Child Neurology: Type 1 sialidosis due to a novel mutation in *NEU1* gene

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A 39-year-old man of Ecuadorian descent presented with a history of seizures, visual impairment, and ataxia. He had a normal birth and early developmental history. His first seizure was a generalized tonic-clonic seizure (GTCS) at 16 years old. Around the same time, he also started experiencing 1–2 myoclonic jerks per day. The myoclonic jerks progressively worsened over a period of 20 years to 15–20 episodes per day. GTCS continued to occur 1–2 times a year until the age of 24 years. EEG revealed multiple brief myoclonic seizures and generalized slow spike/polyspike wave complexes consistent with primary generalized epilepsy. Despite valproic acid, zonisamide, and clonazepam, his seizure control remained poor. When he was 30 years old, he began to have blurring of his vision; ophthalmologic evaluation at that time revealed bilateral cherry-red spots. Optical coherence tomography showed hyperreflectivity in the superficial layers of the retina at the posterior pole consistent with abnormal storage in the ganglion cells. An electroretinogram showed normal rod and cone responses. Flash visual evoked responses demonstrated a delay in the P100 response consistent with dysfunction of the visual pathways. His medical and family history was otherwise noncontributory. Gross physical examination was within normal limits. Neurologic examination demonstrated severe myoclonus of the face interrupting his speech, frequent myoclonus of the arms, truncal and appendicular ataxia, and broad-based ataxic gait. MRI of the brain with and without gadolinium was normal. Chromosome single nucleotide polymorphism microarray revealed long contiguous regions of allele homozygosity (>10 MB) in multiple chromosomes. A query of the regions of homozygosity that was subsequently narrowed down using his clinical presentation identified *NEU1* as a candidate gene. Sequencing of *NEU1* revealed a homozygous missense mutation c.629C>T (p.Pro210Leu). Enzymatic testing in fibroblasts showed sialidase activity to be deficient (0 nmol/h/mg; ref: 23–74). β-Galactosidase activity was within normal limits.

Discussion

Striking clinical features in our patient include progressive myoclonic epilepsy, ataxia, and cherry-red spots. Macular cherry-red spots describe the retinal ophthalmoscopic appearance due to accumulation of abnormal storage material in neurometabolic disorders (table). Progressive myoclonic epilepsies are characterized by myoclonic seizures, tonic-clonic seizures, and progressive neurologic deterioration, typically with ataxia and dementia. Varied etiologies can be considered in broad categories such as genetic epilepsies, mitochondrial disorders, and lysosomal storage disorders. Genetic epilepsies such as Unverricht-Lundborg disease and Lafora disease are typically caused by repeat expansions or point mutations of the disease-causing genes and are clinically characterized by progressive worsening intractable seizures, cognitive decline, dysarthria, and ataxia. Mitochondrial disorders have a wide phenotypic spectrum with multisystem involvement. Myoclonic epilepsy and ataxia are frequently seen in a specific type of mitochondrial disorder, myoclonic epilepsy with ragged-red fibers (MERRF). Lysosomal storage disorders such as Gaucher disease, neuronal ceroid lipofuscinoses (NCL), and sialidosis are caused by defects in the lysosomal proteins, cofactors, or integral membrane proteins leading to intralysosomal accumulation of substrates. A majority of them present with severe neurologic impairment, and progressive myoclonic epilepsy is a common manifestation. In fact, lysosomal storage disorders are the most common cause of the inherited form of

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Table Differential diagnosis for macular cherry-red spot

1	Tay-Sachs disease
2	Sialidosis
3	Niemann-Pick disease
4	Sandhoff disease
5	GM1 and GM2 gangliosidoses
6	Metachromatic leukodystrophy

progressive myoclonic epilepsy. Hepatosplenomegaly, cardiac involvement, and macular cherry-red spots can be seen.

Based on the overlapping characteristics, differential diagnoses considered in our patient include Unverricht-Lundborg disease, MERRF, Lafora disease, NCL, Gaucher disease, and sialidosis. Unverricht-Lundborg disease or epilepsy progressive myoclonus type 1 is the most common progressive myoclonic epilepsy that presents at the age of 6–15 years with stimulus-sensitive myoclonic jerks or generalized tonic-clonic seizures. Patients later develop ataxia, incoordination, intention tremor, and dysarthria. It is associated with defective function of cystatin B, a cysteine protease inhibitor, due to mutations in the *CSTB* gene at 21q22.3.[1] MERRF is a mitochondrial disorder with varied age at onset and clinical severity characterized by myoclonus, generalized epilepsy, ataxia, and ragged-red fibers in muscle biopsy. Additional clinical features include neuropathy, hearing loss, short stature, optic atrophy, and dementia. Brain MRI shows basal ganglia calcifications and cerebral atrophy.[1] Lafora disease typically presents between 12 and 17 years of age with progressively worsening seizures with multiple seizure types including myoclonus, occipital seizures with transient blindness and visual hallucinations, atypical absences, atonic, and complex partial seizures. Progressive dementia and Lafora bodies (Periodic acid–Schiff–positive intracellular polyglucosan inclusion bodies) in neurons, skeletal muscle, heart, and liver are seen. Most affected patients die within 10 years of onset. Mutations in the *EPM2A* (6q24.3) and *NHLRC1* (6p22.3) genes are known to be associated with Lafora disease.[1]

NCL are a group of lysosomal storage disorders with genetically distinct congenital, infantile, late infantile, juvenile, and adult phenotypes based on the age at onset and order of appearance of clinical features. The adult phenotype, which is pertinent to the case described here, can present as early as 11 years of age or later in adulthood and is characterized by progressive myoclonic epilepsy with dementia, ataxia, and late-occurring pyramidal and extrapyramidal signs. Visual impairment is not typically present. Deficient activity of palmitoyl protein thioesterase, tripeptidyl-peptidase 1, cathepsin D, or cathepsin F is seen. Brain MRI shows cerebral and cerebellar atrophy.[1,2] Gaucher disease is caused by deficiency of the enzyme glucocerebrosidase, causing toxic accumulation of glucocerebroside in macrophages. Types 2 and 3 have primary CNS involvement, and progressive myoclonic epilepsy is seen only in type 3, which has a subacute juvenile onset and slow progressive course. These patients also have organomegaly, pulmonary involvement, and cytopenia. Pathogenic variants in the *GBA* gene (1q22) are causative.[3] Macular cherry-red spots are not typically seen in Unverricht-Lundborg disease, MERRF, Lafora disease, NCL, or Gaucher disease.

Sialidosis is an autosomal recessive lysosomal storage disorder caused by homozygous or compound heterozygous mutations in the *NEU1* gene on chromosome 6p21.33, encoding sialic acid cleaving enzyme sialidase 1 or neuraminidase 1.[4] Sialidase is a part of lysosomal multienzyme complex and acts in removing terminal sialic acid molecules from oligosaccharides and glycoproteins. Impaired sialidase activity therefore leads to storage of sialic acid–rich macromolecules in multiple organs including liver, kidneys, brain, skin, conjunctiva, peripheral leukocytes, and bone marrow cells. Diffuse intracytoplasmic storage of lipofuscin-like pigments in neurons, oligodendroglia, endothelial, and perithelial cells with some degree of axonal loss is noted in the CNS. Type 1 sialidosis, also known as cherry-red spot–myoclonus syndrome, is the milder juvenile or adult-onset form characterized by progressive myoclonic epilepsy, visual impairment, and ataxia. The most prominent feature is myoclonus that may be precipitated by voluntary movements, the thought of movement, passive joint movements, light touch, or sound stimuli. Patients have normal to slightly impaired intelligence. Clinical phenotype correlates closely with the type of *NEU1* mutations and the levels of residual enzyme activity.[4–6] Type 2 sialidosis is the severe form that has 3 subtypes: congenital with onset in utero, infantile with onset between birth and 12 months, and juvenile with onset after 2 years of age. Babies with congenital form of the disease develop hydrops fetalis, neonatal ascites, inguinal hernias, and hepatosplenomegaly. They are either stillborn or die shortly after birth. The other 2 subtypes are characterized by myoclonus, coarse facial features, hepatomegaly, dysostosis multiplex, and severe intellectual disability. Life expectancy varies based on genotype and phenotypic severity; however, most patients become wheelchair-bound within few years due to severe myoclonus causing motor deterioration.[4–6] Neuropathologic features include vacuolations with neuronal intracytoplasmic lipofuscin-like pigment storage seen in the neocortex, basal ganglia, thalamus, brainstem, and spinal cord. No abnormalities are seen on brain MRI in early stages of the disease whereas atrophy of the cerebral cortex, pons, and cerebellum may be seen during progression.[5] Diagnosis is usually suggested by increased urinary excretion of sialic acid. Confirmation is by demonstrating enzyme deficiency in cultured fibroblasts or genetic testing.[4,5] Current pharmacologic management involves treating the myoclonic epilepsy. Antiepileptics that have been used include valproic acid, levetiracetam, phenobarbital, zonisamide, and benzodiazepines. It is important to avoid carbamazepine, phenytoin, gabapentin,

and vigabatrin as these can exacerbate myoclonus. Lamotrigine can be used with caution as it exacerbates myoclonus in some patients. Enzyme replacement therapy has been studied in mouse models; however, penetrance through blood–brain barrier was not achieved and severe anaphylactic reactions were seen.[7]

To date, around 50 mutations in the *NEU1* gene have been reported in patients with sialidosis.[4,8,9] To our knowledge, the c.629C>T mutation of *NEU1* found in our patient has not been reported. This missense alteration causes replacement of the amino acid proline by leucine at codon 210. The amino acid substitution is also predicted to be "probably damaging" by the polymorphism phenotyping tool (Polyphen-2). Further, the p.Pro210 residue in *NEU1* has been conserved among species during evolution (Alamut Visual 2.9, interactive-biosoftware.com/alamut-visual). Based on these, and the fact that our patient's clinical presentation and enzyme testing are consistent with sialidosis type 1, we speculate that the missense mutation affecting this highly conserved region is responsible for the phenotype.

Sialidosis should be considered in patients presenting with progressive myoclonic epilepsy and cherry-red spots. Physicians should be aware of the other rare disorders with similar clinical features.

Author contributions

Akilandeswari Aravindhan: drafting and revising the manuscript. Aravindhan Veerapandiyan: revising the manuscript. Chelsea Earley: drafting the manuscript. Venkatraman Thulasi: drafting the manuscript. Christina Kresge: revising the manuscript. Jeffrey Kornitzer: study concept and revising the manuscript.

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Disclosure

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