Acute encephalopathy associated with *Campylobacter jejuni* enteritis

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Running title: Campylobacter jejuni - induced encephalopathy

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ABSTRACT

We present for the first time a case of acute encephalopathy in an adult patient induced by *Campylobacter jejuni* enteritis. Possible pathogenic mechanisms and importance of neuropsychological testing in the assessment of infection related encephalopathy are discussed.

INTRODUCTION

Campylobacter enteritis is a leading cause of acute diarrhea worldwide. The most important species are *Campylobacter jejuni* and *Campylobacter coli*. Campylobacters cause both diarrheal and systemic illnesses [1].

The most common neurological complication associated with Campylobacters is Guillain-Barré syndrome (GBS) [2]. The Campylobacter outer membrane structures containing sialic acid and their resemblance to those seen in the human gangliosides explain the development of GBS following Campylobacter enteritis.

Other neurological complications such as meningoencephalitis and encephalopathy are extremely rare [3-5]. The exact pathogenic mechanisms of those disorders are unknown.

Here we present a case of acute encephalopathy associated with *Campylobacter jejuni* enteritis. Possible pathogenic mechanisms and the importance of neuropsychological testing in the assessment of infection related encephalopathy are discussed.

CASE REPORT

A 22-year old white female was admitted to the hospital because of two-day history of fever, headache, abdominal cramps, watery diarrhea and rapid onset of neurological deterioration.
Her previous medical history was unremarkable. There was no history of behavioral disturbances, herpes labialis, arthritis, rash, hematochezia or melena, head injury, exposure to tuberculosis, toxins and animal bites, drug and alcohol abuse, any kind of eating disorder or other illnesses in recent months.

On admission, she was febrile, dehydrated, hypotensive, confused and drowsy. An attempt to wake her up resulted with excessive fear, hallucinations and aggressivness. On examination the pulse was 98, respiration 14, mean arterial pressure 65 mmHg, central venous pressure (CVP) +4 cm H_2O, SpO_2 96% without supplemental oxygen and temperature 39,5^oC. Glasgow Coma Scale score (GCS) was 11. There were no skin lesions, lymphadenopathy or splenomegaly observed. The abdomen was soft and painless. Neurologic examination revealed transitory divergent strabismus, symmetrically attenuated deep tendon reflexes and generalized hypotonia. Meningismus was present. Plantar reflexes were normal.

Lumbar puncture on admission revealed completely normal cerebrospinal fluid (CSF) with normal opening pressure. CSF PCR assay for HSV, enterovirus, *Epstein-Barr virus*, *West-Nile virus* and *Neisseria meningitidis* were negative. CSF and blood cultures taken before antibiotic administration were negative.

The peripheral white blood cell count was 11,4 x 10^9/L (neutrophils 90%, lymphocytes 4% and monocytes 6%), platelet count 186 × 10^9/L, and hemoglobin level 122 g/L. Erythrocyte sedimentation rate was 10 per hour. C-reactive protein was 93 mg/L. The level of potassium was 3,4 mmol/L. Acid-base status of the patient was normal. Serum concentration of glucose, sodium, chloride, urea nitrogen, creatinine, ionized calcium, phosphorus and magnesium, total bilirubin, aminotransferases, lactate dehydrogenase, creatine kinase and alkaline phosphatase were normal. There were no abnormalities on serum protein electrophoresis. Prothrombin and partial-thromboplastin times were normal.

Chest radiography and electrocardiogram showed no abnormalities. A brain CT scan on admission was unremarkable. An electroencephalogram (EEG) performed on admission detected diffuse background slowing with intermittent diffuse spiky theta waves.

The initial treatment consisted of intravenous ceftriaxone and acyclovir. Fluid replacement with isotonic saline and vasopressor support were required for the first 24 hours. On the second day, the patient`s condition significantly improved. Blood pressure autoregulation was regained and normal urine output was established. Fever, consciousness disturbance as well as diarrhea completely resolved. However, severe headache, fatigue, attention and short time memory difficulties persisted. Neurologic examination was otherwise normal.

The control lumbar puncture again revealed normal CSF. The fundoscopic examination was unremarkable. Optic nerve sheath diameters (ONSD) were within normal range (4,8 mm on the right eye and 4,9 mm on the left eye).

On day 7, the second EEG showed mild background slowing and bilateral temporo-occipital irritative changes. The stool culture grew *Campylobacter jejuni*.

During the following week the headache gradually subsided, however, mild cognitive dysfunction persisted. On day 13, a brain MRI showed normal appearance of the meninges while edema, demyelination, haemorrhage or other abnormalities were not found.

On discharge from the hospital the GCS was 15, Glasgow Outcome Scale score (GOS) was four and Karnofsky perfomance score was 80% (normal activity with effort; some signs or symptoms of disease) [6,7].

One and a half month after admission to the hospital, the patient underwent neuropsychological testing and EEG examination. The following techniques were used in neuropsychological testing: interview, AVLT (audio verbal learning test), FAS (controlled association test), BNT (Boston naming test), PM (progressive matrices) and PIE (emotions profile index). The neuropsychological testing showed above-average intellectual potential and in general regular cognitive functioning. However, minor abnormalities in verbal fluency test were noted. The control EEG was normal and the Karnofsky performance score was 90%.

DISCUSSION

We have described a case of *Campylobacter jejuni* - associated encephalopathy in an immunocompetent patient. As far as we know, this is the first reported case of such encephalopathy in adults. Campylobacter enteritis in our patient had a self-limited course with resolution of symptoms over several days. There was no bacteremia or deep focus of infection. The neurologic symptoms significantly surpassed the signs of Campylobacter infection resulting in diagnostic and treatment doubts. The reports of neurological complications associated with Campylobacters, except for GBS, are scarce and limited to paediatric patients [3-5]. In contrast to previously reported patients, there were considerable differences. The encephalopathy in our patient was characterized with the absence of inflammatory CSF findings, brain edema, demyelination and intracranial hypertension.

The severity of the initial clinical presentation in our patient demanded serious consideration of several diagnostic possibilities before the final therapeutic decision.

The altered mental status accompanied with fever and abnormal eye movements might be suggestive of alcohol withdrawal syndrome or other metabolic encephalopathy precipitated by acute infection. However, this possibility in well-nourished and previously healthy woman without history of drug and alcohol abuse or any kind of eating disorder was very unlikely.

Of particular interest was consideration of possible viral encephalitis or encephalitic form of meningoccocal disease. Up to 10% of patients with viral encephalitis in the early phase of disease can have completely normal CSF findings [8,9]. Therefore, the control lumbar puncture 24-48 hours after admission is absolutely indicated if clinical presentation is suggestive of viral encephalitis. Consciousness disturbance in association with relative or absolute bradycardia could be an ominous sign of intracranial hypertension. In order to assess the intracranial pressure in our patient, optic nerve sheath diameters (ONSD) were measured. ONSD is accepted and considered to be an appropriate technique for noninvasive assessment of intracranial pressure (ICP). In adults ONSD greater than 5.8 mm correlated with a mean cerebrospinal fluid (CSF) pressure of more than 20 mmHg [10].

Encephalopathy in our patient can be easily explained by cerebral hypoperfusion, so often seen in the elderly during sepsis or intestinal infections with dehydration. However, the interruption of the cerebral blood flow (CBF) mechanoregulation, especially in the absence of CO_2 concentration

alterations, in previously healthy young woman with mean arterial pressure (MAP) of 65 mmHg would be quite unusual [11].

Our patient was dehydrated but not hypovolemic (CVP +4 cmH_2O). The co-existence of hypotension, relative bradycardia (absence of tachycardia), consciousness disturbance, hypotonia and attenuated deep tendon reflexes at admission could be attributed to the severe brain and spinal cord dysfunction or neurogenic shock. A transient dysfunction of autonomic pathways within the spinal cord accompanied with unopposed vagal activity potentially caused by endotoxaemia might be a possible explanation. Nevertheless, further course of disease with persisted, although abated, neurological symptoms despite completely resolved infection argued against the toxin-related disorder. In addition, despite Campylobacter's outer membrane containing lipopolysaccharides with endotoxic activity and ability to produce extracellular toxins as well, their concentration was considered generally low and of doubtful clinical significance [1].

The anti-ganglioside antibodies assay unfortunately was not done. However, because of the short time period (24 hours) between enteritis and first neurologic symptoms the probability of anti-ganglioside antibodies involvement in pathogenesis is low.

The possibility of an acute disseminated encephalomyelitis (ADEM), despite of MRI and CSF normality we couldn't completely discard because of several reasons. First, pleocytosis in ADEM tends to be less marked than in acute infectious encephalitis, and it may be completely absent [8]. Second, ADEM does not necessarily produce changes visible by MRI of the brain or spinal cord even if clinical findings clearly reveale injuried level and area, respectively [12]. In some cases of ADEM the appearance of the MRI abnormalities is delayed for several days, even weeks after the clinical onset, while in others MRI remains normal throughout the course of the illness (13,14). Third, the polysymptomatic features including meningism with suggested limbic system affection and the course of disease were compatible with inflammatory CNS disease - autoimmune encephalopathy, primary CNS vasculitis or ADEM. In addition, minor abnormalities demonstrated in verbal fluency test in our patient were congruent with frontal and temporal lobe dysfunction [15].

If we assume the frequent association of diverse neurological complications with Campylobacters, the clinical presentation and the course of disease in our patient accompanied with EEG finding and neuropsychological test is strongly suggestive of immune-mediated acute

encephalopathy. Despite the crucial finding, according to the classic definition (MRI - white matter lesions) is missing, we conclude that our patient most probably suffered from an ADEM.

Since the routine MRI scan of the brain failed to demonstrate brain injury, a diffusion-weighted imaging (DWI) should be provided in similar cases.

Owing to neuropsychological tests, we were able to track the patient's cognitive status and better assess the outcome of disease. The importance of neuropsychological tests in patients with CNS infections and related diseases should be emphasized because such testing provides a number of benefits. Neuropsychological tests enable a clinician to analyze the patient's cognitive status, as well as emotional, psychological, motor and sensory functions. Finally, the results of testing enable focused rehabilitation treatment if needed.

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