Hereditary Orotic Aciduria Heterozygotes Accompanied with Neurological Symptoms

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logical Symptoms. Tohoku J. Exp. Med., 1998, 185 (1), 67–70 — We report a
family with hereditary orotic aciduria heterozygotes. A 3-year-old boy who had
been diagnosed as having cerebral palsy and mental retardation presented himself
with an increase in excretion of urinary orotic acid. Enzymatic studies revealed
that the boy and his healthy mother were hereditary orotic aciduria heterozygote
 carriers. We can not prove that this pyrimidine disorder caused his neurological
symptoms, but his pyrimidine nucleoside supply may have been insufficient in his
neonatal period. orotic aciduria; orotic acid; heterozygotes © 1998
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Hereditary orotic aciduria (McKusick 258900) is a rare autosomal recessive
disorder which occurs in the simultaneous absence of orotate phosphoribosyltrans-
ferase (EC 2.4.2.10; OPRT) and orotidylate decarboxylase (EC 4.1.1.23; ODC)
activities. Our group has reported the only patient in Japan found with hered-
itary orotic aciduria (Morishita et al. 1986). This disease is clinically character-
ized by mental retardation, growth retardation, megaroblastic anemia, immunode-
ficiency, and high levels of orotic acid in the patient’s urine—500 to
1000 times of the normal amount. Reported heterozygote carriers, however,
showed only an increase of orotic acid in their urine while remaining free of the
other symptoms (Webster et al. 1995). In this report, we describe a hereditary
orotic aciduria heterozygote carrier who exhibited severe clinical symptoms.

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CASE REPORT

The patient is a 3-year-old Japanese boy who presented with cerebral palsy and mental retardation. His parents are not consanguineous, and they have no relationship with the previous reported Japanese case (Morishita et al. 1986). The boy was admitted to a newborn intensive care unit the day he was born, because he was premature at 32 weeks of gestation and was a low birth weight baby at 1474 g. Asphyxia was not noted (1-minute Apgar score of 9). The laboratory examination (Table 1) showed that his blood sugar level was slightly low. As feeding difficulties appeared, glucose and minerals were supplied by intravenous infusion (as shown in Fig. 1). He was also treated with oxygen (23 ~25%), because of mild apnea attacks. Cranial computed tomography and cranial ultrasound examinations showed no abnormalities during this period. However, retarded motor development became apparent from the 8th month, and a diagnosis of cerebral palsy (spastic quadriplegia) was made at 13 months. By the age of 3 years slight mental retardation was also apparent. At this time, the patient was admitted to Nagoya City University Hospital for an extensive examination.

The patient was found not to be anemic, and a routine clinical examination revealed no abnormalities. However, when the high-performance liquid chromatographic method was used to screen the patient’s urine for pyrimidine metabolism disorders (Sumi et al. 1995), elevated levels of orotic acid and orotidine were discovered. The level of orotic acid was 10.5 μmol/mmol creatinine (normal children’s level = 1.5 ± 0.4, mean ± S.D., n = 14). And the level

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<th>Table 1. Laboratory findings at admission</th>
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of orotic acid in the patient was 2.6 (normal level = 0.9 ± 0.6). Successive pyrimidine analyses were conducted to verify continuously high values. The level of orotic acid in a urine sample from the patient's father was 0.6 μmol/mmol creatinine (normal adult level is 0.6 ± 0.2), and the level of orotic acid was below the detection threshold (<0.1) (normal adult's level = 0.3 ± 0.1). A urine sample from the patient's mother showed an orotic acid level of 4.3 μmol/mmol creatinine, and an orotic acid level of 2.2. The OPRT and ODC activities in erythrocytes were measured using a method of Fox et al. (1971). The patient's OPRT and ODC activity were both 8.3% of normal levels, respectively. The father's OPRT and ODC activities were 94.3% and 88.6%. The mother's OPRT and ODC activities were 4.4% and 7.9%. Based on these results, it was suggested that the patient and his mother were hereditary orotic aciduria heterozygotes and his father was normal. His mother was a healthy woman showing neither neurological symptoms nor anemia.

Discussion

Sugawara et al. (1995) reported that mother's milk contains pyrimidine nucleosides (nucleotides) such as uridine, suggesting that dietary pyrimidine may play certain roles during a neonatal period. In other periods dietary pyrimidine is not important, because pyrimidine nucleosides are supplied sufficiently by the de novo synthesis. But in a hereditary orotic aciduria homozygote, who lacks the

![Fig. 1. Clinical course in the neonatal period. Intravenous infusion consisted of glucose, mineral and water. Milk: ☯ infant formula which did not contain pyrimidine nucleosides; ☩ mother's milk. FiO₂: Fraction of inspired oxygen content](image-url)
de novo synthesis, oral uridine therapy is necessary during the entire period (Webster et al. 1995). However, in a hereditary orotic aciduria heterozygote, it is unknown whether dietary pyrimidine is important or not.

We have described a hereditary orotic aciduria heterozygote accompanied with neurological symptoms. The patient was not supplied with dietary pyrimidine until mother's milk was started at 9 days after birth. His infant formula did not contain pyrimidine nucleosides, although an infant formula containing pyrimidine has recently become available commercially (Snow Bland Milk Products Co., Ltd., Tokyo). We speculate that pyrimidine nucleosides may have been insufficient during his neonatal period, because both the de novo synthesis and the dietary supply were decreased. We can not prove that the pyrimidine deficiency caused his neurological symptoms. Other factors such as apnea attacks may have also cause the neurological symptoms. Further studies are required to clarify the mechanism of the neurological damage in this patient. The use of an oral uridine therapy during the neonatal period of a heterozygote should be discussed.

References


