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CASE REPORT

Ornithine transcarbamylase deficiency in pregnancy

D. R. Cordero, J. Baker, D. Dorinzi and R. Toffle*
Albert Einstein College of Medicine, 1695 Eastchester Road, Suite 301, New York, NY 10461, USA
*Correspondence: E-mail: vydcordero@yahoo.com

Summary: Women heterozygous for mutations at the ornithine transcarbamylase (OTC) locus may be at risk for hyperammonaemia and its untoward effects including coma and death in the postpartum period. We present the case of a pregnant woman heterozygous for OTC deficiency (McKusick 311250) whose past medical history was significant for two prior pregnancies complicated by postpartum hyperammonaemic coma. In the index pregnancy, increased levels of serum ammonium were noted during labour. Postpartum hyperammonaemia was averted by administration of oral sodium benzoate. Our experience demonstrates that in women at risk, perilous hyperammonaemia can be prevented through appropriate medical management.

CASE REPORT

The proposita, a 24-year-old woman, presumed heterozygous for ornithine transcarbamylase deficiency (OTCD) underwent term induction of labour to provide a controlled environment should she or her male newborn develop hyperammonaemia. OTCD had been diagnosed at age 8 years by liver biopsy following multiple evaluations owing to protein aversion. She self-restricted her protein intake and was relatively asymptomatic before and during pregnancy. To our knowledge, she was never treated with arginine, citrulline or an ammonium scavenger.

Her first pregnancy resulted in the vaginal delivery of an unaffected girl and her postpartum course was unremarkable. Two subsequent pregnancies were complicated by mental status changes followed by hyperammonaemic encephalopathy on postpartum day 3 after term vaginal deliveries of non-affected boys. Recovery occurred after several days of lactulose and intravenous glucose. Between pregnancies she did not require specific medical or dietary intervention, but did follow a self-imposed vegetarian diet.

During the current pregnancy, serum ammonium averaged 52 μmol/L on a 0.5–1.0 g/kg per day protein diet. Although ultrasound revealed a male fetus, neither prenatal testing for OTCD nor transfer to a centre with expertise in genetic metabolic disorders was accepted by the patient. When induction of labour was initiated, she was started on 10% dextrose intravenously to increase caloric intake. At that time her

serum ammonium was 62 μmol/L, which increased to 1 μmol/L prior to the vaginal delivery of a healthy nonaffected boy. Sodium benzoate was initiated at 0.25 g/kg per day orally every 6 h postpartum. Her ammonium stabilized to baseline until postpartum day 3, when her ammonium rose to 137 μmol/L, requiring an increase to 0.5 g/kg per day of sodium benzoate every 6 h. After achieving baseline ammonium levels for 3 days, she was discharged accompanied by her unaffected son with instructions to complete 14 days of sodium benzoate.

DISCUSSION

Females heterozygous for OTCD constitute a lesser-known group of patients who may be at risk for calamitous postpartum hyperammonaemia (Arn et al 1990; Horwich et al 1990). Heterozygous females may exhibit a spectrum of clinical manifestations thought to be a consequence of varying degrees of lyonization (Arn et al 1990). Such females may experience subtle and nonspecific symptoms such as avoidance of dietary protein (Rowe et al 1986) or cerebral dysfunction (Batshaw et al 1980) or present in the puerperium with hyperammonaemic coma (Arn et al 1990; Peterson 2003). Brusilow and his group reported three healthy women with OTCD who developed complications in the puerperium; two of the women had not been diagnosed with OTCD prior to their complicated postpartum course and died as a result; the third patient was a known asyptomatic OTCD carrier who developed gastrointestinal and central nervous system symptoms thought to be due to emotional adjustment on postpartum day 3. On postpartum day 12, she was noted to have hyperammonaemia and was treated with fluids and lactulose. Adequate response was not obtained and on postpartum day 16 intravenous sodium benzoate and sodium phenylacetate were started and the patient improved.

Postpartum metabolic decompensation is not unique to OTCD. For instance, Grunewald and colleagues reported a woman with maple syrup urine disease (MSUD) who tolerated pregnancy well but experienced increased leucine levels 9 days postpartum (Grunewald et al 1998).

It is unclear why women heterozygous for the OTC mutation may be susceptible to overloading the capability of the urea cycle postpartum. One theory is that the normal unaffected fetal liver detoxifies maternal ammonium and, when this relationship is disrupted at the time of delivery, maternal ammonium increases (Arn et al 1990). In our case, hyperammonaemia apparently associated only with an unaffected male fetus also raises the question of a sex bias promoting this complication in a heterozygous female. Grunewald speculated that increased tissue catabolism may have been responsible for the increased leucine in their patient with MSUD (Grunewald et al 1998).

The antepartum period may be unremarkable for women with OTCD because of increased nitrogen demands by the uterus, placenta and fetus. However, following delivery of the fetus and placenta, this symbiotic relation abruptly terminates and the uterus undergoes involution. The uterus, which weighs approximately 1000 g following delivery, decreases in size through a process known as involution; weighing about 500 g after one week and regaining its previous nonpregnant size (100 g or less) within about 4 weeks (Cunningham et al 2001). In the rat model, collagens (types I

and III) are increased in the uterus during pregnancy and are thought to provide the tensile strength required to accommodate the fetus (Burgeson 1988; Harkness and Harkness 1954; Shum et al 2002). Involution of the uterus involves extensive remodelling of the extracellular matrix, primarily resulting from collagen breakdown (reviewed in Salamonsen 2003) along with cell proliferation and apoptosis (Takamoto et al 1998). Degradation of these collagens postpartum returns the uterus to its pre-pregnant state (Harkness and Harkness 1956; Shum et al 2002). Recent data suggest that the interstitial collagenase (matrix metalloproteinase-13; MMP-13) is involved in the process of uterine involution (Shum et al 2002) because it is expressed in the smooth-muscle cells of the uterus during this period (Blair et al 1986; Shum et al 2002). It is likely that a number of MMPs play a role in involution, but the extent of their role in uterine involution is still unclear. Together, these data suggest that the postpartum period is a critical time in which deleterious alterations in the biochemical balance may occur in patients with OTCD and may result from increased metabolic demands secondary to collagen catabolism during involution of the uterus.

Our clinical results differ from those patients described by Brusilow because in our patient, who was known to have OTCD, ammonium levels were monitored closely and sodium benzoate therapy was instituted prior to marked elevations in ammonium. Serum amino acid values were not obtained because the analysis would have been performed at an outside institution, delaying the results and diminishing their usefulness. In institutions where amino acid monitoring is available, measurement of glutamine levels, which may antecede elevations in ammonium (Brusilow et al 2000), may allow the administration of therapy prior to elevations in ammonium. Ideally, intravenous sodium benzoate and/or sodium phenylacetate along with 10% arginine (Brusilow et al 2000) should be used in this setting because a therapeutic level can be obtained expeditiously and the blood levels can be maintained without the fluctuations seen from the oral route due to erratic absorption. However, intra- and-postpartum monitoring of serum ammonium levels, intravenous administration of 10% dextrose to increase caloric intake and oral sodium benzoate may be an effective alternative in preventing postpartum complications when the intravenous route is not available.

In summary, female carriers of OTCD may be at risk of developing hyperammonaemia in the postpartum period and should be monitored and treated early if indicated. Why this period predisposes patients to hyperammonaemia remains unclear but it may involve the metabolic consequences of uterine involution. A more complete understanding of the normal biochemical changes in the postpartum period is warranted if we are to adequately treat or prevent this complication.

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