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Non-stiff anti-amphiphysin syndrome: Clinical manifestations and outcome after immunotherapy

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ABSTRACT

Amphiphysin antibody causes paraneoplastic stiff-person syndrome and can also result in a variety of neurological manifestations. Here, we investigated the clinical spectrum of 20 patients with non-stiff anti-amphiphysin syndrome and their responses to immunotherapy. The most common neurological manifestation was limbic encephalitis (n = 10), followed by dysautonomia (n = 9), and cerebellar dysfunction (n = 6). Cancer was detected in only seven patients. Intravenous immunoglobulin or steroid treatment was effective in most patients, but three improved only after rituximab treatment. Our study suggests that anti-amphiphysin syndrome can manifest as non-stiff encephalomyelitis and is only partially associated with cancer. Active immunotherapy, including rituximab, would be beneficial.

1. Introduction

Amphiphysin is an intracellular synaptic vesicle protein discovered in 1992 (Lichte et al., 1992) that is involved in retrieving vesicle membranes from the axon terminal's plasma membrane after exocytosis of neurotransmitters (Coppens et al., 2006). Amphiphysin antibody was initially described in patients with paraneoplastic stiff-person syndrome (SPS) (De Camilli et al., 1993), but it was later found in many other types of paraneoplastic neurological syndromes (Pittock et al., 2005). Several case reports and small case series have demonstrated that amphiphysin autoimmunity is associated with limbic encephalitis (Dorresteijn et al., 2002; Krishna et al., 2012), brainstem encephalitis (Coppens et al., 2006), myelopathy (Chamard et al., 2011; Flanagan et al., 2011), peripheral neuropathy (Antoine et al., 1999; Perego et al., 2002; Coppens et al., 2006) and cerebellar dysfunction (Coppens et al., 2006). In 2005, Pittock and colleagues reported SPS in 18 of 63 patients (28.6%) with amphiphysin autoimmunity, most of whom had non-stiff encephalomyelitis (Pittock et al., 2005). In addition, according to the report, about 80% of the patients had cancer and about three-fourths had coexisting paraneoplastic antibodies.

To date, only a few reports have shown favorable effects of immunotherapy in amphiphysin-related SPS (Murinson and Guarnaccia, 2008; Dupond et al., 2010). Data on the effect of immunotherapy in non-stiff anti-amphiphysin syndrome (NSAS), however, are very limited. In this study, we describe the clinical features in 20 NSAS patients caused by amphiphysin autoimmunity and the outcome of treatment with immunotherapy.

2. Methods

This study was conducted at Seoul National University Hospital, a tertiary referral hospital, and was approved by its institutional review board. Between October 2012 and March 2014, patients with possible paraneoplastic syndrome (limbic encephalitis, brainstem encephalitis, cerebellar ataxia, dysautonomia, or polyneuropathy of unknown etiology) were screened for classical paraneoplastic (nuclear or cytoplasmic) or autoimmune synaptic antibodies.

Amphiphysin antibody was detected by immunoblotting. Briefly, diluted patient's serum (1:10 to 1:100) or cerebrospinal fluid (1:10) was incubated with recombinant amphiphysin protein and detected by anti-human IgG using an immunoblotting kit (Euroimmun AG,

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Lübeck, Germany). Samples were also tested for the following classical paraneoplastic antibodies and autoimmune synaptic antibodies using detection kits (Euroimmun): anti-Hu, anti-Yo, anti-Ri, anti-Ma2, anti-CV2/CRMP, anti-NMDA receptor, anti-LGI1, anti-Caspr2, anti-AMPA1 receptor, anti-AMPA2 receptor, and anti-GABA-b receptor (Shin et al., 2013). Patients who were positive for amphiphysin antibody were included in the analysis.

For each patient, the following information was recorded: clinical features, laboratory findings, cerebrospinal fluid profile, electroencephalogram, brain magnetic resonance imaging, nerve conduction study and electromyogram, fluoro-deoxyglucose positron emission tomography, and other radiologic screening tests for detecting systemic neoplasm.

3. Results

3.1. Clinical features of anti-amphiphysin syndrome

Between October 2012 and March 2014, amphiphysin antibody was identified in the serum of 20 patients (12 men, eight women; mean age, 57.6 ± 17.2 years). Ten patients were diagnosed with limbic encephalitis, nine with dysautonomia, six with cerebellar dysfunction, and four with brainstem encephalitis. Four patients had peripheral neuropathy and one had myelitis (Table 1). Brain MRI was performed in every patients, which revealed parenchymal T2 high signal intensity (HSI) lesions in three patients and leptomeningeal enhancement in two patients. One patient had T2 HSI lesion in upper cervical spinal cord. CSF pleocytosis was present in four patients. Four patients showed polyneuropathy in nerve conduction studies (Table 2).

Cancer was detected in seven patients (35%), which included non-small cell lung cancer (n = 1), small cell lung cancer (n = 1), ovarian cancer (n = 1), cervical cancer (n = 1), esophageal cancer (n = 1), and gastric cancer (n = 2). To check for hidden malignancies in rest of the patients, chest and abdomen computed tomography or whole body fluoro-deoxyglucose positron emission tomography was performed in all but one patient (case #19), but no additional cancer was detected (Table 2). Patients with cancer were, on average, older than patients without cancer (mean = 71.1 vs. 50.2 years) (Table 3). Among the seven patients diagnosed with cancer, four developed neurological symptoms after (mean time, 5.5 months [range, 2–11]) and three before the diagnosis of cancer. In two cases (cases #4 and #7), cancer was detected during the diagnostic workup for the patient's neurological symptoms. In another (case #5), gait disturbance and orthostatic dizziness were detected 1.5 years before the diagnosis of cancer, and psychotic symptoms appeared 1 month after its detection. In the 13 patients without cancer, neurological symptoms lasted for an average of 32.2 months (range, 2–132). Interestingly, one patient (case #16) had been treated by a psychiatric department for 10 years for psychotic symptoms before amphiphysin antibody was detected.

In two patients, amphiphysin antibodies were detected after prior history of Epstein–Barr virus encephalitis (Table 1). One patient (case #11) initially experienced fever followed by progressive dizziness, dysarthria, spasticity of one leg, and confusion. The other patient (case #20) first complained of progressive headache and dizziness, and later developed brainstem dysfunction and ataxia. In both patients, EBV infections were confirmed by viral PCR of CSF samples and amphiphysin antibodies were revealed more than one month after the onset of initial symptoms.

Additional autoantibodies (Hu, Yo, Ri, and NMDA antibodies) were detected in four patients (cases #3, #7, #16 and #20) (Table 2).

3.2. Effect of treatment

Thirteen patients were treated with immunotherapy, which included intravenous immunoglobulin (IVIG) (n = 12), corticosteroids (n = 9), tacrolimus (n = 4), rituximab (n = 3), cyclophosphamide (n = 1), tocilizumab (n = 1), and mycophenolate mofetil (n = 1) (Table 4). Eleven of these patients had favorable responses. One patient (case #3) did not improve after 10 months of immunotherapy, and in one case (#9), the effect of immunotherapy could not be assessed because the patient was lost to follow-up.

In three patients, symptoms improved after treatment with rituximab but not after treatment with IVIG or corticosteroids. In the first patient (case #5), cognitive impairment improved gradually with IVIG, but gait disturbance remained. This gait disturbance improved significantly after treatment with rituximab. In the second patient (case #10), ataxia and

Table 1
Demographics and clinical characteristics of the patients.

Patient	Sex	Age	Presenting symptoms	LE	BE	Cerebellar dysfunction	Myelitis	PN	Dysautonomia	Other clinical considerations
1	M	73	Seizure, irritability, vertigo, left 6th nerve palsy, right 8th nerve palsy	+	+					
2	F	74	Vertigo, nystagmus, orthostatic hypotension			+			+	
3	F	73	Sensory polyneuropathy					+		
4	M	66	Cognitive impairment (K-MMSE 22)	+						
5	M	65	Cognitive impairment (K-MMSE 20), irritability, dizziness, ataxia, orthostatic hypotension, sensory polyneuropathy	+		+		+	+	
6	M	63	Delayed gastric emptying						+	
7	M	84	General weakness, sensorimotor polyneuropathy					+		
8	F	59	Cognitive impairment (K-MMSE 17), orthostatic hypotension	+					+	DM
9	M	75	Ophthalmoplegia, hoarseness, dysphagia, ataxia, postural instability, orthostatic hypotension (C3 myelitis on MRI)		+		+		+	DM
10	F	71	Postural instability, dysmetria, orthostatic hypotension			+			+	
11	M	42	Altered mentality, bilateral 6th nerve palsy, GEN, dysarthria, right leg weakness, Babinski sign, dysmetria	+	+					CSF EBV PCR(+)
12	M	39	Cognitive impairment (K-MMSE 29), irritability, postural instability	+		+				
13	F	28	POTS						+	Ovarian cyst
14	F	30	Dysarthria, right side weakness, right hand dystonia, right homonymous hemianopsia	+						
15	M	31	Seizure, confusion (bilateral hippocampal atrophy on MRI)	+						
16	F	44	Seizure, cognitive impairment (K-MMSE 17), psychosis (schizophrenia)	+					+	
17	M	63	Sensorimotor polyneuropathy					+		MND + sensorimotor neuropathy
18	F	68	Cognitive impairment (K-MMSE 22), irritability	+						
19	M	62	Dizziness, postural instability			+				
20	M	41	Dizziness, GEN, ataxia, postural instability, POTS		+	+			+	CSF EBV PCR(+)

LE: limbic encephalitis, BE: brainstem encephalitis, PN: polyneuropathy, M: male, F: female, K-MMSE: Korean version of minimental status examination, GEN: gaze evoked nystagmus, POTS: postural orthostatic tachycardia syndrome, DM: diabetes mellitus, CSF: cerebrospinal fluid, EBV: Epstein–barr virus, PCR: polymerase chain reaction, MND: motor neuron disease.