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Endothelial and leukocyte-derived microvesicles and cardiovascular risk after stroke PROSCIS-B

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Opinion and Special Articles: Cerebellar Ataxia and Liver Failure Complicating IPEX Syndrome

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Immunodysregulation, polyendocrinopathy, and enteropathy, X-linked (IPEX) syndrome is an autoimmune condition caused by mutations in the Forkhead Box P3 (*FOXP3*) gene, which maps to chromosome Xp11.23 (OMIM #304790).¹ It typically presents within the first year of life with watery diarrhea, eczematous dermatitis, and endocrinopathy (most commonly diabetes mellitus).¹ Most children have other autoimmune phenomena including Coombs-positive anemia, thrombocytopenia, neutropenia, and tubular nephropathy.¹ Bone marrow transplantation is the only definitive cure for IPEX syndrome.² Neurologic involvement in IPEX syndrome has not been well characterized in the literature, based on a current Ovid MEDLINE search. Without aggressive immunosuppression or bone marrow transplantation, the majority of affected boys die within the first 1 to 2 years of life from metabolic derangements or sepsis.¹ Diagnosis is based on clinical features and whole exome sequencing that reveals a pathogenic *FOXP3* variant.¹

FOXP3, on Xp11.23, comprises 12 exons, encoding a 431-amino acid protein, FOXP3, a member of the Forkhead (FKH) family of transcription factors (OMIM #300292).¹ At least 70 pathogenic variants of *FOXP3* are known, with a wide spectrum of clinical phenotypes associated even in the same variant.²

FOXP3 acts upon the immune system by modulating and suppressing interleukin-2, suppressing effector cytokines, and antagonizing Th17 differentiation.² In effect, the FOXP3 protein plays a critical role in the maturation and function of regulatory T cells (T_{reg}), which are required for effective maintenance of tolerance and prevention of autoimmune diseases, throughout the body.²

Case Description

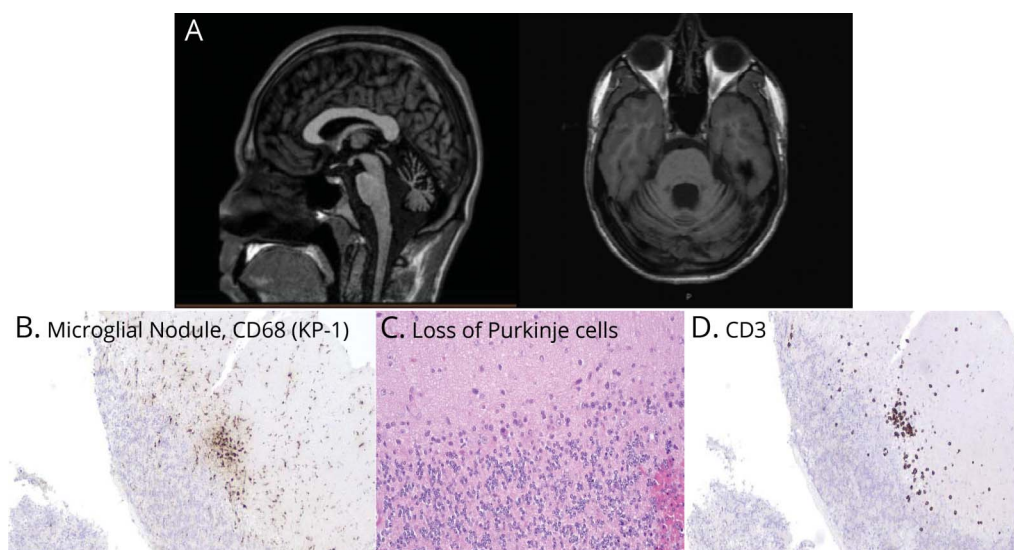
A 19-year-old man at the age of 2 years presented with jaundice and liver failure due to autoimmune hepatitis, for which he received a liver transplant. He had recurrent episodes of rejection of varying severity but was ultimately stable on prednisone 5 mg daily, mycophenolate mofetil 750 mg twice daily, and tacrolimus 2.5 mg twice daily. At age 12 he developed progressive difficulties with handwriting, with bilateral hand tremors beginning by age 14. He developed insulin-dependent diabetes mellitus at age 14 as well. His tremors progressed to the arms and then to the legs by the age of 15, at which time he presented to clinic for further evaluation. He denied any family history of neurologic disease.

The differential diagnosis for a progressive subacute-chronic cerebellar ataxia includes structural lesions, infection, toxic-metabolic derangements, genetic etiologies, and autoimmune etiologies.

Neuroimaging was performed upon presentation to rule out a structural lesion, followed by serum testing for toxic-metabolic causes. Serial brain MRI at ages 15 and 16 revealed stable cerebellar atrophy with ex vacuo dilation of the fourth ventricle. No other lesions were observed (figure, A). Serum vitamin E level was 6.1 µg/mL (normal 4.6–17.8).

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(A) Sagittal and axial MRI brain, from Soldatos et al.¹⁰ (B–D) Cerebellar biopsies with immunostaining, from Soldatos et al.¹⁰

As the patient showed progressive ataxia from an early age, we considered genetic causes and whole exome sequencing was sent. Whole exome sequencing is a next-generation sequencing method that targets only the exons or translated portion of a patient's genome. It is thought to be an effective method for identifying disease-causing mutations.³ Whole exome sequencing at age 16 revealed a *FOXP3* mutation (IVS2+1G>C), consistent with IPEX syndrome.

In addition, a panel testing for mutations and triple repeat expansions of 42 genes associated with hereditary cerebellar ataxia was sent. This panel included those repeat expansion mutations that would have been missed by whole exome sequencing. These genes included *ADCK3*, *SCA28* (*AFG3L2*), *ANO10*, *Aprataxin* (*APTX*), *ATM*, *DRPLA* (*ATN1*), *SCA1* (*ATXN1*), *SCA10* (*ATXN10*), *SCA2* (*ATXN2*), *SCA3/MJD* (*ATXN3*), *SCA7* (*ATXN7*), *SCA8* (*ATXN8OS*), *SCA8* (*CACNA1A*), *CACNA1A*, *CACNB4*, *EEF2*, *FGF14*, *FLVCR1*, *Friedreich Ataxia* (*FXN*), *GRM1*, *ITPR1*, *KCNA1*, *SCA13* (*KCNC3*), *KCND3*, *MRE11A*, *MTPAP*, *PDYN*, *POLG*, *SCA12* (*PPP2R2B*), *SCA14* (*PRKCG*), *SACS*, *SETX*, *SIL1* (*MSS*), *SLC1A3*, *SCA5* (*SPTBN2*), *SYNE1*, *SYT14*, *SCA17*, *TDPI*, *TGM6*, *TTBK2*, *TPPA* (*AVED*), and *VAMP1*. No known pathogenic variants were identified.

The liver failure and insulin-dependent diabetes were well-explained by IPEX syndrome. However, the etiology of the progressive cerebellar atrophy was not yet clear.

The symptoms continued to progress, and by age 17 the patient required assistance to walk. By age 18, he developed scanning speech, bilateral end-gaze nystagmus, bilateral intention tremor (<5 Hz) with ataxic finger to nose testing and heel to shin testing, and a wide-based ataxic gait.

The patient was referred to the NIH for further testing and underwent lumbar puncture and cerebellar biopsy. Routine CSF analysis with flow cytometry and viral PCR were performed at NIH, and serum and CSF autoantibody testing were sent to Mayo Clinic. CSF analysis showed elevated protein (50 mg/dL) and immunoglobulin G index (0.69) (normal ≤ 0.62) as well as paired systemic and CSF oligoclonal bands. Viral PCRs of whole blood and CSF were unremarkable, except for high titers of human herpesvirus 6 (HHV6) (HHV6B PCR serum >2,500,000 copies/mL). One copy of HHV6 viral DNA was found in each of the patient's cells and in the patient's mother, suggesting inherited chromosomally integrated HHV6B. Serum autoantibody results were nonspecific and revealed low titers of N-type calcium channel Ab (0.09 nmol/L) without P/Q type antibodies. Serum and CSF were negative for cell surface neuronal antigen antibodies (NMDA-R, VGKC, GAD65, GABA-B, AMPA-R, ANNA-1/2/3, AGNA-1, PCA-2, PCATr, amphiphysin, CRMP-5, P/Q Ca channel, muscle AChR, AChR ganglionic neuronal, NMO/AQP4 FACS).

Cerebellar biopsy showed loss of Purkinje cells, a CD3 T-cell infiltrate, and CD68 (KP-1) microglial nodules (figure, B–D).

Discussion

Our patient met clinical and whole exome criteria for IPEX syndrome and experienced progressive cerebellar ataxia. The search for acquired causes of his cerebellar atrophy was unrevealing.

The patient's medications, particularly tacrolimus and mycophenolate, are associated with mild to severe neurologic toxicities ranging from uncomplicated headache to posterior

reversible encephalopathy syndrome, but are not known to be associated with global cerebellar atrophy.⁴

Serum and CSF assays for metabolic or infectious causes were unrevealing. Serum vitamin E was normal. Our patient displayed high titers of HHV6B in the blood and CSF. While HHV6 infection is associated with infectious and post-infectious acute cerebellar ataxia, it is not associated with a chronically progressive course as seen in this patient.⁵

Other infectious causes of progressive cerebellar degeneration involve progressive multifocal leukoencephalopathy (PML), Whipple disease, and prion disease. There was no evidence of PML on neuroimaging, and such a slowly progressive course would not be expected in prion disease. The patient has not exhibited altered mentation or the pathognomonic oculo-facial-skeletal myorhythmia of CNS Whipple disease.⁶

We also considered autoimmune causes separate from IPEX syndrome. The autoimmune diseases of the cerebellum generally include paraneoplastic syndromes (associated with Anti-Yo, Hu, Tr, CV2, Ri, Ma2, and VGCC), gluten ataxia, and anti-Gad65 antibody ataxia. A paraneoplastic process would be unlikely in a male patient of teenage years, and gluten ataxia and anti-GAD65 antibody ataxia usually present in older female patients with other autoimmune diseases (T1DM, thyroiditis, hemolytic anemia).⁷ These autoantibodies were not found in CSF analysis.

Other inherited disorders, such as X-linked disorders with cerebellar dysgenesis, are known, and many have been well-characterized.⁸ The cardinal feature of these disorders is a cerebellar defect visible on neuroimaging, caused by gene mutations or genomic imbalances on the X-chromosome.⁸ Some of the disorders are characterized by specific neurologic presentations, but most involve significant developmental delay or intellectual disability, which our patient did not manifest.⁸

In addition, specific mutations on the X chromosome have been characterized in each case, and our whole exome sequencing did not coincide with any known pathogenic variants known to be associated with cerebellar dysgenesis.⁸

The cerebellar biopsy was similarly unrevealing, showing a pattern of inflammation and cell death that is T cell-mediated, yet nonspecific (figure, B–D).

Our patient's cerebellar degeneration may have been a result of his liver failure early in life.⁹ However, it is unusual that his cerebellar degeneration appeared and progressed years following liver transplant. It is therefore most likely that our patient is the first reported to have manifested CNS involvement in IPEX syndrome in the form of progressive autoimmune degeneration.

The patient's brother, age 9, has been found to harbor the same X-linked *FOXP3* mutation, which is known to be carried by their mother. He has manifested features of inflammatory

bowel disease and dermatitis, but no neurologic problems. Bone marrow transplantation is pending for both brothers.

Patients with IPEX syndrome and neurologic decline should have a thorough neurologic examination looking for possible cerebellar degeneration.

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Disclosure

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Appendix Authors

Name	Location	Contribution
Joshua Rim, MD	Cleveland Clinic, OH	Drafted and edited manuscript, liaison between different clinical teams
Melissa Byler, CGC	SUNY Upstate Medical University, Syracuse, NY	Patient's genetics counselor, major role in acquiring data, liaison with patient
Ariane Soldatos, MD, MPH	NINDS, Bethesda, MD	Major role in acquiring data, interpreting data, edited manuscript
Luigi Notarangelo, MD	NIAID, Bethesda, MD	Major role in acquiring data, interpreting data, edited manuscript
Emily Leibovitch, PhD	NINDS, Bethesda, MD	HHV6 research testing, revised intellectual content
Steven Jacobson, PhD	NINDS, Bethesda, MD	HHV6 research testing, revised intellectual content
Mark Gorman, MD	Boston Children's Hospital, MA	Edited manuscript, referring neuroimmunologist
Robert Roger Lebel, MD	SUNY Upstate Medical University, Syracuse, NY	Patient's first geneticist, edited manuscript, revised intellectual content
Klaus Werner, MD, PhD	Duke University, Durham, NC	Patient's first neurologist, edited manuscript, revised intellectual content

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