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LETTER TO THE EDITORS

Co-morbidity of Sanfilippo Syndrome type C and D-2-hydroxyglutaric aciduria

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Dear Sirs,

A 13½-year-old girl was seen at the Neurology and Medical Genetics Clinics with delayed milestones, macrocephaly and developmental regression. She had no history of perinatal complications other than delivery via cesarean section because of breech presentation. Over the preceding 2 years she had developed nystagmus, occurring 4–5 times a week. She had staring spells but had a normal EEG. Her milestones, which included standing at 18 months of age, first words at 2 years of age, walking at 2½ years of age, and writing letters at 6–7 years of age, were delayed. Her developmental regression included enuresis, day time loss of bladder control and use of incorrect words for identification. Her gait had become unsteady, speech less understandable because of mumbling, and she experienced intermittent difficulty in recognizing her mother. Her family history was unremarkable with no consanguinity. On examination she had macrocephaly, mild facial coarsening, thick eye brows, dark coarse hair, mild synophrys, thick lips, high arched palate, low anterior and posterior hairline, intermittent tonic up gaze, nystagmus, and hypotonia with normal muscle bulk. MRI of the brain (Fig. 1) showed enlarged extra-axial spaces, hypoplastic temporal lobes, open Sylvian fissures, mild ventriculomegaly and enlarged perivascular spaces. Skeletal survey was normal. Additional laboratory work up including lactic acid, pyruvic acid, mitochondrial respiratory enzyme analysis, CoQ10 levels, neurotransmitter profile (5-methyltetrahydrofolate, 5-hydroxyindoleacetic acid, homovanillic acid, 3-*O*-methyldopa, neopterin, tetrahydrobiopterin, succinyladenosine and pyridoxal 5 phosphate), karyotype, chromosomal microarray (44K custom Agilent platform), plasma amino acids and acylcarnitine profile was normal. Urine organic acid analysis revealed significant 2-hydroxyglutaric aciduria, which was confirmed to be the D-enantiomer by a LC–MS/MS method that separates D- from the L-enantiomer [1]. Enzyme analysis on skin fibroblast cultures showed severely deficient D-2-hyroxyglutarate dehydrogenase activity. Two disease causing mutations (c.373G>A and c.858C>A) were found in the *D2HGDH* gene. A urine mucopolysaccharidosis (MPS) screen completed during her initial evaluation showed increased heparin sulfate (HS), suggesting co-morbidity with Sanfilippo syndrome. Further investigation showed alpha-glucosaminide *N*-acetyltransferase deficiency and heterozygosity for two disease causing mutations in the *HGSNAT* gene: a splicing mutation defined as c.372-2A>G and a nonsense mutation defined as c.1516C>T.

Sanfilippo Syndrome is the most common of MPS disorders. It is caused by deficiency or absence of any one of the four different enzymes that are necessary to degrade the

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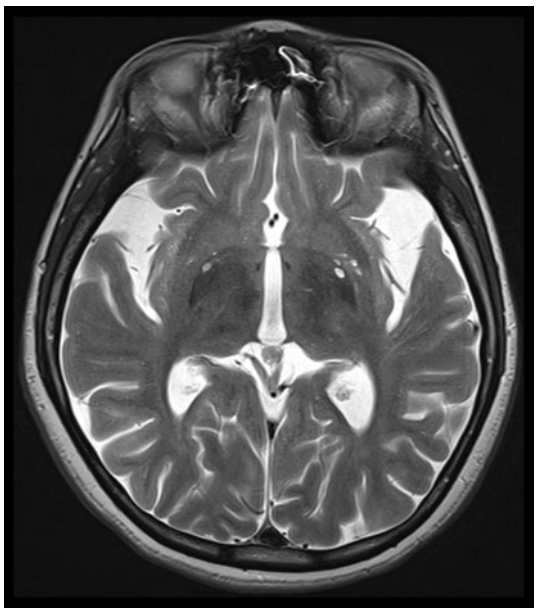

Fig. 1 MRI of the brain

glycosaminoglycan, HS, leading to its accumulation in a variety of tissues. Manifestations include mildly coarse facial features, synophrys, mild hepatosplenomegaly, mild dysostosis multiplex and severe progressive neurologic degeneration. Neurodegeneration ultimately leads to a vegetative state [2]. MRI findings include cerebral atrophy, abnormal or delayed myelination and dilatation of perivascular spaces [3]. Over time, airway obstruction and/or pulmonary infection can lead to cardiopulmonary arrest. A subtype, Sanfilippo type C syndrome is caused by deficiency of alpha-glucosamine *N*-acetyltransferase encoded by *HGSNAT* [4]. No disease-modifying treatment is presently available. Supportive treatment is aimed at improving quality of life.

D-2-hydroxyglutaric aciduria is a rare neurometabolic disorder and organic acidemia characterized by varied clinical symptoms [5]. Clinical presentations vary from asymptomatic to developmental delay, epilepsy, hypotonia, dysmorphic features, neonatal- or early-infantile-onset epileptic encephalopathy, cerebral visual failure and cardiomyopathy. Delayed cerebral maturation, ventricular white-matter abnormalities and subependymal cysts are seen on MRI of the brain. Patients with D-2-hydroxyglutaric aciduria have been found to be homozygous or compound heterozygous for mutations in *D2HGDH* encoding D-2-hydroxyglutarate dehydrogenase or heterozygous for mutations in *IDH2* encoding isocitrate dehydrogenase-2 [6]. No disease-modifying treatment is currently available.

Both of these diseases are characterized by a neurologic phenotype [2, 7]. They are very rare and the likelihood of them occurring together is extremely remote, especially in non-consanguineous unions. Hence, identifying one rare metabolic disorder may induce the physician to stop further diagnostic assessment. Our case demonstrates the need to look further when the phenotype is not completely explained by the disorder detected by laboratory investigation. The physical examination, the unusual MRI findings and an abnormal MPS screen, prompted us to pursue further testing. This case demonstrates the challenges involved in diagnosing rare inborn metabolic disease and correlating discordant laboratory findings with clinical symptoms. An exact and complete genetic diagnosis is essential to providing an accurate prognosis for this patient and for counseling family members.

Conflict of interest None.

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