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Immunotherapy Responsive Recurrent Post-Infectious Ataxia Associated With Recurrent *ATP2B2* Gene Variant

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Abstract

Objectives

We detail a case of recurrent, postinfectious, cerebellar ataxia associated with a likely pathogenic previously documented gene variant in *ATP2B2*.

Methods

The patient was identified after her second hospitalization for postinfectious cerebellar ataxia. Genetic testing was performed after discharge.

Results

An 11-year-old girl with 1 prior episode of self-resolving parainfectious acute cerebellar ataxia at age 4 years presented with acute-onset ataxia, dysarthria, and gait instability in the setting of influenza A infection. The patient had CSF pleocytosis but negative influenza PCR and antibody detection in the CSF. Because of clinical deterioration, she received empiric IV methylprednisolone without improvement. She was subsequently administered IVIg and improved dramatically over the subsequent 7 days. The patient was found to have a rare de novo *ATP2B2* gene (c.3028G>A, p.(Glu1010Lys)) variant previously reported in the literature. The variant was analyzed to have a Combined Annotation Dependent Depletion score of 33 and Polyphen-2 score of 1.0 and was determined to be likely pathogenic according to American College of Medical Genetics PP3 and PM2 criterion.

Discussion

Recurrent episodes of cerebellar ataxia are an especially rare occurrence, and genetic testing may be warranted in these individuals. It is possible that immunotherapy with IVIg may augment clinical outcomes in those with pathogenic *ATP2B2* gene variants.

Introduction

Acute cerebellar ataxia is a rare, parainfectious or postinfectious, phenomenon occurring in both children and adults. In the past 2 decades, a variety of genetic, infectious, and antibody-mediated causes of acute cerebellar ataxia have been identified.[1] Although rare, recurrent cases of acute cerebellar ataxia have been reported, although little is known about the mechanisms of disease in such cases, particularly when long quiescent periods of disease freedom exist. This case report details a case of recurrent parainfectious cerebellar ataxia in a young girl with a likely pathogenic gene variant in the *ATB2B2* gene.

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Table Diagnostic Results From First (Left 2 Columns) and Second (Right 5 Columns) Admission, Notable for CSF With Leukocytosis and Oligoclonal Bands, Positive FAME Panel for HVV6, RSV Panel Positive for Influenza A (Bolded)

First admission			Second admission			
CBC			**CSF**			
WBC	7.00	7.81	*CSF appearance*	Clear	*Myelin basic protein*	<2.0
RBC	5.70 (H)	5.82 (H)	*CSF color*	Colorless	***Oligo Bands CSF***	**PRESENT**
HGB	12.2	12.5	***CSF WBC***	**78 (H)**	*IgG Synthesis Rate*	+0.7
HCT	40.5 (H)	41.0 (H)	*CSF RBC*	1	*IgG Index*	0.61
MCV	71.1 (L)	70.4 (L)	*CSF cells seen*	100	*Albumin CSF*	19.5
MCH	21.4 (L)	21.5 (L)	*CSF lymph %*	95 (H)	*Albumin Serum*	3.5 (L)
MCHC	30.1 (L)	30.5 (L)	*CSF mono/macro %*	5 (L)		
Platelets	275	300	*Glucose*	60		
MPV	10.5	10.4	*Protein*	32		
RDW-CV	10.9 (H)	10.4 (H)	**Paraneoplastic/Enceph Eval, CSF**			
Differential automated			*Detectable antibodies*	None	*LGI1 antibody*	Negative
Seg/Band%	51.8	87.0 (H)	*Anti-neuronal nuclear antibody type 1*	Negative	*mGluR1 Antibody*	Negative
Lymph %	41.1	4.1 (L)	*CASPR2 antibody*	Negative	*NMDA-R Antibody*	Negative
Mono %	5.6	8.2	*DPPX antibody*	Negative	*Aquaporin-4 Antibody*	Negative
Eos %	0.9	0.0	*GABA-B-R antibody*	Negative	*Purkinje Cell Cytoplasmic Antibody*	Negative
Baso %	0.3	0.1	*GAD65 Antibody*	Negative	*Neurochondrin Antibody*	Negative
IG %	0.3	0.6 (H)	*GFAP antibody*	Negative		
Other			**Infectious disease, CSF**			
Sed Rate	44 (H)		*Bacterial culture, CSF*	Negative	*Influenza A Ab, CSF*	<1:1
CMP			*IgG, CSF SO*	3.5	*Influenza B Ab, CSF*	<1:1
Sodium	139	137	**Film array meningitis/enceph panel**			
Potassium	3.8	3.5 (L)	*Escherichia coli K1, FA*	Negative	*Enterovirus, FA*	Negative
Chloride	107	101	*Haemophilus influenzae, FA*	Negative	*Herpes simplex virus 1, FA*	Negative
CO2 total	22	24	*Listeria monocytogenes, FA*	Negative	*Herpes simplex virus 2, FA*	Negative
Anion Gap	10	13	*Neisseria meningitidis, FA*	Negative	***Human herpes virus 6, FA***	**DETECTED**
BUN	10	10	*Streptococcus agalactiae, FA*	Negative	*Human parechovirus, FA*	Negative
Creatinine	0.41 (L)	0.41 (L)	*Streptococcus pneumoniae, FA*	Negative	*Varicella zoster virus, DA*	Negative
Glucose	86	126 (H)	*Cytomegalovirus, FA*	Negative	*Cryptococcus neoformans, FA*	Negative
Mag		2	**Respiratory viral panel**			
Calcium	9.0	9.1	*HHV 6 PCR*	Not detected	*Parainfluenza 1, 2, 3, 4*	Not detected
Phos		4.1 (H)	*Adenovirus*	Not detected	*Respiratory Syncytial Virus*	Not detected
Protein, T	7.5	8.4 (H)	*Coronavirus*	Not detected	*Chlamydia Pneumoniae*	Not detected
Albumin	4.2	4.6	*Metapneumovirus*	Not detected	*Mycoplasma Pneumoniae*	Not detected
Bilirubin	0.43	0.82	*Rhinovirus/enterovirus*	Not detected	*Bordetella pertussis*	Not detected
CRP	<0.5	2.1 (H)	***Influenza A***	**DETECTED**	*Bordetella parapertussis*	Not detected
AST	26	41	*Influenza B*	Not detected		

Continued

Table Diagnostic Results From First (Left 2 Columns) and Second (Right 5 Columns) Admission, Notable for CSF With Leukocytosis and Oligoclonal Bands, Positive FAME Panel for HVV6, RSV Panel Positive for Influenza A (Bolded) *(continued)*

First admission			Second admission				
CBC			**CSF**				
ALT	18	30					
Alk Phos	194	194					
Lipase		169					
CK	56	56					

Case Report

The patient is an 11-year-old girl with a history of parainfectious cerebellar ataxia (secondary to coxsackie virus infection at age 4 years), who presented with recurrent acute ataxia and was admitted with concern for recurrent parainfectious cerebellitis.

Immediately prior to admission, the patient developed headaches for a week, followed by acute ataxia. These symptoms were identical to her episode 7 years prior. Neurologic examination on arrival demonstrated dysmetria; narrow-based stance; and nonfocal, nonataxic gait. Initial workup including a head CT and basic laboratory tests were unremarkable, prompting discharge with a diagnosis of a viral syndrome. Four days later, she represented with worsening headache and new-onset vomiting and was admitted for further evaluation. Although her MRI was normal, respiratory PCR panel was positive for influenza A and she rapidly developed progressive worsening of ataxia over a 24-hour period. Diagnostic data from her first and second admissions are presented in the Table. Notably, she has pleocytosis of 78 cells/hpf (95% lymphocyte) in the CSF. A cell-based antibody panel and influenza PCR and IgG/IgM testing in the CSF were negative. A diagnosis of recurrent cerebellar ataxia was made.

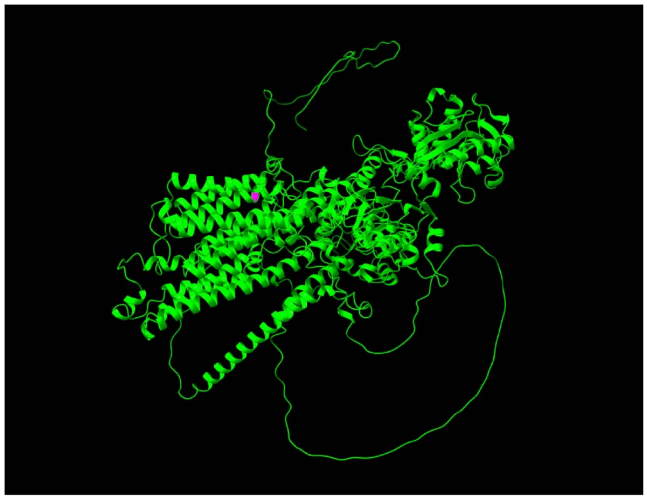
The patient had no response to IV methylprednisolone with further clinical deterioration and was started on IVIg 2 g/kg, which resulted in rapid, sustained clinical improvement. She was discharged on day 19 of admission with minimal residual ataxia on tandem gate and on follow-up 3 months later, had returned to 100% of her previous baseline. Given the atypical nature of recurrent ataxia, whole-exome sequencing (performed using the Illumina HiSeq platform and analyzed in the GENESIS platform) was performed and revealed a heterozygous variant in the *ATP2B2* gene (c.3028G>A, p.(Glu1010Lys)), which was initially reported as a variant of unknown significance according to in silico analysis performed by an *Invitae* panel (Figure).

This variant was found to have been reported previously in an individual with ataxia-dystonia syndrome.[2] In concordance with previous literature, the variant was determined to have a Combined Annotation Dependent Depletion score of 33 and Polyphen-2.0 score of 1.0 indicating "probably damaging" and was determined to be likely pathogenic according to PP3 (*in silico* prediction) and PM2 (population data) classifications from the American College of Medical Genetics.[2-7] Subsequent parental testing revealed that the gene variant was inherited de novo using trio-exome sequencing.

Discussion

Recurrent episodes of ataxia in a child are rare and have a wide differential that may include neuroinflammatory and genetic disorders.[8] Regarding the latter, multiple genes have been identified over the past 2 decades related to parainfectious and postinfectious ataxia, some even in similar ATP-encoding genes.[9-12] In this case, the patient's whole-exome sequencing has revealed a likely pathogenic variant in *ATP2B2*, which may provide a mechanism for the patient's recurrent events.

Figure Three-Dimensional Model of the *ATP2B2* Variant



Three-dimensional structural modeling of the *ATP2B2* gene (c.3028G>A, p.(Glu1010Lys)) variant; noting abnormal residue is in an alpha helix.[13-16] Although the amino acid substitution is not in a defined protein domain, based on the combination of missense substitution (a negatively charged glutamic acid to positively charged lysine) and in silico analysis, this variant is most likely pathogenic.

ATP2B2 codes for PMCA2 Ca2+ pump responsible for ion gradients in specialized cells of cerebellar circuit and vestibular and cochlear systems, and variants of this gene have a well-established association with hearing impairment in both adult humans and mouse models.[12,13] Another study in 2023 suggested an additional association of ataxia with dystonic features and other neurodevelopmental manifestations, including intellectual disability, autism, and seizures.[14]

Of interest, the ATP2B2:c.3028G>A variant was previously reported in 2023 in an individual presenting with motor impairments, ataxia, dystonia responsive to botulism toxin, and optic atrophy and ultimately diagnosed with ataxia-dystonia syndrome.[2] Functional characterization using a histamine-induced Ca2+ export assay demonstrated the variant's compromised ability to export Ca2+ compared with wild type.

In contrast to the prior study, our patient's phenotype was isolated to recurrent ataxia responsive to immunomodulation. Given the negative infectious testing in the CSF and lack of encephalopathy in our case, we believe that the mechanisms of our patient's symptoms are a combination of ion transport failure and cellular injury with secondary immune activation.

We speculate that a heterozygous gene variant in *ATP2B2* may not be sufficient to produce neurologic disease during physiologic homeostasis: that is, second hits may be required for *ATP2B2* variant–mediated ataxia. This is partially supported by the observation of 5 individual heterozygous carriers for this variant identified from the gnomAD version 4.1.0 control database.[15] However, when stressed in the setting of infection (second hit), the energy-dependent export of Ca2+ out of the cell may fail and cause cellular injury.[16] These processes are known to routinely activate central immunologic cascades and could also explain the patient's abnormal CSF findings.[17] Although strictly hypothetical, augmentation of the immune response to cell injury may explain some of the patient's clinical response to immunotherapy.

The use of immunotherapy is not novel in cerebellar ataxia, although the data on this are strictly limited to autoimmune and inflammatory-mediated forms of the condition.[18] As such, this case is unique in that modulation of parainfectious inflammatory cascades with immunotherapy may be a reasonable mechanistic avenue to pursue in cases of recurrent gene-mediated ataxias. The proposed pathophysiology, while logical, is limited by our study's small sample size and our mechanistic understanding of this variant within the context of neuroinflammation. Further study is needed.

Conclusion

This is the first known case of recurrent cerebellar ataxia associated with the ATP2B2:c.3028G>A gene variant, expanding the broad spectrum of neurodevelopmental and cerebellar manifestations in this condition. Given this patient's remarkable clinical response to immunotherapy, the authors propose that immunotherapy may be considered a viable treatment option for patients with symptomatic ataxia presumed secondary to *ATP2B2*, particularly when clear evidence of parainfectious disease is present on neurodiagnostic studies.

Author Contributions

J. Vancura: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data. A.K. Banerjee: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data. N.K. Boyd: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. L. Kazerooni: drafting/revision of the manuscript for content, including medical writing for content. N.A. Nishimori: drafting/revision of the manuscript for content, including medical writing for content. R. Ferris: drafting/revision of the manuscript for content, including medical writing for content. B.N. Vogel: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. L. Nguyen: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data. J.D. Santoro: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data.

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