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MAPLE SYRUP URINE DISEASE : UNCOMMON CAUSE OF ENCEPHALOPATHY

Pediatrics

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ABSTRACT

Maple syrup urine disorder, a rare disorder of inborn error of metabolism may present at anytime during lifetime depending on deficiency of branched chain ketoacid dehydrogenase complex. Classical presents in new born period with encephalopathy which may mimic sepsis , hypoxic injury or metabolic causes. Early diagnosis through newborn screening helps to diagnose MSUD. Prompt treatment may help to decrease severe neurological manifestations.

KEYWORDS

Maple syrup urine disease, encephalopathy , newborn screening

INTRODUCTION -

Maple syrup urine disease (MSUD) is an rare disorder of inborn error of metabolism with a worldwide incidence of one in 185,000 live births with a higher incidence in Menonmite community where incidence as high as 1 : 200 live births(1) . This amino acid disorder is transmitted in autosomal recessive manner. It is caused by defect in the branched chain alpha keto-acid dehydrogenase (BCKDH) complex which results in high level of respective branched amino acids (BCCAs) resulting in significant higher plasma level of leucine, isoleucine and valine (2).

MSUD varies in severity and the clinical spectrum according to deficiency of level of BCKDH complex.. Classical MSUD presents in neonatal period with maple syrup odor in cerumen and urine , irritability , poor feeding , intermittent apnea, opisthotonus bicycling movements. Early diagnosis by newborn screening and prompt management can prevent the severe form of central nervous system irreversible damage. Management mainly focus on BCCAs free formula feeds, hemofilteration and orthotopic liver transplant (4,5). We present an interesting case of MSUD with encephalopathy successfully managed by branch chain free formula feeds and continous veno-venous hemofiltertion.

Case summary -

Male baby born by an elective LSCS to primigravida mother of 25 yrs of age with blood group A positive. Antenatal history was uneventful. There was no history of consanguinity, abortions, previous neonatal deaths in family, no h/o intellectual disability, sudden death in family. Baby cried immediately after birth, apgar scores not known,. Baby was shifted to mother side & discharged on day - 3 of life. Umbilicus was shed off at 5th day.

Baby became symptomatic by day 9 in form of poor feeding, letharginess so was admitted in local hospital & found to have hypoglycemia. Baby was managed with IV fluids, then restarted on feeds & discharged on day 13 of life. But very next day baby again became lethargic with poor feeding so was referred to our hospital .

On admission day 14 of life baby was stuporous with poor reflexes and generalized hypotonia. There was no history of seizures, intermittent posturing with cyclying and fisting movements were noticed. There was no signs of respiratory distress. Baby was hemodynamically stable. Sepsis screen was negative. Blood culture and urine culture were sterile. CSF examination suggested proteins of 48 mg/dl and sugar of 65 mg/dl with 5 cells. CSF culture was sterile. Blood sugar levels were monitored. one value of 43 mg/dl was documented. Blood gas analysis was normal with normal lactate levels. Urine ketones were postive, urine for reducing substance was absent. Serum ammonia was raised (382 ug/dl). Serum electrolytes were normal. TSH was 2.42 uil/ml. Baby was initially kept on IV fluids then gradually feeds were started. In view of clinical presentation on 10th day and metabolic encephalopathy TMS and urine GCMS was sent. Serum homocystein was 6.5 umol/l. Bedside EEG was unremarkable during period of 30 mins.

Diagnosis could be made on 18th day of life on the basis of TMS/GCMS report which revealed very high levels of leucine /isoleucone of 2230 ummol/ l (normal reference range - 22.93- 383.93 u mol/l). Valine was normal (270 umol/l). Urine GCMS suggested raised metabolic products of branched amino acids (2 hydroxy- 3 methylvaleric acid -2,2 hydroxy iso caproic acid 2, 2 hydroxy-isovaleric acid-2, 2 keto iso caproic acid 1) to a significant levels.MRI brain showed abnormal symmetrical hyperintensity in T2/ flair sequences in bilateral frontal cortical-subcortical region, basal ganglia, thalmus, midbrain, pons, cerebral peduncle & deep cerebellum.

Baby was started on BCCAs formula feeds showed improvement so was discharged on day 24 life. Baby was readmittted after 1 day with similar complains of letharginess, So plasma quantification of amino acid was done which showed very high level of lecine - 2556 ummol/L.As plasma level of leucine was significantly higher baby was planned for continous veno- venous hemofiltertion as excess amount of leucine cannot be handled by body excretory systems like renal route.

Pediatric nephrology consultation was taken and baby was started on CVVH (continous veno-venous hemofilteration). Repeat leucine level was 550 at 6hrs, 380 at 21hrs and 270 30 hrs. After stopping CVVH. Ketonex feeds by tube was started & gradually increased to full feeds (ketonex+nan pro). Repeat leucine levels after reaching full feeds were 123 ummol/L. Composition of formula was titrated according to the levels of branched chain amino acids in consultation with the department of genetics and hospital dietician. isoleucine, valine, thiamine and carnitine supplementation started during hospital stay. Last documented branched chain amino acid levels are as follows – isoleucine of 82 umol/l, leucine of 2.4 umol/l and valine of 91 umol/l.

Clinical exome sequence suggested compound heterozygosity in BCKDHA gene on Exon 8 which according to American College of Metabolic and Genetics (ACMG) lies in likely pathogenic variant (c.110T>G).Gradually encephalopathy improved and showed improvement in neurological examination during hospital stay. So was discharged , on discharge baby had spontaneous eye opening, spontaneous movements of all limbs, cry-weak, pupil-normal size and reacting to light, mild hypotonia & neonatal reflexes - moro's incomplete with normal palmar grasp.

DISCUSSION -

MSUD has varied presentation according to deficiency level of

BCKDH. It can be classic, intermediate, intermittent and thiamine responsive. Classical MSUD presents in neonatal period (3). It has activity in whole body , mainly in skeletal muscle (60%), liver (9-13 %), brain and kidney. Increased level branched chain amino acids particularly leucine is very detremental for the growing brain. Markedly increased level of leucine called leucinosis is associated with risk of cerebral edema and death(4,5) .

Neurotoxicity is mainly attributed to a combination of increased level of branched chain amino acid / keto acid level and decreased level of other essential amino acids in brain, as well as neurotransmitter depletion (7). As classical form presents in newborn period it becomes crucial to pick up and diagnose as early as possible as possible by early newborn screening as starting BCCAs formula feeds beyond 10- 14 days are associated with poor neurological outcome (3). Thiamine has role in thiamine responsive type MSUD not in classical form .

Apart from this management relies of BCCAs free prepared formula which become very costly in poor resource country. In acute leucinosis continous veno venous hemofilteration found to be more effective than peritoneal dialysis as higher level cannot be self eliminated from body (8,9). Liver transplantation has also been reported as successful therapeutic options in MSUD (10). So, to summarise MSUD, although an unusual and rare cause of encephalopathy, neurological manifestation can be reversible if diagnosed and manged early.

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