LETTERS TO THE EDITOR

Intracranial venous and dural sinus thrombosis due to protein S deficiency in a patient with AIDS

Protein S is a vitamin K dependent plasma glycoprotein that inhibits blood coagulation through inactivating factors Va and VIIIa in cooperation with protein C. Deficiency of protein S, congenital or acquired, predisposes to thrombotic disease.

In postmortem studies, the prevalence of cerebrovascular disease in HIV infected patients has ranged from 11% to 34%. The causes are diverse, and include embolic and thrombotic stroke, cerebral vasculitis, and cerebral haemorrhage.¹ Decreased free protein S has been commonly found in HIV infected adults and has been associated with systemic venous thrombosis.²

To our knowledge, we report the first case of an HIV infected adult with intracranial dural sinuses and cerebral venous thrombosis due to protein S deficiency.

A 37 year old HIV infected woman was admitted with severe and persistent headache of two weeks duration in January 1994. She had no history of thrombotic events and there were no obvious precipitants of thrombosis. She had never received oral contraceptives or anticoagulants. On admission, vital signs were normal and physical and neurological examinations were unremarkable.

Laboratory studies showed a white blood cell count of $1.7 \times 10^9/L$, a CD4 cell count of $72/mm^3$, platelet count of $18.3 \times 10^9/L$, and erythrocyte sedimentation rate of 10 mm/h. Biochemical indices were within the normal range. Serological tests for syphilis were non-reactive. Tests for antinuclear, anti-DNA, anti-ENA, and antiphospholipid antibodies (anticardiolipin and lupus anticoagulant) were all negative. Prothrombin and partial thromboplastin times, and albumin, fibrinogen, anti-thrombin III, and protein C concentrations were normal. Protein S concentrations, measured by a crossed immunoelectrophoresis method, were 49% (normal 60% to 100%) and 28% (normal 65% to 125%), corresponding to free and functional protein S respectively. The family history was negative for thromboembolic disease and her parents' protein S concentrations were normal.

A urinary monoclonal antibody test concentration of 2.3 hCG/ml (normal <10) excluded pregnancy.

Electrocardiography and two dimensional echocardiography did not disclose any abnormality.

Brain MRI disclosed hyperintense signals on T1 and T2 weighted images in the left venous sigmoid and lateral sinuses. Findings from MR angiography were consistent with obstruction of these sinuses and of the left jugular vein (figure). The patient was initially treated with heparin and when adequate anticoagulation was achieved, heparin was gradually discontinued and long term acenocumarol was started. No recurrence of thrombotic or neurological manifestations have occurred during two years.

Protein S is synthesised by endothelial cells, megakaryocytes, osteoblasts, neural derived tissues, and hepatocytes. Acquired

Coronal MR angiography (venous phase) showing partial thrombosis of the lateral sinus and complete thrombosis (no opacification) of the lateral jugular vein.

decreases in protein S concentrations have been described in liver disease, nephrotic syndrome, systemic lupus erythematosus, disseminated intravascular coagulation, warfarin and oral contraceptive therapies, pregnancy, and HIV infection. The prevalence of decreased free protein S in HIV infected patients has ranged from 31% to 76%.² HIV has been found within endothelial cells of cerebral blood vessels.³ Thus it has been suggested that protein S deficiency can result from abnormal endothelial cell function during HIV infection.² Although the mechanism responsible for the decrease in protein S is unknown, the proinflammatory cytokine tumour necrosis factor- α is increased in HIV infected patients and may induce a procoagulant state on the surface of endothelial cells, down regulating synthesis of protein S.²

Some authors have reported that HIV associated protein S deficiency may predispose to deep vein thrombosis and pulmonary embolism.² Sagittal sinus thrombosis has been reported in a seronegative patient with hereditary protein S deficiency.⁴ Although cerebrovascular disease is not uncommon in patients with AIDS, only a single case of dural sagittal venous thrombosis has been reported to date, in a four month old girl during pneumococcal sepsis.⁵

To our knowledge, the patient herein reported is the first case of intracranial venous and sinuses thrombosis secondary to acquired protein S deficiency in an HIV infected adult. The present case also suggests that long term anticoagulant therapy may prevent further thrombotic events in HIV infected patients with this disorder.

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Serious neurological manifestations of ciguatera: is the delay unusually long?

Ciguatera poisoning is the commonest fish food poisoning encountered in tropical islands, especially in the Pacific.¹ The disease is usually benign, with gastrointestinal and cutaneous manifestations which resolve spontaneously within a few hours. However, serious forms of this fish poisoning, with cardiovascular and neurological disorders, have been described.¹⁻³ The ciguatoxins involved in ciguatera disturbances are competitive inhibitors of the brevetoxins and have a common binding site on neuronal voltage dependent sodium channels.⁴ Even if their action remains partially understood a prolonged axonal sodium channel activation, by contrast with other fish toxins (tetrodotoxin for instance), is now described as the main mechanism by most authors.⁴

We present the results of the retrospective analysis of ciguatera cases admitted to Gaston Bourret hospital (Nouméa, New Caledonia, South Pacific) between January 1991 and December 1995. Fifty six cases were reviewed (19 female and 37 male patients, mean age 37 (SD 15), range 2-62).

Diagnosis of ciguatera was made on clinical grounds—that is, history of fish eating and suggestive clinical manifestations. Two groups were established. In the first, patients had only common signs of ciguatera poisoning including gastrointestinal (nausea, vomiting, abdominal pain, diarrhoea) and cutaneous symptoms (pruritus, itching sensations). Patients with the usual neurological complaints of ciguatera (paraesthesia, muscle pain) were included in this group ("common" group). In the other ("neurological" group) patients had infrequent or severe neurological features—namely, vertigo, ataxia, progressive muscular weakness or sensory loss (polyneuritis), visual blurring, and stupor or confusion. The delay between the consumption of fish and the onset of ciguatera was known in 43 patients (seven of 10 in the "neurological" group and 36 of 46 in the "common" group). There was a significant difference in delay between the groups (46.9 (SD 59) hours in the "neurological" group and 4.8 (SD 5.2) hours in the "common" group ($p=0.0084$, Mann-Whitney test)). Age, sex, number of previous episodes of ciguatera, and type of fish were not significantly different between the groups (χ^2 test).

To our knowledge, this longer delay in serious neurological cases of ciguatera has never been statistically documented, although Allsop *et al* reported a long delay between the first manifestations of ciguatera and the onset of neurological signs.² Further prospective studies are needed to assess this putative characteristic of "neurological ciguatera". Ciguatoxins act on axonal sodium channels and elicit a prolonged activation. By this action, intracellular water and sodium influx could increase and induce neuronal oedema.⁴ In vitro ciguatoxins can provoke a nodal swelling and also a large increase in internodal length and volume.⁴ Changes in membrane sodium current induced by ciguatoxins have been linked to these swelling effects. Slowing of nerve conduction could be explained by both changes (nodal swelling and prolonged activation). In Guillain-Barré

syndrome, internodal length is increased early in the disease and in experimental allergic neuritis the earliest pathological signs are breakdown of the blood-nerve barrier, oedema, and infiltration of activated lymphocytes. Also, we postulate that water and uptake of sodium induced by ciguatoxins could provoke secondary disturbances in nerve fibres, which would explain the long delay in "neurological ciguatera". A striking oedema of the axonal Schwann cell cytoplasm has already been reported in vivo. In this report, the axon was shown to be compressed by axonal oedema.² Raised endoneurial fluid pressure induced by oedema might reduce nerve blood flow. Direct compressive effects or endoneurial fluid pressure could both induce nerve blood supply deficiency. Further nerve (axonal?) disturbances could be due to the ischaemic effects of oedema. In this hypothesis, neuronal oedema would have to be managed as a neurological emergency.³ Mannitol is known to be effective in the treatment of ciguatera,⁴ and its mode of action could be to suppress nodal swelling and sodium channel activation induced by ciguatoxins.

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Isolated ataxia and autonomic dysfunction: a new variant of Guillain-Barré syndrome?

Several variants of Guillain-Barré syndrome have been described including Fisher's syndrome, pure motor Guillain-Barré syndrome, pharyngeal-cervical-brachial weakness, paraparetic pattern, ataxic form, and pure pandysautonomia.¹ The connection between these variants and Guillain-Barré syndrome is based on (1) a close resemblance to some symptoms of the typical disease, (2) overlap phases between typical disease and variant syndromes, (3) electrophysiological and CSF abnormalities that confirm Guillain-Barré syndrome, and (4) exclusion of other, more common, causes of the symptomatology. We report a patient with a possible new variant consisting of progressive ataxia and profound postural hypotension without appreciable weakness or sensory symptoms.

An otherwise healthy 47 year old man developed flu-like symptoms three weeks before admission. He had a history of a bipolar schizoaffective disorder and had been treated for many years with lithium, carbamazepine, and bromoperidol. Five days before admission his gait progressively be-

came unsteady until he could not stand up without support. The day before admission he was seen at the psychiatry outpatient clinic by a consultant neurologist (GT) who concluded that he had a progressive cerebellar syndrome with areflexia of the lower limbs. Brain CT did not show abnormalities of the cerebellum or brainstem. The next day his symptoms worsened, confining him to his bed, and he was admitted to our hospital. Neurological examination of the cranial nerves was unremarkable except for a slight dysarthria. There were no abnormalities of muscle strength or sensory modalities. Finger-nose and heel-knee tests were abnormal showing intention tremor on both sides. He could sit, but not stand, unsupported. He could take a few steps with a wide based gait; the tandem gait could not be performed. Reflexes were slightly decreased in the arms and absent in the legs, and plantar responses were flexor. Serum concentrations of his medication were within the therapeutic range. Routine laboratory examinations did not disclose any abnormalities. The second day after admission he collapsed on sitting up, probably due to postural hypotension resulting from autonomic neuropathy. Sinus bradycardia was recorded on ECG. There were no other signs of autonomic dysfunction. Examination of CSF disclosed a raised protein content of 1.42 g/l with 16 leucocytes/mm³. The CSF/blood albumin ratio was high and the IgG index was slightly raised at 0.89. No oligoclonal bands were present in the CSF. At neurological examination on the second day after admission reflexes of the arms had further decreased and a slight impairment of proximal muscle strength of the legs was noted for the first time. In addition, the patient when specifically asked, complained of paraesthesia in both feet and hands. These findings prompted us to consider the diagnosis of (a variant of) Guillain-Barré syndrome.

Extensive EMG on day 7 disclosed normal conduction velocities and sensory and motor action potentials but absent F waves and delayed H reflexes in the lower limbs without signs of denervation. These findings were thought to be consistent with a proximal nerve lesion and matched early electrophysiological findings in Guillain-Barré syndrome. Serological screening results for neurotropic viruses, *Borrelia burgdorferi*, *Treponema pallidum*, and HIV-1 were negative. IgG antibodies against *Campylobacter jejuni* were detectable in serum but IgM antibodies were absent. Autoantibodies against gangliosides GM1 and GQ1b, and against sulphatides were not detectable in serum. Because of the unusual symptomatology for Guillain-Barré syndrome and the absence of pronounced weakness, treatment with intravenous immunoglobulins (IVIg) was deferred and the patient was kept under close observation.

During the next three weeks his ataxia improved slightly and increased dietary salt intake, abdominal compression using a belt, and fludrocortisone was started to alleviate his postural hypotension. However, after five weeks pronounced postural hypotension was still present which severely disabled the patient by preventing him sitting up for more than a few minutes. Therefore it was decided to treat him with IVIg at 0.4 g/kg during five days. During the next week his blood pressure increased and he was able to sit for more than an hour without collapsing. He was subsequently successfully rehabilitated and discharged from our hospital three months after

admission while capable of sitting in a wheelchair all day. After eight months he was functioning again at his premorbid level and neurological examination was unremarkable except for the inability to walk in a perfect straight line.

The presentation of this patient with isolated ataxia suggested a cerebellar disorder. The subsequent development of autonomic dysfunction and areflexia with very mild and only short lasting motor and sensory disturbances was suggestive of Guillain-Barré syndrome. Abnormalities in CSF and electrophysiological findings supported this diagnosis. During the full observation period ocular movements were repeatedly tested and always found to be normal.

As the patient's postural hypotension did not react to symptomatic treatment, we started treatment with IVIg assuming that his disease was a variant of Guillain-Barré syndrome. After IVIg treatment postural hypotension indeed dramatically improved and did not return. The positive effect of IVIg did not diminish after a few days, suggesting a specific, immunomodulating mode of action rather than a short lasting increase in blood pressure through an increase in blood protein concentrations by high dose IVIg.

A diagnosis of Guillain-Barré syndrome could not be made in our patient because he did not fulfill the diagnostic criteria of the typical syndrome.¹ Intact proprioception and vibration sense combined with pronounced ataxia argue against the presence of the sensory form of GBS and against the sensory ganglionopathies as recently reviewed by Dalakas and Quarles.²

A combination of acute sensory and autonomic neuropathy has been previously described in a 26 year old woman after Cox-sackie B virus infection.³ However, in that case there was also pronounced impairment of cutaneous sensation and extensive muscle weakness. A Japanese patient has been described with ataxia and orthostatic hypotension after infection with Epstein-Barr virus.⁴ By contrast with our patient no CSF abnormalities were noted.

We conclude that the unique combination of ataxia without loss of proprioceptive sense and severe postural hypotension as a result of autonomic neuropathy in our patient suggests either a new variant of Guillain-Barré syndrome or a new overlap syndrome of acute pandysautonomia and acute cerebellar ataxia.

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