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A young woman with persistent nausea, vomiting and hiccups

EDUCATIONAL CASE REPORT

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BACKGROUND

Neuromyelitis optica is an inflammatory syndrome of the central nervous system, associated with anti-aquaporin-4 IgG antibodies. It is associated with severe neurological symptoms and risk of permanent neurological disability. The diagnosis can be established on the basis of clinical core characteristics of neuromyelitis optica, together with serological testing for anti-aquaporin-4 IgG antibodies and magnetic resonance imaging of the central nervous system.

CASE PRESENTATION

We describe the case of a young woman presenting with obstipation, persistent nausea, vomiting and hiccups. The initial diagnostic workup confirmed obstipation, but did not find any underlying gastrointestinal pathology that could explain her persistent symptoms. Her condition deteriorated, she was unable to eat or drink without inducing vomiting, and eventually she received parenteral nutrition. Further diagnostic workup included magnetic resonance imaging of the brain, which revealed a T2-hyperintense lesion in the medulla oblongata, more specifically in the area postrema. Neurological and neuroradiological assessment led to a tentative clinical diagnosis of neuromyelitis optica spectrum disorder with a well-described, but rare, presentation: the area postrema syndrome. The diagnosis was confirmed by serological testing for anti-aquaporin-4 IgG antibodies. She was successfully treated with methylprednisolone with complete remission of symptoms. Patients with neuromyelitis optica spectrum disorders frequently experience relapses of the disease if untreated, and she was therefore treated with rituximab to prevent future relapses.

INTERPRETATION

This case is a reminder that common gastrointestinal symptoms may be caused by diseases of the central nervous system.

A previously healthy young women developed subacute nausea, vomiting and persistent hiccups. The underlying cause proved to be a known presentation of a rare condition.

A young woman was admitted to the medical department of her local hospital after a ten-day clinical history of nausea and vomiting several times a day. The nausea was persistent and without fluctuations in intensity whether the patient was at rest, active or changing position, and she vomited after every meal. The preceding month she had been rather constipated, but otherwise felt well. She was not sensitive to light or dizzy, and did not have abdominal pain or headache. Three days prior to hospitalisation she developed persistent hiccups that kept her awake at night. She had three consultations with an A&E doctor during the week prior to her hospitalisation, and at the last

consultation reported that she had seen blood and mucous in her faeces. The A&E doctor perceived her condition as undiagnosed and in need of immediate assessment, and admitted her to the medical department of the local hospital. On admission she was afebrile with a temperature of 37.2 °C, no respiratory or circulatory distress and a respiratory rate of 12 breaths/minute, pulse 72 beats/minute and blood pressure 118/78 mm Hg. A clinical examination revealed normal organ status. Clinical biochemistry tests revealed hyponatraemia 135 mmol/L (reference range 137–145), hypokalaemia 3.0 mmol/L (3.5–5.0) and slight thrombocytosis 439 × 10^9/L (165–387 × 10^9), but otherwise normal values, including CRP < 1 mg/L (< 5), Hb 13.9 g/dL (11.7–15.3), leukocytes 10.5 × 10^9/L (3.5–11.0 × 10^9/L), ALT < 10 U/L (10–45), ALP 67 U/L (42–102), amylase 51 U/L (25–120) and bilirubin 14 µmol/L (< 21). Analysis of calprotectin in the faeces revealed a slightly elevated value of 215 mg/kg (< 50). An ultrasound scan of the abdomen revealed normal conditions in the pancreas, liver, bile ducts, spleen, kidneys and urinary bladder. An X-ray scan of the abdomen revealed findings consistent with obstipation.

At the time of hospitalisation, obstipation was suspected of being the underlying cause of the symptoms, but osmotic laxatives were ineffective and enema treatment could not be performed because of the pronounced nausea. The nausea and vomiting and the relatively minor abnormality of the blood and calprotectin values were interpreted as secondary to obstipation, which at that time had persisted for a good month. Symptomatic treatment of the nausea with metoclopramide, and subsequently ondansetron, had no effect.

The diagnosis was undetermined, and the patient was referred for endoscopy and further diagnostic imaging. Gastroscopy, colonoscopy, small-bowel follow-through with fluoroscopy and CT abdomen did not reveal any pathology other than slight, distal oesophagitis through gastroscopy and a thickened colon mucous membrane through colonoscopy, which were interpreted as changes secondary to persistent vomiting and obstipation. Microbiological tests revealed negative hepatitis serology and findings consistent with previous infection with cytomegalovirus and Epstein-Barr virus. No antinuclear antibodies or lupus anticoagulant were detected.

The woman had difficulty ingesting sufficient food and drink because of pronounced nausea and vomiting triggered by eating, and therefore had a nasogastric tube inserted shortly after admission. However, she continued to vomit after administration of nourishment and medication through the tube. A week after her admission, AST (57 U/L) and ALT (127 U/L) concentration had risen to respectively 1.6 and 2.8 times the upper reference limits, but normalised spontaneously in the course of the following week.

No definite cause was found for the rise in liver transaminases, and no definite correlation could be found between the rise in values and the drugs administered or the nutrient solutions used in the period. Viral hepatitis was not detected (serological tests for hepatitis A, B and C virus, as well as for cytomegalovirus and Epstein-Bar virus showed patterns consistent with vaccination against hepatitis B and previous infection with cytomegalovirus and Epstein-Barr virus).

Nine days after admission, she received total parenteral nutrition via a venous catheter because of nutritional problems, including via a nasogastric tube. Her general condition improved after this. The patient was evaluated and followed up by a nutritional physiologist, and she managed by degrees to ingest some food by mouth. The parenteral nutrition was tapered and terminated completely after a total of five days. The central venous catheter was removed.

The patient was discharged from the medical department 15 days after admission. No definite evidence was found of a gastrointestinal disorder as the cause of the nausea and vomiting, but the findings of elevated calprotectin and slight thrombocytosis led to a tentative diagnosis of irritable bowel syndrome, mainly reflected in obstipation. The patient was given relevant information leaflets and advice on irritable bowel syndrome, and was instructed to have follow-up blood tests with her GP after a few weeks.

Four days after discharge, the woman was readmitted because of an exacerbation of the problems. The first two days after her discharge she had managed to ingest some food and drink, but then she again experienced acute nausea and vomiting immediately after eating. Clinical biochemical tests were largely unchanged or normalised compared with her first admission: sodium 141 mmol/L, potassium 3.9 mmol/L and slight thrombocytosis 452 × 10^9/L, but otherwise normal values, including CRP < 1 mg/L, Hb 14.0 g/dL, leukocytes 7.7 × 10^9/L, ALT 34 U/L, ALP 71 U/L and bilirubin 6 µmol/L. Thirty days after symptom onset a head MRI was performed on suspicion of a central nervous cause of the nausea. A signal change was detected in the medulla oblongata, measuring 4 mm in the axial plane and 11 mm in the craniocaudal direction (Figure 1). It was hyperintense on T2-weighted images, hypointense on T1-weighted images, and had a weak high signal on diffusion-weighted images. The lesion did not enhance with contrast. There were no other pathological signal changes.

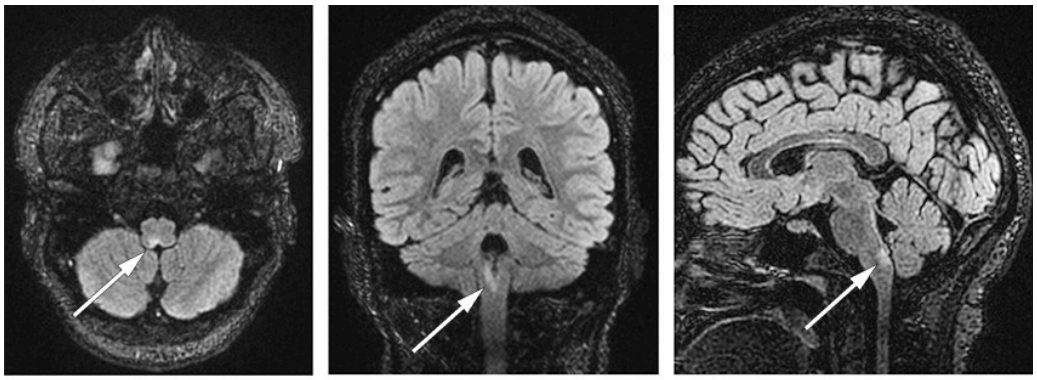

Figure 1 Representative MRI images of lesion in the area postrema: T2-FLAIR in axial (a) coronal (b) and sagittal (c) planes.

In light of the MRI scan, a tentative radiological diagnosis was either subacute phase infarction or demyelinating lesion. The lesion was perceived as the cause of the patient's persistent nausea, vomiting and hiccups, and she was transferred to a hospital with a neurology department. At a clinical neurological examination on admission, 31 days after symptom onset, she was conscious and oriented, and findings on examination of cranial nerves, motility, sensibility and coordination were normal. Her deep tendon reflexes were symmetrically

weak. Her gait was normal, and Romberg's test was negative. A secondary examination of the MRI images after her transfer did not rule out a demyelinating disease, and this, coupled with the clinical picture, gave rise to suspicion of *neuromyelitis optica spectrum disorder*, NMOSD, presenting as so-called area postrema syndrome.

In the course of the illness, the patient had lost 7 % of her body weight. She was still very nauseated, had persistent hiccups, was unable to retain food and drink and was hydrated and received nutrition purely parenterally. As part of the workup for a possible inflammatory lesion in the central nervous system, a lumbar puncture was performed as well as analyses for the presence of antibodies associated with inflammatory disorders of the central nervous system. A slightly elevated cell count was found in the cerebrospinal fluid (4×10^6/L, reference range < 3×10^6) and normal protein concentration (0.21 g/L, 0.15–0.50) and IgG (0.02 g/L, 0.00–0.04). Isoelectric focusing of the cerebrospinal fluid failed to detect an IgG band. A test for antibodies against aquaporin-4 (anti-AQP4) in serum was weakly positive, and for antibodies against myelin oligodendrocyte glycoprotein (anti-MOG) negative. Neither anti-AQP4 nor anti-MOG was detected in the cerebrospinal fluid. Thirty-five days after symptom onset, treatment with high-dose methylprednisolone was started: 1 g intravenously once a day for five days. Two days after the start of treatment, the nausea was substantially improved, the hiccups gone, and the woman was able to start eating and drinking without vomiting. She was discharged at the end of the methylprednisolone therapy, and subsequent treatment with prednisolone 60 mg per day was tapered over a period of 14 days. A week after finishing the prednisolone therapy, she started prophylactic treatment with rituximab, with an initial dose of 1 g and plans for a future maintenance dose of 500 mg every six months, as the untreated condition carries a risk of new inflammatory central nervous system lesions. At follow-up three months after starting treatment, she had made a full clinical recovery. A follow-up MRI showed a reduction in the size and signal intensity of the lesion.

Discussion

Neuromyelitis optica spectrum disorders are a group of autoimmune inflammatory diseases that affect the central nervous system (1). Neuromyelitis optica was first described by the French neurologist Eugène Devic in 1894, and for over a hundred years was believed to be a variant of multiple sclerosis. Neuromyelitis optica spectrum disorder is characterised by subacute episodes of functional neurological deficit as a consequence of focal inflammatory demyelinating lesions in the central nervous system. The disease is normally multiphasic, but monophasic courses occur. In 2005, pathogenic autoantibodies that targeted the water channel protein aquaporin-4 (AQP4) were detected in the majority of patients, which led to the condition being perceived as a separate disease entity (2). Anti-aquaportin-4-IgG binds to aquaporin-4 located in the end-feet of astrocytes at the blood-brain barrier and leads to complement activation and complement-mediated astrocyte lysis.

Antibodies against aquaporin-4 are produced peripherally, and the typical distribution of lesions in the medulla and optic nerve is explained by the distribution of aquaporin-4 in the central nervous system, coupled with a physiologically weaker blood-brain barrier in some areas of the central nervous system. Only in exceptional cases, and then mainly in connection with an episode of acute exacerbation, can antibodies be detected in the cerebrospinal fluid.

The incidence of neuromyelitis optica spectrum disorder is estimated to be about 1 per 100 000 individuals, and the condition is more common in Asia and the Caribbean. The condition takes its name from the two most common clinical manifestations of the disease, transverse myelitis and optic neuritis. A more unusual onset manifestation is the so-called area postrema syndrome (3, 4). The syndrome consists of a triad of clinical symptoms: intractable hiccups, nausea and vomiting, and despite low incidence, these are still viewed as core clinical characteristics of the disorder, on a par with myelitis and optic neuritis.

Signal changes in the area postrema on MRI are not specific for neuromyelitis optica spectrum disorder. The clinical symptom of nausea, vomiting and hiccups, however, is more specific. Area postrema syndrome in anti-aquaporin-4-IgG-positive neuromyelitis optica spectrum disorder is distinguished by acute or subacute onset nausea, vomiting and hiccups (individual or combined symptoms) with a duration of over 48 hours, and the exclusion of other aetiology. The criteria are expanded upon by Shosha et al. (4). The area postrema is located on the dorsal surface at the caudal end of the medulla oblongata and is an emetogenic centre in the brain. It is also, along with the nucleus tractus solitarius and the motor fibres of the vagus nerve, a key area for autonomic regulation of lung and heart function. The blood vessels that supply the area postrema lack a blood-brain barrier (5), and the area is thus directly exposed to substances and pathogenic antibodies in the blood circulation. In a patient series with aquaporin-4-antibody-positive patients with neuromyelitis optica spectrum disorder, area postrema syndrome was cited as the first sign of the condition in 7.1–10.3 % of patients, depending on the population group. Similarly, area postrema syndrome plays a part in a subsequent exacerbation episode in 9.4–14.5 % of patients (4).

As a rule, with neuromyelitis optica spectrum disorder, prophylactic immunotherapy is indicated to prevent new lesions. In a double-blind, randomised, placebo-controlled trial (6), rituximab, a monoclonal antibody against the cell surface marker CD20, proved very effective in preventing relapses, and is usually the first choice. Treatment with monoclonal antibody against interleukin-6-receptor, CD19, and complement factor C5 has also been approved by European and American pharmaceutical authorities. For details of the efficacy of the different therapeutic options, we refer to a recently published review (7).

The prognosis for area postrema syndrome is good as a rule, and complete recovery after starting on methylprednisolone immunotherapy is usual, which was also the case for our patient (4). Functional deficit as a consequence of optic neuritis and myelitis are often more serious, with a high risk of persistence. Typical sequelae are impaired visual field and colour vision after

optic neuritis, and paraparesis with loss of sensibility and autonomous bladder and gastrointestinal disorders after myelitis. Neuromyelitis optica lesions in the area postrema are often reversible, however, and it is therefore important to make the diagnosis and commence immunomodulatory therapy to prevent myelitis and significant functional deficit. Early treatment with methylprednisolone and prompt commencement of prophylactic immunotherapy is recommended. As our case study illustrates, it is important to remember that gastrointestinal symptoms may have a central nervous aetiology.

The patient has consented to the publication of the article. The article has been peer-reviewed.

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