recovery of the cortically evoked diaphragmatic response, but deterioration of the electrophysiologically evoked phrenic nerve response, showing prolonged onset latency and reduced diaphragmatic CMAP. Nerve conduction and needle EMG of the limbs showed a severe, symmetric, axonal, sensorimotor neuropathy. These findings were consistent with a critical illness polyneuropathy. This was not clinically apparent, as myelopathy masked neuropathy. These electrophysiological results showed that a phrenic nerve paceremaker was not necessary.

The patient recovered from critical illness neuroopathy such that on day 121 he was extubated. Respiratory electrophysiological studies on day 129 showed normal diaphragmatic CMAPs after transcortical magnetic and electrical phrenic nerve stimulation. The patient was transferred to his home hospital five months after onset of the disease.

This study demonstrates the value of respiratory electrophysiological studies in localising the site of neurological causes of respiratory failure. An unusual feature occurring during this time of critical illness polyneuropathy. The diaphragmatic CMAP amplitude after phrenic nerve stimulation was lower than the CMAP amplitude evoked by spinal magnetic stimulation. Submaximal stimulation was excluded as a cause. Central enhancement of somatosensory evoked potentials is known to occur in patients with peripheral neuropathy. This phenomenon could be the explanation in our patient.

Moreover, the amplitude of magnetically evoked potentials increases in contracted muscles. In healthy subjects magnetic stimulations during forced inspiration increase the diaphragmatic CMAP by about 100%. Possibly, the increased muscle tone leads to facilitation of the recording muscle resulting in increased CMAP amplitude. Further studies will be necessary to clarify the pathophysiological mechanisms of this phenomenon.

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UDO ZIPKO
BRYAN G YOUNG
CHARLES P BOLTON
Department of Clinical Neurological Sciences, Victoria Hospital, 375 South Street, N6A 4G5 London, Ontario, Canada

Correspondence to: Dr Charles P. Bolton.


Fulminant encephalopathy due to the catastrophic primary antiphospholipid syndrome

The antiphospholipid antibody syndrome is characterised by recurrent arterial and venous thromboses associated with the presence of antiphospholipid antibodies. Neurological features can include cerebral ischaemia, multi-infarct dementia, migraine, epilepsy, transverse myelitis, and chorea. We describe a patient with catastrophic primary antiphospholipid syndrome who presented with right hemispheric dysfunction which rapidly evolved into a fulminant encephalopathy associated with multiorgan failure.

A fifty eight year old woman was admitted with a general malaise, headache, anorexia, and weight loss over a four month period, associated with the development of a painful ulcer over the right lateral malleolus. In the 24 hours before hospital admission she developed gastrointestinal symptoms, urinary incontinence, and left sided facial and limb weakness. She had a history of classic migraine for 35 years, had had several lower limb deep venous thromboses, and had been investigated for pleuritic chest pain for which no cause was established. She developed Graves' disease at 45 years of age and was treated with radioiodine followed by thyroxine. She had no relevant family medical history.

On admission there were no significant abnormalities in the cardiovascular, respiratory, or gastrointestinal systems. She had a 3 cm skin ulceration to the right lateral malleolus. She was disoriented, restless, and unable to give a coherent history. There was no meningism and the optic fundi and eye movements were normal. She had a mild dysarthria associated with a left upper motor neuron facial weakness and a mild left hemiparesis with brisk tendon reflexes and a left extensor plantar response. She also had bilateral periorbital and pout reflexes, and left sided sensory inattention.

She was thrombocytopenic (platelets 125 × 10^9/l) but her full blood count and peripheral blood film were otherwise normal. Her erythrocyte sedimentation rate was 89 mm/h and C reactive protein concentration was 386 mg/l. The prothrombin time was normal, but the activated partial thromboplastin time (aPTT) was prolonged at 37.2 s (normal range 23-35-36.4 s). The D dimer assay was normal but her fibrinogen concentration was low (1-15 g/l, normal 1-5–4-0 g/l). Her plasma urea was slightly increased at 29 mmol/l. Her plasma electrolytes, creatinine, liver function tests, bone chemistry, thyroid function, and blood glucose were normal and a veneral disease research laboratory test was negative. Urine, blood, and CSF cultures were sterile and only skin commensal organisms were isolated from the foot ulcer. A chest radiograph, ECG, echocardiogram, and brain CT were unremarkable. Lumbar puncture disclosed clear CSF, with a normal opening pressure, 6 white blood cells/μl, and normal protein and glucose concentrations.

She was treated with broad spectrum antibiotics for a presumed infection of unknown origin with a provisional diagnosis of right hemispheric ischaemic stroke. However, she became increasingly obtunded, developing signs of bilateral hemispheric dysfunction including pyramidal distribution weakness in all four limbs and bilateral extensor plantar responses. She developed livedo reticulata over her back and lower limbs, and an atrial gallop murmur was noted at the cardiac apex. Her respiratory function deteriorated, she became hypotensive and oliguric, and required assisted ventilation and inotropic support.

Thyroid microsomal antibodies were pre-

sent at a titre of 1 in 400, but other autoan-
tibody titres were negative (including dsDNA-Ab, ANCA, and Anti-GBM-Ab). Her anticardiolipin antibody concentrations were raised (serum IgG aCL 41-5 GPL, IgM aCL 25-9 MPL, normal < 10 GPL). Biopsies of the skin ulcer and an area of livedo reticulata disclosed widespread thrombosis within the small vessels but no vessel wall inflammation. Echocardiography now showed a vegetation on the mitral valve. Abdominal CT was normal and a reported past CT showed no abnormality. An ECG showed diffuse generalised slow wave activity.

After a diagnosis of catastrophic antiphos-
pholipid syndrome who presented with intravenous heparin and immunosup-
pressed with methylprednisolone (1 g intra-
venously/day), cyclophosphamide (500 mg, single dose), and plasmapheresis. Her uri-
inary output increased over the next week and cardiorespiratory support was no longer needed. Her neurological condition did not improve and she remained unaware and unresponsive with no clinical evidence of cortical function but intact brainstorm reflexes. She died 24 days after admission to hospital.

The most striking pathological finding postmortem was of widespread small vessel thrombosis; the tissues involved included the brain, myocardium, lung, kidney, skin, bone marrow, uterus, ovary, bladder, pancreas, stomach, and small intestine. Examination of the heart showed marantic vegetations of the mitral valve which were Gram stain and culture negative. The larger veins and arteries, including the coronary arteries, were patent with only mild atheroma seen.

Macroscopic examination of the cerebral hemispheres showed extensive confluent areas of laminar cortical infarction in the watershed zones. The midbrain, brainstem, cerebellum, and spinal cord were macroscopically unremarkable. Microvascular changes included small arteriolar and venu-
lar thrombotic occlusion in the brain, brainstem, spinal cord, and meninges. There was no associated inflammatory reaction (figure).

In the absence of convincing evidence for infection, the evolution of multorgan fail-
ure, together with livedo reticulata, sug-
gested the possibility of a systemic vasculitis or a coagulopathy. Disseminated intravas-
cular coagulation and the haemolytic uraemic syndrome were excluded by the absence of

Oclusive vascular lesion in the corpus striatum showing an amorphous protein plug with peripheral endothelial and macrophage proliferation. The vessel seems to be dilated at the site of the lesion. The surrounding neuropil shows a pronounced gliosis. There is no evidence of vasculitis. Magnification bar = 100 μm.
blood film or biochemical evidence of haemolysis. The duration of the history made a paraneoplastic syndrome unlikely and the chest X-ray, abdominal and cranial CT showed no evidence of malignancy. Repeated blood cultures before antibiotic therapy were negative reducing the likelihood of bacterial endocarditis. In the absence of positive ANCA or antinuclear antibodies we considered the most likely diagnostic possibilities to be ANCA-negative polyarteritis, systemic lupus erythematosus, vasculitis, thrombotic thrombocytopenic purpura, or widespread non-inflammatory intravascular thrombosis which has been associated with the presence of antiphospholipid antibodies. The negative assay for dsDNA antibodies made systemic lupus erythematosus less likely, and the previous history of recurrent venous thrombosis, leg ulceration, migraine, and the thrombocytopenia on admission were in keeping with a diagnosis of antiphospholipid syndrome.

Acute ischaemic encephalopathy has been described in association with multifocal failure and the antiphospholipid antibody syndrome, and necropsies performed on two cases disclosed similar pathological findings to those in our patient.

There is no universally accepted treatment for the catastrophic primary antiphospholipid syndrome. Various studies have reported beneficial effects from methylprednisolone, cyclophosphamide, and plasmapheresis, alone or in combination, but the role of immunosuppression is far from established.1 In this case, anti-coagulation, immunosuppression, and plasmapheresis improved her cardiac, respiratory, and renal function, but irreversible brain damage led to a fatal outcome.

PF CHINNERY PJ SHAW
Department of Neurology
PG INCE MRC Neurochemical Pathology Unit
GH JACKSON Department of Haematology,
University of Newcastle upon Tyne
RI BISHOP Department of Pathology,
Royal Victoria Infirmary, Newcastle upon Tyne

Correspondence to: Dr PF Chinnery, Department of Neurology, The Medical School, Framlington Place, Newcastle upon Tyne, NE2 4HH, UK.

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Development of the anterior cingulate syndrome in a child due to delayed necrotising methotrexate leukoencephalopathy

 Delayed necrotising leukoencephalopathy may occur after intrathecal, intraventricular, or intravenous treatment with methotrexate (MTX) mostly in combination with radiotherapy.1 A clinical picture dominated by pyramidal parases, ataxia, dysarthria, seizures, and deterioration of consciousness is reported. In one adult case of delayed necrotising leukoencephalopathy, akinetic mutism as a key symptom of one of the frontal syndromes has been reported previously.1 In adults three types of frontal syndromes are discerned: the dorsolateral frontal syndrome, the orbitofrontal syndrome, and the anterior cingulate syndrome.2 Anterior cingulate syndrome is characterised by profoundly apathetic behaviour and severe loss of initiative. Patients show a pattern of response inhibition on go-no go tests, do not speak spontaneously, and answer questions in monosyllables, if at all. They move little, are incontinent, and eat and drink only when fed. They display no emotion, even when in pain, and are indifferent to their circumstancs. The most severe form of anterior cingulate syndrome is akinetic mutism.2 We had the rare opportunity to study the development of anterior cingulate syndrome in a 13 year old boy with delayed necrotising leukoencephalopathy.

In this previously healthy and normally developed right handed boy, acute lymphocytic leukaemia was diagnosed at the age of 11 years. He was treated according to the current acute lymphocytic leukaemia protocol, vincristine, corticosteroids, and L-asparaginase. The CNS prophylaxis consisted of 24 Gray irradiation in 12 fractions and intrathecal injections of MTX delivered in three weeks (total dose 68.75 mg). Subsequently the patient received intravenous MTX and intrathecal MTX during the consolidation phase and on recurrence of acute lymphocytic leukaemia in the tests 18 months after diagnosis. When he was 13 years old he developed a left peripheral facial nerve paresis due to a second recurrence of acute lymphocytic leukaemia. The patient was treated according to a CNS recurrence protocol including intrathecal sandwich therapy of MTX in combination with cytosine-arabinoside (ARA-C) up to a total dosage of 132 mg MTX and 240 mg ARA-C.

Three weeks after the last intrathecal MTX infusion he was admitted because he had changed within four days from a talkative boy of superior intelligence into a child that only answered questions after strong stimulation.

Neurological examination showed a diminished facial expression, eye blinking, and extensor plantar reflexes in addition to a slight left peripheral facial nerve paresis.

Brain CT showed hypodense slightly swollen white matter bilaterally in the frontoparietal part of the centrum semiovale with a slight preponderance on the right side (figure, A). Repeated CSF examinations showed normal cell counts. Immunophenotyping did not show lymphoblasts.

Sponantaneous speech was almost absent. When stimulated he answered in a telegraphic style. By contrast, he could repeat long sentences and read aloud a difficult text, monotonously but without language and articulatory problems. The token test did not show language comprehension problems. No signs of apraxia were present. On a standardised memory test (15 words test) he obtained a very low score (first decile). His IQ was 76 (Groninger intelligence test1). One week later he became severely hypokinetic and developed a paralysis of the left arm and leg and was unable to make voluntary orofacial movements. Involuntary movements such as yawning and swallowing remained intact. He also became mute, but he communicated to yes or no questions by lifting the right hand.

Two weeks after admission CT showed extension of the hypodense white matter lesions into the parietal regions. Desmethylone treatment was started and subcutaneous heparin was given. The hemiparesis ameliorated and voluntary orofacial movements were again possible.

Four weeks after admission he showed a slight left peripheral facial nerve paresis and a slight bilateral pyramidal paresis more so on the left than on the right side. Grasp reflexes could be easily elicited in both hands. He was able to walk independently. He did not attempt to speak and could not be stimulated to talk spontaneously, repeat words, or read aloud. By contrast, he could name objects and answer questions by writing. He obeyed written and spoken commands. He remained in this condition for the next five weeks. Finally he died from an acute subdural haematoma, a sequel of the acute lymphocytic leukaemia.

An extensive recurrence of the acute lymphocytic leukaemia was found with lymphoblast cells in the subarachnoid spaces and in the perivascular spaces, especially of the frontoparietal regions. Large, sharply demarcated necrotic areas were seen bilaterally in the frontal central white matter, not involving the U fibres (figure, B). The cere-