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A Rare Case of Cerebellar Ataxia Due to Voltage-Gated Calcium Channel and Glutamic Acid Decarboxylase Autoantibodies

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Patient: Female, 55
Final Diagnosis: Cerebellar ataxia due to voltage-gated calcium channel and glutamic acid decarboxylase autoantibodies
Symptoms: Ataxia
Medication: —
Clinical Procedure: —
Specialty: Neurology

Objective: Rare disease

Background: Autoimmune cerebellar ataxia can be paraneoplastic in nature or can occasionally present without evidence of an ongoing malignancy. The detection of specific autoantibodies has been statistically linked to different etiologies.

Case Report: A 55-year-old African-American woman with hypertension and a past history of morbid obesity and uncontrolled diabetes status post gastric bypass four years prior to the visit (with significantly improved body mass index and hemoglobin A1c controlled at the time of the clinical encounter) presented to the office complaining of gradual onset of unsteadiness and recurrent falls for the past three years, as well as difficulties coordinating routine daily activities. The neurologic exam showed moderate dysarthria and ataxic gait with bilateral dysmetria and positive Romberg test. Routine laboratory test results were only remarkable for a mild elevation of erythrocyte sedimentation rate, and most laboratory and imaging tests for common causes of ataxia failed to demonstrate an etiology. Upon further workup, evidence of anti-voltage-gated calcium channel and anti-glutamic acid decarboxylase antibody was demonstrated. She was then treated with intravenous immunoglobulins with remarkable clinical improvement.

Conclusions: We present a case of antibody-mediated ataxia not associated with malignancy. While ataxia is rarely related to autoantibodies, in such cases it is critical to understand the etiology of this disabling condition in order to treat it correctly. Clinicians should be aware of the possible association with specific autoantibodies and the necessity to rule out an occult malignancy in such cases.

MeSH Keywords: Calcium Channels, P-Type • Calcium Channels, Q-Type • Cerebellar Ataxia • Glutamate Decarboxylase

Full-text PDF: https://www.amjcaserep.com/abstract/index/idArt/905476

Background

Cerebellar ataxia can be antibody mediated, and this can occur in the setting of paraneoplastic syndrome or in the absence of an ongoing malignancy. Interestingly, the detection of specific types of autoantibodies has been found to be statistically linked to different etiologies. In a recent study, anti-Yo, -Zic, -CARPVIII, -Tr, -Ri, -Hu, -Ma, -CRMP-5, -ANNA-3, -PCA-2, -VGCC, and -mGluR antibodies were more commonly associated with paraneoplastic processes, while anti-GAD, -thyroid, and -gliadin were usually non-paraneoplastic [1]. We present a case of ataxia due to both voltage-gated calcium channel (VGCC) and anti-glutamic acid decarboxylase (GAD) antibodies not associated with malignancy. There are only a few similar cases reported in literature so far.

Case Report

A 55-year-old African-American woman presented to the office complaining of gradual onset of unsteadiness and recurrent falls for the past three years resulting in multiple emergency department visits. She reported difficulties coordinating routine daily activities, such as buttoning a shirt or feeding herself. She visited multiple medical offices and reported that multiple imaging studies ordered in the past were inconclusive. Her past medical history included hypertension and history of morbid obesity and uncontrolled diabetes status post gastric bypass four years prior to the visit (both significantly improved, with a body mass index of 25.9 and hemoglobin A1c of 5.9% at the time of the clinical encounter). Her family history was remarkable for a brother diagnosed with multiple sclerosis at age 25, who died at the age of 40. Her social history was relevant for active cigarette smoking and remote history of heroin abuse (last use eight years prior to the visit). She denied alcohol use. Her list of medications included methadone, enalapril, multivitamin, and cholecalciferol supplementation.

Upon neurologic examination, she was fully oriented to person, place, and time and appeared in no distress. Her cranial nerves function was intact, except for a moderate dysarthria. Her sensory reaction was intact to all four extremities to light touch and pinprick. There was no motor weakness. Her gait was ataxic and wide based with bilateral dysmetria on finger to nose test. Romberg test was positive. The bicipital, tricipital, and patellar reflexes were three+ bilaterally, with plantar responses in flexion bilaterally. Routine laboratory test results were only remarkable for a mild elevation of the erythrocyte sedimentation rate. Infectious diseases or vitamin/mineral deficiencies in the differential diagnosis, which in this specific setting would be highly considered, were ruled out (see Table 1, Section A). The brain MRI, done with contrast, only showed minimal scattered nonspecific white matter changes (see Figure 1). She subsequently underwent lumbar puncture, which showed an opening pressure of 18 cm H_2O and was negative for oligoclonal bands (see Table 1, Section B).

A workup for less common causes of ataxia was then started, and the presence of serum anti-VGCC and anti-GAD antibodies was demonstrated (see Table 1, Section C). The patient subsequently underwent extensive imaging workup to rule out an occult malignancy, and all the studies failed to show evidence of cancer. A treatment cycle of three days of intravenous immunoglobulins was then instituted. Within two weeks from their administration, her coordination and gait improved significantly: she showed ability to walk unassisted without tendency to fall, and the Romberg test became negative.

Discussion

Cerebellar ataxia can be potentially treatable, and a complete understanding of the etiology must be achieved in order to establish an effective management plan. This is especially important because it is usually a disabling condition, and treating it can substantially improve the quality of life of a patient, when possible. The search for a potentially treatable cause should include a broad spectrum of different disorders, and genetic evaluation should be considered only when other etiologies can be ruled out. Disorders commonly encountered in clinical practice such as vitamin B12 deficiency and hypothyroidism can occasionally cause ataxia and in rare cases present with it [2,3]. Adverse reactions to drugs (especially certain antiepileptic and chemotherapeutic agents), systemic autoimmune diseases (such as sarcoidosis, systemic lupus erythematous and Sjogren syndrome) [4–6], deficiencies of vitamin E and B1 (thiamine) as well as mineral deficiencies (such as copper or zinc) have all been occasionally linked with neurological symptoms, including ataxia [7–9]. Antibody-mediated ataxia is another potentially treatable etiology that should be considered. Multiple autoantibodies have been associated with cerebellar ataxia [10], and it has been demonstrated that anti-VGCC and anti-GAD antibodies can directly cause ataxia in experimental models *in vivo* [11]. Anti-VGCC and anti-GAD antibodies have been shown to cause cerebellar synaptic dysfunction *in vitro* as well [1]. In a study of 67 patients with late onset cerebellar ataxia of unknown cause, immunohistochemical and immunoblotting techniques were able to detect the presence of VGCC antibodies in eight patients (11.1%) [12]. Hence, it can be hypothesized that autoimmune cerebellar ataxia may be an underdiagnosed entity in clinical practice [13]. Possible contributing factors could be the lack of specific imaging findings diagnostic of antibody-mediated ataxia [14] and the lack of awareness arising from the paucity of data available in literature. In our case, after ruling out other possible etiologies, evidence of both anti-VGCC and anti-GAD antibodies was found in the serum. Remarkably, the

Table 1. Laboratory test results.

	Result	Reference range
Section A: Initial laboratory tests		
Vitamin B12 level	775 pg/mL	200–950 pg/mL
HIV test	Nonreactive	Nonreactive
TSH	1.02 uLU/mL	0.5–4 uLU/mL
ESR	**33 mm/Hr**	<20 mm/Hr
HTLV I-II Antibody	Nonreactive	Nonreactive
Lyme disease antibod	0.34	(0.00–0.90)
ACE	7 U/L	9–67 U/L
RPR	Nonreactive	Nonreactive
Copper	96 mcg/dL	70–175 mcg/mL
Vitamin E Alpha	9.7	(5.7–19.9)
Vitamin E B-Gamma	1.0	(0.0–4.3)
Vitamin B1	165 nmol/L	(78–185 nmol/L)
Section B: Lumbar puncture results		
Opening Pressure	18 cmH_2O	
Cell Count		
WBC	2/mm^3	
RBC	548/mm^3	
Glucose	47 mg/dL	40–70 mg/dL
Protein	20 mg/dL	15–45 mg/dL
Oligoclonal Bands	Not identified	Not identified
Section C: Autoimmune panel		
Antinuclear antibody	Negative	Negative
DNA antibodies, native	1	(≤4 U/mL)
Rheumatoid factor	Negative	Negative
Pukinje cell cytoplasmic (Yo) Ab	Negative	Negative
tTG IgA	<1 U/mL	<4 U/mL
Immunoglobulin A	249 mg/dL	(81–463 mg/dL)
Anti-VGCC	**>30 pmol/L**	<30 pmol/L
Anti-GAD	**>250 IU/mL**	<5 IU/mL

ACE – angiotensin-converting enzyme; ESR – erythrocyte sedimentation rate; GAD – glutamic acid decarboxylase; HIV – human immunodeficiency virus; RBC – red blood cell; RPR – rapid plasma reagin; TSH – thyroid-stimulating hormone; VGCC – voltage-gated calcium channel; WBC – white blood cells.

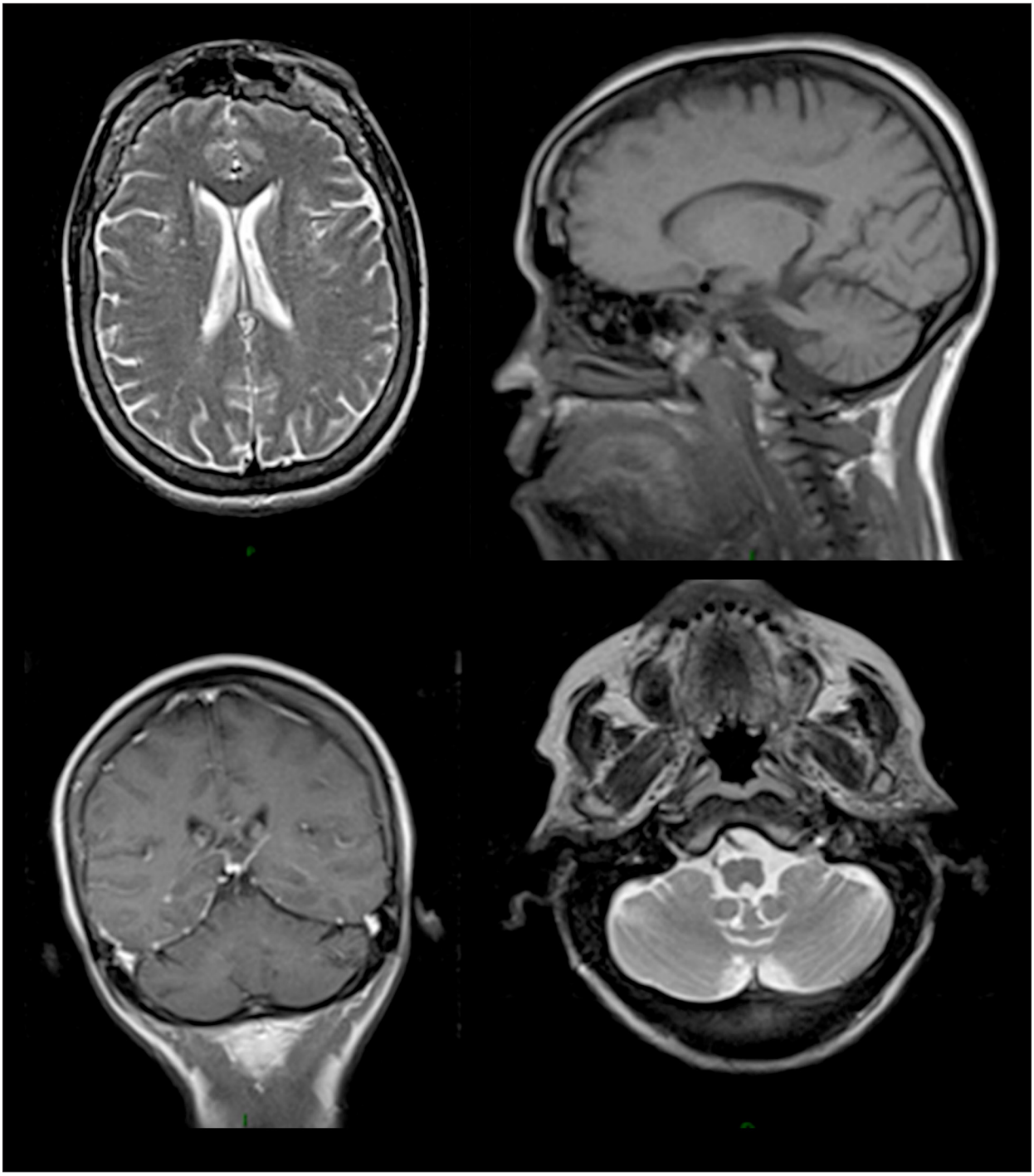

Figure 1. MRI of the brain with contrast showing minimal scattered nonspecific white matter changes.

latter antibody has been associated with type 1 diabetes mellitus and latent autoimmune diabetes of adulthood and could have at least contributed to our patient's history of diabetes as well. The response to the intravenous immunoglobulins confirmed the role played by these antibodies in the pathogenesis of the symptoms, and a plan for periodic infusions was established leading to sustained clinical improvement.

Besides being potentially treatable, antibody-mediated cerebellar ataxia should also prompt a complete cancer workup, since it has been associated with a large number of malignancies and occasionally reported as the presenting sign of an otherwise asymptomatic malignancy [15–17]. The cerebellar ataxia secondary to anti-Yo antibodies has been reported as the most common variant of paraneoplastic cerebellar

degeneration [18], however, the VGCC antibody has been frequently associated with a paraneoplastic process as well. In a study of 236 patients with positive VGCC antibody evaluated for paraneoplastic syndromes, 50 (21%) had at least one malignancy [19]. Human immunodeficiency virus (HIV) has also been linked to autoimmune antibody-mediated cerebellar ataxia without evidence of HIV encephalopathy or malignancy [20]. While rare, autoimmune antibody-mediated cerebellar ataxia should be considered in the differential diagnosis in cases where a clear etiology cannot be found. If an immune-mediated process is indeed demonstrated, a complete workup to rule out an occult malignancy should be instituted before immunosuppressive treatment can be safely started. Studies have shown that treatment of immune-mediated ataxia can make the difference in improving symptoms and quality of life, and favorable responses were noted to be more common among patients with non-paraneoplastic ataxia and those with exclusively ion channel antibodies [10,21,22].

Conclusions

Ataxia can be caused by a wide spectrum of possible etiologies, and understanding the pathogenesis is a critical step needed in order to treat it correctly. Clinicians should be aware of the possible association with specific autoantibodies and the necessity to rule out an occult malignancy in such cases.

Conflict of interest

None.

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