New disease

An adult norovirus-related encephalitis/encephalopathy with mild clinical manifestation

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Summary

Norovirus is an emerging pathogen that causes gastroenteritis outbreaks. Here, we reported an adult female case of norovirus-related encephalitis/encephalopathy (NvREE) with abnormal behaviour, apathy, motor aphasia, bradykinesia and gait disturbance. We treated the patient with intravenous methyl-prednisolone pulse therapy and she recovered quickly. There were slight abnormal signals in the cortex of the opercular part and insula on the MRI fluid-attenuated inversion-recovery (FLAIR) image, generalised slow wave as a background activity in her EEG and cerebrospinal fluid pleocytosis, which restored soon after her recovery. We successfully detected the norovirus genome in stool samples from all seven family members. This is a first case report of an adult NvREE with detection of pathogenic evidence. There could be more cases of NvREE with mild neuropsychiatric symptoms, considering the increasing outbreaks each year.

BACKGROUND

Norovirus is a small RNA virus of the *Caliciviridae* family and is well known as an emerging pathogen that causes gastroenteritis outbreaks in all age group.¹ As the progression of diagnostic technologies helped to determine this pathogen,^{2 3} and its outbreaks increased year by year,⁴ the number of patients with noroviral infection rapidly increased. Although norovirus may rarely cause severe haemorrhagic shock and encephalopathy compared to rotavirus, which is also a cause of gastroenteritis outbreak,⁵ there was a case report presenting encephalopathy related to noroviral infections in early childhood.⁶ However, to date, an adult encephalopathy case related to norovirus infection has not been reported. Here, we present an adult female case of norovirus-related encephalitis/encephalopathy (NvREE) with abnormal behaviour, apathy, motor aphasia, bradykinesia, gait disturbance and severe headache, who recovered soon after corticosteroid treatment. A RT-PCR test was sensitive to detect noroviral genomic RNA in stool samples from the patient and her family members.

CASE PRESENTATION

A 60-year-old woman being treated for hypertension suffered from severe headaches, abnormal behaviour, apathy, motor aphasia, bradykinesia and gait disturbance after mild abdominal pain and fever. There was a small norovirus outbreak in her area of the town and five of her family members living with her—her son, daughter-in-law and three grandchildren—got severe diarrhoea and slight fever. Two days before she visited our hospital, she felt tired and was bedridden with a fever of around 38.0°C. When she got up at 02:00 and went to the bathroom, her husband mentioned that she kept opening a bathroom door contrary to her normal behaviour. She did not say anything when she was asked to answer easy questions. The only thing she could

do to answer was nod. Her husband took her to their family doctor and she was transferred to our hospital. In the emergency room, her body temperature was 36.9°C, and neurological examinations revealed slight dull consciousness, motor aphasia, mild nuchal stiffness and bradykinesia without rigidity of her extremities or paresis. She was able to walk slowly without a stick at that time.

Initially, she was given a CT scan and MRI for suspected brain stroke; however, there was no abnormal finding apart from mild brain atrophy related to her age. Follow-up brain MRI study the next day showed slightly high signals in the cortex of the opercular part and insula at left frontal lobe on the fluid-attenuated inversion-recovery (FLAIR) images, but no abnormal signal in other images, such as diffusion-weighted imaging (DWI), T2WI, T1WI and enhanced T1WI (figure 1). EEG presented generalised slow waves as a background activity without any spike or slow wave complex. Her whole body CT scan and Gallium-67 scintigraphy detected no sign of tumour. Laboratory tests revealed normal red blood cell count ($402 \times 10^4/\mu\text{l}$), a haemoglobin of 13.0 g/dl, normal white blood cell count ($5300/\mu\text{l}$) consisting 65.0% of neutrophils and normal platelet count ($29 \times 10^4/\mu\text{l}$). Blood chemistry studies were also normal including electrolytes: creatine phosphokinase 123 U/l, alanine transaminase 17 U/l, aspartate aminotransferase 13 U/l, triglyceride (TG) 81 mg/dl, high-density lipoprotein cholesterol 39 mg/dl, total cholesterol (T-CHO) 194 mg/dl, HbA1c 5.5%, blood urea nitrogen (BUN) 11.7 mg/dl, creatinine 0.51 mg/dl, Na 137 mEq/l, Cl 100 mEq/l, K 4.1 mEq/l, Ca 8.5 mg/dl and C reactive protein (CRP) 0.16 mg/dl. Her thyroid hormone levels were within normal range: free-T4 1.08 ng/dl, free-T3 2.10 pg/ml, thyroid-stimulating hormone 2.00 $\mu\text{IU/ml}$. No autoimmune antibodies were detected: anti-thyroglobulin antibody 1.8 ng/ml, anti-thyroid peroxidase antibody <0.5 U/ml and she was negative for lupus erythematosus test

Figure 1 MRI on day 2 of hospital admission shown. There is a slight high signal on the cortex of the opercular part and insula at left frontal lobe on the fluid-attenuated inversion-recovery (FLAIR) image, but no signal change on diffusion-weighted image (DWI), T2WI, T1WI or enhanced images.

and rheumatoid factor. There was no detectable antiviral IgG or IgM in her serum against echovirus type 3, 7, 11, 12; coxsackievirus A9, B1, 2, 3, 4, 5, 6; herpes simplex virus; varicella-zoster virus; cytomegalovirus; influenza virus; human T cell lymphotropic virus type 1; hepatitis C virus or hepatitis B virus. β -D glucan was negative: 8.3 pg/ml (<20). On the first hospital day, her cerebrospinal fluid (CSF) study showed normal cerebrospinal pressure (120 mm H₂O) and her cell count was mildly increased (25/mm³) and all mononuclear cells. CSF protein level was 46.4 g/dl and CSF glucose level was 69 mg/dl. Day 2, her CSF was still watery clear tapped with normal pressure (65 mm H₂O) and her cell count was still mildly increased (10/mm³) and all mononuclear cells. CSF protein level was clearly high at 130 mg/dl with lower IgG index (0.63) and CSF glucose level was normal at 59 mg/dl (blood glucose 77 mg/dl). Myelin basic protein level was also normal (31.8 pg/ml) and negative for oligo clonal IgG band. No pathogens that might cause meningitis were detected by PCR in her CSF samples: herpes simplex virus, Epstein-Barr virus, cytomegalovirus and tuberculosis genomic DNA. Cryptococcus antigen was also negative. She was still not able to talk with her family and she did not get well by feeding nutrition, drip infusion of glycerol (1000 ml/day) or and acyclovir (1500 mg/day). On day 3, we decided to treat her with drip infusion of methylprednisolone (1000 mg/day) and globulin (total 12.5 g) for 3 days (from day 3 to day 5). Soon after the first drip infusion she started to speak more than one phrase and ate jelly with

a spoon by herself. She improved quickly over the days and she totally recovered without any further disability on day 10. After recovering, she was able to explain the situation during her severest days: she could understand what she was asked about, but could not say anything to answer.

The RT-PCR (and nested RT-PCR) tests⁷ were done with specific primer pairs for norovirus, sapovirus, astrovirus, aichi-virus, adenovirus, rotavirus group A and C, enterovirus from her CSF and stool samples, following a usual protocol previously described.² In her stool sample, we only detected group 2 of the norovirus RNA genome as well as in those of all six family members. However, even using a nested RT-PCR method, we could not detect any evidence of norovirus genome in her CSF tapped on the first and second hospital day. We clinically diagnosed this patient to be suffering from an adult NvREE on circumstantial evidence.

TREATMENT

She was treated with drip infusion of methylprednisolone (1000 mg/day) and globulin (total 12.5 g) for 3 days.

OUTCOME AND FOLLOW-UP

She made a full recovery without any further disability.

DISCUSSION

This is the first case report of an adult NvREE detected with pathogenic evidence. Although norovirus RNA genome

was not detected in her CSF, her clinical manifestations—fever, severe headache, abnormal behaviour, apathy, motor aphasia, gait disturbance, mild nuchal stiffness and CSF lymphocytic pleocytosis—supported mild meningo-encephalitis due to viral infection as a clinical diagnosis. There was a small norovirus outbreak within her area of the town; moreover, in stool samples from all seven family members, including herself, norovirus genome was detected by RT-PCR but none of the other eight types of enteritis pathogen. Because of acute inflammation due to suspected viral infection (the preceding fever, mildly increased CRP and mildly increased CSF cell counts, all mononuclear cells), we clinically decided that methyl-prednisolone and globulin were good indications as anti-inflammation and anti-infectious treatments. As she recovered quickly after corticosteroid treatment, her mild psychotic manifestations might be caused by humeral immune response against neuronal cells with mild brain dysfunctions, as considered the mechanism of the similar autoimmune encephalopathy.⁸ It is still unclear the cause of her motor aphasia, which might be related to slightly high signals on the FLAIR image.⁹ Although these signals might be an artefact or overestimation, it might reflect the ‘stand-still effect’ of cortical or subcortical neuronal networks due to uncertain humeral factors as autoantibodies or cytokines without destructive mechanism. As discussed in a previous case report describing an adult influenza-associated encephalopathy, an acute surge in cytokine level in the bloodstream or CSF cavity might trigger vaso-dilatation following reversible vasogenic oedema of the myelin.¹⁰ It can also respond to corticosteroid treatment. In 2006, Ito and colleagues described a case of norovirus-related encephalopathy in a child.⁶ In this case, the clinical manifestation was quite severe compared to ours and the norovirus genome was detected by RT-PCR test in the CSF. The possible reasons we could not detect the viral genome in the CSF are: (i) the level of virus genome was not enough for the sensitive nested RT-PCR test or the virions had already disappeared when CSF tapped, (ii) the norovirus never existed inside of the CSF cavity; instead, only cytokine or other humeral factors might cause central nervous system manifestations.

Clinicians should recognise that noroviral infection could potentially cause encephalitis/encephalopathy, even rarely in adulthood, which could respond quickly with immune

treatment. There could be more cases of NvREE with mild neuropsychiatric symptoms considering the increasing outbreaks each year.

Learning points

- ▶ The noroviral infection potentially causes encephalitis/encephalopathy even in adulthood, which could respond quickly with immune treatment.
- ▶ The sensitive RT-PCR test was useful to detect and diagnose the viral genome.
- ▶ This is the first case report of an adult NvREE; however, we suggest there could be more cases with mild neuropsychiatric symptoms considering the increasing outbreaks each year.

Competing interests None.

Patient consent Obtained.

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Please cite this article as follows (you will need to access the article online to obtain the date of publication).

Kimura E, Goto H, Migita A, Harada S, Yamashita S, Hirano T, Uchino M. An adult norovirus-related encephalitis/encephalopathy with mild clinical manifestation. *BMJ Case Reports* 2010;10.1136/bcr.03.2010.2784, date of publication

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