

Case of autoimmune polyendocrine syndrome type 3 complicated with anti-N-methyl-D-aspartic acid-receptor encephalitis

Akira Kurozumi*, Yosuke Okada, Kosuke Nishio, Yoshiya Tanaka

First Department of Internal Medicine, University of Occupational and Environmental Health, Kitakyushu, Japan

Keywords

Anti-N-methyl-D-aspartic acid-receptor encephalitis, Autoimmune polyglandular syndrome type 3, Type 1 diabetes

*Correspondence

Akira Kurozumi
Tel.: +81-93-603-1611
Fax: +81-93-691-9334
E-mail address:
akira@med.uoeh-u.ac.jp

J Diabetes Investig 2021; 12: 290–292

doi: 10.1111/jdi.13341

ABSTRACT

Anti-N-methyl-D-aspartate receptor (NMDA-R) encephalitis is an autoimmune disorder in which autoantibodies in the limbic system bind to GluN1 subunits of NMDA-Rs in the brain. We report a rare case of autoimmune polyendocrine syndrome type 3 complicated by anti-NMDA-R encephalitis. After hospitalization for type 1 diabetes, the 39-year-old patient developed various schizophreniform symptoms and seizures after cold-like symptoms. These findings are consistent with the diagnosis of anti-NMDA-R encephalitis. Immune-related encephalitis was suspected at the early phase of the disease, and cerebrospinal fluid was positive for anti-NMDA-R antibody. Early steroid pulse therapy was initiated during the disease course. The condition improved gradually to full recovery. Early detection and treatment of anti-NMDA-R encephalitis should enhance a positive outcome, considering that besides thyroid diseases and type 1 diabetes, various autoimmune diseases are associated with autoimmune polyendocrine syndrome type 3.

INTRODUCTION

Anti-N-methyl-D-aspartate receptor (NMDA-R) encephalitis is an autoimmune disorder in which autoantibodies in the limbic system bind to GluN1 subunits of NMDA-Rs in the brain. In Japan, anti-NMDA-R encephalitis was first described in 2007¹, and presently, its incidence is 0.33 per million². Early diagnosis and treatment are essential, as anti-NMDA-R encephalitis is a rapidly progressive disorder with a severe and prolonged course, and is often associated with a poor prognosis. In patients with associated neoplastic diseases, the recommended immunotherapies include steroid pulse therapy, plasma exchange, high-dose immunoglobulins and early tumor resection. Cyclophosphamide pulse therapy and rituximab have been used in patients who are refractory to primary immunotherapy³.

Autoimmune polyglandular syndrome (APS) is a disorder associated with autoimmune diseases in multiple organs. APS type 3 (APS-3) includes various autoimmune disorders, such as immune-mediated diabetes and autoimmune thyroiditis. We report a rare case of a patient with APS-3 complicated by anti-NMDA-R encephalitis, who responded to immunotherapy for encephalitis.

CASE REPORT

The patient was a 39-year-old man. In August, he developed hyperglycemia symptoms, and was diagnosed with diabetes and referred to the Hospital of University of Occupational and Environmental Health, Kitakyushu, Japan, in November. He was diagnosed with acute-onset type 1 diabetes based on positivity for the glutamic acid decarboxylase antibody.

On admission, the patient was lean, weighing 45.8 kg. As shown in Table 1, his urinary ketone bodies were 3+, anti-glutamic acid decarboxylase antibodies were 300 U/mL and urinary C-peptide immunoreactivity showed low insulin secretion. Although his thyroid function tests were normal, both the anti-thyroglobulin and anti-thyroid peroxidase antibodies were positive, and thyroid echo showed mild thyroid enlargement. The provisional diagnosis was APS-3 associated with chronic thyroiditis and type 1 diabetes. The results of human leukocyte antigen typing were consistent with disease susceptibility to APS-3.

The patient's diabetes was controlled by multiple insulin therapy with the combination of insulin aspart and degludec. However, the patient developed fever, headache and general fatigue on hospitalization day 4. Furthermore, various mental symptoms started to appear, including hallucinations, delusions and mood depression on day 7. At first, we suspected a mental

Received 19 March 2020; revised 23 June 2020; accepted 24 June 2020

Table 1 | Laboratory data on the admission of the patient

CBC		Biochemistry		Diabetes-related	
WBC (/mm ³)	4100	TP (g/dL)	6.6	FPG (mg/dL)	138
Neutrophils (%)	70.9	Alb (g/dL)	4.3	PPG (mg/dL)	493
Eosinophils (%)	5.1	AST (U/L)	18	HbA1c (%)	14.2
Basophils (%)	0.7	ALT (U/L)	16	24-h urine-CPR (μg/day)	20.5
Lymphocytes (%)	15.3	γ-GTP (U/L)	15	ACR (mg/gCre)	1.3
Monocytes (%)	8.0	LDH (U/L)	153	GAD-Ab (U/mL)	300
RBC (×10 ⁴ /mm ³)	456	ALP (U/L)	341	IA-2 Ab (U/mL)	<0.2
Hb (g/dL)	14.0	CK (U/L)	125	Glucagon load test	
Hct (%)	42.7	LDL-C (mg/dL)	115	Fasting CPR (ng/mL)	0.36
PLT (×10 ⁴ /mm ³)	31.6	TG (mg/dL)	125	After 6 min CPR (ng/mL)	0.77
Urine		HDL-C (mg/dL)	62	Delta CPR (ng/mL)	0.41
pH	5.5	BUN (mg/dL)	16	CPR index	0.28
Glucose	(4+)	Cr (mg/dL)	0.49	Thyroid-related	
Protein	(-)	eGFR (mL/min)	101.7	TSH (μU/mL)	2.43
Ketone	(3+)	Na (mEq/mL)	132	FT3 (pg/mL)	2.10
OB	(-)	K (mEq/mL)	4.8	FT4 (ng/dL)	1.21
VBG		Cl (mEq/mL)	94	TG-Ab (U/mL) (<28.0) [†]	61
pH	7.365	UA (mg/dL)	5.7	TPO-Ab (U/mL) (<16.0) [†]	17
PCO ₂ (Torr)	39			HLA typing	
PO ₂ (Torr)	97			DRB1*04:05	
BE (mEq/L)	-3.2			DQB1*04:01	
HCO ₃ ⁻ (mEq/L)	21.8			DRB1-DQB1 haplotype *04:05-*04:01	

[†]Normal range. ACR, albumin-to-creatinine Ratio; Alb, albumin; ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate aminotransferase; BE, base excess; BUN, blood urea nitrogen; CCr, creatinine clearance; CK, creatine kinase; Cl, chloride; CPR, C-peptide immunoreactivity; Cr, creatinine; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; FT3, free triiodothyronine; FT4, free thyroxine; GAD, glutamic acid decarboxylase; Hb, hemoglobin; HbA1c, hemoglobin A1c; Hct, hematocrit; HDL-C, high-density lipoprotein cholesterol; HLA, human leukocyte antigen; IA-2, insulinoma-associated antigen-2; K, potassium; LDH, lactate dehydrogenase; LDL-C, low-density lipoprotein cholesterol; Na, sodium; OB, occult blood; pH, potential hydrogen; PLT, platelet; PPG, postprandial plasma glucose; RBC, red blood cell; TG, triglyceride; TG-Ab, thyroglobulin antibody; TP, total protein; TPO-Ab, thyroid peroxidase antibody; TSH, thyroid-stimulating hormone; VBG, venous blood gas; WBC, white blood cell; γ-GTP, γ-glutamyl transpeptidase.

disorder; however, on day 13, he developed convulsive seizures, suggesting autoimmune encephalopathy. Accordingly, the Department of Neurology was consulted; electroencephalography showed sustained slow waves and burr head, whereas neck magnetic resonance imaging showed no intracranial abnormalities. Additional tests were carried out for immune-related encephalitis; however, results for the anti-voltage-gated potassium channel complex antibody and anti-amino-terminal of the α-enolase antibody were negative. Analysis of the cerebrospinal fluid showed no abnormalities in the cell number, total protein and glucose, but serological tests showed mild positivity for the anti-NMDA-R antibody, with a titer of 1:10 (normal <1:1). Accordingly, the diagnosis was considered anti-NMDA-R encephalitis. Further neck, chest, abdominal and pelvis computed tomography was negative for apparent malignant tumors, and immunological fecal occult blood test was negative twice.

The patient was administered levetiracetam for seizures, and two courses of steroid pulse therapy (methylprednisolone 1,000 mg infusion for 3 days) were administered. His hallucination, delusions and depression gradually improved after these therapies. The Hasegawa-type dementia scale improved from 9

to 18 points at 1 week, and to 28 points at 3 weeks after steroid pulse therapy. He received rehabilitation before discharge 4 weeks later, and returned to work 3 weeks after that. One year after discharge, the patient was continuing to work and had not experienced any recurrent symptoms.

DISCUSSION

We described a rare case of APS-3 associated with chronic thyroiditis and type 1 diabetes complicated by anti-NMDA-R encephalitis. Regarding the human leukocyte antigen type of APS-3, previous studies reported disease susceptibility in DRB1*04:05 and DRB1*08:02, and disease resistance in DRB1*15:05⁴; the present patient had a disease-susceptible allele. Furthermore, among Japanese patients with acute-onset and slowly progressive type 1 diabetes, those with *04:05-*04:01 and *09:01-*03:03 DRB1-DQB1 haplotypes are susceptible to disease⁵, and again, the present patient had a disease-susceptible allele. Two previously published case reports detailed the association between Graves' disease and anti-NMDA-R encephalitis^{6,7} and APS complicated with anti-NMDA-R encephalitis⁸. In the latter report, a 58-year-old

woman with APS-3 – complicated with type 1 diabetes and Graves' disease – presented with an 8-month history of depressive symptoms. The patient developed encephalitis simultaneously with the onset of type 1 diabetes, and was later found to have an ovarian teratoma. The authors described improvement in the clinical features of encephalitis after resection of the ovarian teratoma without immunotherapy.

Anti-NMDA-R encephalitis occurs predominantly in young women, and ovarian teratoma is a common complication⁹. The presence of a tumor depends on age and sex, being more frequent in women aged >18 years. Notably, patients without tumors generally present with histories of episodic unconsciousness and confusion that can be longer or worse than those in patients with tumors. Non-specific cold-like symptoms are typically observed in the prodromal phase, followed by rapidly progressive schizophreniform symptoms. The disorder can progress to include involuntary movements and unresponsiveness, and recovery is typically slow. Severe complications are observed in 15% of the patients, with an estimated mortality rate of 6%³. The clinical management of anti-NMDA-R encephalitis should initially focus on immunotherapy and the detection/removal of tumors. Most patients receive corticosteroids, intravenous immunoglobulins or plasma exchange as the first-line immunotherapy. These treatments are more effective and show more rapid effects in patients where the underlying malignancy is eradicated. In patients free of tumors or with late diagnosis, additional treatment with second-line immunotherapy is usually required. Early immunotherapy is important, because delayed treatment is associated with poor neurological and life prognoses. The present patient developed various schizophreniform symptoms and seizures after experiencing cold-like symptoms. These findings are consistent with anti-NMDA-R encephalitis. In fact, although the present patient had APS-3 without a tumor, we suspected other autoimmune diseases in APS, and immune-related encephalitis was suspected in the early stages of the disease. Accordingly, early steroid pulse therapy was initiated. Early detection and treatment of anti-NMDA-R encephalitis is critical for enhancing positive outcomes, considering that besides thyroid diseases

and type 1 diabetes, various autoimmune diseases are associated with APS-3.

DISCLOSURE

The authors declare no conflict of interest.

REFERENCES

1. Dalmau J, Tüzün E, Wu HY, *et al.* Paraneoplastic anti-N-methyl-D-aspartate receptor encephalitis associated with ovarian teratoma. *Ann Neurol* 2007; 61: 25–36.
2. Kamei S, Kuzuhara S, Ishihara M, *et al.* Nationwide survey of acute juvenile female non-herpetic encephalitis in Japan: relationship to anti-N-methyl-D-aspartate receptor encephalitis. *Intern Med* 2009; 48: 673–679.
3. Dalmau J, Lancaster E, Martinez-Hernandez E, *et al.* Clinical experience and laboratory investigations in patients with anti-NMDAR encephalitis. *Lancet Neurol* 2011; 10: 63–74.
4. Hashimoto K, Maruyama H, Nishiyama M, *et al.* Susceptibility alleles and haplotypes of human leukocyte antigen DRB1, DQA1, and DQB1 in autoimmune polyglandular syndrome type III in Japanese population. *Horm Res* 2005; 64: 253–260.
5. Kawabata Y, Ikegami H, Imagawa A, *et al.* Differential association of HLA with three subtypes of type 1 diabetes: fulminant, slowly progressive and acute-onset. *Diabetologia* 2009; 52: 2513–2521.
6. De Leu N, Unuane D, Poppe K, *et al.* Seizures and postictal stupor in a patient with uncontrolled Graves' hyperthyroidism. *BMJ Case Rep* 2012; 2012: bcr0220125929.
7. Lu J, Samson S, Kass J, *et al.* Acute psychosis in a pregnant patient with Graves' hyperthyroidism and anti-NMDA receptor encephalitis. *BMJ Case Rep* 2015; 2015: bcr2014208052.
8. Frunza-Stefan S, Whitlatch HB, Rao GG, *et al.* usual case of anti-N-methyl-D-aspartic acid-receptor (NMDA-R) encephalitis and autoimmune polyglandular syndrome (APS). *BMJ Case Rep* 2018; 2018: bcr2018-224821.
9. Dalmau J, Gleichman AJ, Hughes EG, *et al.* Anti-NMDA-receptor encephalitis: case series and analysis of the effects of antibodies. *Lancet Neurol* 2008; 7: 1091–1098.