‘Eyes that look and the Eyes that see’ -common neurological manifestations with uncommon inherited metabolic disorders.

Dr. Abinaya Seenivasan[1], Dr. Nandakumar Nambiyappan[2]

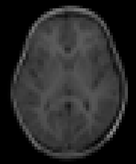
1. Neurology GRID Trainee, Royal Manchester Children's Hospital, UK 2. Consultant Paediatrician, Nambiyappan Hospitals, India

OBJECTIVES Neurologic manifestations often masquerade underlying inherited metabolic conditions. We highlight four children with common neurological presentation who had rare underlying inherited metabolic disorders in a single center in one year.

Case 1 Neonatal Seizures: 31-week preterm born to consanguineous parents with multiple previous abortions and preterm deaths presented with refractory seizures and hypotonia. Genetics showed (second Asian child with) novel nonsense homozygous variant in the ***ALDH4A1 gene*** causing **Type 2 hyperprolinemia (1)**

Case 2 Floppy infant: 4-month girl born to non-consanguineous parents presented with hypotonia, extensor posturing poor feeding and metabolic acidosis. Genetics showed (first Asian child with) homozygous missense variation of the ***RRM2B gene*** causing **mitochondrial DNA deletion syndrome (2)**.

Case 3 Developmental Delay: 1-year girl born to non-consanguineous parents presented with developmental delay, peripheral hypotonia and feeding difficulty. Genetics showed ***POMK+ mutation*** causing **limb girdle muscle dystroglycanopathy**, so far reported in two patients (3).



Case 4 Epilepsy: 11-year boy born to consanguineous parents with normal development presented with recurrent seizures followed by vomiting. Genetics showed ***heterozygous PCCA mutation*** (unlike common homozygous mutation) causing **propionic acidemia (4)**.

Conclusion: All children had hypotonia as a common feature with non-neurological clues. Whole genome sequencing in suspected children can be resourceful and reveal rare diseases in resource limited settings.

References: (1) Kaur R, Paria P, Saini AG, Suthar R, Bhatia V, Attri SV. Metabolic epilepsy in hyperprolinemia type II due to a novel nonsense ALDH4A1 gene variant. Metabolic Brain Disease. 2021 Aug;36(6):1413-7. (2) Bornstein B, Area E, Flanigan KM, Ganesh J, Jayakar P, Swoboda KJ, Coku J, Naini A, Shanske S, Tanji K, Hirano M. Mitochondrial DNA depletion syndrome due to mutations in the RRM2B gene. Neuromuscular Disorders. 2008 Jun 1;18(6):453-9. (3) Johnson K, Bertoli M, Phillips L, Töpf A, Van den Bergh P, Vissing J, Witting N, Nafissi S, Jamal-Omidi S, Łusakowska A, Kostera-Pruszczyk A. Detection of variants in dystroglycanopathy-associated genes through the application of targeted whole-exome sequencing analysis to a large cohort of patients with unexplained limb-girdle muscle weakness. Skeletal muscle. 2018 Dec;8:1-2. (4) Wang H, Meng L, Li W, Du J, Tan Y, Gong F, Lu G, Lin G, Zhang Q. Combinations of exonic deletions and rare mutations lead to misdiagnosis of propionic acidemia. Clinica Chimica Acta. 2020 Mar 1;502:153-8.