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From dizziness to severe ataxia and dysarthria: New cases of anti-Ca/ARHGAP26 autoantibody-associated cerebellar ataxia suggest a broad clinical spectrum

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ABSTRACT

In 2010, a novel anti-neuronal autoantibody, termed anti-Ca, was described in a patient with subacute cerebellar ataxia, and Rho GTPase-activating protein 26 (ARHGAP26) was identified as the target antigen. Recently, three additional cases of anti-Ca-positive cerebellar ataxia have been published. In addition to ataxia, cognitive decline and depression have been observed in some patients. Here, we report two new cases of anti-Ca-associated autoimmune cerebellar ataxia.

Patient 1 presented with dizziness and acute yet mild limb and gait ataxia. Symptoms stabilized with long-term oral corticosteroid therapy but transiently worsened when steroids were tapered. Interestingly, both initial occurrence and worsening of the patient's neurological symptoms after steroid withdrawal were accompanied by spontaneous cutaneous hematomas. Patient 2 initially presented with an increased startle response and myoclonic jerks, and subsequently developed severe limb and gait ataxia, dysarthria, oculomotor disturbances, head and voice tremor, dysphagia, cognitive symptoms and depression. Steroid treatment was started five years after disease onset. The symptoms then responded only poorly to corticosteroids. At most recent follow-up, 19 years after disease onset, the patient was wheelchair-bound.

These cases extend the clinical spectrum associated with anti-ARHGAP26 autoimmunity and suggest that early treatment may be important in patients with this rare syndrome.

1. Introduction

In 2010, a novel serum IgG reactivity, termed anti-Ca with reference to the index patient, was described in a patient with subacute autoimmune cerebellar ataxia (ACA), and the Purkinje cell protein ARHGAP26 RhoGTPase-activating protein 26 was identified as the target antigen (Jarius et al., 2010). That discovery complemented the growing spectrum of Purkinje cell antibodies associated with ACA (Jarius and Wildemann, 2015a, b, c). To date, four patients with cerebellar ataxia and dysarthria (Jarius et al., 2010, 2013; Doss et al., 2014) and one with limbic encephalitis (Jarius et al., 2015) have been reported (Table 1). While a moderate response to steroids, intravenous immunoglobulins or immunosuppressants was noted during the first 12 months after the onset of symptoms, no such effect was observed later in the disease course, leaving the patients severely disabled.

Here, we present two new cases of anti-Ca-associated ACA that extend the clinical spectrum associated with this rare condition and suggest that early treatment is important to prevent irreversible damage to the cerebellum.

2. Case reports

2.1. Case 1

In 2016, a 57-year-old woman presented with a 3-day history of dizziness and spontaneously developing cutaneous hematomas (Fig. 1). Her symptoms had emerged subacutely following an episode of acute urticaria. In 2014, lobular breast cancer (pT1a pN0 cM0) had been treated with surgery and radiotherapy. In 2011, a malignant cutaneous melanoma (pT1a cN0 cM0) had been resected. Regular follow-up

Abbreviations: ACA, autoimmune cerebellar ataxia; ANA, anti-nuclear antibodies; ARHGAP26, RhoGTPase-activating protein 26; CSF, cerebrospinal fluid; CT, computed tomography; IVMP, intravenous methylprednisolone; MRI, magnetic resonance imaging; PET, positron emission tomography

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Table 1
Overview of clinical disease courses in anti-Ca positive patients.

	Patient 1[a]	Patient 2[b]	Patient 3[b]	Patient 4[c]	Patient 5[d]	Patient 6[d]
Age (Years)	33	68	38	24	57	37
Sex	Female	Female	Male	Male	Female	Female
Possible trigger	Common cold	–	?	–	Urticaria	?
Symptoms	Horizontal nystagmus, Dysarthria, Limb and gait ataxia, Hyperekplexia, Depression	Dizziness, Gaze-evoked nystagmus, Dysarthria, Gait ataxia, Nausea and vomiting	Cerebellar ataxia, Dysarthria, Weight loss, Nausea and vomiting	Panataxia, Severe dysarthria, Gaze-evoked nystagmus, Oscillopsia, Weight loss, Headache, Flat affect, Memory disturbances	Dizziness, Cutaneous hematomas, Mild limb and gait ataxia, Disrupted eye movements	Hyperekplexia, Myoclonic jerks, After 5 years: Limb and gait ataxia, Dysarthria, Gaze-evoked nystagmus, Depression
Development of symptoms	Subacute	Progressive	Progressive (?)	Subacute	Subacute	Progressive
Paraneoplastic origin	No	Yes (ovarian carcinoma)	?	No	No	No
Treatment delay	< 1 month (?)	7 months (?)	?	1 month (?)	10 days	5 years
Initial therapy	IVMP with oral tapering (Re-exacerbation at 12.5 mg per day)	Carboplatin + Docetaxel for ovarian cancer	?	IVMP with oral tapering	IVMP followed by continuous oral predniso-lone (Re-exacerbation at 5 mg per day)	IVMP
Other therapies	IVIG, Plasma exchange, Immuno-adsorption	Rituximab, IVIG, Cyclo-phosphamide	?	Plasma exchange	–	Deep brain stimulation
Outcome	Cerebellar signs and hyperekplexia, stable (16 months after onset)	Symptoms still advancing (24 months after onset)	?	Severe gait ataxia and cognitive symptoms after 4 years	Mild ataxia and dizziness, stable (12 months after onset)	Wheelchair-bound with cognitive symptoms after 19 years

[a] Jarius et al. (2010).
[b] Jarius et al. (2013).
[c] Doss et al. (2014).
[d] Our patients. IVMP: intravenous methylprednisolone. IVIG: intravenous immunoglobulins. Please note: No detailed information is available concerning treatment delay in patients 1–4.