Cerebrospinal fluid examination showed absent cells with raised protein of 0.8 g/l, normal glucose concentration, and positive globulin. Bacterial and viral studies were negative.

Sensory loss to touch was elicited in the distal lower extremities in stocking distribution. Reflexes in all four limbs were absent. The clinical features were consistent with the Guillain–Barre syndrome.

In the related Miller–Fisher syndrome, MRI changes have been reported in the subcortical white matter of the cerebellar hemispheres and the posterior limb of the internal capsule. MRI abnormalities on the subcortical white matter (MRC grade 3/5) had difficulty in walking unaided and in tandem walking. Sensory loss to touch was elicited in the distal lower extremities in stocking distribution. Reflexes in all four limbs were absent. The clinical features were consistent with the Guillain–Barre syndrome.

In the related Miller–Fisher syndrome, MRI changes have been documented in the cranial nerves, spinocerebellar tracts, and pons. We postulate that our MRI findings represent a focal manifestation of a wider immunologically mediated reaction within the subarachnoid cerebrospinal fluid bathed space. This focal uveal reaction probably represents a local concentration of proteinaceous fluid and correlates well with the CSF findings of high protein levels but an absence of cells. These MRI changes resolved with immunoglobulin treatment and clinical recovery. While MRI changes have been reported in the subcortical regions in demyelinating neuropathies, most probably from focal demyelination, subcortical changes have not been described. Serial MRI studies are a sensitive technique for documenting cerebral cortical abnormalities in this condition, even in the asymptomatic setting as demonstrated here.

**References**


**Muscle tissue oxygenation as a functional tool in the follow up of dermatomyositis**

Near-infrared spectroscopy (NIRS) is a direct, non-invasive optical method for measuring local oxygenation and haemodynamics in muscle tissue. Although measurement of local oxygenation by NIRS has been used for the diagnosis of metabolic myopathies, the technique has not previously been applied to inflammatory myopathies. Dermatomyositis is a muscle disorder characterised by complement mediated capillary necrosis, resulting in ischaemia and hypoperfusion. We have now employed NIRS to study the effect of corticosteroid treatment on haemodynamics in muscle tissue in dermatomyositis.

The pathological features of dermatomyositis are characterised by a decreased number of capillaries per muscle fibre and necrosis of single muscle fibres or clusters of fibres at the periphery of the fasciculi. Muscle fibre regeneration and an increased number of capillaries have been shown in dermatomyositis after intravenous immune globulin treatment, but corticosteroids are still considered to be the first line of therapy. In the clinical setting, the effect of treatment is mainly assessed by muscle strength and creatine kinase (CK) levels. Direct measurement of capillary and muscle fibre status can only be done by repeated muscle biopsies. However, apart from the fact that muscle biopsies are invasive, they are also a static representation of muscle tissue at a fixed time point and at a particular location (selection bias).

This is the first time that NIRS, a non-invasive optical method for the measurement of oxygenation and haemodynamics in muscle tissue, has been used to study the effect of treatment in a patient fulfilling the clinical and histological criteria of definite dermatomyositis. A young woman from Aruba, aged 24 years, presented with subcutaneous erythema of the facial skin and severe proximal muscle weakness (arm muscles: MRC grade 4; leg muscles: MRC grade 2). Serum CK levels were slightly increased (220 IU/l). Five weeks after the onset of symptoms, treatment with corticosteroids was started in our department at a dose of 60 mg/day (for six weeks), the dose being subsequently tapered. CK levels decreased and muscle strength increased (arm muscles: MRC grade 4; leg muscles: MRC grade 3) in week 12.

Tissue oxygenation was measured by NIRS immediately before treatment was begun and again after three and seven weeks of treatment. NIRS is based on the relative tissue transmittance to light in the near-infrared region, and on the oxygen dependent absorption changes of haemoglobin and myoglobin. Using a modification of the Lambert–Beer law, in which physical path length is incorporated to account for light scattering, it is possible to calculate quantitative values for oxygen consumption and blood flow in skeletal muscle. NIRS is non-invasive and measures oxygenation directly in muscle tissue. Moreover, it is relatively inexpensive, easy to apply, and applicable at the bedside.

In this study, NIRS measurements were obtained using a continuous wave near-infrared spectrophotometer (Oxymon, Bioengineering Department, University of
of Nijmegen, Netherlands). Using this spectrophotometer, which generates light at 950, 850, and 770 nm, it is possible to differentiate between oxyhaemoglobin/myoglobin (O2Hb/O2Mb) and deoxyhaemoglobin/myoglobin (HHb/HMb). The optical fibres were placed on top of the flexor digitorum superficialis muscle in the same location for all the measurements. Data were sampled at 10 Hz.

Quantitative NIRS values for oxygen consumption (mVO2) were calculated by evaluating the rate of decrease in [O2Hb] during arterial occlusion, as previously described.1 Reoxygenation rate ([O2Hb]) was determined as the rate of initial increase in O2Hb measured over three seconds immediately after cessation of arterial occlusion. Both mVO2 and [O2Hb] were calculated at rest and following rhythmic isometric handgrip exercise at various work intensities. Each exercise session consisted of one minute of exercise at a contraction rate of 30/min (80% duty cycle), immediately followed by 45 seconds of arterial occlusion for the calculation of mVO2 and [O2Hb]. Whereas mVO2 is a measure of mitochondrial function at a certain work intensity and is dependent on the vascular capacity of oxygen delivery, [O2Hb] reflects the initial recovery rate at which deoxygenated haemoglobin/myoglobin are resaturated.1 It is therefore directly related to microvascular function. All measurements were performed at the same absolute work intensities.

Figure 1 shows the effect of corticosteroid treatment on measuring non-invasively in the patient with severe dermatomyositis. Before treatment was begun, resting mVO2 was slightly higher than in healthy controls (0.19 ± 0.14 ml O2/min/100 g, respectively). However, mVO2 during exercise was about 60% lower than in the controls over the whole range of exercise intensities (fig 1A). After three weeks of treatment, mVO2 had already markedly increased. After seven weeks, mVO2 had increased even further and was now only 25% below that of the controls, and within the normal range at several work intensities. Serum CK levels were normalised, while muscle strength had increased. [O2Hb] (fig 1B) showed similar results, with slow recovery rates before treatment was begun and an increase over all work intensities at the three week and seven week examinations. [O2Hb] after seven weeks of treatment exceeded the normal mean value.

As NIRS measures local oxygenation and haemodynamics within the muscle, it can give direct insight into the working microvascular system. [O2Hb] increased during treatment, indicating an increase in capillary function. As a result of the increased capillary function and a possible regeneration of muscle fibres, muscular oxygen availability increased, enhancing oxidative capacity—as reflected by the increase in local muscle oxygen consumption.

Although a muscle biopsy will remain indispensable for the diagnosis of dermatomyositis, NIRS is an interesting and non-invasive tool for monitoring the effect of treatment non-invasively and with relative ease. While both serum CK levels and muscle strength are indirect measures, and muscle biopsies provide only a static fingerprint of the muscle, NIRS measures local microvascular and mitochondrial function directly in the intact and working physiological setting.

M C P van Beekvelt, R A Wevers, B G M van Engelen Neuromuscular Centre, Institute of Neurology, University Medical Centre Nijmegen, PO Box 9101, 6500 HB Nijmegen, Netherlands

W N J M Collier Department of Physiology, University Medical Centre, Nijmegen

Correspondence to: Dr B G M van Engelen; bvanengelen@zzzouw.aszn.nl

References


Propofol in myoclonus status epilepticus in comatose patients following cardiac resuscitation

Myoclonus status epilepticus has been identified as a poor prognosticating sign in comatose patients following cardiopulmonary resuscitation.1 These vigorous generalised jerks are considered to be the penultimate phenomenon in a severely damaged brain that is difficult to manage and that may cause difficulty in ventilating the patient. Antiepileptic drugs such as phenytoin or benzodiazepines have not been very successful. When the jerks are particularly severe, neuromuscular junction blockers have been recommended.1 I report on two comatose patients with myoclonus status epilepticus. Propofol in a subanaesthetic dose muted these movements considerably.

A 77 year old patient with a prior history of rheumatoid arthritis was resuscitated at home after sudden collapse. The emergency medical service found no pulse. He was defibrillated, and after resuscitation of approximately 70 minutes, pulse and blood pressure returned. In the coronary care unit, he had generalised myoclonus in the face, limbs, and abdomen muscles and the movements were particularly sensitive to touch. His Glasgow coma score was 3 and brainstem reflexes were intact. These rhythmic jerks interfered with mechanical ventilation and caused repetitive bucking of the ventilator. He was treated with fosphenytoin (phenytoin equivalents 20 mg/kg), which subsequently reduced his blood pressure to 80 mm Hg but which quickly returned to a normal level. He was placed on a propofol infusion titrated to a maximal dose of 65 µg/kg/min, and myoclonus disappeared. After treatment for three hours, propofol was discontinued. An electroencephalogram showed a burst suppression pattern. Myoclonic jerks returned and, in addition, constant blinking was noted. The patient did not awaken after discontinuation of propofol on the second day.

A 19 year old boy was found hypothermic (core temperature of 31°C) in the field after a car rollover. He was resuscitated for 30 minutes before heart rate returned. On admission, his Glasgow coma score was 3. Notable signs were constant facial jerking, biting on the endotracheal tube, and soundsensitive myoclonus jerks in all limbs. Propofol in a dose of 35 µg/kg/min significantly muted myoclonus, although occasional myoclonic jerk was noted in both legs. An electroencephalogram showed a burst suppression pattern. Computed tomography showed poor white-grey matter differentiation, indicating early brain oedema. Care was withdrawn after the patient did not recover from coma after discontinuation of propofol.

Control of generalised myoclonus status epilepticus has been difficult and frustrating. I noted that the use of propofol in a fairly low dose muted myoclonus considerably. The typical dose in the intensive care unit is 5 µg/kg/min, which can then be titrated to 50–
Chronic asymptomatic progressive external ophthalmoplegia with right facial weakness: a unique presentation of mitochondrial myopathy

Because of genetic heteroplasmy, the clinical manifestations of mitochondrialopathies are quite varied. We report an unusual presentation in a patient with asymmetric ophthalmoplegia and unilateral myopathic facial weakness caused by a deletion in mitochondrial DNA.

Case history

The patient, a 42 year old white woman, was evaluated in our neurology clinic for double vision and right sided facial weakness in early 2000. She first noticed these symptoms in 1994. At that time, she had isolated weakness of the right eye and she was felt to have a right internuclear ophthalmoplegia. A demyelinating process was considered initially, but magnetic resonance imaging of the brain on four subsequent occasions (annual scans) did not show any structural lesions to support such a diagnosis. The diplopia remained unchanged and an insidious facial weakness developed.

During the course of her illness she had extensive investigations, including normal cerebrospinal fluid, antinuclear antibodies, erythrocyte sedimentation rate, serum protein electrophoresis, and thyroid profile. Rapid plasma reagin and Lyme’s titre were negative. She received several courses of high dose steroids without any improvement.

There had been no substantial change in her general physical condition since 1994. Her past medical history was otherwise unremarkable. She is a computer operator and quite active in sports. She has smoked moderately for 30 years. She has no history of any neurological disorders. There was no diurnal variation of her symptoms and no complaint of dysphagia, dysarthria, or limb weakness.

Neurological examination revealed a pupillary sparing ophthalmoplegia without ptosis, specifically she had unilateral extroptia on primary gaze, with total paralysis of abduction of the right eye and mild weakness of abduction of the left eye. She also had mild ptosis of infraction of the right eye. Nystagmus was absent in both horizontal and vertical gaze. She had an infranuclear right facial weakness involving both the orbicularis oculi and the orbicularis oris, without lid synkinesis. The strength in the left facial muscles was normal. Ophthalmoscopy showed mild pallor of her fundi without macular involvement.

The patient had several normal MRI scans. Previous attempts at treatment with high dose steroids were unsuccessful and the diagnosis was uncertain. With no structural lesion to explain her clinical condition, we suspected muscular or neuromuscular pathology. An unusual presentation of ocuopharyngeal dystrophy, ocular myopathies, myasthenia gravis, and mitochondrial myopathies were in the differential diagnoses for this progressive ophthalmoplegia. However, we did not have an explanation for her right facial weakness, which we suspected represented a non-neuropathic process. Further investigations showed normal serum lactate levels. Genetic testing in blood tissue was positive for a deletion in mitochondrial DNA in a region that encodes different subunits of the respiratory chain complex. Given the clinical manifestations observed, it is clear that the patient has a significant degree of tissue heteroplasmy.

We would like to emphasise the diagnostic value of the muscle biopsy in cases with atypical clinical presentation and normal serum lactate levels. Genetic testing in blood may become the initial test of choice, with muscle biopsy as an alternative diagnostic aid.

Acknowledgements

Mitochondrial DNA testing was performed at the Emory Molecular Laboratory.

N K Sharma, M Gujarati, J Kumar, J C Kattah
Department of Neurology, University of Illinois College of Medicine at Peoria, One Illini Drive, Box 1649, Peoria, Illinois 61656-1649, USA

Correspondence to: Dr J C Kattah; linnet@uic.edu

References