Clinica Chimica Acta 413 (2012) 1151–1155

Contents lists available at SciVerse ScienceDirect

Clinica Chimica Acta

journal homepage: www.elsevier.com/locate/clinchim

Long-term follow-up of four patients affected by HHH syndrome

Sook Z. Kim [a,*], Wung J. Song [a], William L. Nyhan [b], Can Ficicioglu [c,1], Roseann Mandell [c], Vivian E. Shih [c]

[a] Korea Genetic Research Center, Cheong Ju, Republic of Korea
[b] UCSD Biochemical Genetics Laboratory, La Jolla, CA, United States
[c] Massachusetts General Hospital, Boston, MA, United States

ARTICLE INFO

Article history:
Received 23 April 2011
Received in revised form 20 March 2012
Accepted 21 March 2012
Available online 23 March 2012

Keywords:
Hyperornithinemia
Hyperammonemia
Homocitrullinemia
HHH syndrome
Ornithine

ABSTRACT

Background: In hyperornithinemia–hyperammonemia–homocitrullinemia (HHH) syndrome, impaired ornithine transport across the mitochondrial membrane causes ornithine accumulation in cytoplasm. The resulting mitochondrial ornithine deficiency leads to reduced clearance of ammonia through the urea cycle. First described in 1969, no long-term follow-up has been reported.
Methods: Four patients were followed up for 11 to 38 y. Diagnosis was made by plasma amino acid analysis using ion exchange chromatography, HPLC orotic acid measurement, and ^{14}C-ornithine incorporation study using cultured fibroblasts. DNA from fibroblasts was amplified and sequenced. Blood ammonia was controlled by restriction of protein intake.
Results: All patients had reduced ^{14}C-ornithine incorporation. Mutation analysis revealed two novel mutations in the ORNT1 gene. Neurologic outcome included memory loss, low IQ, tremor, spasticity of extremities, bladder incontinence, and abnormal gait. Neuroimaging revealed subcortical, cerebral and cerebellar atrophy, sparing the basal ganglia. Individual examination showed pyramidal signs, cerebellar signs, paraplegia, movement disorder, dystonia, and epilepsy. One patient had 3 pregnancies, one of which resulted in intrauterine growth retardation.
Conclusions: Our patients expand the clinical phenotype of adults with HHH. Long-term follow-up showed serious neurologic outcomes in all patients; three patients clearly exhibited progression of neurologic dysfunction despite control of hyperammonemia. Intracellular ornithine deficiency may adversely affect brain functions.

1. Introduction

Ornithine is an amino acid and product of the hydrolysis of arginine in the urea cycle. It is metabolized in mitochondria via two pathways — ornithine–carbamoyl phosphate reaction catalyzed by ornithine transcarbamylase (OTC) in the urea cycle, and ornithine-α-ketoglutarate reaction catalyzed by ornithine aminotransferase (OAT) [Fig. 1].

Disorders of ornithine metabolism are associated with many different clinical manifestations. OTC deficient patients have normal plasma ornithine levels while those with hyperornithinemia or hyperornithinemia–hyperammonemia–homocitrullinemia (HHH) have increased concentrations of plasma ornithine. Hyperornithinemia with gyrate atrophy, where OAT is not present, produces a severe retinopathy leading to blindness. In HHH syndrome, the impairment of ornithine transport across the mitochondrial membrane results in accumulation of ornithine in the cytoplasm.

HHH syndrome is an autosomal recessive disorder characterized by reduced ammonia clearance through the urea cycle due to mitochondrial ornithine deficiency. The basic defect is at the level of the mitochondrial ornithine transporter (ORNT1/SLC25A15). The human ORNT1 gene has been mapped to chromosome 13q14. A number of different ORNT1 mutant alleles have been previously reported. The clinical phenotype of the syndrome comprises protein intolerance, episodic vomiting, growth failure, hepatomegaly, and neurologic manifestations — consciousness change, seizures, pyramidal tract signs, and a variable degree of cognitive impairment with or without behavior problems.

Since the first description of the syndrome in l969 [1], >50 patients have been reported. However, there has been no long-term follow-up study of the HHH syndrome. Here, we discuss some previously reported cases of affected adults and examine four adult patients, including the first reported case, who have been observed over many years. This follow-up provides the opportunity to survey the clinical history of the HHH syndrome. Two novel mutations were identified from the mutation analysis of the 4 patients from unrelated families.

* Corresponding author at: Korea Genetic Research Center, Chung Buk, Cheong Ju City, Heung Deok Gu, Woon Cheon Dong 965 361-841, Republic of Korea. Tel.: +82 43 263 8280; fax +82 43 215 8288.
E-mail address: kimgene@unitel.co.kr (S.Z. Kim).
[1] Current address: The Children's Hospital of Philadelphia, Philadelphia, PA.

0009-8981/$ – see front matter © 2012 Elsevier B.V. All rights reserved.
doi:10.1016/j.cca.2012.03.015

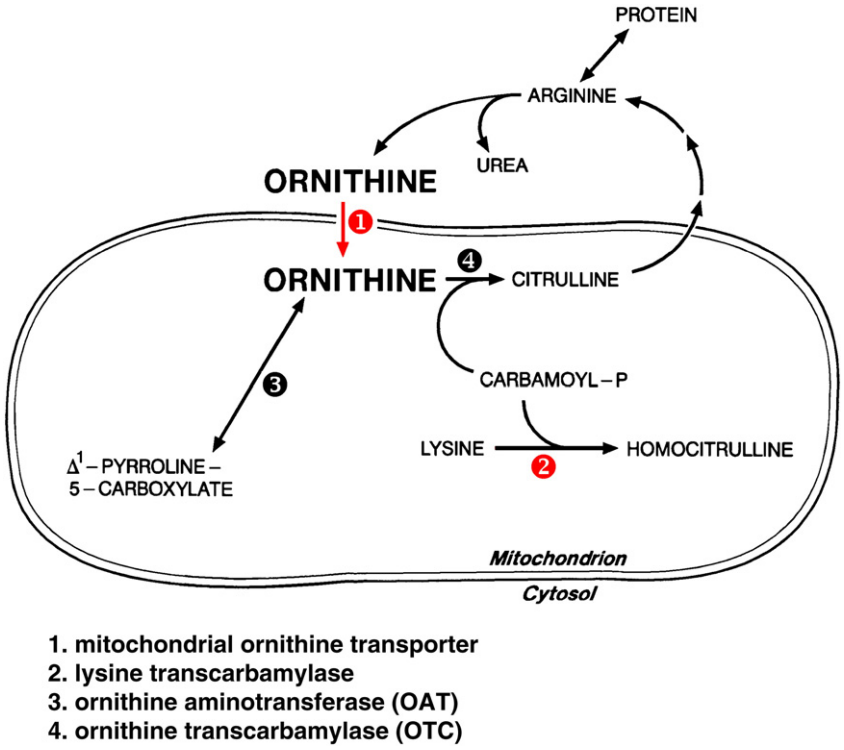

Fig. 1. Pathway. 1 Mitochondrial ornithine transporter. 2 Lysine transcarbamylase. 3 Ornithine aminotransferase (OAT). 4 Ornithine transcarbamylase (OTC).

2. Case reports

2.1. Case 1

A 43 y old man of French-Canadian and English background first presented at the age of 16 months with irritability, seizures, and developmental regression. As an infant, he failed to thrive and had dietary aversion to meat and other high protein foods. He had coarse tremor, head nodding, substantial developmental delay, and hepatomegaly. Upon protein loading, he became irritable and had a seizure. The diagnosis (HHH) was made when 17.5 months old, and he was treated with a diet that restricted protein intake to 1 g/kg/day [1].

The seizures were controlled sufficiently enough to discontinue anticonvulsants within 10 days, and he became more alert and less irritable. His protein tolerance to maintain normal ammonia ranged up to 1.5 g/kg body weight per day. At 4 y, his mental age was 2 y and 5–10 months. He exhibited behavior problems such as biting his sister. He had mild hand tremor, but maintained relatively good hand coordination. At 6 y, his intelligence was below average, scoring an IQ of 80 on the Stanford–Binet Intelligence Scale.

From the age of 8 y, he was started on dexedrine for hyperactivity. His short attention and hyperactivity persisted and medication was changed to Ritalin at 16 y. In his late teens, his hand tremor progressed to hand shaking on intention, interfering with holding objects especially in the morning. He had poor compliance with his low protein diet. His global IQ was 90. After he graduated from high school, he developed a walking problem because of spastic paresis involving particularly the lower extremities and associated with hyperreflexia, ankle clonus and positive Babinski signs. Psychometric testing at 24 y revealed a great difficulty in following verbal instructions, and his IQ ranged between 79 and 82 with preservation of auditory and visual function. He also experienced short term memory loss. In his 20s, his gait worsened; he became less mobile and frequently fell. He was not able to walk without support and had a plastic brace for his right foot. In addition to spastic diplegia, minimal loss of strength, and stiffened gait, he developed right upper extremity dystonic posturing. On the Wechsler memory scale (WAIS-R), he performed particularly poorly in the arithmetic and digital symbol tests, scoring 77. In his 30s, gait and posture further deteriorated, making it more difficult to walk up or down the stairs. Despite physical therapy, both legs were wasted, and there was persistent hyperreflexia and ankle clonus, increasing spasticity and evidence of proximal motor weakness, abnormal gait including circumduction and shuffling. He has since remained on a protein restricted diet, benzoate, and citrulline. His blood ammonia level averages 1.5 times the upper limit of normal. There has been no episode of metabolic crisis.

2.2. Case 2

A 57 y-old French-Canadian woman was first examined for what was thought to be a multiple sclerosis-like clinical problem. Her development was reportedly normal until the age of 2 y when seizures began. Subsequently, her development slowed, and as a result, she attended special classes. She began experiencing gait deterioration from 15 y. Additional testing showed high plasma ornithine and she was referred to Massachusetts General Hospital where diagnosis was made. At 26 y she had child-like conversation, clumsiness and spasticity, with jittery and jerky movements, and uncoordinated gait. She had multiple episodes of injury resulting from falling. From 39 y, she started having frequent drop attacks and progressively spastic and ataxic gait. Radiological study of her spine indicated degenerative changes. She became depressed and attempted suicide 3 times. By 45 y, she displayed general weakness and fatigue, slurred speech and incontinence of bladder and bowel. MRI of her spine showed degenerated disc disease of the cervical spine without any evidence of cord compression and a very small short syringomyelia of the thoracic cord. Brain MRI found cerebral atrophy with white matter hyperintensity and hyperdensity in the pons. She had a myelopathy, and cervical spine imaging revealed a non-expanding, non-enhancing intramedullary signal abnormality. There was EMG evidence of a mixed peripheral neuropathy affecting the lower extremities. She had to use a wheel chair as well as a walker. She