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Maternal Gonadal Mosaicism Causing Ornithine Transcarbamylase Deficiency

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Ornithine transcarbamylase (OTC) deficiency (McKusick 311250), an X-linked inherited disorder, often presents in males with severe neonatal onset of hyperammonemia. Maternal gonadal mosaicism in OTC deficiency was postulated previously, but no cases have been reported. We report on a family in which two consecutive males were affected with OTC deficiency, which was proven biochemically with characteristic metabolites and absent enzyme activity in liver. OTC genotyping in both brothers showed a new mutation in exon 6 (Met206Arg: ATG→AGG), which encodes part of the equatorial H6 α-helix. Biochemical investigations confirmed normal results in the mother and grandmother and the absence of OTC activity in the affected males. Genotyping of the mother and grandmother was performed on peripheral blood leukocytes and skin fibroblasts and showed no mutation in the somatic cells. The recurrence of OTC deficiency in offsprings of a woman with normal genotype strongly suggests gonadal mosaicism. Gonadal mosaicism needs to be considered when counseling couples in which the mother has had a previously affected child with OTC deficiency but apparently is not a carrier. Am. J. Med. Genet. 85:452–454, 1999.

KEY WORDS: urea cycle defects; gonadal mosaicism; ornithine transcarbamylase deficiency; OTC

INTRODUCTION

Ornithine transcarbamylase (OTC) deficiency (McKusick 311250), an X-linked disorder, often presents in males with severe neonatal onset of hyperammonemia. Diagnosis is usually made biochemically from the hyperammonaemia and orotic aciduria and confirmed by liver enzyme assay but can also be made by genotyping. Variable severity of clinical manifestations is apparent in affected males and also in heterozygous females. Most carriers are asymptomatic, but some can present with hyperammonemia. X-inactivation can be skewed, and if the wild-type allele is disproportionately inactivated, the expression of the mutant allele will result in reduced enzyme activity. Carrier detection in asymptomatic females may be made with genotyping [Tsai et al., 1993] or the allopurinol test [Hauser et al., 1990].

The recurrence risk for the disorder in future pregnancies depends on the origin of the mutation. In classical X-linked inheritance, the risk is 50% for males; for sporadic mutations, the recurrence risk is assumed to be very low. Approximately 10% of male cases are assumed to be sporadic [Tuchman et al., 1995a]. Another mechanism of inheritance for X-linked disorders, maternal gonadal mosaicism, can be postulated, but no cases have been reported for OTC deficiency. We report on two consecutive male pregnancies affected with OTC deficiency born to a mother with normal genotype in somatic cells.

MATERIALS AND METHODS

Clinical Report

The first infant was born at term to a healthy, primigravid 28-year-old woman.

The infant presented in the first few days of life and died at age 10 days with biochemically proven OTC deficiency. Genotyping subsequently demonstrated a mutation in exon 6 (Met206Arg: ATG→AGG), which encodes part of the equatorial H6 α-helix [Tuchman et al., 1995b]. Results of biochemical investigation, in-

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cluding allopurinol loading, and genotyping of the mother and maternal grandmother were normal.

One year later, the mother presented pregnant with a male fetus. Prenatal diagnosis was offered. Chorionic villous sampling showed the Met206Arg mutation. Liver tissue obtained after termination at 14 weeks showed no OTC activity and genotyping of liver confirmed the chronic villous sampling (CVS) result. The pedigree is illustrated in Figure 1.

RESULTS

Biochemical investigations (Table I) confirmed normal values in the mother and grandmother and the presence of OTC deficiency in both affected males. Genotyping of the mother and grandmother was repeated on peripheral blood leukocytes and cultured skin fibroblasts and showed no mutation in the somatic cells. Alternate primer sets, which were used to exclude allele dropout in the polymerase chain reaction preparation for sequencing, gave the same result. Thus, the mother, who is unaffected biochemically and has a normal genotype, must have transmitted the disorder to both affected sons.

DISCUSSION

We think this is the first reported case of maternal gonadal mosaicism in OTC deficiency. A woman can be identified as an obligate heterozygote for this disorder if she has had one or more affected children with OTC deficiency and there is another case elsewhere in the pedigree. No other cases were identified in this family (Fig. 1). Two-thirds of clinically normal heterozygotes have plasma glutamine levels above normal and most have orotic aciduria following allopurinol ingestion [Hauser et al., 1990]. A normal response to the allopurinol load in a woman who is heterozygous for a "severe" mutant OTC allele could result from skewed X-chromosome inactivation with a greater number of hepatocytes expressing the normal allele [Ricciuti et al., 1976]. Somatic mosaicism of OTC mutations does occur in families with OTC deficiency, and it can be associated with gonadal mosaicism. Thus, it is possible for

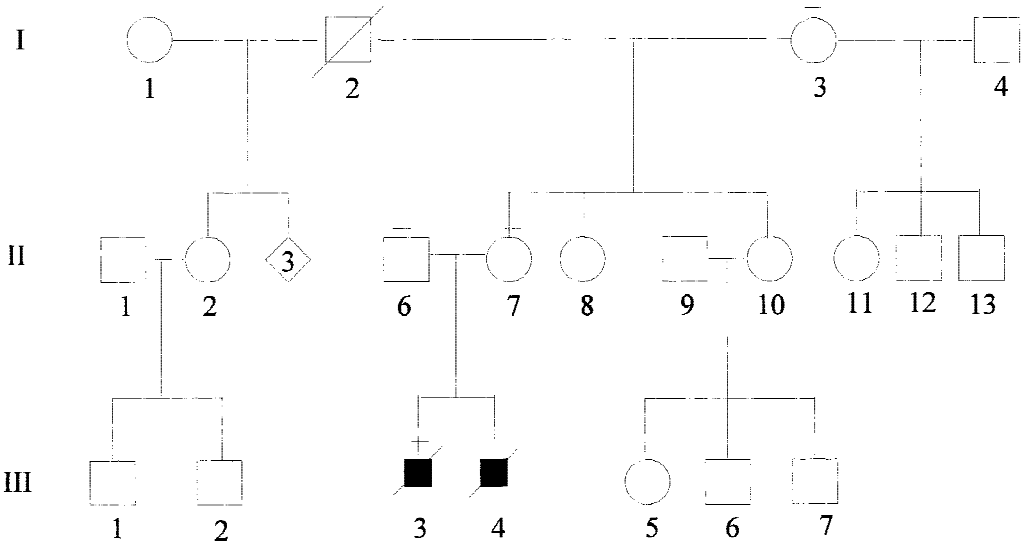

Fig. 1. Pedigree of the family affected with OTC. Individuals I-3, II-7, and II-6 were unaffected clinically with normal biochemistry and wild-type alleles. Individual III-3 was affected clinically with abnormal biochemistry indicating OTC deficiency and Met206Arg genotype. Individual III-4 had abnormal biochemistry and Met206Arg genotype. All other individuals are reported to be clinically normal.

TABLE I. Biochemical Investigations of the Patient and Family

Individual	Plasma ammonium (5–35 μM)	Plasma glutamine (420–700 μM)	Urine orotic acid (0.4–1.2 mmol/mol crest)	OTC activity (Liver) (29–59 U/g protein)	Allopurinol load	Genotype	Phenotype
I-3 maternal grandmother	25	410	<1			Wild type	Unaffected
II-7 mother	22	503	<1		Normal Orotidine (<2mmol/mol crest)	Wild type	Unaffected
II-6 father	18	262	<1			Wild type	Unaffected
III-3 proband	1100	4336	212	<5		Exon 6 (Met206Arg: ATG→AGG)	Affected
III-4 male sib	—	—	—	<5		Exon 6 (Met206Arg: ATG→AGG)	Affected

such individuals to have offspring with severe disease [Staudt et al., 1998]. However, the investigation of two tissues in the mother of the two affected males did not show evidence of OTC mutation, strongly suggesting gonadal mosaicism as the mechanism of recurrence. This phenomenon is known in other X-linked disorders such as Duchenne muscular dystrophy and hemophilia A. A study of spontaneous mutations in males and females with OTC deficiency suggested that the mutation rate is much higher in male germ cells than in eggs [Tuchman et al., 1995a]. This difference in frequency of germinal mutations may reflect the hypermethylation of sperm DNA and higher number of cell divisions. Gonadal mosaicism in a male has been reported in an unusual OTC pedigree in which three daughters were affected (and the mother was unaffected) [Komaki et al., 1997]. However in the study family with two affected male offsprings, the mutation affected only germ cell lines of the ovum, although we can not exclude that some other tissues that were not genotyped were also affected. An index case in an apparently unaffected family may be the result of either a spontaneous mutation or as a result of gonadal mosaicism. Clinicians should be alerted to the existence of maternal gonadal mosaicism in OTC deficiency, and this possibility needs to be considered when counseling couples in which the mother has had a previously affected child but apparently is not a carrier.

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