Title: Hyperornithinemia-Hyperammonemia-Homocitrullinuria Syndrome *GeneReview* – Outcomes and Presentation
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Neonatal (Birth to Age 1 Month) Diagnosis of HHHS – Outcomes

One child, 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 and cognitive development at age six years was normal [Salvi et al 2001].

Female twins, who appeared to have had lethargy and coma during the neonatal period, had developed pyramidal signs by age six years. 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 [Tessa et al 2009].

Two other children 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. One demonstrated severe intellectual disability whereas the other had normal intelligence [Salvi et al 2001].

A male age 23 years with normal intelligence developed progressive pyramidal signs leading to spastic paraparesis at age 20 years [Salvi et al 2001].

A premature (31 2/7 weeks gestation) boy weighing 1.385 kg had respiratory distress, and developed severe hyperammonemia (1,300 µmol/L) after being started on parenteral nutrition, as well as marked hepatic dysfunction and coagulopathy; he recovered with proper medical management [Wild et al 2019].

One child died after developing hyperammonemic coma (1,108 µmol/L) and another child died at age two months. The severe hepatic dysfunction in the former was attributed to the severe hyperammonemia [Shih et al 1992, Tessa et al 2009].

A boy age four weeks initially presented with hyperammonemic coma (2,300 µmol/L). Unable to control metabolic decompensations that had required repeated hospitalizations since age two years, he underwent a liver transplantation at age seven years. His metabolic, cognitive, and neurodevelopmental parameters normalized or improved [Martinelli et al 2015].

Infantile Presentation (Age >1 Month – 1 Year at Diagnosis)

A previously healthy girl age one year whose parents were first cousins was diagnosed with HHH syndrome and secondary fulminant hepatic failure following febrile seizures and pneumonia. She responded quickly to treatment and remained metabolically stable [Mhanni et al 2008].

A boy age six years diagnosed at age one year experienced progressive mild hepatic disease characteristic of untreated HHH syndrome. At age 1-2 months he had prolonged hyperbilirubinemia and hepatomegaly that progressed to mild hepatic dysfunction (elevated ALP, GGT then ALT) without hyperammonemia, followed at age 12 months by coagulopathy and mild hyperammonemia (132 µmol/L). His biochemical profile normalized quickly after protein restriction. At age six years he had maintained good metabolic control; he had subtle gait disturbances [Lee et al 2014].

Four infants underwent successive neuropsychological evaluations: three had gross motor delays; one had normal development (verbal IQ of 104 and performance IQ of 90) [Waisbren et al 2016].

Childhood Presentation (Age >1 Year to 12 Years at Diagnosis)

Two related families represent the type of slowly progressive and variable clinical phenotype [Camacho et al 2006]:

- The oldest of three affected brothers, who had normal growth, was initially evaluated for school difficulties; he had no history suggestive of hyperammonemic episodes. He had dysarthric speech and lower-extremity hyperreflexia. At age ten years, his full scale IQ was 55. He died at age 21 from complications of hyperammonemic crisis. At the time of the initial diagnosis of the older brother, the two younger brothers had normal ammonia levels; plasma ornithine ranged from 370-381 µM. At age three years the youngest affected brother had delayed motor and social skills.

- A boy age five years presented with liver dysfunction (coagulopathy and very high LFTs), hyperornithinemia (697 µM), and mild hyperammonemia (100 µmol/L) during an episode of gastroenteritis. He had learning disabilities but was in regular classes. At age seven years his full scale IQ was 88. His sister (age 13 years) had been asymptomatic all her life and had a full scale IQ of 78. She married and had an uneventful pregnancy.

In a longitudinal French-Canadian study, all 16 affected individuals (13 diagnosed in childhood) sharing the same *SLC25A15* pathogenic variants had virtually no overt hyperammonemic episodes, but demonstrated progressive pyramidal tract involvement, especially of the lower limbs. Variable motor findings included hyperreflexia, clonus, tip-toe gait, and spasticity. All affected individuals had cognitive deficiency (39% severe, 15% moderate, and 46% mild) [Debray et al 2008].

Adolescence/Adulthood (Age >12 Years at Onset) – Outcomes

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 2012].

A man age 39 years and his sister age 42 years diagnosed with HHH syndrome had normal cognitive function but experienced sporadic confusion/disorientation over many years. Hyperammonemia was present in the brother but not the sister during one occurrence. The episodic confusion ended after the start of therapy. The mildness of the phenotype was attributed, in part, to adherence to a vegetarian diet [Tuchman et al 1990].

A practicing physician age 76 years, who was thought to have seizures because he was falling asleep during his clinics, was started on valproate. He subsequently suffered approximately one episode of hyperammonemia (>400 µmol/L) per year. Eventually, at age 80, he was diagnosed with HHH syndrome based on suspicious biochemical findings (consistently elevated plasma ornithine but no homocitrullinuria) and confirmatory molecular testing. Past medical history revealed that he had avoided large protein meals all his life. The patient remained biochemically stable after his diagnosis [L Merritt, personal communication].

A previously healthy woman age 48 years, a lifelong vegetarian, was initially diagnosed as having OTC deficiency at age 27 years after a sudden loss of consciousness lasting two days. At age 40 years she was diagnosed with HHH syndrome based on biochemical and molecular studies. She is currently doing well on a low-protein diet, citrulline supplementation, and glycerol phenylbutyrate [E Font-Montgomery, personal communication].

A male age 48 years with a history of protein intolerance, dyslexia, cognitive difficulties, and recurrent seizures associated with vomiting and loss of consciousness in childhood was diagnosed with HHH syndrome 48 hours after he presented with overnight vomiting, headache, and backache quickly progressing to loss of consciousness in the ER. Severe upper GI hemorrhage triggered the symptoms that progressed to unconsciousness and irreversible long-term neurologic damage that includes aphasia, perception difficulties, and spastic paraparesis requiring a wheelchair for mobility. Of note, in search of an etiology, relatives used his symptoms on a search engine and the result suggested OTC deficiency. Subsequently, his physicians deemed his plasma ammonia at 213 µmol/L without hepatic failure diagnostic for a urea cycle disorder. The HHH metabolic triad was confirmed the next day [Silfverberg et al 2018].

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