P-098 - ATYPICAL PYRUVATE DEHYDROGENASE COMPLEX DEFICIENCY (PDHC) DUE TO PDHA1 GENE DEFECT, PRESENTING AS CHARCOT-MARIE-TOOTH DISEASE (CMT).


Division of Metabolic Disorders. CHOC Children's. Orange-CA-USA.

BACKGROUND: The pyruvate dehydrogenase enzyme complex is composed of 3 catalytic subunits (E1, E2, E3), 2 regulatory subunits, 3 cofactors and one binding protein. Mutations in the X-linked PDHA1 gene are the most common cause of PDHC. The disease typically presents in neonates with lactic acidosis, brain malformations and dysmorphic features, however milder/atypical presentations are known. CMT is the most common hereditary cause of peripheral neuropathy. Mutations in >80 genes are associated with the disease, with an AR, AD or X-linked inheritance. Recently, mutations in one of the PDHC genes, PDK3, were found to be responsible for X-linked CMT type 6, however mutations in the PDHA1 gene have not been associated with CMT.

AIMS: To present a previously unreported association of atypical PDHC deficiency presenting as CMT due to pathogenic variants in PDHA1. Clinical Report: Patient presented at 3 y with toe walking and uncoordinated gait. Later, speech delay, sensory loss, temperature sensitivity, numbness and burning of hands and feet were noted. He was diagnosed with CMT at 5 y based on an abnormal nerve conduction velocity study. Over time he developed ADHD, anxiety, abnormal sleep, migraines, fatigue and leg pain. At 14 y after a CMT gene panel was normal, WES was performed revealing a de-novo pathogenic variant, c.214C>T (p.Arg72Cys) in PDHA1. Biochemical testing showed elevated lactic acid and alanine, and PDHC activity in fibroblasts was 9 % of the control mean, confirming PDHC deficiency. Physical exam was positive for signs of peripheral neuropathy (pes-cavus, absent patellar/achilles reflexes, abnormal gait, tremors) and hypermobility. Brain MRI was normal. He was started on a high-fat/low-carbohydrate diet (20 grams of carbohydrate/day), thiamine (1000mg/day) and gabapentin. Since initiation of treatment, fatigue, headaches, sleep and leg pain have improved. However, there have been no changes in biochemical parameters. CONCLUSION: This case highlights CMT as an atypical presentation of PDHC deficiency and reports on a new association with PDHA1 gene defects. PDHC deficiency should be considered as part of the evaluation for CMT and PDHA1 gene testing should be added to existing CMT/hereditary neuropathy gene panels.