HHH SYNDROME: A CASE REPORT AND REVIEW OF THE LITERATURE

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ABSTRACT

Hyperornithinemia-hyperammonemia-homocitrullinuria (HHH) syndrome is characterized by variable clinical presentation and age of onset [Neonatal onset (~12% of affected individuals)] Infants are normal for the first 24-48 hours followed by onset of symptoms related to hyperammonemia (poor feeding, vomiting, lethargy, low temperature, rapid breathing). Information on long-term outcome is limited. Infancy, childhood and adult presentation (~88%). Affected individuals may present with: Chronic neurocognitive deficits (including developmental delay, ataxia, spasticity, learning disabilities, cognitive deficits and/or unexplained seizures); acute encephalopathy secondary to hyperammonemic crisis precipitated by a variety of factors; and chronic liver dysfunction (unexplained elevation of liver transaminases with or without mild coagulopathy, with or without mild hyperammonemia and protein intolerance). Neurologic findings and cognitive abilities can continue to deteriorate despite early metabolic control that prevents hyperammonemia.

Keywords: HHH Syndrome, Neonatal,

CASE REPORT

A 1yr old female child presented with cough and cold for 12 days, Fever for 6 days, Convulsion (multiple episodes) for 1 day. Cough, which was productive mucoid and frothy, not blood tinged, not related to any posture nor there was any diurnal variation. Developed fever 6 days back which was high grade, continuous in nature, not associated with chills and rigor, was subsiding with medication. On the day of hospitalization developed convulsion multiple episodes, Generalized tonic clonic type of Seizures, each lasting for 3-5 minutes, followed by loss of consciousness for a brief period. She was admitted multiple times to the hospital due to convulsion occurring while onset of fever. Patient was symptom less till 3 months of age, developed convulsion lasting for 5-10 minutes within 24 hours of fever. Patient was admitted to the local hospital, no specific cause was found out, discharged with, calcium and phenobarbitol. Patient developed similar episodes of convulsions with fever multiple times. Admitted multiple times for such complains. Serum electrolytes, CSF studies and neuroimaging (MRI) of brain were normal. Patient was being treated with calcium, vit-D3 and valproic acid. Mother was an educated lady conceived at the age of 26 years, this was her 1st pregnancy, with no history of abortion. Regular ANC done. NO teratogenic drugs were taken by mother, she was having the complain of decreased fetal movement during 3rd trimester. Baby was delivered by LSCS. Cried immediately after birth. Was breast fed within 2 hours of delivery, Birth weight was 2.6 kg. Baby was exclusively breast fed for 6 months. Weaning was done at the age of 6 months with cerelac-1. Baby achieved social smile at the age of 3 months. Patient was not able to hold her neck nor was sitting with support nor having palmer grasp at the time of hospitalization. Patient had no social smile at present. Maternal uncle of the baby died at early infancy of undiagnosed disease. Grand mother is a diabetic and hypertensive patient No sibling death. There was no history of contact with tuberculosis. Immunization status of the baby is as per schedule. Patient received Phenobarbital at a dose of 5mg per kg from 3 month of age till 6 months of age. Then patient received Valproic acid at a dose of 20 mg per kg till date. Patient was with calcium, it D3 and Multivitamins supplement.

ON EXAMINATION

Baby was sick looking, lethargic. Febrile. R/R-46/min P/R-140/min, good volume. B/P-90/60 mmhg Weight-6.7 kg. H.C-40.5 cm, length-67 cm. Armspan-68 cm. US/LS-1.2/1 AF-closed, scalp and facial hygiene were good with no dismorphism. No pallor, no icterus, chest and abdomen were normal in contour. No clubbing. No cyanosis. No lymphadenopathy. CNS-child was lethargic. Not interested in surroundings. No neck holding. Cranial nerves were intact. Hypotonic .plantar flexors, DTR (knee, ankle, bicep, tricep) were diminished. Sensory and ANS were normal P/A-soft, distended, normal in contour, no visible abnormality .No tenderness. Liver palpated 5cm (span-12cm) and spleen 3cm below costal margin. Resp- b/l air entry good, trachea at center, b/l vesicular breath sound with no added sound CVS-apex beat at normal position, S1 ,S2 normally heard with no murmur.

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INVESTIGATIONS

Hb-9.6 g/dl. Her Blood counts, RFT were under normal range, Sepsis screen were negative, LFT was disarranged with aspartate aminotransferase 6428UI/L, alanine aminotransferase 4123UI/L. ABG-PH-7.43. Pco2-19 .Hco3-12.6. serum Na-139mmol/l . K+ -5.05mmol/lt .Ca++,1.31mmol/l. LFT was disarranged with aspartate aminotransferase 6428UI/L, alanine aminotransferase 4123UI/L. serum Na-139mmol/l. Hco3-12.6. K+ -5.05mmol/l . Ca++ -1.31mmol/l. Serum Ornithine-397.15 (ref <278). Sugar-62 mg/dl, protein-36mg/dl. MRI BRAIN-T2 hyper intense signal in bilateral thalami and lentiform nuclei.

**Fig-1:** The pictures of the investigation reports supporting diagnosis

**Fig-2:** The patient at sub conscious level due to acute episode of Hyperammonemia

Impression-HHH syndrome

DISCUSSION

Aetiology and Demographics:

HHH syndrome is caused by mutations in SLC25A15, the gene that encodes ORNT1 (mitochondrial ornithine transporter 1), which is involved in the urea cycle and the ornithine degradation pathway. The metabolic triad of persistent hyperornithinemia, episodic or postprandial hyperammonemia, and urinary excretion of homocitrulline...
establishes the diagnosis of HHH syndrome. These patients often present with the development of progressive problems in muscle control. They can also develop seizures and gradually lose mental function. Growth is abnormal and learning is affected. Common symptoms are seizures and muscle control problems. Patients that have symptoms beginning in adulthood have partial activity of the transporter (mild type of disorder). They typically self-select low protein diets without being aware they have the disease. Diagnosis is difficult since the levels of ornithine can appear normal on laboratory examination if the patient is on a protein restricted diet. The presence of hyperammonemia and homocitrullinuria are helpful in the diagnosis of this disorder.

**Differential Diagnoses:**
Many of the urea cycle disorders have similar symptoms because they affect the body in the same way. Therefore, descriptions of an individual disorder and the method used to diagnose the disorder may be similar or identical to descriptions of other urea cycle disorders. The diagnosis of a urea cycle disorder is based on clinical suspicion and biochemical and molecular genetic testing. A plasma ammonia concentration of 150 μmol/L or higher associated with a normal anion gap and a normal plasma glucose concentration is an indication for the presence of a UCD. Plasma quantitative amino acid analysis and measurement of urinary orotic acid can distinguish between the specific UCDs.

**Treatment and Prognosis:**
A protein-restricted diet with a rapid improvement of the patient's neurological conditions and normalization of liver function tests and blood ammonia. Early identification and treatment of these patients can be life-saving and can avoid liver transplantation. Ornithine and citrulin supplementation reduces ammonia levels in some patients used. Sodium benzoate and sodium phenyl acetate and sodium phenyl butyrate may reduce ammonia levels by providing an alternative pathway. Hyperammonemia crisis might be managed with short-term protein restriction and IV fluids containing large amounts of glucose followed by slow reintroduction of small amounts of protein. In our case we gave the patient protein restricted diet limiting to 6-8 grams total protein per day. MCT OIL was added in the diet to increase calorie intake. The anti convulsant was changed to fosphenytoin from Valparin which precipitates hyperammonemia episodes. we gave supplement of L-Ornithine in the diet at a dose of 500 mg/kg /day.

**Follow up Study:**
We followed up the Patient every 2 weeks interval. After 8 wks mother marked improvement in general condition of the baby. There was regaining of social smile and patient was able hold her neck. There was no intolerance to the food advice we had given, with no further convulsion. The weight and biochemical parameters that we observed after 8 weeks as follows-

<table>
<thead>
<tr>
<th>DATE</th>
<th>26.5.2014</th>
<th>22.7.2014</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight</td>
<td>6.7 kilograms</td>
<td>7.5 kilograms</td>
</tr>
<tr>
<td>Serum Ammonia</td>
<td>150(micro gram/dl)</td>
<td>56(micro gram/dl)</td>
</tr>
<tr>
<td>Serum-aspartate aminotransferase</td>
<td>6428 IU/litre</td>
<td>38.7 IU/litre</td>
</tr>
<tr>
<td>Serum-alanine aminotransferase</td>
<td>4123 IU/litre</td>
<td>27.7 IU/litre</td>
</tr>
</tbody>
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**Genetic Counseling:** HHH syndrome is inherited in an autosomal recessive manner. At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier. Carrier testing for at-risk family members and prenatal testing for pregnancies at increased risk are possible if the disease-causing mutations in the family have been identified. Of note, given the marked phenotypic variability that exists among individuals with the same SLC25A15 mutations it is possible that two affected sibs may have completely different clinical outcomes.

**AUTHORS’ CONTRIBUTIONS IN CASE REPORT:**
Dr Swarupa Panda: Conception and manuscript review and preparation,
Dr Jatin Kumar Majhi: literature search, data acquisition, design, drafting and preparation.

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