

Ataxia associated with anti-glutamic acid decarboxylase antibodies

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Anti-glutamic acid decarboxylase (GAD) antibody-associated ataxia is a rarely diagnosed but potentially curable disease associated with autoimmune damage to and death of Purkinje cells in the cerebellar cortex. In Russia, the authors have provided for the first time descriptions of three own observations of this disease, which had a number of clinical features, such as slow progression, mild ataxia, stroke-like episodes with stem symptoms, concomitant gluten sensitivity, onset of ataxia after hepatitis C with cerebellar hemiataxia and hemiatrophy. In all patients, the diagnosis was verified based on the determination of high anti-GAD antibody titers in serum and cerebrospinal fluid. All the patients lacked intrathecal synthesis of oligoclonal antibodies; protein levels and cytosis were normal. Pulse therapy with methylprednisolone at a total dose of 3–5 g led to a slight reduction in ataxia in one case (a female patient with subacute onset of the disease); the treatment was ineffective in two other cases (patients with a primary chronic course). The paper analyzes the literature covering the pathogenesis and clinical presentations of this type of ataxia, and difficulties in its diagnosis and treatment.

Keywords: ataxia; glutamic acid decarboxylase; antibodies; clinical presentation, diagnosis.

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Autoimmune ataxias present an extensive group of acquired disorders of balance and coordination caused by production of autoantibodies that bind predominantly to antigens of Purkinje cells of the cerebellar cortex, resulting in their destruction [1]. In a large prospective study of patients with progressive ataxia, 32% of all cases had autoimmune origin, with gluten ataxia (27%), paraneoplastic ataxia (3%) and ataxia associated with anti-glutamic acid decarboxylase antibodies (anti-GAD-A, 3%) being the most common. Cerebellar type of Hashimoto's encephalopathy occurs less frequently [2]. The importance of timely diagnosis of anti-GAD-A is driven by the opportunity for immunotherapy, which shows a more pronounced effect in the early stages of the disease. Despite the increasing availability of laboratory tests for the detection of anti-GAD antibodies, a low level of awareness among most practitioners about this type of ataxia is observed due to its relative rarity and lack of any specific symptoms. We report three clinical cases of patients with anti-GAD-A observed at the Research Center of Neurology in 2018–2020. In all cases, the diagnosis was verified by detection of anti-GAD antibodies in serum and cerebrospinal fluid samples.

Case 1. Patient Ch., a 53-year-old woman, presented with unsteady gait, diplopia, action tremor in both hands, and handwriting deterioration. Symptom onset occurred at the age of 50 with acute vertigo and diplopia. Over the next two weeks vertigo decreased, but the patient began to notice handwriting deterioration and unsteady gait, while diplopia persisted. Myasthenia gravis, brain stem and cerebellum lesions were excluded. Brain MRI showed solitary microangiopathic white matter lesions in both cerebral hemispheres (Fazekas grade 1). Gait unsteadiness progressed gradually. The patient was admit-

ted to the Research Center of Neurology with diagnosis of adult-onset cerebellar ataxia.

Past medical history: the patient had arterial hypertension (stage 2, high risk) and type 2 diabetes mellitus since the age of 48, taking metformin and glimepiride; she also had class I obesity.

Neurological examination revealed decreased palpebral fissure width on the right side; the pupils were symmetrical. Extraocular movements were intact. Low-amplitude horizontal nystagmus was observed, being more pronounced when the patient looked to the left; vertical nystagmus in up- and downgaze. Smooth pursuit was impaired, with intermittent saccadic interruptions. The patient developed diplopia in straight-ahead gaze and in all directions of gaze. The nasolabial fold was less prominent on the right side. Mild dysarthria was observed ("scanning" speech). The patient performed finger-to-nose test with mild intention tremor and dysmetria (more pronounced on the left side), heel-to-knee test – with intention tremor on the left side. The patient was unstable while performing the Romberg's test. Her gait was wide-based and ataxic and she could walk <3–4 steps before losing balance on tandem gait test. Ataxia assessment scales scores were the following: 5.5 points on SARA (range: 0–40) and 26 points on ICARS (range: 0–100).

Diagnostic test results:

Blood and urine tests were normal except for high blood glucose level (11.8 mmol/L) and glycated hemoglobin (8.1%).

Thyroid-stimulating hormone (TSH), anti-thyroid peroxidase (TPO) and anti-thyroglobulin (TG) antibodies were all normal.

Anti-gliadin antibodies (IgA) were 61.7 U/mL (normal range <25 U/mL) with no clinical or laboratory findings suggestive of enteropathy, anti-gliadin antibodies (IgG), anti-

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endomysial antibodies (IgA), anti-tissue transglutaminase antibodies (IgG+IgA) were all normal.

Blood serum test for anti-glutamic acid decarboxylase antibodies (IgG) >2000 U/mL (normal range <10 U/mL).

Cerebrospinal fluid analysis: cell count, protein and glucose levels were normal, type 1 pattern on oligoclonal band testing (polyclonal IgG present in both blood serum and cerebrospinal fluid), **anti-GAD antibodies >1000 U/mL (normal range <5 U/mL).**

The patient was treated with intravenous high-dose methylprednisolone 1 g daily for 5 days, demonstrating mild reduction of ataxia severity (SARA 5.0/40 points, ICARS 21/100 points). It was decided to refrain from prescribing oral corticosteroids due to the patient's low adherence to diabetes mellitus treatment and blood glucose monitoring. High-volume plasma exchange therapy and gluten-free diet were recommended. There was no follow-up.

Case 2. Patient Ya., a 67-year-old woman, was admitted to the Research Center of Neurology with complaints of unsteady gait, temporary episodes of double vision and fatigue.

She first noticed slight gait unsteadiness at the age of 65 which worsened over time, with subsequent development of diplopia and fatigue. The patient underwent ambulatory screening: brain MRI showed solitary microangiopathic white matter lesions in both cerebral hemispheres (Fazekas grade 1). Standard cancer screening and tumor marker tests (CEA, hCG, AFP, CA 19-9, CA 15-3, CA 125) which were performed in order to rule out paraneoplastic cerebellar degeneration, demonstrated negative findings. Anti-neuronal antibodies (line blot) were negative. Folic acid and vitamin B12 levels were normal.

Past medical history: the patient had arterial hypertension (stage 2, high risk), brachiocephalic atherosclerosis with a 45–50% stenosis of the right internal carotid artery and 30% stenoses in other arteries; dyslipidemia; autoimmune thyroiditis (receiving L-thyroxine 50 mcg/day), and nephrolithiasis.

Neurological examination revealed low-amplitude horizontal nystagmus, which was more pronounced when the patient looked to the left, and vertical nystagmus in upgaze. Smooth pursuit was impaired. Speech and swallowing were

normal. The patient performed finger-to-nose test with mild intention tremor and dysmetria (more pronounced on the left side), heel-to-knee test – with moderate intention tremor and dysmetria (also more pronounced on the left). Romberg's test was positive. Her gait was wide-based and ataxic and she could not perform tandem walking. SARA score was 10/40 points, ICARS 31/100 points.

Diagnostic test results:

Blood and urine tests, TSH level were all normal.

Anti-TPO antibodies – 591 U/mL (normal range <50 U/mL); anti-TG and anti-gliadin antibodies (IgG, IgA) were not detected.

Blood serum test for anti-GAD antibodies (IgG) >2000 U/mL.

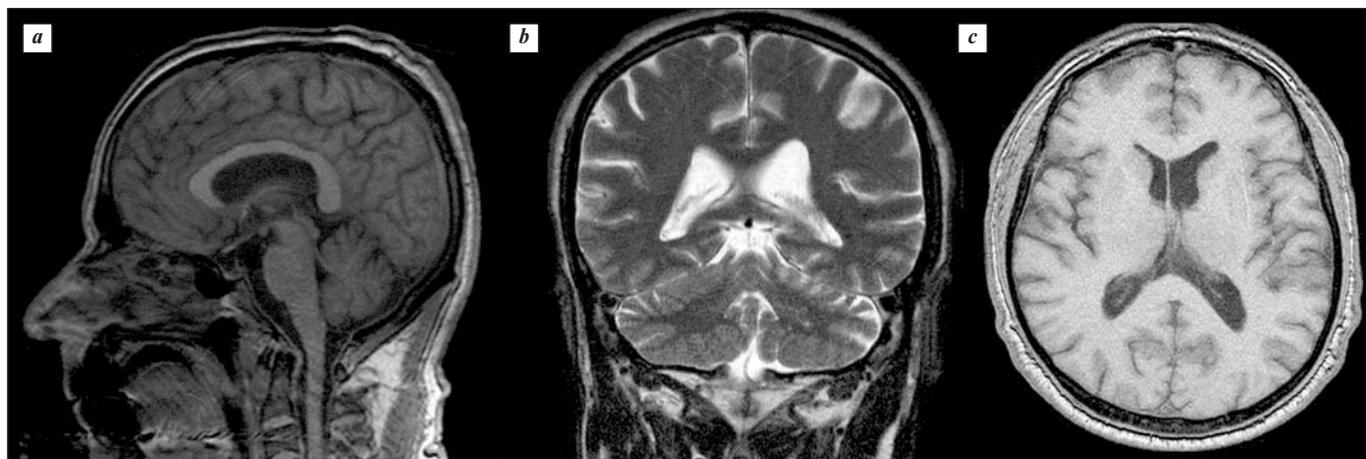
Cerebrospinal fluid analysis: cell count, protein and glucose levels were normal, type 1 pattern on oligoclonal band testing, anti-GAD antibodies >1000 U/mL.

The patient was treated with intravenous high-dose methylprednisolone (total dose 3 g). Intravenous high-dose methylprednisolone therapy was followed by an increase in arterial blood pressure, elevated blood glucose levels and subjective poor tolerance of treatment, with no clinical improvement in the neurological status. High-volume plasma exchange and intravenous human immunoglobulin therapy were recommended. There was no follow-up.

Case 3. Patient B., a 57-year-old man, was admitted to the Research Center of Neurology with complaints of coordination impairment in his left limbs and slurred speech.

He had been noticing a gradual increase of discoordination in his left leg since the age of 54, describing his leg as “alien”. At the age of 55 he developed problems in performing subtle movements with his left hand and speech blurring. These symptoms persisted until admission. Brain MRI showed mild sulcal widening in the left cerebellar hemisphere, asymmetry of the lateral ventricles (Fig.).

Past medical history: the patient was diagnosed with hepatitis C at the age of 48 years with mild inflammatory activity and severe liver fibrosis. After receiving combination antiviral therapy his blood tests returned to normal but the viral load persisted. At the age of 51 he received triple antiviral therapy



A – sagittal view, T1WI: cerebellar vermis has normal morphology and volume; B – coronal view, T2WI: mild sulcal widening in the left cerebellar hemisphere; C – axial view, T1WI: mild enlargement and asymmetry of the lateral ventricles (left lateral ventricle is larger than the right).

(pegylated interferon alfa-2a, ribavirin, telaprevir), achieving viral elimination. He had arterial hypertension (stage 2, high risk), brachiocephalic atherosclerosis with artery stenoses up to 30%, and chronic pancreatitis in remission.

Neurological examination revealed intact extraocular movements. The nasolabial fold was less prominent on the left side. Mild dysarthria was observed (“scanning” speech). Bilateral palmomental reflex was present. Deep tendon reflexes were asymmetrical, being slightly more active on the left than on the right. The patient performed coordination tests well with his right limbs, and with moderate dysmetria, intention tremor, and dysidiadochokinesia in his left limbs. He lifted his left leg in the Babinski trunk-thigh test. The patient was unstable while performing the Romberg's test. He was walking with a slight limp in his left foot and his gait had a slightly wider base than normal. He could walk up to 10 unsteady steps on tandem gait test. SARA score was 5.0/40 points, ICARS 20/100 points.

Diagnostic test results:

Blood and urine tests were normal, except for increased transaminase levels (ALT 130 U/L, AST 44 U/L) along with normal blood bilirubin. Anti-HCV antibodies, HCV-RNA were negative.

Blood tests for TSH, anti-TPO and anti-TG antibodies, anti-gliadin antibodies (IgG, IgA), anti-neuronal antibodies (line blot), vitamin B₁₂, and folic acid were all normal.

Blood serum test for anti-GAD antibodies (IgG) >2000 U/mL.

Cerebrospinal fluid analysis: cell count, protein and glucose levels were normal, type 1 pattern on oligoclonal band testing, **anti-GAD antibodies >1000 U/mL.**

The patient received intravenous high-dose methylprednisolone therapy (total dose 3 g) along with ademetionine infusions. No clinical improvement was observed after the treatment, although there was a reduction in the cytolytic syndrome (autoimmune hepatitis was considered). The patient was referred to a hepatologist in order to determine the further treatment strategy and plan immunosuppressive therapy.

Discussion

Glutamic acid decarboxylase (GAD) is an enzyme that catalyzes the decarboxylation of glutamic acid to gamma-aminobutyric acid (GABA), the most important inhibitory neurotransmitter. GAD is expressed in various structures of the central nervous system, pancreatic beta cells and other organs. It is represented by two isoforms: GAD65 (65 kDa, GAD2 gene) and GAD67 (67 kDa, GAD1 gene), which have different immunogenicity. Antibodies against GAD65, a synaptic membrane-associated protein, play a crucial role in the pathogenesis of anti-GAD-associated disorders. The key element of their pathogenesis is T-cell activation in response to interaction with GAD65 epitopes and cytokine production (IL-4, IL-5, IL-13). However, the cause of the immune response remains unclear, with the mechanism of antigenic molecular mimicry with proteins of cytomegalovirus, Coxsackie viruses and West Nile virus being one of the possible explanations [3]. In anti-GAD-A, antibodies bind to GAD65 epitopes of Purkinje cells of the cerebellar cortex, leading to their destruction, dysfunction of cerebellar, vestibular and other brainstem nuclei, which results in a consistent clinical presentation.

Anti-GAD-associated disorders are characterized by a

wide range of neurological manifestations: stiff-person syndrome, progressive encephalomyelitis with rigidity and myoclonus, cerebellar ataxia, limbic and extralimbic encephalitis, epilepsy without encephalitis, isolated nystagmus and/or oculomotor dysfunction, clinical presentation mimicking Miller Fisher syndrome, palatal myoclonus, as well as their various combinations – overlap syndromes. Frequent identification of concomitant autoimmune pathology (type 1 diabetes, autoimmune thyroiditis, autoimmune polyglandular syndrome, pernicious anemia, vitiligo, etc.) is also typical [3]. This variety of manifestations is currently linked to the production of antibodies to various GAD65 epitopes. Most of these disorders are quite rare. Although there are several clinical cases of anti-GAD-associated stiff-person syndrome described [4–7], we have not encountered any case reports of classic anti-GAD-A published in Russian academic journals, with only a few observations of the overlap syndrome with ataxia (stiff-person syndrome with oculomotor dysfunction and ataxia) present [8–9].

Cerebellar ataxia is one of the most common manifestations of anti-GAD-associated disorders. It is characterized by a subacute or primary progressive onset and is more predominant in women (80%). The clinical presentation of anti-GAD-A is not specific: upon disease onset mainly truncal and locomotor ataxia, “scanning” speech, nystagmus and oculomotor dysfunction are observed, joined later by dynamic ataxia. In 25% of all cases, paroxysmal stroke-like episodes with symptoms of brainstem involvement (upon disease onset in patient Ch.) such as nausea, dizziness, diplopia, nystagmus, bulbar dysfunction and hemiataxia are present [3, 10]. In some cases, ataxia presents in combination with other classic anti-GAD-associated syndromes (axial rigidity, epilepsy, etc.) and, less commonly, cognitive impairment. Brain MRI can be normal; in 57% of all cases, mild to moderate signs of cerebellar atrophy are detected (similarly to many other autoimmune ataxias) [3].

Taking into account the absence of any specific symptoms, verification of anti-GAD-A requires detection of increased titers of anti-GAD antibodies in blood serum and cerebrospinal fluid. In all our patients, intrathecal synthesis of oligoclonal antibodies was absent, protein levels and cell count were normal. However, this does not rule out the autoimmune origin of the disease. In a study by Munoz-Lopetegui et al., in 32% of all cases mild pleocytosis, elevated protein level (42%) and intrathecal synthesis of oligoclonal antibodies (65%) were detected [11]. In 14–20% of all cases, anti-GAD-associated neurological disorders serve as a manifestation of a paraneoplastic process, most frequently occurring in small cell lung cancer, thymoma, and breast cancer [3, 11].

Elevated levels of anti-gliadin antibodies without clinical signs of enteropathy in patients with anti-GAD-A is also noteworthy (patient Ch.). It is shown that high titers of anti-GAD antibodies are found in patients with gluten ataxia (10–40%), and gluten-free adherence diet can reduce ataxia severity and decrease the levels of anti-GAD antibodies [12, 13]. Therefore, it remains unclear whether anti-GAD antibodies represent a pathogenetic factor in patients with gluten sensitivity or they are one of the markers of the systemic autoimmune disease.

Patient B. presenting with left-side hemiataxia, mild atrophy of the left cerebellar hemisphere and a history of hepatitis C is of special interest. A similar clinical observation was described by Wiels W. et al: a 68-year-old woman developed

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subacute ataxia in her right limbs and nystagmus. Two year before the symptoms onset she had been diagnosed with hepatitis C and received combination antiviral therapy. Brain MRI was normal. Elevated titers of anti-GAD antibodies were detected in the blood and cerebrospinal fluid. Intravenous high-dose methylprednisolone (total dose 3500 mg), intravenous human immunoglobulin therapy and treatment with azathioprine showed a clear positive effect [14]. Another clinical case report presented a description of subacute anti-GAD-A in a 48-year-old patient with chronic hepatitis C with remission achieved by corticosteroid and rituximab therapy [15]. It should be noted that hepatitis C is often followed by concomitant autoimmune disorders (mixed cryoglobulinemia, Sjogren's syndrome, autoimmune thyroiditis, thrombocytopenia, etc.) and frequent detection of serological markers of autoimmunity. Some research papers discuss the influence of antiviral therapy on the autoimmune reaction development [16]. In addition, there are case reports of type 1 diabetes (anti-GAD+) in patients with hepatitis C, resulting in the hypothesis of anti-GAD-associated diseases being extrahepatic manifestations of hepatitis C [17, 18].

Various immunotherapy schemes, motor rehabilitation and speech therapy sessions are used for treatment of anti-GAD-A. If necessary, symptomatic therapy and treatment of concomitant autoimmune disorders or the primary oncological disease can be conducted. The best response to treatment is observed in patients with subacute symptom development, but in the vast majority of cases it is not possible to achieve a complete symptom-free state [1, 3].

First-line immunotherapy includes intravenous human immunoglobulin therapy (2 g/kg), intravenous high-dose methylprednisolone therapy (total dose 3000–5000 mg), oral administration of prednisolone (1 mg/kg, average of 50–60

mg/day), high-volume plasma exchange, rituximab (375 mg/m² once weekly), as well as their combinations. Despite the available data on the therapeutic efficacy of corticosteroids as first-line therapy, their use may be limited due to high risk of hyperglycemia in patients with concomitant type 1 diabetes. Second-line immunotherapy includes azathioprine (1–2.5 mg/kg/day), mycophenolate mofetil (2000 mg/day); one study showed a positive effect of cyclophosphamide infusions [1, 3, 19]. For treatment of oculomotor dysfunction (vertical nystagmus, oscillopsia) 10–60 mg/day baclofen and 3,4-diaminopyridine (the drug has not been approved for use in Russia) are used. Currently, treatment guidelines for anti-GAD-A are based on a few small cohort studies, so choosing a specific treatment regimen can be challenging.

Conclusion

There are objective difficulties in diagnosis of anti-GAD-A: absence of pathognomonic symptoms and specific neuroimaging features, various symptom onset (subacute or chronic); in some cases – absence of pleocytosis, increased protein levels and oligoclonal IgG synthesis in the cerebrospinal fluid. Not all patients have concomitant autoimmune pathology, and its presence is not always associated with the production of anti-GAD antibodies. For the first time in Russia, we present a case description of three patients with a number of remarkable clinical features of anti-GAD-A: stroke-like episodes with symptoms of the brainstem involvement, concomitant gluten sensitivity, ataxia onset following hepatitis C with hemiataxia and cerebellar hemiatrophy. The gold standard diagnostic test is the detection of elevated titers of anti-GAD antibodies in the blood serum and cerebrospinal fluid. In our patient cohort corticosteroid therapy had little effect, encouraging development of targeted immunotherapy regimens.

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Conflict of Interest Statement

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