Glutaricaciduria Type II unmasked by neem oil poisoning

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Abstract

A 3 month old male infant presented with intractable seizures following administration of neem oil. Seizures were refractory in nature with features of raised intracranial tension and was managed with thiopentone, mechanical ventilation, midazolam infusion and mannitol. Investigations revealed REYE's syndrome like picture and diffuse cerebral oedema with frontal cortical atrophy in CT brain. Subsequently the child had presented with loss of gained milestone(social smile) and nonattainment of further developmental milestones, persistent hypotonia and myoclonic seizures on follow up at 5th month of life. Inview of myoclonic seizures, hypotonia and developmental regression with parental consanguinity, inborn error of metabolism was suspected. On evaluation, child was found to have significantly elevated levels of 2-hydroxyglutarate, succinate & adipate on Gas chromatography mass spectrometry (GCMS) which was suggestive of gutaric aciduria type II.

Key words: neem oil poisoning, glutaric aciduria.

Introduction

Glutaric aciduria type II is an inherited disorder that interferes with the body's ability to break down proteins and fats to produce energy. Incompletely processed proteins and fats can build up in the body and cause metabolic acidosis. It usually appears in infancy or early childhood as a sudden episode called a metabolic crisis which can be life-threatening, may be triggered by common childhood illnesses or other stresses. It is a very rare disorder, precise incidence being unknown. Mutations in any of three genes, ETFA, ETFB, and ETFDH, can result in glutaric aciduria type II.

Case Report

A 3 month old male infant was brought with history of administration of neem oil ~20 ml orally for cold and cough, following which the baby had severe bouts of cough and choking and brought to the hospital with status epilepticus. Seizure was refractory in nature associated with raised intracranial tension and was managed with thiopentone, mechanical ventilation, midazolam infusion and mannitol. The child also had shock refractory to fluid boluses and was managed with dopamine infusion. Capillary blood glucose was <60 mg/dl which was corrected with 25% dextrose 2ml/kg followed by glucose infusion of 6 mg/kg/min. Ca^{2+} (ionized) was 0.77mmol/lit, Sodium – 147 mmol/lit, Potassium – 3.2mmol/lit, SGOT-115 U/L SGPT – 85 U/L Alkaline Phosphatase – 222 U/L and ABG showed metabolic acidosis. He was extubated after 12 hrs. In the next 48 hrs child was having few brief subtle seizures & was hemodyanamically stable.From the fourth day onwards he was absolutely seizure free, conscious and alert and metabolic parameters normalized. He was started on nasogastric tube feeds and by tenth day of hospitalization he started sucking well and taking direct breast feeds and was discharged on maintenance dose of phenytoin.

On follow up after 2 weeks he was able to recognize mother but muscle tone was reduced and social smile was absent. Follow up after one month (5th month of life) revealed persistence of hypotonia, no head control and nonattainment of any further developmental milestones. Initially the neurological sequelae were attributed to possible hypoxic encephalopathy secondary to refractory seizures. But at 5 months of age, when the child came with recurrence of seizures, myoclonic in type associated with persistent hypotonia, feeding difficulty and hearing deficit, possibility of inborn error of metabolism was considered as CT brain (figure 1) showed a bat wing shaped

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frontal cortical atrophy. Seizures were controlled with sodium valproate and Clonazepam and child was put on early stimulation and occupational therapy. Urine chromatography as a part of metabolic

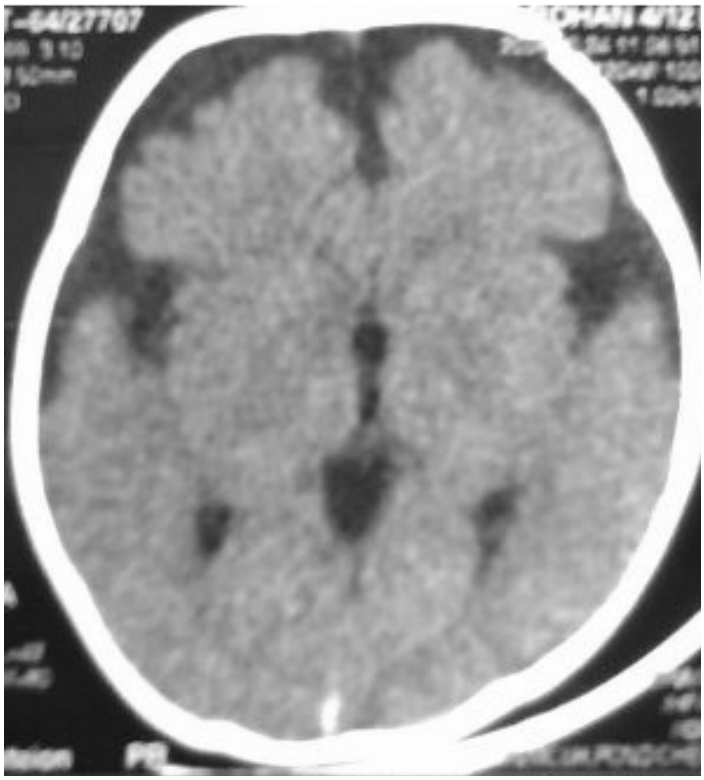

Figure 1: CT brain showing bat wing shaped frontal cortical atrophy

Metabolite	Patient's value	Referrence value
Succinate	6.94	< 0.186
Malate	0.45	< 0.131
Adipate	4.07	< 0.325
Glutamate	0.08	< 0.015
2 hydroxyglutarate	**26.79**	**< 0.473**

Table 1: Urine GCMS result

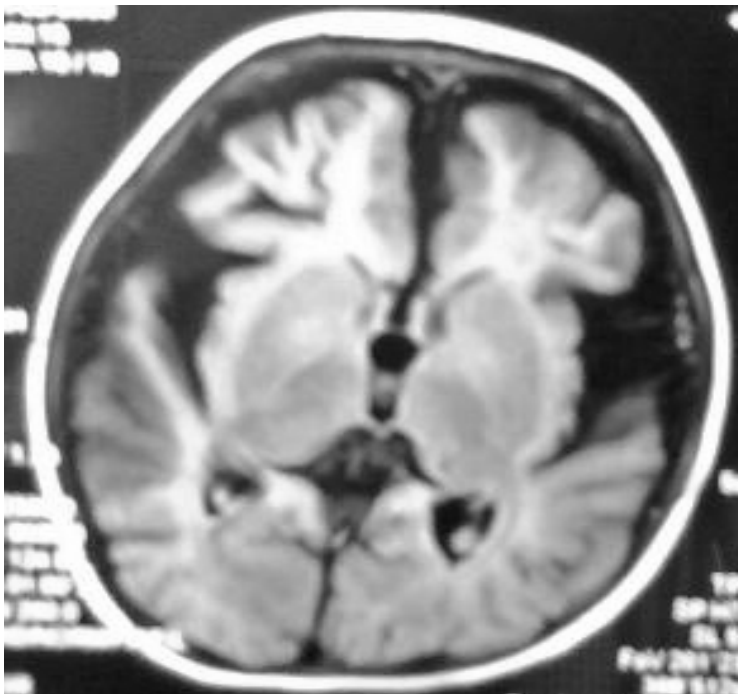

Figure 2: T1 weighted MRI in the same patient showing prominent subarachnoid spaces in frontal, temporal and bilateral sylvian fissure regions

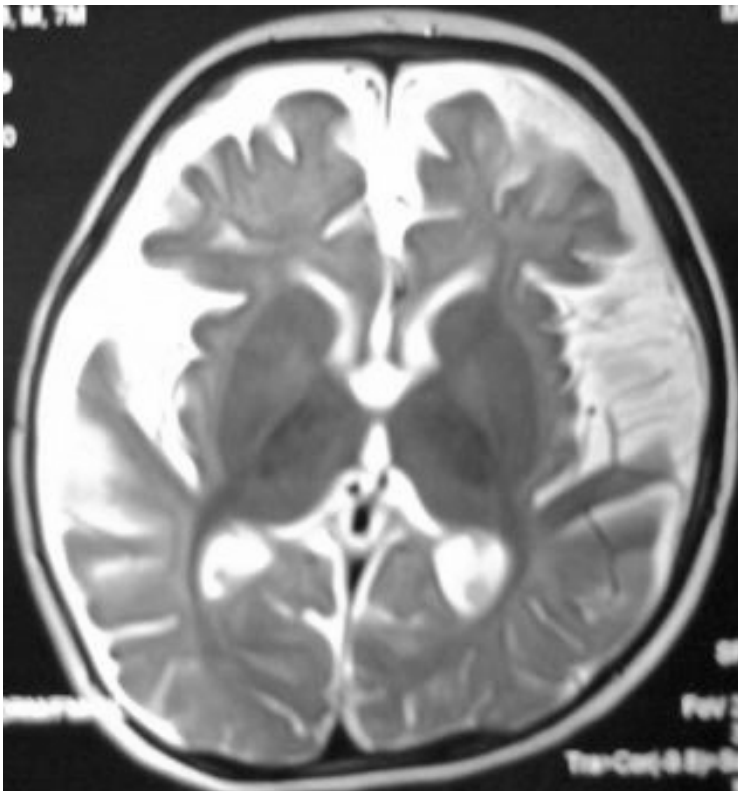

Figure 3: T2 weighted MRI in the same patient

screening revealed non specific aminoaciduria. Urine GCMS report was consistent with glutaric aciduria type II (**Table 1).**

MRI**(Figure2,3)** showed enlarged subarachnoid spaces in both frontal and temporal region & interhemispherical fissure & bilateral sylvian cisterns. There was no evidence of abnormal myelination, hemorrhage, mass lesion, arteriovenous malformation or demyelination.Thalamus, basal ganglia, internal capsule were normal. EEG showed polyspike pattern. Thyroid function test was normal. Neurologist's opinion was obtained and a diagnosis of Glutaric Aciduria Type II was made & the child was put on Carnitine and Riboflavin supplementation along with sodium valproate and protein restricted high calorie diet. BERA done at 1 Yr showed bilateral moderate sensory neural deafness hence was put on hearing aids and speech therapy started. Vision was normal and ophthalmological evaluation revealed a normal anterior chamber, lens and retina. At 1yr of age the child was still not able to sit without support, no social smile & voluntary grasp and child is only cooing & babbling & also developed choreo-athetoid movements involving the upper limbs. At Present the Child is 15 months old and his tone has improved, child is able to sit without support and able to roll over but still neither having voluntary grasp nor speaking bi-syllables.

Discussion

Neem oil a fatty acid rich extract from neem seeds, often administered in infants in Indian subcontinent as a remedy for common cold or to promote good health, has been reported to produce toxic effects in infants. Toxic encephalopathy mimicking REYE's syndrome have been reported after neem oil poisoning.[1,2,3,4,5] Neem oil is shown to induce mitochondrial permeability transition by opening of a high-conductance, cyclosporin-sensitive pore in the mitochondrial inner membrane, causing swelling, depolarization and uncoupling of oxidative phosphorylation.[6] It is also shown to decrease intra mitochondrial levels of acetyl-CoA & acid soluble CoA esters and reduce the mitochondrial ATP content. Of the cases reported majority of survivors have recovered without sequelae but a few of them have been reported to have long term neurological sequelae in the form of developmental delay, hypotonia, feeding difficulty, choreoathetosis and ataxia[4], but none of them had abnormal CT or MRI Brain findings.

Glutaric aciduria type II is a very rare inborn error of metabolism and is inherited in an autosomal recessive pattern[7]. It usually appears in infancy or early childhood as a sudden episodic event referred to as a metabolic crisis, in which metabolic acidosis and hypoglycemia cause weakness, behavior changes such as poor feeding and decreased activity, and vomiting. Hyperammonemia and elevated serum transaminases are demonstrated. The biochemical profile in urine is generally diagnostic, with accumulation of 2-hydroxyglutaric, glutaric, adipic, ethylmalonic acid and so on. The metabolic crisis, which can be life-threatening, is usually triggered by common childhood illnesses or other stresses.Mutations in any of three genes, ETFA, ETFB, and ETFDH can result in glutaric aciduria type II. The ETFA and ETFB genes provide instructions for producing an enzyme called electron transfer flavoprotein. The ETFDH gene provides instructions for making another enzyme called electron transfer flavoprotein dehydrogenase. Glutaric aciduria type II is caused by a deficiency in either of these two enzymes, normally active in the mitochondria, which are the energy-producing centers of cells resulting in impaired fatty acid oxidation and impaired oxidation of several of the amino acids such as leucine and lysine[8]. When one of the enzymes is defective or missing, partially broken down nutrients accumulate in the cells and damage them, causing the signs and symptoms of glutaric aciduria type II. Children with mutations that result in a complete loss of either enzyme produced from the ETFA, ETFB or ETFDH genes are likely to experience the most severe symptoms. Mutations that allow the enzyme to retain some activity may result in milder forms of the disorder.In the most severe cases affected individuals may also be born with physical abnormalities. These may include facial dysmorphism,brain malformations, hepatomegaly, dilated cardiomyopathy, polycystic kidney and other kidney

malformations. Muscle tone abnormality may show either hypotonia or hypertonia with seizures. Some cases present in early childhood with progressive spastic ataxia. Glutaric aciduria type II may also cause a characteristic odor resembling that of sweaty feet. CT and MRI Brain shows macrocephaly, dilated lateral ventricles, cerebral cortical atrophy of the frontal and temporal lobe and rarely atrophy of supratentorial white matter mimicking leukodystrophy. Treatment includes carnitine, high dose of riboflavin (cofactor for ETF, ETFDH and acyl-CoA dehydrogenases) [9] and a protein restricted diet.Glutaric aciemia can now be identified by expanded newborn screening by tandem mass spectrometry[10].

In this particular case, at initial presentation we had a provisional diagnosis of neem oil induced toxic encephalopathy because the onset of status epilepticus was within 30 minutes of neem oil ingestion with the clinical picture being suggestive of Reye like illness and apparently neurologically normal child at presentation. But the possibility of underlying neurological problem could not have been ruled out as the initial CT brain also had shown typical "Bat-Wing" shaped frontal cortical atrophy with prominence of bilateral sylvian fissures. Also on follow-up after 2 months the child had neurological sequelae and after 5 months had a metabolic workup suggestive of glutaric aciduria type II. Hence the neuro-metabolic crisis of glutaric aciduria type II was possibly precipitated by the stress induced by neem oil intoxication which also acts on mitochondrial oxidative phosphorylation.

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References

1. Sinniah D, Baskaran G. Margosa oil poisoning as a cause of Reye's syndrome, Lancet1981; 1(8218):487-92.
2. Sundarvalli N., Raju BB, Krishnamoorthy KA. Neem oil poisoning, Indian J Pediatr 1982; 49(398): 357-359
3. Lai SM, Lim KW, Cheng HK. Margosa oil poisoning as a cause of toxic encephalopathy. Singapore Med J 1990; 31:463-5.
4. Dhongade RK, Kavade SG, Damle RS. Neem oil Poisoning.Indian Pediatr 2008; 45(1):-56-57
5. Ranganathan SS, Fernandopulle R, Abeywardena DSVP, Hathlahawatta HMKN, Gunathilaka KR. Kohomba oil induced Encephalopathy. Srilanka Journal of Child Health 2005; 34(3): 94-5.
6. Trost LC, Lemasters JJ. Mitochondrial permeability transition: a new pathophysiological mechanism for Reye's syndrome and toxic liver injury. J Pharmacol Exp Ther.1996; 278(3):1000-5.
7. Pryzrembel H, Wendel U, Becker K, Bremer HJ, Bruinvis L, Ketting D, Wadman SK. Glutaric aciduria type II: report on a previously undescribed metabolic disorder. Clin Chim Acta 1976; 66(2):227-39
8. Loer JP,Goodman SI., Frerman FE. Glutaric acidemia type II: heterogeneity of clinical and biochemical phenotypes. Pediatr Res1990 27(3):311-5.
9. Mooy PD, Przyrembel H, Giesberts MAH, Schilte HR, Blom W, vanGelderen HH – Glutaric aciduria type II treatment with Riboflavin, Carnitine and Insulin. Eur J Pediatr 1984; 143:92-95.
10. Angle B, Burton BK.Risk of sudden death and life threatening events in patients with glutaric acidemia type II.Mol Genet Metab 2008; 93(1):36-9.