Stupor in an Adolescent Following Yom Kippur Fast, Due to Late-Onset Ornithine Transcarbamylase Deficiency

Nufar Marcus MD[1], Oded Scheuerman MD[1], Vered Hoffer MD[1], Efrat Zilbershot-Fink MD[1], Joel Reiter MD[2] and Ben Zion Garty MD[1]

[1]Department of Pediatrics B, Schneider Children's Medical Center of Israel, Petah Tikva, and Sackler Faculty of Medicine, Tel Aviv University, Ramat Aviv, Israel
[2]Department of Pediatrics, Hadassah-Hebrew University Medical Center (Ein Kerem Campus), Jerusalem, Israel

Key words: ornithine transcarbamylase, hyperammonemia, stupor, urea cycle, late onset

IMAJ 2008;10:395–396

Ornithine transcarbamylase deficiency is the most common urea cycle defect, with an estimated incidence of 1 in 14,000 [1]. This diagnosis is usually considered in catastrophically ill neonates, in whom the characteristic clinical presentation is primarily related to hyperammonemia, prominent liver dysfunction and mental status changes leading to coma. As an X-linked inherited disorder, questioning the parents about their family history is extremely important. Residual or partial activity of OTC (as seen in female hetrozygotes and males with late-onset disease) can alter the age at onset of symptoms, the clinical presentation and the course of disease [1]. Since up to 60% of the patients with OTC deficiency present after the neonatal period [1], a high index of suspicion is mandatory when patients with unexplained episodes of vomiting, alteration in consciousness, or behavioral changes are encountered at any age [1].

This report describes a 14 year old boy who presented after the Yom Kippur* fast with behavioral changes, disorientation and confusion. The clinical condition and family history of two male cousins who died at the age of 3 years led to the discovery of hyperammonemia, and the diagnosis of ornithine transcarbamylase deficiency.

Patient Description

A previously healthy 14 year old boy was hospitalized for investigation of a confusional state that started after the Yom Kippur fast. His parents reported that toward the end of the 25 hour fast he had become disoriented and began behaving strangely. He did not have a fever. Past history showed normal development. He denied alcohol ingestion or drug abuse. His parents were healthy, both of Yemenite descent, and non-consanguineous. The patient had seven healthy brothers and sisters. The family denied a history of illness in other family members.

On physical examination, his pulse rate was 80 beats per minute, blood pressure 155/70 mmHg, temperature 36.7°C, height 180 cm and weight 95 kg. Neurological examination found that the patient was disoriented and unaware of time and place but responded to commands. Perception was preserved. His gait was mildly ataxic. There were no abnormalities in cranial nerves, tendon reflexes, or muscle tone and strength. The rest of the examination was unremarkable.

Laboratory tests revealed white blood cell count of 10,500/mm^3, hemoglobin 14.3 g/dl, platelets 249,000/mm^3, glucose 86 mg/dl, creatinine 0.97 mg/dl, urea 28 mg/dl, sodium143 mEq/L, potassium 4.4 mEq/L, calcium 10.1 mg/dl, bilirubin 1.6 mg/dl, aspartate aminotransferase 40 U/L, alanine aminotransferase 66 U/L, lactate dehydrogenase 671 U/L, alkaline phosphatase 233U/L, gammaglutamyl transpeptidase 14 U/L.

Opening pressure on lumbar puncture was 24 mmH_2O (normal $\leq$ 20 mmH_2O), with no cells in the cerebrospinal fluid; glucose was 52 mg/dl and protein 30 mg/dl. Computed tomography scan and magnetic resonance imaging of the brain revealed no abnormalities.

On the second day of hospitalization the patient became agitated, aggressive and combative. A consulting psychiatrist diagnosed acute psychotic episode and recommended treatment with haloperidol and admission to the psychiatric ward. Following injection of 5 mg haloperidol, the patient became sleepy and a decerebration posture was noted. At this point, further questioning of the parents revealed that one of the mother's brothers developed neurological symptoms and died at the age of 3 years of unknown cause, and the mother's sister had a son who died of an unknown cause at a similar age. These data prompted emergency laboratory tests that revealed serum ammonia of 670 µg/dl (normal < 100 µg/dl), lactate 55 mg/dl (normal < 20 mg/dl), creatine phosphokinase 800 U/L (normal < 130U/L), and AST 100 U/L (normal < 45 U/L). The tentative diagnosis was a urea cycle defect causing hyperammonemia.

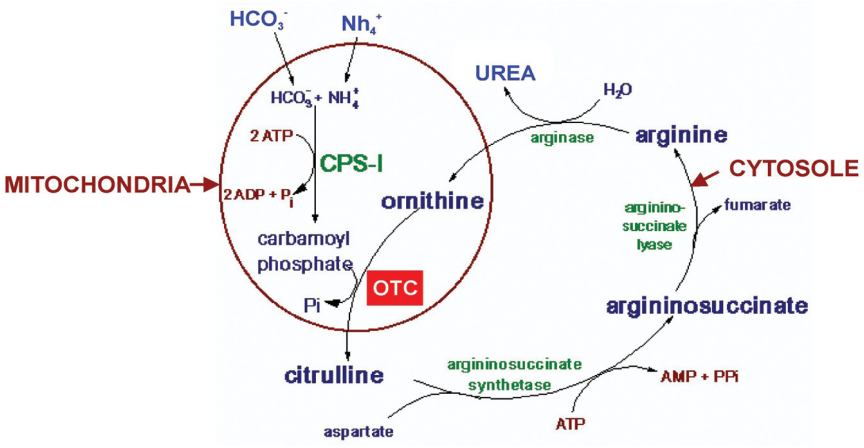
The patient was transferred to the pediatric intensive care unit, underwent intubation and put on a respirator. Blood amino acid analysis showed elevated glutamine level (2552 nmol/ml, normal < 756), reduced citrulline level (6.6 nmol/ml, normal 12–55), and mildly increased levels of ALT. The differential diagnosis now included OTC deficiency, liver disease and mitochondrial dysfunction. A finding of elevated orotic acid levels in urine (93.5 mmol/mol creatinine, normal < 1.3) confirmed the diagnosis of OTC deficiency. The child was treated with intravenous glucose, arginine and sodium benzoate, oral phenylbutyrate and neomycin, and protein restriction.

The patient's condition improved within

OTC = ornithine transcarbamylase

* Day of Atonement, the most holy day in the Jewish calendar.

AST = aspartate aminotransferase
ALT = alanine aminotransferase



The urea cycle: This cycle transforms ammonia to urea via a pathway of several enzymes that are located in the mitochondria or in the cytosole of liver cells. OTC transforms ornithine to citrulline.

5 days, and the neurological examination returned to normal, without any cognitive impairment. Ammonia levels decreased to 27 µg/dl, and serum liver enzymes and CPK normalized.

Molecular analysis revealed a missense mutation in exon 2 of the OTC gene leading to a change in a single amino acid (p.Arg40His). The family was notified that other family members are at risk for the same disease and should be tested. The patient was advised not to fast on Yom Kippur and to avoid large meals rich in protein.

Comment

The clinical features of the classic form of OTC deficiency include lethargy, vomiting and coma in a male baby. If not treated rapidly, death usually occurs within a few days [1-3]. OTC deficiency is an X-linked disorder. Interestingly, it was first reported in 1962 in two girls aged 20 months and 6 years who presented with mental retardation, failure to thrive, stupor and episodic occurrence of vomiting. Only 40% of the patients with OTC deficiency are diagnosed in the neonatal period [2,3]. If symptoms appear after the first year of life, the diagnosis is usually delayed (up to 16–21.5 months in some reports) [2]. In many cases, symptoms appear in response to stimulation with certain triggers, such as protein loading, febrile disease, surgery, weaning from breastfeeding, growth spurt, or treatment with valproic acid.

CPK = creatine phosphokinase

Presentation after fad diets or fasting is uncommon [1-3]. In our patient the clinical manifestations appeared after the Yom Kippur fast. It is unclear whether the fasting itself triggered the metabolic crisis, or the large meals eaten before and after the fast, or a combination of these factors.

The clinical signs that should raise a suspicion of OTC include a triad of vomiting, irritability and lethargy. Encephalopathy, recurrent or intermittent neurological symptoms of unexplained cause, difficult to control gastroesophageal reflux, "intolerance" to baby formula, averseness to protein and dairy products, and a self-selected vegetarian diet are also suggestive [1-4]. Family history of OTC is positive in only 40% of patients [2]. In our patient, the suggestive family history of X-linked disorder was initially hidden by the family and was obtained only when the patient's condition became critical.

If OTC deficiency is suspected, plasma ammonia should be measured immediately. During the acute phase of the illness, ammonia levels are usually above 150 µg/dl, however during asymptomatic periods they may be normal. In addition, plasma amino acids analysis reveals a high glutamine level and very low level of citrulline [Figure]. Elevated urine orotic acid confirms the diagnosis and differentiates the disease from other inborn errors of the urea cycle [1-3]. Other non-specific findings in patients with OTC deficiency include respiratory alkalosis attributed to some degree of cerebral edema, elevation of hepatic enzymes, and low levels of blood urea nitrogen, reflecting chronic reduced protein intake. Allopurinol loading test may also be useful, especially in the diagnosis of female heterozygotes. Unlike male patients, who present in the neonatal period with no residual enzyme activity, patients with late-onset OTC deficiency exhibit an enzyme activity varying from 1% to 30% of the normal range [1-3]. Approximately 340 different point mutations in the OTC gene have been described [5].

In our patient, the hyperammonemic crisis was most likely precipitated by a combination of three factors: the meal before the fast, which loaded the patient with excessive protein, followed by the actual fast, which put the patient in a ketogenic stress, and a rich meal after the fast, which probably loaded the patient with yet another high protein burden, causing a decompensation of the faulty enzyme and resulting in hyperammonemia.

Our case shows that a metabolic crisis in OTC deficiency may occur after Yom Kippur fasting, and clinicians should be alert to this possibility in patients who present with vomiting, delirium or stupor after fasting.

Acknowledgement: We thank Prof. Orly El-Peleg for the consultation and biochemical and genetic analyses.

References

1. Smith W, Kishnani PS, Lee B, et al. Urea cycle disorders: clinical presentation outside the newborn period. *Crit Care Clin* 2005;21:S9–17.
2. Schultz RE, Salo MK. Under recognition of late onset ornithine transcarbamylase deficiency. *Arch Dis Child* 2000;82:390–1.
3. Finkelstein JE, Hauser ER, Leonard CO, Brusilow SW. Late-onset ornithine transcarbamylase deficiency in male patients. *J Pediatr* 1990;117:897–902.
4. Myers JH, Shook JE. Vomiting, ataxia, and altered mental status in an adolescent: late-onset ornithine transcarbamylase deficiency. *Am J Emerg Med* 1996;14:553–7.
5. Arranz JA, Riudor E, Marco-Marin C, Rubio V. Estimation of the total number of disease-causing mutations in OTC deficiency. *J Inherit Metab Dis* 2007;30:217–26.

Correspondence: Dr. N. Marcus, Dept. of Pediatrics B, Schneider Children's Medical Center of Israel, Petah Tikva 49202, Israel.
Phone: (972-3) 925-3681: Fax: (972-3) 925-3257
email: nofarmk@clalit.org.il