Case Report

Recurrent Osteogenesis Imperfecta

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Abstract

Osteogenesis Imperfecta (OI) is a group of inherited disorders characterized by bone fragility. The perinatal lethal form of the disease, type II, has three different mechanisms of inheritance: new dominant mutations, parental germline mosaicism, and autosomal recessive inheritance. We present a case of recurrent OI type II to discuss evolving aspects of diagnosis and to highlight the unique challenges faced when counseling patients.

Keywords: Recurrent Osteogenesis Imperfecta

Introduction

Osteogenesis imperfecta (OI) is a group of inherited connective tissue disorders characterized by bone fragility. Most cases of OI occur due to mutations in the type I collagen genes: COL1A1 located on chromosome 17, or COL1A2 located on chromosome 7, which encode for the proa1 (I) and proa2 (I) chains of type I procollagen, respectively [1]. OI is divided into four subtypes, I-IV, where type II is the perinatal lethal form [2]. We present a case of recurrent OI type II and discuss evolving aspects of diagnosis and counseling.

Case

A 25 year old primiparous woman at 17 3/7 weeks presented for a routine anatomical ultrasound. Her pregnancy had been uncomplicated and she had previously had a dating ultrasound at 6 weeks which was normal. On the anatomical ultrasound, her fetus was found to have short fetal long bones with the appearance of multiple fractures; a contracted chest circumference; irregular to absent mineralization of the ribs, long bones, and skull. The patient was counseled that these findings represented a lethal anomaly, most likely OI type II, and the pregnancy was medically terminated. No specific testing other than examination by a geneticist was performed. Because OI type II is primarily an autosomal dominant abnormality, the patient was counseled that the risk of recurrence was

extremely low, with most cases being due to a spontaneous mutation. The following year, the patient became pregnant again and delivered a normal male fetus at 39 weeks. In the next year, the patient became pregnant for the third time. A dating ultrasound at 7 weeks was normal. An anatomical ultrasound at 17 weeks revealed nearly identical findings as in her first pregnancy. She underwent an amniocentesis to obtain material for genetic testing, and then a medical termination of pregnancy. Genetic analysis revealed mutations in the COL1A1 gene consistent with OI type II. This patient's fourth pregnancy was uncomplicated and she delivered a healthy male infant at 39 weeks.

Discussion

OI type II was first classified as a recessively-inherited disorder based, in part, on observations in consanguineous families [2]. Additional studies over the years have now identified that OI type II inheritance can occur by one of three mechanisms: new dominant mutations, parental germline or mixed germline and somatic mosaicism for a dominant mutation, or a rare occurrence of autosomal recessive inheritance [1,3-5]. Spontaneous mutations appear to be the most common mode of inheritance, and, along with parental germline mosaicism, are associated with mutations in the type I collagen genes COL1A1 and COL1A2 [1,3,4]. Autosomal recessive inheritance involves mutations in the cartilage-associated protein gene (CRTAP), and in two genes

that encode proteins that interact with CRTAP: LEPRE1 and PPIB [4,6]. Population studies have shown the estimated risk of a child being born with OI type II is 1:50,000 live births [1]. The diagnosis of OI type II, followed by identification of the mode of inheritance is important in counseling families of the risk of recurrence in future pregnancies.

The identification of fetal skeletal abnormalities during pregnancy can be achieved with abdominal ultrasound by 14-16 weeks' gestation [1,7]. The differential diagnosis for the skeletal anomalies of micromelia and skeletal undermineralization include OI type II, congenital hypophosphatasia, achondrogenesis, and thanatophoric dysplasia [1,7]. Sonographic findings consistent with OI type II include micromelic limbs, undermineralized skull, multiple fractures in a single bone, marked femoral shortening and beaded ribs [7,8]. Other forms of OI can be distinguished from type II because they are characterized by none to mild limb shortening, and a normal appearing calvaria with slight demineralization and possible wormian bones [8]. Features of achondrogenesis include extreme micromelia with short hands and feet, large head, flat face and short neck [9]. Congenital hypophosphatasia findings include profound skeletal undermineralization, short and deformed limbs, but is usually not characterized by multiple fractures [7,8]. Thanatophoric dysplasia is characterized by severe micromelia, brachydactyly, platyspondyly, narrow thorax with short ribs, and in some cases craniosynostosis [9].

Once OI type II is diagnosed, biochemical and genetic analysis can be performed on both the parents and the affected infant [3,4]. Genetic analysis of dermal fibroblasts from the infant can identify in which gene(s) the mutation is present in. The identification of a mutation in dermal fibroblasts, blood, hair follicles, or sperm samples from the parents can further narrow the mode of inheritance by identifying germline or germline and somatic mosaicism [3-5]. Biochemical analysis of fibroblast cultures from parents and affected infant can identify abnormal type I collagen [4]. The results of the biochemical and genetic analyses in the first affected pregnancy can be used to help identify abnormalities in subsequent pregnancies.

For pregnancies that are known to be at risk for OI type II due to a previously affected pregnancy, early diagnosis may be achieved by transvaginal ultrasound by 13-14 weeks' gestation [1,7]. Several reported cases of OI type II have been diagnosed after finding increased nuchal translucency (NT) during sonography at gestational weeks 11-14 [10]. It has been suggested that fetal biometry be performed in cases of increased NT to look for sonographic evidence of OI type II to aid in early diagnosis [10]. In addition, if biochemical analysis has identified abnormal type I collagen molecules in a previously affected infant or its parents, chorionic villus sampling (CVS) at 10-12 weeks' gestation can be cultured and analyzed for the same abnormalities, with the results

available in 3-4 weeks [1,7]. Alternatively, if DNA analysis has previously identified a mutation within the family, CVS or amniocytes can undergo DNA analysis for the known mutations, with most results being available in 7-14 days [1,7]. Amniocytes do not produce adequate amounts of type I procollagen and cannot be used for the biochemical assay, but they do contain extractable DNA that can be used for DNA analysis [1,7]. DNA analysis for known mutations has the potential to diagnosis OI type II several weeks earlier than sonographic or biochemical data.

Several studies have published recurrence risks for OI type II. In 1988, Beyers et al. [3] reported the empiric recurrence risk for OI type II to be approximately 6%. Additional studies over the following twenty years reported the OI type II recurrence risk to be 1.3-2% after the first affected pregnancy, and 28-32% after the second affected pregnancy [1,4]. Although the reported recurrence risk may change depending on the population sampled, the identification of the type of mutation present is important for genetic counseling [4]. When a family has recurrence of OI type II, the inheritance occurred through parental germline mosaicism or recessive inheritance. In cases with parental germline mosaicism, the risk of recurrence can be as high as 50%, depending on the frequency of the mutated allele in the germline. When both parents are carriers of the recessive mutation the recurrence risk would be 25%. For families with new, spontaneous mutations, without evidence of recessive inheritance or mosaicism, the risk would be less than 0.1% [4].

This case demonstrates the unique challenges of counseling patients whose pregnancies have been affected by OI type II. Our knowledge of the mode of inheritance and the technology available for testing has evolved rapidly in the last several years. Because there appear to be several modes of inheritance, counseling must be tailored to each, individual case. Depending on the mode of inheritance, and the type of mutation, recurrence risk ranges from as low as 0.1% to as high as 50%. We recommend testing for the specific mutation because this can aid in determining the mode of inheritance, better predicting recurrence risk, and aiding in earlier diagnosis in subsequent pregnancies. In patients who attempt future pregnancies, early ultrasound is of value and can lead to substantially earlier diagnosis and therefore earlier and safer pregnancy termination. CVS testing for specific gene mutations or for abnormal type I collagen may also help with early diagnosis. Sperm analysis along with parental blood, dermal fibroblast, or hair follicle DNA testing could be considered in couples who have had a previously affected pregnancy in order to evaluate for cases of somatic and germline mosaicism. Identification of the affected parent might lead some couples to consider a donor egg or sperm to avoid recurrence.

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