Father-to-daughter transmission in two families with late-onset OTC deficiency

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INTRODUCTION

Orotine transcarbamylase deficiency (OTCD), the most common of Inherited Urea Cycle Disorders (UCDs) with an estimated incidence of 1:66,000-70,000, is caused by mutations in the OTCD gene, mapping on Xp11.4 and it is the only UCD inherited as an X-linked recessive trait. Therefore, all hemizygous males are usually affected, whereas the clinical presentation in females varies widely, with at least 20% of carrier women manifesting some degree of disease expression. In late onset forms, clinical presentation is widely variable, from individuals that remain asymptomatic for long periods of time, to a chronic clinical course with symptoms such as recurrent nausea and vomiting, selective feeding behavior with proteins aversion, migraine/headaches, behavioral or personality disturbances or an unexplained hyperammonemia, to intermittent episodes of hyperammonemia, characterized by either acute-onset neurological and psychiatric symptoms (ataxia and movement disorders, stroke-like episodes, psychosis, psychomotor agitation), or an overt encephalopathy with impaired consciousness, seizures and coma, triggered by intercurrent illnesses, dietary changes, assumption of certain drugs (e.g. valproate, aspirin), or catastrophic stressors, such as peripartum parturition, surgical procedures, or prolonged fasting. Although paternal inheritance of X-linked disorders is possible, the best to our knowledge, it has been reported only in 5 pedigrees, all within the Japanese population. Here we describe two Italian families with late-onset OTCD showing a father to daughter transmission pattern.

FAMILY 1

Case report

F1-111 (Female): Onset at 36 y.o. of uneventful episodes of aggriffiveness, irritability by headache and confusion; sometimes associated with reduced alertness and/or emesis, preceded by corticosteroid and/or NSAIDs intake. Died at 43 of hyperammonemic encephalopathy triggered by the intake of high doses of COs, muscle relaxants and NSAIDs to treat a scapulohepatic paralirritis. Metabolic assessment revealed post-mortem glutamine 1295 µmol/l (n. 200 – 800), citrulline 21 (n. 10-35), arginine 63 (n. 30-96) and orotic acid 208 mMol/l normal range. Metabolic assay showed that the X-linked inheritance of late-onset OTCD in this patient is associated with a variable phenotype in female carriers.

F1-110 (male): Received a diagnosis of hepatopathy NOS. Episodic irritability and mood swings. Metabolic assessment performed in absence of symptoms was inconclusive.

F2-110 (female): Chronic headaches, chronic aversion to protein-rich foods. Metabolic assessment showed in range orotic acid and glutamine, alanine 581 µmol/l (n. 150-400)

F2-115 (male): occasional acute episodes of confusion associated with abnormal behavior (verbalized screams and meaningless speeches) lasting for few hours. Metabolic assessment showed glutamine 1088 µmol/l (n. 200 - 800), citrulline 8 (10-35), alanine 1804 µmol/l (n. 350-400)

F2-111 (male): Hospitalized and then died at the age of 30 after an episode of psychomotor agitation and impairment of consciousness progressing to coma. Diagnosed with hepatopathy NOS.

F2-115 (male): mood instability with a tendency to be irritable, along with mild cognitive decline. Hospitalized and then died at the age of 80 after an episode of psychomotor agitation and impairment of consciousness progressing to coma. Rapidly deteriorated after diazepam was administered in ER.

F2-111 (male): F2-117 (male): Hospitalized and then died at the age of 31 after an episode of psychomotor agitation and impairment of consciousness progressing to coma with cerebral edema and hyperammonemia. Rapidly deteriorated after diazepam was administered in ER.

F2-111 (female): History of recurrent headaches, chronic fatigue, transient irritability and aversion to protein-rich food. Metabolic assessment showed elevated alanine (624 µmol/l) (n. 150-400)

F2-116 (female) chronic headaches, chronic aversion to protein-rich foods. Metabolic assessment showed in range orotic acid and glutamine, alanine 581 µmol/l (n. 150-400)

Case report

F2-116 (female): c.662G>A mutation

F2-115 (male): c.652C>T mutation

CONCLUSIONS

Here are reported two Italian OTCD families in which the disease shows the evidence of a father-to-daughter transmission pattern associated with a variable phenotype in female carriers. Paternal inheritance of a X-linked recessive conditions can, in some cases, be attributed to X-linked recessive disorders not impairing the reproductive fitness of affected males, who are then capable of passing the mutation to their daughters, as described, although rarely in other X-linked disorders, such as Duchenne muscular dystrophy and Rett syndrome. As for OTCD, there is an evident lack of reports of paternal transmitted cases in published series. It is possible that the under-reporting of paternal inheritance cases is linked to the underdiagnosis of late onset OTCD cases, as the unequivocal clinical symptoms in adults with UCDs, that tends to mimic more common conditions, leads to frequent misdiagnosis. However, OTCD is a diagnosis not to be missed, as it is a treatable disease and achieving a correct diagnosis can be lifesaving for patients of all ages and gender. Therefore, the absence of a clear maternal transmission pattern in the family pedigree should not exclude OTCD in the differential diagnosis of case of females presenting with hyperammonemia- correlated signs and symptoms.