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Blomstrand osteochondrodysplasia: three novel cases and histological evidence for heterogeneity

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Abstract Blomstrand osteochondrodysplasia (BOCD) is a rare, autosomal recessive, lethal skeletal dysplasia characterized by generalized osteosclerosis and advanced skeletal maturation. The histopathological characteristics of three novel cases (two isolated cases and a sib-pair) of BOCD are presented and correlated with the clinical and radiographical findings, and the relevant literature is reviewed. The results of our study confirm the existence of two separate types of BOCD, which we propose naming type I: the severe, 'classical' form, and type II: a less severe form.

Key words Blomstrand osteochondrodysplasia · Bone density · Clinical heterogeneity · Histopathology · Radiography

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Introduction

Blomstrand osteochondrodysplasia (BOCD) is a rare lethal skeletal dysplasia characterized by generalized osteosclerosis and advanced skeletal maturation. At present only four isolated cases and three cases of sib-pairs have been reported [1, 3, 10–12, 16, 19]. Despite the striking similarities between these cases, complete clinical delineation of this condition awaits further reports. Recently, three mutations in the parathyroid hormone (*PTH*) / PTH-related peptide (*PTHrP*) receptor gene were characterized [5, 7, 8, 20] in three previously described fetuses with BOCD [3, 11, 19]. One of these fetuses showed a markedly less severe phenotype [19], which was associated with some residual activity of the PTH/PTHrP receptors [20]. Based on the histopathological characteristics of two isolated cases and a sib-pair and a review of the literature, we present further evidence for clinical, radiological and histological heterogeneity.

Case reports

Case I was a female infant, born in 1977 to consanguineous Caucasian parents at 32 weeks of gestation after sonographic assessment of fetal death. The 30-year-old mother had previously given birth to two children with neural tube defects. Amniocentesis during the pregnancy culminating in this stillbirth had revealed a normal level of alpha-fetoprotein and a normal female karyotype. At birth the severely macerated infant (Fig. 1) showed a short stature (CRL 22.5 cm) and extreme micromelia of all four limbs. Mild exophthalmos, a hypoplastic nose, micrognathia, and protrusion of the tongue were also noted. Autopsy revealed severely hypoplastic lungs. The heart and the abdominal organs showed no evident abnormalities. Radiography (Fig. 2a–c) showed generalized osteosclerosis and advanced skeletal maturation, a small viscerocranium, short and stubby ribs and ossification of the hyoid bone, the laryngeal cartilage, and most of the carpal and tarsal bones. The extremely short tubular bones showed broad metaphyses and narrow and short diaphyses. Epiphyseal ossification centers were not seen. Histology of tubular bones (Fig. 3a, b) showed the epiphyseal resting cartilage reduced to a narrow rim, without an ossification center. The physes showed short columns of hypertrophic chondrocytes, but hardly any proliferating chondrocytes. The wid-

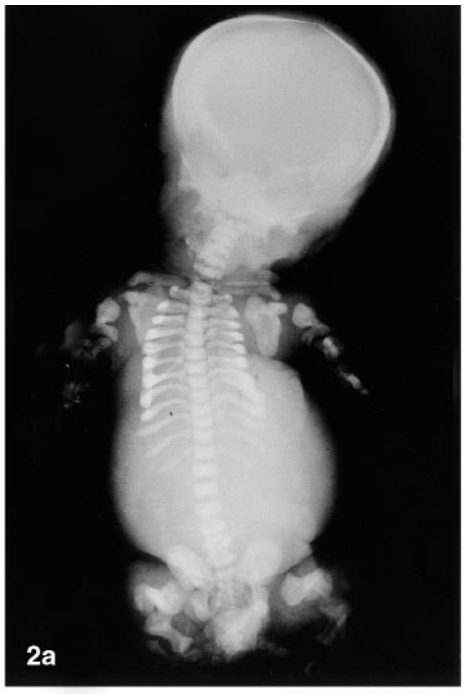


Fig. 1 Case I (32 weeks, type I Blomstrand osteochondrodysplasia; BOCD); external view. Severe maceration, short stature, extreme micromelia and typical protrusion of the tongue can be seen

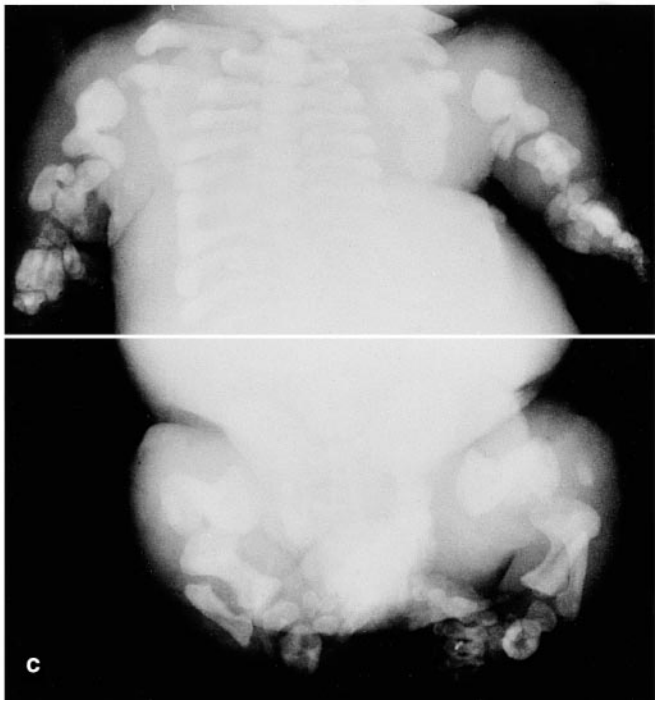


Fig. 2a–c Case I. **a** Whole-body radiograph (antero-posterior). There are short tubular bones and a small thorax with short ribs. **b** Whole-body radiograph (lateral). Micrognathia and ossification of laryngeal cartilage can be seen. **c** Radiograph of the lower part of the body (antero-posterior). Advanced ossification of patella, carpal and tarsal bones are clearly visible

ened metaphyses and narrow diaphyses showed, respectively, irregular enchondral ossification and marked subperiosteal ossification.

Case II was a sib-pair born to Asian parents who were first-degree cousins and who had no family history of skeletal dysplasia. Their first pregnancy had resulted in the birth of a healthy boy. In the second pregnancy, ultrasonography at 19 weeks revealed severe skeletal dysplasia and gross polyhydramnios. The mother, who was 21 years of age at the time, decided to continue with the pregnancy. Prenatal karyotyping was not performed. Postnatal examination of the infant at 33 weeks (Fig. 4) showed normal body length (CRL 30.5 cm) and a normal-sized head (HC 31.5 cm), which appeared enlarged because of a hypoplastic viscerocranium. Bilateral mild exophthalmos, a hypoplastic nose, a protruding tongue, severe micrognathia, and low-set ears were noted. The infant also had a narrow thorax and a mildly protruding abdomen. The limbs, especially the arms, were symmetrically shortened. Resuscitation failed and the child died 5 min after birth. Autopsy revealed hypoplastic lungs. The heart showed a dilated right ventricle, a patent ductus arteriosus, and a pre-ductal aortic coarctation. Abdominal and pelvic organs showed no abnormalities. Radiography (Fig. 5a, b) showed generalized osteosclerosis and advanced skeletal maturation, a small viscerocranium, short ribs, and ossification of the hyoid bone and the laryngeal cartilage. The tubular bones were short, especially the arms, and showed broad and flaring metaphyses. Secondary ossification centers were seen, surprisingly only in the femoral heads. Some of the carpal and tarsal bones were ossified. Histology of tubular bones (Fig. 6a, b) showed a reduction in the resting cartilage, with the presence of secondary ossification centers in the femoral heads. The physes showed irregular columnization of hypertrophic chondrocytes and a few scattered rows of proliferating chondrocytes. The widened metaphyses and narrow diaphyses showed regular bony trabeculae and normal subperiosteal ossification.

One year later, the parents' third pregnancy resulted in the birth of a healthy daughter. The fourth pregnancy was uneventful until ultrasound investigation at 19 weeks of gestation confirmed the presence of severe skeletal dysplasia. The parents elected to have the pregnancy terminated. External examination of the fetus (Fig. 7) showed normal body length (CRL 17.5 cm) and a normal-sized head (HC 17.0 cm). There were marked micrognathia, low-set ears, a narrow thorax, and shortening of all four limbs. At au-

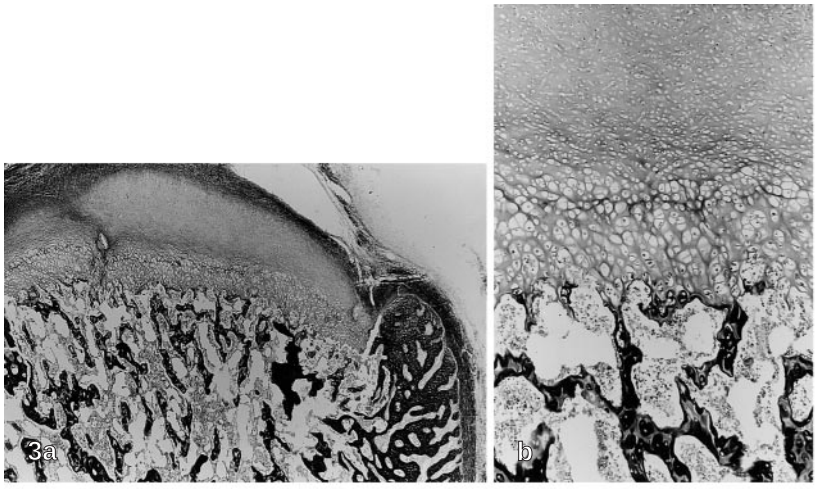


Fig. 3. a Case I: low magnification of the humeral head. There is narrowing of the epiphyseal cartilage. The enchondral growth plate shows slight irregularity with marked thickening of the subperiosteal ossification, which overgrows the growth plate. Ladewig, ×20.6 **b** Detail of **a**. In spite of the severe maceration the hypertrophic cartilage zone is still visible with absence of the proliferative zone. Ladewig, ×82.5

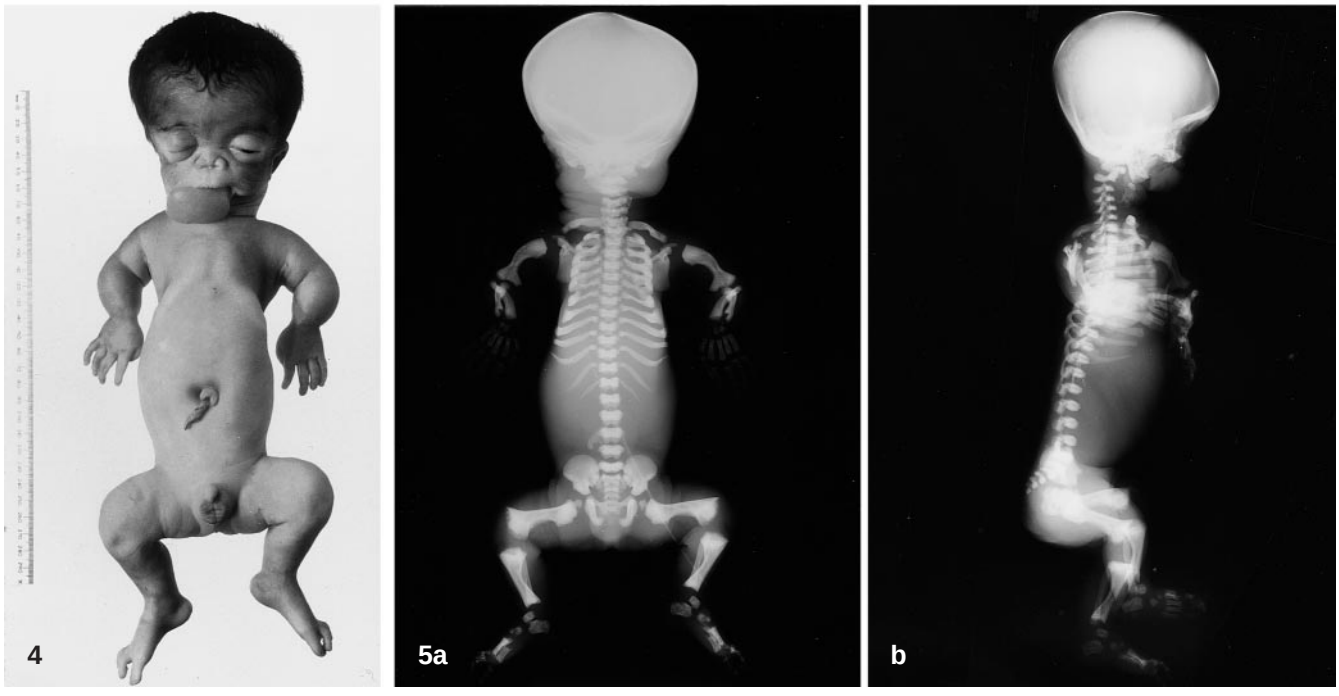


Fig. 4 Case II, older sib (33 weeks, type II BOCD); external view. The length of the trunk is almost normal, and the micromelia is not as severe as in type I (see Fig. 1), but the protrusion of the tongue is striking

Fig. 5a, b Case II, older sib, whole-body radiographs. **a** Anteroposterior view. There is shortening of the tubular bones, hypoplasia of the viscerocranium, short ribs with narrow thorax and advanced ossification of the carpal and tarsal bones. **b** Lateral view showing frontal bossing, severe micrognathia and ossification of the laryngeal cartilage

topsy, the lungs were mildly hypoplastic. The heart and the abdominal organs showed no evident abnormalities. Radiography (Fig. 8a, b) showed generalized osteosclerosis and advanced skeletal maturation, a small viscerocranium, short ribs, and ossification of the hyoid bone and the laryngeal cartilage. The tubular bones were short with broad and flaring metaphyses. Ossification was seen in some of the tarsal bones. Given the younger gestational age, histology of tubular bones (Fig. 9) showed essentially the same picture as seen in the older affected sib.

Case III was in a male fetus examined after termination of pregnancy at 26 weeks of gestation following ultrasonographic assessment of severe skeletal dysplasia. The parents were Asian, but there was no other relevant past medical or family history. The mother was 28 years of age. External examination of the fetus showed normal body length (CRL 25.5 cm) and a normal-sized head (HC 24.0 cm). There were marked micrognathia, low-set ears, a narrow thorax, marked shortening of all four limbs, and a small penis. At autopsy, the lungs were found to be hypoplastic. The heart and the abdominal organs showed no evident abnormalities. Radiography (Fig. 10) showed generalized osteosclerosis and advanced skeletal maturation, a small viscerocranium, short ribs, and ossification of the hyoid bone and the laryngeal cartilage. The tubular bones were short and showed broad and flaring metaphyses. Ossification was seen in some of the tarsal bones and was minimal in the carpal bones. Histology of tubular bones (Fig. 11a, b) showed a reduction of the resting cartilage, short columns of hypertrophic chondrocytes, and a few scattered rows of proliferating chondrocytes. The widened metaphyses and narrow diaphyses showed irregular bony trabeculae; subperiosteal ossification was near normal.

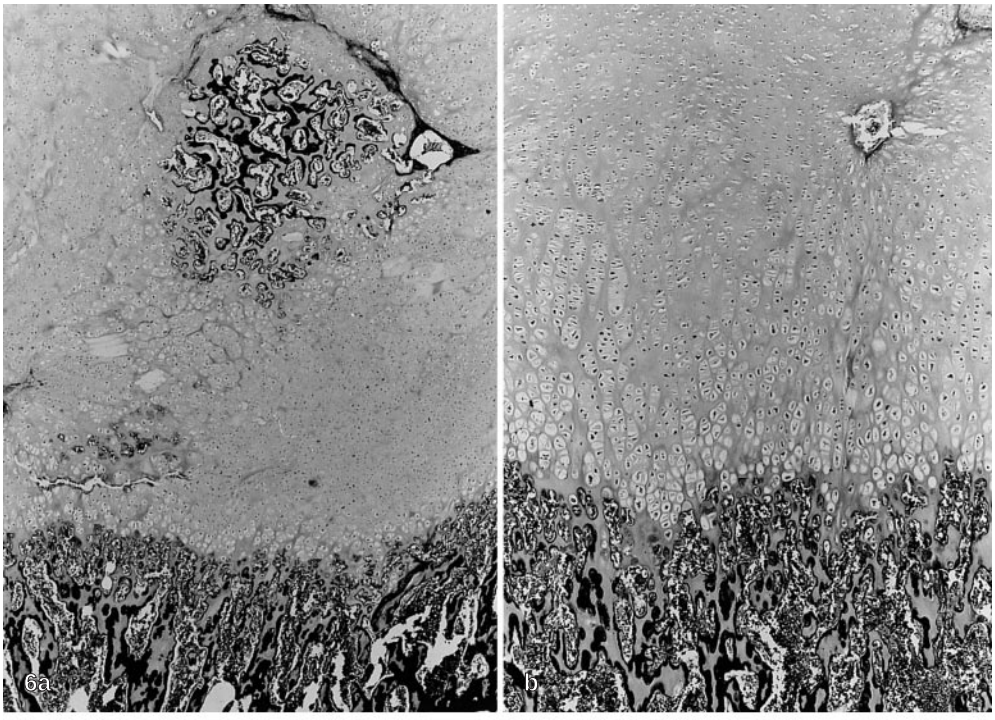


Fig. 6. a Case II, older sib: low magnification of the femoral head showing the enchondral growth plate. There is early ossification of the epiphyseal center. Ladewig, ×20.6. **b** Detail of **a**. The hypertrophic zone shows irregular columnization, and some parallel rows of proliferative cartilage cells are seen near the center. Ladewig, ×41.3

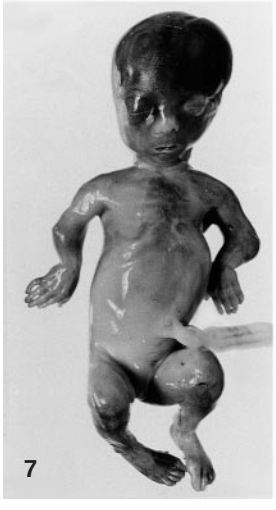


Fig. 7 Case II, younger sib (19 weeks, type II BOCD); external view. The phenotypic presentation in this case is the same as in the older sib, but protrusion of the tongue is lacking

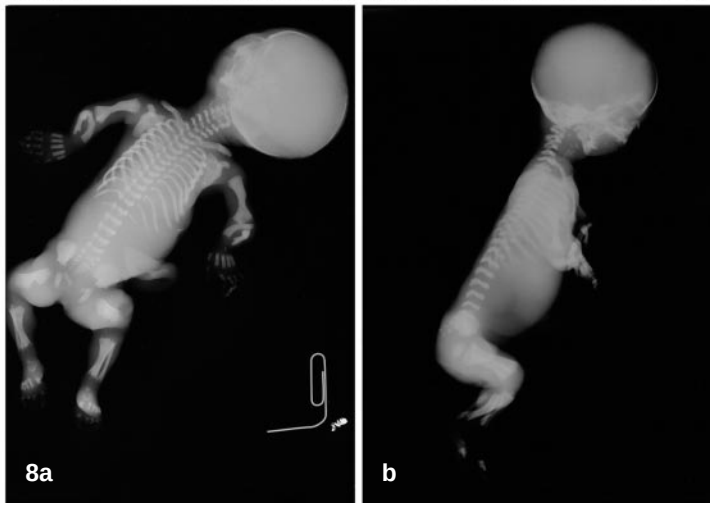


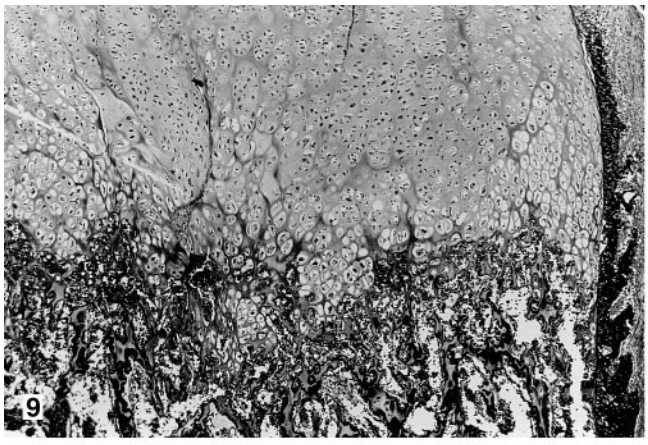
Fig. 8a, b Case II, younger sib; whole-body radiographs. **a** Antero-posterior. The skeleton is comparable with that of the older sib. Ossification of tarsal bones is starting, but not visible in carpal bones. **b** Lateral. The picture is comparable with that of the older sib

Discussion

Our first case presented with clinical, radiographical, and histological peculiarities closely matching the descriptions in almost all other case reports of BOCD. Besides generalized osteosclerosis and advanced skeletal maturation, these descriptions include short stature, extremely short limbs, ossification of all or most carpal and tarsal bones and patellar ossification (at least in those cases that have a gestational age of 30 weeks or more), narrow diaphyseal bone marrow spaces, and thickened cortical bone. The clinical, radiographical and histological characteristics of the presently known cases of BOCD are summarized in Table 1.

As mentioned before, the phenotype of the infant described by Young et al. [19] was different in several aspects from those described in the above reports. She had a normal-sized trunk and less severe shortening of the limbs, especially of the legs. Moreover, radiography showed ossification in only some of the carpal and tarsal bones, the presence of epiphyseal ossification centers in the femoral heads, and the absence of patellar ossification. This profile, which differs from the classical phenotype in that the generalized sclerosis and advancement in bone maturation are less pronounced, was also found in our case II (in both affected sibs) and in case III. These are the second and third cases reported to date with this phenotype. In addition, histology of tubular bones in these cases revealed less abnormal cortical bone and better development of the proliferating and hypertrophic cartilage.

The issue of secondary ossification centers in BOCD deserves special attention. Normally, epiphyseal ossification centers appear in the distal femur between 31 and 34



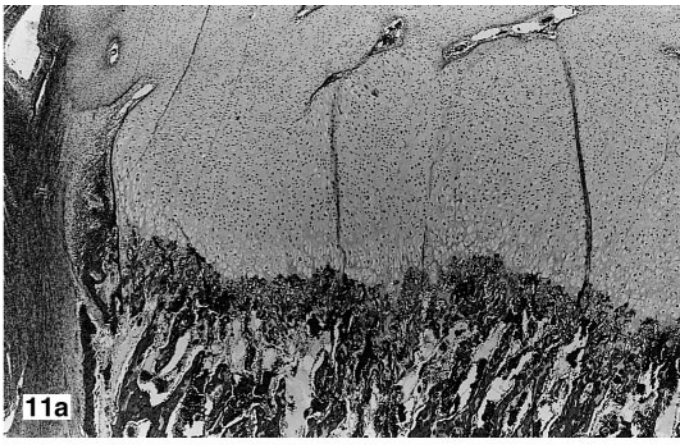


Fig. 9 Case II, younger sib; growth plate of the humeral head. The transformation zone is irregular as well as the hypertrophic zone. In the *center* some parallel rows of proliferative chondrocytes are seen. On the *right side* some overgrowth of the subperiosteal ossification is seen, but the cortex is not thickened. Ladewig, ×41.3

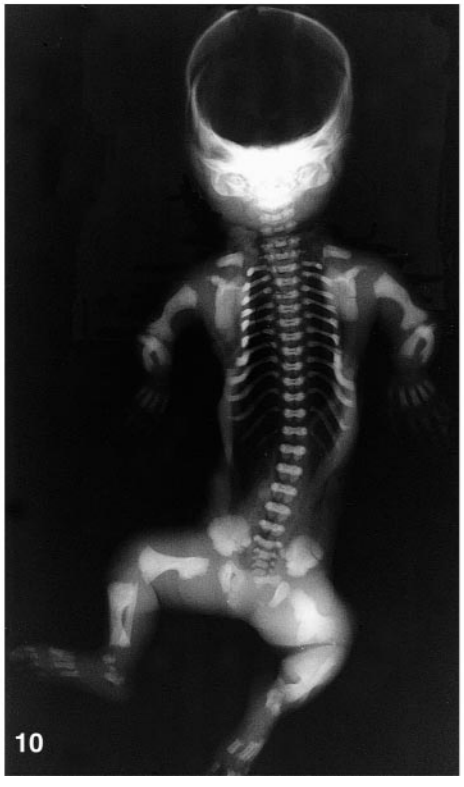


Fig. 10 Case III (26 weeks, type II BOCD); whole-body radiographic composite view (antero-posterior). Although the radiograph was taken after autopsy the picture suggests that this case is comparable with case II (see Fig. 5a). Ossification of carpal bones is starting, but some tarsal bones are seen

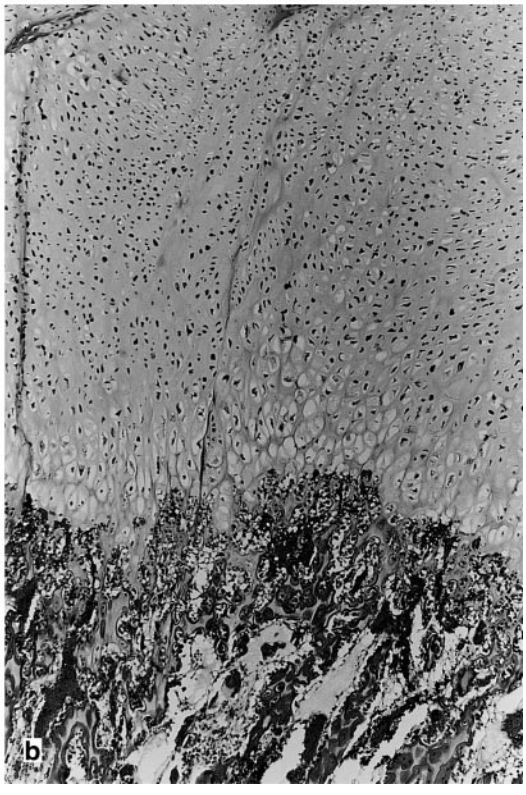


Fig. 11. a Case III: low magnification of the growth plate of the humeral head. Ladewig, ×20.6. The picture is comparable with that of case II (Fig. 6a). **b** Detail of **a**. Some parallel rows of proliferative chondrocytes are seen above the hypertrophic zone. Ladewig, ×41.3

weeks of gestation and in the proximal tibia between the 34th and 40thweeks gestation or neonatally [4], whereas all other secondary ossification centers of the tubular bones appear after birth. In contrast to what one would expect in the view of the highly advanced bone age, there is radiographic and histological absence of visible epiphyseal ossification centers in the classical severe phenotype of BOCD, even in cases with a gestational age of 30 weeks or more. It is assumed that these centers are absorbed by the advancing metaphyseal ossification front [11]. In our opinion, however, the absence of ossification centers might be due to the severe hypoplasia of epiphyseal resting cartilage preventing the development of epiphyseal ossification centers. Therefore, secondary ossification centers would appear if epiphyseal resting cartilage were less hypoplastic, which actually seems to occur in the proximal femora of older fetuses (more than 30 weeks' gestation) presenting with the milder phenotype of BOCD. Ossification of the femoral heads, which normally starts during the 1st year of life, is found both in the case described by Young et al. [19] (30 weeks gestation) and in the older sib of our case II (33 weeks' gestation), whereas no other epiphyseal ossification centers are found in these cases. Indeed, histology of the femoral heads in the older sib of case II shows a larger amount of epiphyseal resting cartilage than in more severe cases of the same gestational age.

To quantify the histologically assessed difference in width of bone marrow spaces between the two phenotypes, the percentage surface area of the bone trabeculae of the humeral head metaphysis/diaphysis was determined by stereology in four cases of BOCD with differ-

Table 1 Phenotypic characteristics of Blomstrand osteochondrodysplasia (BOCD). *Asterisks* indicate pending results, *letters on line* indicate familial cases, figures in round brackets indicate terminated pregnancies (*abs*. absent, *min.* minimal signs of ossification, *n.i.* no information)

	Reported cases									Present cases			
	[1]	[3]		[10][a]	[11]		[12]	[16]	[19]	I	II		III
		a	b		a	b					a	b	
Gestational age (weeks)[3]	29	(19)	(12)	31	(27)	33	?	26	30	32	33	(19)	(26)
Parental consanguinity	Yes	Yes		Yes	No		?	Yes	Yes	Yes	Yes		?
Clinical													
Sex	F	F	F	F	M	F	F	M	F	F	M	F	M
Fetal hydrops	+	+	+	+	+	+	+	?	–	?	–	–	?
Polyhydramnios	+	?	?	+	+	+	?	?	+	?	+	?	?
Flat nasal bridge	+	?	?	+	+	+	+	?	+	+	+	+	?
Protruding tongue	+	+	?	–	+	+	+	?	–	+	+	+	–
Micrognathia	+	+	?	+	+	+	+	?	+	+	+	+	+
Short trunk	+	+	+	+	+	+	+	+	–	+	–	–	–
Extremely short limbs	+	+	+	+	+	+	+	+	–	+	–	–	–
Aortic coarctation	+	–	?	+	+	+	?	?	–	–	+	–	–
Radiographical													
Generalized sclerosis and advanced bone age	+	+	+	+	+	+	+	+	+	+	+	+	+
Hypoplastic viscerocranium	+	+	?	+	?	?	+	+	+	+	+	+	+
Calcified laryngeal cartilage and hyoid bone	+	+	?	+	+	+	+	+	+	+	+	+	+
Short ribs	+	+	+	+	+	+	+	+	+	+	+	+	+
Extreme shortening of long bones	+	+	+	+	+	+	+	+	–	+	–	–	–
Recognizable epiphyses	–	–	–	–	–	–	–	–	+	–	+	–	–
Broad metaphyses	+	+	+	+	+	+	+	+	+	+	+	+	+
Ossified carpal bones	Most	Most	?	7	Most	Most	6	Most	3	Most	3	None	min.
Ossified tarsal bones	Most	6	?	7	Most	Most	7	Most	4	Most	4	Some	Some
Patellar ossification	?	–	?	+	?	+	+	?	–	+	–	–	–
Bony tail	?	?	?	?	?	?	+	?	+	?/+	+	+	?
Histological						n.i.	n.i.	n.i.	n.i.				
Reduced epiphyseal cartilage	++	++	++	++	+					++	+	+	+
Epiphyseal ossification center	–	–	–	–	–					–	+	–	–
Thin proliferating cartilage	+	+	+	+	+					+	+	+	+
Thickened cortical bone	+	+	+	+	+					+	–	–	–
Biochemical													
Expression of functional PTH/PTHrP receptor	n.i.	abs.	n.i.	n.i.	abs.	n.i.	*	n.i.	<10%	*	*		*

[a] No clinical data were available with respect to the affected sib

ent phenotypes and in ten normal controls. For the severe phenotype we used histological slides of a case described by Den Hollander et al. [3] in a fetus of 19 weeks' gestation, and a case described by Leroy et al. [10] in a fetus of 31 weeks' gestation, because the material of our case I was too macerated. The milder phenotype was represented by slides of cases II (second affected sib; 19 weeks' gestation) and III (26 weeks' gestation). The slides were imaged using the QPRODIT interactive video overlay device (Leica, Cambridge, UK) [2]. In short, points of a six-point Weibel grid overlying bone trabeculae and bone marrow were counted up to a minimum of 500 points at a final on-screen magnification of approximately 30× (10× objective), and the ratio of the area of bone trabeculae to marrow was calculated as a percentage (points on bone × 100/points on bone + points on marrow). The correlation between the values obtained from the controls and their gestational age fits best with a linear regression. The fetal bone density seems to decrease slightly with increasing age: the bone density in the severely affected cases was significantly increased ($P<0.05$), whereas the mildly affected cases showed no significant difference from normal in bone density. The results are summarized in Fig. 12.

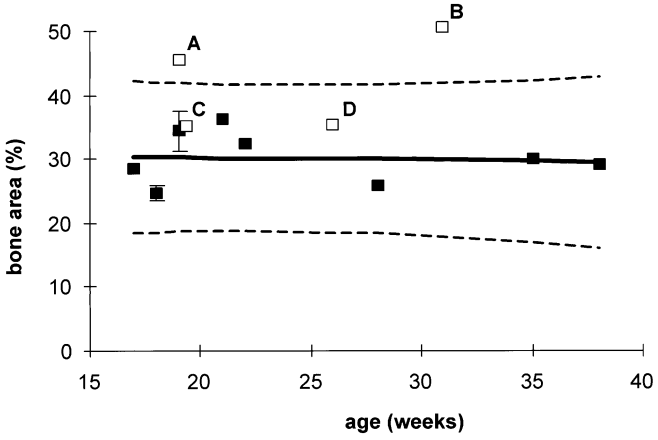


Fig. 12a–d Stereologically assessed surface area percentage of the bone trabeculae of the humeral head metaphysis/diaphysis in ten normal fetuses at various gestational ages (*filled squares*) and in four cases of BOCD (*unfilled squares*). *Dashed line*s indicate 95% confidence interval of the regression line (*bold line*). The bone area percentage (*y*-axis) shows a slight linear decrease with progression of gestational age (*x*-axis) in the normal controls. The severe phenotype (**a**, **b**) shows a significantly increased bone density ($P<0.05$), whereas the milder phenotype (**c**, **d**) has density values within the confidence interval

Differences in the severity of the phenotype could result from variable expression of the same mutation. However, with BOCD this seems unlikely, for two reasons. First, in the reported familial cases and in the sib-pair described here (case II) the affected sibs presented with the same degree of severity. Secondly, the various mutations described in BOCD to date result in either absence or residual presence of functioning PTH/PTHrP receptor, which correlates with a severe or a less severe phenotype, respectively. It is interesting to note that all the cases with the less severe phenotype currently identified, being our cases II and III and the case described by Young et al. [19], were the children of Asian parents. In the latter case a homozygous point mutation in the *PTH* / *PTHrP* receptor gene was found, both by Zhang et al. [20] and by Karaplis et al. [7]; this mutation causes an amino acid change (proline to leucine) at position 132 of the protein. Results of DNA investigation in cases II and III, to find out whether this mutation is a founder mutation in the Asian population in England, are pending.

Although the mutations in BOCD were found quite recently, it has already been known for some years that the PTH/PTHrP receptor is involved in skeletal dysplasias, both in mice and in humans. Advanced skeletal maturation, as seen in BOCD, was found both in PTH/PTHrP receptor (-/-) [9] and, to a lesser degree, in PTHrP (-/-) knock-out mice [6]. Conversely, in Jansen metaphyseal chondrodysplasia, which is characterized by delayed skeletal maturation, mutations have been reported in the *PTH* / *PTHrP* receptor gene that result in a constitutively active receptor that is independent of PTHrP [13, 14]. Similar maturation defects were seen in transgenic mice with a constitutively active PTH / PTHrP receptor [15] or a targeted overexpression of PTHrP [18]. Apart from maintaining calcium homeostasis in adults, the complex of the PTH/PTHrP receptor and its ligand PTHrP plays a part in several embryonic processes, especially in the rate of chondrocyte differentiation in the growth plate of developing skeletal structures [9]. PTHrP suppresses this differentiation when binding to the PTH / PTHrP receptors of prehypertrophic chondrocytes [6, 9]. Expression of PTHrP by hypertrophic chondrocytes is stimulated through the release of an evolutionary conserved protein called Indian hedgehog (Ihh) by the pre-

Table 2 Clinical, radiographical, histological and biochemical differences between the two proposed types of BOCD

Types	I	II
Clinical		
Short trunk	Yes	No
Arms	Extremely shortened	Severely shortened
Legs	Extremely shortened	Moderately shortened
Radiographical[a]		
Recognizable epiphyses	No	Yes
Ossified carpal bones	All or most	Some or minimal
Ossified tarsal bones	All or most	Some
Patellar ossification	Yes	No
Histological[a]		
Epiphyseal ossification centers	No	Yes
Reduced resting and proliferative cartilage	Severely	Less severely
Diaphyseal bone marrow spaces	Reduced	Normal
Cortical bone thickening	Profound	Mild
Biochemical		
Expression of functional PTH/PTHrP receptor	Absent	Severely reduced

[a] Beyond 30 weeks' gestation

hypertrophic chondrocytes, which in its turn enhances chondrocyte differentiation [17]. In this way, the whole process is subjected to a negative feedback loop.

We conclude that the previously reported biochemical and molecular results, supported by our own clinical, radiographical and histological findings, indicate that there are two separate types of BOCD, which we propose to name type I (the severe, classical form) and type II (the less severe form). The characteristics of these types are summarized in Table 2. Although the presently described mutations in BOCD were found in the *PTH* / *PTHrP* receptor gene, resulting in absent [5, 8] or severely reduced [20] expression of functional receptors, no mutations were found in either the receptor gene itself or the upstream untranslated region of the paternal allele of the case described by Joubert et al. [5], despite the absence of its expression. This may indicate that mutations in sequences that regulate the expression of the receptor gene (those involved in the negative feedback loop) may also result in BOCD, either as a homozygous mutation or in combination with a receptor gene mutation. There is therefore scope for further phenotypic and genotypic diversity in the syndrome of advanced skeletal maturation.

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References

1. Blomstrand S, Claësson I, Säve-Söderbergh J (1985) A case of lethal congenital dwarfism with accelerated skeletal maturation. Pediatr Radiol 15:141–143
2. Brugghe J, Baak JPA, Meijer GA, Diest PJ, Brinkhuis M (1998) Rapid and reliable assessment of volume percentage of epithelium in borderline and invasive ovarian tumours. Anal Quant Cytol Histol 20:14–20
3. Den Hollander NS, Van der Harten JJ, Vermeij-Keers C, Niermeijer MF, Wladimiroff JW (1997) First trimester diagnosis of Blomstrand lethal osteochondrodysplasia. Am J Med Genet 73:345–350
4. Dimmick JE, Kalousek DK (1992) Developmental pathology of the embryo and fetus. Lippincott, Philadelphia, p. 667
5. Joubert AS, Zhang P, Couvineau A, Bonaventura J, Roume J, Le Merrer M, Silve C (1998) Absence of functional receptors for parathyroid hormone and parathyroid hormone-related peptide in Blomstrand chondrodysplasia. J Clin Invest 102:34–40
6. Karaplis AC, Luz A, Glowacki J, Bronson RT, Tybulewicz VL, Kronenberg HM, Mulligan RC (1994) Lethal skeletal dysplasia from targeted disruption of the parathyroid hormone-related peptide gene. Genes Dev 8:277–289
7. Karaplis AC, He B, Nguyen MTA, Young AD, Semeraro D, Ozawa H, Amizuka N (1998) Inactivating mutation in the human parathyroid hormone receptor type 1 gene in Blomstrand chondrodysplasia. Endocrinology 139:5255–5258
8. Karperien M, Van der Harten JJ, Van Schooten R, Farih-Sips H, Nijweide P, Papapoulos SE, Loewik CWGM (1999) A frame-shift mutation in the type I parathyroid hormone/parathyroid hormone-related peptide receptor causing Blomstrand lethal osteochondrodysplasia. J Clin Endocrinol Metab (in press)
9. Lanske B, Karaplis AC, Lee K, Lutz A, Vortkamp A, Pirro A, Karperien M, Defize LHK, Ho C, Mulligan RC, Abou-Samra AB, Jüppner H, Segre GV, Kronenberg HM (1996) PTH/PTHrP receptor in early development and Indian hedgehog regulated bone growth. Science 273:663–666
10. Leroy JG, Keersmaekers G, Coppens M, Dumon JE, Roels H (1996) Blomstrand lethal osteochondrodysplasia. Am J Med Genet 63:84–89
11. Loshkajian A, Roume J, Stanescu V, Delezoide A, Stampf F, Maroteaux P (1997) Familial Blomstrand chondrodysplasia with advanced skeletal maturation: further delineation. Am J Med Genet 71:283–288
12. Oostra RJ, Baljet B, Dijkstra PF, Hennekam RCM (1998) Congenital anomalies in the teratological collection of Museum Vrolik in Amsterdam, The Netherlands. II. Skeletal dysplasias. Am J Med Genet 77:116–134
13. Schipani E, Kruse K, Jüppner H (1995) A constitutively active mutant PTH/PTHrP receptor in Jansen-type metaphyseal chondrodysplasia. Science 268:98–100
14. Schipani E, Langman CB, Parfitt AM, Jensen GS, Kikuchi S, Kooh SW, Cole WG, Jüppner H (1996) Constitutively activated receptors for parathyroid hormone and parathyroid hormone-related peptide in Jansen's metaphyseal chondrodysplasia. N Engl J Med 335:708–714
15. Schipani E, Lanske B, Hunzelman J, Luz A, Kovacs CS, Lee K, Pirro A, Kronenberg HM, Jüppner H (1997) Targeted expression of constitutively active receptors for parathyroid hormone and parathyroid hormone-related peptide delays enchondral bone formation and rescues mice that lack parathyroid hormone-related peptide. Proc Natl Acad Sci USA 94: 13689–13694
16. Spranger J, Maroteaux P (1990) The lethal osteochondrodysplasias. In: Harris H, Hirschhorn K (eds) Advances in human genetics, vol 19. Plenum Press, New York, pp 1–103
17. Vortkamp A, Lee K, Lanske B, Segre GV, Kronenberg HM, Tabin CJ (1996) Regulation of rate of cartilage differentiation by Indian hedgehog and PTH-related protein. Science 273: 613–622
18. Weir EC, Phibrick WM, Amling M, Neff LA, Baron R, Broadus AE (1996) Targeted overexpression of parathyroid hormone-related peptide in chondrocytes causes chondrodysplasia and delayed enchondral bone formation. Proc Natl Acad Sci USA 93:10240–10245
19. Young ID, Zuccollo JM, Broderick NJ (1993) A lethal skeletal dysplasia with generalized sclerosis and advanced skeletal maturation: Blomstrand chondrodysplasia? J Med Genet 30: 155–157
20. Zhang P, Joubert AS, Couvineau, Silve C (1998) A homozygous inactivating mutation in the parathyroid hormone / parathyroid hormone-related peptide receptor causing Blomstrand chondrodysplasia. J Clin Endocrinol Metab 83:3365–3368