Treatable Rapid Progressive Dementia: A First Case Report of Anti-dipeptidyl-peptidase-like Protein 6 Encephalitis in Taiwan

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Abstract

Purpose: Anti-dipeptidyl-peptidase-like protein 6 (DPPX) encephalitis is a rare but treatable autoimmune disorder, characterized by gastrointestinal symptoms, cognitive dysfunction, and central nervous system hyperexcitability.

Case Report: Herein, we report a case of an 80-year-old male patient who presented with unexplained diarrhea, weight loss, rapidly progressive dementia, tremors, and myoclonus. His serum tested positive for anti-DPPX antibodies. He was treated with plasma exchange, oral prednisolone, and azathioprine. All his symptoms improved substantially after treatment.

Conclusion: Early recognition of anti-DPPX encephalitis is important because it can be treated with immunotherapy. To the best of our knowledge, this is the first reported case of anti-DPPX encephalitis in Taiwan.

Keywords: anti-DPPX encephalitis, autoimmune encephalitis, rapidly progressive dementia, diarrhea, myoclonus.

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INTRODUCTION

First described in 2013 by Boronat et al. [(1)], anti-dipeptidyl-peptidase-like protein 6 (DPPX) encephalitis is a rare autoimmune disease characterized by diarrhea, weight loss, central nervous system hyperexcitability, and encephalopathy. DPPX is an important regulatory subunit of Kv4.2 potassium channels, which plays an important role in inhibiting currents in the central and peripheral nervous systems [(1)]. Autoantibodies to DPPX cause Kv4.2 function impairment, resulting to neuronal hyperexcitability [(2)]. Anti-DPPX encephalitis is easily misdiagnosed; however, timely recognition is crucial for prompt treatment. Herein, we report the first case of anti-DPPX encephalitis in Taiwan.

CASE REPORT

An 80-year-old male patient was admitted with a two-month history of involuntary muscle jerks in all limbs, rapidly progressive dementia, depressive mood, agitation, abdominal pain, severe diarrhea, and weight loss of 20

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kg. The patient had gastric cancer history and undergone subtotal gastrectomy 20 years ago. He had gallstones with cholangitis and had undergone percutaneous transhepatic gallbladder drainage 3 years earlier. He had smoked for >40 years, but quitted 10 years ago. No alcohol consumption was reported. Two months before admission, the patient developed frequent diarrhea and abdominal pain. He was admitted to the department of gastroenterology. All tests, including imaging, gastroscopy, and colonoscopy showed unremarkable findings. Two weeks before admission, his wife found him with severe diarrhea approximately 10 times a day, incoherent speech, depressive mood, drowsiness, apathy, intermittent irritability, bizarre behavior (walking naked on the street), tremor, and involuntary muscle jerks in the limbs. Initially, he visited the department of psychiatry, where blood tests including complete blood count and differential counts, liver and renal function tests, electrolytes, glucose, thyroid function tests, and computed tomography of the brain without contrast were unremarkable. The patient was diagnosed with acute delirium and probable neurotic depression. He was transferred to the department of neurology due to persistent symptoms. The patient was alert; however, mental status examination showed impaired cognitive function with disorientation, inattentiveness, flat affect, and passively cooperative attitude. The Mini-Mental State Examination (MMSE) score was 7, with intact domains of naming and reading. Cranial nerves, muscle strength, muscle tone, deep tendon reflexes, and plantar reflexes were normal. He had postural tremor and myoclonus in all limbs, which disappeared during sleep. The myoclonus involved both the proximal and distal

Table 1. Blood and CSF examination results of the patient

	Results (at Diagnosis)	Results (17M later)	Normal Range
ANA	1:640 (nucleolar pattern), 1:80 (speckled pattern)	1:320 (nucleolar pattern), 1:80 (cytoplasmic pattern)	< 1:80
Anti-cardiolipin IgM	60	5.7	< 40 U/mL
Lupus anticoagulant	1.31	1.13	< 1.2
Protein S	48.1	79.5	72.2–126.0 %
C3	70.3	106.2	87.0–200.0 mg/dL
C4	14.1	31.3	19.0–52.0 mg/dL
TSH	2.44	1.71	0.25-5.00 μIU/mL
Free T4	1.68	1.53	0.89-1.78 ng/dL
T3	86.11	99.93	78.00-182.00 ng/dL
Anti-TPO	3.70	1.25	0.0-16.00 IU/mL
Anti-TSH	2.3	<0.1	0.0-1.0 U/L
Tumor markers: CEA, SCC antigen, CA19-9, AFP, PSA	Within normal limits	Not performed	
DPPX antibody in serum	Positive	Positive	
Autoantibodies to Tr, GAD65, Zinc4, titin, SOX1, recoverin, Hu, Yo, Ri, PNMA2, CV2, and amphiphsyin in serum	Negative	Not performed	
Autoantibodies to NMDAR, AMPAR1, AMPAR2, GABABR, LGI1, and CASPR2 in serum and CSF	Negative	Not performed	

Abbreviations: CSF = cerebrospinal fluid; ANA = antinuclear antibody; TSH = thyroid stimulating hormone; TPO = thyroid peroxidase; CEA = carcinoembryonic antigen; SCC = squamous cell carcinoma; CA19-9 = cancer antigen 19-9; AFP = alpha-fetoprotein; PSA = prostate specific antigen; DPPX = Dipeptidyl peptidase-like protein 6; GAD = glutamic acid decarboxylase; NMDAR = N-methyl-d-aspartate receptor; AMPAR = α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; LGI1 = leucine-rich glioma-inactivated 1; GABABR = gamma aminobutyric acid receptor; CASPR2 = contactin-associated protein-like 2

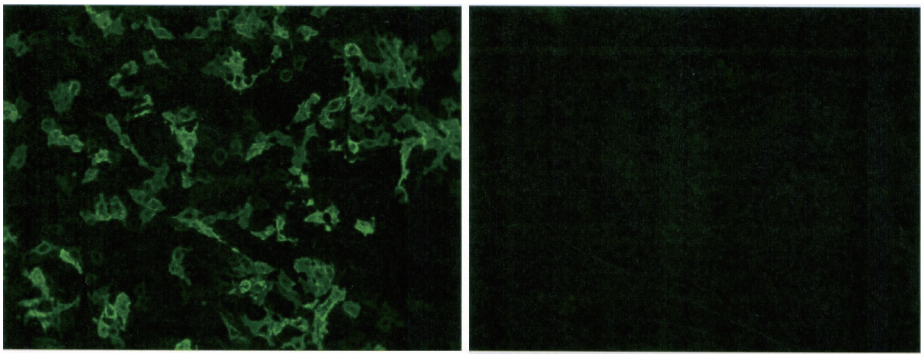

Figure 1. The patient's serum shows reactivity with DPPX-expressing cells (left) compared with a control extract without DPPX (right).

parts of the limbs and was tactile-sensitive. His gait was ataxic. Dysmetria was absent in the upper or lower limbs. Abdominal examination revealed generalized tenderness on palpation, without peritoneal signs. Cerebrospinal fluid (CSF) analysis demonstrated normal opening pressure of 7.5 cm H_2O, 0 white blood cells, 0 red blood cells, 115 mg/dL total protein (normal range 15–45 mg/dL), and 57 mg/dL glucose (serum glucose 131 mg/dL). Blood tests were notable for elevated antinuclear antibody (ANA) titers (1:640 for nucleolar pattern, 1:80 for speckled pattern); presence of anti-cardiolipin IgM, lupus anticoagulant (LA), and anti-thyroid stimulating hormone (TSH) antibody; and low C3, C4, and protein S (Table 1). Antibodies against DPPX were tested positive in his serum (Fig. 1). Relevant blood and CSF tests results are summarized in Table 1. His electroencephalogram showed a slowing background activity. Brain magnetic resonance imaging (MRI) with contrast showed senile atrophy. A diagnosis of anti-DPPX encephalitis was made, and the patient was administered with prednisolone (orally, 30 mg daily) with simultaneous plasma exchange. After completing 10 times of plasma exchange, his tremor and myoclonus disappeared and diarrhea subsided (2–3 times a day). However, cognitive impairment persisted, with an MMSE score before discharge of 9. Four weeks after discharge, his cognitive impairment showed no progression, ataxic gait improved, and he could walk slowly with a cane.

The steroid dosage was gradually tapered with a final maintenance of 5 mg daily of prednisolone. Azathioprine 25 mg daily was also added. On his last follow-up at our outpatient department (17 months after diagnosis), his cognitive function had recovered, with an MMSE score of 19. His serum still tested positive for anti-DPPX autoantibodies and the ANA titers remained elevated (1:320 for nucleolar pattern, 1:80 for cytoplasmic pattern). Other autoimmune antibodies, including anti-cardiolipin IgM, LA, and anti-TSH antibody, were not detected. C3, C4, and protein S levels were within normal limits.

DISCUSSION

Anti-DPPX encephalitis is a rare autoimmune disorder that was first described in 2013 by Boronat et al., who described four patients presenting with symptoms of central nervous system hyperexcitability, including agitation, confusion, myoclonus, tremors, and seizures, as well as severe prodromal diarrhea [(1)]. The cause was determined to be an autoantibody to a surface antigen called DPPX, which serves as an important regulatory subunit of Kv4.2 potassium channels. Kv4.2 channels are widely expressed in neuronal somata and dendrites, which play an important role in inhibiting neural activity in the central and peripheral nervous systems [(3)]. Animal studies using mice showed that Kv4.2 channels are expressed in the cerebral cortex, hippocampus, striatum, cerebellum, brainstem, spinal dorsal horn neurons, myenteric and submucosal plexuses, and kidneys [(4)]. Anti-DPPX autoantibodies indirectly impair the function of Kv4.2 channels, leading to neuronal hyperexcitability in these brain areas and organs.

Anti-DPPX encephalitis shows male predominance, with an onset median age of 57 years [5]. Typical clinical presentations of anti-DPPX encephalitis are subacute-to-chronic onset of encephalopathy (involving the cortex, cerebellum, and brainstem), hyperkinetic movement disorders, and myelopathy preceded by prodromal diarrhea [1]. Rarer presentations of anti-DPPX autoantibodies include neurological syndromes such as opsoclonus-myoclonus syndrome [6], progressive encephalomyelitis with rigidity and myoclonus [7], and stiff-person syndrome [8]. Findings of CSF examination, brain MRI, and electroencephalography are nonspecific and variable [5]. Brain MRI may reveal nonspecific T2/fluid-attenuated inversion recovery white matter abnormalities or atrophy of the temporal lobes. A recent case report showed hypometabolism in the bilateral temporal lobes and thalamus by positron emission tomography-MRI [9]. A diagnostic tool for this disease is the detection of anti-DPPX autoantibodies in the patient's blood or CSF. Once the diagnosis is made, immunotherapy should be initiated promptly since most patients are responsive to treatment. Multiple treatment options, including steroids, plasma exchange, plasmapheresis, intravenous immunoglobulin administration, azathioprine, rituximab, cyclophosphamide, and mycophenolic acid, have been reported [2,5]. However, efficacies of these treatments have not been compared in a randomized trial to date. Our patient was initially treated with plasma exchange and oral prednisolone, followed by a tapered dosage of prednisolone and an additional azathioprine. He responded well, with significant improvement in diarrhea, cognitive impairment, tremors, and myoclonus. Long-term maintenance immunotherapy may be warranted since the disease tends to progress or relapse [10,11]. Paraneoplastic causality in anti-DPPX encephalitis is yet to be established. However, performing diagnostic tests for underlying B-cell non-Hodgkin lymphoma is important, which is also associated with chronic immunosuppressive therapy. Five cases were reported to develop B-cell lymphoma during follow-up [2,5,11,12].

At the initial presentation, the patient had coexisting serum autoantibodies, including ANA, anti-cardiolipin IgM, LA, and anti-TSH antibody. However, he did not have any associated clinical features, and most of the autoantibodies disappeared after treatment, except for the anti-DPPX antibody and ANA. This epiphenomenon is possibly caused by the initial co-activation of T-cell or B-cell pathways, which subsequently subsided after immunomodulatory treatment. However, these coexisting autoantibodies may truly indicate underlying autoimmune diseases since concurrent lupus [2] and autoimmune thyroid disease [2] with anti-DPPX encephalitis were reported. Whether the presence of these autoantibodies is pathognomonic or just an epiphenomenon of immune activation is challenging for clinicians. Therefore, detailed history taking, physical examinations, further diagnostic workup, and long-term follow-up are warranted to confirm the diagnosis.

CONCLUSION

To the best of our knowledge, this is the first reported case of anti-DPPX encephalitis in Taiwan. Anti-DPPX encephalitis should be considered as a differential diagnosis when patients present with subacute onset of unexplained diarrhea, encephalopathy, and neuronal hyperexcitability. The presence of anti-DPPX antibodies in either the serum or CSF is diagnostic. Timely diagnosis is important since most patients respond well to immunotherapy.

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