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ORIGINAL COMMUNICATION

Antineuronal antibodies in sporadic late-onset cerebellar ataxia

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Abstract Sporadic late-onset cerebellar ataxia of unknown cause is considered a neurodegenerative disorder whose underlying mechanisms are still unknown. To identify antineuronal autoantibodies, immunohistochemical and immunoblotting techniques were performed in 67 patients with sporadic cerebellar degeneration of unknown cause. Elevated P/Q-type voltage-gated calcium channel (VGCC)-specific antibodies were found in eight patients (11.9%). There was no hint of a paraneoplastic disorder in any of the patients. The present findings suggest an autoimmune contribution to the pathophysiology of a subgroup of sporadic late-onset cerebellar ataxia.

Keywords Voltage-gated calcium channels · VGCC · Idiopathic late onset cerebellar ataxia · Multiple system atrophy · Paraneoplastic cerebellar degeneration

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Introduction

Idiopathic late-onset cerebellar ataxia (ILOCA) comprises a variety of cerebellar syndromes of apparently unknown cause that may present with a purely cerebellar syndrome or with additional extracerebellar features [1]. Multiple system atrophy also is a sporadic neurodegenerative disorder of unknown origin that may cause prominent cerebellar symptoms (MSA-C). In both conditions, diagnosis is made after exclusion of symptomatic ataxia. Paraneoplastic cerebellar degeneration (PCD) may clinically resemble ILOCA/MSA. The detection of different antineuronal antibodies (Abs) and the cloning and sequencing of their target antigens established PCD as an immune-mediated disorder occurring as a tumor-related complication [2]. In ILOCA and MSA-C, the pathogenic mechanisms still have to be elucidated. Little attention has been paid to a possible involvement of immune mechanisms. Therefore, patients with sporadic ataxia of unknown cause were screened for circulating Abs commonly associated with PCD.

Patients and methods

Sixty-seven patients (38 male, 29 female, mean age 57 ± 12 years, range 29–76 years, mean age of onset

50 ± 14 years, range 18–68 years, mean disease duration 8 ± 5 years, range 1–22 years) fulfilled the following inclusion criteria: (1) progressive cerebellar ataxia and dysarthria, (2) disease onset after the age of 18 years, (3) absence of any neurodegenerative disorder in relatives, no evidence for consanguinity of parents, and negative molecular genetic testing for Friedreich's ataxia and the most frequent spinocerebellar ataxias (SCA1, SCA2, SCA3, SCA6), and (4) exclusion of symptomatic causes of ataxia (infectious disease, disease of the thyroid, Wilson's disease, hypovitaminosis, alcoholism, chronic anticonvulsive therapy, and intracranial ischemia or neoplasm) [1]. CSF was examined for cell count, protein, albumin, immunoglobulin, lactate contents, and electrophoresis of the CSF. None of the 67 cerebellar patients had CSF abnormalities. Tumor screening including differential blood cell count, X-ray, or CT scan of the chest and abdominal ultrasound and/or CT scan were performed in patients with disease durations of 4 years or less. An additional mammogram and pelvic examination were performed in females. These radiological and physical screens for cancer were negative in all subjects. Written consent was obtained from all participants.

Antineuronal Abs were determined using immunofluorescence test (IFT) on cerebellum slides (Euroimmun) at a serum dilution of 1:60 and in positive or ambigious cases by immunoblot with recombinant antigens according to the manufacturer's instructions (Euroimmun GmbH, Lübeck, Germany; Milenia Biotech, Bad Nauheim, Germany) and as described earlier [3]. P/Q-type voltage-gated calcium channel (VGCC)-specific Abs in the patients' sera were assessed using a highly specific commercially available ^{125}I-radioimmunoprecipitation assay (DLD Diagnostika, Hamburg, Germany). The manufacturer set the cutoff for positivity at 20 pmol/l [4, 5].

Results

Clinical findings

Twenty-three patients had a disease duration of less than 4 years (see Table 1). Twenty-two patients fulfilled the diagnostic criteria of probable multiple system atrophy of the cerebellar type (MSA-C) according to the consensus criteria [6].

Brain imaging studies

CT/MRI scans were available for retrospective analysis in 57 patients (2 CT, 55 MRI). Six patients showed no abnormalities of the posterior fossa. Thirty patients had cerebellar atrophy and 21 combined cerebellar and brainstem atrophy. In ten patients, imaging studies excluding symptomatic causes such as infarction or tumor had been performed by the referring centers and were therefore not available for detailed retrospective analysis.

Table 1 Clinical symptoms in addition to cerebellar ataxia and dysarthria

Symptom	%
Cerebellar oculomotor deficits (nystagmus, impaired smooth pursuit)	96
Impaired proprioception	60
Spasticity	40
Bladder dysfunction	39
Dysphagia	36
Double vision	27
Reduced deep tendon reflexes	27
Basal ganglia features	25
Postural hypotension	24
Dementia	15
Gaze palsy	13
Impaired exteroception	10
Amyotrophy	6

Antibody testing

The immunofluorescence test (IFT) was negative in 59 patients, while 8 sera showed weak nuclear staining. These sera were further subjected to additional immunoblotting (Hu, Ri, Yo, amphiphysin). In all, there was no evidence for any paraneoplastic antineuronal Abs. Eight of 67 (11.9%) had elevated VGCC Abs concentrations. In six subjects, VGCC Abs ranged between 20 and 40 pmol/l. Two female individuals showed highly significant levels of 69.6 and 43.1 pmol/l. None of the controls (64 patients with myasthenia gravis, 28 with motor neuron disease, 25 with other immunologically mediated disorders) had Abs levels above the threshold of 20 pmol/l.

Patients

Disease duration, clinical symptoms and Abs levels of the patients who tested positive for levels of VGCC Abs are given in Table 2. Mean disease duration at the time of the study was 10 ± 8 years (range 1–24 years). Both patients with highly elevated concentrations presented with probable MSA-C with rapid disease progression. Meanwhile, the first patient aged 77 years has been followed for 10 years without any evidence of paraneoplastic disease. The clinical features include cerebellar ataxia, autonomic dysfunction and basal ganglia symptoms. The second patient developed rapidly progressive ataxia at the age of 52. She

Table 2 Characteristics of patients showing elevated VGCC Abs levels

Patient	Clinical diagnosis	Sex	Disease duration (years)	Anti-VGCC Abs concentration (pmol/l)	Imaging	Extracerebellar features
1	ILOCA	M	10	21.1	CA	Mild cognitive deficits, slowed saccades, spasticity, impaired proprioception, mild bladder dysfunction
2	ILOCA	F	18	22.9	CA	Action tremor
3	MSA-C	M	1	23.5	OPCA	Cogwheel rigidity, akinesia, severe autonomic dysfunction
4	ILOCA	F	13	29.6	CA	Spasticity, impaired proprio- and exteroception, mild bladder dysfunction
5	ILOCA	M	8	35.3	CA[a]	Pale discs, dysphagia
6	ILOCA	M	24	35.9	CA	Pale discs, double vision, hypacusis
7	MSA-C	F	1	43.1	OPCA	Autonomic dysfunction
8	MSA-C	F	7	69.6	CA	Dysphagia, rigidity, akinesia, severe autonomic dysfunction, impaired proprioception

[a] CA + asymptomatic brainstem cavernoma

ILOCA Idiopathic late onset cerebellar ataxia; *MSA-C* multiple system atrophy of the cerebellar type; *CA* cerebellar atrophy; *OPCA* olivopontocerebellar atrophy

was first examined 1 year later. At that time she had severe autonomic dysfunction. Unfortunately, this patient was lost to follow-up after another 2 years.

Discussion

Surprisingly, we found evidence for elevated VGCC-specific Abs in 11.9% of 67 patients with sporadic cerebellar degeneration of unknown cause (ILOCA and MSA-C), while 'classical' paraneoplastic antineuronal Abs were negative. In sporadic late-onset cerebellar ataxia of unknown cause, the underlying mechanisms still have to be elucidated. During the last years, there has been increasing evidence that some of these patients actually suffered from immunologically mediated disease: gluten ataxia, for example, is linked to celiac disease, a disorder characterised by defective innate and adaptive immune responses [7, 8], although the autoimmune mechanisms linking gluten sensitivity to the nervous system remain a matter of debate.

Abs against VGCC are commonly considered typical for PCD [2]. The clinical syndrome of sporadic cerebellar ataxia of unknown cause and MSA does not differ significantly from PCD since many PCD patients develop additional extracerebellar symptoms such as limbic or brainstem encephalitis with eye movement abnormalities, parkinsonian features, chorea or peripheral neuropathy [2]. In small imaging series of PCD, the cerebellum has been reported to range from normal to clearly atrophic [9]. Since cerebellar atrophy with or without additional brainstem atrophy represents a typical morphological feature of sporadic cerebellar ataxia, MRI may not be appropriate to distinguish PCD from other types of cerebellar degeneration [10]. In PCD, CSF examination usually reveals mild pleocytosis, as well as slightly elevated protein and IgG content. Pleocytosis may escape the diagnostic proof since it disappears several weeks after the onset, but protein abnormalities may persist [9, 11]. In the current series, CSF abnormalities represent an exclusion criterion. This may explain the absence of paraneoplastic Abs in the current series. The most striking argument against PCD though is the long disease duration (mean 10 ± 8 years) without any evidence of a tumor.

Voltage-gated calcium channels consist of a complex of distinct subunits. The Ca^{2+} conducting pore is formed by the α1 subunit, whereas the other subunits mainly modulate the gating. There are several kinds of VGCC that share structural homologies, but differ in their physiological properties and their inhibition by characteristic toxins. P/Q-type VGCCs are mainly located in presynaptic terminals that synapse on cell bodies and dendritic shafts of many types of neurons. Interestingly, human hereditary cerebellar ataxia (e.g., spinocerebellar ataxia type 6 and episodic ataxia type 2) as well as familial hemiplegic migraine (FHM) are contingent upon mutations in the gene CACNA1A encoding the α1 subunit of the P/Q-type VGCC.

In degenerative ataxia, such as ILOCA or MSA, VGCC Abs could theoretically contribute to cerebellar dysfunction provided that these Abs are capable of crossing the blood-brain barrier. In the current study, the highest VGCC Abs concentrations were found in patients with aggressive disease with rapid progression. Thus, it cannot be excluded that these Abs represent a secondary phenomenon due to massive degeneration. Even if this proves to be true, autoimmunity may contribute to neuronal dysfunction and could therefore offer new therapeutic approaches to incurable cerebellar ataxia.

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Conflict of interest statement None.

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