Atypical Diagnosis Of Neuraminidase Deficiency: A Case Report

Catherine Groden, MS, CRNP[1], Ellen Macnamara[2], Cynthia J. Tifft[3], Camilo Toro[1], Alessandra D'Azzo[4].

[1]NIH/NHGRI, Bethesda, MD, USA,
[2]National Institutes of Health NHGRI, Bethesda, MD,
[3]National Human Genome Research Institute, Bethesda, MD,
[4]St Jude Research Hospital, Memphis, TN, USA.

Atypical diagnosis of neuraminidase deficiency: a case reportCatherine Groden, MS, CRNP, Ellen Macnamara, ScM,., Camilo Toro, MD, Alessandra D'Azzo PhD, Cynthia J. Tifft MD PhDGalactosialidosis (GSL) (OMIM 256540) caused by biallelic mutations in CTSA (20q13), is a lysosomal storage disease associated with a combined deficiency of beta-galactosidase and neuraminidase secondary to a defect in protective protein/cathepsin A (PPCA). The juvenile/adult form is characterized by myoclonus, ataxia, cherry red spots, angiokeratoma, intellectual disability, seizures, neurologic deterioration, bone abnormalities, and heart disease.We present a 15-year-old African American female with ophthalmologic, neurologic and biochemical findings consistent with sialidosis type 1 including elevations in urine oligosaccharides. Her presumed diagnosis of sialidosis type 1 was confirmed by finding deficient neuraminidase activity in cultured fibroblasts and neurologic findings consistent with the disorder. Repeated sequencing and deletion/duplication testing of NEU1 did not identify any variants. The proband was enrolled in the Undiagnosed Disease Network for a broader evaluation and genetic testing to identify her diagnosis. Her history was significant for intentional myoclonus, mild cerebellar ataxia and generalized convulsive epilepsy, successfully treated with levetiracetam. Neurologic findings on exam showed slight tongue myoclonus but normal tongue strength and movement, positive Hoffman reflex consistent with myoclonus/C-reflex on the right side, mild postural tremor of both hands with intermittent negative myoclonus with wrists held extended, and intention tremor with dysmetria on finger to nose bilaterally. She had a mildly wide-based stance and gait with foot inversion and difficulty with tandem gait.MRI brain imaging was normal. Somatosensory evoked responses following bilateral median nerve stimulation showed amplitude increase in giant waveforms (25U, upper limit of normal). Her ophthalmologic findings include poor visual acuity, significant myopic astigmatism and bilateral cherry red maculae. Prior optical coherence tomography showed diffuse storage in macular ganglion cells.Her history is also significant for a mood disorder (depression and anxiety), a chronic headache disorder with frequent use of NSAIDs, a sleep disorder (previously suspected due to narcolepsy with cataplexy), dysmenorrhea and a history of significant episodic systolic and diastolic hypertension suggestive of autonomic dysfunctionThe UDP performed genome sequencing on the patient and her mother that identified compound heterozygous variants in CTSA; consistent with a diagnosis of galactosialidosis.This case demonstrates the value of agnostic genome sequencing when biochemical testing and phenotype is inconsistent with single gene sequencing. While our patient had undergone numerous sequencing and deletion/duplication tests in an effort to discover her NEU1 variants, exome or genome sequencing earlier in the diagnostic process might have shortened the diagnostic odyssey.

"Repeated sequencing and deletion/duplication testing of NEU1 did not identify any variants."
"The UDP performed genome sequencing on the patient and her mother that identified compound heterozygous variants in CTSA; consistent with a diagnosis of galactosialidosis."
"This case demonstrates the value of agnostic genome sequencing when biochemical testing and phenotype is inconsistent with single gene sequencing. While our patient had undergone numerous sequencing and deletion/duplication tests in an effort to discover her NEU1 variants, exome or genome sequencing earlier in the diagnostic process might have shortened the diagnostic odyssey."
Just Now