Uncontrolled inflammation of the nervous system

Inherited CD59 deficiency

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CD59 regulates the complement activation cascade at the final step by inhibiting formation of membrane attack complex.¹ The lack of CD59 allows uncontrolled complement amplification following spontaneous, viral, or postviral induced complement activation.² Inherited CD59 deficiency is a rare autosomal recessive disorder characterized by chronic hemolysis, early-onset recurrent peripheral neuropathy resembling Guillain-Barré syndrome or chronic inflammatory demyelinating polyneuropathy, and together with recurrent strokes.^{3–6}

PRACTICAL IMPLICATIONS

Ecilizumab may be effective in reversing neurologic symptoms of inherited CD59 deficiency.

We describe a family with isolated CD59 deficiency with peculiar findings: acute-onset immune-mediated cerebellitis, hemorrhagic longitudinal myelitis, acute disseminated encephalomyelitis (ADEM)–like demyelination in CNS, and subclinical mild chronic neuropathy. This report extends the clinical spectrum of inherited CD59 deficiency syndrome.

Patient 1 is an 11-year-old girl who presented with acute fever, vomiting, and fatigue within a day. The pedigree is presented in figure e-1 (links.lww.com/CPJ/A44). Her father had a form of acute peripheral neuropathy beginning at age 28 years and died shortly after the onset of the disease. Her aunt could not walk after a febrile illness, later developed scoliosis, and died at age 16 years. Another aunt died with presumed meningitis at 3 months of age. One sibling was admitted to the hospital a few days before patient 1's admission (see patient 2). Twelve years prior, her sister had died due to rapidly ascending neurologic signs at age 13 months.

On admission, patient 1 had dysarthric speech, horizontal nystagmus, dysmetria, and ataxic gait. There was pes cavus and thenar atrophy. She could only walk 10 meters.

The patient was admitted with a diagnosis of acute cerebellitis. Initial laboratory values were white blood cell count 8,350/ μ L (69% neutrophils), hemoglobin 11 g/dL, platelet count 204×10^3 / μ L, C-reactive protein 116 mg/L. CSF examination showed abundant leukocytes (2,000/ mm^3), protein 450 mg/dL, glucose 54 mg/dL (blood glucose 114 mg/dL), with normal culture. MRI at presentation revealed diffuse cerebellar cortical edema with pial enhancement suggestive of acute cerebellitis, accompanied by diffuse linear enhancement of the cauda equina. Additional T2 hyperintense lesions in bilateral middle cerebellar peduncles were present (figure 1). She was started on IV immunoglobulin. She partially responded with improvement of ataxia and nystagmus after the fifth dose. Oral prednisolone therapy was added. Two days later, hypertension accompanied by seizures and nystagmus developed once again. MRI 5 days later shows pial and ependymal enhancement. Cortical and subcortical lesions at bilateral occipital and frontoparietal lobes were noticed on T2-weighted imaging. Simultaneous thoracic spinal MRI shows myelopathy by T2 hyperintensity involving both gray and white matter of the cord at the T7–T9 level (figure e-2, links.lww.com/CPJ/A44). Furthermore, thenar atrophy, mild pes cavus, and hypoactive deep tendon reflexes were suggestive of a neuropathic disorder. Three months into the diagnostic journey, CD59 deficiency was detected by flow cytometry.

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Figure 1 MRI at presentation

MRI at the time of presentation reveals diffuse cerebellar cortical edema (A; yellow arrows) with pial enhancement (B) suggestive of acute cerebellitis, accompanied by diffuse linear enhancement of the cauda equina (C, D; green arrow). Additional T2-hyperintense lesions in bilateral middle cerebellar peduncles are shown (A). Although there is no supratentorial meningeal enhancement at initial MRI (not shown), an MRI at 5 days later shows pial and ependymal enhancement (E; white arrow). Cortical and subcortical lesions at bilateral occipital (F) and frontoparietal lobes (not shown) consistent with "posterior reversible encephalopathy syndrome" are seen on T2-weighted imaging. Simultaneous thoracic spinal MRI shows myelopathy by T2 hyperintensity involving both gray and white matter of the cord at the T7-T9 level (G, H; red arrows).

CD59 mutation analysis revealed a homozygous missense mutation (c.146A>T[p.Asp49Val]). Based on previous reports, the patient was put on eculizumab. Within 7 months of onset, she gradually improved with no ataxia and full ambulation at the last visit. She continues to take this drug according to the scheme.

Patient 2, the younger sibling of patient 1, presented at age 10 years with acute urinary incontinence and walking difficulty. On examination, he had lower extremity weakness. One day later, the patient's consciousness decreased and neck stiffness developed. In the CSF, there were 25 leukocytes/ μ L, and protein was elevated at 70 mg/dL. This boy's MRI showed T2-hyperintense lesions in bilateral middle cerebellar peduncles and right cerebellar hemisphere with many additional lesions in the deep and peripheral cerebral white matter. From cervical level 3 down to the conus medullaris, profound acute myelopathy and radiculopathy with hemorrhage were present on T1 (figure e-2, [links.lww.com/CPJ/A44](https://www.annals.org/lookup/suppl/doi:10.1212/WNL.0000000000004444/-/DC1)). The boy received IV steroids, plasma exchange, erythrocyte infusions, and life support. He died on the 86th day of admission. The CD59 mutation analysis of this patient was identical to that of his sister, which was shown postmortem.

Genetic analyses

CD59 gene sequence analysis was performed with MiSeq next-generation sequencing platform (Illumina, San Diego, CA).

Genomic DNA was isolated from peripheral lymphocytes according to the manufacturer's standard procedure with Anatolia magnetic bead kit (Anatolia, Turkey). Coding exons and flanking regions were amplified with in-house designed PCR primers, designed with Primer Designer v.2.0 (Scientific & Educational Software program, Denver, CO) software. Library preparation was carried out with the Nextera XT kit (Illumina). Sequences were aligned to the hg19 genome within MiSeq Reporter software (Illumina) and visualized with IGV 2.3 (Broad Institute, Cambridge, MA) software.

As shown in figure 1, the CD59 mutation analysis in patients 1 and 2 showed a homozygous deletion (c.146A>T [p.Asp49Val]). Heterozygous deletion was detected in their mother's analyses. The parents are not relatives; rather, they are individuals from the same village.

Discussion

Mutations in CD59 leading to loss of function have been described previously in 12 patients, all of whom had neurologic findings. Eleven of 12 patients presented with recurrent peripheral neuropathy while 6 of them presented with recurrent strokes.² The age at onset of the first symptoms of previously described cases was generally reported during infancy.²⁻⁸ Our cases presented with acute neurologic features at a later age. However, the examination findings were

consistent with chronic neuropathy, suggesting that both cases actually may have had symptoms before the acute presentation.

Remarkably, caudal involvement and middle cerebellar peduncle lesions were also present in previously reported patients.^{3,4,8} Previously unknown longitudinal diffuse hemorrhagic myelopathy, ADEM-like cerebral demyelinating patchy lesions, and acute cerebellitis findings were detected by neuroimaging. Different from the cases in the literature, cerebrovascular events were not present. We follow 4 other patients who are treated with eculizumab. There have been no new neurologic insults (unpublished clinical observations). At this stage, eculizumab therapy was initiated in the index case. After 5 months with eculizumab (7 months into the symptoms), her ataxia has resolved completely.

Author contributions

D. Yuksel: acquisition of data and interpretation. K.K. Oguz: acquisition of data and interpretation. E. Azapagasi: acquisition of data. S. Kesici: acquisition of data. B. Cavdarli: acquisition of data. B. Konuskan: acquisition of data. H. Topaloglu: acquisition of data and interpretation.

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Disclosure

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