Blomstrand’s lethal chondrodysplasia

Authors: Doctor Caroline Silve\textsuperscript{1} and Doctor Harald Jüppner\textsuperscript{2}

Scientific Editor: Doctor Valérie Cormier-Daire

\textsuperscript{1}INSERM U. 426, Faculté de Médecine Xavier Bichat, 16 rue Henri Huchard, 75018 Paris, France; \textsuperscript{2}Endocrine Unit, Department of Medicine, and Pediatric Nephrology unit, MassGeneral Hospital for Children, Massachusetts General Hospital and Harvard Medical School, Boston, MA 02114, USA.

Caroline.Silve@bichat.inserm.fr

Abstract

Blomstrand’s lethal chondrodysplasia (BLC) (OMIM215045) is a rare recessive human disorder characterized by early lethality, advanced bone maturation and accelerated chondrocyte differentiation. Infants with BLC are typically born prematurely and die shortly after birth. They present a severe dysmorphic syndrome characterized by extremely short limbs. Radiologic studies reveal pronounced hyperdensity of the entire skeleton and markedly advanced ossification. Diagnosis can be made as early as 12-13 gestational weeks by transvaginal ultrasound. BLC is associated with loss-of-function mutation in the gene encoding the PTH/PTHrP receptor (PTHR1).

Keywords

chondrodysplasia, advanced endochondral bone maturation, lethal, PTHR1 gene

Disease name/Synonyms

Blomstrand’s lethal chondrodysplasia (BLC), Blomstrand osteochondrodysplasia (BOCD)

Definition/Diagnostic methods

Blomstrand’s lethal chondrodysplasia (BLC) (OMIM 215045) is a rare recessive human disorder characterized by early lethality, advanced bone maturation and accelerated chondrocyte differentiation (1, 2). The diagnostic criteria are based on the clinical and radiographic characteristics observed in patients with this dysmorphic syndrome, early lethality, and, in most cases, parental consanguinity.

Clinical features

The first patient was described by Blomstrand and colleagues in 1985; descriptions of several other patients followed (3-9). Infants with BLC are typically born prematurely and die shortly after birth. Birth weight, when corrected for gestational age, appears to be normal, but may be overestimated because most infants are hydropic. The placenta can be immature and edematous. Nasal, mandibular, and facial bones are hypoplastic; the base of the skull is short and narrow; the ears are low set; the thoracic cage is hypoplastic and narrow with short thick ribs and hypoplastic vertebrae. In contrast, the clavicles are relatively long and often abnormally shaped.


http://www.orpha.net/data/patho/GB/uk-BlomstrLethChondrodysplasia.pdf
the limbs are extremely short, and only the hands and feet are of relatively normal size and shape. At autopsy, internal organs show no apparent structural or histological anomalies, but preductal aortic coarctation is observed in some published cases. The lungs are hypoplastic and the protruding eyes typically show cataracts. Defects in mammary gland and tooth development, previously overlooked, were demonstrated in two recently studied fetuses with BLC (10). Although these analyses have not been performed, it is most likely that fetuses with BLC present severe abnormalities in mineral ion homeostasis.

Radiologic and histologic analysis of the skeleton
Radiological studies of patients with BLC reveal pronounced hyperdensity of the entire skeleton and markedly advanced ossification. As mentioned above, the long bones are extremely short and poorly modeled, show markedly increased density, and lack metaphyseal growth plates. Endochondral bone formation is dramatically advanced, and is associated with a major reduction in epiphyseal resting cartilage preventing the development of epiphyseal ossification centers. The zones of chondrocyte proliferation and of column formation are lacking, and the zone that normally comprises the layer of hypertrophic chondrocytes is poorly defined, narrow and irregular. Cortical bone is thickened, bone trabeculae are coarse with reduced diaphyseal marrow spaces. Capillary ingrowth, bone resorption, and bone formation are reported by some authors as being unaltered, while others describe these bone remodeling events as deficient. Based on the severity of the phenotype, two types named type I (the severe, ‘classic’ form) and type II (a less severe form) are described (9). The less severe phenotype is associated with a mutation leading to some residual activity of the PTHR1 mutated receptors (see below).

Pathogenesis
Studies in transgenic mice demonstrated that the PThrp/PTHR1 signaling pathway is an essential regulator of endochondral bone development (11) and epithelial-mesenchymal interactions during the formation of the mammary glands and teeth (12). The findings in patients with BLC recapitulate the phenotype observed in the mouse Pthr1 and Pthrp "knock-out" (13, 14). They are the mirror image of those observed in Jansen chondrodysplasia (OMIM 156400) (15).

Molecular genetics
Four different defects in the PTHR1 gene were described in genomic DNA from patients affected by BLC. The first reported case, a product of non-consanguineous parents, was shown to have two distinct abnormalities in the PTHR1 gene (16). Through a nucleotide exchange in exon M5 of the maternal PTHR1 receptor allele, a novel splice acceptor site was introduced which led to a mutant mRNA encoding an abnormal receptor that lacks a portion of the fifth membrane-spanning domain (∆373-383). For yet unknown reasons, the paternal PTHR1 allele from this patient is very poorly expressed, suggesting an unidentified mutation in one of the different promoter regions or in a putative enhancer element. A second patient with BLC, the product of a consanguineous marriage, was shown to have a nucleotide exchange that leads to a proline to leucine mutation at position 132 (P132L) (17, 18). A homozygous deletion of G at position 1122 (exon EL2) was identified in a third case of BLC (19). This mutation led to a shift in the open reading frame, which resulted in a truncated protein that completely diverged from the wild-type receptor sequence after amino acid 364 (∆365-593).

All mutant receptors have been demonstrated by in vitro studies to have greatly reduced agonist-stimulated cAMP accumulation, with or without impaired cell surface expression and/or PTH binding. It is worth noting the P132L mutation inactivates the PTHR1 incompletely (17). Abnormalities in skeletal development in the fetuses carrying that mutation are less severe than those observed in most cases, particularly with regard to the bones of the lower limbs. This led to the proposal that two forms of BLC can be distinguished clinically and on the basis of the in vitro characteristics of the mutant PTHR1 (9). Of note, mutations in the PTHR1 gene have been associated to three diseases in addition to BLC. Jansen's metaphyseal chondrodysplasia (JMC) (OMIM 156400) (20), Eiken familial skeletal dysplasia (21), and enchondromatosis (Ollier's disease) (OMIM 166000) (22).

Jansen's metaphyseal chondrodysplasia (JMC)
JMC is a rare form of short limb dwarfism associated with laboratory abnormalities that are typically observed only in patients with either primary hyperparathyroidism, or the humoral hypercalcemia of malignancy syndrome. Four different heterozygous missense mutations (H223R, I458R, T410P, and T410R) in the PTHR1 gene have been identified in patients with JMC (15, 23). All mutations are associated
with constitutive activation of the PTHR1 in vitro. The T410R mutation shows a less pronounced constitutive activity than the previously reported T410P substitution, and is associated with a less severe form of JMC.

**Eiken familial skeletal dysplasia**

Eiken familial skeletal dysplasia has been described in a unique consanguineous family (24). It is characterized by multiple epiphyseal dysplasia, with extremely retarded ossification, as well as by abnormal modeling of the bones in hands and feet, and abnormal persistence of cartilage in the pelvis and mild growth retardation. Serum calcium and phosphate levels have been found to be normal in all the patients examined, serum PTH level was measured in one patient and found to be slightly elevated with normal 1,25-(OH)2VitD. A recessive mutation in one patient and found to be slightly elevated with an abnormal persistence of the PTHR1, has been recently identified in a kindred with Eiken syndrome (21). Although the mutant receptor has not been characterized in vitro, it is hypothesized that the truncated receptor is associated with an unbalance in the signaling pathways activated by the PTHR1.

**Enchondromatosis**

Enchondromatosis (Ollier's disease) is a non familial disorder characterized by the presence of multiple enchondromas. A mutant PTHR1 (R150C) has been identified in enchondromas from some patients affected with enchondromatosis (22). However, neither the R150C mutation (35 patients) nor any other (11 patients) mutations in the PTHR1 gene could be identified in another study, suggesting a molecular heterogeneity (25).

**Genetics/Prevalence**

Thirteen cases of BLC have been reported in the literature. The disorder occurs in families of different ethnic backgrounds and appears to affect males and females equally. Most affected infants are born to consanguineous parents (only in one instance were unrelated parents reported to have two offspring that are both affected by Blomstrand’s disease) (5).

**Genetic counseling**

It is the genetic counseling of a rare recessive lethal disorder. Mothers at risk to have a child affected with BLC should be encouraged to have transvaginal ultrasound as early as 12-13 gestational weeks (6).

**Antenatal diagnosis**

Diagnosis can be made as early as 12-13 gestational weeks by transvaginal ultrasound.

**Treatment**

There is no treatment.

**References**

is associated with abnormal breast development and tooth impaction. *J Clin Endocrinol Metab* 86, 1788-1794


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