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Case Report

HHH Syndrome: A Case Report and Review of Literature

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ABSTRACT

HHH Syndrome is a rare autosomal recessive disorder of urea cycle. Diagnosis is done by variable clinical presentation and biochemical triad of hyperammonemia, hyperornithinemia and homocitrullinuria. We report a day 3 neonate presented with lethargy, poor feeding, hypotonia, diagnosed by plasma ammonia and amino acid analysis by mass spectrometry.

Key words: HHH Syndrome, Hyperammonemia, Hyperornithinemia, Homocitrullinuria.

INTRODUCTION

HHH syndrome represents a heterogeneous disease with high clinical variability, ranging from a mild form with learning difficulties and slight neurological involvement, to a more severe form with coma, lethargy, hepatic signs and seizures. Asides from the severe neonatal form, there is no evidence of a direct correlation between age of onset, which is variable, and disease severity. [1] As for other urea cycle disorders (UCDs), early diagnosis in infancy or childhood may improve the clinical outcome. We report a case of HHH syndrome in a neonate.

CASE REPORT

A day 3 male child (figure A) born out of non consanguineous marriage was admitted to NEWBORN Unit of SVPPGIP, Cuttack with complaints of lethargy and poor feeding. He was 2nd order, term, adequate for gestational age, born out of elective LSCS with no history of birth asphyxia and passed urine and meconium within 24 hours of life. Exclusive breast feeding was started on day 1 of life. Mother was a booked case received 2 doses of Tetanus toxoid and IFA tablets during antenatal period. No history of gestational diabetes, hypertension, fever with rash during antenatal period and no history of thyroid disease, fetotoxic medication or radiation exposure in mother. There was no history of premature rupture of membranes, prolonged labour, foul smelling liquor and antepartam haemorrhage. History of unexplained sibling death on day 1 of life. Child was clinically diagnosed as a case of Early Onset Sepsis with Shock. After admission patient developed recurrent apnoea not recovered by tactile stimulation, suctioning of airway or bag and mask ventilation (BMV) so the baby was intubated and ventilated in NICU on day 4 of life. Sepsis screening was negative and ABG revealed Respiratory Alkalosis. Apart from Mechanical Ventilation baby was treated with antibiotics and vasopressors. Baby was extubated on day 11 of life. The baby was again intubated on day 12 of life for apnea and lethargy. Plasma Ammonia

was elevated so to rule out metabolic disorder IEM Panel was sent. During the course of NICU stay the baby was repeatedly intubated and extubated 4 times for same reason and ultimately the baby died on day 28 of life.

On examination weight was 2.7 kg, length 49 cm, head circumference 31.5 cm. There was no dysmorphisms, hepatosplenomegaly and specific odour in urine.

Figure A.

S95 - CUTTACK LAB HOME VISIT
MANGAL BAGH, PRACHI AGENCIES, MAIN MKT
CUTTACK

Name	: B.O GAYATRI SAHOO			Collected	: 18/8/2014 9:54:00AM
				Received	: 18/8/2014 11:14:45AM
Lab No.	: 209593051	Age: 20 Days	Gender: Male	Reported	: 1/9/2016 6:34:07PM
A/c Status	: P	Ref By : Dr. SISHUBHABAN HOSPITAL		Report Status	: Final

Test Name	Results	Units	Bio. Ref. Interva
IMD PANEL, QUANTITATIVE , BLOOD *Amino Acids*Organic Acids* Fatty Acid oxidation disorders @ (Tandem Mass Spectrometry)			
AMINO ACIDS			
Alanine	280.00	µmol/L	<1270
Arginine	7.00	µmol/L	<132
Citrulline	15.00	µmol/L	<70
Glycine	437.00	µmol/L	<505
Leucine	188.00	µmol/L	<385
Methionine	18.20	µmol/L	<77
Ornithine	**354.00**	µmol/L	<278
Phenylalanine	80.40	µmol/L	<165
Tyrosine	69.51	µmol/L	<550
Valine	215.00	µmol/L	<306
Ornithine / Citrulline	**23.69**	µmol/L	<1.50
FREE CARNITINE (C0)	8.81	µmol/L	8 - 100
ACYLCARNITINES			
Acetylcarnitine (C2)	**3.83**	µmol/L	8 - 150
Propionylcarnitine (C3)	0.32	µmol/L	<6
Butyrylcarnitine (C4)	0.15	µmol/L	<2
Isovalerylcarnitine (C5)	0.15	µmol/L	<1.70
Glutarylcarnitine (C5DC)	0.21	µmol/L	<0.84
C5OH	0.11	µmol/L	<0.68
Hexanoylcarnitine (C6)	0.08	µmol/L	<0.72
Octanoylcarnitine (C8)	0.44	µmol/L	<0.51
Decanoylcarnitine (C10)	0.23	µmol/L	<0.40
Lauroylcarnitine (C12)	0.07	µmol/L	<0.94
Myristoylcarnitine (C14)	0.11	µmol/L	<0.70
Palmitoylcarnitine (C16)	0.83	µmol/L	<12.50
Octadecanoylcarnitine (C18)	**0.42**	µmol/L	0.60 - 3.50

Impression
Raised Ornithine & Ornithine /Citrulline ratio indicates Hyperornithinemia-Hyperammonemia Homocitrullinuria (HHH) Syndrome. This is an Aminoacid disorder which can manifest in neonates, childhood or in late adulthood. Affected individuals have Hyperammonemia and Homocitrullinuria after feeding. Lethargy, vomiting, coma, mental retardation, progressive weakness , spasm in legs, seizures and learning difficulties may occur. Protein restricted diet and supplimentation with ornithine is recommended.

Page 1 of 3

Figure B.

Investigation revealed Hb-14.1 gm/dl, TLC- 12700 mm^3, Lymphocyte-11%, Neutrophil-84%, CRP-2.4 mg/dl, serum sodium-140 meq/dl, potassium-4.6 meq/dl, calcium-1.08 meq/dl, serum urea-32.8 mg/dl, creatinine-0.5 mg/dl, serum bilirubin total-14.53 mg/dl, direct-0.49 mg/dl, and Blood culture revealed no growth. CSF study revealed cell count nil, sugar 76 mg/dl, protein 27 mg/dl, gram stain negative and culture revealed no growth. ABG: PH-7.46, Pco2-22, Hco3-14. Metabolic workup revealed plasma ammonia-152 ug/dl (normal value-27-90 ug/dl), urinary reducing sugar and ketone body were negative.

Blood amino acid analysis (µmol/L) by tandem mass spectrometry (Figure B):
Ornithine: 354.0 (<278)
Ornithine/Citruline: 23.69 (<1.50)

DISCUSSION

In 1969, Shih et al. described a 3 years-old boy with cognitive impairment and myoclonic seizures, in whom intermittent hyperammonemia was associated with abnormal high plasma ornithine levels and homocitrullinuria. [2]

These authors coined the name "hyperornithinemia hyperammonemia-homocitrullinuria (HHH) syndrome".

HHH Syndrome is a rare genetic disorder of urea cycle caused by mutations in the SLC25A15 or ORNT1 gene which encodes for the mitochondrial ornithine carrier ORC1. [1]

In this rare autosomal recessive disorder, the defect is in the transport of ornithine from cytosol into mitochondria, resulting in accumulation of ornithine in the cytosol and deficiency of this amino acid in mitochondria. The former causes hyperornithinemia and the latter results in disruption of urea cycle and hyperammonemia. Homocitrulline is formed from the reaction of mitochondrial carbamyl phosphate with lysine which may give rise to. [3]

Age at onset, type and severity of the symptoms in HHH syndrome are highly variable. Clinical symptoms usually start from early infancy, including the neonatal period, to childhood and, more rarely, in adulthood. 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 longterm 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. [4]

The metabolic triad of hyperammonemia, hyperornithinemia, and urinary excretion of homocitrulline establishes the diagnosis of HHH syndrome. HHH syndrome is characterized by a lower degree of hyperammonemia if compared with other UCDs [1] and plasma ammonia level usually normalizes in response to pharmacological treatment. Homocitrullinuria is a hallmark of the disease, however some patients may show absent or only minimal excretion of homocitrulline in urine. [5] Similarly to other UCDs, [1] plasma glutamine concentrations and urinary orotic acid may be elevated.

Acute treatment is similar to other UCDs. [1] Rapid control of hyperammonemic episodes done by discontinuation of protein intake, intravenous infusion of glucose and, as needed, infusion of supplemental arginine or citrulline and the ammonia removal drugs, sodium benzoate and sodium phenylacetate. [4] Long-term treatment is based on a low-protein diet supplemented with citrulline or arginine ornithine supplementation has been tried in the past with contradictory results in the attempt to correct ornithine depletion in the mitochondria, however its use is not recommended. [6] Protein restriction may be combined with sodium benzoate or sodium phenylbutyrate.

Prognosis is highly variable ranging from mild neurological involvement to a severely disabling disease. 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. [4]

CONCLUSION

HHH syndrome is a rare genetic disorder. The combination of variable clinical features and the biochemical triad of hyperammonemia, hyperornithinemia, and

urinary excretion of homocitrulline allow the diagnosis. In India due to poor resources the screening and diagnosis are rarely made. Metabolic disorders are not uncommon in India. A high index of suspicion is needed for early diagnosis and timely intervention to improve the outcome.

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