The Combined Neurogenetic Disorders; Blended Phenotype of Metachromatic Leukodystrophy (MLD) and Glutaric Aciduria Type 1 (GA -1) in an Indian Child

Dear Editor,

The introduction of next-generation sequencing (NGS) has revolutionized the field of genetics. NGS involves the sequencing of multiple genes at a faster speed and can identify millions of sequence changes. Multilocus pathogenic variants (MPV) are a form of mutational burden where two or more Mendelian disorders can occur in the same patient. The clinical features in patients with MPVs can occur in concurrence or can occur sequentially over time. NGS has helped patients with MPV phenotype.[1,2] Consanguinity plays an important role in the development of MPVs.[3] Glutaric aciduria type-1 (GA-1) is caused by mutations in the *GCDH* gene which encodes the enzyme Glutaryl CoA dehydrogenase. The GA-1 usually presents in the infancy with features of dystonia and macrocephaly.[4] Metachromatic leukodystrophy (MLD) is caused by mutations in the *ARSA* gene which encodes arylsulfatase A. The disorder is classified based on the age of presentation into late-infantile, juvenile, and adult forms.[5] We present an Indian boy with a dual diagnosis of GA-1 and MLD.

A 21-month-old male child born to a consanguineous marriage, with uneventful birth history, presented with developmental delay along with regression of attained milestones post a diarrheal illness at the age of 18 months. Prior to onset of regression, developmentally, in the gross motor domain, the child attained neck control at 4 months, sitting with support at around 8 months, and standing with support at 16 months. In the fine motor domain, attained uni-dexterous approach by 9 months and bi-dexterous approach by 13 months. Social milestones, recognition of mother by 8 months, waving bye-bye by 17 months, used to point at objects and understand emotions and speak bisyllables by 16 months followed by 1–2 words with meaning. Following diarrheal illness at the age of 18 months, acute regression of motor milestones in the form of no neck control and not reaching toward objects were noted. He later recovered partially, and at presentation had neck control,

and sits when made to sit along with an immature pincer grasp. On examination, the child had right eye esotropia and mild facial dysmorphism. Anthropometry showed a head circumference of 47 cm (0 to -1 SD), a weight of 8.85 kg (-2 to -3 SD), and a length of 83 cm (0 to -1 SD). The child was conscious but irritable with cranial nerve examination revealed right eye esotropia, nonparalytic with brisk gag reflex. Motor system examination was suggestive of generalized wasting with spasticity (lower limbs more than upper limbs) and dystonia (open mouth with tongue thrusting movements), power of 3+/5 to 3-/5 across the joints along with sluggish deep tendon reflexes, and extensor plantar bilaterally.

Investigations revealed normal complete blood counts; arterial blood gas showed a pH: 7.366, pCO2: 32.4 (normal: 35–45 mmHg), $HCO3^-$: 18.1 (22–28 mEq/L), and base deficit of –6.3 mmol/L suggesting compensated metabolic acidosis. Serum ammonia 32.8 (normal: 13–56 µmol/L) and lactate-17.03 (normal: 4.5–19.8 mg/dL) were normal. MRI of the brain showing hyperintensities in bilateral cerebral deep white matter and periventricular white matter regions with hyperintensities noted in the bilateral putamen. [Figure 1a]. Prominent extra ventricular CSF spaces were noted in bilateral sylvian fissures and frontotemporal regions [Figure 1b and c] hemorrhage was seen in the left frontal sub-calvarial region [Figure 1c]. T2 FLAIR symmetrical hyperintensities in periventricular, deep white matter giving the Tigroid appearance [Figure 1d]. Tandem mass spectrometry revealed low free carnitine (C0: 4.82: Normal: 9.00–69.00), acetyl carnitine (C2: 1.43: 2.00–63.00) with elevated glutaryl carnitine (C5-DH: 0.82: 0.00–0.38) suggestive of glutaric aciduria type-1. Serum arylsulfatase A levels were low- 0.07 (normal 0.6–5.0 nmol/h/mg/protein). Motor nerve conduction studies showed prolonged distal latency and reduced conduction velocity with normal compound muscle action potential amplitude in the bilateral posterior tibial and common peroneal nerves. Sensory conduction studies showed reduced conduction velocity in the bilateral sural nerves with normal distal latency and sensory nerve action potential amplitude. Above features are suggestive of sensory motor demyelinating neuropathy of bilateral lower limbs. The whole exome sequencing showed homozygous pathogenic variants in both GCDH and *ARSA* genes. *GCDH*: NM_000159.4: c.532G>A, p.(Gly178Arg) in exon 7 and *ARSA*: NM_000487.6: c.413C>T, p.(Pro138Leu) in exon 2, thus giving us a dual diagnosis in a single patient. Sanger sequencing showed homozygous status in the child and heterozygous status in both parents for both genes [Figure 2a to f]. The child is currently put on a standard

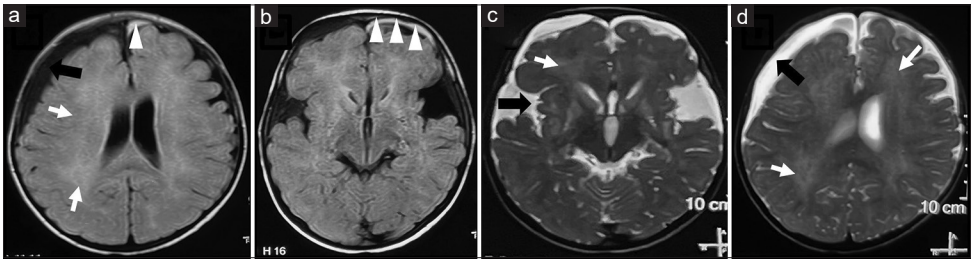

Figure 1: MRI of brain with axial fluid attenuated inversion recovery (a and b) and T2 Weighted (c and d) images showing hyperintensities in bilateral cerebral deep white matter and periventricular white matter regions (thin white arrows). Hyperintensities noted in the bilateral putamen (1c). Prominent extra ventricular CSF spaces noted in bilateral sylvian fissures and fronto-temporal regions (thick black arrows). Mild subdural haemorrhage seen in left frontal subcalvarial region (white arrow heads)

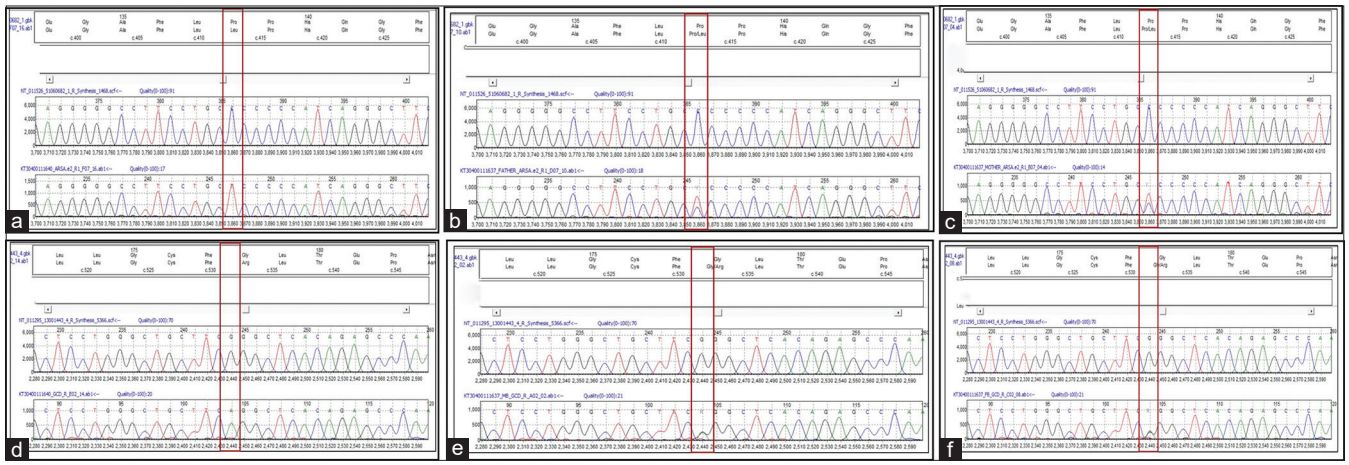

Figure 2: Sanger sequencing-Electropherogram showing nucleotide change at c. 413C > T, p.(Pro138Leu) in *ARSA* gene in the child (a), mother (b), father (c) c. 532G > A, p.(Gly178Arg) in *GCDH* gene in the child (d), mother (e), father (f)

diet for GA type-1 along with carnitine, and riboflavin supplementation.

Here we present an Indian child with features of neuroregression, spasticity, and dystonia with sluggish deep tendon reflexes with neuroimaging findings of wide and prominent Sylvian fissure, basal ganglia lesion, and periventricular white matter signal changes, and tigroid appearance. The clinical differentials considered in the current case were ***glutaric aciduria type-1 and other organic acidemias. The unusual features in the current case in addition to classic GA-1 were normal head size, sluggish deep tendon reflexes, and tigroid appearance on neuroimaging. Nerve conduction studies showed demyelinating motor polyneuropathy involving all limbs.

Seventy-five percent of cases have macrocephaly which forms an important diagnostic clue that was absent in the current case.[6] Many genetically confirmed cases may not have this feature. Tigroid appearance on the MRI of the brain is described in a case of GA-1.[7] This feature is classically described in MLD and Pelizaeus Merzbacher disease.[8] The feature of absent deep tendon reflexes and demyelinating neuropathy has not been reported in GA-1. Hence a second etiology was looked for. Exome sequencing helped us in identifying the *ARSA* variant and correlated with biochemically low Arylsulfatase A levels.

The *GCDH* variant c.532G>A, results in the amino acid substitution p.Gly178Arg and has a minor allele frequency of 0.00001 in gnomAD exomes and genomes. The *ARSA* variant c.413C>T results in the amino acid substitution p.Pro138Leu. According to ACMG, both the variants are classified as likely pathogenic.

Treatment becomes very challenging as GA-1 is a manageable disorder if treatment is started early with a lysine-free tryptophan-restricted diet and additional supplementation of carnitine and riboflavin, whereas MLD requires hematopoietic stem cell therapy. Detailed clinical examination and analysis of laboratory investigations are helpful in differentiating whether there is a phenotypic expansion of one disease or multiple disorders causing blended phenotypes.

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Conflicts of interest

There are no conflicts of interest.

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