

eP028

Neurological manifestations in PMM2 related congenital disorders of glycosylation (CDG): Insights into clinico-radiological characteristics and recommendations for follow-upKarthik Muthusamy¹, Anna Ligezka¹, Christin Johnsen¹, Suzanne Boyer¹, Eva Morava-Kozicz¹¹Mayo Clinic

Introduction: PMM2-CDG is the most common N-linked glycosylation disorder. Neurological involvement is one of the major clinical features in individuals with PMM2-CDG. Understanding the neurological phenotype is essential as many treatments are on the horizon, and their ability to modify the neurological manifestations are yet to be understood.

Objectives: Prospective neurologic evaluation of patients with PMM2-CDG to systematically explore the neurologic phenotype, predict severity and to derive recommendations for clinical practice and research.

Methods: Patients with biochemical and molecular confirmation of PMM2-CDG who were recruited along with other CDG to the Frontiers of Congenital Disorders of Glycosylation (FCDGC) natural history study were evaluated for neurological manifestations as a part of standard care.

Results: Thirty-two patients were included (7 females and 25 males). Mean age at diagnosis was 7 months (range 4 months to 32 years). Various diagnosis like spinal muscular atrophy, Prader-Willi syndrome and congenital muscular dystrophy were considered initially, before suspecting CDG. Mean age at assessment at our clinic was 11.42 years (range of 2 to 34 years). Only two patients were walking unassisted, the rest required assistance to walk. Socio-adaptive and language domains were relatively preserved when compared to motor development. Retinopathy was present in 10 (31%) and hearing loss requiring aids was seen in 6 (19%) patients.

Cerebellar ataxia was the most common finding (97%) followed by myopathy (78%), neuropathy (78%), movement disorder (50%) and spasticity (19%). Seizures were present in 69% of patients with mean age at onset being 3 years (range 3 months to 24 years). Eleven of them both febrile and afebrile seizures, 4 had only febrile and 7 only afebrile seizures. Status epilepticus requiring hospital admission was seen in 28%. Antiepileptics tried were levetiracetam, oxcarbazepine, carbamazepine, phenytoin, clobazam, clonazepam and lacosamide. Three had medically refractory seizures, 3 with initially refractory seizures were currently under control, 16 had good seizure control from beginning.

Total of 7 stroke like episodes (SLE) were seen in 6 patients, with precipitating factor being seizures in 4, infection in 2 and an accidental fall in one. Most of them recovered in a day. Two patients had normal imaging, whereas all others revealed progressive cerebellar atrophy. Mean score in Nijmegen Pediatric CDG rating scale was 23.1 (range of 14 to 33). Statistically significant correlation was seen with seizures and SLE ($p=0.004$). No statistical significance was seen with head circumference, clinical features, imaging findings, Nijmegen scores or transferrin values with the severity of involvement, seizures, or SLE.

Conclusion: Cerebellar ataxia is the most common neurological sign in PMM2-CDG. Patients with seizures are prone to develop SLE. Adequate seizure control might prevent SLE and progressive neurologic deterioration. Transferrin profile and Nijmegen scoring does not appear to correlate with neurological involvement or severity.

<https://doi.org/10.1016/j.gim.2022.01.066>

eP029

Response of an infant with presumed type II multiple Acyl-CoA dehydrogenase deficiency to ketone supplementationBryce Schuler¹, Erica Nelson¹, Natalie Owen¹, Ellen Strickler¹, Neena Agrawal¹, Rizwan Hamid¹, Angela Grochowsky¹, Thomas Morgan¹, John Phillips¹¹Vanderbilt University Medical Center

Background: Multiple acyl-CoA dehydrogenase deficiency (MADD) type II has neonatal onset without congenital anomalies. In those who survive the neonatal period, recurrent metabolic decompensation and hypertrophic cardiomyopathy can occur. Deficiency of the electron transfer flavoprotein (ETF alpha and beta subunits, *ETF A* and *ETF B*) or the ETF flavin adenine dinucleotide (FAD)-dependent dehydrogenase (*ETFDH*) negatively impacts electron transfer in the mitochondria which subsequently affects fatty acid oxidation (FAO) and the metabolism of some amino acids. The diagnosis of MADD is established via detection of a characteristic pattern of metabolite derangements on newborn screen (NBS), acylcarnitine profiles (ACP), and urine organic acids (UOA) and/or identification of biallelic pathogenic variants in *ETF A*, *ETF B*, or *ETFDH*. Here we report a patient who presented with a biochemical phenotype consistent with MADD who developed cardiomyopathy that responded to ketone supplementation therapy but whole genome sequencing (WGS) failed to identify the molecular cause of his phenotypes.

Case presentation: Consent was obtained from the family to present this case. The patient presented with repeated NBS showing elevated C5, C16, C18:2, C18:1, C18, C16:1, and C16-OH. ACP results paralleled the NBS results and revealed additional elevations of C4, C5DC, C8, C10, C12, C14, and C14:1. UOA revealed elevations in lactic, glutaric, 2-hydroxyglutaric, ethylmalonic, adipic, suberic, and sebacic acids (among other elevations). All were characteristic of MADD but DNA testing including WGS failed to detect variants in the ETF genes or other genes that could explain his phenotype. He was treated with riboflavin (150mg daily) and levocarnitine (adequately supplemented with 150mg daily). At three months of age, he developed severe cardiomyopathy (EF as low as 20%) and a pericardial effusion in the context of a presumed viral infection. We initiated a low-fat, modified-protein, high-carbohydrate diet and, following the addition of ketone supplementation (max dose of 3g/kg/day), he rapidly improved clinically. His EF increased to 45% and the elevated metabolites on ACP and UOA decreased. Complications including emesis, electrolyte abnormalities, and nephrocalcinosis resulted from the high calcium content in the high doses of ketone supplementation necessitating decreasing his dose; there was a corresponding decrease in EF to 32%.

Conclusion: The patient's biochemical phenotype and presentation are consistent with MADD type II which is associated with fatal hypertrophic cardiomyopathy. His biochemical phenotypes and EF quickly responded to high dose ketone supplementation. Ongoing work to optimize his ketone supplementation without causing electrolyte derangements and to identify the underlying molecular cause of this MADD clinical and biochemical phenotype is in progress.

<https://doi.org/10.1016/j.gim.2022.01.067>