“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 paraesthesiae 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 hypoaesthesia 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. Electromyographic 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 creatine 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...
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 amyloidotic polyneuropathy (FAP). (fig 1E) leading to the diagnosis of familial amyloidotic polyneuropathy (FAP).

This patient presents a chance association of B-CLL with “sporadic” FAP. Several cases of a B-CLL associated chronic sensorimotor neuropathy, either caused by neoplastic nerve fibres. Protein and DNA analysis showed heterozygosity for normal TTR and the amyloidogenic mutation ATTR(Val30Met) (fig 1E) leading to the diagnosis of familial amyloidotic polyneuropathy (FAP).

In most cases FAP is caused by a point mutation in the TTR gene. About 80 different mutations of the TTR gene have been identified. The initial tentative diagnosis of CLL associated neuropathy was revised when amyloid plaques immunoreactive for TTR were found in the sural nerve biopsy and the ATTR(Val30Met) mutation was demonstrated.

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.

M Buttmann, M Marzinick, K V Toyka, C Sommer Neurologische Klinik und Poliklinik, Julius-Maximilians-Universität, Josef-Schneider-Str 11, 97080 Würzburg, Germany

K Altland Institut für Humangenetik, Justus-Liebig-Universität, Schlümpenstraße 14, 35392 Gießen, Germany

Correspondence to: Dr Claudia Sommer; sommer@mail.uni-wuerzburg.de

References


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

The syndrome of glossopharyngeal pain and/or 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,1,2 the elongated styloid process,3 and multiple sclerosis.4 However, aneurysm of the cervical portion 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

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Figure 1  Contrast axial computed tomography scan (A) at the level of the atlas and (B) through the base of the skull. There was a large aneurysm of the extracranial internal carotid artery.

Figure 2  (A) Blaisdell line (dashed oblique line) between the angle of the mandible and the tip of the mastoid process. (B, C) Anteroposterior and lateral view of left carotid angiography showing an aneurysm on the extracranial internal carotid artery. It started near the Blaisdell line and ended at the base of the skull. (D) Postoperative angiography showing the patent venous graft.
Acute hyperperfusion syndrome complicating EC-IC bypass

The extracranial-intracranial (EC-IC) arterial bypass study has been criticised for failing to demonstrate a benefit for patients with chronic hemodynamic 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 cerebral vascular reserve, which was complicated by intraoperative hyperperfusion syndrome. Hyperperfusion syndrome with the presence of a dense vascular blush throughout the middle cerebral tree from pial collaterals.

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 bypass. Postoperative serial computed tomography revealed intracranial haemorrhage and cerebral oedema with progressive neurological deterioration. After discussion with the family, aggressive supportive measures were withdrawn and the patient died.

Symptoms of intracranial stenotic lesions are usually haemodynamic iniology and develop after the collateral blood supply fails to compensate for the stenosis. The patient's case demonstrates the importance of the collateral blood supply in maintaining cerebral perfusion and the potential for hyperperfusion syndrome to occur even in patients with compromised collateral flow.
to support metabolic demands despite maximal oxygen extraction. Management of patients refractory to treatment with anitiplatelet 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 and involvement of 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. Intracerebral haemorrhages can complicate both superficial 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. The vascularity 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. 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 clamping 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. By comparison, STA-MCA bypasses generate flows through the graft in the range of 10–28 ml/min. 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 incrementual 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 without the risk of 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.

Correspondence to: Dr Shirley I Stiver, Beth Israel Deaconess Medical Center, Boston, Massachusetts, USA; stiver@caregroup.harvard.edu

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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 19. There was also a history of antidepressive drug treatment. Her symptoms worsened and after a few months she developed weakness in all of her limbs, slurred speech, and diplopia, and began having difficulty with breathing. She was first presented in 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 160 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, dysmetria, dysdiadochokinesis, limb ataxia, limb dystonia, and hyporeflexia. Her muscle tone, sensory perception, 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. She was also hypoproteinaemic. 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, anti-endorphin 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 sternocleido-mastoid 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 on paraffin sections showed a marked infiltration of mononuclear inflammatory cells (data not shown). 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 dyspnoea 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...
were markedly similar to those seen in the
Apart from the limitation of her extraocular
atrophy with no staining of chondroitin
lar movement limitation, and proximal mus-
Our patient showed the following clinical fea-
staining was demonstrable (fig 1C).
neurone disease in 1993, chondroitin sulphate
vessels in the patient's muscle (fig 1B). In dis-
results and the absence of an inflammatory infiltrate on histochemi-
classification, all other clinical features
were markedly similar to those seen in the
only other reported case.2 As the antibody
used in our immunohistochemical analysis
could not discriminate between subtypes of
chondroitin sulphate, we were unable to con-
clude that our patient's deficient subtype was
definitely type C, though the clinical similari-
ties with the other reported case suggest that
this was the case.
Type 2 muscle fibre atrophy has been
reported in the muscles of malnourished
patients.1 Our patient was certainly malnour-
ished as a result of severe bulbar involvement.
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 malnu-
trition.
Chondroitin sulphates are major constitu-
ents 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.2 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 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 as cases of atypical ocuolopa-
ryngeal myopathy of unknown origin.

Yabe, S Kikuchi, T Higashi, K Tashiro
Department of Neurology, Hokkaido University
School of Medicine, N-15 W-7 Kita-ku, Sapporo
060-8638, Japan
Correspondence to: Dr Yabe;
yabe@med.hokudai.ac.jp

Fulminant progression of hyperammonaemic
encephalopathy after treatment with
valproate in a patient with
uretrosigmoidostomy

In the absence of liver disease, hyperammo-
naemia is often not considered in the differ-
ential diagnosis of encephalopathy and, there-
fore, the diagnosis of hyperammonaemic
encephalopathy may be delayed. We report a
case of fulminant progression of hyperammon-
aemic encephalopathy after valproate treat-
ment in a patient with uretrosigmoidostomy.
A 31 year old patient was admitted because of
disturbance of confusion and agitation. Uretrosigmoidos-
tomy for congenital bladder exstrophy was
performed when he was 9 years old. Over the
past years, he was repeatedly hospitalised with
episodes of abnormal behaviour, which were blamed on his abuse of various illegal
drugs. At this admission, he was disorientated,
with lapses into somnolence as well as agitation.
Apart from that, his general and
neurological status was unremarkable. C
reactive protein was 80.5 mg/l, leucocytes
16160 x10³/l, and blood urea 12.6 mmol/l. Venous
ammonia concentration was mildly increased
(63 µmol/l). Arterial blood gas analysis
showed respiratory alkalosis. All other labora-
tory analyses including toxicological screen-
ing, microbiological analysis, and cranial computed tomography were unremarkable. Plasma amino acids,
organic acids, and orotic acid were normal. After treatment with fluids and
amoxicillin with clavulanate for urinary infec-
tions, he developed generalised tonic-clonic seizures. Antiepileptic treatment
was introduced with 900 mg valproate intra-
venously followed by continuous infusion
(2000 mg/day). Because of repeated seizures, phenytoin was added two days later (1000 mg bolus followed by 1000 mg/day). Despite the
antiepileptic treatment, the patient developed
a status epilepticus and had to be intubated.
The seizures finally stopped after barbiturate coma (with thiopental (2 × 50 mg/kg
+ 10 000 mg/day) was induced. Arterial blood
ammonia concentration was now massively increased (2875 µmol/l). Emergency dialysis
was started, and paromomycin and lactulose
were administered. Under dialysis, the blood
ammonia concentration decreased to
812 µmol/l. However, the patient developed
diarrhoea, and multiple abscesses were found. The patient died a few hours later, five days after admission. Total plasma carnitine (6 µmol/l,
normal range 33–77 µmol/l) and free carnit-
ine (3 µmol/l, normal range 25–54 µmol/l)
concentrations were decreased. Acylcarnitine
profile also showed decreased but no abnor-
mal individual acylcarnitine species. Repeated
analyses of amino acids in plasma and urine,
urinary organic acids, and orotic acid showed
no significant abnormalities. On postmortem
test, the liver was normal. In both
kidneys, multiple abscesses were found. There
was massive cerebral oedema and cerebellar
herniation.
Uretrosigmoidostomy has been repeatedly
associated with episodic hyperammonaemic
encephalopathy.1 In this condition, the urine
is excreted directly into the sigmoid colon and
then excreted during defecation. Frequent
discomforts include recurrent pylonephri-
tis, faecal incontinence, intestinal malabsorp-
tion, and hyperchloraemic acidosis.1 Hyper-
ammonaemia develops as a result of the
increased production of ammonia in the colon
from bacterial ureolysis and subsequent ab-
sorption of ammonia in the colon. The bowel
wall is much more permeable to ammonia
than the bladder mucosa, allowing rapid
absorption of the ammonia produced within
the sigmoid colon. This exceeds the liver's
capacity to detoxify ammonia by the urea
cycle. In addition, a proportion of the reab-
absorbed ammonia is minimally absorbed
through the oesophageal and haemorrhoidal veins. Thus, hyperammonaemic encephalopathy can de-
velop even if liver function is normal.
In the present patient, the diagnosis of
hyperammonaemic encephalopathy was not
established until the ammonia concentration
had risen greatly and the patient was already
in critical condition. Urea cycle disorders and
organic acidurias were excluded. The labour-
tory analysis and postmortem examination
did not find any signs of hepatic dysfunction.
There were no signs of inborn systemic carnit-
ine deficiency. The ammonia concentration
increased massively after the introduction of
valproate. This can hardly be explained as a

Figure 1  (A) Muscle biopsy from our
patient showing a predominant type 2 fibre
atrophy [adenosine triphosphatase 10.4
staining, ×50]. (B) Immunohistochemical
staining of muscle obtained from our patient
and (C) from disease control subjects, using
a chondroitin sulphate specific antibody
(×66). Chondroitin sulphate staining was
absent from the muscle of our patient.

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consequence of ureterosigmoidostomy: 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 constipation, which theoretically can lead to very high ammonia concentrations. However, during the final episode, he was not constipated. Therefore, in our patient, pre-existing episodic hyperammonaemia with encephalopathy and seizures was obviously severely aggravated by valproate induced hyperammonaemia and depletion of carnitine. Patients with valproate induced encephalopathy have been repeatedly described, the pathophysiology of which seems to be heterogeneous. In some patients, previous subclinical urea cycle defects have become manifest after treatment with valproate. However, these disorders could be ruled out in our patient. Hyperammonaemia is a frequent side effect of valproate treatment and is often asymptomatic. It seems to occur more frequently in children but is also common in adults, particularly in the presence of other antiepileptic drugs, as was the case in our patient. The exact mechanism of valproate induced hyperammonaemia is unknown but it may appear independently of hepatotoxicity. Valproate has repeatedly been shown to reduce serum and liver carnitine, which may reduce carnitine concentrations by forming an ester with carnitine, which is excreted with organic acids into the urine, or by altering renal reabsorption of acylcarnitine and free carnitine.

In conclusion, our case shows that valproate may greatly aggravate pre-existing, mild hyperammonaemia. We suggest that valproate should be avoided in patients with even slight hyperammonaemia and normal liver function. Equally, we advise the close monitoring of ammonia and carnitine concentrations in patients with ureterosigmoidostomy, such as the one described here, if valproate cannot be avoided.

S Schwarz, D Georgiads, S Schwab
Department of Neurology, University of Heidelberg, INF 400, Heidelberg, Germany

S Zoubaa
Department of Pathology, Division of Neuropathology

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Correspondence to: Dr Stefan Schwarz, Department of Neurology, Klinikum Mannheim of the University of Heidelberg, Theodor-Kutzer-Ufer 1-3, 68167 Mannheim, Germany; schwarz@neuro.ma.uni-heidelberg.de

References

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 460 and 461 in 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 and this 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 lower 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 the clinical features included cognitive decline, palatal tremor. These features extend the phenotype of this condition from those previously reported.

The patient was a 49 year old man who developed lingual and oral dyskinetic movements and a slurring dysarthria at the age of 10 years. Over the next 10 years, he developed dysphagia, unsteadiness, and cognitive decline, particularly of frontal lobe function. His father, paternal uncle, and paternal grandmother had all developed a movement disorder in middle age. A diagnosis of Huntington’s disease was made at that time and was assumed in the patient until disproved by a negative genetic test result. The family continued to seek diagnostic clarification to enable life planning for the patient’s children.

On examination, he was alert and oriented. He scored 7/10 on a mini mental state examination. Detailed cognitive testing showed particular impairment of non-verbal abstract reasoning, with some word retrieval difficulties. He tended to perseverate, and his cognitive estimates were poor. He exhibited pout, palmonial, and grasp reflexes. He manifested appreciable oral, lingual, and facial dyskinesias. Eye movements were abnormal, with saccadic intrusion into pursuit and use of head thrust to initiate saccades. He had apraxia of eyelid opening. There was no evidence of a pigmentary retinopathy or Kayser-Fleisher rings, and the optic discs were normal. There was a palatal tremor at a frequency of 1 Hz. Examination of the limbs showed pronounced choreiform movements and dystonic posturing. There was no evidence of a peripheral neuropathy or myoclonus.

The following blood tests were normal or negative; full blood count and film, copper studies, creatine kinase levels, ferritin levels (60 µg/l, normal range 25-350 µg/l), liver function tests, and genetic tests for Huntington’s disease (HD), dentatorubral pallidolysian atrophy, and spino cerebellar ataxia 1-3, 6, and 7. Nerve conduction studies were normal. A muscle biopsy was normal. Cerebrospinal fluid analysis was normal, with no evidence of xanthochromia. Magnetic resonance imaging of the brain (fig 1) showed considerable hyperintensity, with a band of surrounding hypointensity on T2 weighting involving the putamen, pallidum, thalamus, substantia nigra, and dentate nucleus. The cerebral cortex was atrophic. A computed tomography scan showed no evidence of cerebral calcification.

Mindful of the clinical features, ferritin deposits, dominant inheritance, and family origin reported in neuroferritinopathy, further genetic testing confirmed the presence of the same A insertion at position 460-461 of the ferritin light chain gene. Investigation of genotypes at six polymorphic microsatellite markers close to the gene location on chromosome 19 showed sharing of one allele at each marker. Thus, it is likely that the patient potentially shares the disease associated haplotype with all affected individuals of the originally described families and is another example of inheritance of an initial founder event. Additional evidence comes from the north-west geographical origin of his family.

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
(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 myokymia) and may arise from vascular lesions, such as idebenone, such as idebenone, 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 nuclei. 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 hypokalaemic periodic paralysis

The use of cocaine has been associated with a number of peripheral and central, neurological 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 Science Center after the abrupt onset of ascending generalised 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 problems, 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 awake, alert, and oriented person. Heart rate, respiratory rate, blood pressure, and blood gases were normal. Two laboratory investigations were noted. The sensory examination was normal. Cranial nerves were intact. Motor examination found normal bowel and bladder function.

Physical examination found an awake, alert, and oriented person. Heart rate, respiratory rate, blood pressure, and blood gases were normal. Two laboratory investigations were noted. The sensory examination was normal. Cranial nerves were intact. Motor examination found normal bowel and bladder function.

Stroke

A 72 year old man with no significant medical history was evaluated at the Texas Tech Health Science Center after the abrupt onset of ascending generalised 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 problems, 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 awake, alert, and oriented person. Heart rate, respiratory rate, blood pressure, and blood gases were normal. Two laboratory investigations were noted. The sensory examination was normal. Cranial nerves were intact. Motor examination found normal bowel and bladder function.

Physical examination found an awake, alert, and oriented person. Heart rate, respiratory rate, blood pressure, and blood gases were normal. Two laboratory investigations were noted. The sensory examination was normal. Cranial nerves were intact. Motor examination found normal bowel and bladder function.

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 noted 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–Barré syndrome.

The patient was initially referred to an orthopaedic surgeon for possible lumbosacral spondylotic 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 neurological opinion.

Nerve conduction studies revealed significantly prolonged distal motor latency (median motor distal latency 6.7 to 9.4 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) 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 culture and viral studies were negative.

The first MRI of the brain, obtained to establish a central cause for weakness and gait abnormalities during the first week of admission, showed left parietal and superior occipital sulcal hyperintensities on the fluid attenuated inversion recovery (FLAIR) sequence, in addition to subtle enhancement with contrast administration (fig 1). A repeat MRI one week later showed mild improvement. A third MRI two months after initial presentation showed resolution of the focal abnormalities.

In the related Miller–Fisher syndrome, MRI changes have been documented in the cranial nerves, spinocebellar 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 sulcal 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, sulcal 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.

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 transient 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 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 subacute erythema of the facial skin and severe proximal muscle weakness (arm muscles: mean Medical Research Council (MRC) grade 3; 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.

Muscle 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 concentration of oxygenated and reduced haemoglobin and myoglobin. Using a modification of the Lambert–Beer law, in which physical path length is incorporated into 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 the muscle. 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 (Oxycon, Bioengineering Department, University of Applied Sciences, Zurich, Switzerland). A young woman from Aruba, aged 24 years, presented with subacute erythema of the facial skin and severe proximal muscle weakness (arm muscles: mean Medical Research Council (MRC) grade 3; 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.

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of Nijmegen, Netherlands). Using this spectrophotometer, which generates light at 905, 850, and 770 nm, it is possible to differentiate between oxyhaemoglobin/myoglobin (O2Hb/ O2Mb) and deoxyhaemoglobin/myoglobin (Hb/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 (mV2) were calculated by evaluating the rate of decrease in [O2Hb] during arterial occlusion, as previously described.1 Reoxygenation rate (ΔO2Hb) was determined as the rate of initial increase in O2Hb measured over three seconds immediately after cessation of arterial occlusion. Both mV2 and ΔO2Hb 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 (30% duty cycle), immediately followed by 45 seconds of arterial occlusion for the calculation of mV2 and ΔO2Hb. Whereas mV2 is a measure of mitochondrial function at a certain work intensity and is dependent on the vascular capacity of oxygen delivery, ΔO2Hb 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, measured non-invasively and with relative ease by NIRS, in the patient with severe dermatomyositis. Before treatment was begun, resting mV2 was slightly higher than in healthy controls (0.19 ± 0.14 ml O2/min/100 g, respectively). However, mV2 during exercise was about 60% lower than in the controls over the whole range of exercise intensities (fig 1A). After three weeks of treatment, mV2 had already markedly increased. After seven weeks, mV2 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. ΔO2Hb (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. ΔO2Hb 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. ΔO2Hb 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; b.vanEngelen@czzoneaz.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 The 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 sound sensitive 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–
100 g/kg/min. Propofol has been suggested as a possible treatment for refractory status epilepticus, although hard data of its therapeutic effect are not yet available.1 Propofol has not been used in this condition before but has been effective in two earlier case reports of severe myoclonus— one patient had chloralose poisoning and one had “encephalopathy.”11 In this condition a catastrophic anoxic-ischaemic injury may have damaged the cortex, basal ganglia, brain stem, and spinal cord and thus the origin of myoclonus remains undetermined. Propofol may terminate myoclonus through enhancement of γ amino butyric acid type A receptor. Further experience is needed, but these case reports indicate that good control can be achieved. Propofol’s additional benefit is that intermittent neurological assessment remains reliable after discontinuation of propofol.

E F M Wijdicks
Department of Neurology, Mayo Clinic, Rochester, Minnesota, USA

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Correspondence to: Dr E F M Wijdicks, Department of Neurology, Mayo Clinic-WBB, 200 First Street SW, Rochester, MN 55905, USA; wijde@mayo.edu

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Chronic asymmetric 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 adduction of the right eye and she was felt to have a right internuclear ophthalmoplegia. The patient had a chronic asymmetrical pupil and ptosis which was noted on routine examination. Our patient had a chronic asymmetrical pupil and ptosis which was noted on routine examination. She had an infranuclear right facial weakness with both orbicularis oculi and orbicularis oris, without lid synkinesis. The strength in the left facial muscles was normal. Ophthalmoplegic myopathy was suspected, and mitochondrial myopathy was confirmed by muscle biopsy as an alternative diagnostic aid.

Figure 1 Observe the wide palpebral fissure on the right, flattening of the right nasolabial fold, and a right exotropia. There was no ptosis of the upper eyelid.

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 is quite active in sports. She has smoked moderately for 30 years. She has no family 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. She had bilateral exotropia in primary gaze, with total paralysis of adduction of the right eye and mild weakness of abduction of the left eye. She also had mild paresis of the right external rectus. She had mild ptosis of the upper eyelid.

The blink reflex was normal and symmetrical, thus suggesting a non-neuropathic facial weakness, which was confirmed by electromyography. The presentation of this disorder in our patient shows how supranuclear, brain stem, neuromuscular, or myopathic abnormalities may be encountered in patients with mitochondrial disorders, either in isolation or in combination. Mitochondriopathies should be included in the differential diagnosis of progressive asymmetric facial palsies, while asymmetrical myopathic facial weakness should be included in the differential diagnosis of infranuclear facial palsies. Our patient’s genetic study identified a deletion of 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.

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N K Sharma, M Gjurati, 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

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