Auto-immune cerebellar ataxia with anti-GAD antibodies accompanied by de novo late-onset type 1 diabetes mellitus

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Abstract

Autoantibodies to glutamic acid decarboxylase (GAD-Ab) have been described in stiff-man syndrome, type 1 diabetes mellitus and in patients with auto-immune polyglandular failure. In addition, a few patients with progressive cerebellar ataxia show high titres of GAD-Ab, suggesting an auto-immune origin.

Aim. – This is a report of a patient presenting with cerebellar ataxia associated to late-onset type 1 diabetes and polyendocrine auto-immunity.

Case report. – A 47-year-old woman with a past medical history of vitiligo and Graves’ disease presented with late-onset type 1 diabetes. For two years, she had complained of progressive gait instability and oscillopsia. Neurological examination revealed multidirectional, horizontal rotatory fixation and gaze nystagmus, gait ataxia and mild limb ataxia in the left upper arm.

Methods. – Imaging studies, electrophysiological studies, routine biological and detailed immunological screening as well as a study of cerebrospinal fluid (CSF) were performed.

Results. – Brain magnetic resonance imaging showed cerebellar atrophy. Routine biological screening was normal. Immunological screening showed positivity for numerous antibodies (Ab), including GAD-Ab, thyroid peroxidase-Ab, thyroglobulin-Ab, 21-hydroxylase (adrenal)-Ab, gastric parietal cell-Ab and GM1 ganglioside IgG-Ab. CSF was normal, with no oligoclonal bands detected. GAD-Ab were positive in CSF, suggesting an auto-immune origin of the cerebellar ataxia. Treatment with intravenous immunoglobulin led to a slight improvement in nystagmus and gait instability.

Conclusion. – Auto-immune cerebellar ataxia related to GAD-Ab is a rare condition that typically affects women with late-onset type 1 diabetes or other auto-immune disorders, including auto-immune polyendocrinopathy. Immunomodulatory treatment may be effective.

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Résumé

Ataxie cérébelleuse auto-immune avec anticorps anti-GAD et diabète de type 1 à début tardif.

Les anti-GAD, auto-anticorps dirigés contre la décarboxylase de l’acide glutaminique ont été décrits dans le syndrome de l’homme raide, dans le diabète de type 1 et dans les polyendocrinopathies auto-immunes. Il existe en outre plusieurs observations de patients avec ataxie cérébelleuse progressive et des titres élevés d’anti-GAD qui ont fait évoquer une origine auto-immune. Nous rapportons l’observation d’une patiente présentant une ataxie cérébelleuse, associée à un diabète de type 1 à début tardif et à une polyendocrinopathie auto-immune.


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**Conclusion.** – L’ataxie cérébelleuse auto-immune liée aux anti-GAD est une affection très rare qui doit surtout être évoquée chez des femmes atteintes d’un diabète de type 1 à début tardif ou terrain dysimmunitaire. Un traitement immunomodulateur peut être efficace.

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**Keywords:** Auto-immunity; GAD antibodies; Type 1 diabetes; Cerebellar ataxia; Polyendocrinopathy

**Mots clés :** Auto-immunité ; Anticorps anti-GAD ; Ataxie cérébelleuse ; Diabète de type 1 ; Polyendocrinopathie

1. **Introduction**

Autoantibodies to glutamic acid decarboxylase (GAD-Ab) were first described in stiff-man syndrome [1] and type 1 diabetes mellitus [2]. They are also found in patients with auto-immune polyglandular failure [3,4], and in neurological disorders such as drug-resistant epilepsy [5] and Batten disease [6]. In addition, high levels of GAD-Ab have been detected in the serum and cerebrospinal fluid of a few patients with progressive cerebellar ataxia, suggesting an auto-immune origin [4,7,8]. We report here on the case of a patient presenting with cerebellar ataxia associated to late-onset type 1 diabetes and polyendocrine auto-immunity.

2. **Case report**

A 47-year-old woman, with a past medical history of vitiligo and Graves’ disease, presented in June 2006 with unusual thirst, polyuria and weight loss associated with readily detectable concentrations of glucose and ketone bodies in the blood and urine. She was diagnosed with late-onset type 1 diabetes. Furthermore, for two years, she had complained of progressive gait instability and oscillopia. General clinical examination showed extensive vitiligo and exophthalmia. Neurological examination revealed multidirectional, horizontal rotatory fixation and gaze nystagmus, gait ataxia and mild limb ataxia in the left upper arm. Her arterial blood pressure was low, with a systolic level of 100 mmHg. In the standing position, systolic rates dropped to below 75 mmHg.

3. **Investigations and treatment**

Magnetic resonance imaging (MRI) of the brain showed cerebellar atrophy (Fig. 1). Videonystagmography and oculography identified spontaneous and fixation nystagmus with substantial ocular instability. Further electrophysiological exploration, including nerve conduction studies, somatosensory and acoustical evoked potentials, heart frequency variability and sympathetic skin potential responses detected no abnormality. Routine biological screening was normal. Immunological screening showed positivity for numerous antibodies (Ab): GAD-Ab (111 IU/mL), thyroid peroxidase-Ab (1500 IU/mL), thyroglobulin-Ab (517 IU/mL), 21-hydroxylase (adrenal)-Ab (11.9 IU/mL), gastric parietal cell-Ab (1/50); and GM1 ganglioside IgG-Ab (1/160). The following Ab were absent: tissue transglutaminase-Ab, antinuclear-Ab, antineuronal-Ab, GQ1b-Ab, acetylcholine receptor-Ab, thyroid-stimulating hormone (TSH) receptor-Ab, and insulinoma antigen 2 (IA2)-Ab. The cerebrospinal fluid (CSF) was normal with respect to cell count, protein level and IgG index, and no oligoclonal bands were detected. GAD-Ab were positive in CSF (40 IU/mL). GAD-Ab were tested by RIA using human recombinant GAD65. In type 1 diabetes and multiple auto-immune abnormalities, the presence of high titres of GAD-Ab in both the serum and CSF strongly suggest a diagnosis of auto-immune cerebellar ataxia. After six months of intravenous immunoglobulin (IVIg) treatment (0.4 g/kg per day for five days per month), the patient showed slight regression of nystagmus and gait instability. Her neurological status continued to improve even after the IVIg dose was decreased.

4. **Discussion**

Auto-immune cerebellar ataxia related to GAD-Ab has been described in several case reports [4,7]. In a series of 14 patients [8], the following clinical features were noted:

- a large majority were women;
- the median age at onset was 51 years (range 20–74);
- nystagmus was commonly found;
- gait ataxia was more frequent than limb ataxia;
- dysarthria may also be present.

Symptoms progress slowly in most patients. An association with late-onset type 1 diabetes and other auto-immune disorders is frequently seen, and a few cases of cerebellar ataxia with GAD-Ab and auto-immune polyendocrinopathy have been reported [4,8]. MRI may be normal or reveal cerebellar atrophy, and CSF analysis frequently detects oligoclonal IgG bands.

The pathophysiology of cerebellar ataxia with GAD-Ab is unknown. GAD is an enzyme that catalyzes the conversion of glutamic acid to the neurotransmitter gamma-amino butyric acid (GABA). GAD-Ab in ataxic patients appears to cause selective presynaptic suppression of GABA-ergic transmission in the rat cerebellum [9]. IgG from patients with GAD-Ab and neurological involvement led to neuronal dysfunction, when administrated to rats in intracerebellar and paraspinal regions, whereas IgG from patients with diabetes and GAD-Ab without neurological complications did not [10]. Thus, stiff-person syndrome and cerebellar ataxia are thought to be the direct consequence of antibody-mediated neuronal dysfunction.

Recently, the autopsy of a woman with cerebellar ataxia, late-onset type 1 diabetes and later associated stiff-person syndrome showed severe Purkinje cell loss in the cerebellar cortex with proliferation of the Bergmann glia in the absence of a specific inflammatory response. In the pancreas, a marked decrease
of islets in the tail and lymphocytic infiltration of islets in the pancreas body were also noted [11].

Treatment with IVIg appears to be effective in stiff-man syndrome, but remains uncertain in auto-immune ataxia as well as in other GAD-Ab-related disorders [12]. In our patient, as in another case report [7], IVIg brought about regression of the neurological symptoms, but controlled studies are lacking. Alternatively, oral and high-dose intravenous corticosteroids may be used [13], although diabetes may be a limiting factor.

Auto-immune cerebellar ataxia with GAD-Ab is a rare condition that has to be considered in cases of sporadic cerebellar ataxia, especially in women with late-onset type 1 diabetes and other diffuse auto-immune disorders.

References