NEUROMYELITIS OPTICA IN A CHILD WITH AICARDI-GOUTIÈRES SYNDROME

Aicardi-Goutières syndrome (AGS) is a monogenic inflammatory disorder typically presenting in infancy as a progressive encephalopathy demonstrating phenotypic overlap in some cases with both congenital infection and systemic lupus erythematosus (SLE), with mutations in 7 genes identified. All forms are associated with a perturbation of type I interferon metabolism, with a defect in the removal, or sensing, of endogenously produced nucleic acid species that activate the immune system. Recently, immunoglobulin G staining of astrocytes in brain sections of 3 deceased patients with AGS were reported, but no specific antigen was identified and the staining patterns were not typical for neuromyelitis optica (NMO). We describe a girl with a heterozygous mutation in IFIH1 who developed NMO with aquaporin-4 antibodies (AQP4-Ab) who clearly responded to immunotherapy.

Case. A patient was previously considered to have isolated motor delay with lower limb spasticity and microcephaly (head circumference <0.4 centile), of undetermined origin. MRI of the brain and spine at 31 months had shown subtle posterior periventricular signal changes (figure, A and B). Her father had been diagnosed with lower limb cerebral palsy, with normal brain and spinal imaging. A clinical diagnosis of unclassified hereditary spastic paraparesis was made. She has a younger brother who is developmentally normal.

At age 36 months, she presented with a 2-week history of retching and vomiting, reduced appetite, and weight loss. Her cognition was age appropriate, and vision and hearing were normal. Regression became evident over the following 6 months, with evolution of her motor disorder, retching, irritability, and new-onset oculogyric crises. Repeat imaging demonstrated diffuse white matter signal change, more posteriorly, with normal spine (figure, C). She continued to deteriorate, and at 44 months she developed acute flaccid monoparesis of her right upper limb. She was too unstable for an MRI to be performed, and was thus clinically diagnosed with transverse myelitis (TM). Imaging, when the patient was clinically stable, confirmed a longitudinally extensive TM (figure, D). At that time, she was strongly positive for serum (1:1,000) and CSF (1:100) AQP4-Ab. NMDA receptor and myelin-oligodendrocyte glycoprotein Abs were negative, but antinuclear antibodies (ANA) (1:160), antineutrophil cytoplasmic antibodies (ANCA), and double-stranded DNA (dsDNA) (82.6 IU/mL) antibodies were detected, consistent with NMO. In addition, CSF neopterin (1,035 nmol/L, normal range 7–65 nmol/L) was significantly elevated, and a provisional diagnosis of an interferon-related disorder was made, subsequently confirmed by the finding of a pathogenic mutation (c.1483G>A; p.Gly495Arg) in the IFIH1 gene, and upregulation of interferon stimulated genes in both the patient and her father. The father’s serum AQP4-Ab was negative, as were his anti-dsDNA and ANCA antibody titers, but ANA titer was also 1:160. A dramatic improvement of the child’s monoparesis and level of engagement, with cessation of vomiting, was observed following treatment with steroids (6 weeks tapering oral steroid course supplemented by IV pulse steroids every 4 weeks). She was treated with rituximab (CD19 cells undetectable at 3 months) and is currently maintained on mycophenolate mofetil.

Serum AQP4-Ab tested 6 months later were markedly reduced (1:100). Repeat imaging demonstrated resolution of the white matter signal abnormalities and improvement in the previously observed cerebral atrophy (figure, E and F). There have been no clinical relapses over a period of 3 years. Bowel and bladder control are intact. She retains a movement disorder with mixed spasticity and dystonia and is accessing mainstream school with significant support. Despite weakness and clawing of hands, there has been recovery of function and she can use a powerchair. She remains under investigation for poor growth.

Discussion. AGS is a genetic disorder associated with an inflammatory milieu that might, theoretically, render patients susceptible to CNS antibody-mediated diseases. Identification of AGS with clinically and serologically confirmed NMO raises the possibility that other such patients may also develop NMO or other antibody-mediated disease.
Despite the patient’s broader neurodevelopmental problems, she had a dramatic response to immunotherapy with improved brain and spinal cord imaging.

The discovery of AQP4-Ab has influenced the diagnosis and management of NMO, with steroids and B-cell-targeting treatments reducing relapse rates and improving outcomes. NMO can co-occur with SLE, but AQP4-Abs are rarely found in patients with other autoimmune diseases.

Interestingly, the proband’s father, with the same mutation and a similarly marked induction of type I interferon signaling, has normal neuroimaging, despite a slowly progressive spastic paraparesis. These phenotypic differences may reflect intercurrent illnesses, modifying genetic polymorphisms, or variable engagement and perturbation of a secondary adaptive immune response towards the myelinating brain. Accurate diagnosis and management in similar patients may result in clinical improvement with a reduction of disability and likely prevention of further relapses.

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RECESSIVE HEREDITARY MOTOR AND SENSORY NEUROPATHY CAUSED BY IGHBMP2 GENE MUTATION

Hereditary motor and sensory neuropathy (HMSN), also known as Charcot-Marie-Tooth disease (CMT), is a genetically heterogeneous disorder that affects both sensory and motor peripheral nerves. HMSN is characterized by distal and symmetric muscle atrophy in the feet and hands, presenting with atrophies of bilateral distal muscles and scoliosis at 6 years of age. Loss of sensory abilities and electrophysiologic findings were also similar to those of the proband (table e-2).

In order to identify the disease-associated genetic abnormality of this pedigree, we had previously excluded 50 known HMSN genes by targeted throughput sequencing. Because we did not identify any known HMSN gene mutations, we performed exome sequencing in the proband. Using ANNOVAR and previously described methods (table e-3), we obtained a list of candidate genes; 2 novel compound heterozygous mutations in the IGHBMP2 gene, c.344C>T (p.Thr115Met) and c.1794G>C (p.Asn598Lys), were highlighted. The IGHBMP2 gene c.344C>T variant is listed in the dbSNP as rs181657861, with an estimated minor allele frequency of 0.00054 in the Exome Variant Server (EVS; 1/12,987) having no identified homozygote, whereas the c.1794G>C variant is not listed in the EVS, and the 2 mutations passed SIFT and PolyPhen-2 filtering. Therefore, both variants are rare and predicted to be pathologic. In addition, we found that the 2 mutations were fully cosegregated with the HMSN phenotype and absent in 500 ethnically matched controls, thereby confirming the pathogenicity (figure e-2).