Different clinical phenotype of WARS2 mutation: Case report

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Introduction:

Mitochondrial form of tryptophanyl-tRNA synthetase is encoded by WARS2 gene. Neurodevelopmental disorder with abnormal movements and lactic acidosis and with or without seizures (NEMMLAS) is an ultra-rare disorder and is caused by homozygous or compound heterozygous mutation in the WARS2 gene (OMIM 604733).

Mutations of WARS2 gene have been associated a wide spectrum of clinical manifestations which ranges from movement disorders and mental retardation to severe fatal neonatal lactic acidosis. Cardiomyopathy, movement disorder, retinitis pigmentosa, optic atrophy, hypoglycemia, liver injury, epilepsy, leukoencephalopathy, intellectual disability and elevated lactate levels suggestive of mitochondrial dysfunction have been reported in patients with WARS2 mutation. Although, progressive hearing loss has been described in a mouse model with the Wars2 mutation, hearing loss has not been reported in patients with WARS2 mutation. Here we report a girl with WARS2 novel mutation who manifested by recurrent hypoglycemia, hyperuricemia, hyperlactatemia, seizures and sensorineural deafness.
Case report:
The patient was hospitalized on the 3rd day of life due to hypoglycemia. She was diagnosed as a case of fructose 1,6-bisphosphatase deficiency based on her recurrent clinical manifestations of vomiting, hypoglycemia, hyperuricemia, hyperlactatemia, hypertransaminasemia and glucagon unresponsive fasting hypoglycemia at 18 months. Bilateral sensorineural deafness was determined at 12 months of age. A cochlear implant was inserted. The patient had seizures with requiring multiple-drug which started at 18 months of age. Her cranial MR was normal. Recurrent clinical manifestation was continued until seven years of age. Mental and growth retardation were detected during the follow-up. No mutation was detected in the genetic analysis for fructose 1,6-bisphosphatase (FBP1) gene when the patient was 9 years old. The patient lost to follow-up for three years. When the patient was admitted again at the age of 13, a coarse granular appearance was detected in the liver in her ultrasonography. Her echocardiography was normal. Blood amino acid levels, serum acylcarnitine profile, coagulation parameters (Prothrombin time: 10.1 seconds, partial thromboplastin time: 29.4 seconds, international normalized ratio: 1.15), direct bilirubin (0.25 mg/dl) and indirect bilirubin (0.32 mg/dl) and serum ammonia level were normal. Homozygous c.797C>T(p.pro266Leu) novel mutation was detected in the WARS2 gene by whole exome sequencing analysis and the patient was diagnosed as NEMMLAS.
Discussion:
Herein we presented a patient with novel WARS2 mutation who manifested different clinical findings from those reported in the literature. Twelve patients with WARS2 mutation have been reported in the literature. A patient with WARS2 mutation who developed liver failure associated with valproate has been reported. However, our patient had hypertransaminasemia and coarse granular appearance in liver according to her ultrasound unrelated to valproate exposure. Additionally, progressive hearing loss, which was not previously described in the literature, but observed in a mouse model of wars2 mutation, was observed in our patient. Furthermore, our patient had mild neurological involvement, unlike the previously reported patients which they presented with severe neurological disease.

Conclusion
WARS2 mutation should be considered in patients who presented with recurrent hypoglycemia, hyperuricemia, hyperlactatemia, seizures. Additionally, our patient’s findings suggest that WARS2 mutation can cause heterogeneous clinical features such as liver involvement, sensorineural deafness, no movement disorder or no progressive leukoencephalopathy. Also, patients with WARS2 mutation should be monitored for progressive sensorineural hearing loss.

References: