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*Clinical Report*

# Prenatal Cortical Hyperostosis With *COL1A1* Gene Mutation

**Agnès Kamoun-Goldrat,[1]* Jelena Martinovic,[2] Julien Saada,[3] Pascale Sonigo-Cohen,[4] Ferechte Razavi,[2] Arnold Munnich,[1] and Martine Le Merrer[1]**

[1]Paris Descartes University, INSERM U781, Hôpital Necker, Paris, France
[2]Unit of Fetal Pathology, Hôpital Necker, Paris, France
[3]Unit of Fetal Medicine, Hôpital Necker, Paris, France
[4]Department of Pediatric Radiology, Hôpital Necker, Paris, France

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Infantile cortical hyperostosis (Caffey disease) is benign and self-limiting when it presents near or after birth but it is usually lethal when it presents earlier. We present the clinical, ultrasonic, radiographic, and pathologic findings in an instructive case of early onset prenatal cortical hyperostosis. The pregnancy of a 21-year-old woman was medically terminated at 30 weeks of gestation after a diagnosis of severe osteogenesis imperfecta. Prenatal ultrasounds showed short long bones. Postmortem radiographs showed hyperostosis in long bones, ribs and mandible. The affected skeleton showed marked bony sclerosis and ballooning of the diaphyses of the long bones with periosteal sclerosis. A complete autopsy showed characteristic histologic findings of infantile cortical hyperostosis in affected bones. A missense mutation (3040C → T) in exon 41 the gene encoding the alpha 1 chain of type I collagen was found in fetus pulmonary tissue. Neither the severe form nor the mild form of prenatal cortical hyperostosis were thought to be related to collagen I mutations. Our study indicates that a heterozygous 3040C → T mutation can also be found in lethal prenatal cortical hyperostosis. © 2008 Wiley-Liss, Inc.

**Key words:** collagen type I; collagen disease; cortical hyperostosis; infantile prenatal diagnosis

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## INTRODUCTION

Infantile cortical hyperostosis (Caffey disease) is usually a relatively benign, self-limiting disease. It is manifested by cortical thickening of affected bones and swelling of the contiguous soft-tissues. The condition usually occurs in young infants (i.e., before 5 months of age) and is occasionally seen in neonates. Another form of infantile cortical hyperostosis, a lethal prenatal form, has been proposed [Lecolier et al., 1992]. The authors found angulations of long bones, an apparent rib fracture and polyhydramnios at 20 weeks of gestation in a pregnancy aborted at 23 weeks due to fetal-placental anasarca. The fetus was diagnosed postnatally as having cortical hyperostosis. Additional cases of hydramnios, anasarca, pulmonary hypoplasia, and hyperostosis were described by others [Drinkwater et al., 1997; Schweiger et al., 2003]. The prognosis is poor, mostly due to prematurity [Turnpenny et al., 1993; Drinkwater et al., 1997]. Radiological and histological findings correspond to those of the classical infantile cortical hyperostosis form. The occurrence in siblings of both sexes born to unaffected parents led to the suggestion of autosomal recessive inheritance [Turnpenny et al., 1993; De Jong and Muller, 1995; Drinkwater et al., 1997].

Recently, a novel missense mutation in *COL1A1*, the gene encoding the alpha 1 chain of type I collagen, was found in all affected individuals from three unrelated families [Gensure et al., 2005]. All individuals affected by the classical form of infantile cortical hyperostosis were heterozygous for the identical mutation, a 3040C → T transition resulting in the substitution of an arginine by a cysteine at

*Correspondence to: Agnès Kamoun-Goldrat, Paris Descartes University, INSERM U781, Hôpital Necker, 149 rue de Sèvres, 75015 Paris, France. E-mail: agnes.kamoun@yahoo.fr

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position 836 (R 836 C). This substitution is within the helical domain of the alpha 1 chain of type I collagen. Two cases of lethal prenatal cortical hyperostosis were also studied by Gensure et al. [2005], but the 3040C → T mutation was not found in these fetuses. Here, we describe a patient suffering from lethal prenatal cortical hyperostosis in which the 3040C → T mutation was observed in the *COL1A1* gene.

## CLINICAL REPORT

The fetus represented the first pregnancy of a young, healthy, nonconsanguineous couple. The family history was unremarkable especially for skeletal diseases. The woman (21 years old) was referred at 28.5 weeks of gestation due to an increased volume of amniotic fluid observed at a first ultrasonic examination performed at 22.5 weeks of gestation. The ultrasonic study showed a skeletal disorder: short and irregularly delineated long bones (humeri, femora, and lower limbs). The femora were angulated. The fronto-occipital diameter was normal with abnormal pressure-induced skull deformability. Thorax, pelvis, and spine were sonographically unaffected. The suspected diagnosis was osteogenesis imperfecta type IIb. Chromosomes were normal (46,XY). Infection parameters were not examined.

The pregnant woman elected to terminate the pregnancy at 30 weeks of gestation. A male infant was born weighing 1,680 g (50th centile), measuring 38 cm (10th centile), and with a head circumference of 26.5 cm (10th centile). The fetus had generalized edema with a fragile skin, rhizomelic shortening with angulated thighs and legs, relative macrocephaly with pressure-induced skull deformability, retrognathia, microstomia, protuberant abdomen, camptodactyly, and talipes equinovarus. The placenta was abnormally large, weighing 577 g (appropriate weight for gestational age: $260 \pm 20$ g).

Radiographs of the whole skeleton (Fig. 1) showed striking changes of the long bones. The humeri and femora were short and slightly angulated without fractures. Most prominent were the bloated diaphyses of the long bones with a double contour of the cortex (Fig. 2). The bony substance appeared sclerotic. Metaphyses were intact. Ribs were irregularly shaped and showed less severe signs of periosteal thickening. Some vertebral bodies were slightly enlarged (Fig. 3). Clavicular involvement was not found. The trabecula of the mandible and scapula was irregular and flocculent (Fig. 4).

The autopsy demonstrated ascites, a marked hepatomegaly (106 g for an expected value of $67.9 \pm 20.8$ g), a splenomegaly (14 g with an expected value of $3.0 \pm 1.3$ g), a nephromegaly (21.8 g with an expected value of $12.9 \pm 3.6$ g), and adrenomegaly (7.4 g with an expected value of

Fig. 1. Frontal radiograph of the whole skeleton of the fetus at 30 weeks gestation showing short and slightly angulated long bones.

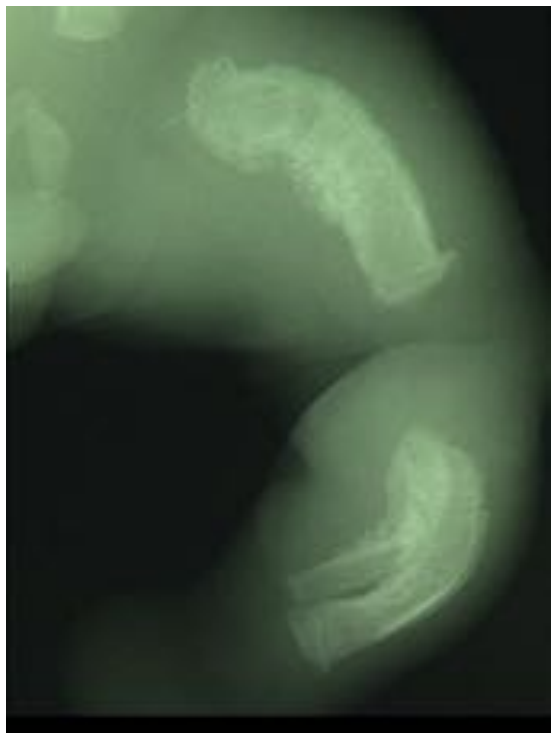

Fig. 2. Lower limb radiograph: see the bloated diaphyses of the bones with a double contour of the cortex and the sclerotic bony substance. Femurs, tibiae, fibulae are all angulated.


FIG. 3. Lateral radiograph of the whole skeleton of the fetus at 30 weeks of age, showing a few mildly enlarged lumbar vertebral bodies and the irregularly shaped ribs. There is decreased skull ossification and a dense mandible.

$4.1 \pm 1.4$ g). The pulmonary weight was within the normal range (weight: 21.9 g, expected for body length/weight combined, $30.2 \pm 9.5$ g). Histological examination showed global visceral congestion and normal histogenesis.

A histologic study of the long bones showed typical changes of cortical hyperostosis including a periosteal hyperostosis with a widened fibrous periosteum and an incomplete and irregularly demarcated cortex without acute inflammatory exsudate. An abnormal abundance of hematopoietic cells was found in the medulla. A histological study of the placenta showed nonspecific villous hydrops.

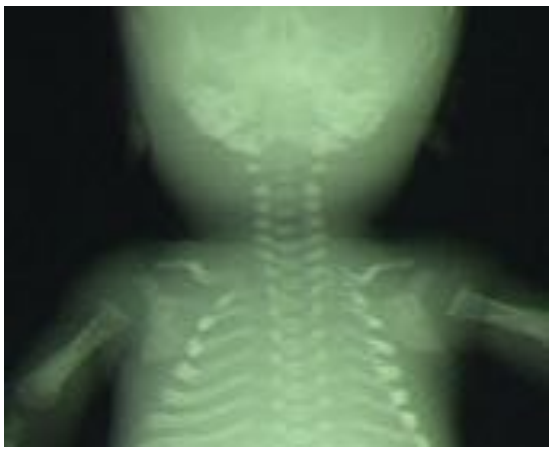

FIG. 4. Radiograph of the irregular and flocculent dense ossification of the mandible and scapulae, with normal appearing clavicles.

Genomic DNA was isolated from three fragments of the pulmonary tissue by standard methods and the *COL1A1* gene was sequenced using the Big Dye Terminator Cycle Sequencing kit V1 (ABI Prism, Applied Biosystems, Foster City, CA) on a 3100 automated sequencer. A heterozygous mutation ($3040C \rightarrow T$) was found in all three samples.

## DISCUSSION

A total of 44 affected infants have been reported in 34 unrelated families with antenatal onset of cortical hyperostosis, that is, with any manifestation in utero or at birth [Schweiger et al., 2003]. The authors found that two groups can be distinguished among the different prenatal manifestations: a severe form and a mild form. Severe prenatal cortical hyperostosis (with any prenatal or postnatal complication) was present in 26 patients from 23 families [Schweiger et al., 2003]. Most fetuses died during pregnancy (in some cases due to elective termination), at birth or shortly after birth. Eleven of the 26 fetuses were stillborn. Six of them had pulmonary hypoplasia, and 6 of the 14 liveborn babies died due to respiratory problems. In most of these pregnancies, polyhydramnios was the first detected manifestation, as it was in the case we report here. Other signs include fetal hydrops or skin edema (frequency: 50% of cases), and hepatosplenomegaly (frequency: 31% of cases). We also observed these signs in our patient. The earliest manifestation of bowing or shortness of the limbs has been reported at the 14th week of gestation [Drinkwater et al., 1997], on average bone changes were seen at 27 weeks of gestation. In the fetus we report here, these signs were observed at the ultrasonic examination performed at 28.5 weeks of gestation. In severe cases of prenatal cortical hyperostosis, nearly all long bones are affected antenatally or at birth in 81% of the cases reported [Schweiger et al., 2003], as is the case in the fetus described in our report.

The second group of prenatal cortical hyperostosis has been defined as a mild form (uncomplicated form) by Schweiger et al. [2003] and was present in 18 patients from 13 families. In this group, all patients were born at term and polyhydramnios was mentioned only in one case (in an otherwise uncomplicated pregnancy). Fetal hydrops, edema, and hepatosplenomegaly were not reported and skeletal manifestations were not detected before the 35th gestational week by ultrasonography or radiography. The clinical course of the fetus we observed could without doubt be classified in the first group defined by Schweiger et al. [2003], that is, a severe form.

Some perinatally lethal conditions with diaphyseal periosteal new bone that require differentiation from

intrauterine cortical hyperostosis include mucolipidosis type II, but there are in this latter disease there are other radiological changes with coarse trabeculae and metaphyseal irregularity [Michels et al., 1982]. When bowed or angulated long bones are identified prenatally by ultrasound, differentiation is required from the severe form of osteogenesis imperfecta [Bercau et al., 1991]. In the fetus described here, the lack of fractures, the normality of the bone mineralization observed in prenatal cortical hyperostosis, findings of radiological study and histopathological studies allowed us to eliminate the diagnosis of both mucolipidosis type II and osteogenesis imperfecta.

The inheritance of the classical (infantile) form and the prenatal form of cortical hyperostosis has been claimed to be different. Autosomal dominant inheritance of the classical form has been suggested by many reports [Gerrard et al., 1961; Van Buskirk et al., 1961]. Male-to-male transmission has also been observed [Van Buskirk et al., 1961]. Two affected sisters have been found [Bull and Feingold, 1974], one of whom had an affected son and daughter and the other a normal daughter and affected son. Since then, many other reports have been published, confirming autosomal dominant inheritance [Fried et al., 1981; Newberg and Tampas, 1981; Emmery et al., 1983]. More interestingly, a report of 24 affected members of a family segregating infantile cortical hyperostosis [Gensure et al., 2005] identified a 3040C → T mutation in the *COL1A1* gene, and showed only 19 of the family members had experienced an episode of cortical hyperostosis and 5 obligate carriers had not, consistent with reduced penetrance.

On the contrary, autosomal recessive inheritance has been suggested for the prenatal form of cortical hyperostosis. Sporadic occurrence of the disease was documented in two-thirds of cases with information on family history; in four cases, two or more siblings were born to unaffected parents [Clemett and Williams, 1963; Turnpenny et al., 1993; De Jong and Muller, 1995; Drinkwater et al., 1997]. Consanguinity was reported only once [Turnpenny et al., 1993] and there were equal numbers of male and female patients [Schweiger et al., 2003]. In some other reports, autosomal dominant inheritance has been suggested: in two cases, patients had one affected parent [Faul, 1961; Schärer and Szabo, 1966]. A case of prenatal cortical hyperostosis was detected in utero in a familial nonlethal case [Stevenson, 1993]. Ultrasound examination at 35.5 weeks of gestation showed curvature of the tibia and irregularity of the cortex of the radius. Mild leg curvature was present at birth at 39 weeks; involvement of all long bones was documented radiographically at the age of 2.5 months. A sister, the mother, and a maternal uncle had documented infantile cortical hyperostosis. So, the mechanism of inheritance of prenatal cortical hyperostosis seems uncertain.

Gensure et al. [2005] searched for the 3040C → T mutation of the *COL1A1* gene in two cases of severe prenatal hyperostosis. The fetus of 27 weeks reported by Schweiger et al. [2003] showed, at prenatal ultrasound examination, polyhydramnios and markedly short and angulated long bones, which had led to the incorrect diagnosis of lethal osteogenesis imperfecta, but radiological and histopathological findings were compatible with the diagnosis of prenatal cortical hyperostosis. The 3040C → T mutation was not found in the tissues of the fetus [Gensure et al., 2005]. The second case was a sporadic case which resulted in early death at 30 weeks of gestation [Dahlstrom et al., 2001]. The mother presented polyhydramnios. The infant showed extensive symmetrical diaphyseal subperiosteal cortical thickening throughout the skeleton with short extremities. Hepatomegaly and lung hypoplasia were present. The 3040C → T mutation was not detected in the fetal tissues [Gensure et al., 2005]. Our patient was, indeed, the first case of the 3040C → T mutation of the *COL1A1* gene observed in a case of prenatal cortical hyperostosis. It is noteworthy that this mutation was also not observed in a sporadic case reported by Gensure et al. [2005], as well as in one of our patients (unpublished result), both suffering from a classical (infantile) form of cortical hyperostosis.

So, the genetic heterogeneity of the cortical hyperostosis (Caffey disease) now needs to be addressed. It is likely that the mutation of an unknown gene is responsible for some cases of cortical hyperostosis, either classical (infantile) or prenatal forms. A heterozygous mutation of this unknown gene could also be responsible for the classical (infantile) form, as well as the 3040C → T mutation of the *COL1A1* gene. In this hypothesis, the severe prenatal cortical hyperostosis could be related to a homozygous mutation of the unknown gene or maybe to the simultaneous presence of the heterozygous 3040C → T mutation and other mutations of unknown genes.

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