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【 CASE REPORT 】

Spinocerebellar Ataxia Type 31 Exacerbated by Anti-amino Terminal of Alpha-enolase Autoantibodies

Satoshi Zeniya[1], Nobuo Sanjo[1], Hiroya Kuwahara[1], Kinya Ishikawa[2], Miwa Higashi[1], Akiko Matsunaga[3], Makoto Yoneda[4], Hidehiro Mizusawa[5] and Takanori Yokota[1]

Abstract:

We herein report a 61-year-old woman who was genetically diagnosed with spinocerebellar ataxia type 31 whose symptoms were modified by anti-amino terminal of alpha-enolase (NAE) antibodies, known as a biomarker of Hashimoto's encephalopathy (HE), and ultimately responded to immunotherapy. The relative titers of anti-NAE antibodies increased when her cerebellar ataxia showed acute deterioration and decreased after immunotherapy. This is the first report of cerebellar ataxia associated with genetic spinocerebellar ataxia with concomitant cerebellar type HE. Physicians should be mindful of measuring anti-NAE antibodies to prevent overlooking patients with genetic spinocerebellar ataxia with treatable simultaneous ataxic diseases.

Key words: spinocerebellar ataxia, hashimoto's encephalopathy, anti-amino terminal of alpha-enolase antibody, autoimmune cerebellar ataxia, immune-mediated cerebellar ataxia

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Introduction

Spinocerebellar ataxia type 31 (SCA31) is one of the most common genetic cerebellar ataxic neurodegenerative diseases in Japan (1). Hashimoto's encephalopathy (HE) is an autoimmune encephalopathy distinct from hypothyroid encephalopathy (2); the latter presents various neurological and psychiatric manifestations and is generally responsive to immunotherapy. Anti-amino terminal of alpha-enolase (NAE) antibodies have been reported to be specific diagnostic biomarkers for HE (3, 4). The cerebellar type of HE has been reported to be an immune-mediated cerebellar ataxia presenting with clinical features of genetically pure cerebellar ataxic diseases (5).

We herein report a 61-year-old woman who was genetically diagnosed with SCA31, whose symptoms were modified by anti-NAE antibodies, and who responded to immunotherapy.

Case Report

A 56-year-old woman experienced an unstable gait. She presented with chief complaints of slowly progressive unsteady gait and dysarthria for 5 years (until 61 years old) that were associated with cerebellar ataxia. She was diagnosed having SCA31 when a genetic analysis revealed a TGGAA repeat expansion in the SCA31 locus. She had a family history of slowly progressive ataxia in her brother, father, grandmother, and uncle, with symptoms at 58 years old and in their 60s, 60s, and 60s, respectively; however, genetic analyses were not performed in those subjects.

Since her ataxia had suddenly deteriorated during the last two months before presentation, without any other neurological symptomatic deteriorations, such as muscle weakness, sensory disturbance, or cognitive impairment, we speculated an additional intercurrent immunological disease. The first laboratory blood tests before the sudden deterioration were weakly positive for serum anti-NAE antibodies

[1]Department of Neurology and Neurological Science, Tokyo Medical and Dental University, Japan, [2]The Center for Personalized Medicine for Healthy Aging, Tokyo Medical and Dental University, Japan, [3]Second Department of Internal Medicine, Faculty of Medical Sciences, University of Fukui, Japan, [4]Faculty of Nursing and Social Welfare Sciences, Fukui Prefectural University, Japan and [5]National Center Hospital, National Center of Neurology and Psychiatry, Japan
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Correspondence to Dr. Nobuo Sanjo, n-sanjo.nuro@tmd.ac.jp

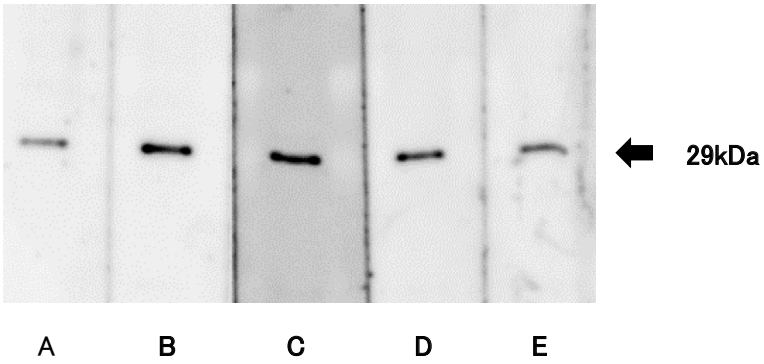

Figure. **Immunoblots detecting anti-N-terminal of α-enolase (NAE) autoantibodies in the serum of the patient with a combination of spinocerebellar ataxia 31 and Hashimoto's encephalopathy. A recombinant human NAE fragment (amino acid residues 1-157) expressed in cultured human embryonic kidney (HEK) 293 cells was purified using a His column (ProBond Protein Purification kit; Invitrogen, Carlsbad, USA). An immunoblotting analysis of serum antibodies against the recombinant NAE fragment was performed using a gel electrophoresis system (BE-220; BIO CRAFT, Tokyo, Japan) and 12% sodium lauryl sulfate-polyacrylamide gel electrophoresis, as previously described (3). In each lane of the polyacrylamide gel, 1 μg of the recombinant fragment was loaded and electrophoresed, and the separated proteins were then electroblotted onto a polyvinylidene difluoride membrane (Hybond-P; GE Healthcare UK, Buckinghamshire, UK) with a blotting apparatus (KS-8453; Oriental Instrument, Tokyo, Japan) at 0.3 mA/cm^2 for 8 h at 4°C. To detect the band specific against the recombinant NAE fragment, serum (diluted to 1/320) was applied to the membrane, which was then incubated in 1% gelatin for 1 h at 20°C. Horseradish peroxidase-conjugated anti-human goat IgG Fc (ICN Pharmaceuticals, CostaMesa, USA) was then applied to the membrane as the secondary antibody, and the membranes were fluorescently labeled and imaged using Fusion (Vilber-Lourmat, Collégien, France). Serum samples of the patient collected at various time points - when the patient was first diagnosed with genetic spinocerebellar ataxia 31 (A: baseline), at the time of acute deterioration of ataxia (B), before the second immunotherapy (C), at the time of the second immunotherapy (D), and at 4 years after the second immunotherapy (E) - were analyzed on the same membrane, and the titers are presented as measured optical densities in Table 1 as multiples (%) of the baseline optical density (A). The arrow shows recombinant human NAE fragments (29 kDa).**

Table. **Clinical Course and Anti-NAE Antibody Titers.**

Duration from onset of the disease (months)	60 (Baseline)	62	63	79	80	125
Clinical features	Slowly progressive cerebellar ataxia	Rapid progression and diagnosed having Hashimoto's encephalopathy	After the first immunotherapy	Before the second immunotherapy	After the second immunotherapy	Four years after the last immunotherapy
SARA	N.E.	14	8	17	12.5	20.5
SARA progression (/months)	N.E.	0.23	0.13	0.22	0.16	0.16
Anti-NAE antibody titers (% of the density of the baseline)	100	266	N.E	332	176	126
anti-thyroid peroxidase antibody titers (U/mL)	1.4	1.3	1.1	7.5	3.6	15.4
anti-thyroglobulin antibody titers (U/mL)	0.3	0.5	1.5	1.6	0.9	5.8
anti-thyroid-stimulating hormone receptor antibody titers (U/mL)	1.1	0.8	0.4	0.8	N.E.	N.E.

Titers of the anti-N-terminal region of α-enolase antibody were described as measured signal densities of the bands in Figure using densitometry as the multiple numbers (%). SARA progression=SARA score/duration from onset of the disease. SARA: the Scale for the Assessment and Rating of Ataxia. NAE: amino terminal of alpha-enolase

(lane A in Figure). The antibody titer was evaluated again during the acute deterioration; the result revealed a 2.7-fold elevation from the baseline optical density (lane B in Figure, Table). Other blood tests, including those for the anti-glutamic acid decarboxylase, anti-deamidated gliadin peptide, anti-Hu, anti-Yo, anti-voltage-gated-calcium-channel antibodies; vitamins; toxic chemicals; and thyroid functions, were negative. However, tests for anti-thyroid peroxidase,

anti-thyroglobulin, and anti-thyroid-stimulating hormone receptor autoantibodies were positive [1.4 (<0.3) U/mL, 0.3 (< 0.3) U/mL, and 1.1 (<1.0) U/mL, respectively]. An examination of the cerebrospinal fluid was unremarkable, including findings for the immunoglobulin G-index, and systemic imaging did not reveal any evidence of malignancy. No epileptic discharges were detected on an electroencephalogram. Brain magnetic resonance imaging (MRI) showed atrophy of the cerebellum with widening of the cerebellar sulci and the fourth ventricle without any abnormal signal intensities. Cerebellar hypoperfusion was not detected on single-photon emission computed tomography. Based on these findings, we diagnosed the patient with SCA31-associated chronic cerebellar ataxia with acute deterioration caused by a simultaneous cerebellar type of HE.

The deterioration of her cerebellar ataxia was so rapid that she needed a walking cane for ambulation. After intravenous administration of high-dose methylprednisolone (1,000 mg/day) for 3 days, followed by oral administration of prednisolone (30 mg/day), her ataxia improved dramatically, and she recovered the ability to walk alone without any supportive equipment. We did not administer additional immunosuppressive agents. The Scale for the Assessment and Rating of Ataxia (SARA) score (6) improved from 14 to 8 points (Table).

However, her cerebellar ataxia gradually progressed after discharge (SARA score, 17), and the relative titer of anti-NAE antibodies increased to 332% of the baseline optical density (lane C of Figure, Table). We performed plasma exchange, following which her SARA score improved from 17 to 12.5, and the relative titers of anti-NAE antibodies decreased to 176% of the baseline optical density (lane D of Figure, Table). Although the titer of anti-NAE antibodies returned to the baseline 4 years after the second treatment, her SARA score worsened to 20.5, probably because of SCA31 progression.

Discussion

Immunotherapy, including steroid pulse therapy and plasma exchange, was effective in treating the acute deterioration of the ataxia, especially gait instability, and facilitated the simultaneous reduction of the serum anti-NAE antibody titers. The natural history and fluctuation of SCA31 symptoms remains under investigation (1). An average SARA score progression (calculated by SARA score/duration) of about 0.8 points per year has been reported in patients with SCA31 (7). Compared with the progression score, the rate of progression was 3.3-3.45 times higher in patients with acute deterioration than the average score progression in SCA31 (Table).

In our patient, the SARA score and relative titers of anti-NAE antibodies increased when her cerebellar ataxia showed acute deterioration and decreased after immunotherapy; this suggests that anti-NAE antibody may be useful not only as a diagnostic marker but also as a disease progression marker in HE. However, there has been no other report of the relative titers of anti-NAE antibody as a disease activity or progression marker.

The mechanism by which anti-NAE antibodies cause cerebellar ataxia has not been clarified. Alpha-enolase is a multifunctional protein expressed in almost all human tissues and functions as a key glycolytic enzyme and plasminogen receptor (8). Anti-NAE antibodies have been detected in the cerebrospinal fluid (CSF) of patients with cerebellar type HE, and these antibodies may disturb synaptic transmission (9). Anti-NAE antibody may be a dual function marker - a marker of the diagnosis as well as deterioration and recovery of cerebellar type HE. We previously reported the prevalence of anti-NAE antibodies in healthy subjects, Hashimoto's thyroiditis, HE, and cerebellar type of HE as 0%, 11.8%, 68%, and 62%, respectively (3-5), but there has been no report on the prevalence in genetic spinocerebellar ataxia. Excellent responses were described in a previous report (5). However, to our knowledge, there is no published report concerning cerebellar ataxia associated with genetic spinocerebellar ataxia with concomitant HE monitored by assessing anti-NAE antibody titers. The prevalence of autoimmune diseases in patients with genetically characterized ataxia is only 8%, and they are mostly reported as non-cerebellar diseases (10). It is extremely rare for patients with genetic spinocerebellar ataxia to present with coexisting anti-NAE antibodies. Physicians should be mindful of measuring anti-NAE antibodies to prevent overlooking patients with genetic spinocerebellar ataxia with treatable simultaneous ataxic diseases, especially those with relatively rapid progression.

The protocol followed all ethical requirements and was approved by the Institutional Ethics Committee of the Tokyo Medical and Dental University; written informed consent was obtained from the participant. This study was performed in accordance with the ethical standards laid down by the 2013 Declaration of Helsinki.

The authors state that they have no Conflict of Interest (COI).

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