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Case Report

HHH SYNDROME- A RARE CAUSE FOR CHILDHOOD APHASIA- SINGLE CASE STUDY

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ABSTRACT

Hyperornithinemia-hyperammonemia-homocitrullinuria (HHH, MIM #238970) syndrome is a rare genetic disorder of the urea cycle (UC) caused by mutations in the SLC25A15 or ORNT1 gene (MIM*603861), which encodes for the mitochondrial ornithine carrier ORC1. 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. This paper presents the rare cause for childhood aphasia – HHH syndrome; its onset of the problem, severity during the course of treatment, various tests that enlighten the cause, learning/literacy difficulties, Pre and Post morbid history of the child, Speech and language diagnosis, cranial nerve examination and intervention in addressing the muscle weakness associated with spontaneous recovery and prognosis. This paper also reflects the awareness of this rare cause for childhood aphasia to improve the quality of life in an affected child.

Keywords: Hyperornithinemia-hyperammonemia-homocitrullinuria syndrome, childhood aphasia, cranial nerve examination, spontaneous recovery, awareness of the condition.

INTRODUCTION

Hyperornithinemia-hyperammonemia-homocitrullinuria (HHH, MIM #238970) syndrome is a rare genetic disorder of the urea cycle (UC) caused by mutations in the *SLC25A15* or *ORNT1* gene (MIM*603861), which encodes for the mitochondrial ornithine carrier ORC1. 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.

INCIDENCE AND PREVALENCE

Based on DNA analysis, we estimated that the heterozygote frequency for the mutant allele for HHH syndrome to be about 1 in 19 individuals, predicting one affected child with HHH syndrome for approximately every 1,500 individuals (1 in 1,550 live births; 1 child every 12 years) in this isolated population. The male to female ratio is unknown.

EPIDEMOLOGY

Since the original description, more than 100 patients with HHH syndrome have been reported. Overall, according to a recent survey based on newborn screening data on over 6 million births in United States (US) and data from two large US and European longitudinal registries, the incidence of all UCDs is estimated as 1:35.000 live births; however, figures reporting the incidence of HHH syndrome are still lacking. Based on the few available large series studies on UCDs, HHH syndrome accounts for 1% – 3,8% of all UCDs. On the basis of the available information in the literature for 97 out of 111 patients the male/female ratio is approximately 2:1. Data derived from the Neogene screening program (www.neogene sceening.com) suggest an incidence of citullinemia of 1/86,000. While prevalence is unknown as an overall incidence of 1/8200 for UCD has been estimated.

Onset can be divided into four different age periods: neonatal, first three years of life, childhood, and adolescence to adulthood. Neonatal onset accounts for about 12% of affected individuals. Usually, the prenatal and perinatal courses are uncomplicated. The neonatal-onset presentation is indistinguishable from that of other neonatal-onset urea cycle disorders: the infant is asymptomatic for the first 24-48 hours and, thereafter, has episodes of poor feeding, vomiting, lethargy, low temperature, and/or rapid breathing related to hyperammonemia. Little is known about the long-term outcome of individuals with the neonatal onset form of HHH syndrome: One child with neonatal-onset who had an initial plasma ammonia concentration of 317 µmol/L had normal growth, development, and neuroimaging studies at age 18 months. Follow-up brain imaging at age six was normal [Salvi et al 2001]. By age six years female twins who appeared to have had lethargy and coma during the neonatal period had developed pyramidal signs [Tessa et al 2009]. The twin with the higher plasma ammonia concentration (700 µmol/L) had seizures and significant intellectual disability, whereas the twin with the lower plasma concentration of ammonia (100 µmol/L) had only mild cognitive impairment. Two other neonatal-onset cases evaluated in their late teens had pyramidal signs of the lower limbs (hyperreflexia, clonus, tip-toe gait, and/or spastic ataxia) and moderate cortical atrophy on neuroimaging [Salvi et al 2001].

Infancy, childhood, and adult presentation account for approximately 88% of affected individuals. Onset at or before age three years occurs in about 40%, childhood onset in about 29%, and adolescent to adult onset in about 19% [Salvi et al 2001, Korman et al 2004, Fecarotta et al 2006, Al-Hassnan et al 2008, Debray et al 2008, Mhanni et al 2008, Tessa et al 2009, Tezcan et al 2011].Affected individuals in this group come to medical attention for findings related to a mild degree of hyperammonemia with or without liver dysfunction or for evaluation of developmental delay, intellectual

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disability, learning disabilities, recurring vomiting, school difficulties, ataxia, and/or seizure activity. Even when ammonia levels are normal, a history of protein intolerance or neurologic symptoms suggestive of hyperammonemia (periods of lethargy, nausea, vomiting, decreased appetite, headaches, changes in mood, or altered behavior) may sometimes be elicited during the initial evaluation of a patient. A college-educated male age 35 years with adult onset disease who had no history of learning disabilities, liver disease, psychiatric illness, or neurologic deficits was diagnosed with HHH syndrome after deviating from a vegetarian diet [Tezcan et al 2011]. Two previous accounts of sibs with adult-onset HHH syndrome attributed the mildness of the phenotype, in part, to adherence to a vegetarian diet [Tuchman et al 1990].

The cognitive development of persons with HHH syndrome ranges from normal to severe impairment, with the majority having mild neurocognitive impairment. In some reports persons with adolescent-onset and adult-onset disease have significant neurologic deficits such as spasticity and ataxia without cognitive impairment. Of note, pyramidal signs of the lower extremities (hyperreflexia, clonus, tip-toe gait, and/or spastic ataxia) may develop years after the initial diagnosis [Salvi et al 2001, Debray et al 2008]. Despite early detection and adequate metabolic control (i.e., absence of hyperammonemia), some individuals with HHH syndrome continue to worsen neurologically with progressive pyramidal tract disease and cognitive deterioration [Debray et al 2008]. In some individuals with early childhood onset, gait abnormalities and spasticity are the predominant findings.

Liver dysfunction, present in 20%-25% of affected individuals, generally manifests as mild coagulopathy and elevated liver enzymes (AST and ALT) with or without hyperammonemia. In a few reports acute liver failure prompted consideration of liver transplantation [Fecarotta et al 2006, Mhanni et al 2008]. However, the liver dysfunction that may occur during the initial clinical presentation does not appear to cause long-term complications. Once the hyperammonemia is treated with standard intravenous infusion of dextrose and arginine and protein intake is restricted, the liver dysfunction subsides [Korman et al 2004, Camacho et al 2006, Fecarotta et al 2006, Debray et al 2008, Mhanni et al 2008, Tessa et al 2009].

CLINICAL CHARACTERISTICS

Hyperornithinemia-hyperammonemia-homocitrullinuria (HHH) syndrome is characterized by variableclinical 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.

CASE STUDY

Background Information:

XXX, 9 years old male child came to the department of Speech and Language pathology with the complaint of not speaking age adequately since 03/06/2016. Birth history was not significant. The child was born to non- consanguineous parents with no significant family history of communication delay or any other Speech and Language problems

ONSET AND SEVERITY OF THE PROBLEM:

The onset of the problem was reported on 03/06/2016. The child was reported to have developmentally normal growth. The child had clinically presented with the symptoms of fever, vomiting, loose tools for 2 days and reported to have one episode of generalized tonic-clonic seizures lasting for more than 20 minutes. This results in poor GCS and hypotension and developed right sided hemi paresis with right UMN facial palsy. The child had been diagnosed as Status Epilepticus/ HHH Syndrome/ Right hemi paresis with right facial nerve palsy

TESTS THAT ENLIGHTEN THE CAUSE: (Histopathological report)

Initial MRI showed bilateral sub cortical edema, corpus callosum changes with (?) inflammatory etiology. Repeated MRI showed left cerebral hemisphere, anterior limb of internal capsule, carpus callosum and right fronto- temporo-parietal lobe diffusion restriction suggestive of encepahalitis. The metabolic triad of persistent hyperornithinemia, episodic or postprandial hyperammonemia, and urinary excretion of homocitrulline establishes the diagnosis of HHH syndrome.

LEARNING LITERACY DIFFICULTIES

PRE & POST MORBID HISTORY:

Pre morbid history reveals that the child is able to read, write and speak well on English language; able to speak on Tamil language. Post morbid history reveals that the child has difficulty to read, write and speak English language and able to speak Tamil Language.

SEECH AND LANGUAGE DIAGNOSIS:

On Speech and Language evaluation the child comprehends simple step verbal commands on repetitions and prompts, family members, and emotions, able to discriminate strangers from family members. The child expresses his needs predominantly in non-verbal mode and able to vocalize /a. and says /m/.

CRANIALNERVE EXAMINATION AND OPM EXAMINATION:

On examining the oral peripheral mechanism all the structures are normal and functions are restricted on his right side. Lip seal is present. Lips puckering and pursuing are inadequate. Lingual movements of elevation, protrusion and lateralization are restricted. Functions of soft palate are normal and velopharyngeal closure is adequate. Jaw movements are also restricted. The child has difficulty in maintaining intra-oral pressure. Vegetative skills of sucking, biting, chewing and swallowing are present but it is inadequate. Blowing skills are absent. Drooling is absent.

Cranial nerve examination reveals as follows:

CN I optic nerve		
CN II Olfactory nerve		
CN III Occulomotor nerve		
CN IV Trochlear		
CN V Trigeminal nerve	✓	the ability to chew
	✓	masseter & temporal muscle strength
	✓	Opening the jaw against resistance
	✓	pressure sensation
	✓	sensation of temperature
	✓	differentiate the sensation of touch
CN VI Abducens nerve		
CN VII Facial nerve	✓	Checking ability to whistle
	✓	facial symmetry at rest
	✓	facial symmetry during voluntary movements
	✓	Close both eyes
	✓	Ability to smile
	✓	frown their forehead
	✓	Show their teeth as saying eee
	✓	Puff out cheeks
	✓	strength by trying to apart tightly close eyelids
CN VIII Vestibular nerve		
CN IX Glosso pharyngeal nerve	✓	Elicitation of pharyngeal gag.
	✓	Asking the patient to say "ah
CN X Vagus nerve	✓	Laryngoscoping examination to check motor status of the larynx & pharynx
	✓	sensory status of the larynx & pharynx by stimulating the back of the throat on each side
	✓	motor status by asking the patient to say "ah"
	✓	Listen to the patient's voice
	✓	Ask patient to swallow
CN XI Spinal accessory nerve	✓	ability of patient to shrug shoulders by keeping your hand against the clients
	✓	ability of patient to turn the head towards one shoulder against resistance along with that watch palpate the sternomastoid muscle on the opposite side
	✓	ability of patient to put hand on head
	✓	, look for atrophy or asymmetry of the trapezius muscles
CN XII Hypoglossal nerve	✓	Testing of tongue strength by pushing patient's tongue tip against the clinician's finger resistance.
	✓	Checking of deviation of tongue upon protrusion
	✓	Observe the tongue as it lies in the mouth
	✓	Notice of atrophy/ tremor of tongue

INTERVENTION

MUSCLE WEEKNESS:

Oral exercises to facial nerve functioning

1. Massage the cheeks in circular motion both clockwise and anticlockwise for 20 times on each side
2. To and fro massage in upper part of the upper lip
3. Massage the lower part of the chin in upward and downward direction as in circular motion
4. Ask the client to say "ooo" with exaggerated lip movement. Then say "eee." Combine them for "oo-ee."
5. Ask the client to make a big smile and ask them to Relax and repeat the same
6. Prefer using straw for drinking rather than drinking from a cup.
7. Ask the client to Whistle by using whistling material
8. Upper lip stretch by keeping both your index finger on both the sides of their upper lip and stretch it gently and continue the same for lower lip. Repeat the same for 20 times Other exercises to be followed

Lip closure:

- Children should be able to close their lips when requested to do.
- Lip protrusion:
- Children should be able to push their lips forward as kissing.
- Lip retraction:
- Children should be able to pull their lips back as in a smiling
- Exercises for lips:

Lip Retraction

- Smile. Hold for 5 seconds.
- Relax and Repeat 5 times.

Lip Protrusion

- Pucker your lips as if you were going to give someone a kiss. Hold for 5 seconds. Relax and Repeat 5 times.

Lip Retraction and Protrusion

- Smile then pucker your lips. Use exaggerated movements. Relax and Repeat 5 times
- Lip Closure: Press lips tightly together for 5 seconds. Relax and Repeat 5 times.
- Lip press on tongue depresser. Tightly press lips around tongue depressor, while the clinician tries to remove it. Perform for 3 to 5 seconds. Relax and Repeat 5 times.

Puff Cheeks

- Fill cheeks with air, move air from one cheek to the other 5 to 10 times.
- No air should escape from around the lips or the nose.
- Relax and Repeat 5 times.

Crunch chew:

- Have the child to take small bite of a crunchy food. Ask the child to keep his closed as he chews, doing ten chews per bite for five bite

Humming:

- Have the child hum a favourite tune, make sure his lips stay closed through the song.

Brushing

- Objective: To increase tactile stimulation/awareness for the lips.
- Procedure: Brush lips with different textures (i.e. toothbrush, cotton swab, tongue depressor, spoon)

Whistle

- Objective: To increase lip strength.
- Procedure: Have child pucker lips and blow attempting to whistle.

Fish Mouth

- Objective: To increase oral-motor strength.
- Procedure: Pucker lips and suck cheeks in to make a "fish-face"

Pucker-Smile

- Objective: To increase oral-motor coordination.
- Procedure: have child close mouth with back teeth together. Have child pucker lips (while keeping back teeth together). Once mastered, have child alternate a pucker with a smile.

Sucking

- Objective: To increase lip strength.
- Procedure: Suck on banana, sucker, popsicle, etc.

Water Hold

- Objective: To increase lip strength.
- Procedure: Hold a small amount of warm water in mouth with cheeks puffed out.
- Objective: To increase lip strength.
- Procedure: Put a small cotton pad between the upper lip and upper gum and hold it there. Repeat with lower lip and lower gum.

Wide Mouth Grog Pulls

- Objective: To increase lip strength.
- Procedure: Gently pull on sides of mouth laterally while child tries to pucker.

Tactile Stimulation for Lips

- Objective: To increase tactile stimulation and awareness.
- Procedure: have child rub chapstick on lips and wash off while rubbing lips.

Tongue-Ins

- Objective: To increase lip strength.

Procedure: Open mouth wide and continuously move the tongue forward and backward toward the throat.

SPEECH AND LANGUAGE GOALS:

Goals have been focused on to improve his comprehension of simple verbal commands, lexical items, daily living activities, expression of family members and to improve hi oro- motor movements.

SPONTANEOUS RECOVERY:

Recovery is a theoretical construct that implies regaining lost or impaired functions following brain damage. Physiological mechanism includes 4 processes.

- ***Diaschisis :*** When the active areas are treated then the referred pain is reduced and the area with referred pain functions normally
- ***Regenerative sprouting:*** Branching of the axons and dendrites gives rise to new synapses from the affected spot leading to recovery of the functions
- ***Collateral sprouting:*** Neighboring nerve cells gives a branch to the affected nerve there by restoring the functions that are affected
- ***Relative ineffective synapsis:*** Newly formed synapses stimulate the inefficient synapses to function effectively

Structural/ anatomy mechanism involves

Redundancy:

- Extra or additional information makes the task easier
- There are two types of cues.
  - External redundancy
  - Internal redundancy

Multiple controls:

- Similar to redundancy
- Many structures control the same function
- When one area is affected, it can be taken over by other structures that are intact

Behavioral mechanism includes

Functional substitution:

- Restoration of the affected function

Plasticity:

- Occurs in children
- One hemisphere takes over the function of another hemisphere

Relearning:

- Learns compensatory strategies or relearns the affected function for communication and other tasks

Re-organization:

- When the particular function is affected reorganization occurs

Periods of recovery:

- Heilman & valenstein (1979) stated that Recovery continues at a maximal rate for up to 3months & then slows.
- Groher(1977) reported that Significant improvement in both language and memory functioning occur often within a 1 month period.
- Spontaneous recovery occur till 6-7 months (Luria1963)
- Spontaneous recovery occurs in first month itself (Culton(1969)
- Spontaneous recovery take place around 2-3 months (Kertesz & Mc cabe,1977)
- Spontaneous recovery of language in patients with aphasia between 4 and 34 weeks (W.Lenderm and N.B.Lincoln,1985)

Spontaneous recovery:

The standard doctrine about childhood aphasia claims that recovery of language function is rapid and complete. However, this claim is largely supported by the earlier literature and contradicted by more recent reports. there was less improvement in the abscess cases (1 out· of 3) and no improvement after thrombosis. Guttmann provided further evidence that recovery was related to an initial motor type of aphasia as well as by the size of the lesion and the fact that "aphasic signs were still present 4 weeks after onset". Additional information with respect to school achievements is not available.

Woods and Carey (1979) showed that left hemisphere lesions, if they caused initial aphasia, left significant residual impairment on most of the language tasks. A study of Vargha-Khadem *et al.,* (1985)

confirmed this finding. These authors concluded that in cases from age 5 onwards left hemisphere lesions the impairments were most marked. From their test data it appeared that this tendency was more evident with respect to naming rather than with respect to auditory comprehension deficits.

The study of Martins *et al.* (1981) in which 19 children, 3 years after the onset of the aphasia were assessed, showed that only 2 had recovered according to the results on standardized language tests. Goorhuis-Brouwer and Deelman (1983) presented a follow-up study of lO children over a period of 2 to 5 years. A complete recovery was observed only in 2 children. The optimistic view that recovery of aphasia in children would be rapid and complete, has not been confirmed in recent studies. Now, a number of unfavourable prognostic signs are known: aetiology, size of lesion, type of aphasia and age at onset.

PROGNOSIS

Vimalan is attending Speech and Language therapy since July, 2016. He is able to attend and concentrate to the verbal stimuli with the consistency of 70%. He is able to express *"Amma"* with the consistency of 55% with verbal and tactile prompts. He says *"Anna"* with 30% consistency only on prompts. He is able to comprehend simple verbal commands with the consistency of 80%. He is able to comprehend the semantic intentions of appearance, disappearance, existence, non-existence, rejection, location, very few basic actions and few objects. He is able to comprehend body parts of eyes, ears, nose, mouth, head, hands, legs and stomach with the consistency of 90%. He is able to comprehend lexical of fruits (Apple, Banana, mango, strawberry and papaya) with the consistency of 30; Animals (dog, cat, cow and elephant) with the consistency of 20%.He is able to comprehend Functional words of "*va, tha and po*" with the consistency of 95% and able to express "*/v/"* with the consistency of 30% on tactile prompts and "*/ɬ/"* with 20 % consistency only on verbal and tactile prompts. The child is able to say "hi" verbally and *"bye"* nonverbally with the consistency of 50%.Lips puckering and lips pursuing have been improved as the child is able to alternate /e/ and /u/. He is able to lateralize his tongue towards right side with 80% consistency on imitations. Elevation and protrusion of the lingual movements have been improved. He is able to maintain intra- oral pressure for 2-3 seconds. He has started chewing on his right side.

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