Clinical Case Report

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Analysis and discussion of the rare complication of autoimmune encephalitis

Two case reports

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Abstract

Rationale: Autoimmune encephalitis related to many antibodies against neuronal cell surface or synaptic proteins, it is increasingly recognized as the cause of a variety of neuropsychiatric syndromes.

Patient concerns: The two pediatric cases were about autoimmune encephalitis with rare complication. One patient was a 11-year-old girl and was diagnosed with Voltage-Gated Potassium Channel complex (VGKC) antibody-mediated encephalitis with rhabdomyolysis; the other was also a 11-year-old girl and was diagnosed with anti- N-methyl-D-aspartate receptor (NMDAR) encephalitis.

Diagnoses: Both patients were diagnosed as autoimmune encephalitis with rare complication.

Interventions: Intravenous methylprednisolone, oral prednisone and intravenous immunoglobulin was administered to both patients.

Outcomes: One patient was discharged after a half month's hospitalization; the other was finally with intestinal function failure, gradually developed multiple organ failure, and eventually died.

Lessons: The pathogenic mechanism of autoimmune encephalitis associated with autoimmune disease is not fully understood, but may be related to a common immune pathological mechanism with variance in susceptibility caused by genetic or environmental factors.

Abbreviations: AIE = autoimmune enteropathy, Caspr2 = contactin-associated protein-like 2, CK = creatine kinase, DRBs = dopamine receptor blockers, EEG = electroencephalogram, MOF = multiple organ failure, NMDAR = anti-*N*-methyl-D-aspartate receptor, VGKC = voltage-gated potassium channel complex.

Keywords: autoimmune encephalitis, children, intestinal failure, multiple organ failure, rhabdomyolysis

1. Introduction

One study[1] showed that 19% of children with anti-*N*-methyl-D-aspartate receptor (NMDAR) encephalitis had a positive family history of autoimmune or immune-mediated disease. The mechanism of autoimmune encephalitis associated with autoimmune disease is not yet fully understood. It may be due to a common immunological mechanism with genetic or environmental factors affecting the susceptibility of individuals. We retrospectively analyzed 2 pediatric patients with autoimmune encephalitis associated with autoimmune disease with the aim of improving the diagnosis and treatment of this disease and its complications. This study was approved by the ethics committee of the Children's Hospital of Chongqing Medical University and was conducted in accordance with the latest version of the Declaration of Helsinki. The written informed consent and assent were obtained from the parents of the patients.

2. Case 1

An 11-year-old Chinese girl was brought to the hospital on August 8, 2015, with a 3-day history of progressive insomnia, altered mental status, and abnormal behaviors. She had begun to experience sleeplessness without obvious cause on August 5, sleeping only 6 to 7 hours per day with the help of a sleep aid, followed by altered mental status on August 6. She then developed mental and behavioral disorders including delirium, irritability, auditory and visual hallucinations, and inflexibility. At times, she had involuntary movements of the head, neck, and limbs. There were no convulsions, hematuria, hematochezia, myalgias, or rash.

Editor: N/A.

The written informed consent was obtained from the parents of the participant for the publication of this case report.

The authors alone are responsible for the content and writing of the paper.

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The physical examination showed dull eyes, decreased mathematical ability, and she could only answer simple questions. Brain magnetic resonance imaging and electroencephalogram (EEG) was normal. EEG showed sinus arrhythmia. Serologic testing for creatine kinase (CK) was 1517 U/L and CK-MB was 56 U/L on August 7. Liver and kidney function tests, complete blood count, electrolytes, thyroid function tests, and tumor markers were normal. Repeat serologic testing on August 8 showed a CK of 3005 U/L, a CK-MB of 6.98 U/L, a myoglobin of 156 μg/L, an AST of 78.5 U/L, and a uric acid of 457 mol/L. Voltage-gated potassium channel complex (VGKC) antibody were positive in both the serum and cerebrospinal fluid. The admission diagnosis was VGKC antibody-mediated encephalitis and acute rhabdomyolysis.

Intravenous methylprednisolone was initiated at 20 mg/kg/d for 3 days followed by oral prednisone at 1.5 mg/kg. Intravenous immunoglobulin was administered at a dose of 2 g/kg. On hospital day 5, repeat serologic testing showed the following: CK of 922 U/L, CK-MB of 2.45 U/L, and myoglobin of 78.7 μg/L. Liver and kidney functions recovered to normal. After a half month's hospitalization, the patient asked to be discharged on prednisone for another 1 month. She presented again, however, with recurrent mental and behavioral abnormalities without rhabdomyolysis in November 2015. She recovered with appropriate treatment and had returned to school when seen for 1-year follow up.

3. Case 2

An 11-year-old girl presented for evaluation of acutely altered mental status on May 9, 2014, with a 5-day history of paroxysmal nonsensical speech, headache, and yelling at night. The presentation worsened, gradually developing into disturbance of logical thinking, confusion, and the inability to care for herself. She began to have episodes of involuntary limb movements with upturning of the mouth lasting for 20 minutes about 4 to 5 times per day. There was no fever, seizures, nausea, vomiting, diarrhea, coma, or auditory or visual hallucinations.

EEG showed 2 to 3 Hz slow rhythm in the frontal leads without epileptic discharges (Fig. 1A). Brain magnetic resonance imaging was normal. Anti-NMDAR antibodies were positive in both the serum and cerebrospinal fluid. Screening tests for liver and kidney functions, electrolytes, thyroid function, autoantibodies, and tumor markers were negative. Computed tomography of the thorax and abdomen were unrevealing. The diagnosis of anti-NMDAR encephalitis was made.

After admission, she had a high-grade fever to 39.5°C. Intravenous immunoglobulin was initiated at 1 g/kg/day for 2 days, and methylprednisolone was begun at 20 mg/kg/d for 5 days followed by oral prednisone. The body temperature was normal on May 29. Gradually, she showed improved consciousness, communication. Repeat EEG was significantly improved with focal slow-wave disappearance (Fig. 1B).

Unexpectedly, however, liver function testing indicated damage, with an alanine transaminase of 725 U/L and an AST of 335 U/L on May 31. She then developed widespread urticaria and recurrent fever to 40°C. Drug eruption was diagnosed by the dermatologist. All the suspected triggering medicines were discontinued and antiallergy medicines were given. Intravenous immunoglobulin was repeated at 1 g/kg for 1 day. At the same time, liver-protective drugs were added to improve liver function. The rash gradually resolved on June 8.

The patient ate a large amount of food on June 4 and developed vomiting accompanied by abdominal pain on June 5. Emergency abdominal ultrasound examination was unrevealing and incomplete ileus was suspected from the abdominal X-ray findings. Nonsurgical treatment was chosen, including fasting, rehydration, gastrointestinal decompression, pumping the stomach with cold hypertonic saline, and maintenance of water, electrolyte, and acid-base balance. Abdominal X-ray was normal on June 6. However, the patient then developed a lower gastrointestinal bleed with approximately 150 to 300 mL per day of bloody stool on June 7. The bloody stool gradually increased to 500 mL per day, and she was transferred to the intensive care unit on June 10.

During her intensive care unit course, she continued to have sporadic fevers. The lower gastrointestinal bleeding improved for a while. *Candida albicans* was cultured from her stool on June 11, but the following 3 stool cultures were negative. Analysis of fecal flora showed third-degree intestinal flora imbalance. *Enterococcus faecium* grew from the patient's urine and central venous catheter culture. He began to eat on June 24, vomiting occasionally. The diarrhea frequency increased from June 26 and progressively worsened (Table 1: urinalysis, Table 2: stool routine, Table 3: abdominal X-ray and computed tomography, Table 4: abdominal ultrasonography). Treatment included total parenteral nutrition therapy, many kinds of antibiotics, improving the intestinal microbial environment, albumin infusion, low doses of glucocorticoid, and intravenous immunoglobulin. Platelet count declined progressively from July 24 onward (Table 5), accompanied by increased volume of bloody stool, excreted intestinal mucosa tissue, and blood pressure instability. Intravenous platelets and fresh frozen plasma transfusions were given to improve blood coagulation, and suspended red blood cell transfusions to correct anemia. The IgG4 level in the peripheral blood was normal, IL-6 was >1000 pg/mL, IL-8 was 268 pg/mL, IL-10 was >1000 pg/mL, IL-1B was 30.3 pg/mL, and TNF-α was 104.0 pg/mL. Testing of exfoliated cells of intestinal mucosa showed many neutrophils, a few monocyte-macrophages, and scattered epithelioid cells (Fig. 2A and B). Colonoscopy revealed colitis changes on August 4 (Fig. 3), with autoimmune enteritis suspected. An immunohistochemistry study of the intestinal mucosa showed ulcerative colitis changes: IgG1 (−), IgG3 (−), IgG2 (+), scattered lymphocytes (+) with <5/HPF (0–1/HPF on average), IgG4 focal (+), and plasma cells (+) with <5/HPF (mean of 0–1/HPF). Repeat EEG showed scattered 2 to 4 Hz slow waves (Fig. 1C). The patient died of multiple organ failure (MOF) on August 12.

4. Discussion

Rhabdomyolysis is a clinical syndrome in which the cell contents of striated muscle (such as myoglobin, CK, and small molecular substances) are released into the circulation, destroying cell membranes and membrane channels and affecting the energy metabolism of striated muscle. Consequently, striated muscle is damaged, typically with acute kidney function failure and metabolic disorders. A variety of viral encephalitis patients with rhabdomyolysis have been reported, with West Nile virus as the most common viral cause. One study of 244 patients with West Nile virus encephalitis or meningitis included 9 cases of rhabdomyolysis patients. Rhabdomyolysis in these patients was presumably because of the proliferation of or allergy to virus particles. Autoimmune diseases such as dermatomyositis,[2] hyperthyroidism,[3] and systemic lupus erythematosus[4] may also result in rhabdomyolysis.

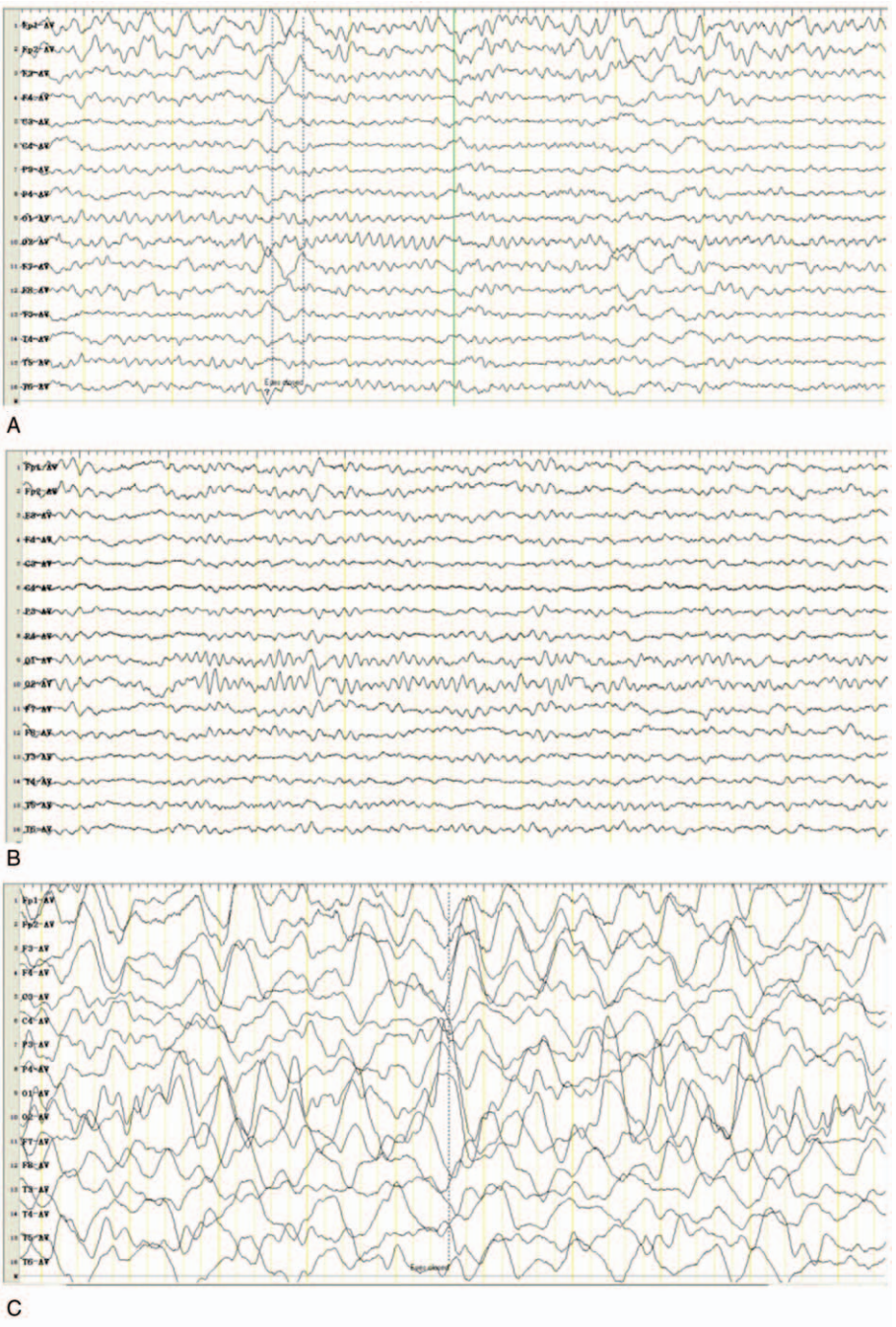

Figure 1. EEG for Patient 2. Paper speed: 10 mm/s, sensitivity: 10 uv/mm; time constant 0.3 s. (A) 2–3 Hz slow rhythm in the left frontal leads. (B) Repeat EEG showed the focal slow waves had disappeared and the background had advanced. (C) A 3rd EEG test showed scattered 2–4 Hz slow waves.

Table 1

Urinalysis of Patient 2.

Date	U-occult blood	U-Pro	U-Ket	U-RBC, cells/μL	U-WBC, cells/mL	Others
18/05/2014	++	−	+	14	22	−
04/06/2014	+	−	−	39	141	−
16/06/2014	++	±	−	−	±	−
18/06/2014	+++	++	−	439	1483	−
22/06/2014	−	−	−	28	−	−
29/06/2014	−	−	−	22	±	8 hyaline cast per μL, 5 pathocast per μL

RBC = red blood count, WBC = white blood count.

Table 2

Routine stool studies of Patient 2.

Date	Character	WBC, cells/HPF	RBC, cells/HPF	Occult blood
10/06/2014	Normal	Full field	–	+
19/06/2014	Mucus and blood	3–5	++++	+
21/06/2014	Loose and mucousy stool	++++	4–7	+
05/07/2014	Yellow and a little loose	–	–	+
14/07/2014	Normal	+++	1–2	+
20/07/2014	Normal	–	–	+
25/07/2014	Brown and watery	–	–	+
26/07/2014	Red and loose	–	Full field	+
30/07/2014	Yellowish-brown and loose	0–3	1–3	+

RBC = red blood count, WBC = white blood count.

Lim et al reported 9 patients with anti-NMDAR encephalitis complicated with rhabdomyolysis: 7 patients occurring after immunotherapy and 2 patients, before treatment. There are no correlations between disease severity and rhabdomyolysis development. CK level was higher in patients who received dopamine receptor blockers (DRBs), and abnormal movements were aggravated by the introduction of DRBs, suggesting DRBs use increased the risk of rhabdomyolysis.[5] There are no reports of VGKC antibody-mediated encephalitis complicated with rhabdomyolysis. The pathogenic effects of the VGKC antibodies are mediated by their combining with leucine-rich glioma inactivated protein 1 (LGI1) and contactin-associated protein-like 2 (Caspr2).[6] These antibodies are considered to play an important role in neuronal excitability. LGI1 is a neuronally secreted protein most strongly expressed in the hippocampus.[7–9] The syndrome is characterized by intractable hyponatremia and faciobrachial dystonic seizures.[10] It is more likely to result in permanent memory impairments compared with Caspr2. Anti-Caspr2 is an axonal transmembrane protein of the neurexin superfamily that binds to contactin-2 and may contribute to the normal function of myelinated axons. It is highly enriched at the juxtaparanodes of myelinated axons and expressed in the

Table 3

Abdominal X-ray and CT of Patient 2.

Date	Item	Results
05/06/2014	X-ray	Incomplete intestinal obstruction cannot be excluded
06/06/2014	X-ray	Normal
09/06/2016	X-ray	Enlarged stomach bubble
16/06/2014	X-ray	Normal
25/07/2014	CT	It showed slightly thickened intestinal walls and peritoneal effusion, hazy and disorganized ileocecal mesentery images, possibly caused by intraabdominal infection. Abdominal radionuclide Te-99 scanning was unremarkable
01/08/2014	X-ray	The lumen of intestinal is a little narrowed, and the shadows of gas are continuous; the shapes are not natural
02/08/2014	X-ray	Scattered and irregular bowel in the low-abdomen
05/08/2014	X-ray	An isolated arc inflatable shadow in the left upper abdomen which may be a stomach bubble, considering the combination of intestinal paralysis and inflammation

CT = computed radiography.

Table 4

Abdominal ultrasonography of Patient 2.

Date	Results
05/06/2014	Normal
09/06/2014	Ultrasound images showed obvious expansion and fluid accumulated in part of the intestinal cavity; the components of the fluid is mud-like, and there is also intestinal bleeding, obstruction, and a small amount of pelvic effusion
12/06/2014	The intestinal wall was generally slightly thickened, with no obvious expansion or obstruction; bowel movements were normal; abnormal dilatation of the intestine in the low-abdomen and the liquid in it was thick. The sonographic features are similar to the former study. Intestinal deformity cannot be excluded (intestinal duplication deformity?) but no obvious seroperitoneum is seen
16/06/2014	The intestinal wall was generally slightly thickened; parts show expansion and accumulation of excess fluid. The fluid was turbid, possibly consistent with intraluminal rebreeding. Bowel dilatation was significantly improved compared with June 9; no obvious seroperitoneum
18/06/2014	The intestinal wall was generally slightly thickened; there was no obvious expansion and obstruction; there exists a small amount of seroperitoneum. Cholestasis seen in the gallbladder, and there was no obvious abnormality of the liver, pancreas, spleen, and kidney
25/07/2014	The liver and the spleen were slightly enlarged. Cholestasis seen in the gallbladder, and the common bile duct was slightly enlarged. A small amount of seroperitoneum
01/08/2014	The location of the liver has slightly gone down. The sizes of the liver and spleen were slightly enlarged; parts of the intestinal wall were slightly thickened and the peristalsis was slow. A small amount of seroperitoneum
02/08/2014	Part of the intestinal wall was slightly thickened; a small amount of seroperitoneum
04/08/2014	Slightly enlarged liver and spleen; a small amount of pleural effusion on both sides

Table 5

Routine blood tests of Patient 2.

Date	WBC, 10^9/L	PLT, 10^9/L	Hb, g/dL	CRP, mg/L	PCT, ng/mL	Date	WBC, 10^9/L	N, 10^9/L	PLT, 10^9/L	Hb, g/dL	CRP, mg/L	PCT, ng/mL
17/05/2014	15.25	326	114	41	—	7.20	25.98	0.88	125	112	24	—
19/05/2014	3.19	229	89	49	0.52	7.20	25.63	0.86	125	113	15	—
23/05/2014	5.00	306	88	<8	—	7.24	33.37	0.85	57	99	22	—
01/06/2014	13.53	424	100	36	<1	7.25	18.77	0.88	31	81	58	—
16/06/2014	17.04	281	132	<8	—	7.26	9.75	0.86	97	86	58	—
02/06/2014	14.40	270	108	21	—	7.28	8.62	0.70	46	75	40	—
22/06/2014	10.07	288	115	19	—	7.29	10.36	0.9	40	97	69	—
27/06/2014	26.58	390	134	72	1.57	7.30	5.29	0.78	32	96	26	—
29/06/2014	28.83	207	131	116	—	7.31	3.64	0.84	13	74	42	—
30/06/2014	14.90	84	91	35	—	8.1	2.81	0.68	6	98	91	—
02/07/2014	23.26	46	101	60	—	8.2	5.20	0.70	6	77	47	—
05/07/2014	45.52	142	105	16	—	8.3	12.38	0.76	8	104	42	—
10/07/2014	23.25	321	137	<8	—	8.4	7.11	0.79	7	96	91	—
13/07/2014	37.80	276	115	<8	3.97	8.5	6.58	0.86	3	10	94	—
18/07/2014	21.47	176	74	<8	—	8.6	16.72	0.93	14	57	—	—

CRP = C-reactive protein, Hb = hemoglobin, PCT = procalcitonin, PLT = blood platelet, WBC = white blood count.

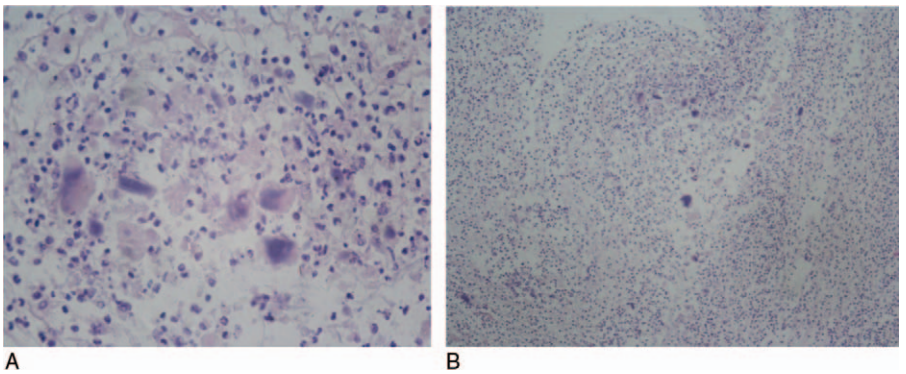

Figure 2. The exfoliated cells of the intestinal mucosa showed a large number of neutrophils, a few monocyte-macrophages, and scattered epithelioid cells.

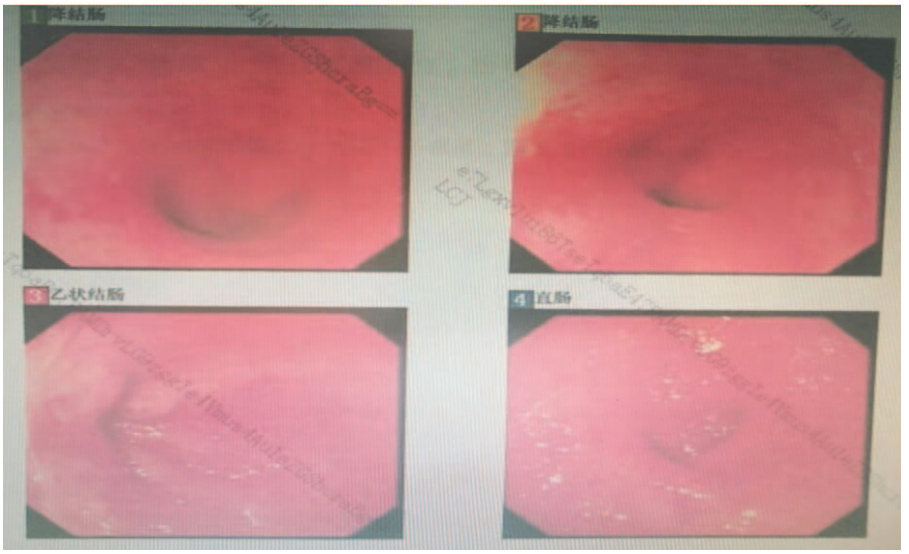

Figure 3. Colonoscopy of Patient 2 revealed colitis changes.

hippocampus and cerebellum.[5] Common clinical features include various syndromes involving the peripheral and central nervous systems, such as Morvan syndrome,[11] neuromyotonia,[7] peripheral nerve hyperexcitability,[12] and limbic encephalitis.[8] At present, it is unclear whether VGKC antibodies expressed in striated muscle were the exact mechanism of the rhabdomyolysis in this patient. It is speculated that there may be a common immunopathogenesis with VGKC antibody-mediated encephalitis.

Patient 2 had anti-NMDAR encephalitis and developed rash, diarrhea, and gastrointestinal bleeding. Treatment against antibiotic-associated colitis and autoimmune enteropathy (AIE) were ineffective, and the patient eventually died of intestinal and MOF. It is not known if AIE was the exact cause of the gastrointestinal bleeding in this case. Perhaps AIE is a rare complication of autoimmune anti-NMDAR encephalitis. Reports related to AIE report primarily intractable diarrhea, malabsorption, and hypoproteinemia in the setting of various types of autoimmune disease, including rheumatoid arthritis, systemic lupus erythematosus, thyroiditis, and autoimmune myopathy. The pathogenesis of AIE is related to a disorder of immune regulation. When mucosal barrier function is destroyed, intestinal mucosa antigens are exposed to blood and induce an autoimmune response. At the same time, an inflammatory response is induced by the invasion of lymphocytes and macrophages into the intestinal lamina propria. Antibodies to NMDAR are not just expressed in the central nervous system, but are also detected in other tissues, such as the kidney, parathyroid glands, osteoblasts, osteoclasts, pancreatic beta cells, cardiac muscle, lung, red blood cells, and lymphocytes. NMDAR or NMDAR subunits are also found in myelinated and unmyelinated axons in the peripheral nervous system. Generally, these antigens do not induce an autoimmune response, but when this organ is infected or damaged, the body's immune tolerance is broken and will lead to autoimmune reactions.[13] Whether the antibodies against NMDAR directly influence the gastrointestinal tract leading to destruction of intestinal mucosal barrier function remains to be further confirmed. The mechanism underlying anti-NMDAR encephalitis accompanied by AIE may be autonomic nerve dysfunction caused by antibodies against NMDAR acting on the dopaminergic, noradrenergic, and cholinergic systems, which leads to visceral dysfunction, including disorders of gastrointestinal function and the secretion of digestive juice.

On the one hand, the digestive system is a metabolic organ and the largest immune organ in addition to the thymus. It is also a natural mechanical barrier from the outside world, plays a crucial role in immune defense and homeostasis, and contributes to stabilization of the internal milieu. On the other hand, it has the largest pool of bacteria and toxins and acts as a communication channel between in vitro and in vivo. Once the mucosal barrier function is damaged, bacteria translocation from the gut occurs and bacterial endotoxins are released into the circulation resulting in the systemic inflammatory response syndrome and secondary intestinal function failure, and even possible MOF. Patient 2 grew *Enterococcus faecalis* from both the central venous catheter and urine cultures, which suggests the barrier of the intestinal mucosa may have been severely damaged, resulting in bacteria shifting from the gut to other organs.

The main findings on Patient 2's colonoscopy showed ulcerative colitis changes and an overactive immune response. At the same time, the overwhelming release of serum proinflammatory cytokines and antiinflammatory cytokines, such as IL-6, IL-8, TNF-α, IL-1B, and IL-10, led to overactive immune responses. Endotoxins from the intestine may be the main cause of intestinal failure or MOF in patients with no definite infection source.[14] Early protection of the intestinal barrier and gut function may play an important role in improving the prognosis of patients.

Author contributions

Conceptualization: Yue Hu, Min Zhong.
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