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case report of glutaric aciduria type 1

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Abstract : Inborn errors of metabolism are a heterogenous group of disorders which present with developmental delay or regression, episodes of lethargy, poor feeding, vomiting and seizures. Majority of the conditions are inherited as autosomal recessive trait(1). Therefore history of consanguinity in the parents or an unexplained death in the neonatal period may raise the question of an inherited metabolic disease in the sick infant. Glutaric aciduria type 1 is an organic academia presenting with developmental arrest or regression, extrapyramidal disorder in infancy(2). Macrocephaly is a common finding in these infants(1,2). It is one of the differential diagnosis for extrapyramidal cerebral palsy. Early diagnosis and aggressive may prevent striatal necrosis and ensures a favourable prognosis(2).

Keyword : Glutaric aciduria, extrapyramidal cerebral palsy, striatal necrosis

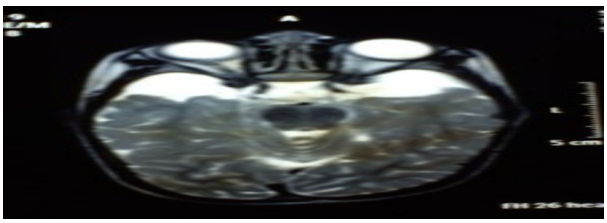
INTRODUCTION Glutaricaciduria type 1 is an organic academia, also known as glutarylcoA dehydrogenase deficiency.It is an autosomal recessive condition caused by deficiency of glutarylcoA dehydrogenase activity. The reported prevalence is 1 in 100000 population(1). It presents as a movement disorder with choreoathetosis, dystonia and opisthotonus in infancy(2).

CASE HISTORY One and a half year old female child, 5th child of third degree consanguineous parents, born by a full term normal delivery and there was no history perinatal asphyxia or neonatal jaundice. The child presented with fever, lethargy, refusal of feeds. There was no history of seizures. Child was normal upto 4 months of age. Child had a similar episode of illness at 4 months of age following which did not attain any further milestones and has lost head control also. History of 2 similar such episodesat 7th month and 1 year of life and they were managed as sepsis and respiratory infections in a nearby hospital. Her 4 elder siblings with similar history has died at 1-2 years of age without diagnosis. On examination, the child was lethargic, febrile, dehydrated. There was pallor, but had no respiratory distress. There was no dysmorphicfacies or neurocutaneous markers. Macrocephaly was present. Central nervous system examination revealed increased tone in all 4 limbs with brisk deep tendon reflexes along with choreiform movements involving all four limbs with upper limbs being more involved than lower limbs. Child also had choreiform movementsof tongue and dystonic posturing.

Cardiovascular and respiratory system examination were normal. Ther was no organomegaly.

In view of the current clinical picture with past history of repeated sepsis like illnesses and positive family history, a diagnosis of inborn errors of metabolism was thought of. Complete blood count and peripheral smear revealed a microcytic, hypochromic anemia. Septic work up like CRP was negative and blood culture showed no growth.Metabolic parameters including serum bicarbonate, ammonia and lactate were normal. Urine screening tests were negative. Ophthal examination did not show any abnormality. CSF examination was unremarkable. CT brain showed bilateral frontotemporal atrophy.

MRI brain showed atrophy of both frontal and temporal lobes with typical bat wing appearance.



MRI Brain-Bat wing appearance

Tandem mass spectrometry revealed 6 fold elevation ofglutaric acid and low carnitine levels. Urine organic acid profile confirmed marked elevation of glutaric acid in the urine. Child was treated with haloperidol, clonazepam,trihexyphenidyl for the movement disorder. Folic acid, riboflavin and carnitine supplementation was given. Nutritional advice regarding restriction of lysine and tryptophan was given. Now the patient is 3 and a half years old and currently isfree from episodic illnesses , some

improvement in choreiform movements has been observed. But the child has not regained the lost milestones.

DISSCUSSION

GLUTARIC ACIDURIA TYPE 1 Glutaricaciduria type 1 is an organic academia, also known as glutarylcoA dehydrogenase deficiency. It is an autosomal recessive condition caused by deficiency of glutarylcoA dehydrogenase activity. The reported prevalence is 1 in 100000 population. Chromosomeinvolvedis 19p13(1).

It presents as a movement disorder with choreoathetosis, dystonia, opisthotonus in infancy(2). Glutarylcoa dehydrogenase is the key enzyme in degradation pathway for lysine, hydroxylysine, tryptophan. Deficiency of the enzyme leads to accumulation of glutarate and to a lesser extent of 3 OH glutarate and glutaconate in body tissues, blood, csf and urine.Increased glutarate and 3 OH glutarate levels induce an imbalance in glutamatergic and GABAergic neurotransmission by

inhibiting glutamate decarboxylase, key enzyme in GABA synthesis or through direct damage to striatal GABAergic neurons. 3OH glutarate mimic excitatory neurotrasmitter glutamate and thereby cause excitotoxic cell damage mediated through activation of NMDA receptors.Irreversible focal striatal necrosis can occur after an acute illness(2). CLINICAL FEATURES: Characterised by macrocephaly, hypotonia evolving to rigidity and dystonia, opisthotonus, choreoathetosis, developmental regression and seizures(1,2). The symptoms may occur suddenly in a seemingly normal infant after a minor infection. Recovery from the first attack usually occurs slowly, but some residual neurologic abnormalities, especially dystonia and extrapyramidal symptoms may persist(1,2). Additional acute episodes resembling the first one usually occur during an intercurrent infection. In other patients, these signs and symptoms may develop gradually in the first few years of life and hypotonia and choreoathetosis may gradually progress into rigidity and dystonia. The intellectual abilities usually remain relatively normal in most patients(2,3). LABORATORY FINDINGS: Metabolic acidosis, hypoglycemia, hyperammonemia usually do not occur, but may occur in some cases during acute episodes(1,2). CT Brain shows early fronto temporal atrophy manifested by enlarged pre temporal subarachnoid spaces with the sylvian fissures often showing bat wing configuration(5). MRI Brain shows symmetric widening of sylvian fissure with poor operculization(BAT WING APPEARANCE) caused by frontotemporal atrophy or hypoplasia.Basal ganglia injury, subdural effusions, ventriculomegaly and delayed myelination can be seen(2). Tandem mass spectrometry will reveal high levels of glutaric acid and low carnitinebecause glutaric acid, like other organic acids is detoxified by carnitine and causes secondary carnitine deficiency(2,4). Urine organic acid analysis will show highly elevated glutarate and lesser elevation of 3OH glutarate and glutaconate(2,4). Some children with a classic phenotype have low or undetectable levels of these metabolites, so called low excretors. Low excretors will be mised in tandem mass spectrometry(2). PRENATAL DIAG NOSIS Prenatal diagnosis is possible by detecting increased concentration of glutaric acid in amniotic fluid, assay of enzyme activity in amniocytes or chorionic villi samples or by identification of mutant gene(6).

TREATMENT

Treatment consists of restriction of lysine, hydroxylysine and tryptophan intake in the diet(1,2), total protein intake from 1.5-3g/kg/day, limited intake of natural protein(0.5-2g/kg/day) and supplementation with synthetic protein(0.5-2g/kg/day), fasting should be prevented, carnitine(50-100 mg/kg/24hr) and riboflavin (200-300 mg/24hr) supplementation, rapid intervention in times of intercurrent illness with intravenous glucose, fluids, intravenous carnitine to get rid of harmful substances and antibiotics(7), GABA analog like baclofen, and valproic acid, anticholinergic drugs like trihexyphenidyland botulinum toxin for generalised or focal dystonia and stereotactic pallidotomy in cases of disabling dystonia(2). Foods to be avoided or strictly inhibited include milk, cheese and other dairy products, meat and poultry, fish, eggs, dried beans, legumes and nuts(7).

PROGNOSIS

Early identification and aggressive management can prevent striatal necrosis and disabling dystonia but permanent neurologic damage occurs in approximately one third of patients (2).

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