

# Increased nuchal translucency and short femur length as possible early signs of osteogenesis imperfecta type III

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## Summary

**Objective:** this paper reports an association between an increased Nuchal Translucency (NT) and Osteogenesis Imperfecta (OI), a type of skeletal dysplasia. Measurement of fetal NT at 10-14 weeks of gestation is a sensitive and effective screening method for chromosomal abnormalities.

**Methods:** a 35-year-old Caucasian woman in her fourth pregnancy was referred to our clinic for an ultrasound scan at 12 weeks of gestation, that confirmed increased Nuchal Translucency. Chorionic villi sampling was performed, showing a normal karyotype. The patient was evaluated by a team of experienced ultrasonographers for pregnancy follow-up at our Department, that is a tertiary center.

**Results:** in our case the ultrasound scan at 12 week of gestation revealed only an increased NT (3 mm). Cytogenetic analysis on chorionic villi demonstrated a normal male karyotype. US follow-up, performed every 3-4 weeks, confirmed normal anthropometric parameters except for shortening of both femurs, but at 23 weeks an incorrect attitude of the feet was revealed. A clinical and radiographic diagnosis of OI type III was made only at birth, and through follow-up continuing to date.

**Discussion:** NT screening was successful for chromosomal abnormalities at 11-14 weeks of gestation. An increased NT thickness is also associated with numerous fetal anomalies and genetic syndromes in a chromosomally normal fetus. In our case there were no sonographic signs of imperfect osteogenesis in the first trimester, although there was an increased NT with a normal karyotype.

**Conclusion:** currently, in literature, there are not other cases of OI type III associated with an increased NT. Our report is the first to suggest an association between an increased nuchal translucency, short femur length and osteogenesis imperfecta type III.

**Key words:** osteogenesis imperfecta, skeletal dysplasia, nuchal translucency, ultrasound scan.

## Introduction

Osteogenesis Imperfecta (OI) is an inherited disease caused by a defective maturation of collagen. It is more common in women, and has an incidence of one per 25,000 - 30,000 pregnancies (1). There are four main OI types, that differ in term of clinical, pathologic and radiologic characteristics (Tab.1).

OI type I is an autosomal dominant condition with a prevalence of approximately 1:30,000 births. Affected individuals have fragile bones, blue sclerae and progressive deafness, although life expectancy is normal. In the second and third trimesters of gestation ultrasonography may show long bones fractures (2).

OI type II is the most severe form because newborns do not survive the prenatal period. Causes of death can be malformations, hemorrhages in the central nervous system, extreme fragility of the ribs or pulmonary hypoplasia. At ultrasound scannings, infants may show multiple intra-uterine fractures, affecting the skull, long bones and vertebrae, narrow ribs, and severe deformity of the long bones. The vast majority of cases are new, autosomal dominant mutations (3).

OI type III can be either an autosomal dominant or a recessive condition, and has a prevalence of 1:300,000 births. It is characterized by blue sclerae, multiple fractures usually present at birth and resulting in scoliosis, a very short stature, chest and long bones deformities featuring a specific structural alteration of the metaphyses and epiphyses defined as a "popcorn appearance" (4).

OI type IV is the most variable form of OI, ranging in severity from mild to moderately severe; it is therefore difficult to make a diagnosis of this type (4).

Although there have been many reports of molecular or biochemical tests for a prenatal OI diagnosis, in utero sonography is still the primary diagnostic modality (5).

The main defect is a dominant negative mutation affecting the COL 1A1 or COL1A2 alleles, which encode the pro A1 (I) and pro A2 (I) chains of type I collagen, a protein of paramount importance for normal skin and bone development. The mutation results in the production of an abnormal quantity (OI type I) or quality (OI types II, III, IV) of collagen (6).

This paper reports a case of OI type III that was clinically diagnosed postnatally, but had already shown an increased Nuchal Translucency (NT) and short femur length at US performed in the first trimester.

## Case report

A 35-year old Caucasian woman in her fourth pregnancy was referred to our clinic for an ultrasound scan at 12 weeks of gestation, that confirmed an increased Nuchal Translucency.

Her first pregnancy had been voluntarily interrupted at 22 weeks of gestation because the fetus was affected by the Dandy Walker Syndrome. The second pregnancy ended in a miscarriage at 16 weeks of gestation, due to cervical incompetence. The third pregnancy was a blighted ovum.

Table 1. Clinical Features of OI by type.

Type	Inheritance	Severity	Fractures	Bone Deformities	Stature	Sclerae	Hearing Loss
I	AD	Mild	Few to 100	Uncommon	Normal or slightly short for family	Blue	Present in about 50%
II	AD	Perinatal lethal	Multiple fractures of ribs, minimal calvarial mineralization, platyspondyly, marked compression of long bones	Severe	Severely short stature	Dark blue	—
III	AD; rare recessive	Severe	Thin ribs, platyspondyly, thin gracile bones with many fractures, "popcorn" epiphyses common	Moderate to severe	Very short	Blue	Frequent
IV	AD	Moderate to mild	Multiple	Mild to moderate	Variably short stature	Normal to grey	Occasional

**Prenatal findings**

Our first ultrasound scan at 12 weeks of gestation revealed an increased NT thickness (3 mm) (Fig.1), normal CRL (60 mm, corresponding to the 50<sup>th</sup> centile), normal nasal bone, normal trans-tricuspid and ductus venosus flow, and no other sonographic signs of abnormalities except for a slightly short femur length (5 mm, between the 10<sup>th</sup> and the 50<sup>th</sup> centile).

Since increased Nuchal Translucency is associated with many aneuploidies, chorionic villus sampling was performed. Cytogenetic analysis showed a normal male karyotype.

The parents were informed about the fact that an increased NT could be associated with various syndromes despite the normal cytogenetic analysis and normal ultrasound scan. They chose to continue the pregnancy.

US follow-up, performed every 3-4 weeks, confirmed normal anthropometric parameters except for shortening of both femurs (at 21 and 25 weeks of gestation long bones was between the 5<sup>th</sup> and the 10<sup>th</sup> centile; at 29 and 32 weeks of gestation long bones was between the 3<sup>th</sup> and the 5<sup>th</sup> centile) but at 23 weeks of gestation an incorrect attitude of the feet was revealed. The ultrasound examination at 26 weeks of gestation

showed polyhydramnios (AFI 290 mm). Because of worsening of the polyhydramnios, at 34 weeks of gestation, when AFI was 350 mm, amnioreduction was performed and the pregnancy was ended by caesarian section at 36 weeks.

**Neonatal findings**

At birth, the neonatal weight was 2100 g (average weight for gestational age), the Apgar score was 8/9 and the first clinical evaluation showed some anthropometrical changes, such as slightly triangular facies, facial asymmetry, low-set ears, club-foot, overlap of the IV finger on the V, hypospadias and undescended testes, as well as hypotonia. Echocardiography and MRI and transcranial ultrasound were normal. Seven days later, in the nursery the baby suffered fractures of the humerus and ribs; he was transferred to the Policlinico Umberto I in Rome, where a clinical diagnosis of Osteogenesis Imperfecta was made and bisphosphonate therapy was started.

**Laboratory and instrumental tests**

Genetic analysis of the COL-1 and COL-2 genes was carried out by Prof. Venturi from the University of Verona, and yielded negative results (COL 1 genes: rs 1007086 homozygote; rs 2734272 homozygote; rs 1800215 homozygote. COL-2 genes: rs 42518 heterozygote; rs 42519 heterozygote; rs 412777 heterozygote; rs 42524 heterozygote). When the child was five he underwent bone biopsy for femur fragments performed by Prof. Bianco from the Policlinico of Rome, that demonstrated "Osteogenesis Imperfecta". The results of the biopsy together with clinical criteria and radiological signs allowed the diagnosis to be completed as OI type III.

**Follow-up**

Follow-up carried out after 11 months showed a normal psychomotor development, no fractures, blue sclerae and normal muscle tone. The subsequent follow-up, at 16 months after birth, revealed a normal psychic development but difficulties in



Figure 1. Abnormal NT thickness at 12 weeks of pregnancy.

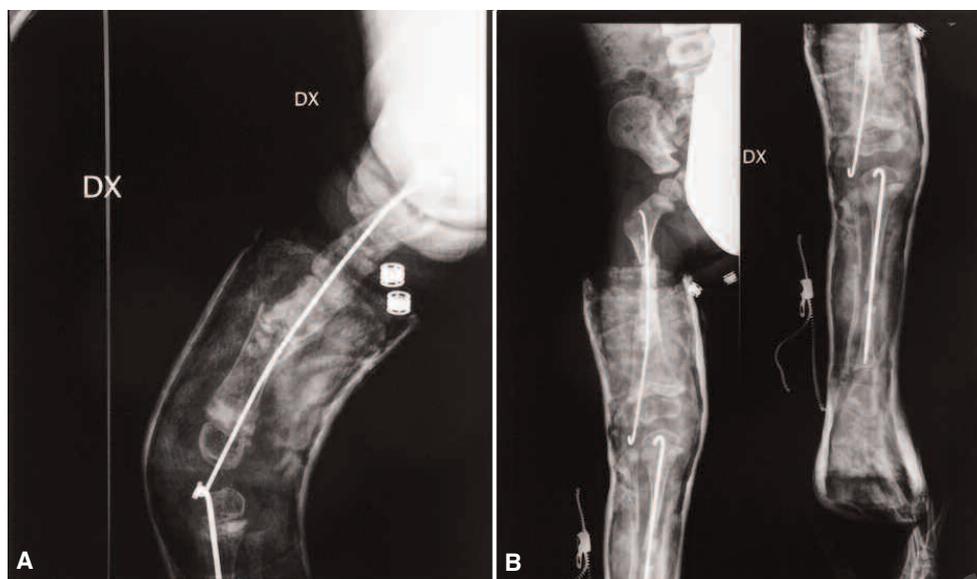


Figure 2 A, B. Radiological images of tibia and femur fractures.

Table 2. Prenatal diagnosis of OI triggered by detection of increased Nuchal Translucency thickness.

Authors	Case	NT scan (weeks+days)	Gestational age for the diagnosis	Abnormalities found on ultrasound	OI Type	Outcome
Makrydimas et al. (2)	1	11(CRL, 46 mm)	15	Shortened long bones, Multiple long bones and ribs fractures	II	abortion
Makrydimas et al. (2)	2	11	11(CRL,60 mm)	Shortened long bones and ribs	II	abortion
Viora et al. (7)	3	13+2	16+5	Short both femur and humerus, long bones fractures	II	abortion
Viora et al. (8)	4	13+0	16+4	Short both femur and humerus, long bones fractures	II	abortion
Hsieh et al. (5)	5	12+3	14+3	Shortened long bones, Multiple long bones and ribs fractures	II	abortion
Present study	6	12+0	—	Both femurs shortened	III	Caesarian section at 36 weeks

maintaining the upright posture and some episodes of bronchopneumonia.

Surgery was performed to correct abnormal ossification of the tibia and femur fractures (Fig. 2 A, B), and the bisphosphonate therapy was continued.

The child is now 5 years old, and has a delayed motor development and abnormal ability to maintain the upright posture because of continual long bone fractures. He also has slight difficulties in speaking, that he has overcome with the aid of speech therapy.

## Discussion

NT screening was successful for chromosomal abnormalities at 11-14 weeks of gestation. An increased NT thickness is associated with numerous fetal anomalies and genetic syndromes even in a chromosomally normal fetus.

In literature, 28 cases of Osteogenesis Imperfecta type II diagnosed only by ultrasonographic scan have been reported. Only in five cases there was an increased NT in the first trimester but the karyotype was normal (Tab. 2).

Possible mechanisms underlying the association between an increased accumulation of nuchal fluid and OI include mediastinal compression by the narrow thoracic cage, reduced fetal movements due to limb fractures, and an altered composition of the dermis (2).

The measurement of fetal NT at 10-14 weeks of gestation has been set as a sensitive, accurate and effective method of screening for chromosomal abnormalities (9). In addition, Souka reported the association of an increased NT with other structural defects, rare genetic syndromes and skeletal dysplasia. There is substantial evidence that in fetuses with an increased NT and normal karyotype there is a greater prevalence of skeletal dysplasia (10).

In our case there were no sonographic signs of osteogenesis imperfect in the first trimester despite the increased NT. In the third trimester the only signs indicating skeletal dysplasia, but not specific to OI, were the short femur length and incorrect attitude of the feet.

A clinical and radiographic diagnosis of OI type III was made only at birth and through follow-up continuing to date. The bone biopsy confirmed the diagnosis of OI, completed as OI type III.

Although in most patients the disorder is caused by mutations in one of the two genes encoding collagen type 1, in some individuals no such mutations are detectable, as in our case (11).

Currently, in literature, there are no other descriptions of cases of OI Type III associated with an increased NT. This is the first report of an association between an increased nuchal translucency, short femur length and osteogenesis imperfecta type III.

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