Acute transverse myelitis as a rare manifestation of Campylobacter diarrhoea with concomitant disruption of the blood brain barrier

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ABSTRACT

We describe a case of acute transverse myelitis following Campylobacter diarrhoea in an adult. The patient presented with diplegia due to a longitudinal spinal cord lesion. The CSF demonstrated an aseptic meningitis. Oligoclonal bands and *C. jejuni*-specific IgG were detected in serum and cerebrospinal fluid at the beginning of the neurological illness. The patient was treated with antimicrobial therapy and steroids. A near full recovery was made and there were no relapses.

C. jejuni is strongly implicated in the aetiology of acute motor axonal neuropathy and Miller Fisher syndrome through molecular mimicry of neuronal gangliosides. These gangliosides are expressed throughout the nervous system yet *C. jejuni* related central nervous system disease is exceedingly rare. We conclude that disruption of the blood-brain barrier was the key event in the pathogenesis of immune mediated post-infectious myelitis in our patient.

1. Introduction

Acute transverse myelitis (ATM) is characterised by focal inflammation of the spinal cord. Diseases which commonly cause ATM fall into three broad categories: (1) demyelination; (2) multi-system inflammatory disorders; (3) infection. A diagnosis of ATM is supported by demonstrating new intramedullary inflammatory lesion(s) radiologically, and by demonstrating evidence of an intrathecal inflammatory process.

C. jejuni is commonly implicated in the aetiology of acute motor axonal neuropathy (AMAN) and Miller Fisher syndrome (MFS).[1] The pathogenic mechanism is molecular mimicry of neuronal gangliosides expressed throughout the nervous system. Yet *C. jejuni* related central nervous system (CNS) disease is exceedingly rare. There have been two previous case reports of isolated transverse myelitis associated with *C. jejuni*.[2,3]

2. Case study

A 39 year old Caucasian male, previously fit and well, developed non-dysentery diarrhoea whilst on a business trip in rural Côte d'Ivoire. The diarrhoea settled after 12 days. The patient sought medical attention 8 days later complaining of persistent headache and fever, prompting a number of investigations in the community including a stool culture which isolated Campylobacter species (fluoroquinolone sensitive). Oral ciprofloxacin was commenced. On day 22 (post diarrhoea) the patient re-presented with a 12 hr history of urinary retention, constipation, and clumsiness of gait together with sensory disturbance in the legs. By day 23 the patient had developed lower limb weakness and was unable to walk. He was subsequently admitted to our unit for investigation and treatment.

On examination the patient was lucid and orientated; his temperature was 38 °C, pulse was 75 bpm, blood pressure was 140/80 mmHg. In the lower limbs, the only demonstrable voluntary movement was of the toes. By contrast, the upper limbs showed only mild (MRC grade 4) distal left sided weakness. All of the limb reflexes were pathologically brisk. There was loss of sensation to pinprick up to the level of T10 bilaterally. The patient was incontinent of urine and faeces. Cranial nerve function was normal and there were no signs of meningism.

Blood leukocyte count was normal. The patient's C-reactive protein was 32 mg/l, and his erythrocyte sedimentation rate was 10 mm/h. Blood cultures showed no growth and serology was negative for HIV, HTLV 1&2 and schistosomiasis. Cryptococcal antigen was not detected in blood. A full autoantibody screen was normal including ANA, anti-DNA, anti-ENA and complement levels. Nerve conduction and needle electromyography studies were normal.

MRI imaging showed intrinsic intramedullary high signal from C3 to T1 consistent with myelitis (Fig. 1a). A further area of expansion and increased signal was demonstrated from T3 to T12 (Fig. 1b).

A lumbar puncture was performed immediately after initiation of empirical antibiotic treatment. Cerebrospinal fluid (CSF) findings included a white cell count of 228/mm^3 (predominantly neutrophils), a red cell count of 29/mm^3, a raised CSF protein of 5.2 g/l, and a low CSF glucose of 1.7 mmol/l (as compared with a plasma value of 5.9 mmol/l). The CSF IgG was raised at 814 mg/l, this was consistent with passive transfer of IgG across the blood-brain barrier (serum IgG was 10.3 g/l). The CSF albumin was similarly raised at 3330 mg/l (serum albumin was 30 g/l). The cerebrospinal IgG electrophoresis pattern was oligoclonal, with an identical pattern found on isoelectric focusing of serum. No organisms were seen or cultured from the CSF, including mycobacteria. CSF polymerase chain reaction (PCR) tests for herpes simplex virus, Varicella-Zoster virus, and enteroviruses were negative, as was cryptococcal antigen.

A serum sample, collected in parallel with the CSF, was tested for *C. jejuni*-specific antibodies using a CE-certified enzyme-linked immunosorbant assay (ELISA) (Virion \ Serion). Specific IgA and IgM antibody levels were normal, in keeping with infection 3–4 weeks previously, *Campylobacter jejuni*-specific IgG was raised. This test is not validated for use on CSF, however intra-thecal IgG was also detected by the test at levels in keeping with transfer of antibody across the blood brain barrier. The antibody index was 0.5.

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Fig. 1. (a) T2-weighted sagittal MRI of the spine from craniocervical junction to T12. Intrinsic expansion and high signal can be seen within the spinal cord from C3 to T1. Some degenerative vertebral change is incidentally noted from C3 to C7. (b) T2-weighted sagittal MRI of the spine from T8 to sacrum. Here a further area of expansion and increased signal is demonstrated from T3 to T12.

The patient received empirical ceftriaxone (2 g twice daily), acyclovir (950 mg three times per day intravenously), and doxycycline (100 mg daily). Antimicrobial therapy was given for one week and then stopped. High dose dexamethasone was administered from the time of admission and gradually tailed off over a period of two months. One month after admission the weakness in the left hand had resolved and the patient was able to move his proximal lower limb muscles voluntarily. Interval scanning at this point showed complete radiological remission of the lower cord lesion and near complete resolution of the upper lesion. After two further months of rehabilitation the patient was able to walk independently. The neurological recovery was sustained for three years, with no further relapses.

3. Discussion

Our patient developed an ATM, associated with stool culture positive *C. jejuni* enteritis. The clinical sequence appeared to involve resolution of diarrhoeal symptoms within 12 days, followed 8 days later by meningeal symptoms and the development of ATM. There was CSF evidence of meningitis accompanying

MRI evidence of ATM. The diagnosis of prior campylobacter gastroenteritis was further substantiated by raised serum campylobacter-specific IgG. There was evidence of passive transfer of these antibodies into the CSF.

The aetiological role of *C. jejuni* in two other neurological diseases (AMAN and MFS) has been explained by the molecular mimicry between particular lipopolysaccharides expressed on certain strains of *C. jejuni*, and particular human gangliosides (sialylated glycosphingolipids highly concentrated in plasma membranes of the peripheral and central nervous system), namely GM1, GD1a, and GQ1b.[4] In a study of 33 AMAN patients, 64% demonstrated anti-GM1 IgG and 45% anti-GD1a.[5]

Gangliosides are highly expressed in the CNS but autoimmune CNS disease is exceptionally rare. The blood-CNS barrier, which is usually much tighter than the blood-nerve barrier, is likely to be protective against *C. jejuni* related autoantibodies in most cases. In our patient the transverse myelitis CSF picture was one of an aseptic neutrophilic pleocytosis, and our antibody index calculation of 0.5 (for anti-*C. jejuni*) was consistent with passive transfer of antibodies through a disrupted blood-brain barrier. The event which caused this blood-brain barrier disruption in unknown, but we propose that such a disruption occurred concomitantly with the *C. jejuni* infection.

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Patrikios syndrome in two patients with treatable flail-leg weakness

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ABSTRACT

Flail-leg syndrome or lower limb diplegia is a form of motor neuron disease characterized by a slower progression rate. The differential diagnosis with motor neuropathy is important. We present two patients with a previous diagnosis of amyotrophic lateral sclerosis (ALS)–flail-leg syndrome, in whom neurophysiological studies suggested proximal conduction block.

Both patients responded to immunomodulatory therapy, which suggested an immunologically mediated, treatable flail-leg syndrome phenotype. We stress the importance of fasciculations in the diagnosis of ALS, and the study of nerve root conduction in the differential diagnosis.

1. Introduction

In his 1918 thesis supervised by Pierre Marie, Jean Patrikios described 21 patients with amyotrophic lateral sclerosis (ALS). In five of them he performed autopsies. The typical "paraplégie flasque complete á aspect polynévritique" (distal flail-leg syndrome) was observed in four patients. In two of these four, post-mortem studies confirmed a severe loss of lower motor neurons in the lumbosacral spinal cord.[1] Clinical progression was slow and lower limb deep tendon reflexes were weak or absent, suggesting a diagnosis of polyneuropathy.[1]

Since then similar cases have been reported, but not all corresponded to a syndrome of predominantly distal weakness without upper motor neuron signs.[2–4] Wijesekera et al.[3] noted slower progression, longer diagnostic delay and better survival (mean survival of 69 months) in this group of patients. Those reports did not differentiate between distal onset, as described by Patrikios, and predominant proximal weakness. We describe two patients, with a previous diagnosis of distal flail-leg syndrome, who showed electrophysiological features of proximal motor neuropathy, and improved with immunomodulatory therapy.

2. Case report

2.1. Patient 1

A 41-year-old woman was referred to us for a second opinion. She gave a 5-year history of progressive lower limb weakness beginning with distal weakness of the left leg, which slowly progressed to involve proximal muscles of the same limb and to involve the contralateral leg. She had been confined to a wheelchair for 6 months. She did not report fasciculations, cramps or bulbar, upper limb or sphincter symptoms.

On examination, the patient had severe asymmetrical distal leg weakness (Table 1). In the legs, tendon reflexes and plantar responses were absent, and there was moderate generalized atrophy but no fasciculations. Sensory examination did not reveal

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