Prenatal Diagnosis of Osteogenesis Imperfecta Associated With Nuchal Edema: A Case Report

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Abstract

This report describes a case of osteogenesis imperfecta associated with nuchal edema at 16 weeks of gestation. A 32-year-old, gravida 3, para 1, abort 1 woman admitted to our antenatal clinic in the first trimester of her third pregnancy. The fetal crown-rump length and nuchal translucency thickness were measured 63.2 mm and 2.7 mm by ultrasound at 12+5 weeks of gestation, respectively. The estimated risk for trisomy 21, calculated by a combination of maternal age, nuchal translucency thickness and first trimester maternal biochemistry, was 1/868. At 16 weeks of gestation, ultrasound showed evolution of translucency into nuchal edema. Amniocentesis performed owing to nuchal edema revealed a normal 46, XX karyotype. Maternal serology for toxoplasmosis, cytomegalovirus, and parvovirus B19 were normal. Ultrasound at this gestational age showed innumerable fractures and shortening and bowing of the fetal long bones, rib fractures, and hypomineralization of the skull. These findings suggested osteogenesis imperfecta type II. Termination of pregnancy was offered, but the patient decided to carry on her pregnancy. Unfortunately, hydrops fetalis developed at 20 weeks of gestation and fetal intrauterine death occurred. A postmortem examination established the diagnosis of osteogenesis imperfecta type II and the diagnosis was also confirmed radiographically and by pathological examination.

Keywords: prenatal diagnosis, nuchal edema, osteogenesis imperfecta

Özet

Nukal Ödemin Eşlik Ettiği ve Prenatal Tanı Konulan Osteogenezis İmperfekta: Olgu Sunumu

Bu yazıda, 16. gebelik haftasında tanı konulan ve nukal ödemin eşlik ettiği bir osteogenezis imperfekta vakası tarif edilmektedir. Otuz iki yaşında, gravidası 3, parite 1 ve abortusu 1 olan kadın, gebeliğinin ilk trimesterinde antenatal kliniğimize başvurdu. Gebeliğin 12. haftasında yapılan ultrasonografi ile fetal baş-popo uzunluğu ve nukal translusensi kalınlığı sırasıyla 63.2 mm ve 2.7 mm olarak ölçüldü. Anne yaşı, nukal translusensi kalınlığı ve birinci trimester maternal serum biyokimyası kullanılarak hesaplanan trizomi 21 riski 1/868 olarak bulundu. Gebeliğinin 16. haftasında, nukal translusensi kalınlığının nukal ödeme dönüştüğü görüldü. Nukal ödem nedeniyle yapılan amniyosentez sonucu normal karyotip (46, XX) olarak geldi. Maternal serumda bakılan toksoplazmozis, sitomegalovirüs ve parvovirüs B19 testleri normaldi. Aynı gebelik haftasında ultrasonografik olarak fetal uzun kemiklerde çok sayıda kırıklar ve uzun kemiklerde kısalma ve eğilme, kosta kırıkları ve kafatası kemiğinde hipomineralizasyon tespit edildi. Bu bulgular fetal osteogenezis imperfekta tip II ile uyumluydu. Hastaya gebelik terminasyonu önerildi fakat, hasta gebeliğini devam ettirmek istedi. Ancak, 20. gebelik haftasında hidrops fetalis gelişti ve fetus uterus içinde öldü. Postmortem inceleme bulguları osteogenesis imperfekta tip II ile uyumluydu. Radyografik ve patolojik inceleme bulguları da tanıyı doğruladı.

Anahtar sözcükler: prenatal tanı, nukal ödem, osteogenezis imperfekta

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Introduction

Osteogenesis imperfecta is a relatively common dysplasia, with an incidence of 4 per 100 000 live births and about half of which represents type II (1). Abnormal collagen production results in weak bone vulnerable to fracture and secondary deformity. Osteogenesis imperfecta presents with fragility of bones, blue sclerae, loose joints and growth deficiency. Osteogenesis imperfecta type II is a lethal disorder, which is increasingly diagnosed in utero by ultrasound demonstrating bowed and shortened limbs owing to multiple fractures affecting the long bones.

A small black space under the skin of the fetus behind the neck is called a *nuchal translucency* (NT) between 10-14 weeks and a *nuchal fold* (NF) between 15-22 weeks. It is well known that in chromosomally normal fetuses there may be an association between increased NT and a wide range of fetal abnormalities, skeletal dysplasias and genetic syndromes (2).

In this report, we present a prenatally diagnosed case of osteogenesis imperfecta with increased NF thickness (nuchal edema) in a chromosomally normal pregnancy.

Case Report

A 32-year-old, gravida 3, para 1, abort 1 woman started to visit our antenatal clinic in the first trimester of her third pregnancy. Her husband was 36 years old, and they had no consanguinity. The woman's obstetric history was significant. Her first pregnancy in 1992 had resulted in a birth of a girl with cerebral palsy of unknown etiology. This infant was delivered at term by cesarean section. The woman had also had an abortion at 2 months gestation in 1999. Her medical and family histories were unremarkable. At 12+5 weeks of gestation, the crown-rump length (CRL) was 63.2 mm, and the NT thickness was 2.7 mm. The estimated risk for trisomy 21, calculated by a combination of maternal age, NT and, first trimester maternal biochemistry was 1/868. At the 16th week of gestation, ultrasound showed an increase in NF thickness defining nuchal edema (6.8 mm) (Figure 1). Amniocentesis was performed to rule out chromosomal abnormalities, and this revealed a normal 46,XX karyotype. At this time, ultrasound showed multiple fractures and global shortening and bowing of the fetal long bones with lengths below the third percentile, rib fractures and hypomineralization of the skull. Maternal serology for toxoplasmosis, cytomegalovirus, and parvovirus B19 were normal. The presumptive diagnosis was osteogenesis imperfecta type II. Termination of the pregnancy was offered, but the patient declined. Subsequently, hydrops fetalis developed at the 20th week of gestation (Figure 2) and fetal intrauterine death occurred. Ultrasound at this stage showed that fetal limb measurements were still below the third percentile. After fetal abortion, the parents consented to full postmortem assessment, including photography and bone-cartilage histology. The postmortem examination showed nuchal edema, severe limb shortening, and bowing and contracture of the extremities (Figure 3). The diagnosis of osteogenesis imperfecta type II was confirmed radiographically and by pathological examination. Radiographic examination revealed multiple fractures of the long bones and ribs and hypomineralization of the skull (Figure 4). Histology showed thin trabeculae. The parents were informed of the pattern of inheritance and the risk for recurrence in future pregnancies.

Discussion

Osteogenesis imperfecta is a genetically heterogeneous group of disorders presenting as fragility of bones, loose joints, blue sclerae, and growth deficiency. A dominant negative mutation affecting COL1A1 or COL1A2 alleles, which encode the proa1 (I) and proa2 (I) chains of type-I collagen (a protein of paramount importance for normal skin and bone development) is the main underlying defect. There are 4 types. Osteogenesis imperfecta type I does not present prenatal deformities, and the diagnosis is made after birth. It is an autosomal dominant condition. Osteogenesis imperfecta type II is the most severe form with a birth prevalence of 1 in 60 000, which usually appears as

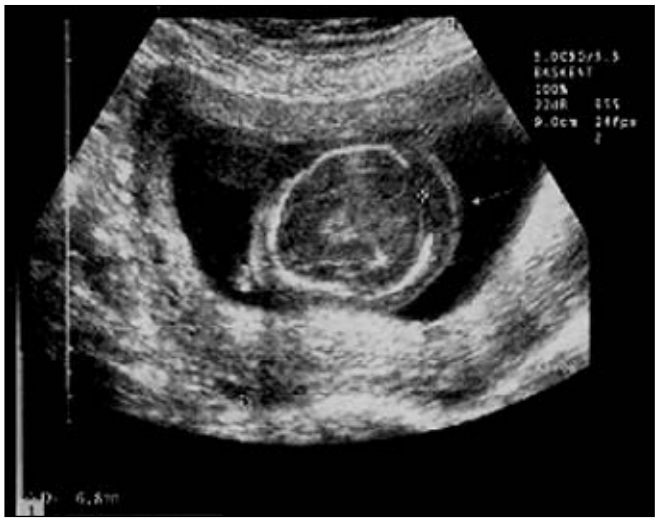

Figure 1. Ultrasound appearance of fetal nuchal edema.

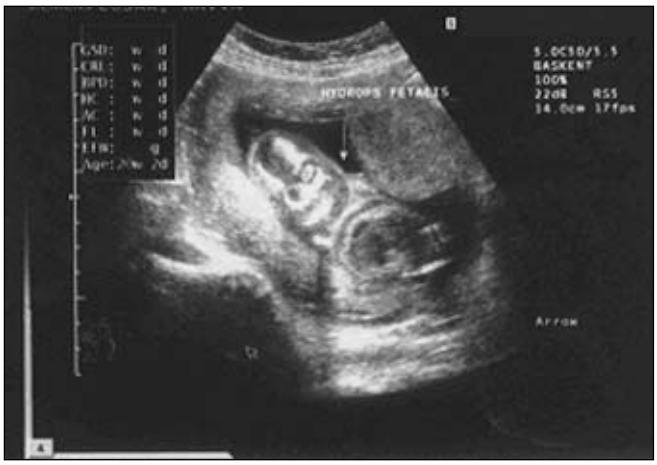

Figure 2. Ultrasound appearance of hydrops fetalis.

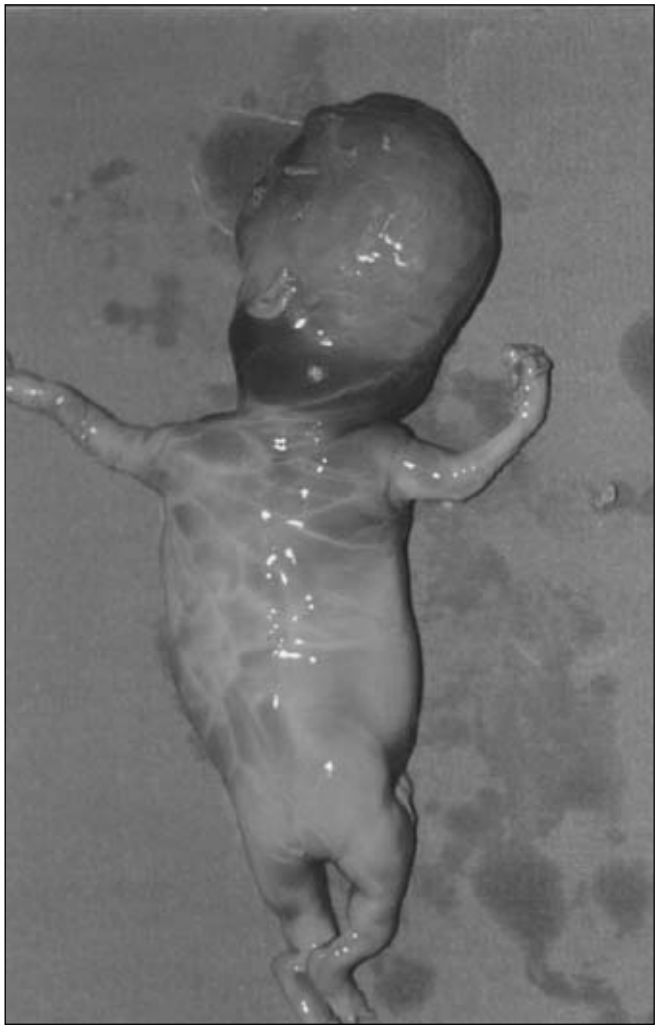

Figure 3. Postmortem photograph of the fetus showing severe limb shortening and bowing.

the result of a sporadic new mutation. Recurrence (6-7%) is usually due to parental mosaicism, even though, in a small number of families, autosomal recessive inheritance has been observed (3). It is characterized by early prenatal onset of severe bone shortening and bowing of the long bones due to multiple fractures, poor demineralization of the skull, narrow and bell-shaped chest caused by fractures of the ribs, abnormal skull shape, and abnormal face. Findings of associated polyhydramnios and chest compression (indicated by a relatively high cardio-thoracic ratio) and associated nonspecific abnormalities (such as hydrops) on ultrasound signal a poor prognosis. Death occurs either prenatally or shortly after birth owing to respiratory failure. Chorion villous sampling and DNA analyses or demonstration of abnormal collagen production can make the prenatal diagnosis in high-risk pregnancies (4). However, the diagnosis is usually made by routine ultrasound examination in midpregnancy, since the majority of the affected pregnancies are the result of sporadic mutations of an autosomal dominant gene. Osteogenesis imperfecta type III is less severe than type II and usually presents as multiple fractures at birth. Osteogenesis imperfecta type IV is the mildest form and is not detectable prenatally.

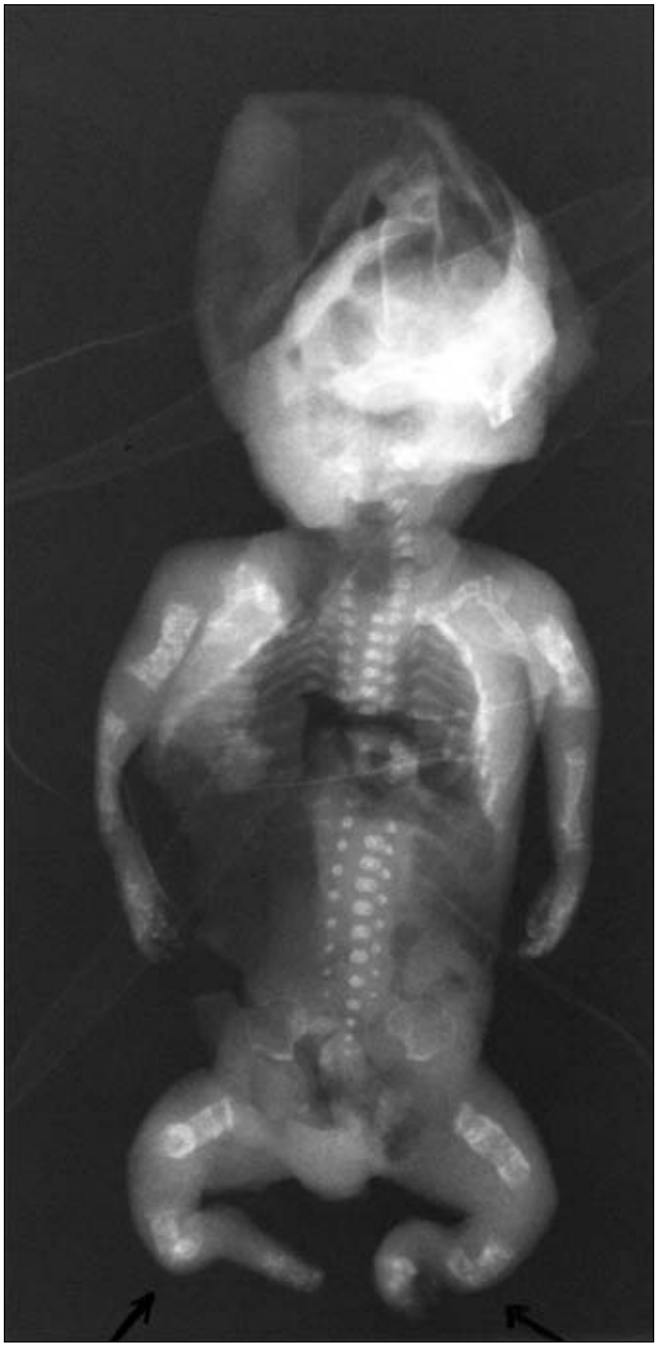

Figure 4. Postmortem X-ray shows the fetus with osteogenesis imperfecta type II, with short and bowed long bones crumpled by innumerable fractures and general undermineralization.

Osteogenesis imperfecta can be associated with increased NT thickness in the first trimester without any chromosomal abnormality (5). The abnormal accumulation of fluid behind the fetal neck during the second and third trimesters of pregnancy can be defined as nuchal edema. It has a diverse etiology; chromosomal abnormalities are found in about one third of the fetuses, and in about 75% of cases, the abnormality is trisomy 21 or 18. Nuchal edema is also associated with fetal cardiovascular and pulmonary defects, skeletal dysplasias, congenital infection and metabolic and hematological disorders without any chromosomal abnormalities (6).

In our case, increased NT thickness was observed at the 12th week of gestation. The estimated risk for Down syndrome, calculated by a combination of maternal age, NT thickness, and first trimester maternal biochemistry did not necessitate fetal cytogenetic analysis. Subsequently, ultrasound examination performed at the 16th week of gestation showed the evolution of translucency into nuchal edema. At this gestational age, the typical ultrasonographic features of osteogenesis imperfecta type II including multiple fractures and global shortening and bowing of the fetal long bones, rib fractures and hypomineralization of the skull were seen by fetal sonography. At the 20th week of gestation, nuchal edema progressed to severe hydrops.

In fetuses with increased NT, special care should be taken to confirm whether NF thickness is increased or not and to carry out a detailed fetal scan at the 20th week of gestation to diagnose or exclude major abnormalities that could not be identified at the 11-13+6 weeks scan (7). The persistence of unexplained increased NT at the 14-16 weeks scan or evolution to nuchal edema or hydrops fetalis at 20-22 weeks, raises the possibility of a wide range of fetal abnormalities, congenital infection, or a genetic syndrome. Maternal blood should be tested for toxoplasmosis, cytomegalovirus, and parvovirus B19 to rule out congenital infection.

In conclusion, increased fetal NT and also nuchal edema may be associated with skeletal dysplasias such as osteogenesis imperfecta in chromosomally normal fetuses. The probable explanations for nuchal fluid accumulation in osteogenesis imperfecta consist of mediastinal compression due to a narrow chest and decrease in fetal movements because of limb fractures. An additional or alternative mechanism may be the altered composition of the extracellular matrix.

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