HIGH PROTEIN DIET MIMICS HYPERTYROSINEMIA IN NEWBORN INFANTS

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Tyrosinemia resulting from administration of protein-dense infant diets was detected by newborn screening in two infants. Change of formula resulted in rapid resolution of the hypertyrosinemia. These cases identify nonstandard infant diets as a benign and reversible cause of tyrosinemia and a potential cause of positive newborn phenylketonuria screening. (J Pediatr 2005;146:281-2)

Tyrosinemia is a group of inborn errors of metabolism that presents with a variable phenotype. There are many causes of hypertyrosinemia in the newborn and infancy periods, including tyrosinemia type 1, transient tyrosinemia of the newborn infant, and cytomegalovirus infection. Tyrosinemia type 1, caused by fumarylacetoacetate hydrolase deficiency, presents in infancy with jaundice, progressive cirrhosis, and generalized symptoms of hepatic dysfunction such as clotting abnormalities and/or the renal Fanconi syndrome. Treatment includes tyrosine (protein) restriction, therapy with NTBC [2-(2-Nitro-4-Trifluoromethylbenzoyl)-1,3-Cyclohexanedione (Nitisinone)], and/or liver transplantation. Transient tyrosinemia of the newborn infant results from a combination of immature function of 4-hydroxyphenylpyruvate dioxygenase (4HPPD), high protein diet, and ascorbate deficiency. Treatment with oral ascorbate and/or protein restriction usually results in normal plasma tyrosine within weeks to months. The incidence of transient tyrosinemia has decreased with more breast-feeding and the use of lower-protein commercial formulas.

We report two cases of tyrosinemia caused by inappropriately high dietary protein intake with nonstandard infant diets that resolved after dietary normalization.

METHODS

Case 1

A term male infant was reported to have a presumptive positive phenylketonuria (PKU) newborn screen. The birth weight and length were 3.5 kg and 50 cm, respectively. He was initially fed on Enfamil (Mead Johnson Nutritional, Evansville, Ind), and his first newborn screen (at 24 to 48 hours of life) was normal. Because of spitting up and jaundice, he was fed with on Shaklee Slim Plan Drink Mix (Shaklee Corporation Pleasanton, Calif) at 5 days of age by his mother, providing about 7 g/kg per day of dietary protein (Table). A routine second newborn screen at 7 days of age was positive for PKU. At 2 weeks, he was a healthy, normal infant with normal growth parameters. Plasma tyrosine was elevated to 2330 μmol/L (normal value <148) and plasma phenylalanine was increased to 220 μmol/L (normal value <138), resulting in the positive newborn PKU screen. Large amounts of p-hydroxyphenyllactic acid and p-hydroxyphenylacetic acid were in the urine. Transient tyrosinemia was considered, and he was given Isomil (Ross Products, Columbus, Ohio) (providing 2 g of protein/kg per day) and vitamin C (100 mg/kg per day). The plasma tyrosine and phenylalanine was normal within 5 days. Vitamin C was discontinued at 3 months of age and plasma tyrosine remained normal at follow-up at 1 year of age. At 1 year of age, his growth parameters were at the 50 percentile and his development was normal.

Case 2

A term 2.7-kg female infant was fed with Similac Advance (Ross Products, Columbus, Ohio) with iron from birth, and her first newborn screen at 24 hours was...
Because of constipation, the mother switched the formula at 4 days of age to Pet evaporated milk (J.M. Smucker Co., Minneapolis, Minn) 2 cans per day, which provided approximately 10 g/kg (Table). A routine second newborn screen performed at 1 week of age (because the first screen was done at <2 days of age) was positive for PKU. The infant appeared healthy and normal at 3 weeks of age, with weight and height at the 25 percentile. The plasma tyrosine and phenylalanine were markedly elevated (tyrosine, 1822 μmol/L; phenylalanine 306 μmol/L). Urine organic acids showed large amounts of 4-hydroxyphenyllactic acid and 4-hydroxyphenylacetic. Liver function tests were normal, including α-fetoprotein (490 μmol/L; normal value <10,000 μmol/L).4 The infant was switched to Similac advance with iron at 5 weeks of age. Her tyrosine and phenylalanine returned to normal within 4 days, with no other treatment.

**DISCUSSION**

These cases demonstrate the effect of an extremely high protein diet on plasma phenylalanine and tyrosine concentrations. In each case, the infant had a presumptive positive PKU screen. The phenylalanine in both cases was higher (2 to 3 times) than normal but not as high as the tyrosine concentration (>10 times normal). The urine organic acids in both cases demonstrated compounds commonly found in tyrosinemia. Both patients were being fed nonstandard high protein diets at the time of high plasma tyrosine, and the plasma tyrosine returned to normal within a short period of time after a change to an appropriate infant formula. The usual protein requirement in infancy is 2.2 g/kg per day,5 and the infants received 3 to 4 times more protein than normally recommended. These 2 patients would not have been identified if newborn screening had not been repeated during the high protein administration. Both patients were normal at the time of diagnosis, but the long-term effects of high protein intake in infants have not been systemically studied. These cases highlight the importance of following infant nutritional guidelines.

A high protein diet is a known risk factor for transient tyrosinemia in the newborn infant. Most patients with transient tyrosinemia have no complications or long-term effects from a short period of high plasma tyrosine.1,2 However, Rice et al6 and Mamunes et al7 reported learning disabilities without gross motor developmental effects after 8-year follow-up, especially in a group having very high tyrosine levels (>1100 μmol/L). Corneal crystals were reported by Driscoll et al8 in one patient with transient tyrosinemia. Some patients with transient tyrosinemia will not be diagnosed, and those diagnosed with transient tyrosinemia are not followed for long-term effects.

### REFERENCES


### Table. Nutritional analysis and phenylalanine/tyrosine content of formula per kilogram per 24 hours of administration

<table>
<thead>
<tr>
<th>Patient 1</th>
<th>Patient 2</th>
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</thead>
<tbody>
<tr>
<td><strong>Formula</strong></td>
<td><strong>Shaklee Slim Plan</strong></td>
</tr>
<tr>
<td>Calories (kcal/kg)</td>
<td>105</td>
</tr>
<tr>
<td>Protein (g/kg)</td>
<td>6.1</td>
</tr>
<tr>
<td>Phenylalanine (mg/kg)</td>
<td>594</td>
</tr>
<tr>
<td>Tyrosine (mg/kg)</td>
<td>589</td>
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</tbody>
</table>

*Formula recipe: 2 cup (60 g) Shaklee Slim Plan powder with 1 tsp olive oil and enough water to make 20 oz per batch. Formula intake: averaged 5 oz every 4 hours or 30 oz every 24 hours.
†Formula recipe: 12 oz evaporated milk, 2 tsp corn syrup with 18 oz water, and boiled. Formula intake: averaged 4 oz every 2 hours or 48 oz every 24 hours.