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Case Report

Campylobacter jejuni-induced acute transverse myelitis

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Study design: Case report.
Setting: University Hospital of Antwerp, tertiary referral hospital of the University of Antwerp, Edegem, Belgium.
Case report: *Campylobacter jejuni* infection is related to various syndromes in which the peripheral nervous system is involved. An immune response is triggered through molecular mimicry between gangliosides of the peripheral nervous system and lipo-oligosaccharides of *C. jejuni*. We report a case of a previously healthy 17-year-old girl, who developed clinical manifestations of acute transverse myelitis (ATM) 7 days after a culture-proven *C. jejuni* enteritis. High titres of serum IgG antibodies to the ganglioside GM1 were found in the acute phase of disease, which decreased with clinical recovery. These antibodies cross-reacted with *C. jejuni* lipo-oligosaccharides, indicating that *C. jejuni* infections may induce ATM.
Conclusions: Only a few cases of *C. jejuni* infection associated with demyelination of the central nervous system or spinal cord have been described. Physicians should be aware that *C. jejuni* might be another cause of transverse myelitis.
Sponsorship: None.
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Introduction

Campylobacter jejuni is the most frequent cause of antecedent infection in Guillain–Barré syndrome (GBS).[1] Patients with GBS as a postinfectious sequel from a *C. jejuni* enteritis often have detectable anti-GM1 antibodies.[2]

We report a case of acute transverse myelitis (ATM) in a 17-year-old female after she developed a *C. jejuni* enteritis treated with antibiotics. Cross-reactive IgG antibodies to *C. jejuni* lipo-oligosaccharides and GM1 were demonstrated in serum, indicating that *C. jejuni* by molecular mimicry may also induce ATM similarly as in GBS.

Case report

A 17-year-old previously healthy female was admitted to our hospital with a rapidly evolving quadriparesis, severe back pain and atony of the urinary bladder. Her history started 12 days before admission, when she consulted her general physician because of diarrhoea and fever. Stool cultures revealed a *C. jejuni* infection, which was treated with oral ofloxacine (200 mg 2 × / day). Her neurological symptoms started 1 week later: she consulted her general practitioner because of generalised muscle pain, a rigid neck and a painfully rigid left hand. Routine blood investigations at that moment only showed a slight increase in leucocytes (10 690/mm^3, reference value 4000–10 000/mm^3) and SGPT (28 U/l, reference value <22 U/l). A symptomatic treatment consisting of paracetamol q6h and an intramuscular injection with diclofenac was prescribed. Four days later, the patient was admitted to our hospital for further diagnostic work-up. On clinical examination, we found a bilateral rotatory nystagmus, a T4 sensory level, weakness of both arms and legs (most pronounced in the left upper leg with MRC grade 2/5 of the quadriceps muscle), symmetrical hyper-reactive tendon reflexes, a bilateral non-sustained ankle clonus and an atony of the bladder with a residual volume of 3 l. Magnetic resonance imaging (MRI) of the cervical and thoracic spinal cord showed T2-hyperintense lesions, involving cervical and upper thoracic segments of the cord. The signal abnormalities were most pronounced

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from C2 to C7 (Figure 1). After intravenous contrast administration, there was some enhancement along the anterior surface of the cervical spinal cord (not shown). A brain MRI, obtained on the same day, revealed inhomogeneous signal changes in the medulla oblongata and in the posterior part of the pons on T2-weighted imaging and fluid attenuation with inversion recovery (FLAIR) (Figures 2 and 3). These lesions were contiguous with the medullary lesions in the spinal cord. As no other lesions were found supratentorially on MR examination, the diagnosis of multiple sclerosis could not be retained.

Both the clinical and the radiological findings pointed to the diagnosis of ATM of the cervical spinal cord also with brainstem involvement.

An extended aetiological screening for infectious or systemic diseases was carried out.

Blood analysis revealed normal leucocytes, normal electrolytes, normal liver enzymes, a normal C-reactive protein level, elevated creatine kinase of 237 U/l (normal value 30–135 U/l), a normal serum angiotensin-converting enzyme level and normal titres of rheumatoid factor and antinuclear antibodies.

Serological studies in the acute phase, 5 days after onset of her neurological complaints and after 3 weeks during reconvalescence, showed no evidence for infections with *Mycoplasma pneumoniae,* toxoplasma, cytomegalovirus (CMV), herpes simplex virus (HSV), varicella–zoster virus (VZV), Epstein–Barr virus (EBV),

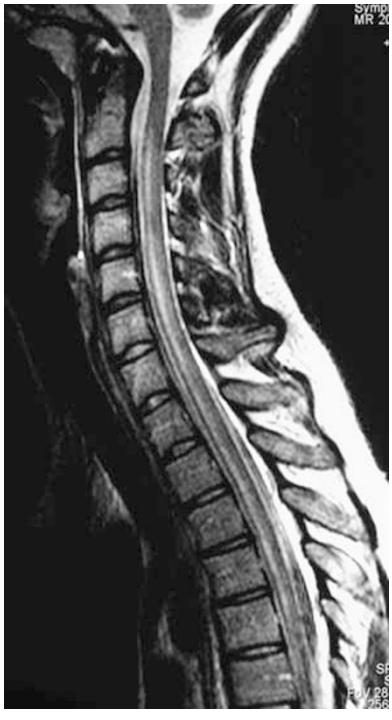

Figure 1 Midsagittal turbo spin echo T2-weighted image (TR/TE: 2900/98 ms) through the cervical spine. Within the spinal cord, there is a long linear area of hyperintensity, involving the cervical and upper thoracic segments of the cord

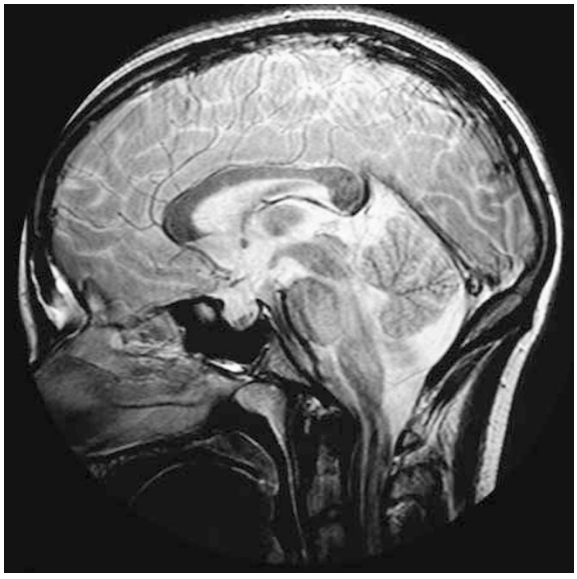

Figure 2 Midsagittal turbo spin echo T2-weighted image (TR/TE: 3800/74 ms) shows an ill-defined area of increased signal intensity in the brainstem. The hyperintensity predominantly involves the posterior pons and extends into the medulla oblongata

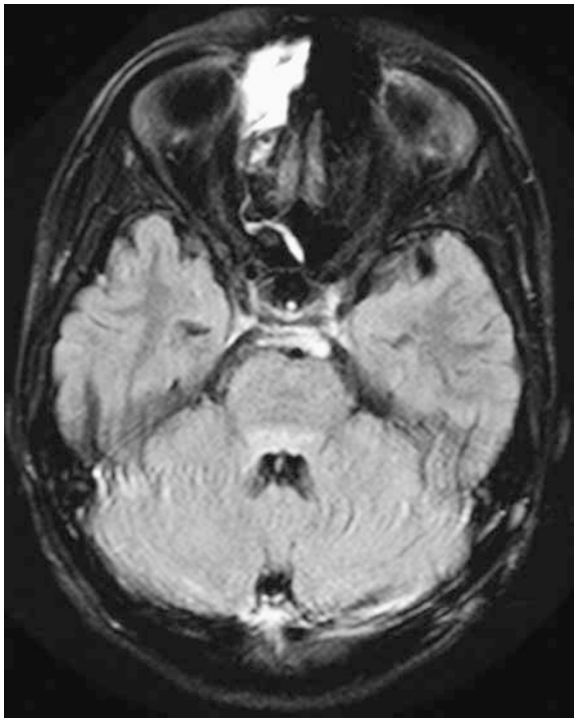

Figure 3 Axial turbo fluid attenuation with inversion recovery (FLAIR) image (TR/TE/TI: 9000/108/2500 ms) through the brainstem at the level of the mid-pons. There is a focal area of increased signal intensity in the posterior part of the pons, near the floor of the fourth ventricle

measles, human immunodeficiency virus (HIV) 1 and 2, hepatitis A, B and C virus, influenza A and B virus, Coxsackie B virus, polio 1–2–3 virus, *Borrelia burgdorferi* and *Treponema pallidum*. Also blood cultures remained negative.

Analysis of cerebrospinal fluid (CSF) revealed 12 leucocytes/mm^3 with predominantly lymphocytes (98%), <2 erythrocytes/mm^3, a normal glucose of 61 mg/dl, a normal protein of 32 mg/dl, normal lactate acid and normal protein electrophoresis. Serological studies on CSF were negative for CMV, HSV, VZV, *Borrelia*, *T. pallidum* and EBV. CSF cultures were sterile and polymerase chain reaction (PCR) for enteroviruses, HSV and EBV all remained negative.

Electromyography did not show any abnormalities ruling out peripheral nervous involvement.

The patient was transferred to the intensive care unit and treated with methylprednisolone 1000 mg q24h (for 5 days) and acyclovir 10 mg/kg q8h intravenously (until the PCR on HSV and EBV was carried out and remained negative). Levofloxacine 500 mg q24h orally was continued in view of the previous *C. jejuni* infection.

The clinical condition of our patient did not improve until 6 days after the onset of the symptoms. On day 11 however, she could walk again and she had regained most of her muscle power. Sensory function had also returned to normal, but reflexes remained brisk in the lower limbs. Bladder function remained compromised for a longer time, probably owing to the initial distension, but after 23 days this problem resolved too and urodynamic examination showed no abnormalities. The patient could leave the hospital after 24 days in good condition, with slight muscle weakness especially at the left side, more prominent in the leg than the arm and small difficulties in fine motor movement. She was further treated with physiotherapy.

An MRI of the thoracic spine after 6 weeks was normal.

Antibody testing as aetiological confirmation

Serum was tested in ELISA for IgG and IgM antibodies to gangliosides according to methods previously described.[3] Acute-phase pretreatment serum contained high titres of anti-GM1 IgG (1:6400) and IgM (1:400) antibodies, which were decreased in a serum sample obtained at 6 months: IgG (1:200) and absent IgM. Both samples were negative for IgG and IgM antibodies to GM2, GM3, GD1a, GD1b, GD2, GD3, GT1a, GT1b and GQ1b. In the acute-phase serum sample also IgG antibodies were found to lipo-oligosaccharides (LOS) from the *C. jejuni* 11 168 reference strain, which is known to contain mimicry with GM1. No or low titre antibodies were found to LOS from two GM1 mimicking *C. jejuni* isolates from GBS patients with anti-GM1 antibodies (GB2 and GB11) or to LOS from a *C. jejuni* enteritis control without ganglioside mimicry (O:3). In inhibition ELISA it was demonstrated that serum anti-GM1 IgG antibodies from the patient cross-reacted with LOS from *C. jejuni* 11 168 and in less amount with GB2 and GB11, but not with from the *C. jejuni* control strain.

Discussion

ATM is a heterogeneous clinical syndrome, characterised by the development of a focal inflammation of the spinal cord, resulting in motor, sensory and autonomic dysfunction. It is a rare disorder of infectious, postinfectious or inflammatory aetiology with an incidence of 1–4 new cases per million per year. Other diseases such as compressive myelopathy, syphilis, malignant neoplasm and spinal arteriovenous malformation should be excluded.[4] In most of the cases there is a clearly defined border of sensory dysfunction and common symptoms are paraparesis of the legs, bladder dysfunction and paresthesias. Spinal MRI and lumbar puncture often show evidence of acute inflammation. ATM usually is a monophasic disorder and is treated with high doses of corticosteroids and antimicrobial agents if an infectious aetiology is suspected. The prognosis is variable and sequelae are common.

Our patient had developed a *C. jejuni* enteritis, proven by stool culture, followed by a postinfectious ATM. We based our diagnosis of ATM on the criteria proposed by the Transverse Myelitis Consortium Working Group.[4] To differentiate idiopathic ATM from ATM attributed to an underlying disease, we executed another set of examinations, guided by the history and clinical examination: there was no evidence for exposure to virtually all microbial and viral organisms known to cause ATM as proven by culture, serology or PCR. Autoimmune diseases or other causes were also excluded.

Because of the antecedent *C. jejuni* infection, we performed another test: serology for antiganglioside antibodies. Very high levels of IgG antibodies against GM1 were found also in the early phase of the disease (day 6 after onset) as in the late phase (6 months after the acute onset). Together with the presence of high titres of IgM antibodies in the early but not the late phase, these data are conclusive of recent exposure to *C. jejuni* and *C. jejuni*-related demyelination. Unfortunately, the *C. jejuni* strain from our patient was not available for cross-reactivity studies but studies, with different *C. jejuni* species, demonstrated the expected cross-reactivity with the antibodies from our patient.

C. jejuni is a genetically highly variable spiral, flagellated bacillus. *C. jejuni* enteritis is characterised by watery diarrhoea and abdominal cramps. *C. jejuni* is the most common antecedent infection of GBS and has been reported in up to 4–66% of cases.[5] Clinical enteritis may be absent in 30% of *C. jejuni*-associated GBS: in these cases there is only serologic evidence of the previous bacterial infection. From the known incidences of GBS and documented *C. jejuni* enteritis, it can be deduced that only about one in a thousand cases of symptomatic *C. jejuni* enteritis is followed by GBS. A large number of strains are recognised, based on their antigenicity or direct DNA comparisons. Uncommon strains of *C. jejuni* are often isolated from GBS cases.

Anti-GM1 antibodies are most frequently associated with *C. jejuni* enteritis preceding GBS[1] but electromyo-

Table 1 Overview of all reported cases of *C. jejuni*-related central nervous system demyelination

Reference	*Type of CNS demyelination*	*Age/ gender*	*C. jejuni diagnostics*	*Anti-GM1 antibodies*	*Peripheral nerve damage*	*Outcome > 6 months after onset*
Nasralla *et al*[12]	Vasculitis predominantly involving grey matter No demyelination	4/F	Stool	NT	NT	Unknown
Huber *et al*[14]	ADEM	23/M	Serology	IgG positive in acute phase, unchanged after 6 months	Acute motor axonal polyneuropathy	Mild distal paresis legs, slight frontal lobe disturbances
Aberle *et al*[11]	TM	32/M	Stool serology	NT	None	No sequelae
Orr *et al*[13]	ADEM	24/M	Stool	NT	NT	No sequelae
Gaig *et al*[15]	ADEM	38/F	Stool	IgG positive in acute phase, negative after 5 months	Possible on clinical grounds, not supported by EMG	Neurogenic bladder dysfunction
Present case report	TM	17/F	Stool	IgM and IgG positive in acute phase, reduced after 6 months	None	No sequelae

ADEM, acute disseminated encephalomyelitis; CNS, central nervous system; TM, transverse myelitis; M, male; F, female; NT, not tested

graphic studies in our patient showed no abnormalities, excluding the existence of a concurrent GBS.

Anti-GM1 antibodies are directed against gangliosides. These are glycosphingolipids characterised by the presence of sialic acid (*N*-acyl neuraminic acid) linked to the oligosaccharide core.[6] Sialic acid is also found as a surface antigen on *C. jejuni*.[7] An antibody response against this surface antigen can therefore cross-react with human gangliosides and cause clinical disease.[8] This process is called molecular mimicry.

Anti-GM1 titres can also be increased in patients with lower motor neuron disease, sensorimotor or motor neuropathy with or without multifocal conduction blocks. However, they do not increase nonspecifically after neural injury or inflammatory disease.[9]

The mechanism of molecular mimicry with anti-GM1-antibodies has been suggested in one other case report about ATM. In this case the myelopathy was part of an antiphospholipid syndrome and was triggered by a pinworm infestation (*E. vermicularis*). This pinworm also contains ganglioside GM1 in its lipid composition. The authors argued that anti-GM1 antibodies also bind to oligodendrocyte–myelin glycoprotein, which is a constituent of the myelin of the central nervous system.[10] This suggests that anti-GM1 antibodies can also cause central nervous disease as in our case.

The association between *C. jejuni* and central nervous system disease was found in only a few other cases, summarised in Table 1:[11–15] one other case of TM[11] with specific antibodies in serum and CSF, one of a postinfectious encephalopathy in a child,[12] in which case brain biopsy confirmed vasculitis predominantly involving the grey matter, and three cases of acute disseminated encephalomyelitis (ADEM). In one of these ADEM cases, only a temporal association was demonstrated and concurrent peripheral nervous system involvement was not excluded by nerve conduction studies.[13] In another case there was a proven coexisting acute motor axonal neuropathy.[14] In the third case, as in our case study, the authors also demonstrated anti-GM1 antibodies.[15]

It is not clear why in neurological sequelae of *C. jejuni* enteritis nearly always only peripheral nerves are involved. Moreover, in some articles ATM is considered as an overlap syndrome with GBS and cases have been described of patients with evidence of both diseases.[16] Remarkably, all patients with *Campylobacter*-associated acute demyelination survived and, as far as reported, evolution to a good clinical neurological recovery was observed (Table 1). ATM is a rare heterogeneous disorder often associated, however, with poor neurological outcome, that is, persistent paresis. In view of the low number of *Campylobacter*-associated cases, any comment on the prognosis of *Campylobacter*-associated acute demyelination is not useful.

There are some remarkable parallels in this case of ATM with GBS in which the crucial role of *C. jejuni* in the pathogenesis has firmly been established. Firstly, the patient had a culture-proven *C. jejuni* enteritis 7 days before the first neurological symptoms. Secondly, the ATM clearly had a monophasic course in which the patient recovered completely. Thirdly, high titres of IgM and IgG antibodies to GM1 were demonstrated in the acute phase, which declined during clinical improvement. Fourthly, these antibodies could cross-react with

GM1-mimicking LOS from *C. jejuni* strains from GBS patients. Physicians should be aware that *C. jejuni* might be another cause of transverse myelitis.

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