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

Prafulla Kumar Dash[1], Sagar H. S[2]

[1]Assistant Professor, Department of Radio-diagnosis, Kalinga Institute of Medical Sciences, Bhubaneswar, Odisha, India.
[2]Junior Resident, Department of Radio-diagnosis, SCB Medical College, Cuttack, Odisha, India.

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.

HOW TO CITE THIS ARTICLE: Dash PK, Sagar HS. A rare case of inherited metabolic disorder causing macrocephaly-glutaric aciduria type 1. J. Evid. Based Med. Healthc. 2017; 4(25), 1498-1500. DOI: 10.18410/jebmh/2017/292

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 bought 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.

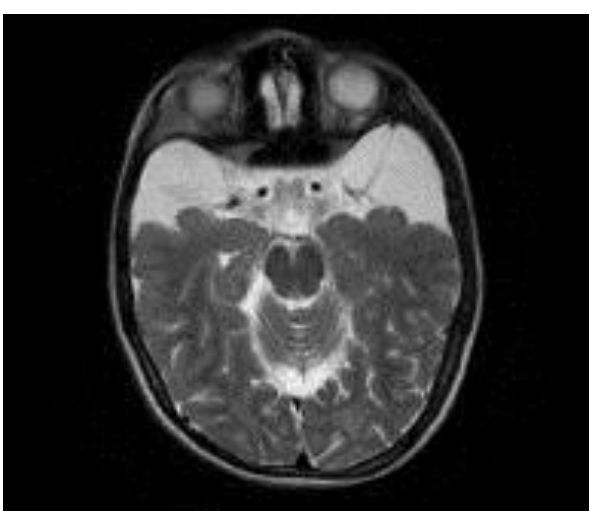

Figure 1 : Axial T2 Weighted Image showing increased Extraaxial Space in Bilateral Anterior Temporal Region with Traversing Vessels

Financial or Other, Competing Interest: None.
Submission 01-03-2017, Peer Review 07-03-2017,
Acceptance 20-03-2017, Published 27-03-2017.
Corresponding Author:
Dr. Prafulla Kumar Dash,
Assistant Professor, Department of Radio-diagnosis,
Kalinga Institute of Medical Sciences,
Bhubaneswar, Odisha, India.
E-mail: sagarhs98@gmail.com
DOI: 10.18410/jebmh/2017/292

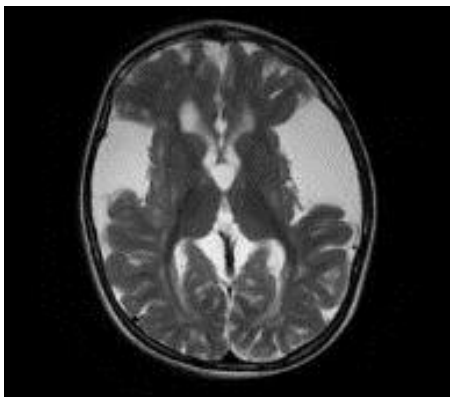

Figure 2 : Axial T2 Weighted Image at the level of Basal Ganglia showing open Sylvian Fissure

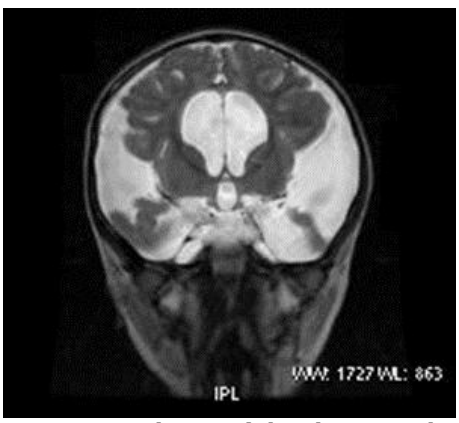

Figure 3: Coronal T2 Weighted Image showing Dilated Ventricles and Extra-axial Spaces

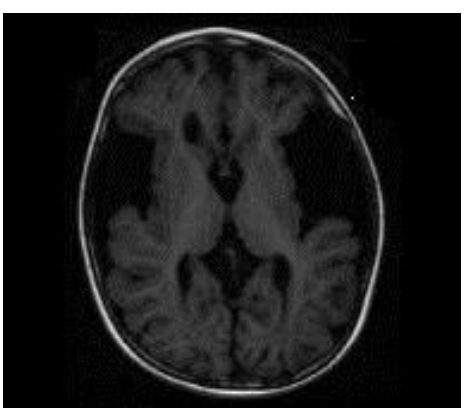

Figure 4: Axial T1 Weighted Image showing Atrophy of Grey and White Matter

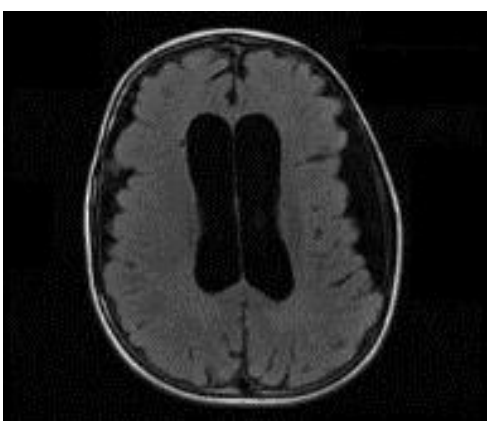

Figure 5: Axial T1 Weighted Image showing Dilated Ventricles

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 dyskinetic 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

huge CSF collection anterior to the temporal lobes in proportion to the prominence of other extracerebral CSF spaces. Operculation normally takes place during the last trimester of gestation, and the presence of this anomaly thus suggests that the toxic effects in glutaric acidaemia type 1 started already in utero. In severe cases, diffuse white matter abnormalities are also seen.[9]

During acute crisis infant brain shows increased signal intensity in symmetrically enlarged basal ganglia (putamen and caudate nuclei) in T2 weighted image with Diffusion restriction suggestive of cytotoxic oedema and disturbed oxidative metabolism. In chronic stage, due to neuronal loss and astrogliosis, there will be atrophy of brain with enlarged CSF spaces. The volume loss may tear bridging veins that cross the brain surface to the dura resulting in recurrent subdural haematomas.[9] The lesions do not enhance on contrast enhanced images. Magnetic Resonant Spectroscopy shows non-specific findings like elevated lactate peak due to impaired cerebral oxidative metabolism. Decline in NAA and Increased Choline to creatine ratio is also seen.

The diagnosis of GA-1 can be confirmed by the demonstration of urinary excretion of glutaric acid, 3-hydroxyglutaric acid, and glutaconic acid by tandem mass spectrometry (TMS).[5]

The differential diagnosis for the infants presenting with macrocephaly include hydrocephalus, benign enlargement of the subarachnoid space in infancy, benign familial macrocephaly, and other inherited metabolic disorders like mucopolysaccharidosis, Canavan disease, and Alexander disease. Hydrocephalus presents with signs of increased intracranial pressure effacement of sulci and extra-axial spaces. Benign enlargement of the subarachnoid space usually involves frontal lobe subarachnoid spaces with frontal bossing and these infants are neurologically normal. Mucopolysaccharidosis shows prominent perivascular spaces in posterior white matter and in corpus callosum and Canavan disease shows striking NAA peak in spectroscopy. The subdural haematoma which occurs in Glutaric aciduria type 1 due to tearing of bridging veins has to be differentiated from head injury. Absence of skull fracture and associated increased extra-axial space fluid collection in glutaric aciduria type 1 helps in excluding head injury as a cause for subdural haematoma.

The mainstay of treatment is diet modification with restriction of lysine and tryptophan. Dietary supplementation of riboflavin and L-carnitine is done as GCDH requires riboflavin as cofactor and patient will be having L-Carnitine deficiency which is normally synthesised in body from amino acid lysine. Acute crisis patients are managed with anticonvulsants.

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

[1] Knerr I, Zschocke J, Trautmann U, et al. Glutaric aciduria type III: a distinctive non-disease? Journal of Inherited Metabolic Diseases 2002;25(6):483-490.
[2] Goodman SI, Stein DE, Schlesinger S, et al. Glutaryl-CoA dehydrogenase mutations in glutaric acidemia (type I): review and report of thirty novel mutations. Hum Mutat 1998;12(3):141-144.
[3] Funk CB, Prasad AN, Frosk P, et al. Neuropathological, biochemical and molecular findings in a glutaric acidemia type 1 cohort. Brain 2005;128(Pt 4):711-722.
[4] Hoffmann GF, Zschocke J. Glutaric aciduria type I: from clinical, biochemical and molecular diversity to successful therapy. J Inher Metab Dis 1999;22(4):381-391.
[5] Hoffmann GF, Trefz FK, Barth PG, et al. Glutaryl-coenzyme a dehydrogenase deficiency: a distinct encephalopathy. Pediatrics 1991;88(6):1194-1203.
[6] Ullrichy K, Flott-Rahmel B, Schluff P, et al. Glutaric aciduria type I: pathomechanisms of neuro-degeneration. J Inherit Metab Dis 1999;22(4):392-403.
[7] Kolker S, Ahlemeyer B, Krieglstein J, et al. 3-hydroxyglutaric acid and glutaric acids are neurotoxic through NMDA receptors in vitro. J Inher Metab Dis 1999;22(3):259-262.
[8] Muhlhausen C, Ergun S, Strauss KA, et al. Vascular dysfunction as an additional pathomechanism in glutaric aciduria type I. J Inherit Metab Dis 2004a;27(6):829-834.
[9] Osborne AG. Glutaric aciduria type 1. Inherited metabolic disorders. Osborns's brain imaging, pathology and anatomy. Salt Lake, UT: Amirsys 1st edn. 2012:897-898.
[10] Poge AP, Autschbach F, Korall H, et al. Early clinical manifestation of glutaric aciduria type I and nephrotic syndrome during the first months of life. Acta Paediatrica, International Journal of Paediatrics 1997;86(10):1144-1147.