A RARE CASE OF INHERITED METABOLIC DISORDER CAUSING MACROCEPHALY-
GLUTARIC ACIDURIA TYPE 1
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ABSTRACT

BACKGROUND
Glutaric aciduria type 1 is an inborn error of metabolism characterised by deficiency or defect of mitochondrial DNA-mediated enzyme, glutaryl-coenzyme A dehydrogenase. Deficiency of glutaryl-coenzyme A dehydrogenase leads to accumulation of glutaric acid in brain which affects operculisation during foetal brain development. Central nervous system is affected early because of its high energy demand. It causes macrocephaly despite significant brain atrophy and has characteristic imaging findings which helps in its diagnosis. It can be treated with suitable dietary supplementation and amino acid restriction, thereby necessitating its early detection. We are presenting a case of Glutaric Aciduria Type 1 in a male child who presented with macrocephaly and movement abnormalities.

KEYWORDS
Glutaric Aciduria Type 1, Mitochondrial DNA-mediated Enzyme, Macrocephaly.

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BACKGROUND
Glutaric aciduria Type 1 is an autosomal recessive Inborn Metabolic Brain Disorder caused by deficiency or abnormality of the mitochondrial enzyme Glutaryl-coenzyme A dehydrogenase. Glutaryl-coenzyme A dehydrogenase is required for metabolism of amino acids like lysine, hydroxylysine and tryptophan. Its deficiency or abnormality leads to accumulation of amino acid intermediate breakdown products like glutaric acid, glutaryl-CoA, 3-hydroxyglutaric acid and glutaconic acid in brain and other organs. These metabolites are potent neurotoxic which preferentially involve of basal ganglia and white matter with relative preservation of thalami. The characteristic appearance of brain in MRI along with macrocephaly helps in identification of this disorder.

CASE: A 7-month-old male child of third degree consanguineously married couple was brought to our hospital complaining of seizure, abnormal body movements and decreased milestone since 4 months. There was no history of fever, jaundice or head trauma. Antenatal and birth history was normal. On general physical examination, there was macrocephaly and decreased motor milestones. There was no pallor, jaundice, neck rigidity. Central nervous system examination showed choreoathetoid and myoclonic jerks. Routine blood investigations were within normal limits. MRI brain was done to look for any abnormalities as patient presented with abnormal movements. T1 and T2 weighted images showed macrocrania, bilateral open Sylvian fissures with increased extra-axial fluid collection (Figure 1-4)). Brain parenchyma including subcortical white matter and basal ganglia appears atrophied with dilatation of ventricles (Figure 4). Flair image shows increased signal in periventricular white matter. Based on these characteristic findings diagnosis of glutaric aciduria type 1 was made and was confirmed by urinary organic acid analysis by gas chromatography which showed increased concentration of glutaric acid and 3-hydroxyglutarate in urine.

Figure 1: Axial T2 Weighted Image showing increased Extraaxial Space in Bilateral Anterior Temporal Region with Traversing Vessels
DISCUSSION

Glutaric acidurias are metabolic disorders resulting in an increased urinary excretion of glutaric acid caused by deficiency of metabolising enzymes. Glutaric acidurias are classified as type 1, 2 and 3 depending on the specific enzymatic defects. In glutaric aciduria type 1, there is a deficiency in the Flavin adenine dinucleotide dependent glutaryl-coenzyme A dehydrogenase which is required for the metabolism of amino acids like lysine, hydroxylysine and tryptophan. Glutaric aciduria type 2 results from a defect in the mitochondrial electron transport chain at coenzyme Q. Glutaric aciduria type 3 is possibly by peroxisomal glutaryl-CoA oxidase deficiency.¹

Glutaric aciduria type 1 is inherited as an autosomal recessive pattern with heterogeneous mutation at glutaryl-CoA dehydrogenase gene located in chromosome 19p13.2.² The deficiency of glutaryl-coenzyme A leads to an accumulation of glutaric acid and other amino acids in serum and tissues. As Glutaryl-coenzyme A is a mitochondrial enzyme, its deficiency adversely affects mitochondrial energy dependent organs like basal ganglia of the brain. Glutaric acid and 3-hydroxyglutaric acid can accumulate in the brain of affected infants even though their serum and urinary excretion of glutaric acid is low.³ Glutaric acid and 3-hydroxyglutaric acid then stimulate the NMDA-2b receptors in brain as they are structurally similar to an excitatory neurotransmitter glutamate. As the foetal brain consists of numerous NMDA-2b receptors, the damage begins in in-utero foetal brain.⁴,⁵,⁶,⁷ The repeated excitation of brain leads to neuronal damage in basal ganglia which may be precipitated during the time of sepsis or fever due to the production of cytokines and nitric oxide.³ The neuronal death is followed by lymphocytic infiltration and subsequent glial proliferation and atrophy. Abnormalities of the development of blood vessels or blood flow also contribute to striatal injury.⁸ Typical microscopic features include spongiform changes with neuronal loss, myelin splitting and vacuolation, and intramyelinic fluid accumulation.⁹

The majority of infants with glutaric aciduria type 1 are initially normal and usual age of presentation is 6 months to 2 years of life.⁴,¹⁰ Macrocephaly is a constant feature which may be absent at birth and later develops after 4th month. Acute striatal necrosis is usually triggered by febrile illness or immunisation causing neuroregression and dystonia. Seizures, mental retardation, and dysskinetic movements are also common mode of presentation. Patients may also develop Reye-like encephalopathy with ketoacidosis and vomiting. In infants presenting with hypoglycaemia with elevated urinary acids, glutaric aciduria type 1 should be suspected. Serum and urine metabolites may be completely normal between metabolic crises.⁹

MRI is the modality of choice for imaging glutaric aciduria type 1. The three characteristic findings seen are macrocrania, bilateral widened Sylvian fissures and bilateral symmetric basal ganglia lesions. The anomaly may range from a complete lack of operculation to visible widening of the Sylvian fissures. Complete lack of operculation is associated with gross hypoplasia of the temporal lobes with
CONCLUSION
Clinical presentation of Glutaric aciduria Type 1 varies depending upon degree of brain involvement and associated systemic illnesses. Accurate diagnosis is possible through imaging studies which shows characteristic findings which can be confirmed by biochemical test. Early institution of treatment through diet modification increases survival possibility and decrease of symptoms.

REFERENCES