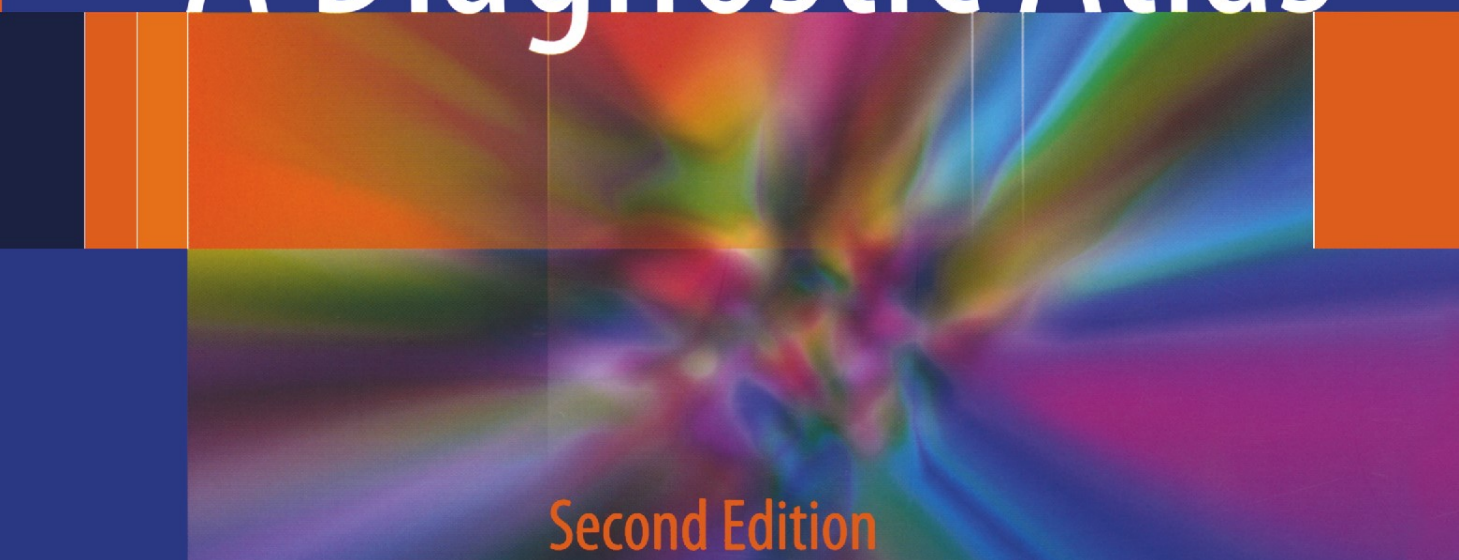
Reinhard Schumacher
Laurie H. Seaver
Jürgen Spranger

Fetal Radiology
A Diagnostic Atlas



Second Edition

Springer

R. Schumacher · L. Seaver · J. Spranger

Fetal Radiology

2nd Edition

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With 113 Figures in 238 Individual Illustrations
and 51 Tables

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Preface to the Second Edition

The first edition of Fetal Radiology was sold out fast necessitating a second edition within a relatively short period of time. This second edition preserves the character of the book as an illustrated reference for the stages of normal prenatal skeletal development and as a structured tool for the radiologic diagnosis of fetal anomalies. The authors have refrained from including MR images. This method is at the moment not suitable for a detailed skeletal diagnosis.

The following major changes have been made.

Chapter 1 now covers the skeletal development between the 9th and 24th gestational week. The often very subtle milestones during the development are illustrated separately and enlarged.

Chapter 2 has been revised and the spectrum of differential diagnoses has been expanded. Illustrations of key findings have been separately enlarged to stress their importance.

Chapter 3 has been thoroughly revised to keep up with the progress made in the field of osteochondrodysplasias during the last few years.

The Authors

Contents

Acknowledgements

This book could not have been written without the help of many physicians who provided material for consultation. Our heartfelt thanks go to Horst Müntefering, who during his long tenure as head of the Department of Pediatric Pathology of the University of Mainz oversaw the diagnosis and classification of fetal material, securing the establishment of a remarkable collection of fetal specimens. We gratefully acknowledge the help of Dr. Tim Tralau, who faithfully assisted in the radiographic documentation and selection of cases. We are indebted to Springer-Verlag, notably to Dr. U. Heilmann, Mrs D. Mennecke-Bühler, Mr C.-D. Bachem and Mr J.W. Schmidt, for their commitment, patience and expertise in producing this book.

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Introduction

Intrinsic errors of skeletal development are individually rare but of clinical importance because of their overall frequency and their impact on patients' lives. Conventionally they are divided into *malformations* – defects of single bone – and *dysplasias* – systemic defects of chondro-osseous tissue. Depending on the type of surveillance system, limb reduction defects, one major category of skeletal malformations, are recognized in 3.1–6.9 of 10,000 newborns (Eurocat 2002; Makhoul et al. 2003; McGuirk et al. 2001; Stoll et al. 2000). Due to spontaneous or induced fetal loss, the prevalence in fetuses is higher, up to 15.7 of 10,000 (A. Queisser 2003, personal communication). The overall prevalence of neonatally manifested skeletal dysplasias is about 2 out of 10,000, half of them lethal (Andersen 1989; Gobben et al. 1990; Gonnor et al. 1985; Rasmussen et al. 1996).

As sonography has become a routine component of prenatal care, many of these disorders are diagnosed prenatally confronting family and physician with the question of elective termination of pregnancy. Ideally, this question is discussed on the basis of a specific diagnosis. However, such a diagnosis is difficult to achieve by fetal sonography. Even under optimal conditions it is missed in at least 35% of cases (Schramm et al. 2009; Parilla 2003; Stoll et al. 2000) meaning that many abortions are performed on the basis of diagnostic suspicion.

Postnatally, the prenatal diagnosis has to be verified. To do this, fetal radiography becomes important. It is an effective, simple and economic way to establish a diagnosis or to narrow the number of diagnostic possibilities sufficiently to direct pathological, biochemical or molecular studies in their quest for a specific diagnosis. A specific diagnosis is required for various reasons. It permits sonographic quality control. It provides the clinical basis for research. More importantly, it is required for proper parental counseling. Parents who have gone through the termination of a pregnancy have a right to know all the available facts as to possibilities of recurrence.

This book has been written to assist in fetal postnatal radiological diagnosis. It is divided into three chapters:

1. *Development of the normal fetal* skeleton between gestational weeks 10 and 24. The chapter presents age-dependent standards with which to compare diagnostic films.
2. *Radiological differential diagnosis* of conspicuous defects of single bones such as pre- or postaxial limb deficiencies or vertebral segmentation defects. These malformations occur alone or combined in numerous conditions which are tabulated to assist in differential diagnosis. Starting from a given specific abnormality, malformation patterns can be recognized leading to a specific diagnosis or to a narrowing of the number of diagnostic possibilities.
3. *Fetal osteochondrodyspiasias.* Skeletal diseases caused by factors that continue to express themselves after the earliest stages of fetal development result in osteochondrodysplasias, systemic alterations of form, structure, and maturation of bone. Recognition of the expression pattern allows for a specific diagnosis with its prognostic, genetic, and often molecular information. In this chapter are found illustrations of the salient radiological manifestations of the most common lethal and nonlethal osteochondrodysplasias manifesting in fetal life.

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1 Development of the Normal Fetal Skeleton

Introduction

The fetal skeleton ossifies in a time-dependent sequence of patterns. The elements of these patterns – foci of mineralization within preformed mesenchymal templates – can be recognized by radiography and ultrasound.

Radiographic sequential patterns will be presented in this atlas using images of normal fetuses at specific gestational ages (**Figs. 1.1–1.14**). The images were selected from about 150 normal fetuses. Only those X-rays were used, where gestational age, clinical age based on foot length, and radiographic age were in accordance.

Recognition of a pattern of ossified structures allows the determination of the developmental stage of a given fetus within the range of normal variability (**Tables 1.1–1.5**). With few exceptions, variability ranges for the first appearance of marker bones, such as the ischial bone or the middle phalanx of the fifth finger, are not known. The standard error for the appearance of a specific ossification center is estimated to be approximately ± 1 week. Variability increases with gestation; it is smaller in a fetus of 12 weeks than in a fetus of 23 weeks gestational age. To add precision to this admittedly coarse estimate, age-related percentiles of the femoral length will be provided in the legends to the age-specific images. These are taken from published percentiles of normal femoral growth, which were obtained in population-based sonographic and radiographic studies (Merz 1988; Scherf 2001). In a normal fetus, pattern age (Eurin et al. 1993) and femoral length age will be identical. Lack of congruence points to developmental abnormalities. For instance, a femur length of less than 15 mm in a 16th gestational week fetus suggests intrauterine growth retardation. On the other hand, absent ossification of the cervical vertebral bodies in a fetus with a femur length of 22 mm suggests delayed ossification of the axial skeleton, as seen in some skeletal dysplasias.

The images of normally developed fetuses at specific ages will also provide the normative basis with which to compare abnormal looking bones. While crude abnormalities such as longitudinal or transverse limb defects, are easily recognized, discrete abnormalities such as developmental delay, minor formative and structural abnormalities of single bones or the entire skeleton, are not easily diagnosed without resource to abnormal features.

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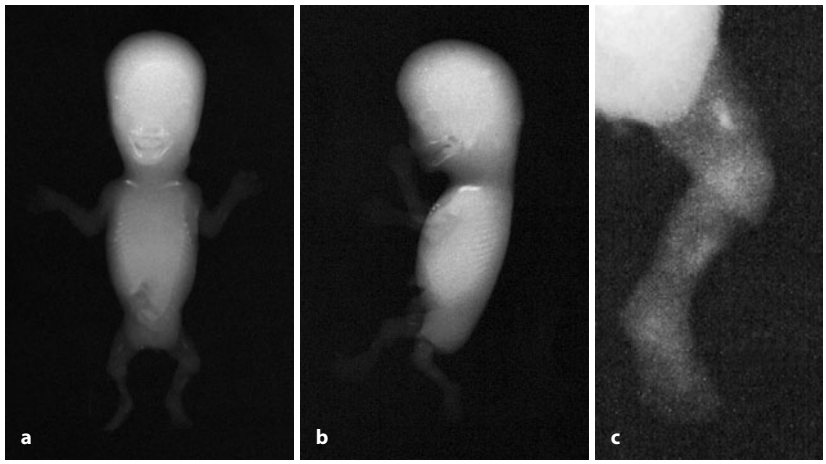
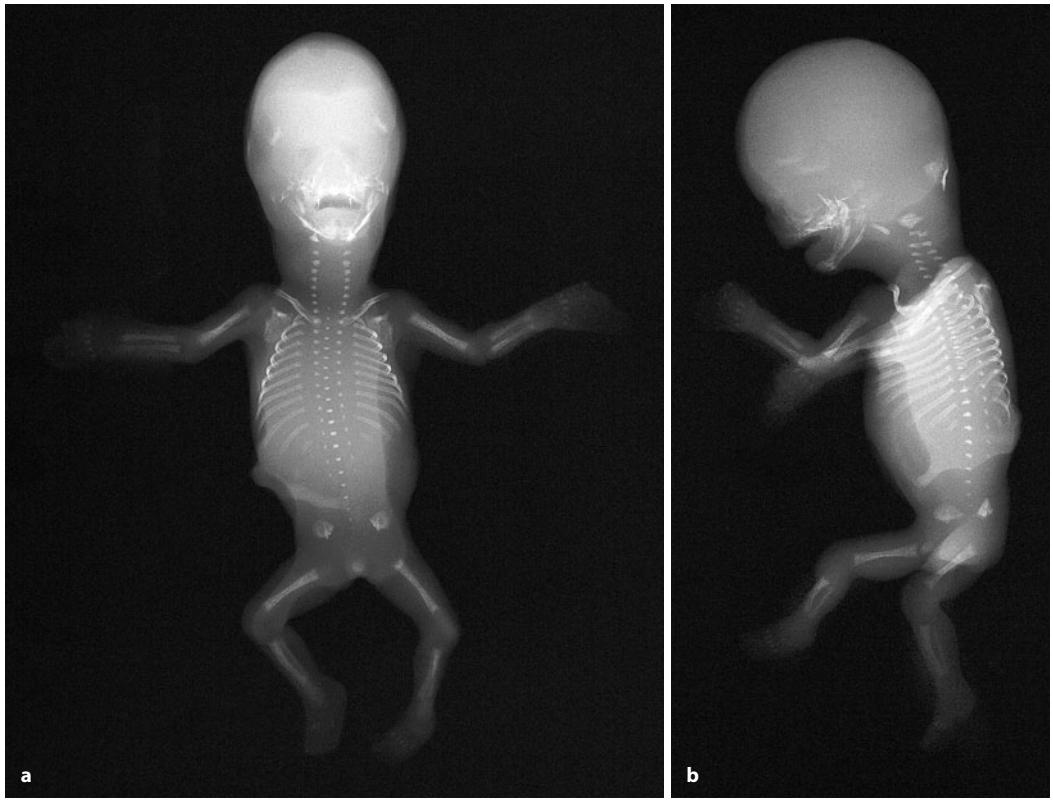


Fig. 1.1a, b (Original size) ***Week 9–10.*** Length of femur: 2 mm
Milestone: The clavicles are ossified; there is no ossification of the vertebral bodies and the neural arches
Earliest ossification centers are seen in the clavicles, mandible and maxilla. The basiocciput, the orbital roofs and the ribs are faintly visible. Small condensations are present in the diaphyses of the long bones
c (Detail) Enlargement left leg



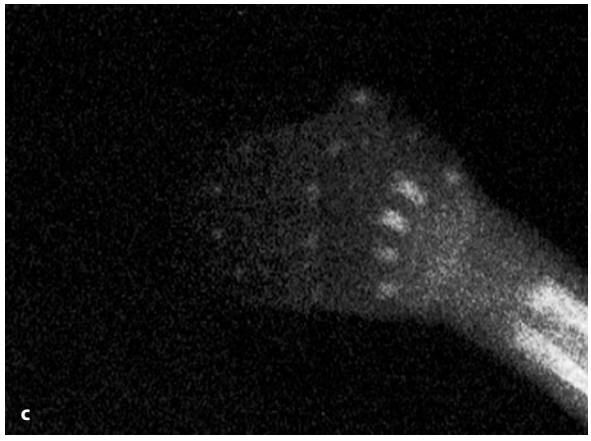


Fig. 1.2a, b (Original size) ***Week 11–12.*** Length of femur: 7 mm
Ossification centers appear in orbital roofs, the occiput, maxillae, and mandibulae. There is still a symphysis menti. The calvaria is not ossified. The clavicles grow toward their acromial ends. Ossification centers of the neural arches are visible from C1 to the upper lumbar vertebrae. The vertebral bodies are ossified in the thoracic and lumbar spine. Iliac bones and scapulae are seen as well-rounded structures. There is incipient modeling of the long tubular bones demarcating diaphyses from metaphyses. The metacarpals and metatarsals appear. The proximal phalanges of digits 2–5, both phalanges of the thumb, and one ossification center of the great toe appear

◁
c (Detail) *Milestone:* Metacarpals and terminal phalanges become visible

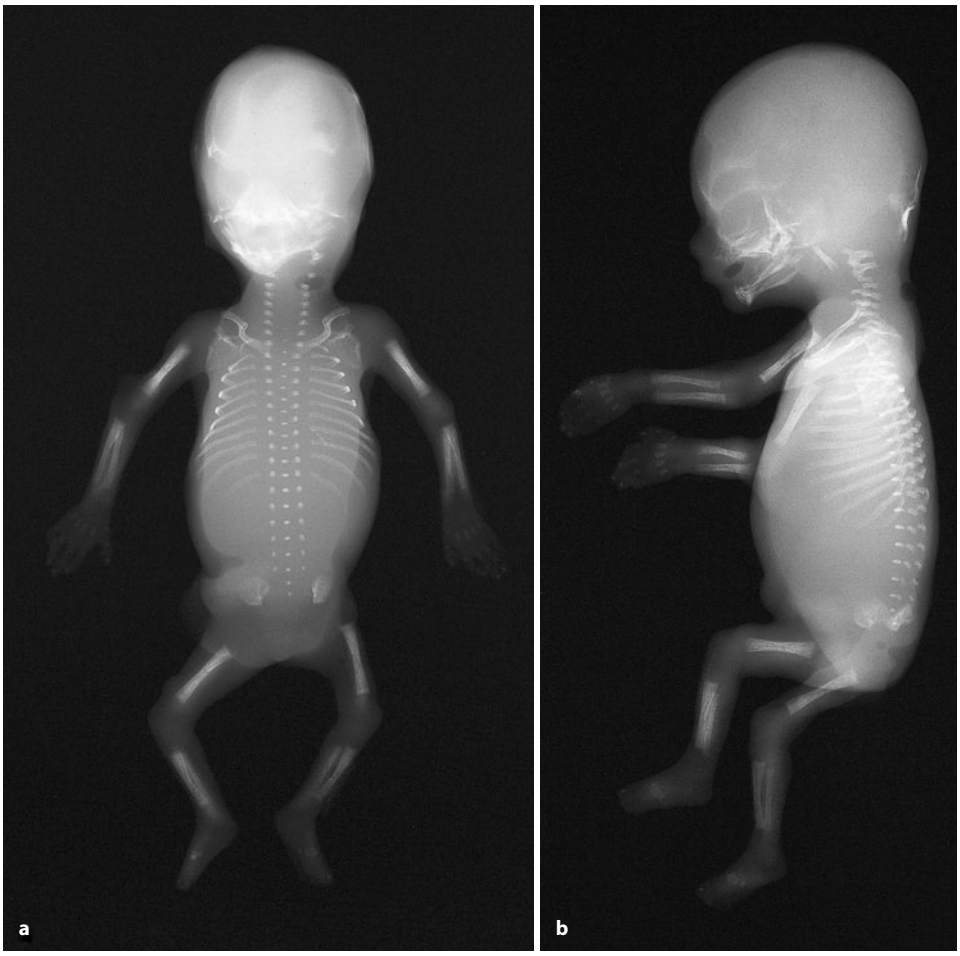
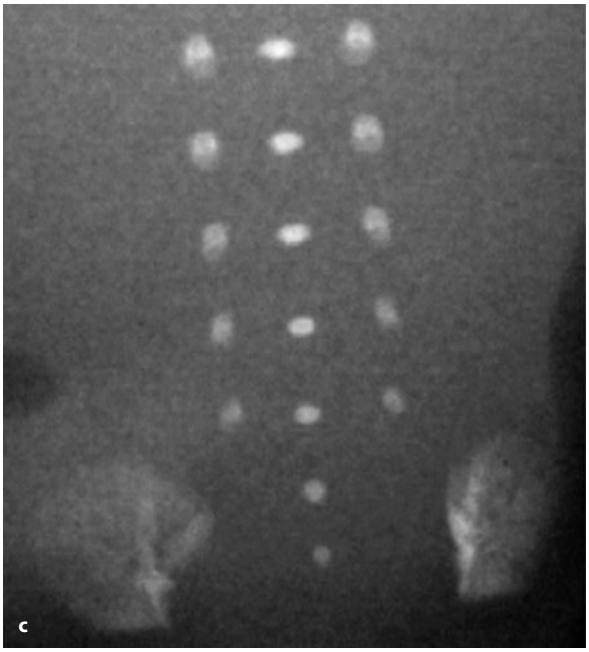


Fig. 1.3a, b (Original size) ***Week 13.*** Length of femur 10–11 mm (normal range 10–15 mm)
Ossification of the zygomatic bone progresses and the lower lateral angle of the orbit becomes visible. The medial parts of the orbits are now delineated. In the lateral projection, a dot-like ossification dorsal to the orbits marks the lesser wing of the sphenoid bone. In the AP projection, they are faintly seen in the medial parts of the orbits. The clavicles have assumed their characteristic S shape. This fetus has 11 pairs of ribs. Neural arches have appeared in the lower lumbar spine and upper sacrum. The distal phalanges of the toes are visualized



▷
c (Detail) *Milestone:* Ossification of the neural arches extend to the sacrum

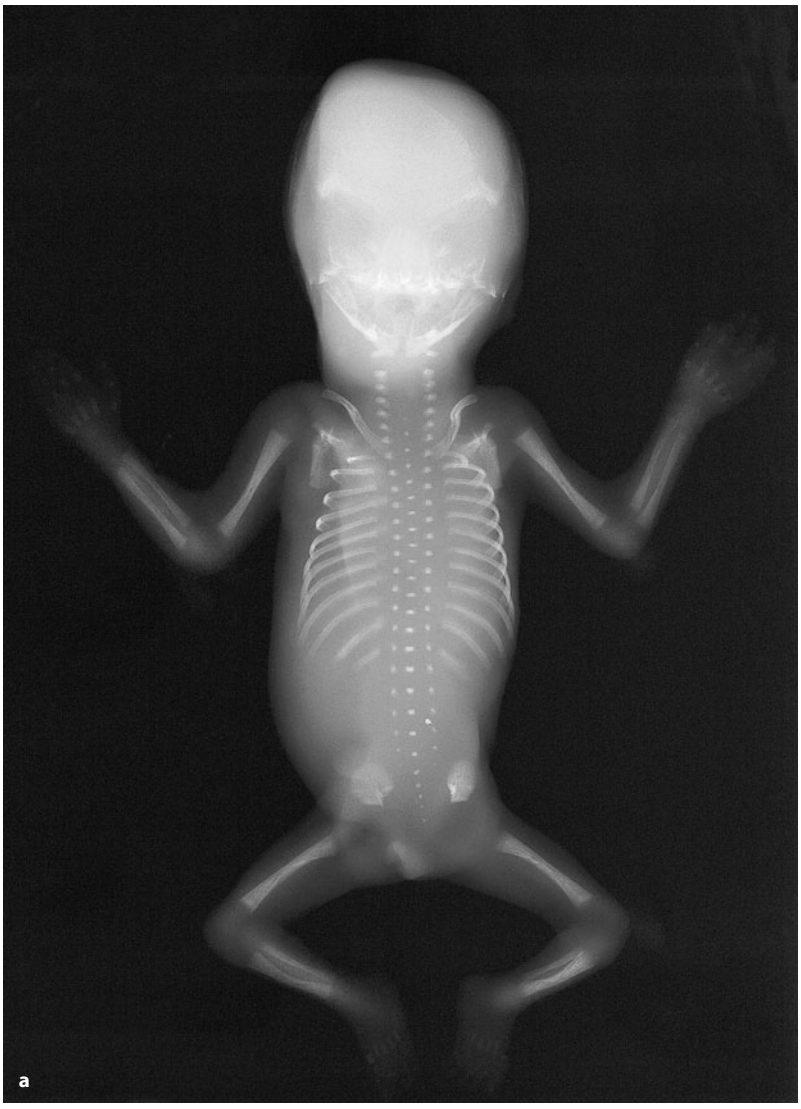


Fig. 1.4a, b (Original size) ***Week 14.*** Length of femur 15 mm (normal range 10–18 mm)
The nasal bones are now ossified and the lesser wings of the sphenoid bone are more clearly seen. Sacral bodies 1–4 are ossified. The lumbar bodies have grown in their AP dimension. A coronal cleft or small notches in their upper and lower plates may be present. All phalanges of the fingers are ossified except the middle phalanx of digit V. In the feet the proximal and distal phalanges are inconsistently ossified

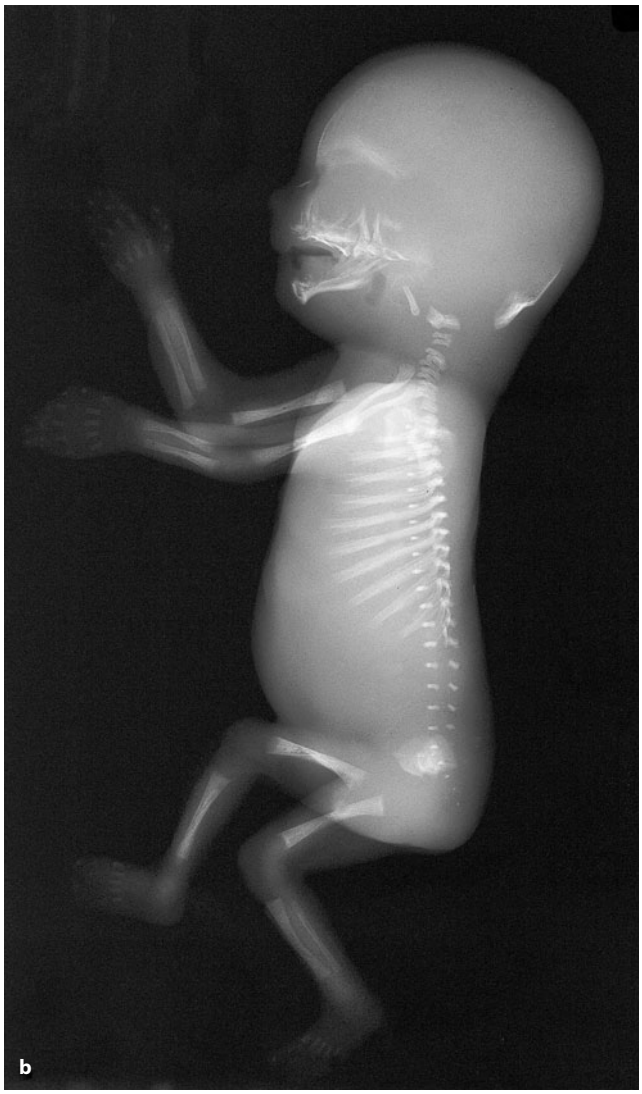


Fig. 1.4b

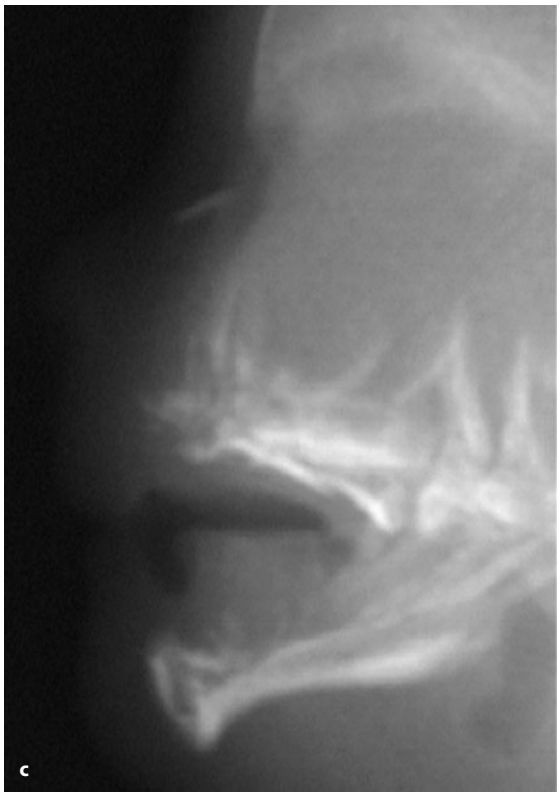


Fig. 1.4c (Detail) *Milestone:* The nasal bone is ossified

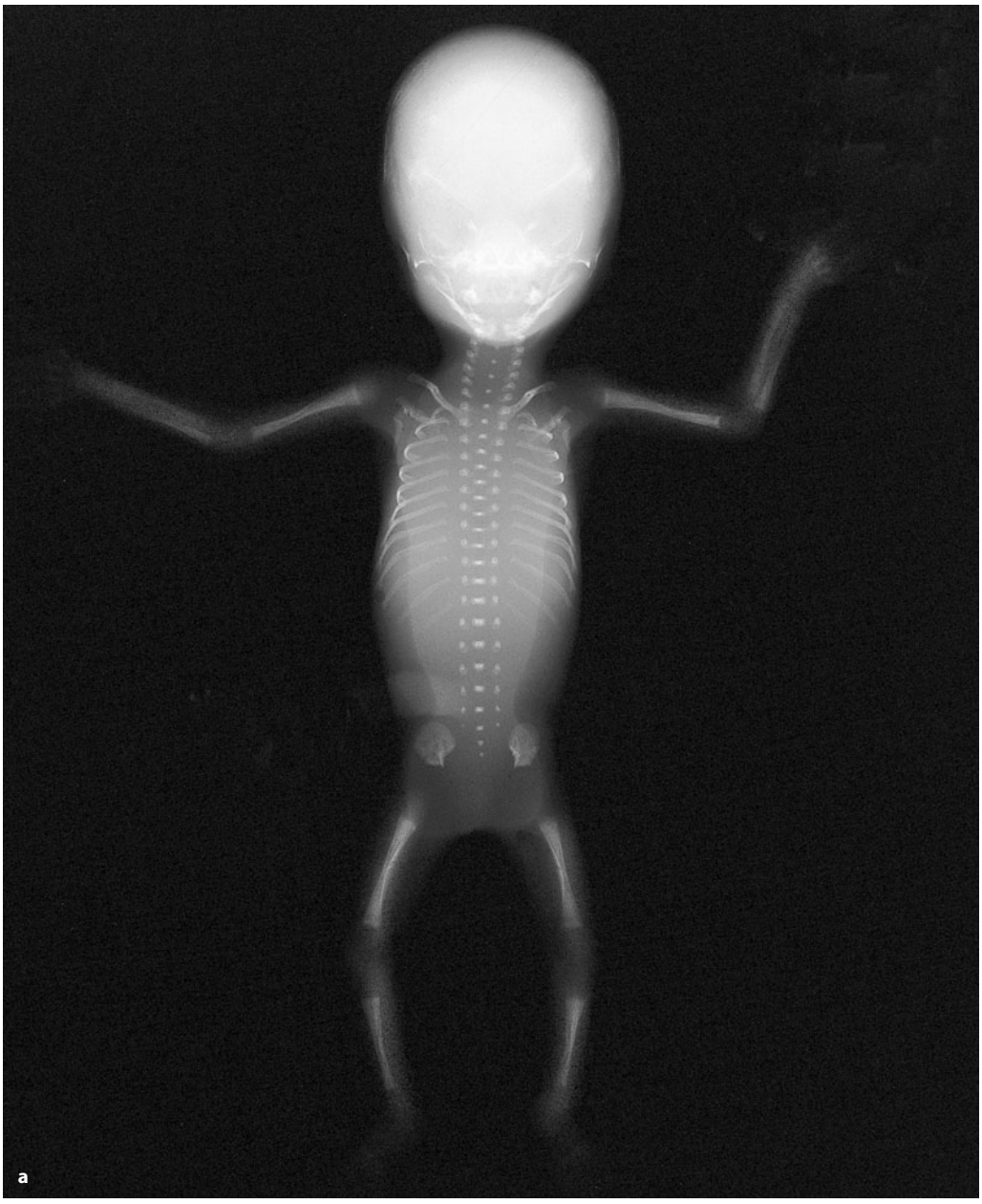


Fig. 1.5a, b (Original size) ***Week 15.*** Length of femur 16 mm (normal range 12–21 mm)
Hand phalanges are more distinct
The maxillary palatine processes are ossified. The symphysis mentis is still visible. Ossification of the vertebral bodies is now complete from C3 to S5 with some variability in the mineralization of the upper cervical and lower sacral bodies. The coracoid process of the scapula appears. In this fetus all short tubular bones of the hands are visible – including the middle phalanx of the fifth finger. The proximal phalanges of the toes are more distinct

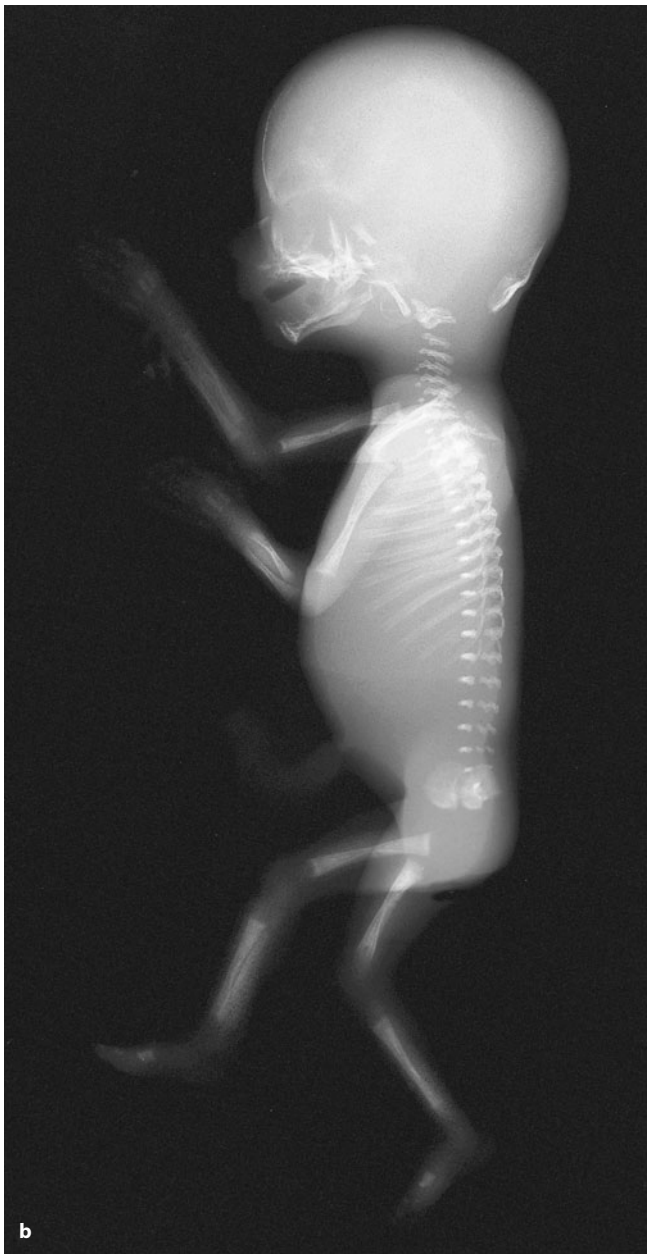


Fig. 1.5b

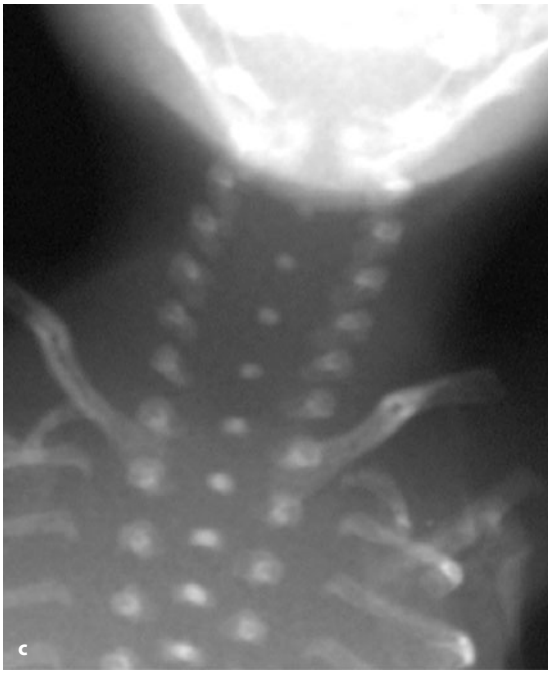


Fig. 1.5c (Detail) *Milestone:* Ossification of the cervical vertebral bodies has occurred

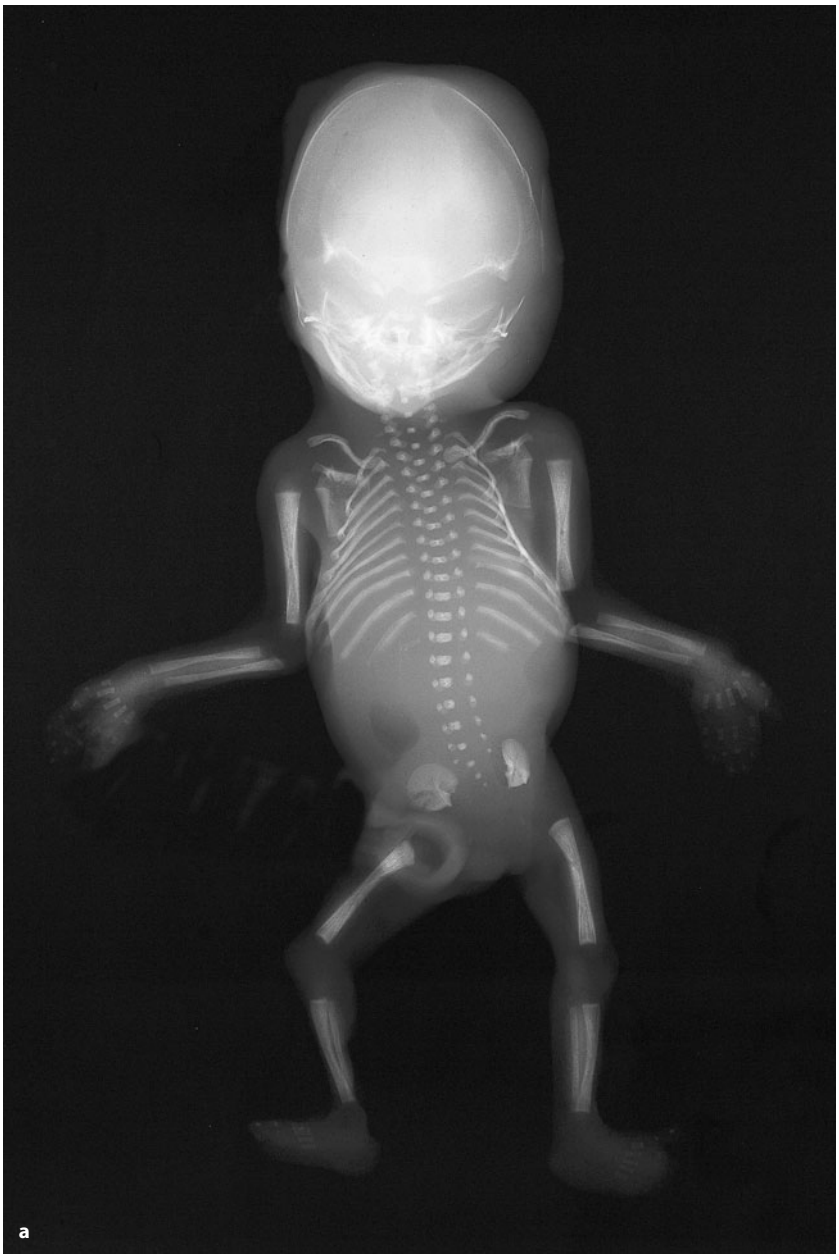


Fig. 1.6a, b (Original size) ***Week 16.*** Length of femur 18 mm (normal range 15–24 mm)
The lower nasal cavity is well modeled. Both wings of the sphenoid are clearly seen. The vertebral bodies assume a more cubic shape and the AP diameter of the neural arches of the lumbar spine increases. The ischial bones become visible in about 35% of fetuses. The phalanges of the fingers are well visualized except the middle phalanx of the 5th finger. Ossification of the distal phalanges of the toes is variable

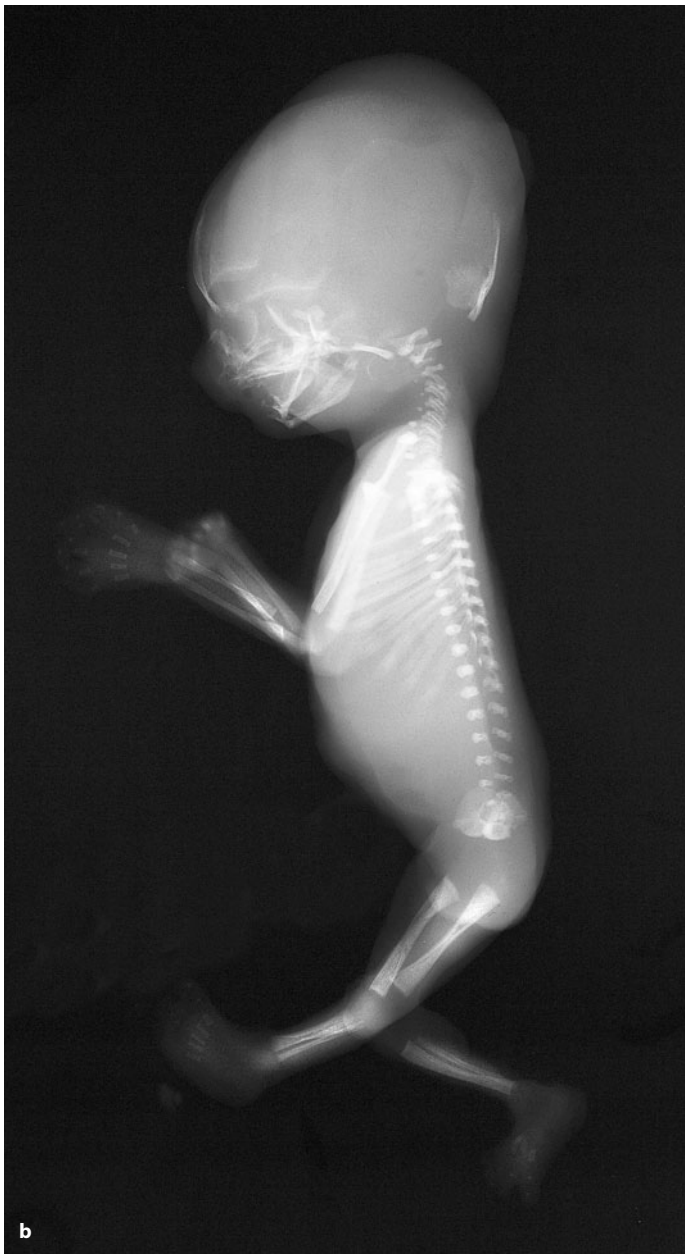


Fig. 1.6b

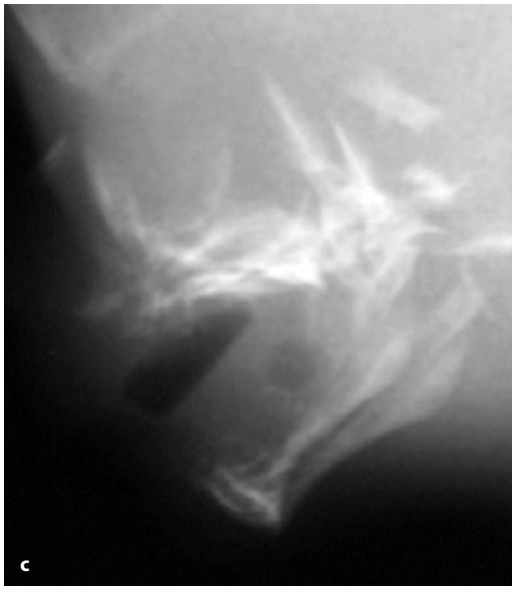


Fig. 1.6c (Detail) *Milestone:* First tooth buds develop in the anterior part of the maxilla and mandible. A discrete angulation develops in the mandible

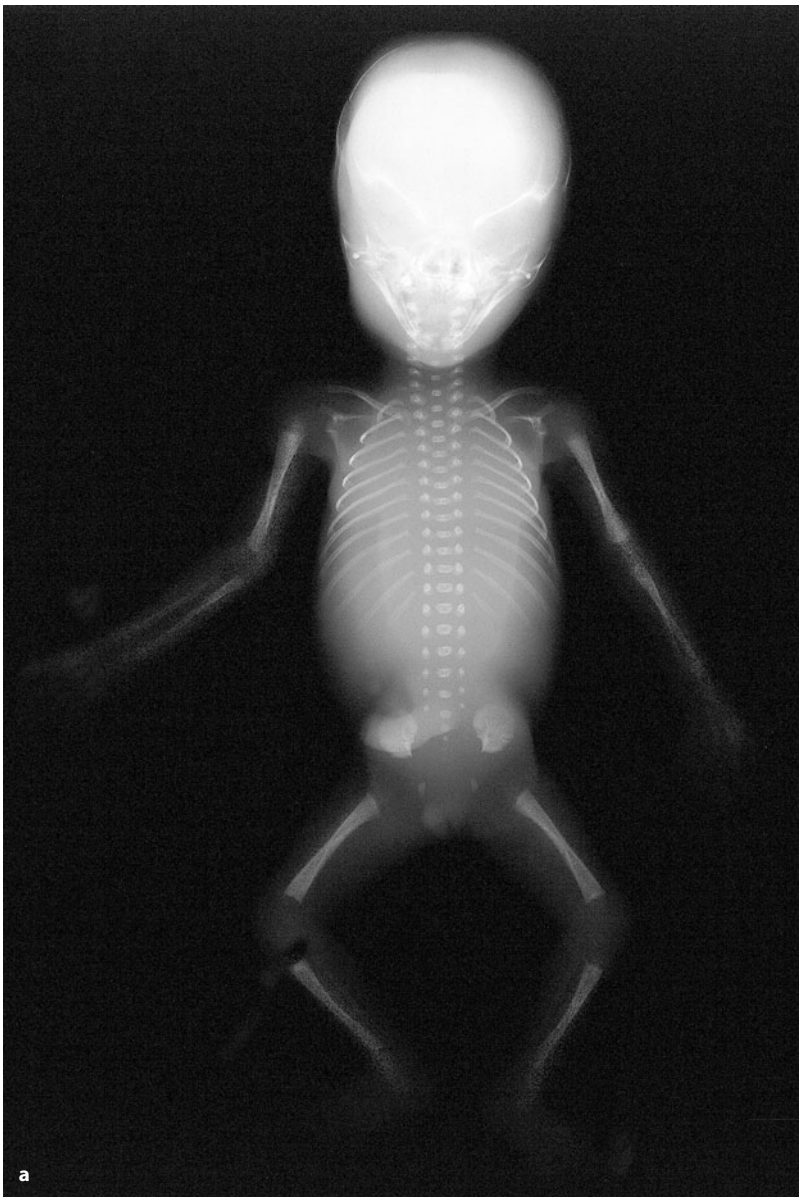


Fig. 1.7a, b (75% of original size) ***Week 17.*** Length of femur 23 mm (normal range 18/27 mm)
In this fetus the vertebral bodies caudal of S2 are not yet ossified. In approximately 95% of fetuses the ischial bone is seen and assumes a more vertical orientation. The middle phalanx of the 5th digit becomes visible but is smaller than the distal phalanx. In the lateral projection the proximal metaphysis of the ulna is slightly angulated

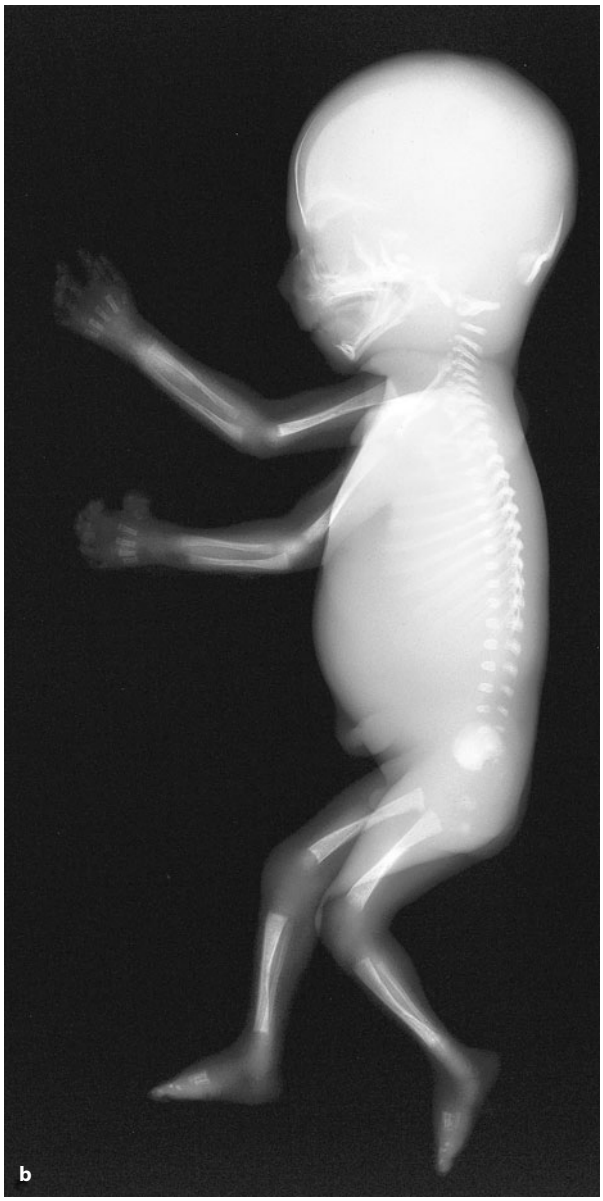


Fig. 1.7b

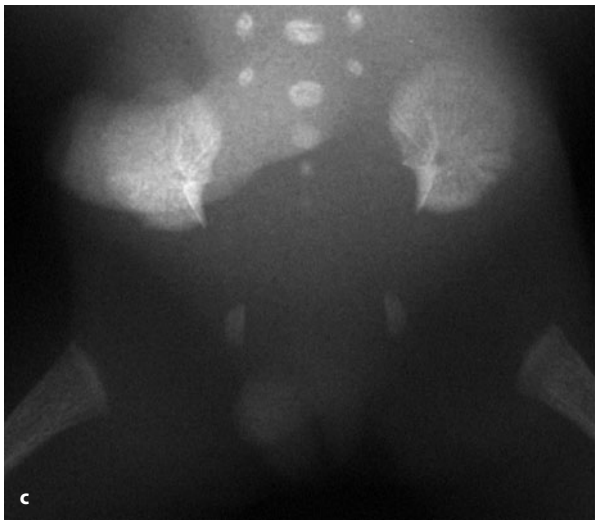


Fig. 1.7c (Detail) *Milestone:* The os ischium is visible (> 95%)

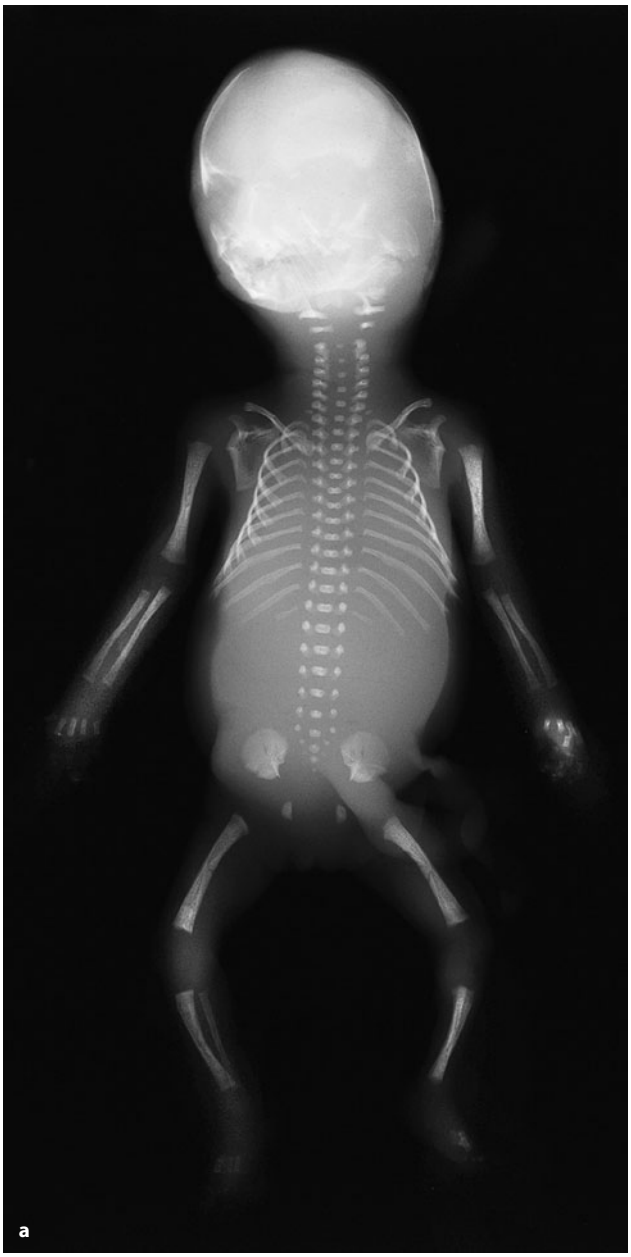


Fig. 1.8a, b (75% of original size) ***Week 18.*** Length of femur 24 mm (normal range 20–30 mm)
The odontoid process is not yet visible. The body of C3, as well as the bodies and neural arches of S3 to S4 are now ossified. There is incipient development of the lower ilium with a small osseous spur at the medial end pointing inward and downward. The proximal ulna is still slightly angulated. Cervical ribs and sagittal clefts of the upper thoracic vertebral bodies are seen in this fetus

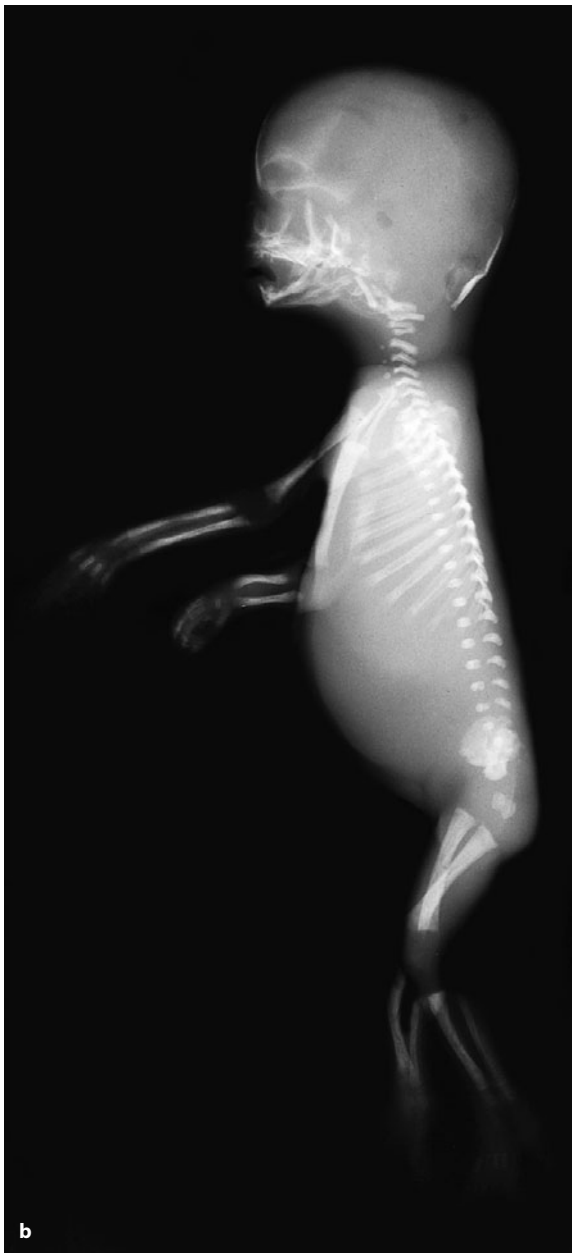


Fig. 1.8b

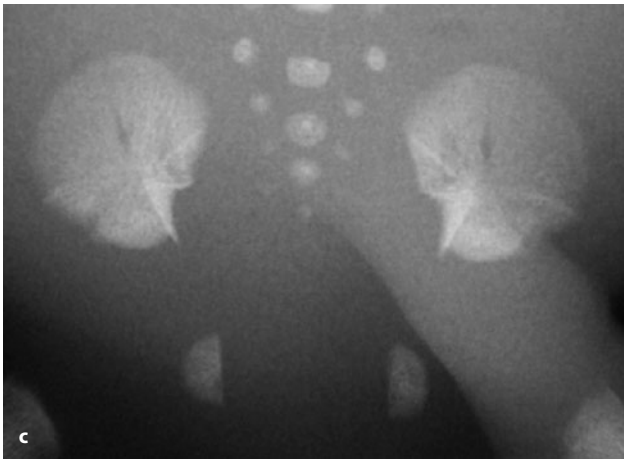


Fig. 1.8c (Detail) *Milestone:* A small osseous spur at the lower end of the os ilium appears pointing inward and downward

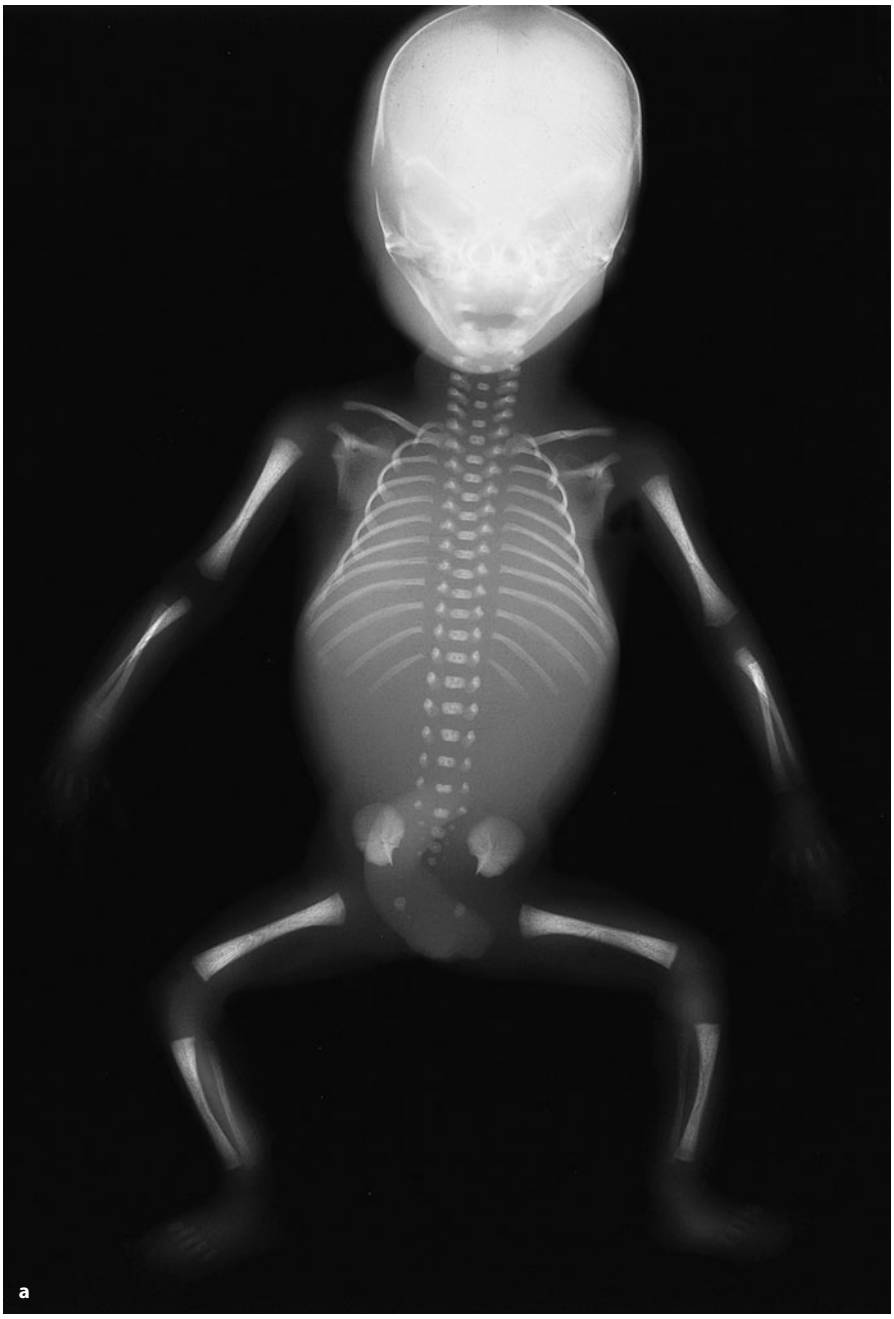


Fig. 1.9a, b (75% of original size) ***Week 19.*** Length of femur 29 mm (normal range 23/33 mm)
The first tooth buds appear in both maxilla and mandible. Ossification of the cervical spine progresses with complete ossification of the bodies of C2-C7 and a decreasing distance between vertebral bodies and arches. The odontoid is not yet ossified
Modeling of the proximal ulna begins to form a concave articular surface. The calcaneus is visible in about 13% of fetuses

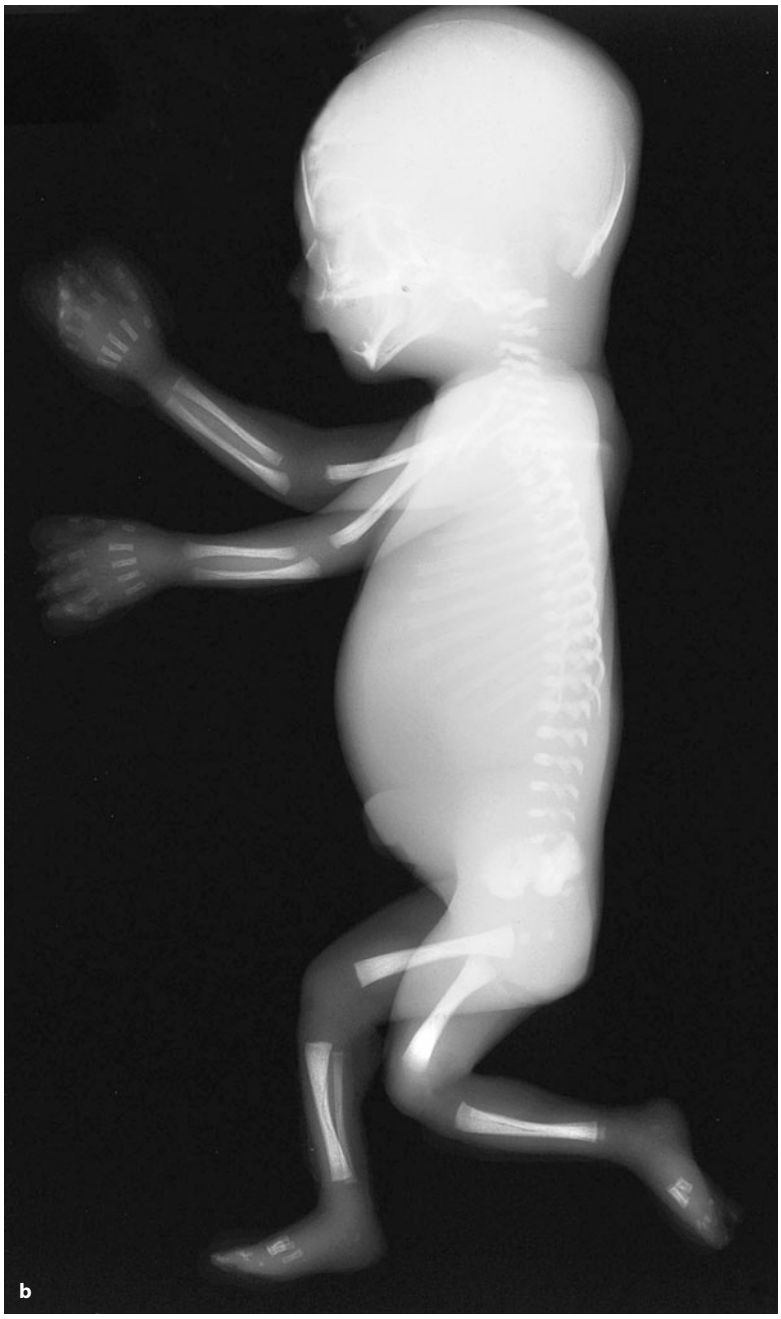


Fig. 1.9b

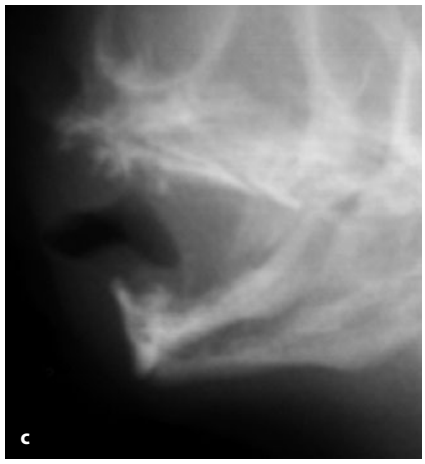


Fig. 1.9c (Detail) *Milestone:* Tips of the upper incisors become visible

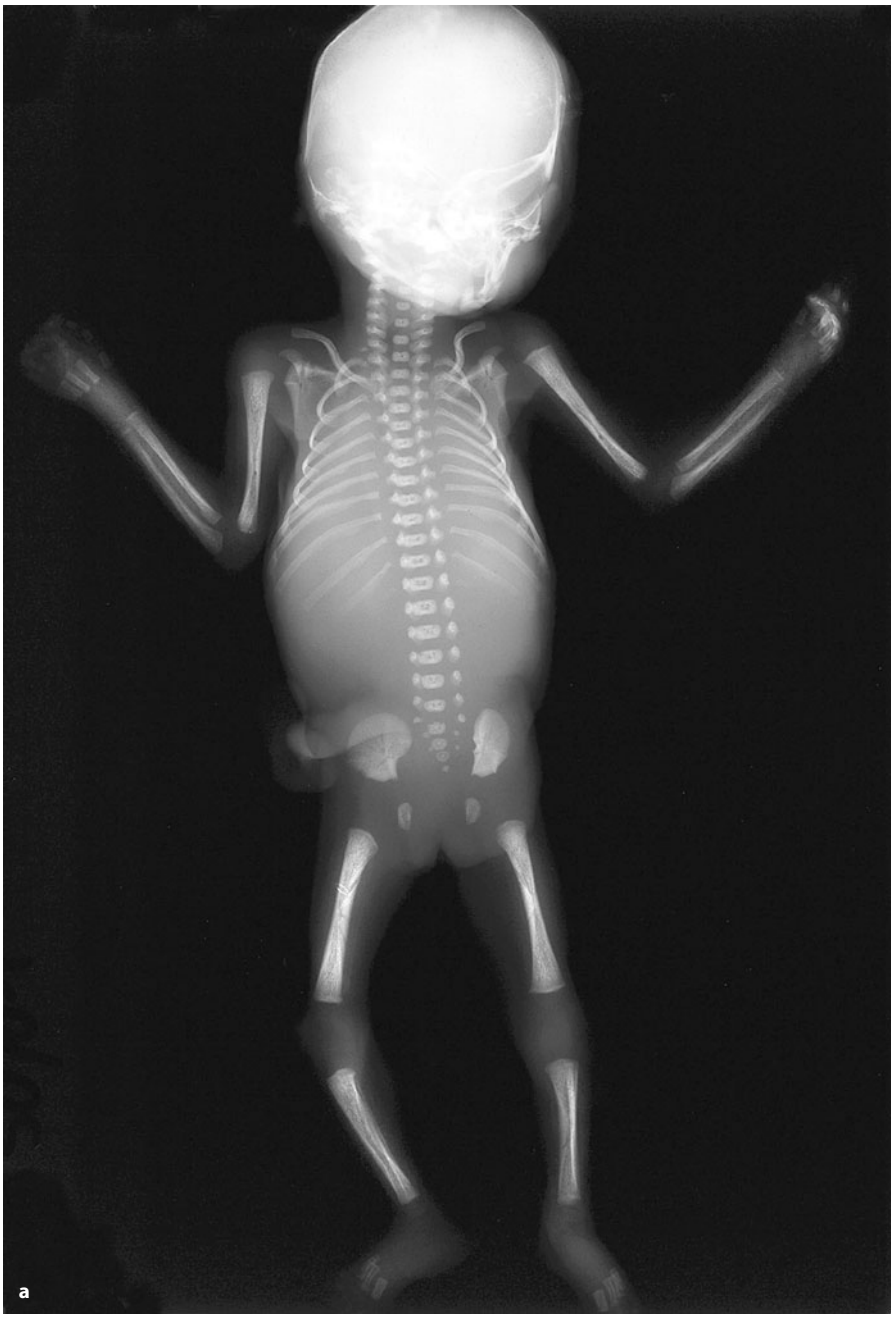


Fig. 1.10a, b (75% of original size) ***Week 20.*** Length of femur 31 mm (normal range 26–36 mm)
The upper semicircular ducts (petrous bone) are visible. Ossification of the vertebral bodies is complete from C2 to S4. A lateral indentation demarcates the iliac wings from the lower ilium. The acetabular roof is horizontal with a spur extending downward and inward from its medial aspect. The medial edge of the ischium is slightly concave. In the early maturing fetus the calcanei become visible. Modeling of the proximal ulna progresses to form a concave articular surface ventrally and a convex olecranon dorsally

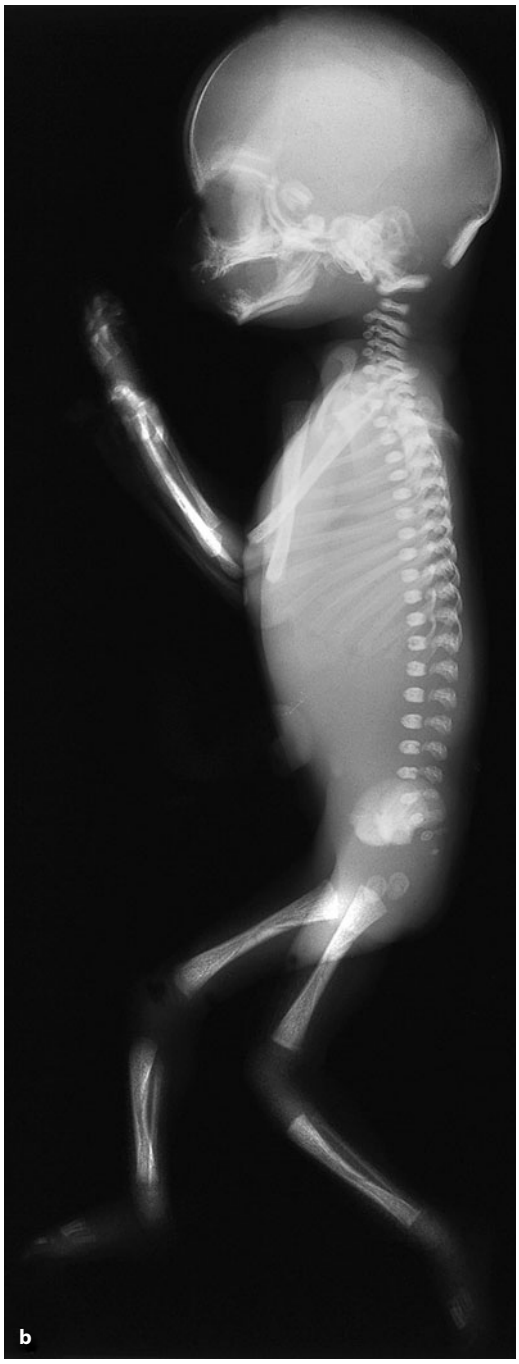


Fig. 1.10b

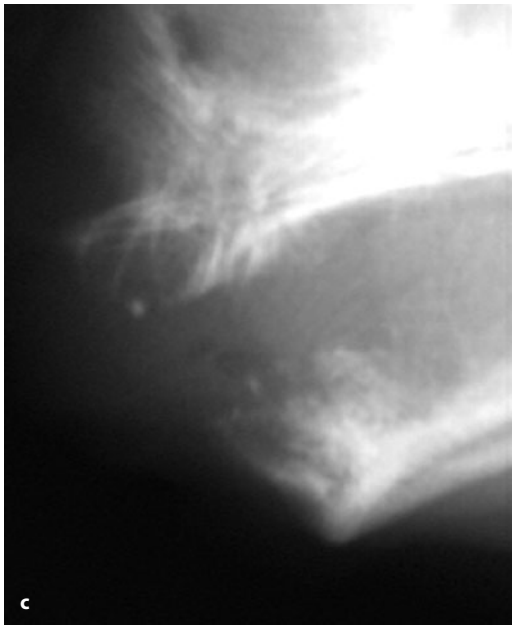


Fig. 1.10c (Detail) *Milestone:* Tips of the incisors are regularly visible

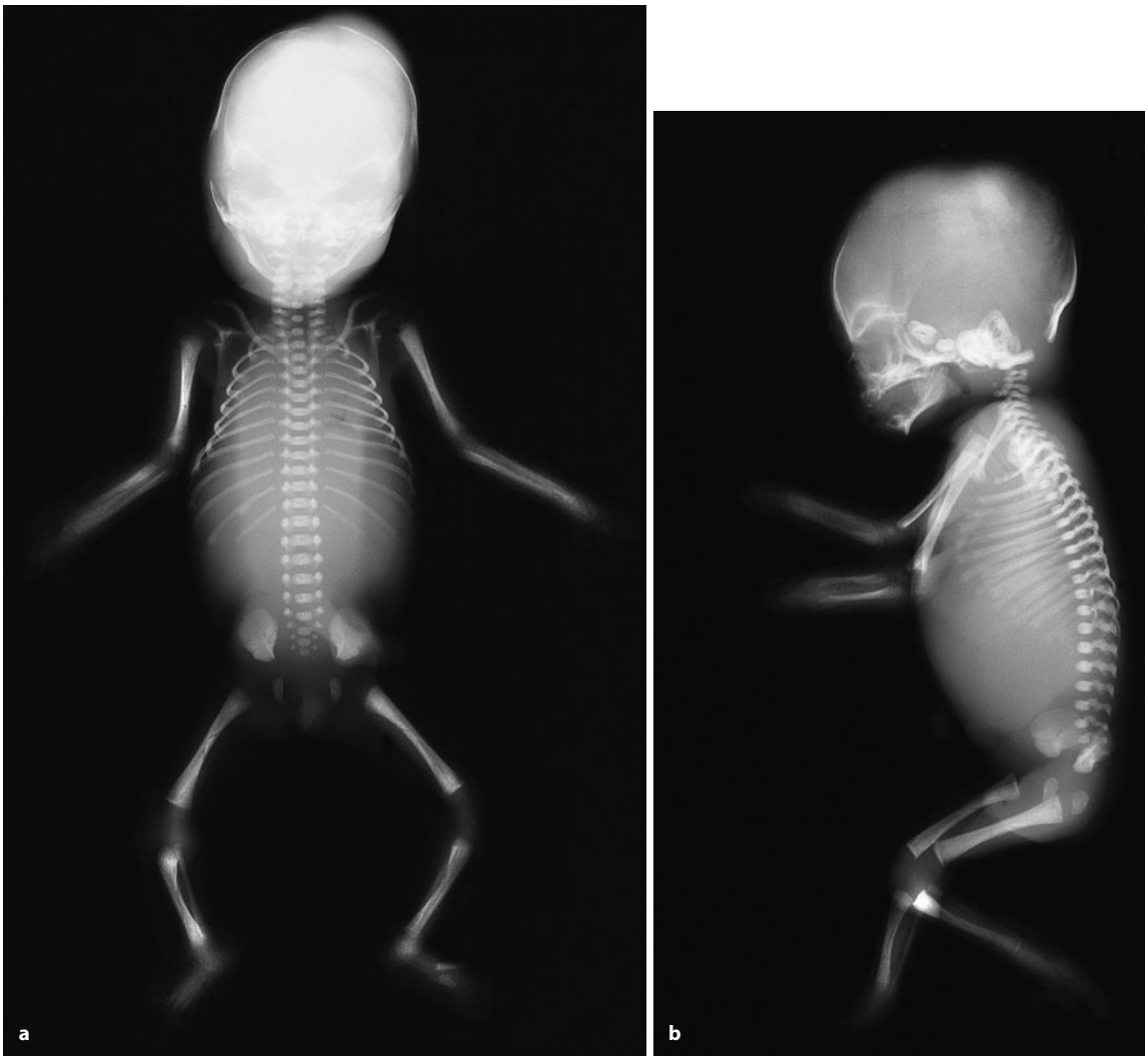
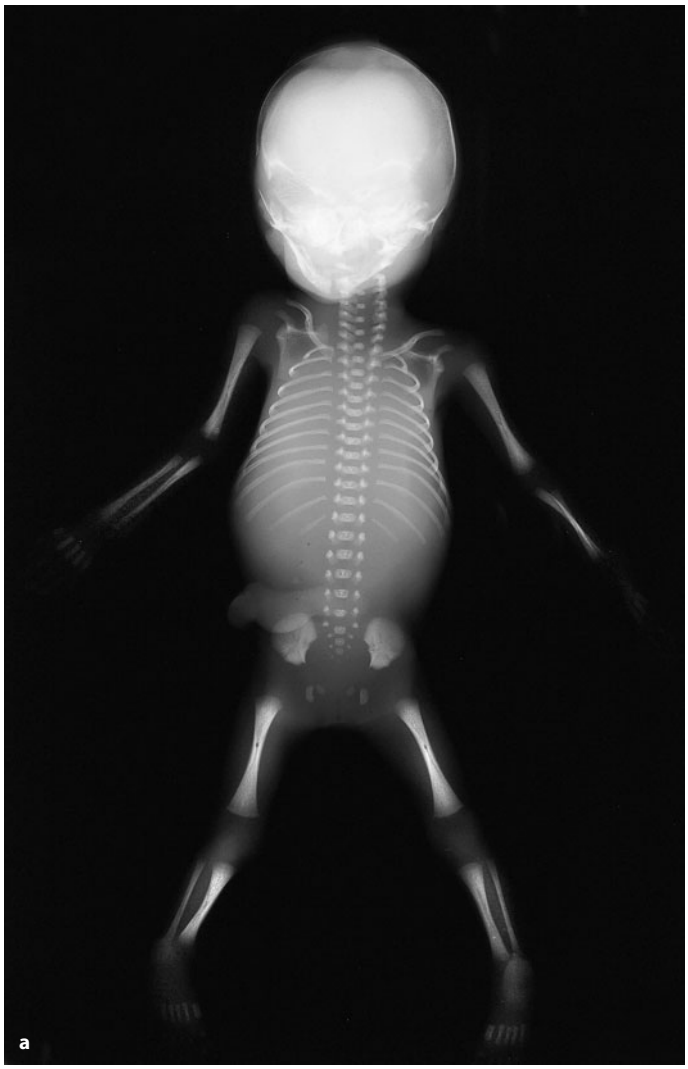


Fig. 1.11a, b (Half original size) ***Week 21.*** Length of femur 36 mm (normal range 29–39 mm)
Milestone: There is an increased number of deciduous teeth
The vertebral bodies become more voluminous with a decreasing distance between bodies and neural arches. There is progressive thickening of the ischial bones



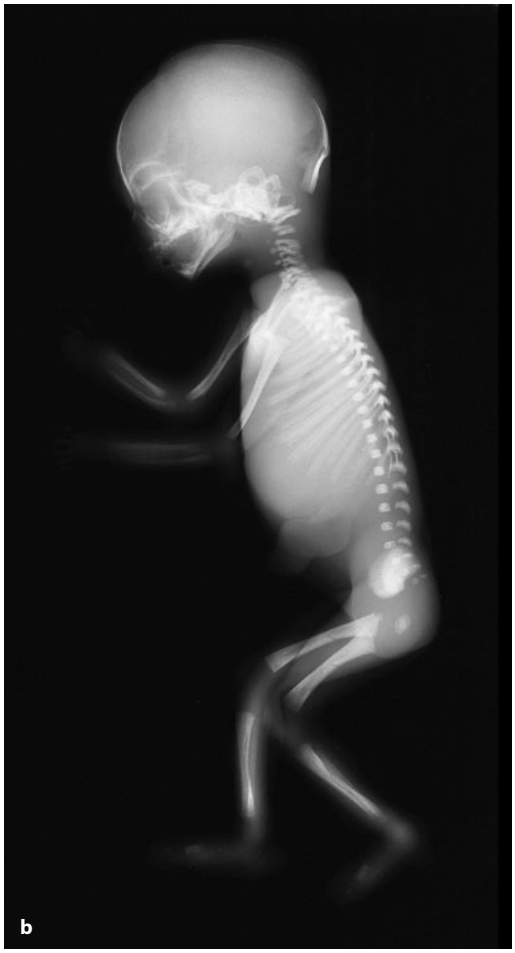
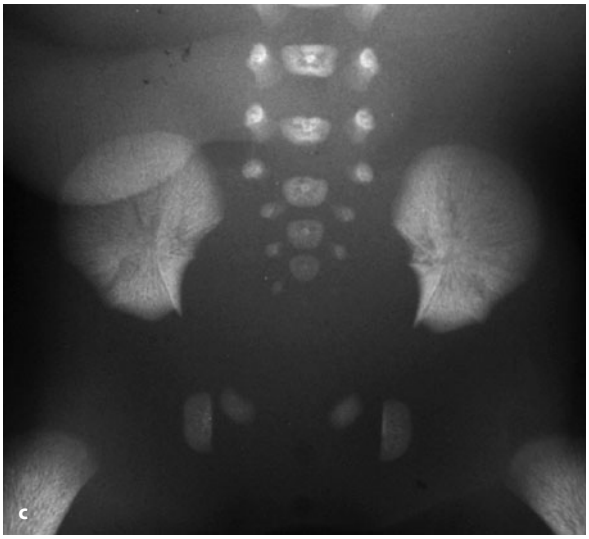


Fig. 1.12a, b (Half original size) ***Week 22.*** Length of femur 35 mm (normal range 31–41 mm)
More tips of the teeth are seen including the canines. The odontoid process is visualized above the body of C2. The pelvis matures with a distinct iliac body, disappearance of the downward projecting medial spur, and incipient ossification of the pubic bone. In this fetus, the calcaneus is not yet ossified



▷
Fig. 1.12c (Detail) *Milestone:* The pubic bones become visible

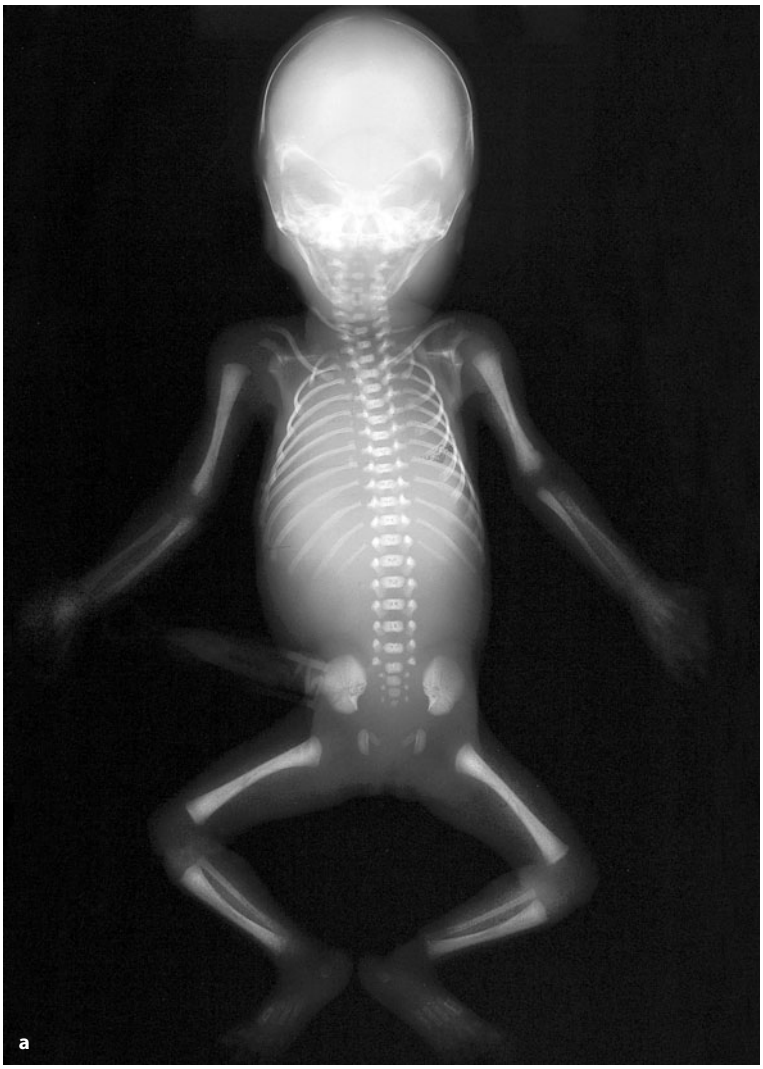


Fig. 1.13a, b (Half original size) ***Week 23.*** Length of femur 39 mm (normal range 34–44 mm)
Sternal ossification starts with the simultaneous appearance of ossification centers in the manubrium and corpus sterni. Pubic bones are clearly seen and the calcanei are ossified in approximately 50% of fetuses

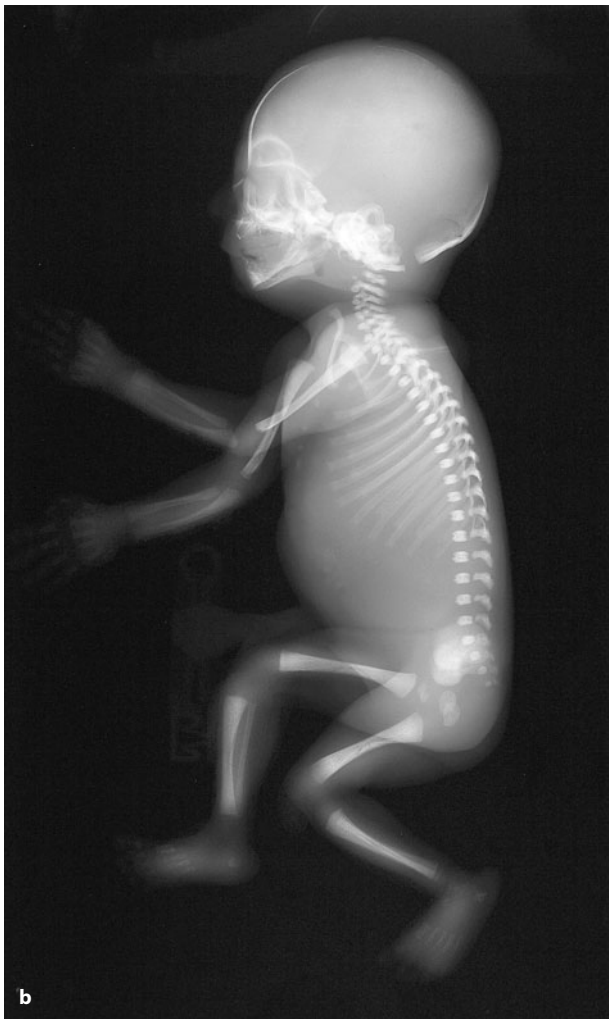


Fig. 1.13b

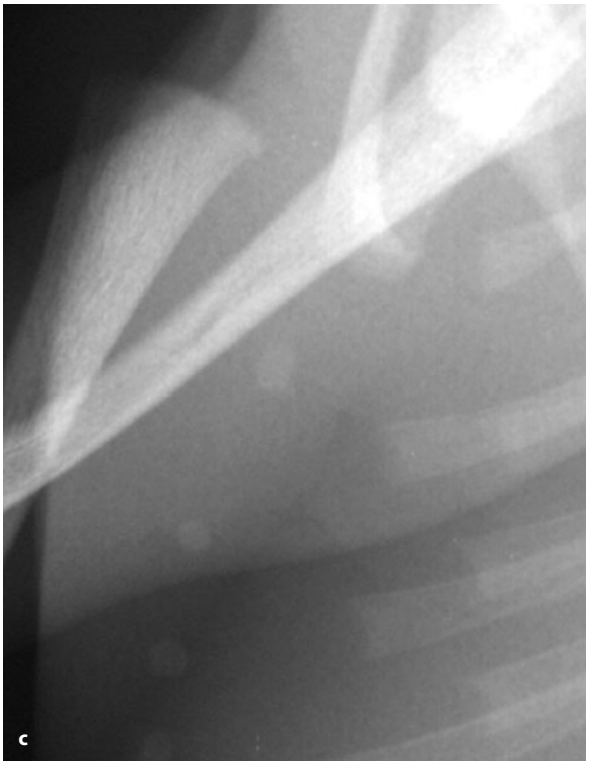


Fig. 1.13c (Detail) *Milestone:* Sternal ossification centers become visible

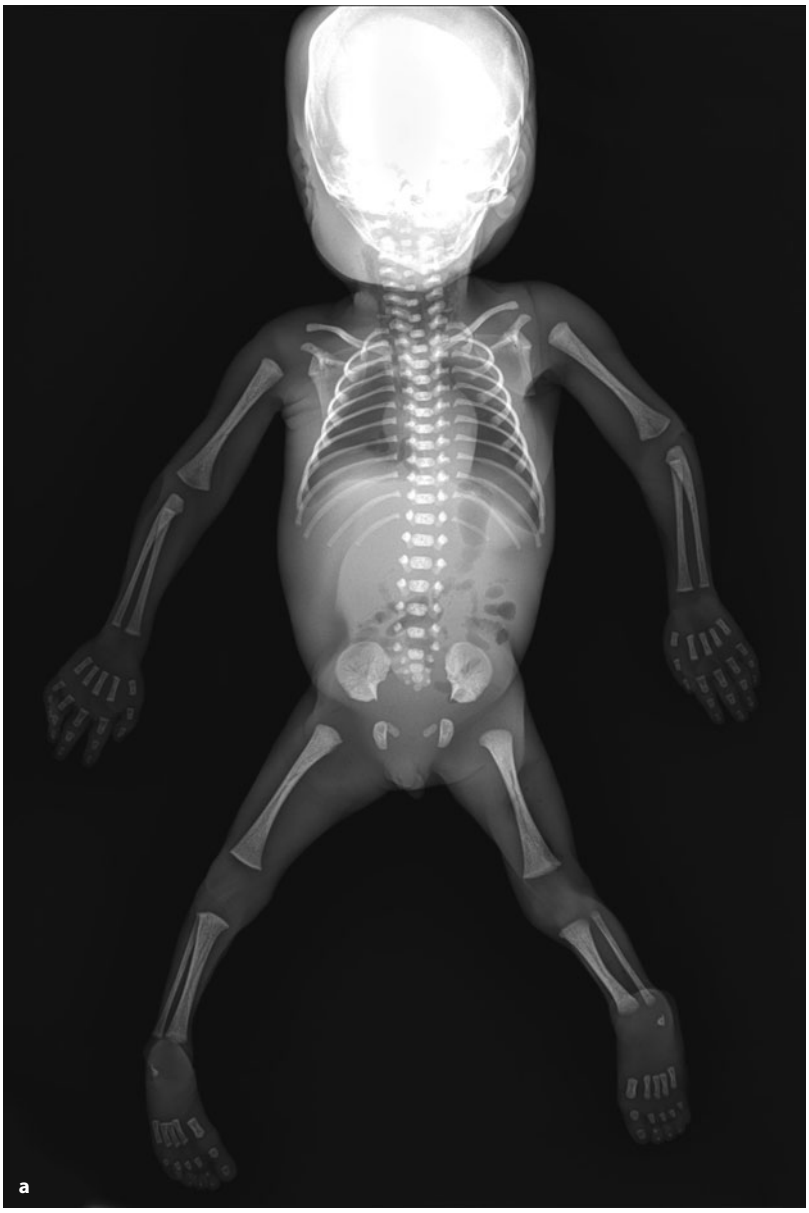
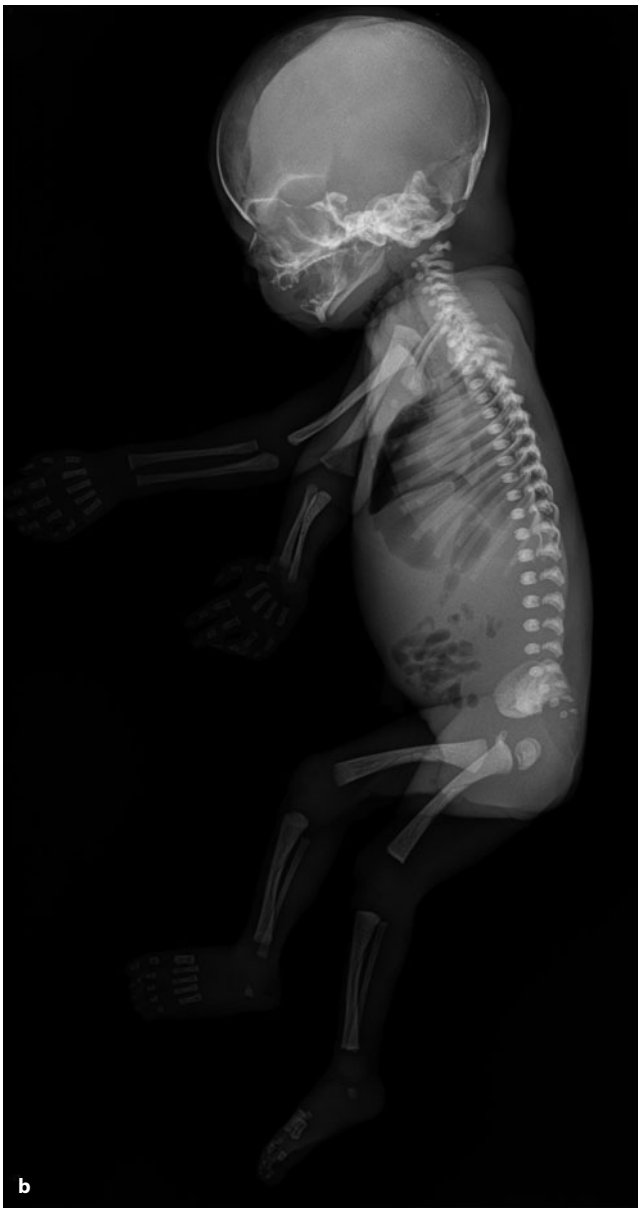
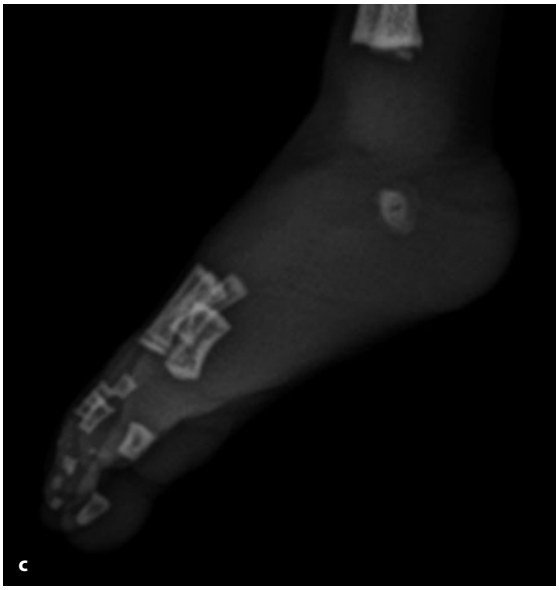


Fig. 1.14a, b (Half original size) ***Week 24.*** Length of femur 40 mm (normal range 36–47 mm)
The odontoid is well rounded





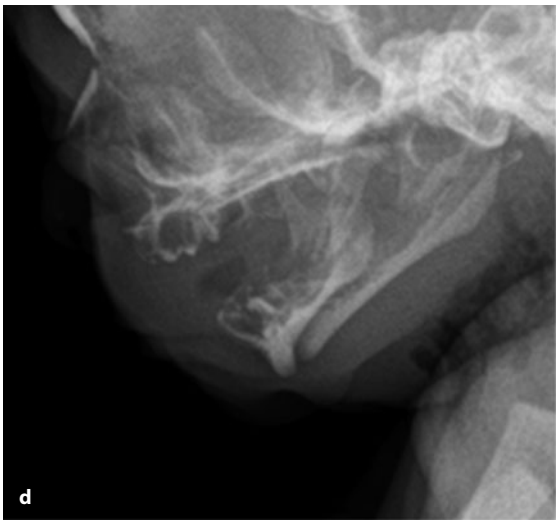


Fig. 1.14b

Fig. 1.14c (Detail) *Milestone:* The calcaneous becomes visible with an irregular outline

Fig. 1.14d (Detail) The crowns of the upper and lower incisors are clearly visible as well as the lower canine

Femur

Table 1.1. Relation of diaphyseal length (mm) and gestational week in the femur (adapted from Merz 1988, with permission of the author)

	Gestational week		
mm	5%	50%	95%
10	12	13	14
11	12	13	14
12	12	13	15
13	13	14	15
14	13	14	15
15	13	14	16
16	14	15	16
17	14	15	16
18	14	15	17
19	15	16	17
20	15	16	18
21	15	17	18
22	16	17	18
23	16	17	19
24	16	18	19
25	17	18	19
26	17	18	20
27	17	19	20
28	18	19	20
29	18	19	21
30	18	20	21
31	19	20	22
32	19	20	22
33	19	21	22
34	20	21	23
35	20	22	23
36	20	22	24
37	21	22	24
38	21	23	24
39	21	23	25
40	22	23	25
41	22	24	25
42	23	24	26
43	23	25	26
44	23	25	27

	Gestational week		
mm	5%	50%	95%
45	24	26	27
46	24	26	27
47	24	26	28
48	25	27	28
49	25	27	29
50	26	27	29
51	26	28	30
52	26	28	30
53	27	29	30
54	27	29	31
55	28	29	31
56	28	30	32
57	28	30	32
58	29	31	32
59	29	31	33
60	30	31	33
61	30	32	34
62	30	32	34
63	31	33	35
64	31	33	35
65	32	34	36
66	32	34	36
67	32	34	36
68	33	35	37
69	33	35	37
70	34	36	38
71	34	36	38
72	35	37	39
73	35	37	39
74	36	38	40
75	36	38	40
76	36	39	41
77	37	39	41
78	37	40	42
79	37	40	42

Tibia

Table 1.2. Relation of diaphyseal length and gestational week in the tibia (adapted from Merz 1988, with permission of the author)

	Gestational week				Gestational week		
Mm	5%	50%	95%	Mm	5%	50%	95%
8	11	13	14	38	23	25	27
9	12	13	14	39	23	25	27
10	12	13	15	40	24	26	28
11	13	14	15	41	24	26	28
12	13	14	16	42	25	27	28
13	13	15	16	43	25	27	29
14	14	15	16	44	26	28	29
15	14	15	17	45	26	28	30
16	14	16	17	46	27	29	30
17	15	16	18	47	27	29	31
18	15	16	18	48	28	30	31
19	15	17	18	49	28	30	32
20	16	17	19	50	28	31	33
21	16	18	19	51	29	31	33
22	17	18	20	52	29	32	34
23	17	18	20	53	30	32	34
24	17	19	20	54	31	33	35
25	18	19	21	55	31	33	35
26	18	20	21	56	32	34	36
27	18	20	22	57	32	34	36
28	19	20	22	58	33	35	37
29	19	21	23	59	33	35	38
30	20	21	23	60	34	36	38
31	20	22	23	61	34	37	39
32	20	22	24	62	35	37	39
33	21	23	24	63	36	38	40
34	21	23	25	64	36	38	41
35	22	23	25	65	37	39	41
36	22	24	26	66	37	40	42
37	23	24	26	67	38	40	43

Humerus

Table 1.3. Relation of diaphyseal length and gestational week in the humerus (adapted from Merz 1988, with permission of the author)

	Gestational week		
Mm	5%	50%	95%
9	11	13	14
10	12	13	14
11	12	13	15
12	12	14	15
13	13	14	16
14	13	14	16
15	13	15	16
16	14	15	17
17	14	16	17
18	14	16	17
19	15	16	18
20	15	17	18
21	16	17	19
22	16	18	19
23	16	18	19
24	17	18	20
25	17	19	20
26	17	19	21
27	18	19	21
28	18	20	22
29	19	20	22
30	19	21	22
31	19	21	23
32	20	22	23
33	20	22	24
34	21	22	24
35	21	23	25
36	21	23	25
37	22	24	26
38	22	24	26

	Gestational week		
Mm	5%	50%	95%
39	23	25	26
40	23	26	27
41	23	25	27
42	24	26	28
43	24	26	28
44	25	27	29
45	25	27	29
46	26	28	30
47	26	28	30
48	27	29	31
49	27	29	31
50	28	30	32
51	28	30	32
62	29	31	33
53	29	31	34
54	30	32	34
55	30	32	35
56	31	33	35
57	31	34	36
58	32	34	36
59	32	35	37
60	33	36	38
61	34	36	38
62	34	36	39
63	35	37	39
64	35	38	40
65	36	38	41
66	37	39	41
67	37	40	42
68	38	40	43

Radius

Table 1.4. Relation of diaphyseal length and gestational week in the radius (adapted from Merz 1988, with permission of the author)

	Gestational week				Gestational week		
Mm	5%	50%	95%	Mm	5%	50%	95%
6	11	13	14	31	22	24	26
7	11	13	15	32	22	24	27
8	12	13	15	33	23	25	27
9	12	14	16	34	23	26	28
10	12	14	16	35	24	26	29
11	13	15	16	36	24	27	29
12	13	15	17	37	25	27	30
13	14	15	17	38	25	28	30
14	14	16	18	39	26	28	31
15	14	16	18	40	26	29	32
16	15	17	19	41	27	30	32
17	15	17	19	42	28	30	33
18	16	18	20	43	28	31	34
19	16	18	20	44	29	32	34
20	16	19	21	45	30	32	35
21	17	19	21	46	30	33	36
22	17	19	22	47	31	34	37
23	18	20	22	48	32	35	37
24	18	20	23	49	32	35	38
25	19	21	23	50	33	36	39
26	19	21	24	51	34	37	40
27	20	22	24	52	35	38	41
28	20	22	25	53	36	39	42
29	21	23	25	54	36	40	43
30	21	23	26	55	37	40	44

Ulna

Table 1.5. Relation of diaphyseal length and gestational week in the ulna (adapted from Merz 1988, with permission of the author)

	Gestational week		
Mm	5%	50%	95%
7	11	13	14
8	12	13	14
9	12	13	15
10	12	14	15
11	13	14	16
12	13	15	16
13	13	15	16
14	14	15	17
15	14	16	17
16	15	16	17
17	15	16	18
18	15	17	18
19	16	17	19
20	16	18	19
21	16	18	19
22	17	18	20
23	17	19	20
24	17	19	21
25	18	19	21
26	18	20	22
27	19	20	22
28	19	21	22
29	19	21	23
30	20	22	23
31	20	22	24
32	21	22	24
33	21	23	25
34	21	23	25

	Gestational week		
Mm	5%	50%	95%
35	22	24	26
36	22	24	26
37	23	25	27
38	23	25	27
39	24	26	28
40	24	26	28
41	25	27	29
42	25	27	29
43	26	28	30
44	26	28	30
45	27	29	31
46	27	29	31
47	28	30	32
48	28	30	33
49	29	31	33
50	29	32	34
51	30	32	34
52	31	33	35
53	31	34	36
54	32	34	36
55	33	35	37
56	33	36	38
57	34	36	39
58	35	37	39
59	36	38	40
60	36	39	41
61	37	40	42
62	38	40	43

2 Differential Diagnosis of Single Skeletal Defects

Introduction

This section focuses on the radiographic differential diagnosis of single defects of the fetal skeleton. Complying with the character of this book as a radiographic tool, the number of conditions in the differential lists has been limited in two ways:

1. The disorder should have at least one radiographic sign in addition to the key feature, thus allowing one to make a diagnosis or suspect a diagnosis by radiographic analysis alone. For instance, the combination of an amputated limb with anencephaly – both recognizable on a fetogram – leads to a diagnosis of the ADAM complex. On the other hand, isolated vertebral segmentation defects in the upper thoracic spine without additional radiographic findings are relatively unspecific and can be seen in a great number of disorders. As radiology does not help in the differential diagnostic process, these isolated defects have not been included.
2. The disorder should be relatively common, i.e., have an entry in the OMIM database. Isolated case reports without an OMIM number have not been included in the differential diagnostic lists. Comprehensive lists of all possible disorders associated with a given defect are available in databases such as POSSUM or the London dysmorphology databases.

The radiodiagnostic process requires the complete and thorough analysis of the available radiographs. Form, size, position, proportions, structure, and maturational status of all skeletal elements must be scrutinized. Soft tissue changes must be recorded. A pattern of findings may emerge from which a key skeletal feature is selected. Consulting the subsection devoted to this key feature, a diagnosis may emerge from a match between the given and a listed pattern. The presence of widespread, often symmetric, skeletal abnormalities raises the possibility of a generalized skeletal dysplasia (see Chap. 3). Tables in the appendix simplify this approach.

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Limbs

Amelia – Amputation – Phocomelia

Definition

- Amelia: no formation of extremity
- Amputation: transverse terminal defects of limb (**Fig. 2.1**)
- Phocomelia: band-like transverse or segmental defects within a limb (**Fig. 2.2**)

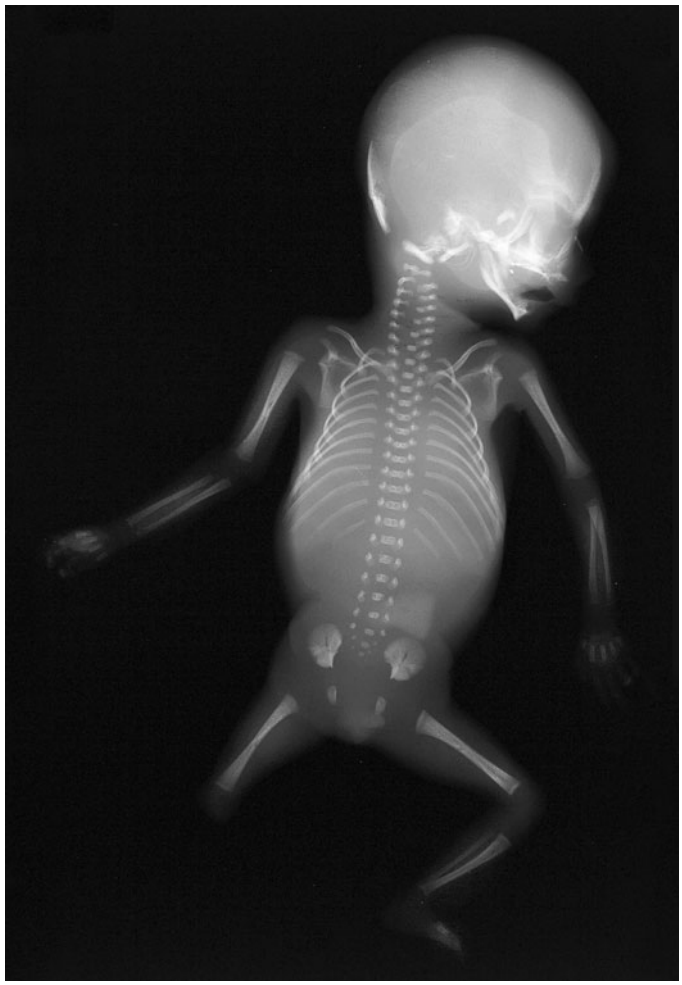

Fig. 2.1. ***18th gestational week.*** Amputation of the right shank in amniotic disruption sequence, otherwise normal skeleton

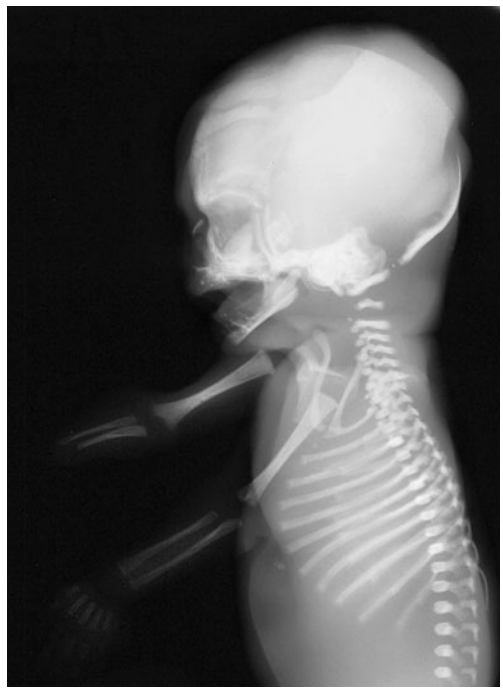

Fig. 2.2. ***23rd gestational week.*** Phocomelia of the left forearm with tiny fingers and a few dot-like phalangeal ossification centers

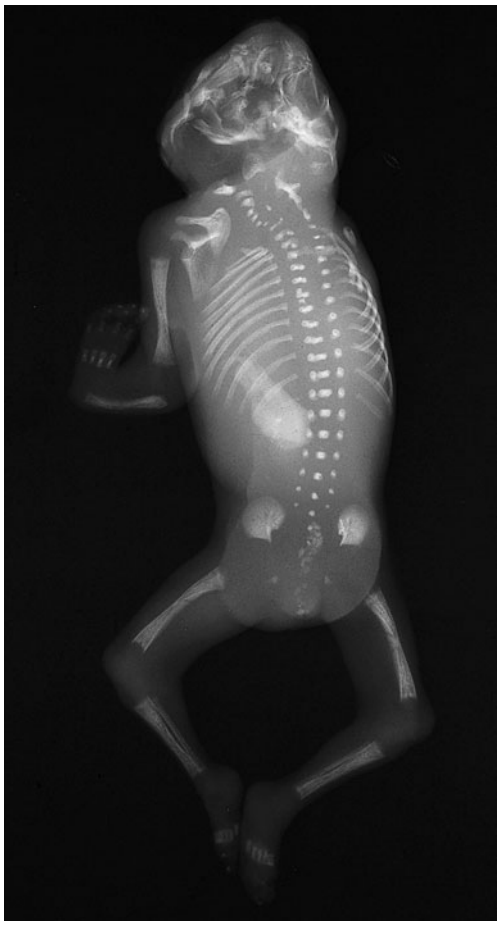

Fig. 2.3. ***15th gestational week.*** Amputation of the left arm in ADAM complex. Aplasia of the right radius and thumb; anencephaly, duplication of right scapula, hypoplastic clavicle

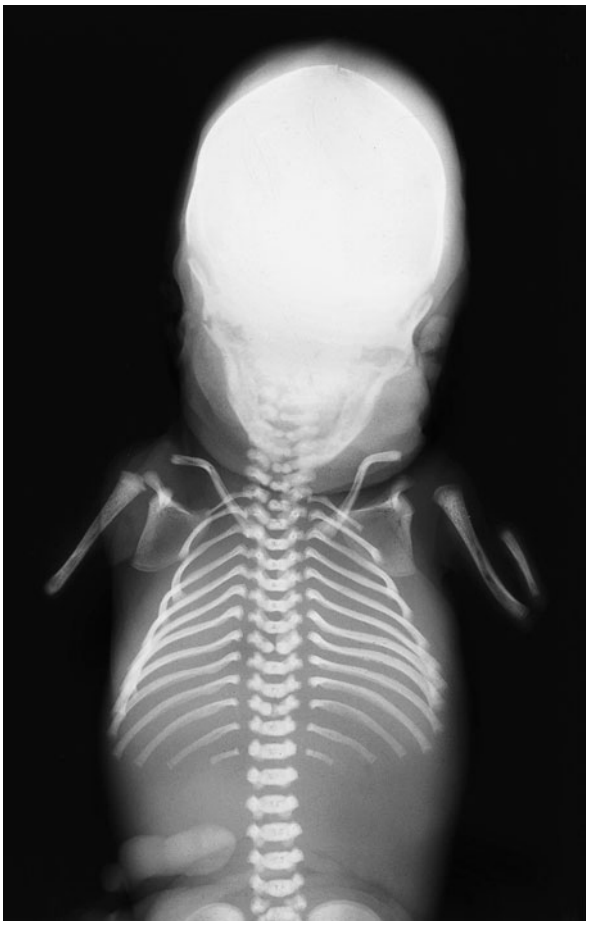

Fig. 2.4. ***27th gestational week.*** Asymmetric reduction defects of the forearms in oromandibular-limb hypogenesis syndrome. Hypoplasia of humeri. Sagittal clefts of the vertebral bodies of D8 and D11. Thirteen pairs of ribs

Diagnosis	Accessory radiological findings in the fetus
Acrofacial dysostosis, type Rodriguez [1] MIM 201170	Phocomelia of arms, defective ulnar ray, short humerus and fibula, hypoplastic scapula
Amelia, autosomal recessive [2] MIM 601360	Amelia of upper limbs and terminal transverse defect through femora, micrognathia
Amnioic band/disruption sequence ADAM complex *(Amniotic* Deformity, Adhesions, Mutilations); **Fig. 2.3** Limb-bodywall complex [3] MIM 217100	Terminal limb defects, constriction bands, distal lymphedema, different degree of mutilations, craniofacial clefts, ectopia cordis, cephalocele/anencephaly, body wall defects
Diabetic embryopathy [4]	Caudal regression, segmentation defects of the spine, defects of ulna and tibia, femoral aplasia
DK phocomelia [5] von Voss-Cherstvoy syndrome MIM 223340	Microcephaly; upper limb anomalies: absent or hypoplastic humerus, radius, ulna, metacarpals, thumb; oligodactyly; syndactyly of fingers
Disorganisation-like syndrome [6] MIM 223200	Anencephaly, asymmetry, pre-/postaxial polydactyly, lower limb aplasia/duplication

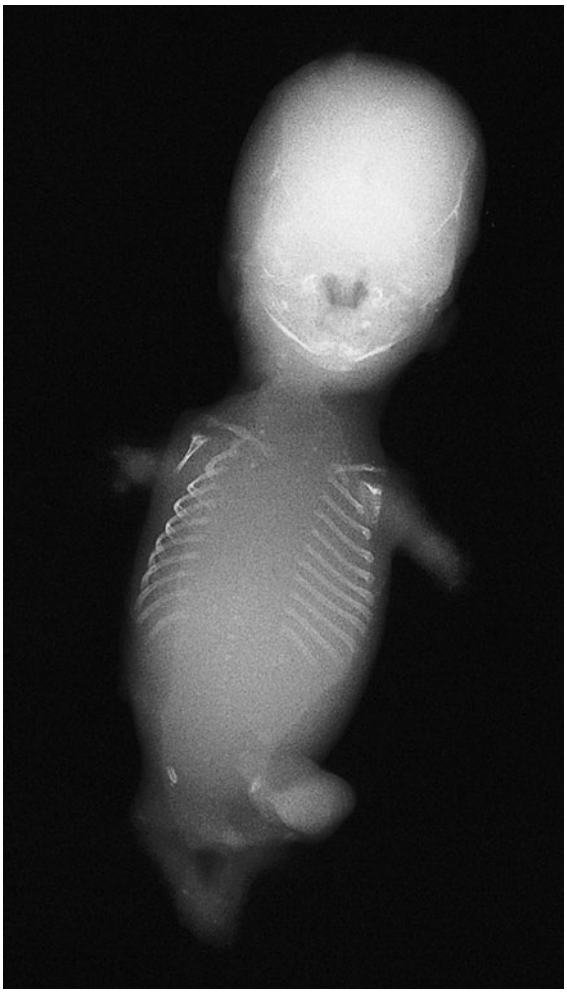

Fig. 2.5. ***10th gestational week.*** Short limbs. Roberts syndrome. Absent ossification of most tubular bones and age related absent ossification of the vertebrae

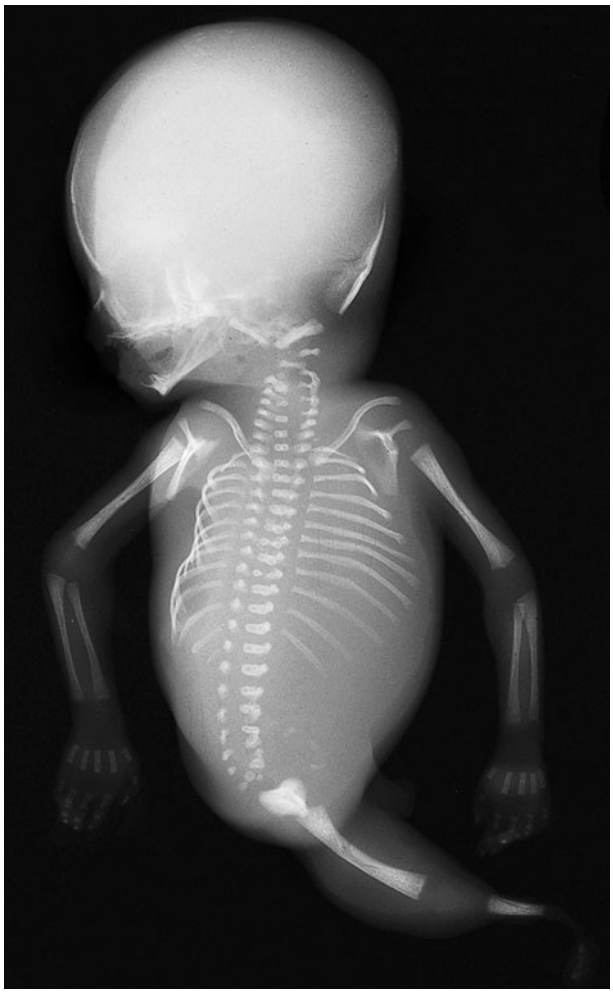

Fig. 2.6. ***19th gestational week.*** Monopodic sirenomelia. Pelvic fusion, sagittal cleft defects of the thoracic vertebral bodies. Accessory rib on the right at L1

Diagnosis	Accessory radiological findings in the fetus
Femur-Fibula-Ulna complex (FFU-syndrome) [7] MIM 228200	Asymmetric absent upper and/or lower limbs, phocomelia, absent or hypoplastic femur, fibula, ulna, humero-ulnar/-radial synostosis, oligodactyly.
Limb/pelvis hypoplasia/aplasia syndrome Includes: Schinzel phocomelia [8] MIM 268300 AL-Awadi/Raas-Rothschild syndrome [9, 10] MIM 276820 Fuhrmann syndrome MIM 228930	Variable and possibly asymmetric lower limb deficiency including primarily femur, tibia and fibula; absent toes; upper limb defects including absent/hypoplastic radius, ulna; radio-humeral synostosis; abscence of carpals, metacarpals, and phalanges; hypoplastic pelvis including irregular pubis, ischium; hip dislocation; thoracic involvement including wide or fused ribs, pectus carinatum
Oromandibula-limb hypogenesis syndromes (incl. Hanhart syndrome) [11] MIM 103300 **Fig. 2.4**	Nearly symmetric terminal limb reduction anomalies, micrognathia, hypoglossia
Roberts (pseudothalidomide) syndrome [12] MIM 268300 **Fig. 2.5**	Tetraphocomelia, severe limb shortening, radial defects, oligodactyly, nuchal cystic hygroma, cleft palate, sometimes craniostenosis

Diagnosis	Accessory radiological findings in the fetus
Sirenomelia [13] (part of caudal regression sequence); MIM 182940 **Fig. 2.6**	Fusion and varying degrees of hypoplasia of lower extremities; pelvic bone fusion; fusion of femurs, sometimes both tibiae and fibulae rotated by 180 degrees (see Fig. 2.38), spinal segmentation anomalies, bladder exstrophy, meningomyelocele, hypoplastic/absent radius
Splenogonadal fusion – limb defects [14] MIM 183300	Micrognathia, caudal regression, spinal dysraphism, transverse limb reduction with or without digits
Tetraamelia with multiple malformations [15] MIM 301090	Anencephalus, hydrocephalus, facial cleft, segmentation defects of spine, aplasia of pelvic bones, severe reduction defects of upper and lower limbs, no digits; other defect: anal atresia
Thalidomide embryopathy [16]	Amelia, proximal phocomelia, fingers present, often attached directly to the shoulders
Thrombocytopenia-absent radius (TAR) syndrome (severe form) [17] MIM 274000	Bilateral severe phocomelia of the upper limbs with hands, including thumbs, attached to the shoulders
Vacterl association [18] MIM 192350	Acronym of associated malformations: *V*ertebral malsegmentation, *a*nal atresia, *c*ardiac malformation, *t*racheoesophageal fistula, *e*sophageal atresia, *r*adial/*r*enal anomalies, *l*imb anomalies (absent upper limb, ray defects such as hypoplasia of fibula, tibia, aplasia of metatarsals, oligo-/preaxial polydactyly of fingers)

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Radius and/or Thumb: Aplasia, Hypoplasia [1]

Entities with isolated aplasia of the radius or radial ray without other radiological apparent defects are not listed.

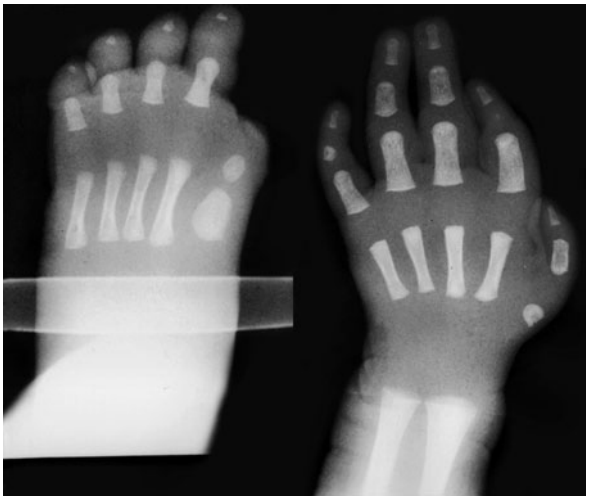

Fig. 2.7. ***Newborn.*** Isolated hypoplasia of metacarpal and phalanges of thumb; Brachymesophalangy II and V. Hypoplasia of metatarsal and aplasia of terminal phalanx of hallux in fibrodysplasia ossificans progressiva

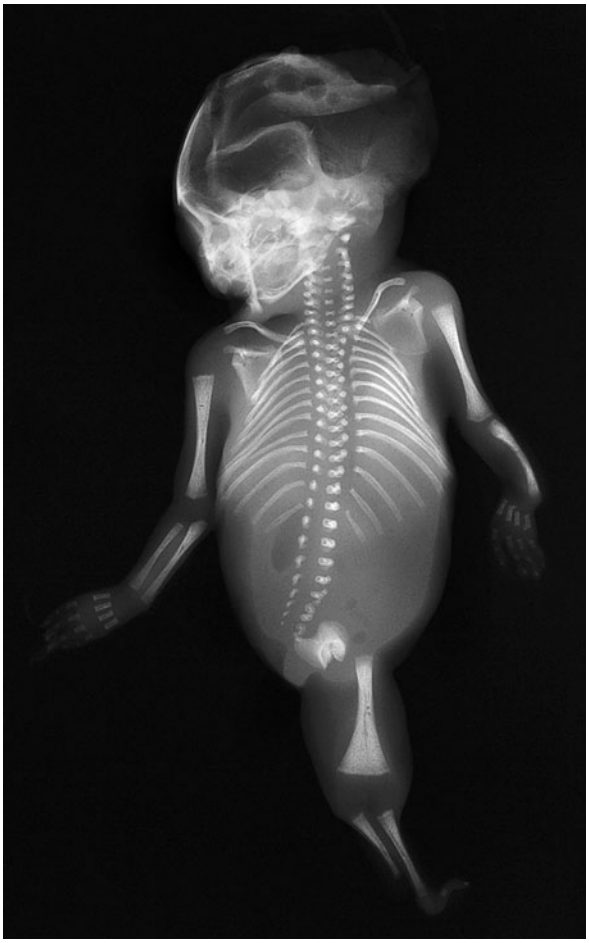

Fig. 2.8. ***19th gestational week.*** Dipodic sirenomelia. Aplasia of the thumb in both hands, aplasia of the left radius, 13 pairs of ribs, and accessory cervical ribs. Fusion of femora, aplasia of fibulae, hypoplastic tibiae. (Postmortem laceration of the neurocranium)

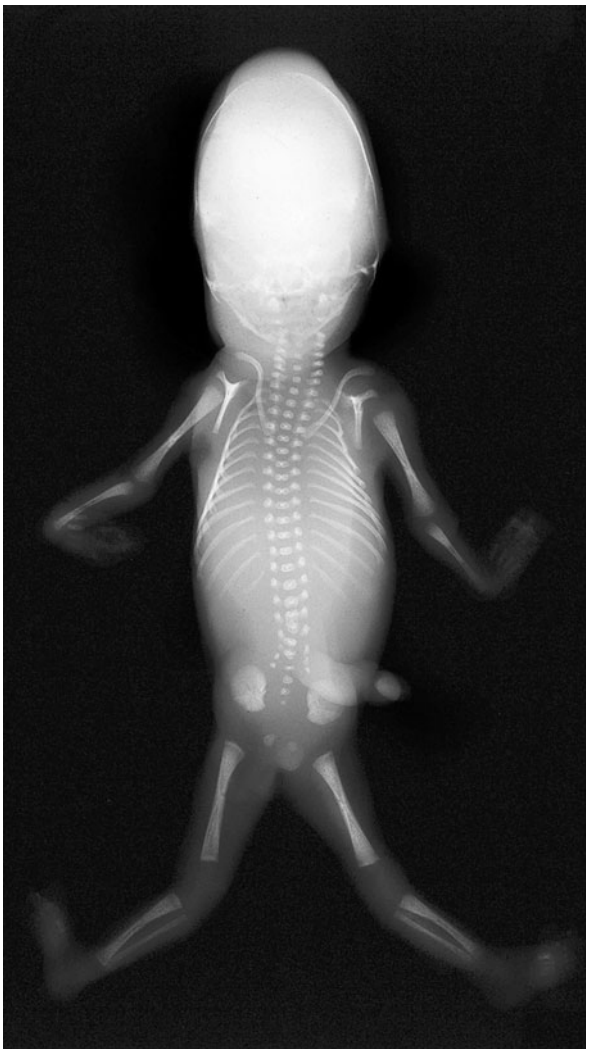

Fig. 2.9. ***18th gestational week.*** Aplasia of radius on both sides in VACTERL association. Segmentation defects of the lumbar and sacral vertebrae. Vertebral fusion. Hyperextended knees are a sequelae of intrauterine malposition due to anhydramnios. Asymmetric shape and narrow position of the ischia suggest an underlying urethral pathology – see "Pelvic-Sacral Abnormalities". Other findings: esophageal atresia Vogt II; urethral atresia; multicystic, dysplastic horseshoe kidney

Diagnosis	Accessory radiological findings in the fetus
Aase syndrome [2] MIM 205600 Blackfan-Diamond syndrome [3]	Radio-ulnar synostosis
Acrofacial dysostosis, type Rodriguez [4, 5] MIM 263750	Micrognathia, forearm anomalies mostly on the radial side, short forearm, radio-ulnar synostosis, preaxial polydactyly, fibular hypoplasia
Amniotic band/disruption sequence ADAM complex (Amniotic Deformity, Adhesions, Mutilations) [6] Limb-body wall complex MIM 217100	Terminal limb defects, constriction bands, distal lymphedema, different degree of mutilations, craniofacial clefts, ectopia cordis, cephalocele/anencephaly, body wall defects
Baller-Gerold Syndrome [7] MIM 218600	Asymmetric radial defect; shortened, bowed ulna; variable premature craniosynostosis; preferable coronal suture
Brachmann-de Lange Syndrome [8] MIM 122470	Primordial dwarfism; hand with ray reduction, mainly ulnar aplasia

Diagnosis	Accessory radiological findings in the fetus
Cerebro-cardio-radio-rectal community [9] MIM 223340 Overlap with VATER + hydrocephalus Association	Microcephaly, absent or hypoplastic humerus, radius, ulna, metacarpals, thumb; oligodactyly; syndactyly of fingers
Chromosome abnormality Trisomy 18 (Edwards' disease) [10]	Slender ribs (11 pairs), vertical iliac bones, limb reduction, radioulnar synostosis, rocker-bottom foot, typical flexion deformity of fingers and overlapping of 2nd finger (see Fig. 2.41b,c), omphalocele
Chromosome 13 q- syndrome [11] see Fig. 2.32	Growth retardation, absent thumb, proximal synostosis of metacarpals/tarsals 4 and 5
Duane anomaly-radial defects [12] MIM 126800	Fusion of verteba, hypolplastic or absent fibula
Fanconi pancytopenia [1] MIM 227650 Thrombocytopenia-absent radius (TAR) syndrome [1] MIM 274000	Range from aplastic thumb to duplication Bilateral aplasia of radius but present thumbs
Fetal valproate syndrome [13, 14]	Prominent metopic ridge, bifrontal narrowing, clinodactyly, distal phalangeal hypoplasia, absent or hypoplastic radius, absent or hypoplastic thumb, talipes equinovarus
Fibrodysplasia ossificans progressiva [15] MIM 135100 **Fig. 2.7**	Isolated aplasia/hypoplasia of metacarpal and phalanges of thumb and metatarsal and phalanges of hallux
Fryns syndrome – acral defects [16] MIM 229850	Distal ray hypoplasia; other finding: diaphragmatic hernia
Goldenhar syndrome (oculo-auriculo-vertebral dysplasia) [17] MIM 164210 see Fig. 2.33	Sporadic, unilateral malformation syndrome of the first and second branchial arches (hypoplastic mandible and maxilla), vertebral anomalies, radial hypoplasia
Holt-Oram (cardiomelic) syndrome [1] MIM 142900	Triphalangeal thumb, radio-ulnar synostosis, absent radius, absent ulna, hypoplastic humerus
Mesomelic dyspiasias [18] see p. 173 ff	Symmetric mesomelic (forearm, shank) shortening of the extremities, different types
MURCS association [19] MIM 601076 see Fig. 2.35	Acronym of associated malformations: Mullerian duct aplasia/hypoplasia, renal aplasia/ectopia, cervical somite (spinal) dysplasia; upper limb defects
Nager acrofacial dysostosis [20] MIM 154400	Forearm anomalies, aplasia/hypoplasia on the radial side, radio-ulnar synostosis, micrognathia
OPD II (oto-palato-digital syndrome II) [21] See p. 136 MIM 304120	Curved long bones, wavy ribs, platyspondyly, omphalocele, overlapping of 2nd finger (trisomy 18-like; see Fig. 2.41b,c) narrow pelvis
Poland syndrome [22] MIM 173800	Different degrees of finger and radius defects, vertebral anomalies; other defect: aplasia of pectoralis muscle
Roberts (pseudothalidomide) syndrome [23] MIM 268300 see Fig. 2.5	Tetraphocomelia, severe limb shortening, radial and ulnar defects, oligodactyly, nuchal cystic hygroma, sometimes craniostenosis
Sirenomelia [24] (part of caudal regression sequence); MIM 182940 **Fig. 2.8**	Fusion and varying degrees of hypoplasia of lower extremities, pelvic bone fusion, fusion of femurs; overlap with VACTERL association
VACTERL Association [1] MIM 192350 **Fig. 2.9**	Acronym of associated malformations: *V*ertebral malsegmentation, *a*nal atresia, *c*ardiac malformation, *t*racheoesophageal fistula, *e*sophageal atresia, *r*adial/*r*enal anomalies, *l*imb anomalies (ray defects such as hypoplasia of fibula, tibia, aplasia of metatarsals, oligo-/preaxial polydactyly of fingers)
XK-aprosencephaly [25] MIM 207770	Anencephaly, absent radius, radio-ulnar synostosis

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Radio-ulnar Synostosis (Fig. 2.10)

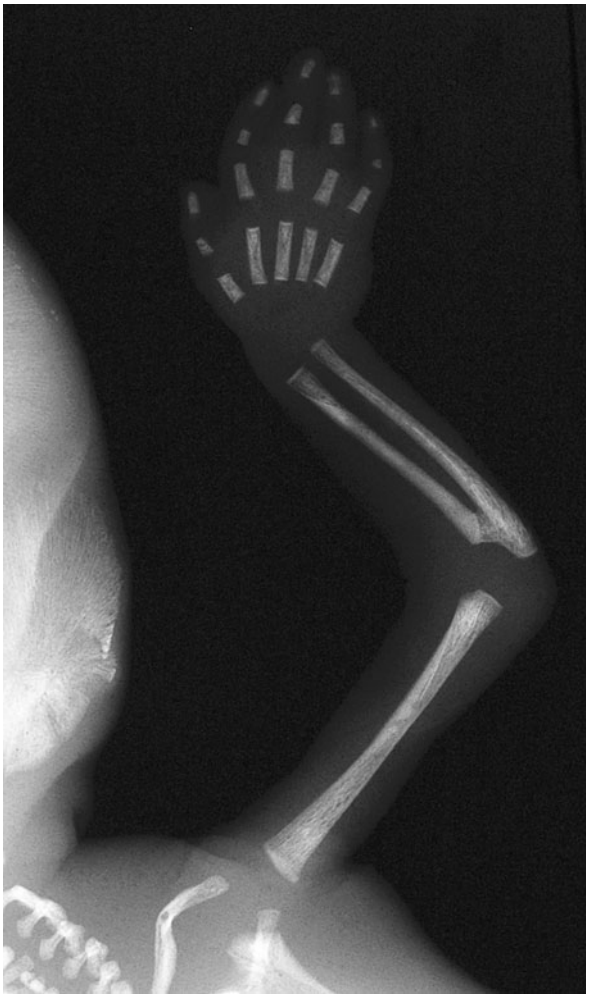

Fig. 2.10. ***19th gestational week.*** Radioulnar synostosis in Triploidy. Bone bridge between the proximal parts of radius and ulna

Diagnosis	Accessory radiological findings in the fetus
Aase syndrome [1] MIM 205600 Blackfan-Diamond syndrome [2]	Triphalangeal thumb, duplication of thumb
Antley-Bixler syndrome MIM 207410 see p. 126	Craniosynostosis, multiple synostoses.
Cenani-Lenz syndrome [3] MIM 212780	Extensive phalangeal synostosis and proximal metacarpal fusion; oligodactyly; thoracic hemivertebrae
Cloverleaf skull – limb anomaly, type Holtermüller-Wiedemann [4] MIM 148800	Trilobed skull deformity (congenital cranial synostosis), ankylosis of elbow
Chromosome abnormality Trisomy 18 [5]	Slender ribs (11 pairs), vertical iliac bones, rocker-bottom foot, hypoplasia of first metacarpal, typical flexion deformities and overlapping 2nd finger (see Fig. 2.41b,c), omphalocele, limb reduction

Diagnosis	Accessory radiological findings in the fetus
Chromosome (Sex-) abnormality Klinefelter syndrome [6]	No specific radiologic signs in the fetus
Ectrodactyly AD [7] MIM 183600, 600095 Ectrodactyly AR [7] MIM 225300	Cleft hand/foot, reduction deformity of arms or legs, triphalangeal thumbs
Fetal alcohol syndrome [8]	Intrauterine growth retardation, vertebral segmentation defects, Klippel-Feil syndrome, reduction deformity of upper extremities, hypoplasia! aplasia of ulna, tetradactyly; clubfoot
Genitopatellar syndrome [9] MIM 606170	Dislocation of hip, hypoplasia of ischia and pubic rami, brachydactyly
Holt-Oram syndrome (cardiomelic syndrome) [10] MIM 142900	Triphalangeal thumb, hypoplastic/absent radius, hypoplastic/absent ulna, hypoplastic humerus
Larsen syndrome MIM 150250, 245600 see p. 161	Multiple luxations of great joints, especially of hips, knees, elbows, coronal vertebral cleft
Nager acrofacial dysostosis [11] MIM 154400	Forearm anomalies: aplasia/hypoplasia on the radial side, radio-ulnar synostosis; micrognathia
Radio-ulnar synostosis, autosomal dominant [12] MIM 179300	Bilateral or single-sided proximal synostosis
XK-aprosencephaly [13] MIM 207770	Anencephaly, absent/hypoplastic thumb and radius,

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Ulna: Aplasia, Hypoplasia

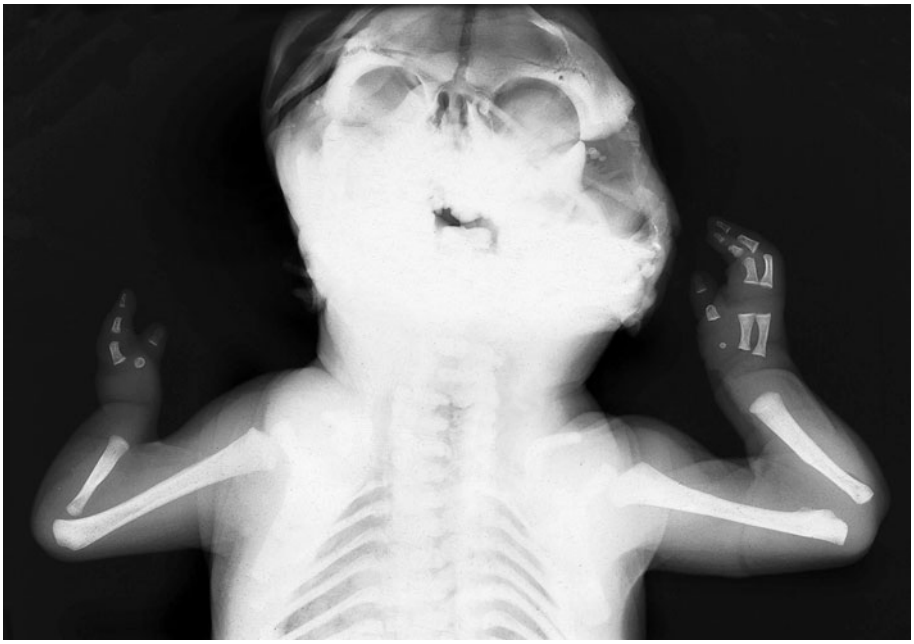

Fig. 2.11. ***33rd gestational week.*** Complex tubular bone aplasia/hypoplasia in Brachmann-De Lange syndrome: bilateral aplasia of the ulna and ulnar rays of the hands, aplasia of the middle finger and proximal phalanx of the thumb on the right side. Hypoplastic radii. Luxation of the left humeroradial joint

Diagnosis	Accessory radiological findings in the fetus
Acrofacial dysostosis with post-axial defects [1] MIM 263750	Different degrees of postaxial hypoplasia in all four limbs, shortened forearm
Acrofacial dysostosis, type Rodriguez [2] MIM 263750	Micrognathia, forearm anomalies mostly on the radial side, short forearm, radio-ulnar synostosis, preaxial polydactyly, fibular hypoplasia
Brachmann-de Lange syndrome [3] MIM 122470 **Fig. 2.11**	Variable reduction deficiency of upper limb, including ulna, humerus, radius, carpals; ectrodactyly
Femur-fibula-ulna complex (FFU syndrome) [4] MIM 228200	Asymmetric hypoplasia/aplasia of femur, fibula, humerus, ulna; humero-ulnar/-radial synostosis; oligodactyly
Fetal alcohol syndrome [5]	Intrauterine growth retardation, vertebral segmentation defects, Klippel-Feil syndrome, reduction deformity of upper extremities, hypoplasia/aplasia of ulna, radioulnar synostosis, tetradactyly, clubfoot
Grebe syndrome [6,7] and related osteochondrodyspiasias; see p. 177 MIM 200700	Dislocated radial heads, aplasia/hypoplasia of ulna, radius, femur; absent or hypoplastic proximal and middle phalanges; syndactyly; absent or hypoplastic metacarpals; absent or hypoplastic carpals; carpal fusion; very short tubular long bones (lower limbs more severe than upper limbs), hypoplastic tarsals, short and broad metatarsals
Holt-Oram-Syndrome (cardiomelic syndrome) [8] MIM 142900	Asymmetric aplasia of radius, triphalangeal thumb, hypoplasia of humerus
Humero-radial synostosis-ulnar defects [9] MIM 236400	Humero-radial synostosis, fibular aplasia, patellar aplasia
Lethal osteochondrodyspiasias [10] see p. 167	For example, atelosteogenesis II (de la Chapelle dysplasia)

Diagnosis	Accessory radiological findings in the fetus
Leri-Weill dyschondrosteosis [11] MIM 127300	Mesomelia, bowed radius, hypoplasia of tibia
Mesomelic dysplasias [11] see p. 173 ff	Severe mesomelic i.e, forearm, shank) shortening of the extremities, different types
Mietens-Weber syndrome [12] MIM 249600	Proportionate short stature, hypo-/aplasia of ulna, radius, fibula, elbow dislocation, hip dislocation, mesomelia of upper limb
Neu-Laxova syndrome [13] MIM 256520	Severe microcephaly, hypoplasia of radius/ulna, postaxial oligodactyly
Neurofibromatosis 1 [14] MIM 162200	Pseudarthrosis; pathologic fracture of the diaphysis due to focal fibrous dysplasia; most often in the tibia
Odontotrichomelic syndrome [15] MIM 273400	Spilt hand, oligodactyly,
Pfeiffer Absent ulna/fibula with oligodactyly [16] MIM 228930	Bowed femur, split hand
Roberts (pseudothalidomide) syndrome [17] see Fig. 2.5 MIM 268300	Tetraphocomelia, severe limb shortening' radial defects, oligodactyly, nuchal cystic hygroma, sometimes craniostenosis
Thrombocytopenia-absent radius (TAR) syndrome [18] MIM 274000	Bilateral aplasia of radius but present thumbs
Ulnar-mammary syndrome type Pallister [19] MIM 181450	Ulnar ray deficiency, aplasia of phalanges, bowed radius, hypoplasia of humerus; other: anal atresia/stenosis
Weyers syndrome of deficiency of ulnar and fibular rays [20] MIM 602418 (similar with De la Chapelle syndrome? see p. 167) MIM 256050)	Hypoplasia of ulna and fingers, split hand, absent clavicles, cleft palate; see also "Fibula: Aplasia. Hypoplasia"

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Humerus: Aplasia, Hypoplasia

Diagnosis	Accessory radiological findings in the fetus
Acrofacial dysostosis, type Rodriguez [1] MIM 201170	Phocomelia of arms, defective ulnar ray, short humerus and fibula, hypoplastic scapula
Atelosteogenesis 1 [2–4] and related osteochondrodyspiasias; see p. 163 MIM 108720, 108721, 112310	Hypoplastic vertebral bodies, especially of cervical and thoracic spine; hypoplastic and tapered (distal) humerus and femur; bowed radius, ulna and tibia; absent or hypoplastic fibula; absent or hypo-ossified metacarpals and phalanges
Brachmann-de Lange syndrome [5] see Fig. 2.11 MIM 122470	Variable reduction deficiency of upper limb, including ulna, humerus, radius, carpals; ectrodactyly
CHILD syndrome [6] (Congenital hemidysplasia, ichthyosiform erythroderma, limb defects) MIM 308050	Unilateral hypoplasia of limb(s) including absent or hypoplastic scapula, humerus, radius, ulna, femur, tibia, fibula; joint contracture or pterygium; punctate epiphyseal calcification; other features: congenital ichthyosiform erythroderma ipsilateral to limb deficiency, visceral anomalies
Chondrodysplasia punctata, rhizomelic type [7, 8] see p. 159 MIM 215100	Punctate calcifications primarily around the ends of the long bones, hypoplasia of humerus and femur, wide or splayed metaphyses, platyspondyly
Chondrodysplasia punctata, tibia-metacarpal type [9] MIM 118651	Stippling of sacrum and carpals; dislocation of hip, knee, elbow; short tibia, femur, metacarpals, phalanges; asymmetry
DK phocomelia [10] Phocomelia-encephalocele-thrombocytopenia-urogenital malformation von Voss-Cherstvoy syndrome MIM 223340	Microcephaly; absent or hypoplastic humerus, radius, ulna, metacarpals, thumb; oligodactyly; syndactyly of fingers; other features: genitourinary, cardiac anomalies, platelet abnormalities
Femur-fibula-ulna complex (FFU syndrome) [11] MIM 228200	Asymmetric hypoplasia/aplasia of femur, fibula, humerus, ulna; humero-ulnar/-radial synostosis; oligodactyly
Fetal thalidomide syndrome [12]	Amelia; proximal phocomelia; fingers present, often attached direct to the shoulders
Fetal valproate syndrome [13, 14]	Prominent metopic ridge, bifrontal narrowing, clinodactyly, distal phalangeal hypoplasia, absent or hypoplastic radius, absent or hypoplastic thumb, talipes equinovarus
Holt-Oram syndrome [15, 16] Cardiomelic syndrome MIM 142900	Absent or hypoplastic humerus, radius, ulna, first metacarpal, thumb; triphalangeal thumb; absent or hypoplastic carpals; delayed ossification or fusion of carpals; other polydactyly; radioulnar synostosis; hypoplasia of the clavicle, scapula; Sprengel anomaly; pectus excavatum or carinatum; rib hypoplasia or fusion; vertebral fusion or hemivertebra, scoliosis; other anomalies: cardiac defects (secundum-type atrial septal defect most commonly)
Omodysplasia [17 – 19] see p. 161, 170 MIM 164745, 251455	Rhizomelia of upper limbs by distal hypoplasia of humeri, milder such involvement of lower limbs; dislocation of radial heads
Oromandibular – limb hypogenesis syndromes; see Fig. 2.20 Aglossia-adactylia, hypoglossia-hypodactylia Hanhart syndrome [20, 21] MIM 103300	Asymmetric, variably absent or hypoplastic humerus, radius, ulna, carpals, metacarpals, femur, tibia, fibula, tarsals, metatarsals; oligodactyly; syndactyly; microretrognathia; aplasia/hypoplasia of tongue
Thrombocytopenia-absent radius (TAR) syndrome (severe form) [22] MIM 274000	Bilateral severe phocomelia of the upper limbs with hands attached to the shoulders, thumbs present
Ulnar-mammary syndrome type Pallister [23] MIM 181450	Ulnar ray deficiency; aplasia of phalanges; bowed radius; hypoplasia of humerus; other feature: anal atresia

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Tibia: Aplasia, Hypoplasia

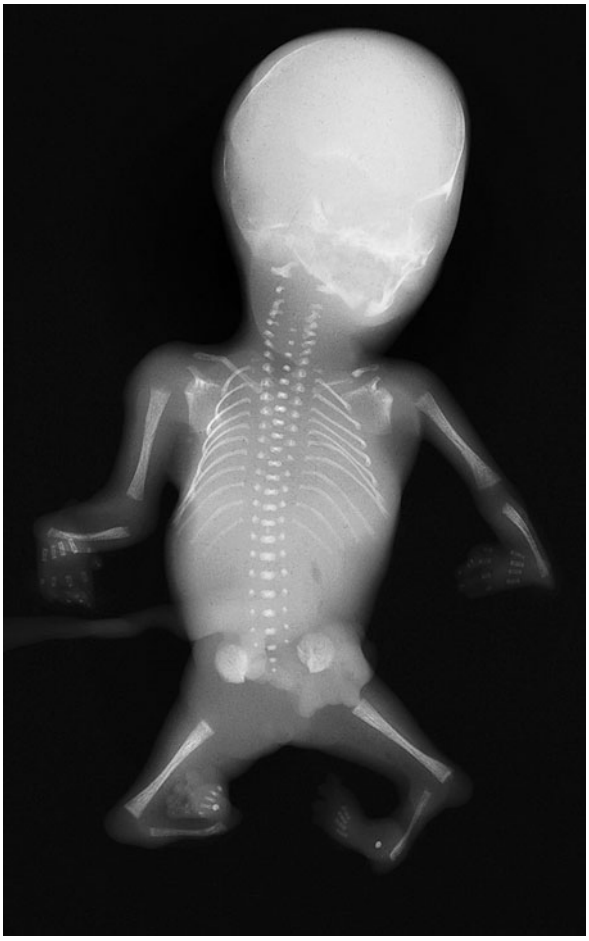

Fig. 2.12. ***18th gestational week.*** Aplasia of both radii and tibiae in Trisomy 18. Aplasia of the first ray of the left hand and foot. Punctate calcifications in the calcaneus. 11 pairs of slender ribs. (Note retarded maturation!)

Diagnosis	Accessory radiological findings in the fetus
Acro-renal-mandibular syndrome [1] MIM 200980	Severe mandibular hypoplasia, variable and asymmetric limb reduction defects incl. hypoplastic or absent radius, oligodactyly, syndactyly, vertebral segmentation defects
Amniotic band disruption sequence ADAM complex (Amniotic Deformity, Adhesions,Mutilations) Limb-body wall complex [2] see Fig. 2.24 MIM 217100	Usually asymmetric transverse terminal limb reductions/amputations and variable terminal syndactyly/pseudosyndactyly; sometimes also oligodactyly, hypoplasia of long bones, craniofacial and ventral wall disruption
Chondrodysplasia punctata, tibia-metacarpal type [3] MIM 118651	Stippling of sacrum and carpals; dislocation of hip, knee, elbow; short tibia and femur; short metacarpals and phalanges; asymmetry
Chromosome abnormality Trisomy 18 [4]; **Fig. 2.12**	In rare cases tibial aplasia is present; for Trisomy 18 see "Aplasia, Hypoplasia of Radius and Thumb"
Grebe syndrome [5] see p. 177 MIM 200700	Severe, proportionate shortening of extremities, mild shortening of trunk, absent proximal phalanges, distal phalanges always present, oligo/polydactyly
Leri-Weill dyschondrosteosis [6] MIM 127300	Mesomelia, bowed radius, hypoplasia of tibia and ulna

Diagnosis	Accessory radiological findings in the fetus
Mesomelic dyspiasias [6] see p. 173 ff	Different types and degree of mesomelic shortening of the extremities combined with or without phalangeal involvement.
Mesomelic dwarfism of hypoplastic tibia-radius type [7] MIM 156230	Isolated bilateral shortening of radius and tibia
Neurofibromatosis 1 [8] MIM 162200	Tibial pseudarthrosis; pathologic fracture of the diaphysis due to a focal mesenchymal defect; rare in other long bones
Split hand/foot, tibial defect [9] MIM 119100	Split hand and/or foot; hypoplasia of ulna, femur; bifurcation of distal femur; postaxial polydactyly
Tibial hemimelia [10] MIM 275220	Isolated aplasia of the tibia, clubfoot
Tibial hypoplasia, polydactyly and triphalangeal thumb (Werner syndrome) [11] MIM 188770	Triphalangeal thumb, (multiple) preaxial polydactyly of feet, polydactyly of hands, radio-ulnar synostosis. In rare cases tibial aplasia is present
VACTERL association	For VACTERL association see: "Radius and Thumb: Aplasia, Hypoplasia"

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Fibula: Aplasia, Hypoplasia

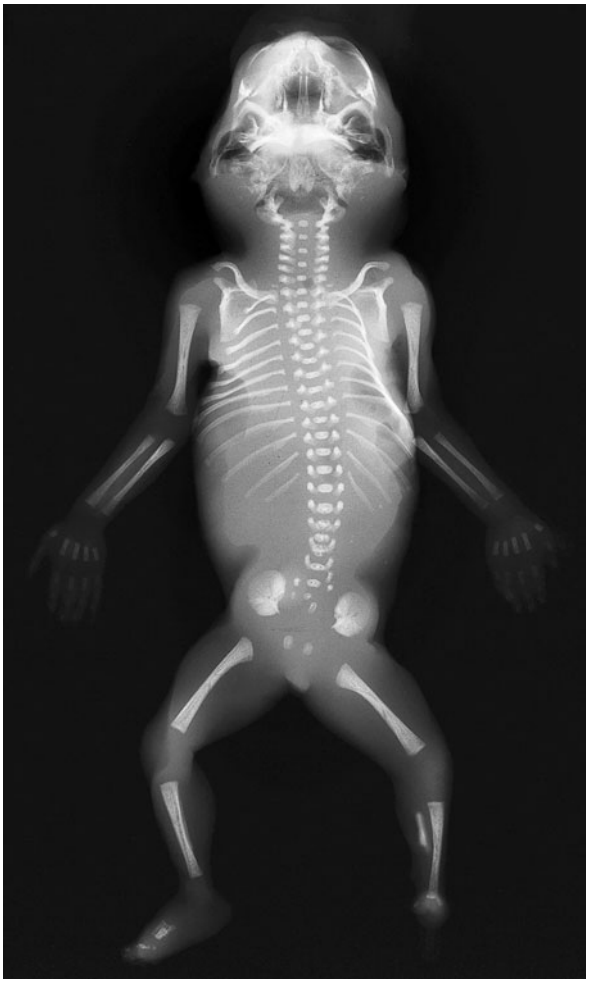

Fig. 2.13. ***18th gestational week.*** Hypoplasia of left fibula in VACTERL association. Small left foot with only one ray. Fused vertebrae L3–5 Segmentation errors and hypoplasia of the sacrum (caudal regression). Urethral pathology is suggested by narrow and asymmetric pubic bones. Other findings: esophageal atresia Vogt IIIb; anal atresia; absent urethra, bladder, and kidneys

Diagnosis	Accessory radiological findings in the fetus
Acrofacial dysostosis, type Rodriguez [1] MIM 201170	Phocomelia of arms, defective ulnar ray, short humerus, hypoplastic scapula
Atelosteogenesis 1 [2–4] and related osteochondrodyspiasias; see p. 163 MIM 108720, 108721, 112310	Hypoplastic vertebral bodies, especially of cervical and thoracic spine; hypoplastic and tapered (distal) humerus and femur; bowed radius, ulna and tibia; absent or hypo-ossified metacarpals and phalanges
Campomelic dysplasia; see p. 124 MIM 114150	Bowing of femur and tibia, pear-shaped iliae; hypoplasia of claviculae, scapulae; cervical kyphosis
Chondroectodermal dysplasia Ellis-van Creveld [5] see p. 153	Postaxial polydactyly; narrow chest; short, thick, bowed humeri and femurs; hypoplasia/aplasia tibiae; triradiate acetabula
Chromosome abnormalities	Rare
De la Chapelle dysplasia [6] including atelosteogenesis II; see p. 167 MIM 256050	Deficiency of fibular and ulnar rays; hemivertebrae; platyspondyly; coronal clefts; thin, short ribs

Diagnosis	Accessory radiological findings in the fetus
Du Pan brachydactyly, fibular aplasia [7] see Grebe dysplasia p. 177 MIM 228900	Dislocation of elbow, knee, or hip; complex brachydactyly
Ectrodactyly-fibular aplasia [8] MIM 113310	Variable absence or hypoplasia of ulna, carpals, metacarpals, phalanges, fibulae, tarsals, metatarsals; brachydactyly; syndactyly; triphalangeal thumb
Femoral hypoplasia, unusual facies syndrome [9] MIM 134780	Small mandible, cleft palate, bowing of femur, hypoplastic/absent fibula or tibia, hypoplastic acetabula, preaxial polydactyly
Femur-fibula-ulna complex (FFU syndrome) [10] see Fig. 2.14 MIM 228200 Fibular aplasia – oligodactyly – camptomelia MIM 246570	Asymmetric hypoplasia/aplasia of femur, fibula, humerus, ulna; humero-ulnar/radial synostosis; oligodactyly
Fibular aplasia/hypoplasia [11] Limb/pelvis-hypoplasia/aplasia syndrome [12] MIM 276820	Isolated defect of the fibula Hypoplastic femurs and feet; aplastic fibulae; oligodactyly; short, bent ulnae
Leri-Weill dyschondrosteosis [13] MIM 127300	Mesomelia, bowed radius, hypoplasia of tibia and ulna
Mesomelic dyspiasias [13] see p. 173	Different types and degrees of mesomelic shortening of the extremities with or without phalangeal involvement
Seckel syndrome [14] MIM 210600	Severe intrauterine growth retardation; microcephaly; craniosynostosis; radial head luxation, absent ribs
VACTERL association; **Fig. 2.13**	Aplasia of fibula in rare cases (see: "Aplasia, Hypoplasia of Thumb and Radius")

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Femur: Aplasia, Hypoplasia

Aplasia or hypoplasia of the femur is rare, most often associated with other radiological signs helping to solve the differential diagnosis. See "Amelia, Amputation, Phocomelia"

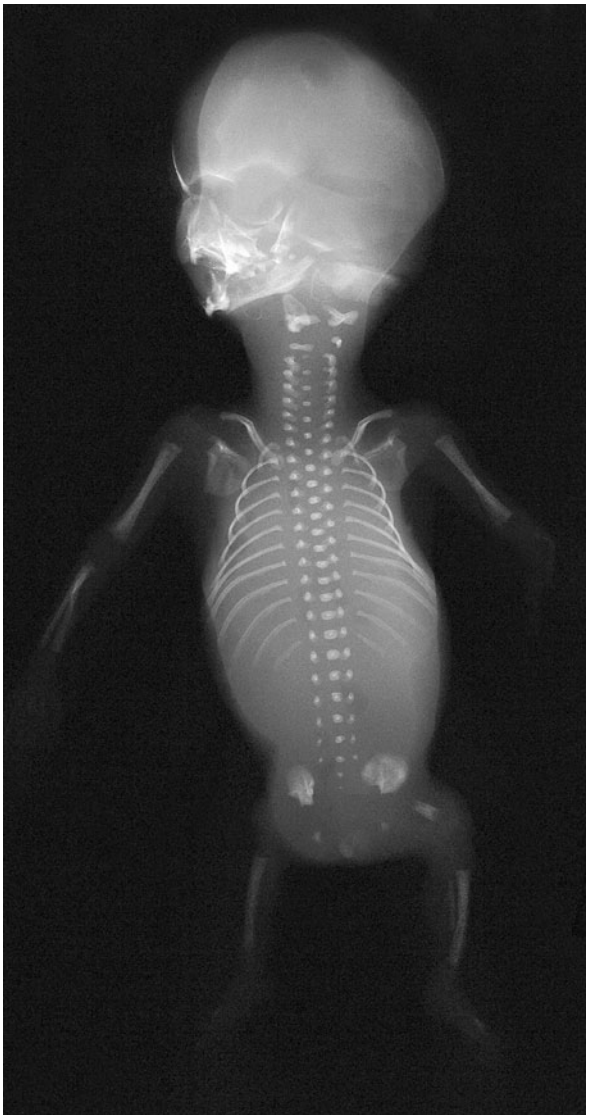

Fig. 2.14. ***17th gestational week.*** Complex tubular bone aplasia/hypoplasia in femur-fibula-ulna complex. Aplasia of the right femur, hypoplasia of the left femur, hypoplastic fibulae, aplasia of left radius, hypoplasia of the left ulna, two triphalangeal digits on the left

Diagnosis	Accessory radiological findings in the fetus
Atelosteogenesis I [1–3] and related osteochondrodysplasias; see p. 163 MIM 108720, 108721, 112310	Hypoplastic vertebral bodies, especially of cervical and thoracic spine; hypoplastic and tapered (distal) humerus; bowed radius, ulna and tibia; absent or hypoplastic fibula; absent or hypo-ossified metacarpals and phalanges
Diabetic embryopathy [4] see Fig. 2.37	Caudal regression, segmentation defects of the spine, defects of ulna and tibia
Ectrodactyly-tibial hypoplasia [5] MIM 119100	Split hand and/or foot, polydactyly, ulnar hypoplasia, tibial hypoplasia, bifid femur
Femoral hypoplasia, unusual facies syndrome [6] MIM 134780	Small jaw, cleft palate, radio-ulnar synostosis, absent fibula, absent tibia, hypoplastic acetabula, preaxial polydactyly of feet

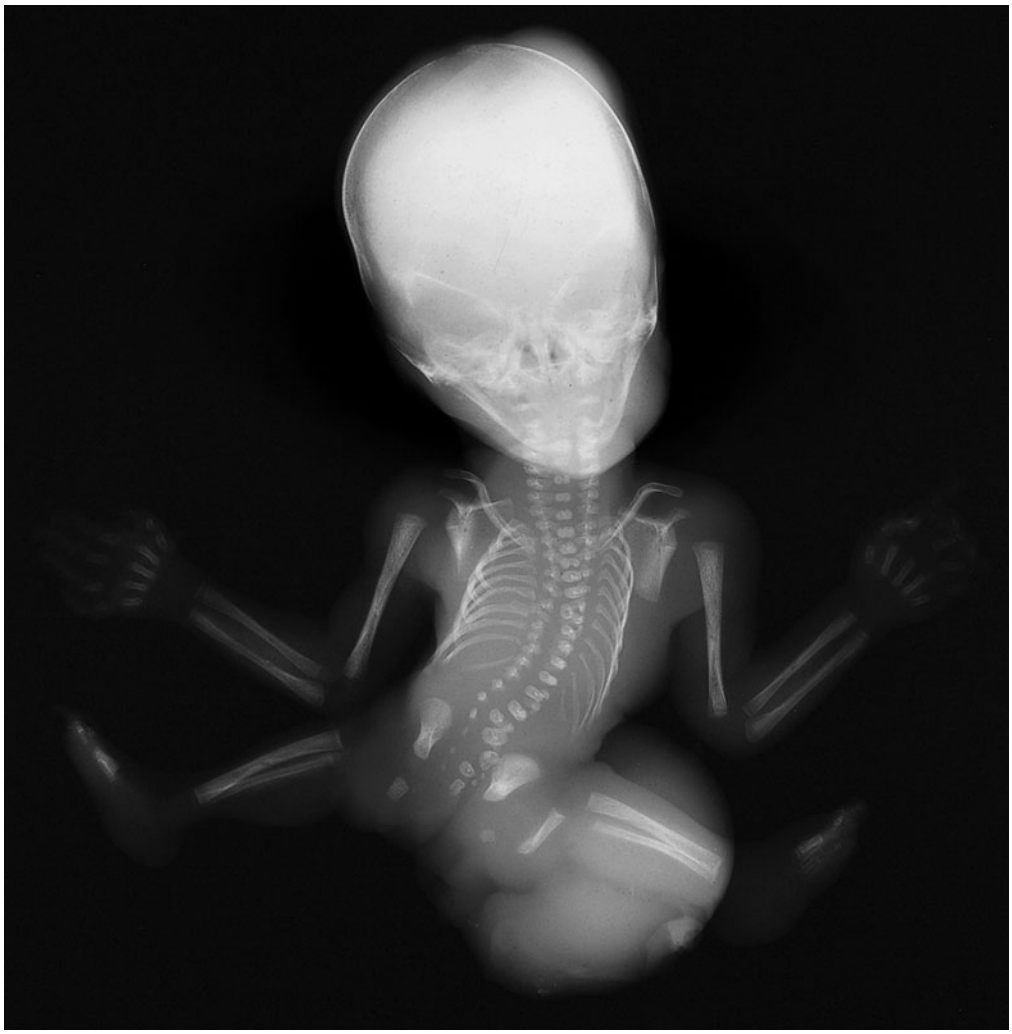

Fig. 2.15. ***20th gestational week.*** Femoral aplasia/hypoplasia in limb-body wall complex. Aplasia of the right femur, hypoplasia of left femur. Disproportionately short trunk. vertebral segmentation defects. Abdominal wall defect and bladder exstrophy. The upper extremities are normal

Diagnosis	Accessory radiological findings in the fetus
Femur-fibula-ulna syndrome (FFU complex) [7] **Fig 2.14** MIM 228200	Asymmetric hypoplasia/aplasia of femur, fibula, humerus; humero-ulnar/-radial synostosis; oligodactyly
Limb, body wall complex [8] **Fig. 2.15** MIM 217100	Defect of lower abdominal wall, bladder exstrophy, pubic diastasis, segmental defects of lower extremities, spinal segmentation defects
Limb/pelvis-hypoplasia/aplasia syndrome [9] MIM 276820	Hypoplastic femur; aplasia of fibula; hypoplastic feet; oligodactyly; short, bent ulnae
Omodysplasia [10–12] see p. 170 MIM 164745, 251455	Rhizomelia of upper limbs by distal hypoplasia of the humeri, milder involvement of lower limbs; dislocation of radial heads
Proximal focal femoral deficiency [13] MIM 228200	Unilateral short femur due to proximal reduction defect, hip joint preserved

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Femur: Bowing

Bowing of the femur is a quite common sign. It is helpful to evaluate at first whether length and structure are normal or not.

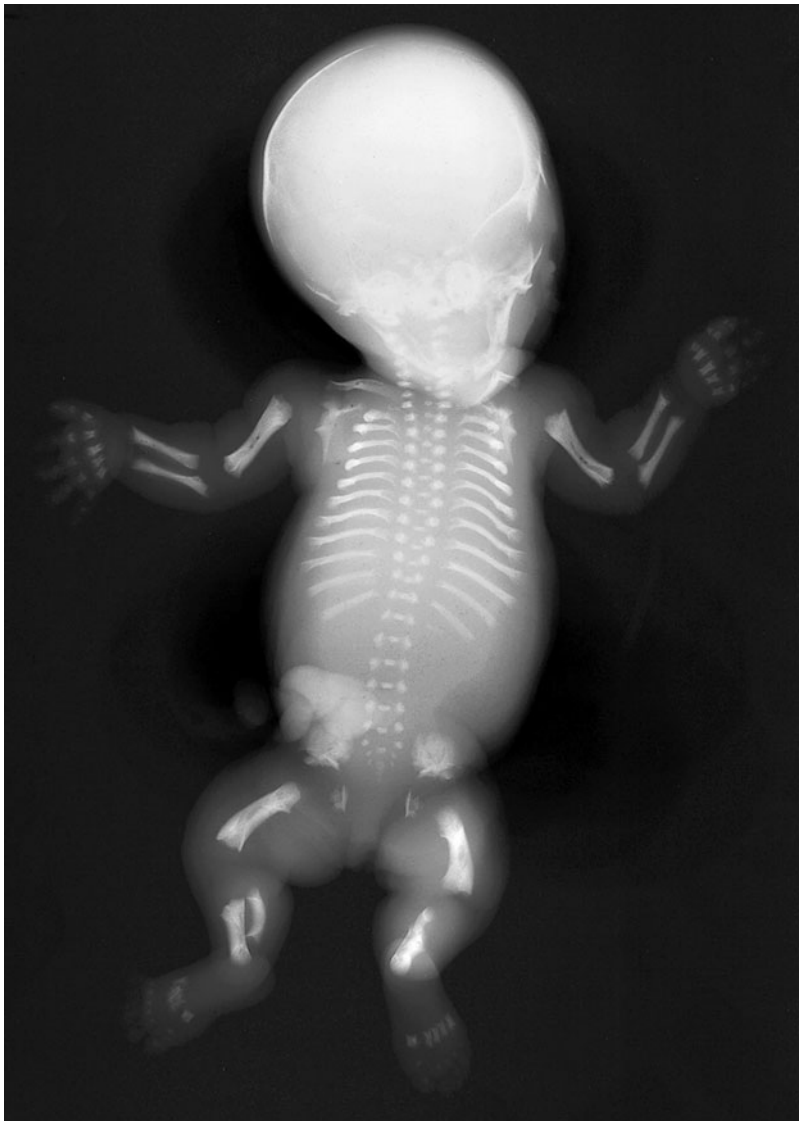

Fig. 2.16. ***23rd gestational week.*** Short bowed femora in thanatophoric dysplasia I. Narrow thorax, platyspondyly. All short and long tubular bones are markedly short and broad with flared and cupped metaphyses. Postaxial polydactyly right foot

Structure of femur	Diagnosis
A: short, thick, metaphyseal abnormalities but normal bone structure; **Fig. 2.16**	Mostly lethal osteochondrodyspiasias [4] (see Chap. 3, "Skeletal Dysplasias with Shortened Tubular Bones", p. 100 ff, "Skeletal Dysplasias with Congenital Bowing", p. 120 ff); exception: kyphomelic dysplasia [1]
B: normal structure, slight to moderate bowing; **Fig. 2.17**	Unspecific radiological sign in many syndromes and chromosomal abnormalities with otherwise normal skeleton or luxations [3]; exceptions: Antley-Bixler syndrome MIM 207410; campomelic dysplasia MIM 211970 (see p. 124), OPD II MIM304120 (see p. 136)

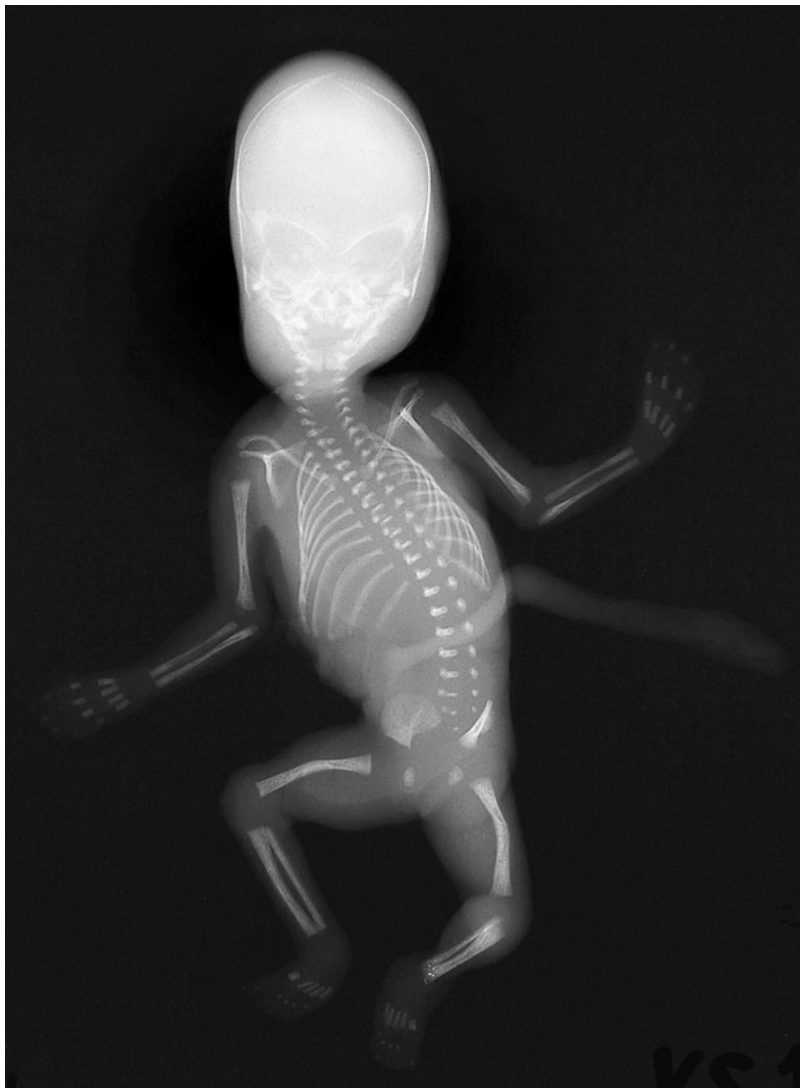

Fig. 2.17. ***15th gestational week.*** Mild femoral bowing of the normally structured femora in Trisomy 18. Eleven pairs of ribs. Disharmonic skeletal maturation: absent ossification of the cervical vertebrae but well-ossified ischia

Structure of femur	Diagnosis
C: abnormal structure (fractures, abnormal density), any size	
Osteogenesis imperfecta II [4] see p. 128 MIM 120150, MIM 166200	– broad irregular diaphyses due to multiple fractures, multiple rib fractures, hypo-ossified calvarium
Hypophosphatasia, infantile form [2] **Fig. 2.18** MIM 241500	– bowing of long bones (rectangular), metaphyseal ossification defects, transverse midshaft spurs, hypo-ossified calvarium, erratic ossification of vertebrae
Neurofibromatosis 1 [5] MIM 162200	– pseudarthrosis of femur (more often tibia)

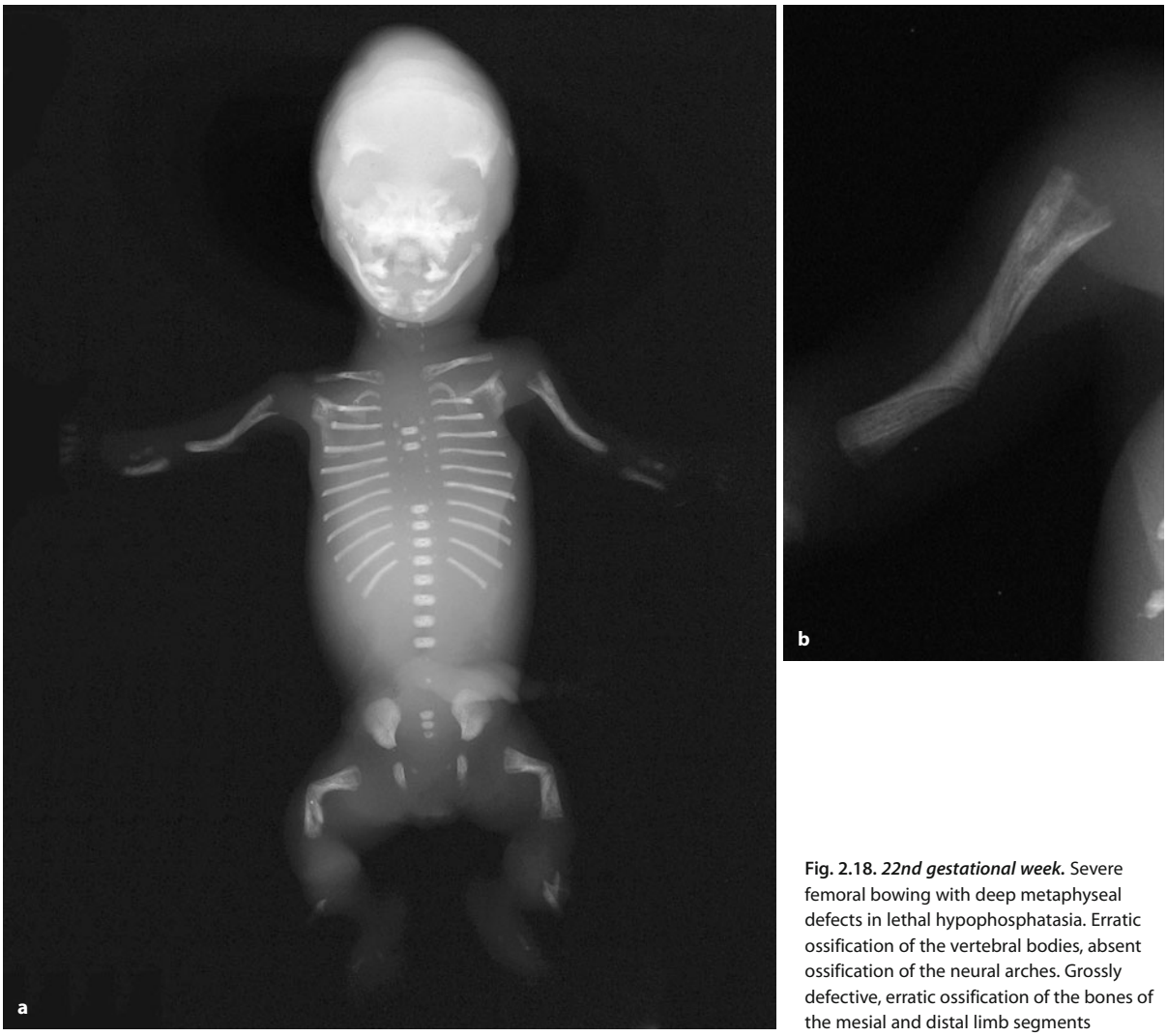

Fig. 2.18. ***22nd gestational week.*** Severe femoral bowing with deep metaphyseal defects in lethal hypophosphatasia. Erratic ossification of the vertebral bodies, absent ossification of the neural arches. Grossly defective, erratic ossification of the bones of the mesial and distal limb segments

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Stippled Epiphyses – Stippled Ossification of Cartilage

For skeletal dysplasias with punctuate calcification see p. 155 ff (Greenberg dysplasia; dappled diaphysis dysplasia; chondrodysplasia punctata, different types; CHILD syndrome)

Definition

– Syndromatic or symptomatic premature stippled calcification of epiphyses or apophyses of high radiographic density

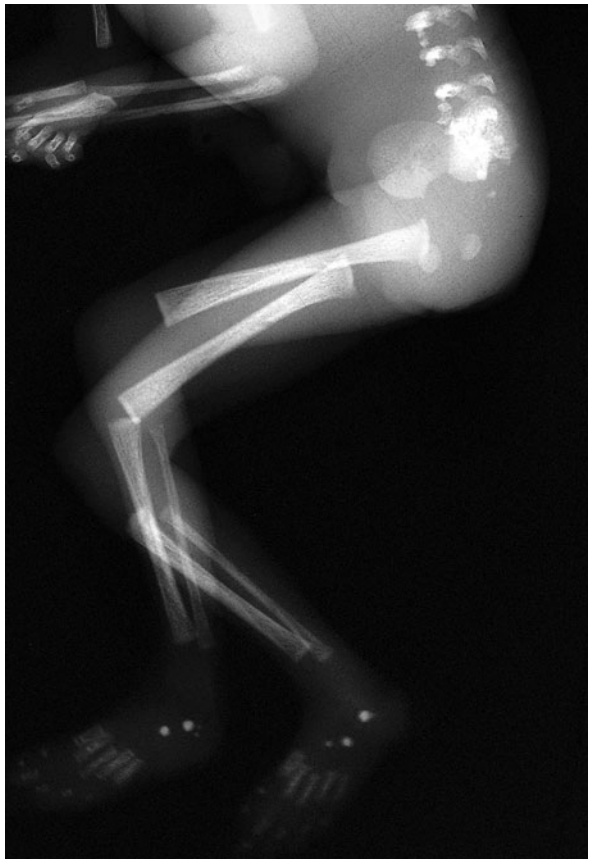

Fig. 2.19. ***22nd gestational week.*** Short femora in triploidy: femur length of 18th gestational week. Puncta in the tarsus and intervertebral disks

Diagnosis	Accessory radiological findings in the fetus
Chromosome abnormalities: Triploidy Trisomy 13 Trisomy 18 Trisomy 21 [1] Turner syndrome, X-Y translocation **[2]**	Besides the other signs which specific disorders expose (such as dystrophy, hypo-ossified calvaria, hypotelorism, nuchal cystic hygroma, umbilical hernia, radius aplasia, coronal vertebral clefts) most often only the calcaneus with a premature, dot-like, very dense ossification; especially in triploidy, intervertebral disks with a central calcification (see Fig. 2.19)
Fetal alcohol syndrome [3]	Intrauterine growth retardation, microcephaly, hemivertebra, Klippel-Feil syndrome
Hydantoin embryopathy [4] MIM 261720	Microcephaly, distal hyperphalangism or hypoplasia
Smith-Lemli-Opitz syndrome [5] MIM 270400	Growth retardation, microcephaly, postaxial polydactyly, split hand, clubfoot
Warfarin embryopathy [6, 7]	Short, broad hand; calcification of larynx and trachea; shortened limbs; occipital encephalocele
Zellweger syndrome [8] (cerebro-hepato-renal syndrome) MIM 214100	Microcephaly, no specific radiologic signs, stippled calcifications of the patella and mostly grouped around the pelvis

Chromosome 16p duplication, DeBarsy-Syndrome (progeroid syndrome), show, except for stippled epiphyses, no other radiologic signs in the fetus helping to solve the differential diagnosis.

Single cases of undetermined origin have been published.

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Hands/Feet: Absent

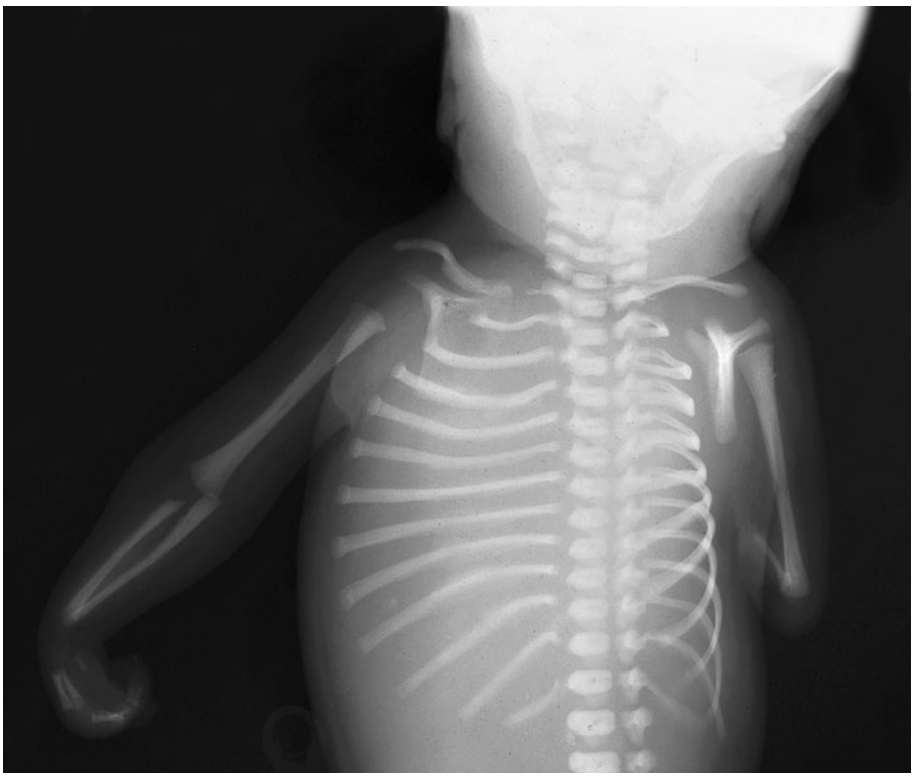

Fig. 2.20. ***30th gestational week.*** Complex aplasia/hypoplasia: aplasia of the left radius and hand in oromandibular-limb hypogenesis syndrome, hypoplasia of the left ulna. On the right side, slightly dysplastic radius and ulna, absent ossification of the 4th and 5th digits and of the phalanges of the 3rd digit

Diagnosis	Accessory radiological findings in the fetus
Acheiropodia [1] MIM 200500	Transverse terminal limb reductions, usually involving all extremities with variable deficiency of radius, ulna, humerus, tibia, and fibula; variable presence of Bohomoletz bone (hypoplastic bone at the tip of the upper limb stump with triphalangeal component)
Adams-Oliver syndrome [2,3,4] MIM 100300	Occipital skull and/or scalp defect associated with highly variable clinical findings; variable transverse limb reduction including phalanges, metacarpals, metatarsals. and occasional tubular long bones, ectrodactyly, syndactyly
Amniotic band disruption sequence [5] ADAM complex (Amniotic Deformity, Adliesions, Mutilations) MIM 217100	Usually asymmetric transverse terminal limb reductions/amputations and variable terminal syndactyly/pseudosyndactyly; may also include oligodactyly, hypoplasia of long bones, craniofacial and ventral wall disruption
Brachmann-de Lange syndrome [6,7] MIM 122470 see Fig. 2.11, Fig. 2.21	Asymmetric and variable upper limb deficiency including absent or hypoplastic humerus, radius or ulna, carpals, metacarpals, and phalanges; other skeletal findings including microcephaly, micrognathia, supernumerary ribs, fused ribs, hemivertebrae, or vertebral fusion
Femur-fibula-ulna complex [8] MIM 228200	Asymmetric hypoplasia/aplasia of femur, fibula, ulna, humerus; humero-ulnar/-radial synostosis; oligodactyly
Holoprosencephaly-transverse limb defect [9]	Quadrilateral transverse terminal limb defects, holoprosencephaly

Diagnosis	Accessory radiological findings in the fetus
Oromandibular – limb hypogenesis syndromes; **Fig. 2.20** Aglossia-adactylia Hypoglossia-hypodactylia Hanhart syndrome [10,11] MIM 103300	Asymmetric and variable absent or hypoplastic humerus, radius, ulna, carpals, metacarpals, femur, tibia, fibula, tarsals, metatarsals; oligodactyly; syndactyly; microretrognathia; aplasia/hypoplasia of the tongue

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Hands/Feet: Split/Cleft/Ectrodactyly

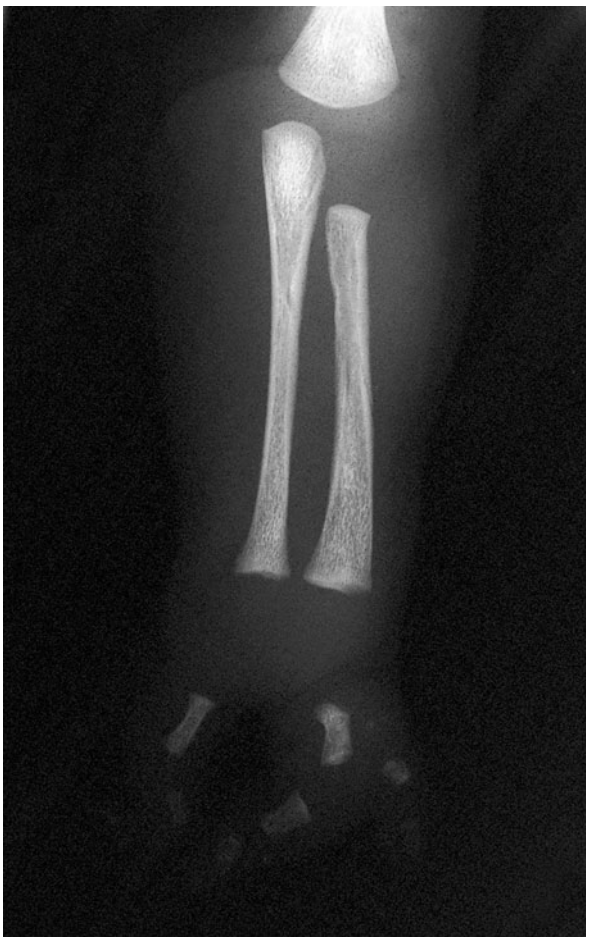

Fig. 2.21. ***32nd gestational week.*** Split hands with three incomplete rays bilaterally in Brachmann-de Lange syndrome

Diagnosis	Accessory radiological findings in the fetus
Acro-renal-mandibular syndrome [1] MIM 200980	Severe mandibular hypoplasia; variable and asymmetric limb reduction defects including hypoplastic or absent radius or tibia, oligodactyly, syndactyly, vertebral segmentation defects; other defects including renal agenesis/renal dysplasia, diaphragmatic hernia
Brachmann-de Lange syndrome [2]; **Fig. 2.21** MIM 122470	Asymmetric and variable upper limb deficiency including absent or hypoplastic humerus, radius or ulna, carpals, metacarpals, and phalanges; other skeletal findings including microcephaly, micrognathia, supernumerary ribs, fused ribs; hemivertebrae or vertebral fusion
Chromosome abnormality trisomy 13 [3]	Microcephaly, hypotelorism, small orbits, hypo-ossification of calvarium, spinal dysraphism, hemivertebrae, absent/supernumerary/fused ribs, hypoplasia of pelvis, oligodactyly, polydactyly, syndactyly, camptodactyly, vertical talus; other defects including cardiac anomalies, omphalocele, holoprosencephaly, neural tube defect, cystic hygroma, hydrops fetalis

Diagnosis	Accessory radiological findings in the fetus
Chromosome abnormality trisomy 18 [4 – 7]	Microcephaly, hypo-ossification of calvarium, hypoplasia of maxilla and/or mandible, microretrognathia, absent or thin ribs, short sternum, spinal dysraphism, hypoplasia of pelvis, hypoplasia of first metacarpal, flexion deformities and overlapping fingers, vertical talus, short first toe, hammertoes; other defects: intrauterine growth retardation, cardiac anomalies, omphalocele, neural tube defect
Cleft palate-cardiac defect-genital anomalies and ectrodactyly [8] Acrocardiofacial syndrome, ACFS MIM 600460	Proximal placed thumb, short first metacarpal, syndactyly of toes, hypoplasia of metatarsal, absent phalanges, cleft lip +/- palate, congenital heart defect, genital anomalies
DK phocomelia [9, 10] Phocomelia-encephalocele-thrombocytopeniaurogenital malformation von Voss-Cherstvoy syndrome MIM 223340	Microcephaly; encephalocele; absent or hypoplastic humerus, radius, ulna, metacarpals, thumbs; oligodactyly; syndactyly
Ectodermal dysplasia-ectrodactyly-macular dystrophy [11] EEM syndrome MIM 225280	Syndactyly, camptodactyly, phalangeal agenesis/hypoplasia, duplication of phalanges, sparse scalp hair, eyebrows and eyelashes, macular dystrophy
Ectrodactyly-Ectodermal dysplasia – Clefting syndrome [12] MIM 129900, 604292	Cleft lip ± palate; variable absence or hypoplasia of carpais, metacarpals, tarsals, metatarsals, phalanges; variable oligodactyly; variable syndactyly; other finding: renal dysplasia
Ectrodactyly-fibular aplasia [13] MIM 113310	Variable absence or hypoplasia of ulna, carpals, metacarpals, phalanges, fibulae, tarsals, metatarsals; brachydactyly; syndactyly; triphalangeal thumb
Ectrodactyly, isolated malformation MIM 183600, MIM 313350, MIM 600095, MIM 605289, MIM 606708	Variable and usually asymmetric absence or hypoplasia of phalanges, metacarpals and/or metatarsals, carpals and/or tarsals, radius, dna, tibia, and fibula
Ectrodactyly-tibial aplasia [14, 15] MIM 119100	Variable absence or hypoplasia of radius, ulna, carpals, metacarpals, phalanges, tibia, tarsals, metatarsals; bifid distal femur; bowed tibia, absent or hypoplastic patella; preaxial or postaxial polydactyly; variable oligodactyly; variable syndactyly; may present as four-extremity monodactyly or transverse hemimelia
Femur-fibula-ulna complex [15] MIM 228200	Asymmetric hypoplasia/aplasia of femur, fibula, ulna, humerus; humero-ulnar/radial synostosis; oligodactyly
Holoprosencephaly-ectrodactyly and bilateral cleft lip/palate [16] MIM 300571	Craniosynostosis, hypertelorism, absent or hypoplastic radius, ulna phalanges; other defects: cleft lip ± palate, holoprosencephaly, neural tube defect
Monodactylous ectrodactyly and bifid femur Wolfgang-Gollop syndrome [17, 18] MIM 228250	Variable absence or hypoplasia of radius, ulna, carpals, metacarpals, phalanges, tibia, patella, tarsals, and metatarsals; bifid femur; talipes equinovarus; vertebral body fusion; hemivertebrae
Oromandibular – limb hypogenesis syndromes: aglossia-adactylia, hypoglossia-hypodactylia, Hanhart syndrome [19,20]; see Fig. 2.4 MIM 103300	Asymmetric and variably absent or hypoplastic humerus, radius, dna, carpals, metacarpals, femur, tibia, fibula, tarsals, and metatarsals; oligodactyly; syndactyly; microretrognathia

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Hands/Feet: Preaxial Polydactyly

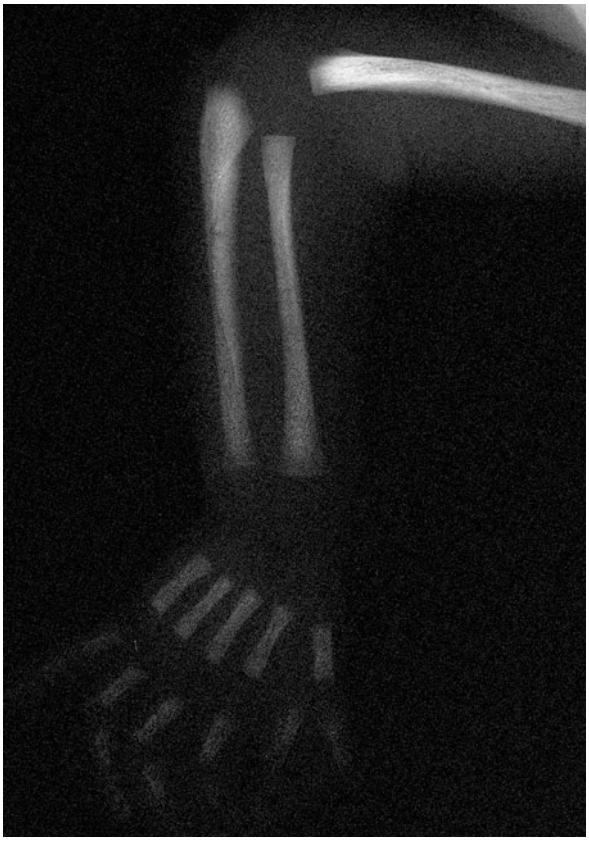

Fig. 2.22. ***24th gestational week.*** Preaxial polydactyly in Townes-Brock syndrome. Duplication of triphalangeal thumbs; defective ossification of the middle and distal phalanges. Other findings: imperforate anus, triphalangeal thumbs, ear anomalies

Diagnosis	Accessory radiological findings in the fetus
Aase syndrome [1] MIM 205600 Blackfan-Diamond syndrome Anemia and triphalangeal thumbs [2]	Broad thumb, triphalangeal thumb, hypoplastic thumb, radial hypoplasia, abnormal clavicles; other features: cleft palate, congenital heart defect, congenital hypoplastic anemia
Acrocallosal syndrome [3, 4] MIM200990	Macrocephaly, prominent forehead, large fontanelles, hypertelorism, bifid terminal phalanges of thumbs, duplicated hallux, syndactyly, brachydactyly, postaxial polydactyly; other features: absent corpus callosum, other brain defects, cleft palate, heart defect
Carpenter syndrome [5, 6] Acrocephalopolysyndactyly, type 2 MIM 201000	Craniosynostosis, Kleeblattschädel (cloverleaf skull), absence or hypoplasia of middle phalanges, double ossification center of proximal phalanx of thumb, postaxial polydactyly, broad first metatarsal, syndactyly, coxa valga, genu vara, pes varus
Chromosome abnormalities	Variable according to specific segmental aneuploidy
Diabetic embryopathy [7]	Hemivertebrae, absent or hypoplastic femora, hypoplastic tibia, postaxial polydactyly, spinal dysraphism, neural tube defect, congenital heart defect
Greig cephalopolysyndactyly [8,9] MIM 175700	Macrocephaly, prominent forehead, large fontanelles, hypertelorism, postaxial polydactyly of hands (rarely of feet), broad thumbs, broad hallux

Diagnosis	Accessory radiological findings in the fetus
Holt-Oram syndrome [10, 11] Cardiomelic syndrome MIM 142900	Absent or hypoplastic humerus, radius, ulna, first metacarpal, and thumb; triphalangeal thumb; absent or hypoplastic carpals; delayed ossification or fusion of carpals; other polydactyly; radioulnar synostosis; hypoplasia of the clavicle and scapula; Sprengel anomalyr; pectus excavatum or carinatum; rib hypoplasia or fusion; vertebral fusion or hemivertebra and scoliosis; other anomalies:cardiac defects (secundum type atrial septal defect the most common)
Hydrolethalus syndrome [12, 13] MIM 236680	Macrocephaly, keyhole-shaped deformity of foramen magnum, severe micrognathia, postaxial polydactyly of hands, tibial hypoplasia, bowing of tubular long bones, duplicated hallux, hallux varus, short first metatarsal; other anomalies: major brain defects including hydrocephalus, cleft lip/palate, laryngotracheobronchial malformation, pulmonaryr hypoplasia
Isolated defect MIM 174200, 174400, 174500,174600, 174700	May include postaxial polydactyly and syndactyly
Laurin-Sandrow Syndrome [14] MIM 135750	Ulnar duplication, fibular duplication, absent radius, absent tibia, accessory metacarpals, capral fusion, preaxial and postaxial polydactyly, triphalangeal thumb, syndactyly, hypertelorism, broad nose with cleft of nares
Orofacial digital syndromes [15] Type 1 MIM 311200 Type II MIM 252100 Type IV MIM 258860 Type VI MIM 277170 Type VIII MIM 311200	Absence or hypoplasia of phalanges, metacarpals, metatarsals; clinodactyly; camptodactyly; forked or bifid metacarpals; duplication of hallux; postaxial polydactyly; irregular modeling of bones in hands and feet; syndactyly; tibial hypoplasia; talipes equinovarus; other features: microcephaly, lobulated or cleft tongue, cleft lip/palate, malformations of brain and other organs
Pfeiffer syndrome [16, 17] Acrocephalopolysyndactyly, type 5 MIM 101600	Craniosynostosis, Kleeblattschädel, hypertelorism, ocular proptosis/shallow orbits, broad first metacarpals and phalanges of the thumb, radial deviation of thumb, syndactyly, broad first metatarsals and phalanges of hallux, deviation of hallux, absence or hyrpoplasia of other phalanges, symphalangism, radioulnar or radiohumeral synostosis
Pseudo-trisomy 13 syndrome [17] MIM 264480	Microcephaly, micrognathia, hemivertebrae, absent or hypoplastic radius or ulna, postaxial polydactyly, absent or hypoplastic tibia, broad hallux, talipes equinovarus; other defects: omphalocele, malformations of brain and other organs
Short rib-polydactyly syndromes [19, 20], different types; see p. 147 ff MIM 269860, 263520	In common: short horizontal ribs, short tubular bones, postaxial polydactylyr, hypoplastic ilia
Townes-Brocks syndrome [21, 22]; **Fig. 2.22** MIM 107480	Bifid or broad thumb, triphalangeal thumb, syndactyly, clinodactyrly, hyrpoplasia or absent carpals, carpal and/or tarsal fusion, pseudoepiphyses of metacarpals, metatarsal fusion other features: ear anomalies, imperforate anus
VATER Association [23] VACTERL Association MIM 192350	Vertebral fusion, hemivertebrae, missing or extra ribs, rib fusion, absent or hypoplastic radius, absent or hypoplastic thumb, triphalangeal thumb, other limb deficiencies are reported less commonly. Other defects include anal atresia, esophageal atresia, tracheoesophageal fistula, cardiac defect, renal agenesis or dysplasia.
VATER Association with hydrocephalus [24] (MIM 276950, 314390)	Macrocephaly secondary to hydrocephalus, hydranencephaly, vertebral fusion, hemivertebrae, missing or extra ribs, rib fusion, absent or hypoplastic radius, absent or hypoplastic thumb, triphalangeal thumb, other limb deficiencies are reported less commonly. Other defects include anal atresia, esophageal atresia, tracheoesophageal fistula, cardiac defect, renal agenesis or dysplasia.

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Hands/Feet: Postaxial Polydactyly

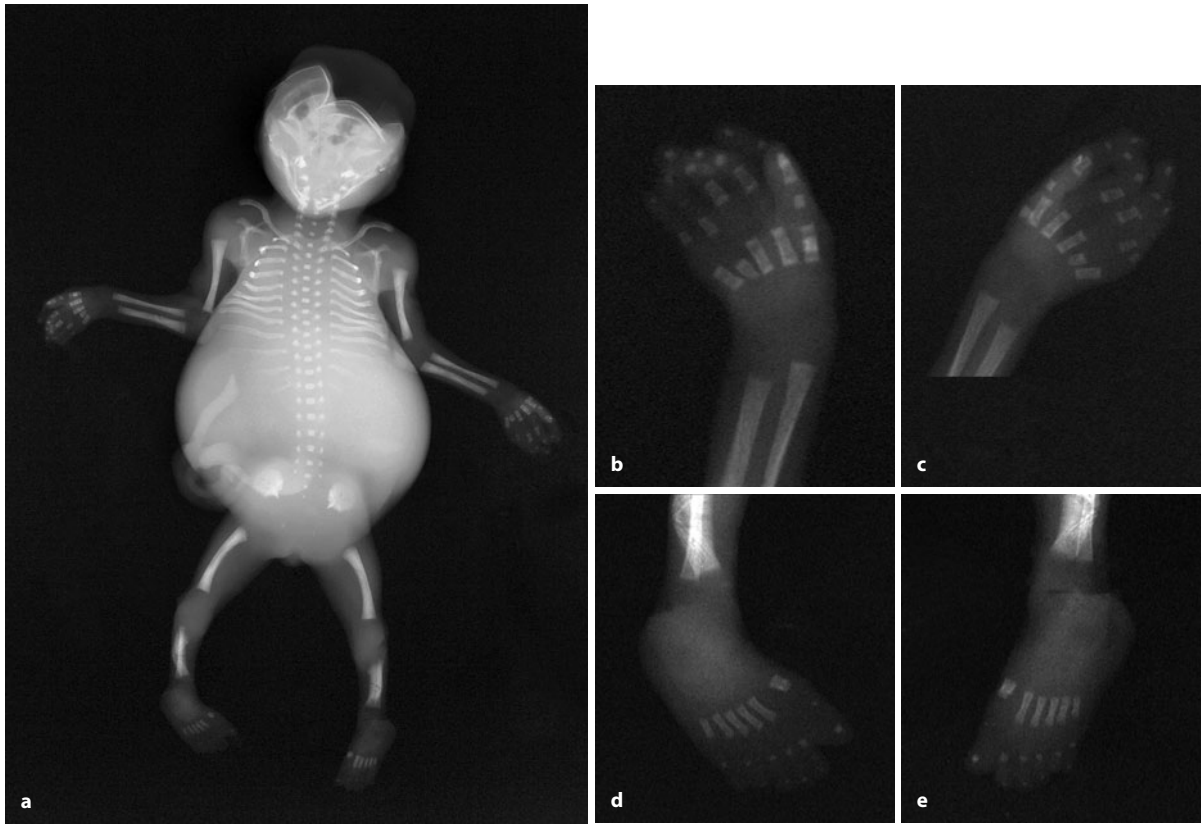

Fig. 2.23. ***16th gestational week.*** Postaxial polydactyly in Meckel-Gruber syndrome. Six toes, shortened tibia and fibula (mesomelia), slight bowing of femora. Ruptured encephalocele

Fig. 2.23b – e. (Detail) Postaxial polydactyly

Diagnosis	Accessory radiological findings in the fetus
Acrocallosal syndrome [1] MIM 200990	Macrocephaly, prominent forehead, large fontanelles, hypertelorism, bifid terminal phalanges of thumbs, duplicated hallux, preaxial polydactyly, syndactyly, brachydactyly: other features: absent corpus callosum, other brain defects, cleft palate, heart defect
Asphyxiating thoracic dystrophy [2, 3]; see p. 150 Jeune syndrome MIM 208500	Long narrow thorax with short, horizontal ribs, irregular costochondral junctions; short and flared iliac bones; triradiate acetabulae; ischial and pubic bones with medial and lateral spurs; premature ossification of the capital femoral epiphysis; shortened long tubular bones with irregular metaphyses; short and/or broad phalanges
Carpenter syndrome [4, 5] Acrocephalopolysyndactyly, type 2 MIM 201000	Craniosynostosis, Kleeblattschädel, absence or hypoplasia of middle phalanges, double ossification center of proximal phalanx of thumb, preaxial polydactyly, broad first metatarsal, syndactyly, coxa valga, genu vara, pes varus
Chromosome abnormality, trisomy 13 [6]	Microcephaly, hypotelorism, small orbits, hypo-ossification of calvarium, spinal dysraphism, hemivertebrae, absentlsupernumerary/fused ribs, hypoplasia of pelvis, oligodactyly, syndactyly, camptodactyly, vertical talus: Other defects: heart defects, omphalocele, holoprosencephaly, neural tube defect, cystic hygroma, hydrops fetalis

Diagnosis	Accessory radiological findings in the fetus
Chromosome abnormality, other [6]	Variable according to specifsc segmental aneuploidy
Elejalde syndrome [7] Acrocephalopolydactylous dysplasia MIM 200995	Craniosynostosis, hypertelorism, shortening of all long bones: Other features: generalized overgrowth, cystic hygroma, hydrops fetalis, omphalocele
Ellis-van Creveld syndrome [8]; see p. 153 Chondroectodermal dysplasia MIM 225500	Mild narrowing of thorax with short ribs, small and flared ilia, triradiate acetabulae, short tubular long bones, bowing of humerus and femur, premature ossification of capital femoral epiphysis, hypoplasia of proximal tibial ossifscation center, genu valgum, short fibula, carpal fusion, short and broad middle phalanges, hypoplasia of distal phalanges, cone-shaped epiphyses of phalanges; other features: heart defect, sparse hair, hypoplastic nails, oral frenula
Focal dermal hypoplasia [9, 10] Goltz syndrome MIM 305600	Absent or hypoplastic clavicles; clavicular pseudoarthrosis; bifsd or fused ribs; asymmetric oligodactyly; ectrodactyly; syndactyly; preaxial polydactyly; bifid thumb; bifid hallux; hemimelia; short phalanges, metacarpals, metatarsals; osteopathia striata; other features: skin, eye, and visceral malformations
Grebe syndrome [11,12]; see p. 177 MIM 200700	Absent or hypoplastic proximal and middle phalanges; syndactyly; absent or hypoplastic metacarpals and carpals; carpal fusion; very short tubular long bones (lower limbs more severe than upper limbs); dislocated radial heads; aplasia/hypoplasia of ulna, radius, and femur
Greig cephalopolysyndactyly [13, 14] MIM 175700	Macrocephaly, prominent forehead, large fontanelles, hypertelorism, preaxial polydactyly of feet, broad thumbs, broad hallux
Hydrolethalus syndrome [15, 16] MIM 236680	Macrocephaly, keyhole-shaped deformity of foramen magnum, severe micrognathia, preaxial polydactyly, tibial hypoplasia, bowing of tubular long bones, duplicated hallux, hallux varus, short first metatarsal; other anomalies; major brain defects including hydrocephalus, cleft lip/palate, laryngotracheobronchial malformation, pulmonary hypoplasia
Isolated defect MIM 174200	May include preaxial polydactyly, syndactyly
Laurin-Sandrow syndrome [17] MIM 135750	Ulnar duplication, fibular duplication, absent radius, absent tibia, accessory metacarpals, capral fusion, preaxial and postaxial polydactyly, triphalangeal thumb, syndactyly, hypertelorism, broad nose with cleft of nares
Meckel-Gruber syndrome [18,19]; **Fig. 2.23** MIM 249000	Rarely preaxial polydactyly or bifsd thumb, talipes equinovarus; other features: polycystic kidneys; CNS anomalies including microcephaly, occipital encephalocele (most common), Dandy-Walker malformation, hydrocephalus
McKusick-Kaufman syndrome [20] MIM 236700	Mesoaxial polydactyly, syndactyly, congenital heart defect, hydrometrocolpos, vaginal stenosis/atresia, polycystic kidney. Some cases may be allelic with Bardet-Biedl syndrome (MIM 209900)
Orofacial digital syndromes [21] Type II MIM 252100 Type III MIM 258850 Type IV MIM 258860 Type V MIM 174300 Type VI MIM 277170 Type VIII MIM 300484	Absent or hypoplastic of phalanges, metacarpals, metatarsals; clinodactyly; camptodactyly, forked or bifid metacarpals; duplication of hallux; preaxial polydactyly; irregular modeling of bones in hands and feet; syndactyly; tibial hypoplasia; talipes equinovarus; other features: microcephaly, lobulated or cleft tongue, cleft lip/palate, malformations of brain and other organs

Diagnosis	Accessory radiological findings in the fetus
Pallister-Hall syndrome [22] MIM 146510	Central polydactyly, bifid third metacarpal, hypoplastic fourth metacarpal, metacarpal synostosis, syndactyly, subluxation or dislocation of radial head, mild shortening of long tubular bones, bifid hallux;. other features: hypothalamic hamartoma, imperforate anus, laryngeal cleft, visceral defects
Pseudo-trisomy 13 syndrome [23] MIM 264480	Microcephaly, micrognathia, hemivertebrae, absent or hypoplastic radius or ulna, preaxial polydactyly, absent or hypoplastic tibia, broad hallux, talipes equinovarus; Other defects: include omphalocele, malformations of brain and other organs
Short rib-polydactyly syndromes, different types [24 – 28]; see p. 147 ff MIM 263530, 263510, 263520, 269860	In common: relative macrocephaly, very short horizontal ribs, short tubular long bones, hypoplasia of scapula, small ilia, preaxial polydactyly
Simpson-Golabi-Behmel syndrome [29] MIM 312870	Macrocephaly, supernumerary ribs, vertebral anomalies, hypoplasia of distal phalanges, syndactyly, clinodactyly, broad hallux other features: hepatosplenomegaly, congenital heart defect, diaphragmatic hernia, renal dysplasia, and hydrops fetalis
Smith-Lemli-Opitz syndrome [30, 31] MIM 270400	Microcephaly, micrognathia, thin ribs, hypoplastic first metacarpal, brachydactyly, syndactyly, talipes equinovarus, vertical talus; other features include CNS anomalies, cleft palate, heart defect, renal dysplasia, hydrops fetalis, genital hypoplasia, sex reversal
Synpolydactyly [32, 33] MIM 186000	Syndactyly of third and fourth fingers, mesoaxial polydactyly, camptodactyly and/or clinodactyly of fifth finger, accessory metacarpal and/or metatarsal, Y-shaped metacarpal, syndactyly of fourth and fifth toes, preaxial polydactyly, mid-phalanx hypoplasia, triangular shaped distal phalanges of feet

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Skull

Premature Cranial Synostosis/Cloverleaf Skull

Fibroblast growth factor receptor mutations cause some of the main short-limb skeletal dysolasias and craniosynostosis syndromes, of which some present a cloverleaf skull (Kleeblattschädel) [1]

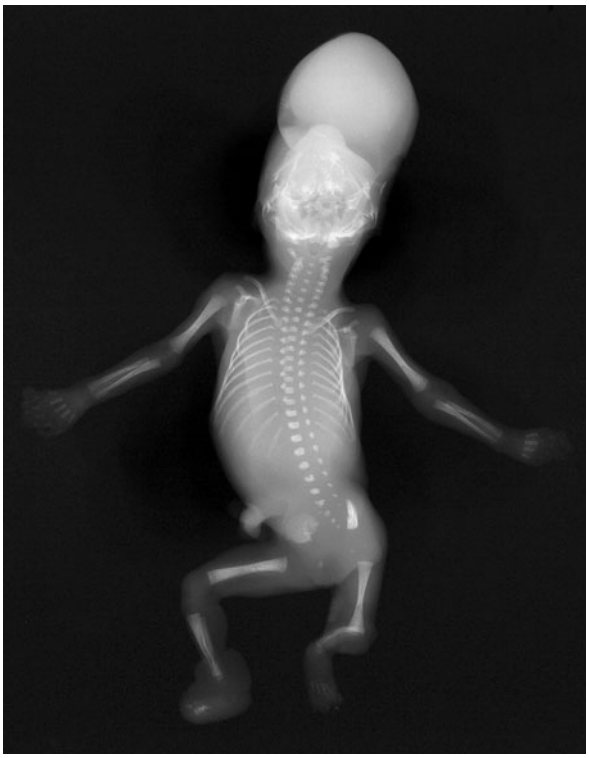
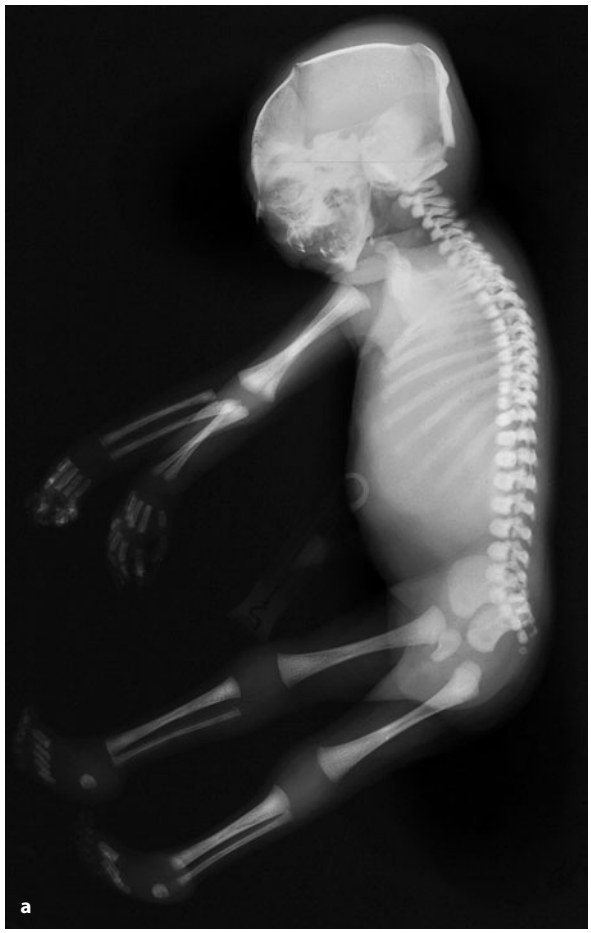


Fig. 2.24. ***17th gestational week.*** Cloverleaf skull in amnion band disruption sequence. Amputation of distal phalanges, aplasia of left tibia, ring constriction at the right shank with distal edema



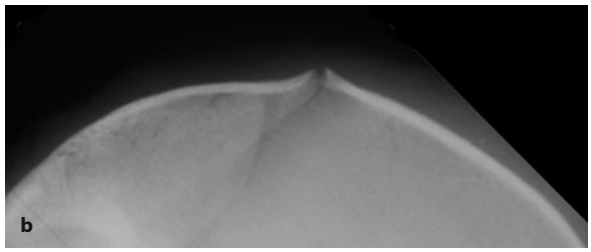


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Fig. 2.25a–c. ***29th gestational week.*** **a** Premature craniosynostosis (donkey's back deformity of the coronal suture) in microcephalic Seckel syndrome with lissencephaly. Very thick calvaria
b (Detail) Ogee arch-like deformation of the ridged, nonfunctional coronal suture
c Orgee arch (Lintel from Jewish Chapel in Mainz, 19th century)

Diagnosis	Accessory radiological findings in the fetus
Acrocephalosyndactyly 1 (Apert) [1] Acrocephalosyndactyly V (Pfeiffer) [1] Acrocephalopolydactyly II (Carpenter) [1] MIM 101200,101600,201000	Distal bony syndactyly of hands and feet Occasionally duplication of first toe Preaxial poly-syndactyly of feet
Amniotic band/disruption sequence ADAM complex (Amniotic Deformity, Adhesions and Mutilations) [2]; **Fig. 2.24** Limb-body wall complex MIM 217100	Usually asymmetric transverse terminal limb reductions/amputations and variable terminal syndactyly/pseudosyndactyly; may also include oligodactyly, hypoplasia of long bones, craniofacial and ventral wall disruption
Antley-Bixler syndrome [3]; see p. 126 MIM 207410	Synostosis of coronal and lambdoid sutures, depression of nasal bridge, frontal bossing, radiohumeral synostosis, bowing of ulnae and femora, fractures
Baller-Gerold Syndrome [4] MIM 218600	Asymmetric radial defect; shortened bowed ulna; variable premature craniosynostosis (coronal suture most commonly)
Cloverleaf skull-limb anomalies, type Holtermüller-Wiedemann [5] MIM 148800	Trilobed skull deformity, ankylosis of the elbows
Craniosynostosis, nonsyndromic isolated	No further radiologic signs
M. Crouzon [6,7] MIM 123500	Coronal and lambdoid suture synostosis, frontal bossing, midface hypoplasia, brachycephaly
Microcephaly: Holoprosencephaly with fetal akinesia/hypokinesia sequence [8] MIM 306990 Fetal brain disruption sequence [9]	Due to reduced intracranial pressure: growth failure of the brain i.e. migrational disorder or intruterine brain destruction
Osteocraniostenosis [10, 11, 12]; see p. 140	Intrauterine dwarfism, thin ribs, slender long bones with diaphyseal fractures, hypo-ossified calvaria, craniostenosis with mild cloverleaf skull appearance
Osteoglophonic dysplasia [13, 14] MIM 166250	Bizarre premature cranial synostosis, rhizomelia, metaphyseal defects
Seckel syndrome [15]; **Fig. 2.25** MIM 210600 Lissencephaly syndromes [16] MIM 247200	Severe intrauterine growth retardation, microcephaly, craniosynostosis, absent fibula
Short rib (polydactyly) syndrome Beemer-Langer type [17]; see p. 149 MIM 269860	Intrauterine dwarfism; short ribs; narrow thorax; marked bowing of long bones, especially radius and ulna; hydrops; pre-postaxial polydactyly
Thanatophoric dysplasia II [1]; see p. 102 MIM 187600	Short stature, short ribs, platyspondyly, mild shortening of long bones, straight femora

Such malformations can also be seen in some partial trisomy syndromes of chromosome **4, 9, 13**.

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Unossified and Hypo-ossified Calvaria

Some skeletal dysplasias, such as atelosteogenesis, boomerang dysplasia, dappled diaphysis dysplasia, lethal male Melnick-Needles syndrome, and others, show a hypo-ossification of the calvaria. These all show striking additional skeletal findings (see p. 136, 163).

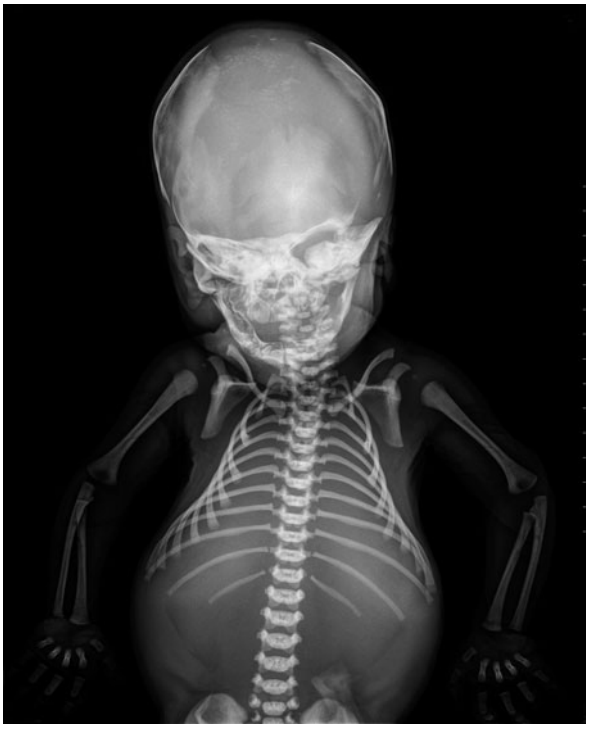

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Fig. 2.26. ***Renal tubular dysplasia. Stillborn, 40 GW.*** Hypocalvaria, broad sutures, bell shaped thorax (lung hypoplasia)

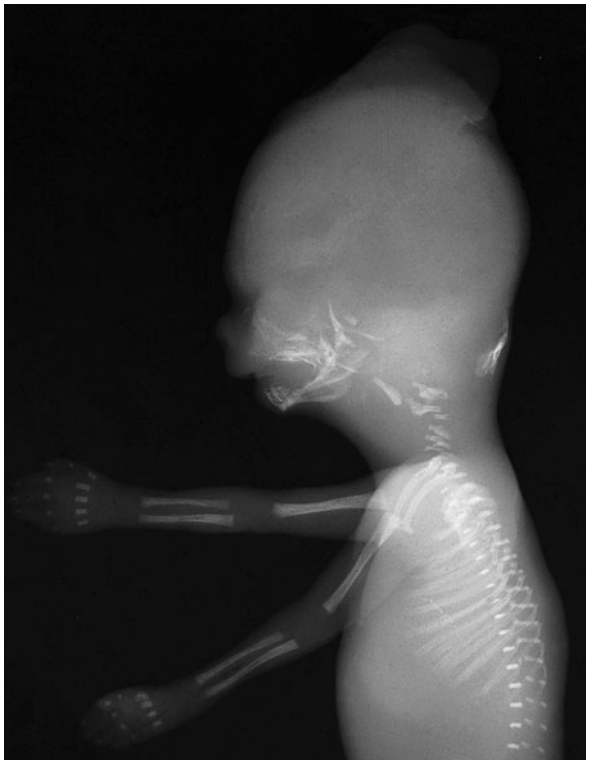

Fig. 2.27. ***15th gestational week.*** Unossified calvaria. in Trisomy 18

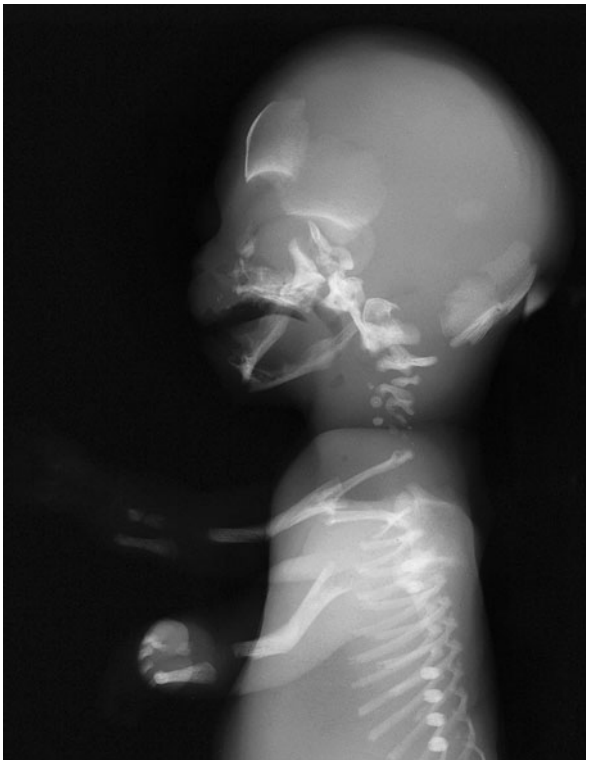

Fig. 2.28. ***22nd gestational week.*** Deficient calvarial ossification in lethal hypophosphatasia. Absent ossification of a major part of the spine. Incomplete or missing ossification of metacarpals and phalanges. Bowing of humeri with deep metaphyseal defects

Diagnosis	Accessory radiological findings in the fetus
Acalvaria [1]	May be associated with omphalocele, spina bifida
Aminopterin/methotrexate fetopathy [2] MIM 600325	Retardation, mesomelia of upper limbs
Angiontensin converting enzyme (ACE) inhibitor fetopathy [3] Same pathomechanism: Renal tubular dysplasia [4]; **Fig.2.26** MIM 267 430	Renal insufficiency, oligohydramios, hypoplasia of lungs, bell shaped thorax, severely underossified calvarial bones (wide sutures), growth retardation, otherwise normal skeleton, perinatal death
Chromosome abnormality [5]; Trisomy 13 and 18 **Fig. 2.27**, see Fig. 2.41	Intrauterine growth retardation microcephaly, hypo- ossification of calvarium, hypoplasia of maxilla and/or mandible, microretrognathia, absent or thin ribs, short sternum, spinal dysraphism, omphalocele
Hyperparathyroidism, neonatal familial [6] MMI 239200	Gross underossifscation, subperiosteal bone resorption, metaphyseal fractures (resembling mucolipidosis type II)
Hypophosphatasia, infantile form [7]; **Fig. 2.28** see p. 131 MIM 241500	Poorly ossifled skeleton, erratic ossification of vertebrae, deep metaphyseal defects, angulation of long bones, especially femur (see Femur: Bowing)
Mucolipidosis type II (I-cell disease) [8] MIM 252500 see p. 145	Decreased bone mineralization, short vertebral bodies, diaphyseal cloaking, signs of hyperparathyroisism, pelvic dysplasia.
Osteocraniostenosis [9, 10]; see p. 140	Intrauterine dwarfism, thin ribs, slender long bones with diaphyseal fractures, hypo-ossified calvaria, craniostenosis with mild cloverleaf skull appearance
Osteogenesis imperfecta II [11]; see p. 128 MIM 120150, 166200	Multiple fractures of ribs and long bones, shortening and angulation of long bones. Hypo-ossification present in all types

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Encephalocele

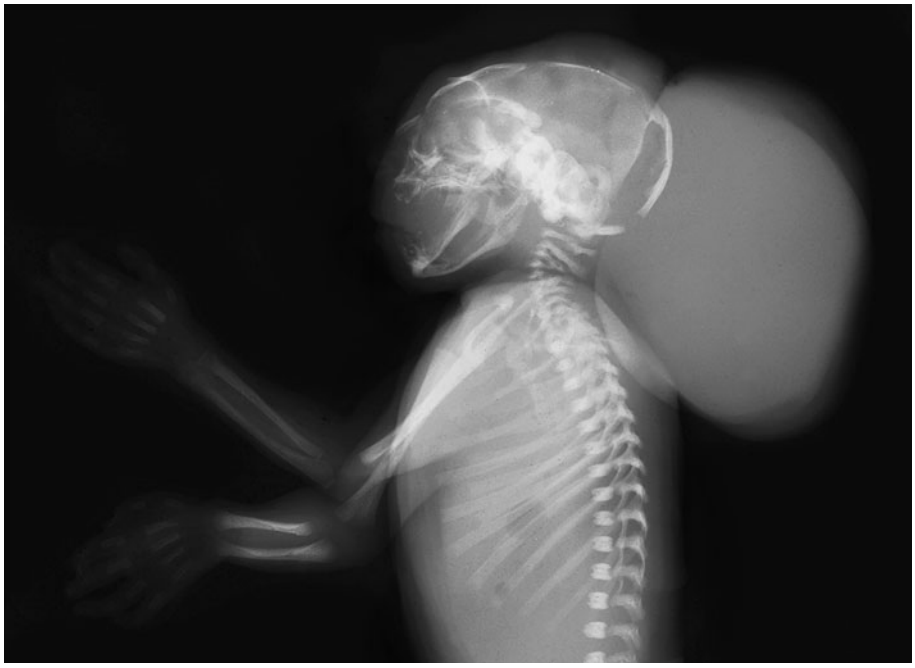

Fig. 2.29. ***23rd gestational week.*** Microcephaly with encephalocele. Note lückenschädel (craniolacunia)

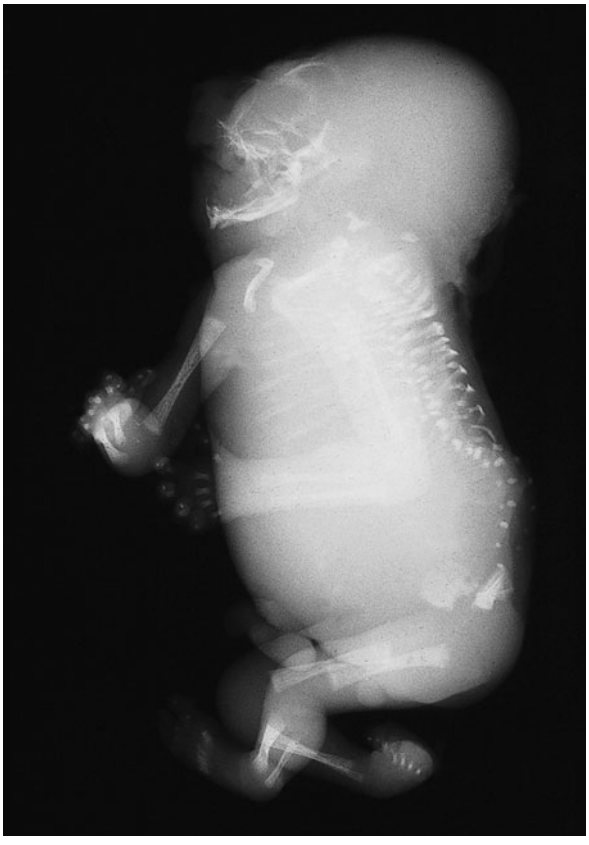

Fig. 2.30. ***15th gestational week.*** Iniencephaly. Retroflexion of head, "missing" neck by fusion of the soft tissue of the head and the shoulders. Defective ossification of the spine. Thoracolumbar kyphosis

Diagnosis	Accessory radiological findings in the fetus
Amniotic band/disruption sequence [1] ADAM complex (*A*mniotic *D*eformity, *A*dhesions, *M*utilations) Limb-body wall complex MIM 217100	Usually asymmetric transverse terminal limb reductions/amputations and variable terminal syndactyly/pseudosyndactyly. Mayr also include oligodactyly, hypoplasia of long bones, craniofacial and ventral wall disruption
Chromosome abnormalities	Variable according to specific segmental aneuploidy
DK phocomelia [2] Phocomelia-encephalocele-thromobocytopeniaurogenisal malformation von Voss-Cherstvoy syndrome MIM 223340	Microcephaly; absent or hypoplastic humerus, radius, ulna, metacarpals, thumb; oligodactyly; syndactyly of fingers; other features: genitourinary, cardiac anomalies, platelet abnormalities
Dyssegmental dysplasia; see p. 120 Silverman-Handmaker type [3, 4] MIM 224410	Severe irregularity in shape and size of vertebral bodies; hypoplastic thorax with short ribs; short and wide, bowed tubular long bones with wide metaphyses (dumbbell-shaped); hypoplasia ofbasilar portions of ilia; broad and thick ischium and pubis
Fukuyama congenital muscular dystrophy [5] MIM 253800	Hydrocephalus, neuronal migration defect, optic atrophy, retinal detachment, myocardial fibroelastosis
Isolated finding; **Fig. 2.29**	Isolated encephalocele, microcephalus, no other radiologic findings
Iniencephaly [6]; **Fig. 2.30**	Cervical spinal retroflexion, elevated face, occipito-spinal association, cervical spina bifida, rhizomelia of upper limbs, omphalocele
Joubert syndrome and related cerebellooculorenal syndromes [7] MIM 213300	Macrocephaly, enlarged cisterna magna hypoplasia or Aplasia of cerebellar vermis, hypoplasia of cerebellar hemispheres and/or brainstem, postaxial polydactyly, renal cysts
Knobloch syndrome [8] MIM 120329	Occipital skull defect, cerebellar hypoplasia, vermian agenesis or hypoplasia, neuronal heterotopia, vitreoretinal degeneration, high myopia
Laryngeal atresia, encephalocele and limb anomalies (LEL syndrome) [9] MIM 607132	Fetal hydrops, anterior and/or parietal skull defect, facial cleft, enlarged echogenic lungs, laryngeal atresia, hypoplasia or aplasia of radius and/or tibia, aplasia of metacarpals, metatarsals and phalanges, syndactyly, renal anomaly
Meckel-Gruber syndrome [10]; see Fig. 2.23 MIM 249000	Post-axial polydactyly, rarely pre-axial polydactyly, talipes equinovarus; other features: polycystic kidneys; CNS anomalies including microcephaly, anencephaly, Dandy-Walker malformation, hydrocephalus
Roberts syndrome [11] Roberts-SC phocomelia syndrome Pseudothalidomide syndrome see Fig. 2.5 MIM 268300	Microcephaly, wormian bones, sometimes craniostenosis, hypertelorism, cleft lip and palate, variable absence or hypoplasia of tubular bones (usually asymmetric, and upper limbs typically more severe than lower limbs), fusion of tubular long bones, bowing of tubular long bones, contractures of large joints, absent carpals, absent first metacarpal and thumb, absent fifih metacarpal and phalanges, clinodactyly, syndactyly, talipes equinovarus or equinovalgus, calcaneovalgus: anomalies common in GNS, heart, kidneys
Sakoda complex [12] MIM 610871	Microcephaly, cerebral dysgenesis, agenesis of corpus callosum, cleft lip +/- palate, microphthalmia, hemivertebrae, scoliosis, heart defect, bifid thumb
VACTERL association with hydrocephalus [13] MIM 276950	See “Aplasia, Hypoplasia of Thumb and Radius”
Walker-Warburg syndrome [14] Hydrocephalus, agyria, retinal dysplasia-encephalocele HARD ± E syndrome MIM 236670	Microcephaly, wide or delayed fusion of cranial sutures, joint contractures, talipes equinovarus; other features: retinal dysplasia, cataract, ear anomalies, Dandy-Walker malformation, hydrocephalus, heart defect

Diagnosis	Accessory radiological findings in the fetus
Warfarin embryopathy [15] Coumadin embryopathy Fetal warfarin syndrome	Frontal bossing; depressed nasal bridge; very small/short anteverted nose; short tubular long bones; short metacarpals, metatarsals, and phalanges; stippling or punctate calcification of epiphyses, spine, proximal femur, and calcaneus

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Anencephaly/Myelomeningocele/Spina Bifida

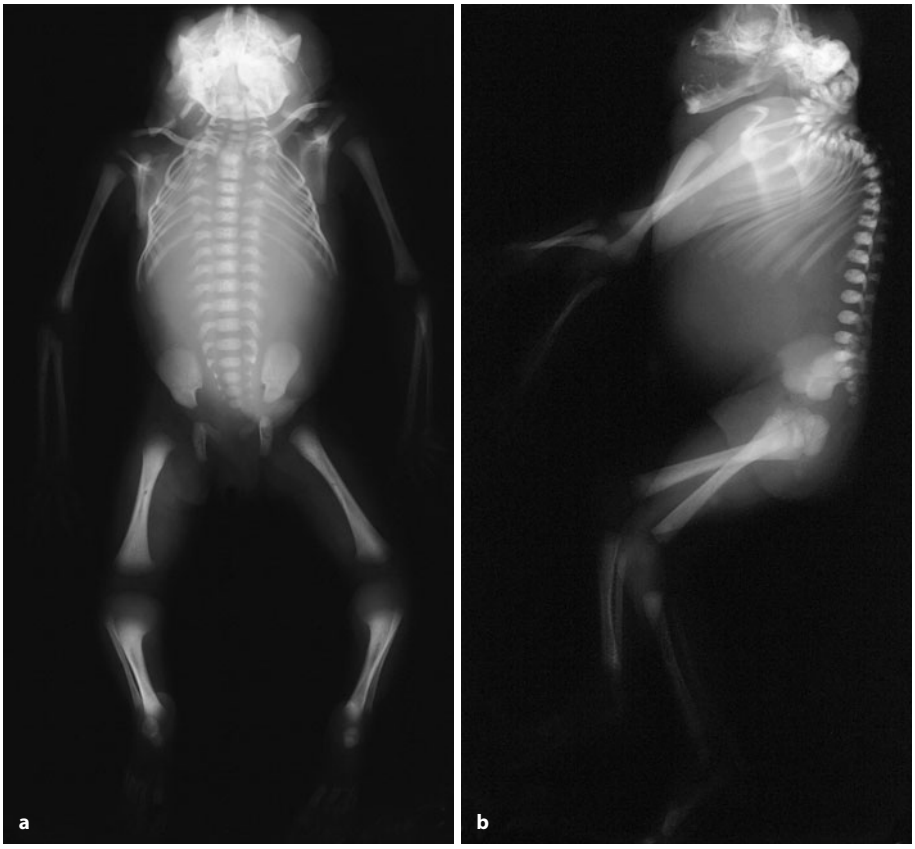

Fig. 2.31a, b. ***29th gestational week.*** Anencephaly with total craniorachischisis, aplasia of the cranial vault. Wide open spinal canal, severe kyphosis and swan's neck deformity of the cervical spine resulting in a disproportionately short trunk

Diagnosis	Accessory radiological findings in the fetus
Amniotic band/disruption sequence ADAM complex (Amniotic Deformity, *Adhesions, Mutilations)* Limb-body wall complex [1] MIM 217100	Usually asymmetric transverse terminal limb reductions/amputations and variable terminal syndactyly/pseudosyndactyly; may also include oligodactyly, hypoplasia of long bones, craniofacial and ventral wall disruption
CHILD syndrome [2] (Congenital hemidysplasia, ichthyosiform erythroderma, limb defects) MIM 308050	Unilateral hypoplasia of limb(s) including absent or hypoplastic scapula, humerus, radius, ulna, femur, tibia, fibula; joint contracture or pterygium; punctate epiphyseal calcification; other features: congenital ichthyosiform erythroderma ipsilateral to limb deficiency, visceral anomalies
Chromosome abnormality trisomy 18 (Edward syndrome) [3]	Intrauterine growth retardation; microcephaly; prominent occiput; micrognathia; thin or absent ribs; short sternum; absent or hypoplastic radius, first metacarpal, thumb; camptodactyly; vertical talus; talipes equinovarus; short or dorsiflexed great toe; other defects: tracheoesophageal fistula, heart defect, absent or cystic kidneys, omphalocele
Chromosome abnormalities, other	Variable according to specific segmental aneuploidy
Diabetic embryopathy [4]	Hemivertebrae, absent or hypoplastic femora, hypoplastic tibia, preaxial or postaxial polydactyly, spinal dysraphism, neural tube defect, congenital heart defect
Disorganisation-like syndrome [5] MIM 223200	Anencephaly, asymmetry, pre-/postaxial polydactyly, lower limb aplasia/duplication
Fetal aminopterin syndrome Folate antagonist chemotherapeutic agents [6]	Delayed mineralization of calvarium, craniolacunae, craniosynostosis, hypertelorism, micrognathia, rib anomalies including fusion, joint contractures, absence or hypoplasia of digits including thumbs, syndactyly, talipes equinovarus

Diagnosis	Accessory radiological findings in the fetus
Fetal valproate syndrome [7, 8]	Prominent metopic ridge, bifrontal narrowing, clinodactyly, distal phalangeal hypoplasia, absent or hypoplastic radius, absent or hypoplastic thumb, talipes equinovarus
Iniencephaly [9]	Severe retroflexion of the head, occipital encephalocele, spinal defects, mandibular aplasia, cleft palate
Isolated defect with or without rachischisis [10]; **Fig. 2.31a, b**	No other radiological signs
Laterality sequence [11] MIM 304570	Visceral heterotaxy, sacral agenesis.
Meckel-Gruber syndrome [12, 13]; see Fig. 2.23 MIM 249000	Post-axial polydactyly, rarely pre-axial polydactyly, talipes equinovarus;. other features include polycystic kidneys; CNS anomalies including microcephaly, occipital encephalocele (most common), Dandy-Walker malformation, hydrocephalus
Omphalocele-exstrophy of the bladder-imperforate anus-spinal defects (OEIS) complex [14] MIM 258040	Hemivertebrae, absent sacrum, widely spaced pubic bones, spinal dysraphism, talipes equinovarus, ventral wall defect
Pentalogy of Cantrell [15] Thoracoabdominal syndrome; see Fig. 2.40 MIM 313850	Sternal defects including agenesis, clefting or bifid sternum, absence of lower third of sternum; other defects include supraumbilical midline defect (omphalocele), central diaphragmatic hernia, pericardial defect, congenital heart defect
Short-rib polydactyly syndrome, type II (Majewski type) [16, 17]; see p. 152 MIM 263520	Relative macrocephaly, prominent forehead, thoracic hypoplasia with protuberant abdomen, short and horizontal ribs, short tubular long bones, ovoid tibia smaller than fibula, preaxial or postaxial polydactyly; other features include hydrops fetalis, cleft or lobulated tongue, multiple visceral and brain anomalies
X-linked neural tube defects [18] MIM 301410	Dysraphias within families as an X-linked condition.

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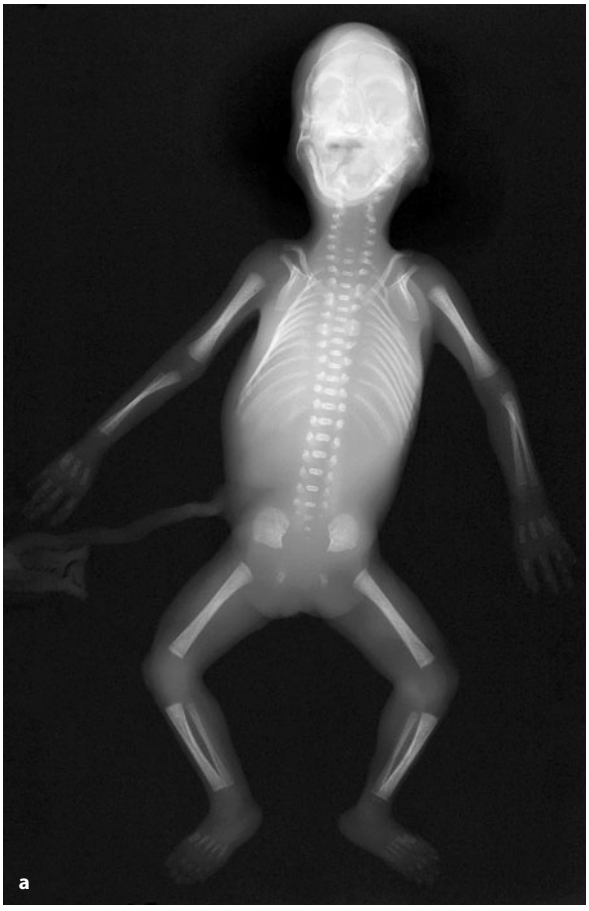
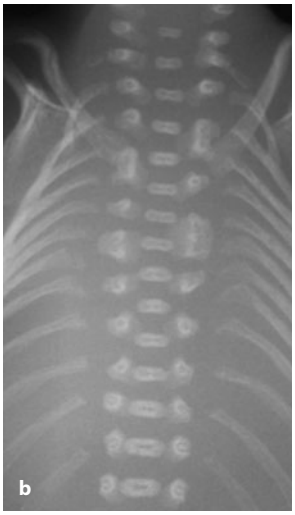
Spine

Vertebral Segmentation Defects/Hemivertebrae/Vertebral Fusion





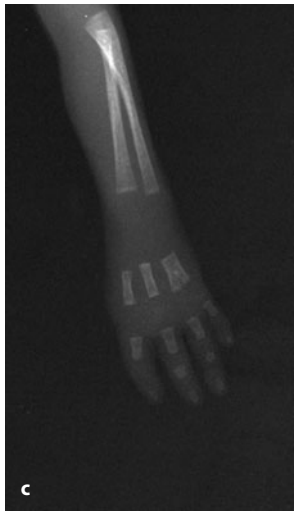
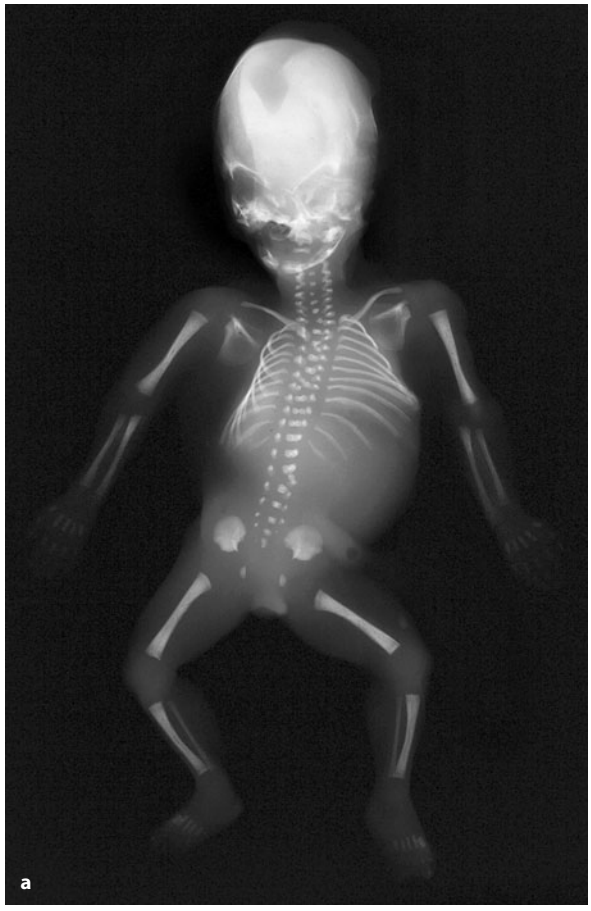
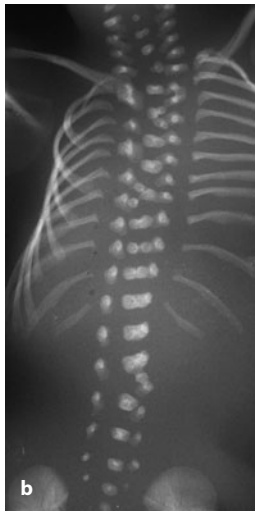


Fig. 2.32. ***18th gestational week.*** Fusion of neural arcs in the upper half of the thoracic spine in partial monosomy 13 q-. Microcephaly, defective ossification C1–C5. Oligodactyly; aplasia of thumb. Proximal fusion of metacarpals 4 and 5. **b** (Detail) Segmentation defects in the thoracic spine. **c** (Detail) Preaxial oligodactyly





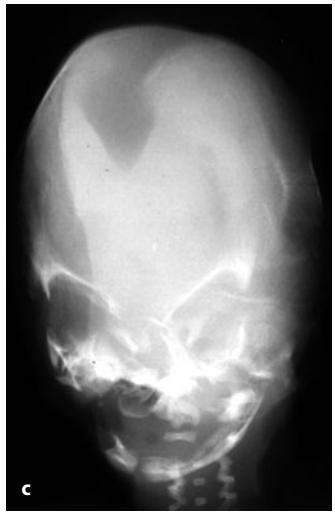


Fig. 2.33. ***18th gestational week.*** Multiple vertebral segmentation defects with hemivertebrae and butterfly vertebrae in Goldenhar syndrome. Mandibular hemihypoplasia (absence of the right corpus mandibulae). **b** (Detail) Hemivertebrae in the thoraxic spine. **c** (Detail) Aplasia of the right corpus mandibulae

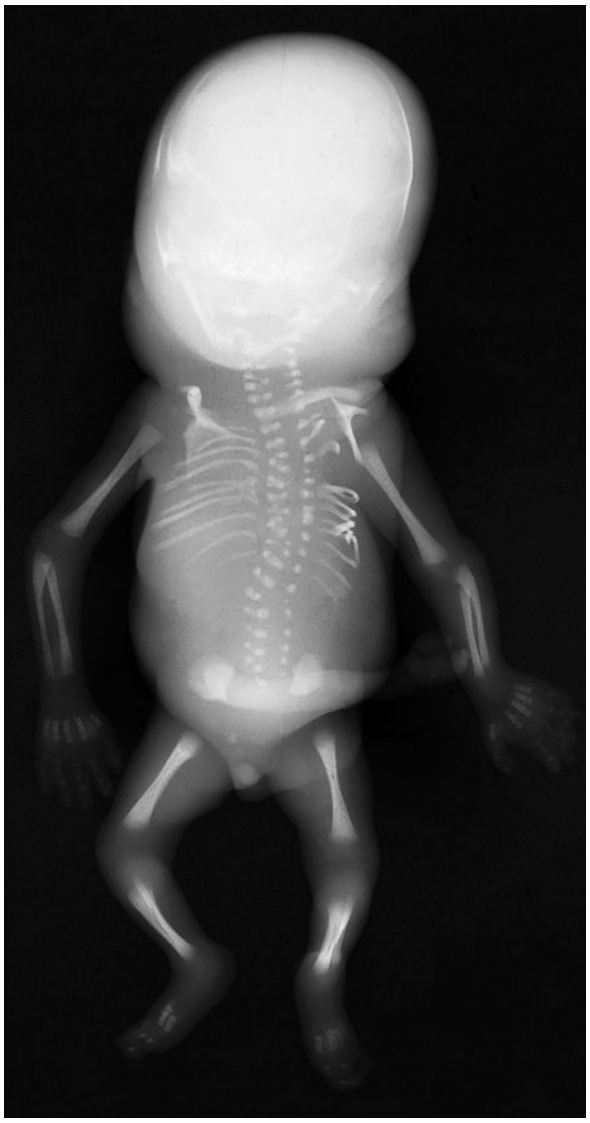


Fig. 2.34. ***17th gestational week.*** Multiple vertebral segmentation defects in the dorsal and upper lumbar spine in spondylothoracic dysostosis. Fusion of ribs (10 ribs on the right, 12 on the left). Short thorax. Nuchal lymphedema

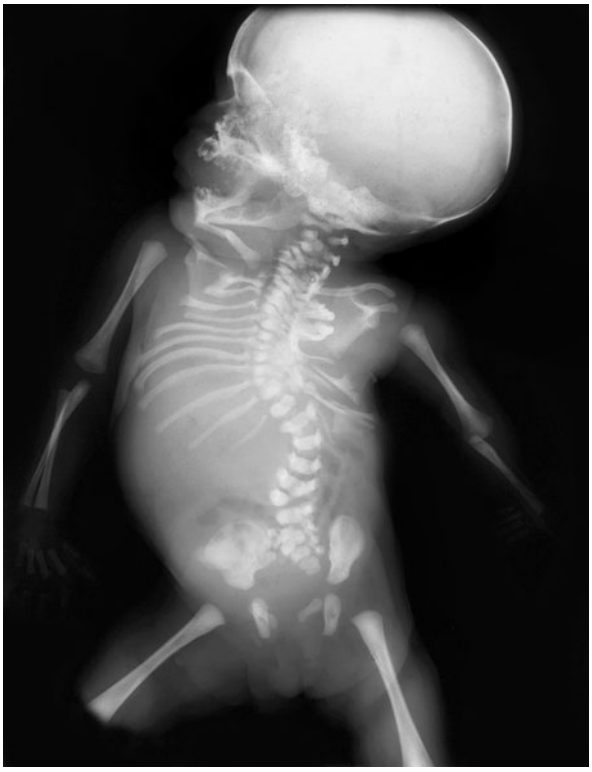


Fig. 2.35. ***30th gestational week.*** Multiple segmentation defects of the vertebrae in MURCS association. Asymmetric vertebral aplasia/hypoplasia, left-sided rib fusions, resulting in an S-shaped scoliosis. Aplasia of the radius and right thumb

Classification of vertebral segmentation defects has considerably changed during the last few years. Spondylocostal dysplasias cover all phenotypes with the characteristics of the 3 molecularyly defined types. Spondylothoracic dysplasia is used for the specific phenotype with "crab-like" chest. Diagnoses like Jarcho-Levin, Klippel-Feil should no longer be used: Their indiscremenate use refers erroneously to a whole variety of heterogenous phenotypes that should be named specifically.

Diagnosis	Accessory radiological findings in the fetus
Acro-renal-mandibular syndrome [1] MIM 200980	Severe mandibular hypoplasia, variable and asymmetric limb reduction defects including hypoplastic or absent radius or tibia, oligodactyly, ectrodactyly, syndactyly
Aicardi Syndrome [2] MIM 304050	Absent, extra and/or fused ribs, scoliosis, microcephaly, cleft lip +/- palate, central nervous system defects, microphthalmia, coloboma, chorioretinal lacunae, cataract

Diagnosis	Accessory radiological findings in the fetus
Alagille syndrome [3] MIM 118450	Mostly butterfly vertebrae, further: rib anomalies, short ulnae, short distal phalanges
Butterfly vertebrae, isolated	Can be seen in Alagille syndrome, Aicardi syndrome
Campomelic dysplasia [4]; see p. 124 MIM 114290	Mandibular hypoplasia; hypoplastic scapulae;, small, bell-shaped thorax; absent ribs; hypoplastic vertebrae; usually short and bowed femur and tibia; joint dislocation may include hip and radial head; absent or delayed ossification of distal femur, proximal tibia, sternum, ischium, pubis; hypoplasia of ischium and pubis; talipes equinovarus
CHARGE association [5] MIM 214800	Aconym of associated malformations: *C*oloboma, *H*eart anomaly, choanal *A*tresia, *R*etardation, *G*enital and *E*ar anomalies. Small mandible, cleft palate, hemivertebra, rarely limb anomalies (ectrodactyly, bifid distal femur)
Chromosome abnormalities [6, 7] Trisomy 13 Partial monosomy 13 q; **Fig. 2.32** Trisomy 18 Triploidy	Growth retardation, hypo-ossified calvaria, hypotelorism, nuchal cystic hygroma, umbilical hernia, radial aplasia, hemivertebrae (especially fusion of the vertebral arches), coronal clefts in the lumbar spine; see Fig. 2.38
Diabetic embryopathy [8]; see Fig. 2.36	Hemivertebrae, absent or hypoplastic femora, hypoplastic tibia, preaxial or postaxial polydactyly, spinal dysraphism, caudal dysplasia
Duane anomaly-radial defects [9] MIM 126800	Hypolplastic or absent fibula
Dyssegmental dysplasia [10]; see p. 120 Silverman-Handmaker type [11], MIM 224410 Rolland-Desbuquois type, MIM 224400	Severe irregularity in shape and size of vertebral bodies, hypoplastic thorax with short ribs, short and wide bowed tubular long bones with wide metaphyses (dumbbell shaped), hypoplasia of basilar portions of ilia, broad and thick ischium and pubis
Fetal alcohol syndrome [12]	Intrauterine growth retardation, microcephaly, vertebral segmentation defects, cervical ald thoracic segmentation anomaly, reduction deformity of upper extremities, hypoplasia/aplasia of ulna tetradactyly, clubfoot
Goldenhar syndrome/hemifacial dysplasia (oculo-auriculo-vertebral dysplasia) [13,14] see **Fig. 2.33** MIM 164210	Sporadic, unilateral malformation syndrome of the first and second branchial arches (hypoplastic mandible and maxilla), vertebral anomalies, radial hypoplasia
Klippel-Feil syndrome [15]; MIM 148900) Better use specific diagnoses.	Spectrum of cervical and upper thoracic spinal fusions; hemivertebrae and occipitoatlantal fusion; Sprengel deformity; spina bifida; may be a part of Mayer-Rokitansky-Küster syndrome, MURCS association (Fig. 2.34), alcohol embryopathy, Duane anomaly-radial defects, or Goldenhar syndrome (Fig. 2.32)
Limb/pelvis hypoplasia/aplasia syndrome Includes: Schinzel phocomelia, Al-Awadi/Raas-Rothschild syndrome [16, 17, 18, 19, 20], MIM 276820 Fuhrmann syndrome MIM 228930	Variable and possibly asymmetric lower limb deficiency including primarily femur, tibia and fibula; absent toes; upper limb defects include absent/hypoplastic radius, ulna, carpals, metacarpals, and phalanges; radio-humeral synostosis; hypoplastic pelvis including irregular pubis, ischium; hip dislocation; thoracic involvement including wide or fused ribs, pectus carinatum
(Jarcho-Levin syndrome [21]); see: spondylothoracic dysostosis **Fig. 2.34**	Severe vertebral defects including block vertebrae; butterfly vertebrae; hemivertebrae; ribs that: have sagittal clefts with malsegmentation including fusion, are bifid, are absent or hypoplastic, appear "fan-like" or "crablike"; spinal dysraphism; neural tube defects; congenital heart defects; and other visceral anomalies frequently reported

Diagnosis	Accessory radiological findings in the fetus
Lethal multiple pterygium syndrome [22] MIM 253290 X-linked lethal multiple pterygium syndrome [23] MIM 312150	Fusion of cervical vertebrae, hypoplastic scapulae, wide ribs, contractures of large joints with pterygia formation, radio-ulnar synostosis, camptodactyly of fingers, talipes equinovarus; other features: cystic hygroma and hydrops fetalis, diaphragmatic hernia
Microphthalmia-esophageal atresia [24] Anophthalmia-esophageal-genital AEG syndrome MIM 206900	Absent, extra or fused ribs, hypoplastic vertebrae, microcephaly, anophthalmia/microphthalmia, congenital heart defect, esophageal atresia, genital defects, central nervous system defects
MURCS association [25]; MIM 601076 **Fig. 2.35**	Acronym of associated malformations: *M*ullerian duct aplasia/hypoplasia, *R*enal aplasia/ectopia, *C*ervical *S*omite (spinal) dysplasia, and upper limb defects
Omphalocele-Exstrophy of the bladder- Imperforate anus-Spinal defects (OEIS) complex [26] MIM 258040	Hemivertebrae, absent sacrum, widely spaced pubic bones, spinal dysraphism, talipes equinovarus
Robinow syndrome, autosomal recessive [27] Costovertebral segmentation defects with mesomelia COVESDEM MIM 268310	Macrocephaly, large fontanelle, frontal bossing, hypertelorism, depressed nasal bridge, pectus excavatum, absent or fused ribs, scoliosis, mesomelia, brachydactyly, brachymesophalangism, broad thumbs and halluces, bifid terminal phalanges, congenital heart defect, umbilical hernia, genital defects, renal duplication, hydronephrosis
Simpson-Golabi-Behmel syndrome [28] MIM 312870	Macrocephaly, supernumerary ribs, hypoplasia of distal phalanges, syndactyly, clinodactyly, broad hallux, postaxial polydactyly, hydrops fetalis
Spondylocostal dysostosis 1 (DLL3) [29,30] MIM 277300 Spondylocostal dysostosis 2 (MESP2) MIM 608681 Spondylocostal dysostosis 3 (LFNG) MIM 609813	Diffuse segmentation disorder (whole spine). no scoliosis, rib anomalies. Pebble beach sign Diffuse segmentation disorder (whole spine), pronounced in cervico-thoracic region, block vertebrae Diffuse segmentation disorder (whole spine), multiple hemivertebrae and rib anomalies, kyphoscoliosis
Spondylothoracic dysostosis (AR) [31] MIM 277300 (formerly covered by Jarcho-Levin syndrome)	Severe trunk shortening, fan-like or crab-like thorax, rib fusion at their origin, spinal dysraphism
Sprengel deformity [32] MIM 184400	Clavicular anomalies, rib segmentation defects, omovertebral bone, scoliosis, diastematomyelia, cleft palate, may be associated with Klippel-Feil syndrome
Spinal dysraphism	Vertebral segmentation defects (such defects are also part of Arnold-Chiari II malformation, hydrocephalus)
Urorectal septum malformation sequence [33]	Vertebral fusion, hemivertebrae, extra or missing ribs, absent or hypoplastic sacrum, hypoplastic radius, absent or hypoplastic thumb; other defects: megacystis ("prune belly"), anal atresia, esophageal atresia, tracheoesophageal fistula, cardiac defect, renal agenesis or dysplasia, absent or ambiguous external genitalia
VATER Association [34] MIM 192350 VACTERL Association	Vertebral fusion, hemivertebrae, missing or extra ribs, rib fusion, absent or hypoplastic radius, absent or hypoplastic thumb, triphalangeal thumb, preaxial polydactyly, other limb deficiencies less commonly; other defects: anal atresia, esophageal atresia, tracheoesophageal fistula, cardiac defect, renal agenesis or dysplasia

Diagnosis	Accessory radiological findings in the fetus
VATER Association with hydrocephalus [35] MIM 276950,314390	Macrocephaly secondary to hydrocephalus, hydranencephaly, vertebral fusion, hemivertebrae, missing or extra ribs, rib fusion, absent or hypoplastic radius, absent or hypoplastic thumb, triphalangeal thumb, pre-axial polydactyly, other limb deficiencies less commonly; other defects: anal atresia, esophageal atresia, tracheoesophageal fistula, cardiac defect, renal agenesis or dysplasia

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Pelvic-Sacral Abnormalities

Sacral Agenesis/Hypogenesis/Caudal Dysplasia; Pubic Bone Dysgenesis

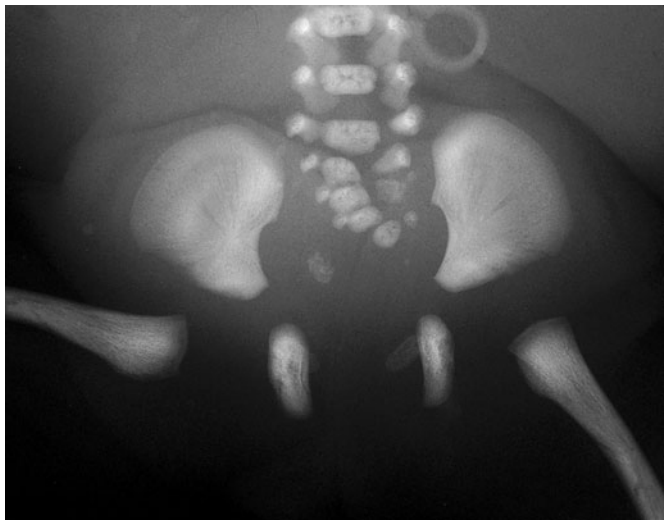

Fig. 2.36. ***34th gestational week.*** Semilunar dysostosis of the sacrum (scimitar shape) due to an anterior meningocele. (Currarino triad)

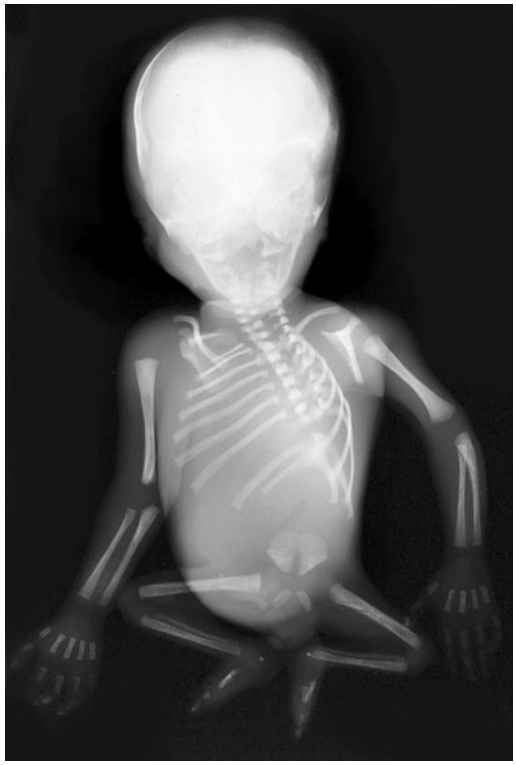

Fig. 2.37. ***22nd gestational week.*** Aplasia of the lower spine in Diabetic embryopathy. Posterior, fork-like fusion of the 8th and 9th ribs, partial fusion of iliac bones, narrow pelvis. Slender tibia and fibula due to hypokinesia. Stippled ossification of calcaneus

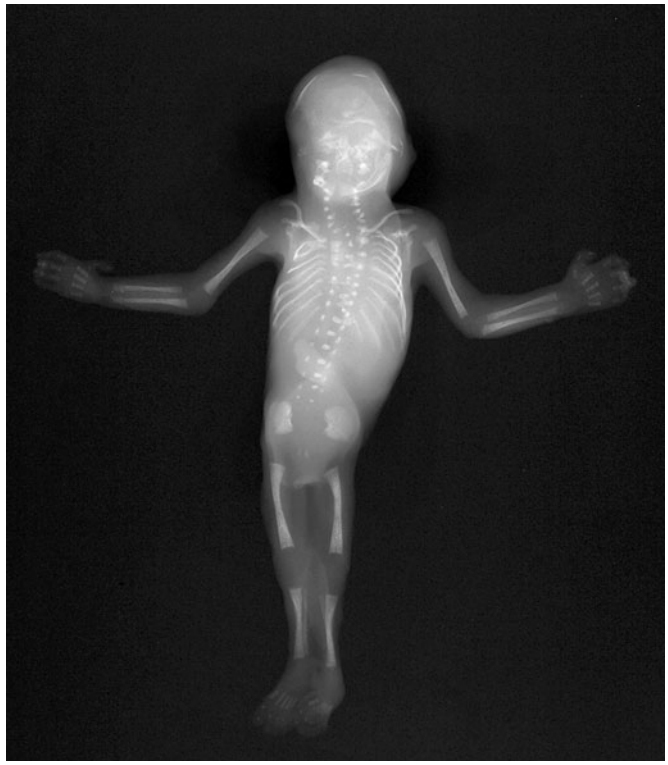

Fig. 2.38. ***16th gestational week.*** Narrow pubic distance in dipodic sirenomelia. Multiple vertebral segmentation defects and fusion of neural arches. Desmal fusion of lower legs. Mirroring of shanks and feet (tibia and hallux on the outside). Sacrum not ossified, narrow ossa ischii

Diagnosis	Accessory radiological findings in the fetus
Achondrogenesis, type 2; see p. 114 Hypochondrogenesis MIM 200600 Lethal type II collagenopathies [1] MIM 200610	Absent or severely delayed ossification of vertebral bodies, short and horizontally oriented ribs, absent or delayed ossification of pubic and ischial bones, small iliac bones with concave borders, small scapulae, very short long bones with cupped metaphyses, fetal hydrops
Boomerang dysplasia[a] [2]; see p. 163 MIM 112310	Similar to atelosteogenesis 1, hut more severe; hypoossification of calvarium; relative macrocephaly; micrognathia; absent or severely retarded ossification of vertebral bodies; long clavicles with normal ossification; narrow interpedicular distance of the thoracic spine with widening in the lumbar spine; very short and deformed long tubular bones (the femur may be fan- or boomerang-shaped); absent pubic ossification centers; hydrops fetalis
Campomelic dysplasia[a] [3]; see p. 124 MIM 211970	Mandibular hypoplasia; hypoplastic scapulae; small bell-shaped thorax; absent ribs; hypoplastic vertebrae; usually short and bowed femur and tibia; joint dislocation may include hip and radial head; absent or delayed ossification of distal femur, proximal tibia, sternum, ischium, pubis; hypoplasia of ischium and pubis; talipes equinovarus
Cleidocranial dysostosis [4]; see p. 171 MIM 119600	Partially absent clavicles, delayed ossification of the pubic bones, cleft mandible, cleft palate
Currarino triad [5, 6, 7]; MIM 176450 **Fig. 2.36**	Sickle-shaped sacrum, presacral mass, anterior meningocele
Diabetic embryopathy [8]; **Fig. 2.37**	Hemivertebrae, absent or hypoplastic femora, hypoplastic tibiae, preaxial or postaxial polydactyly, spinal dysraphism, rib fusion in the midline
Axial mesodermal dysplasia spectrum [9]	Caudal dysplasia, hemivertebrae, scoliosis, absent or bifid ribs, lower limb contractures, talipes equinovarus, hemifacial microsomia
Isolated defect [10]	Variable lumbar vertebral agenesis; fused iliac wings; lower limb contractures with pterygia; hypoplasia of femur, tibia, fibula; talipes equinovarus
Limb-body wall complex [11]; MIM 217100 see Fig. 2.15	Defect of lower abdominal wall, bladder exstrophy, pubic diastasis, segmental defects of lower extremities, spinal segmentation defects
Limb/pelvis hypoplasia/aplasia syndrome [12,13,14,15,16] Includes: Schinzel phocomelia syndrome, MIM 268300 Al-Awadi/Raas-Rothschild syndrome MIM 276820 Fuhrmann syndrome MIM 228930	Parieto-occipital skull defect, femoral hypoplasia, bowing, absent ulnae and fibulae, radial agenesis, oligodactyly, preaxial polydactyly, diaphragmatic hernia, absence or coalescence of tarsal and metatarsal bones
Omphalocele-Exstrophy of the bladder-Imperforate anus-Spinal defects (OEIS) complex[a] [17] MIM 258040	Hemivertebrae, widely spaced pubic bones, spinal dysraphism, talipes equinovarus
Opsismodysplasia[a] [18] MIM 258480	Delayed skeletal maturation, shortening of hand bones. rhizomelic shortening of limbs, severe platyspondyly. absent ossification of vertebrae, narrow thorax, delayed ossification of ischiopubic bones
Pubic distance, extended[a] see Fig. 2.15	Hint of an underlying epispadia, bladder exstrophy, ventral wall defect; syndromatic or non-syndromatic
Pubic distance, narrow[a] see Fig. 2.13	Hint of an underlying urethral aplasia/atresia, prune belly syndrome; syndromatic or non-syndromatic

Diagnosis	Accessory radiological findings in the fetus
Sacral defect with anterior meningocele [7] MIM 600145	Caudal regression, in case of urinary tract obstruction: narrow pubic distance
Sirenomelia [19]; **Fig. 2.38** MIM 182940	Hemivertebrae, fusion of vertebrae, bifld or fused ribs. spinal dysraphism, single or fused lower limb with single or fused femora and tibiae, variable foot abnormalities depending on degree of fusion, sometimes both tibiae and flbulae rotated by 180 degrees, hypoplastic/absenT radius
Spondyloepiphyseal dysplasia congenita[a] [1, 20]; see p. 118 MIM 183900 Spondylometepiphyseal dysplasia (Strudwick)[a] [21, 22] MIM 184250	Short trunk, short limbs; similar radiologic signs of both diseases during fetal period; growth retardation, ovoid vertebrae; no ossification of pubic rami
Urorectal septum malformation sequence[a] [23]	Hemivertebrae, hypoplasia of femur and/or tibia, talipes equinovarus, polydactyly, radial agenesis, megacystis ("prune belly")
VATER Association[a] [24] MIM 192350 VACTERL Association; see Figs. 2.9, 2.13	Vertebral fusion, hemivertebrae, missing or extra ribs. rib fusion, absent or hypoplastic radius, absent or hypoplastic thumb, triphalangeal thumb, preaxial polydactvly, other limb deficiencies less common; other defects include anal atresia, esophageal atresia, tracheoesophageal fistula, cardiac defect, renal agenesis or dysplasia
X-linked visceral heterotaxy syndrome [25,26] MIM 306955	Dextrocardia, heart defect, situs inversus, visceral heterotaxy, gastrointestinal atresia, malrotation, meningomyelocele

[a] Syndromes with pubic bone dysgenesis/a- hypoossified pubic bones

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Coronal Clefts of Vertebral Bodies

Coronal clefts of vertebral bodies in the fetus may be a temporal variation of normal enchondral ossification [1]. In our experience this type is most often seen in chromosomal aberrations. (Fig. 2.38 b,c)

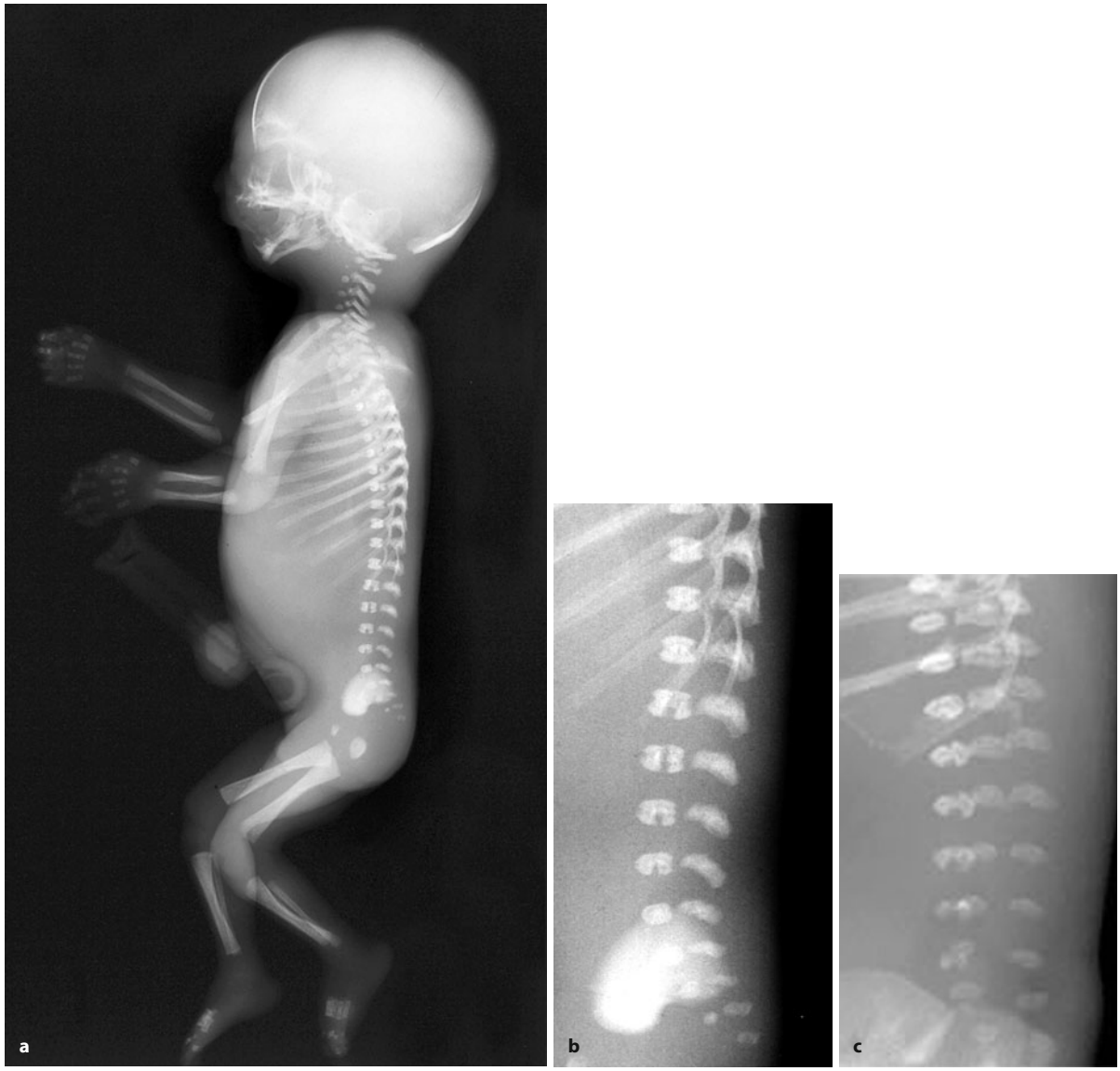

Fig. 2.39. ***18th gestational week.*** Coronal clefts of the thoracic and lumbar vertebral bodies in Trisomy 21. Otherwise normal skeleton **b** (Detail) Coronal clefts of the lumbar vertebrae. **c** Coronal clefts in another fetus, illustrating the spectrum of clefting

Diagnosis	Accessory radiological findings in the fetus
Atelosteogenesis 1 [2 – 4] and related osteochondrodyspiasias; see p. 163 MIM 108720, 108721, 112310	Hypoplastic vertebral bodies, especially of cervical and thoracic spine; hypoplastic and tapered (distal) humerus and femur; bowed radius, ulna, tibia; absent or hypoplastic fibula; absent or hypo-ossified metacarpals and phalanges
Chondrodysplasia punctata, rhizomelic type [5,6]; see p. 159 MIM 215100	Punctate calcifications primarily around the ends of long bones, hypoplasia of humerus and femur, wide or splayed metaphyses, platyspondyly

Diagnosis	Accessory radiological findings in the fetus
Chondrodysplasia punctata, tibia-metacarpal type [7]; see p. 159 MIM 118651	Stippling of sacrum and carpals; dislocation of hip, knee, elbow; short femur, tibia, metacarpals, phalanges; asymmetry
Chromosome abnormalities Trisomy 13 [8] Trisomy 18 [9] Trisomy 21 [10]; **Fig. 2.39** Triploidy [11] Turner syndrome	Besides the other signs (such as growth retardation, hypo-ossified calvaria, hypotelorism, nuchal cystic hygroma, umbilical hernia, radius aplasia), hemivertebrae (especially fusion of the vertebral arches), coronal clefts in the lumbar spine
CODAS (cerebral-ocular-dental-auricular-skeletal syndrome) [12] MIM 600373	Hip dislocation, delayed ossification of pubic bones
De la Chapelle dysplasia [13] see p. 167 MIM 256050	Short tubular bones, deficiency of ulna and to a lesser degree radius, hemivertebrae, platyspondyly, short ribs
Desbuquois syndrome [14, 15]; see p. 165 MIM 251450	Mild platyspondyly, hypoplasia of the ilia (base), short femoral neck and greater trochanter ("monkey wrench" appearance), mild shortening of long bones with flared metaphyses, multiple large and small joint dislocations, advanced carpal and tarsal ossification, accessory ossification centers of metacarpals and metatarsals (digits 1 and II)
Fibrochondrogenesis [16, 17]; see p. 108 MIM 228520	Micrognathia; absent or hypo-ossification of vertebral bodies, especially posteriorly; platyspondyly; short ribs with splayed ends; short, broad ilia with basilar spurs, short long tubular bones with metaphyseal flaring ("dumbbell-shaped")
Larsen syndrome [18]; see p. 161 MIM 150250, 245600	Multiple joint luxations, bifid calcaneus,
Lethal Kniest-like dysplasia [19], MIM 245190 Kniest dysplasia [20], MIM156550; see p. 118	Relative macrocephaly, micrognathia, platyspondyly, broad ilia with hypoplasia of the base, short tubular bones with wide metaphyses, short femoral neck, hydrops fetalis
OPD II (oto-palato-digital syndrome type II) [21] MIM 304120	Curved long bones, wavy ribs, platyspondyly, absent frist digits, omphalocele, overlapping of 2nd finger (trisomy 18-like; see Fig. 2.41b,c) narrow pelvis in case of infravesical obstruction
Oto-spondylo-megaepiphyseal dysplasia (OSMED)[a] [22,23,24] see p. 118 MIM 215150	Micrognathia, depressed midface, rhizomelic shortening of long bones, dumbbell-shaped femora, square or broad iliac wings, brachydactyly, platyspondyly, anterior vertebral wedging, absent-small capital femoral epiphyses (newborn), enlarged epiphyses (late)
Short rib-polydactyly syndrome, type 1 (Saldino-Noonan) [25]; see p. 147 MIM 263530	Relative macrocephaly, very short horizontal ribs, hypoplasia of scapula, small ilia, very short femur and humerus with pointed ends, absent or hypo-ossification of other long tubular and short tubular bones, postaxial polydactyly, hydrops fetalis
Weissenbacher-Zweymüller syndrome[a] [22,26] MIM 277610	Micrognathia, midface hypoplasia, rhizomelic shortening of long bones, dumbbell-shaped femora and humeri, broad iliac wings, enlarged epiphyses

[a] related disorders due to defects in type 11 collagen genes and/or type II collagen

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Platyspondyly

This is an unspecific radiographic sign most often recognized in skeletal dysplasias (see chapter 3). It becomes only diagnostic with a combination of other findings (e.g. short extremities, unossified pubic bone, multiple fractures, unossified calvaria, coronal clefts of vertebral bodies...).

Ventral Body Wall Defects

Ectopia Cordis

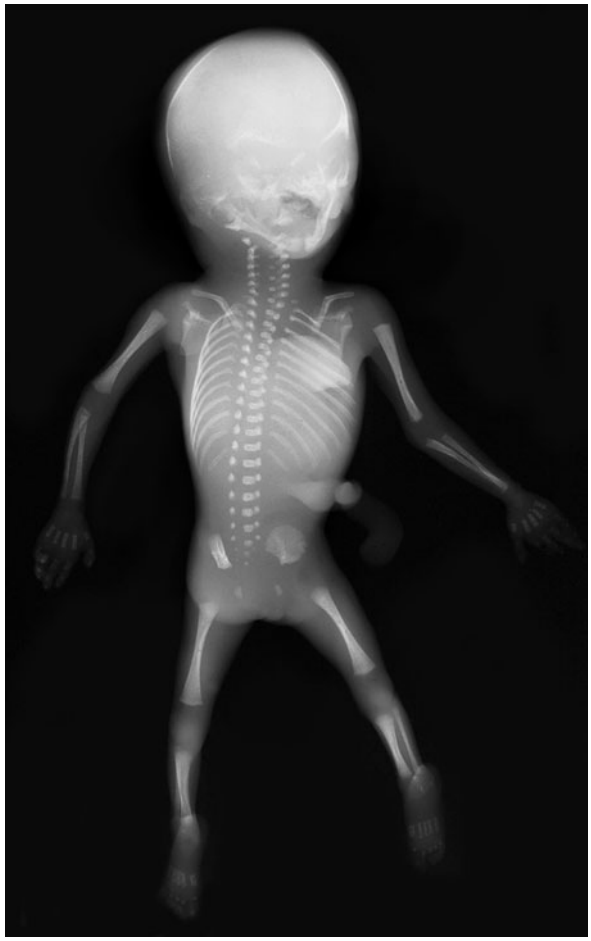

Fig. 2.40. ***18th gestational week.*** Body wall defect: ectopic heart in pentalogy of Cantrell. The shadow of the ectopic heart projects onto the upper part of the left hemithorax. Slender abdomen. Otherwise normal

Diagnosis	Accessory radiological findings in the fetus
Amniotic band/disruption sequence [1, 2]; ADAM complex (Amniotic Deformity, Adhesions, Mutilations) Limb – body wall complex MIM 217100	Usually asymmetric transverse terminal limb reductions/amputations and variable terminal syndactyly/pseudosyndactyly; may also include oligodactyly, hypoplasia of long bones, craniofacial and ventral wall disruption.
Pentalogy of Cantrell [3] Thoracoabdominal syndrome; MIM 313850 **Fig. 2.40**	Sternal defects including agenesis, clefting or bifid sternum, absence of lower third of sternum; other defects include supraumbilical midline defect (omphalocele), central diaphragmatic hernia, pericardial defect, congenital heart defect
Sternal malformation-vascular dysplasia association [4] Sternal clefts-telangiectasia/hemangiomas Hemangiomas – midline abdominal raphe [5] MIM 140850	Absent or bifid sternum, pectus excavatum, absent or hypoplastic clavicles; micrognathia, cleft mandible; other features include midline hemangiomas of face and/or chest, midline supraumbilical raphe

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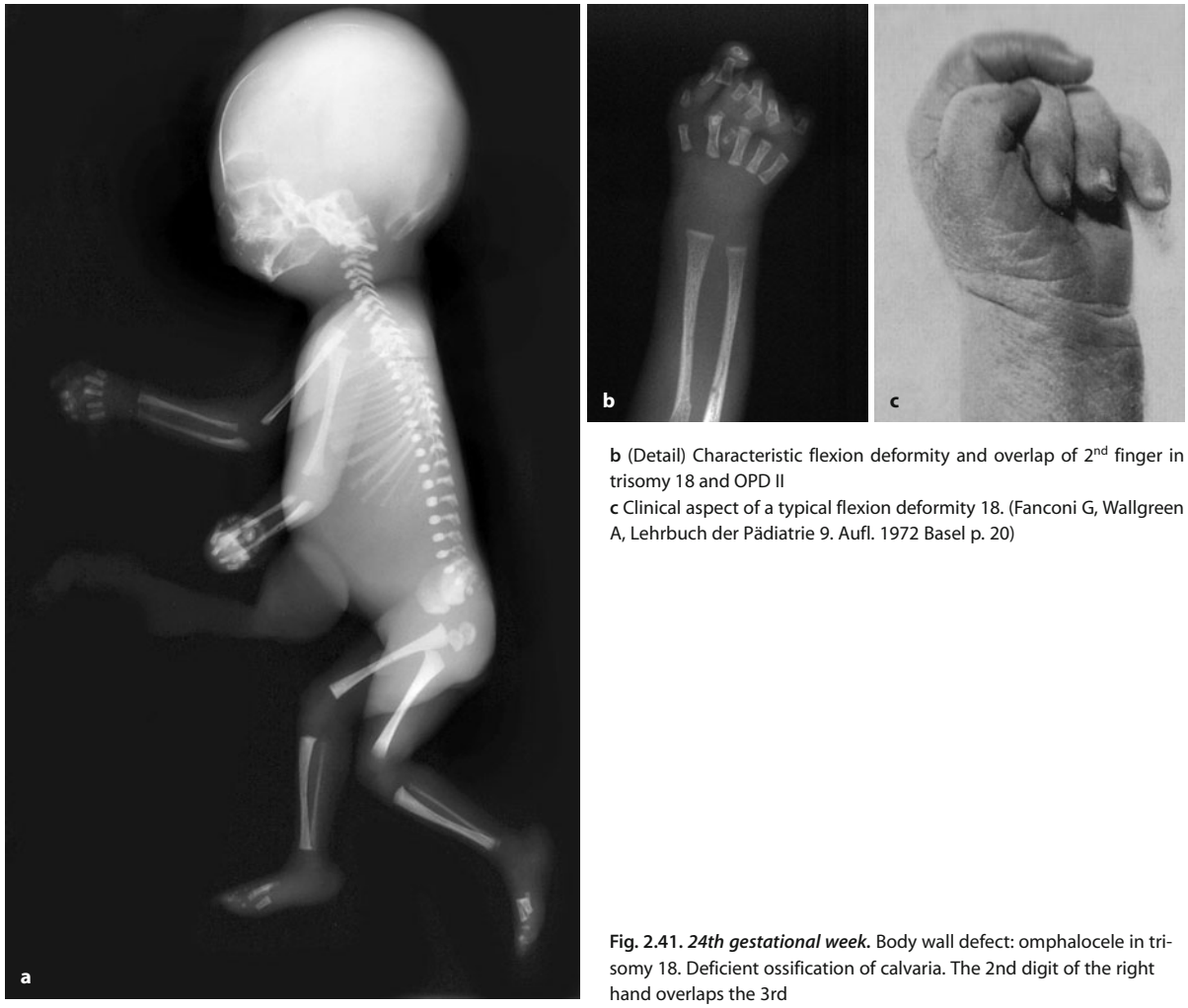
Ventral Wall Defects/Omphalocele/Gastroschisis



b (Detail) Characteristic flexion deformity and overlap of 2nd finger in trisomy 18 and OPD II

c Clinical aspect of a typical flexion deformity 18. (Fanconi G, Wallgreen A, Lehrbuch der Pädiatrie 9. Aufl. 1972 Basel p. 20)

Fig. 2.41. ***24th gestational week.*** Body wall defect: omphalocele in trisomy 18. Deficient ossification of calvaria. The 2nd digit of the right hand overlaps the 3rd

Diagnosis	Accessory radiological findings in the fetus
Amniotic band/disruption sequence ADAM complex (*Amniotic* Deformity, *Adhesions*,Mutilations) Limb-body wall complex [1]; MIM 217100 see Fig. 2.15	Usually asymmetric transverse terminal limb reductions/amputations and variable terminal syndactyly/pseudosyndactyly; may also include oligodactyly, hypoplasia of long bones, craniofacial and ventral wall disruption
Arthrogryposis multiplex congenita Amyoplasia [2] MIM 108110	Extension contractures of elbows and knees, dislocated or adducted hips, flexion of wrists and hands, slender long bones, metacarpophalangeal and interphalangeal joint contractures, pterygia, absent patellae, hypoplastic genitalia, gastroschisis, nonduodenal intestinal atresia
Beckwith-Wiedemann syndrome [3] MIM 130650	Macrosomia, cardiomegaly, omphalocele, abdominal visceromegaly

Diagnosis	Accessory radiological findings in the fetus
Boomerang dysplasia [4,5]; see p. 163 MIM 112310	Similar to atelosteogenesis 1, but more severe; hypoossification of calvarium; relative macrocephaly; micrognathia; absent or severely retarded ossification of vertebral bodies; long clavicles with normal ossiflcation; narrow interpedicular distance of the thoracic spine with widening in the lumbar spine; very short and deformed long tubular bones (the femur may be fan- or boomerang-shaped); hydrops fetalis
Chromosome abnormality, trisomy 13 [6]	Microcephaly, hypotelorism, small orbits, hypo-ossification of calvarium, spinal dysraphism, hemivertebrae, absent/supernumerary/fused ribs, hypoplasia of pelvis, oligodactyly, polydactyly, syndactyly, camptodactyly, vertical talus; other defects: heart ahnormalities, omphalocele, holoprosencephaly, neural tube defect, cystic hygroma, hydrops fetalis
Chromosome abnormality, trisomy 18 [6, 7]; **Fig. 2.41**	Microcephaly, hypo-ossification of calvarium, hypoplasia ofmaxilla and/or mandible, microretrognathia, absent or thin ribs, short sternum, spinal dysraphism, hypoplasia of pelvis, hypoplasia of first metacarpal, flexion deformities and overlapping fingers, vertical talus, short first toe, hammertoes; other defects: intrauterine growth retardation, heart abnormalities, omphalocele, neural tube defect
Donnai-Barrow syndrome [8] MIM 222448	Macrocephaly, wide metopic suture, large anterior fontanelle, agenesis of corpus callosum, hypertelorism, heart defect, diaphragmatic hernia or eventration, omphalocele, intestinal malrotation, bicornate uterus
Elejalde syndrome [9] MIM 200995	Craniosynostosis, hypertelorism, shortening of all long bones, postaxial polydactyly; other features include generalized overgrowth, cystic hygroma, hydrops fetalis.
Fryns syndrome [10] MIM 229850	Macrocephaly, wide metopic suture, large anterior fontanelle, agenesis of corpus callosum, hypertelorism, heart defect, diaphragmatic hernia or eventration, omphalocele, intestinal malrotation, bicornate uterus
Melnick-Needles osteodysplasty [11, 12] MIM 309350 Oto-palato-digital syndrome, type II [13, 14]; see Fig. 2.41b,c see p. 136 MIM 304120	Hypo-ossification of calvarium, sclerosis of skull base, large anterior fontanelle, micrognathia, thin/wavy/beaded ribs with irregular cortex, hypoplastic scapula, flared ilia with hypoplastic base, kyphosis, scoliosis, lordosis, S-shaped bowing of long bones, metaphyseal flaring, coxa valga, genus valga, short distal phalanges, absent or hypoplastic metacarpals and metatarsals, absent or hypoplastic thumb and/or hallux; other defects: urinary obstruction, multiple joint dislocations
*O*mphalocele-*E*xstrophy of the cloaca-*I*mperforate anus-*S*pinal defects (*OEIS* complex) [15] MIM 258040	Absent or hypoplastic sacrum, hemivertebrae, scoliosis, spinal dysraphism, pubic diastasis, talipes equinovarus
Omphalocele, diaphragmatic hernia and radial ray defects [16] Gershoni-Baruch syndrome MIM 609545	Diaphgramatic hernia, bell-shaped chest, scoliosis, hepatic cysts, radioulnar synostosis, absent thumb, triphalangeal thumb, absent metacarpal
Osteopathia striata with cranial sclerosis [17] OSCS MIM 300373	Macrocephaly, trapezoidal shaped skull, hypertelorism, frontal bossing, cleft lip +/- palate, cleft palate, linear striations of long bones, scoliosis, increased bone density, cranial sclerosis, absent or hypoplastic fibulae, talipes equinovarus, camptodactyly, hydrocephalus, heart defect, omphalocele, intestinal malrotation, multicystic kidney, Males are more severely affected.
Pseudotrisomy 13 syndrome [18, 19] MIM 264480	Microcephaly, micrognathia, hemivertebrae, absent or hypoplastic radius or ulna, postaxial polydactyly, preaxial polydactyly, absent or hypoplastic tibia, broad hallux, talipes equinovarus

Diagnosis	Accessory radiological findings in the fetus
Short rib-polydactyly, Beemer-Langer type [20]; see p. 149 MIMIM 269860	Short horizontal ribs, short tubular bones, tibia short but longer than fibula, bowed radius and ulna, preaxial or postaxial polydactyly, hypoplastic ilia; other defects: CNS abnormalities, cleft lip, heart, kidneys, hydrops fetalis
Tetraamelia [21] MIM 273395	Tetraamelia, microphthalmia, cleft lip +/- palate, choanal atresia, diaphragmatic defect, abnormal lung lobation, gastroschisis, agenesis of kidney, adrenal, spleen, absence or malformation of external and internal genitalia, persistent cloaca,
Thoracoabdominal syndrome Pentalogy of Cantrell [22, 23] MIM 313850	Short, cleft or bifid sternum, central/anterior diaphragmatic hernia; other defects include ectopia cordis, congenital heart defect

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3 Skeletal Dysplasias

Introduction

The presence of widespread, often symmetric, skeletal abnormalities raises the possibility of a generalized skeletal dysplasia. Osteochondrodysplasias are structural or formative defects that continue to evolve after blastogenesis, i.e., approximately the 8th gestational week. At this time, the patterning of individual bones as organs, i.e., of the single constituents of the axial skeleton and limbs, is complete. Many genes involved in the early patterning and development of the skeleton are no longer expressed. On the other hand, defects of growth, maturation, and homeostasis may continue to manifest until adulthood and thereafter, producing abnormalities recognizable by the histologic study of chondroosseous tissue.

In this book only osteochondrodysplasias manifesting during fetal life are depicted. Many of them are lethal. Their recognition in utero and differentiation from early-manifesting nonlethal osteochondrodysplasias by sonography is difficult and has been the subject of many studies (Avni et al. 1996; Doray et al. 2000; Rouse et al. 1990; Spirt et al. 1990; Tretter et al. 1998). Postnatally, anterio-posterior and lateral radiographs of the entire fetus and of selected sites, notably the hands, often allow for a specific diagnosis with only a limited number of differential diagnoses. In that respect the conditions presented here differ from those in Chap.-2 of the book which occur less specifically in a great number of diseases.

More fetal osteochondrodysplasias exist than are illustrated in this book. Some of them may be variant expressions of known dysplasias. Other represent bona fide entities waiting for future delineation (e.g., Akaba et al. 1996; Al Gazali et al. 1996; Brodie et al. 1999; Goldblatt 1998; Kerner et al. 1998; Khosravi et al. 1998; Kozlowski et al. 1995; Morton et al. 1998; Müller et al. 1992; Nishimura et al. 1998; Pinto et al. 1993; Saito et al. 1989; Saint-Martin et al. 1979; Seller et al. 1996).

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A. Skeletal Dysplasias with Prominent Shortness of the Tubular Bones

Thanatophoric Dysplasia I MIM 187600

Synonym: Thanatophoric Dwarfism I. Includes San Diego variant of platyspondylic chondrodysplasia.

Major Radiographic Features:

- Enlarged skull; rarely craniosynostosis with cloverleaf formation
- Narrow thorax due to short ribs
- Flattened vertebral bodies with central depression of upper and lower plates in most cases; waver-thin vertebral bodies in San Diego variant
- Hypoplastic iliac wings with horizontal inferior margins, often medially extending radiolucent band or multiple ossification centers in inferio-lateral aspects of ilia , narrow sacrosciatic notches, unossified pubic bones
- Short, broad and bowed tubular bones with flared metaphyses
- Rounded, radiolucent appearance of proximal femoral end in most cases, squared proximal end with ragged metaphyseal margin in San Diego variant
- Very short and broad tubular bones of hands and feet

Mode of Inheritance: Autosomal dominant.

Molecular Basis: Various mutations of the *FGFR3* gene encoding the fibroblast growth factor receptor 3. The most common mutations are Arg248Cys and Tyr373Cys.

Prenatal Diagnosis: By ultrasound in 2nd trimester. Confirmation by mutation analysis of *FGFR3* in cultured amniotic cells or cord blood cells.

Differential Diagnosis: *Thanatophoric dysplasia II* differs by the straight tubular bones and the more frequent occurrence of craniosynostosis with cloverleaf formation.

The appearance of the vertebral bodies, pelvis and tubular bones rules out other lethal chondrodysplasias including the various types of a*chondrogenesis* and *Schnekkenbecken dysplasia* with which thanatophoric dysplasia has been confused. A radiologically similar disease with good prognosis is *achondroplasia.* The bone changes in that disorder are similar but milder than those in thanatophoric dysplasia.

Prognosis: Most patients are stillborn or die shortly after birth from cardiorespiratory failure. With appropriate life support a few patients are known to have survived beyond the age of 9 years showing growth failure,

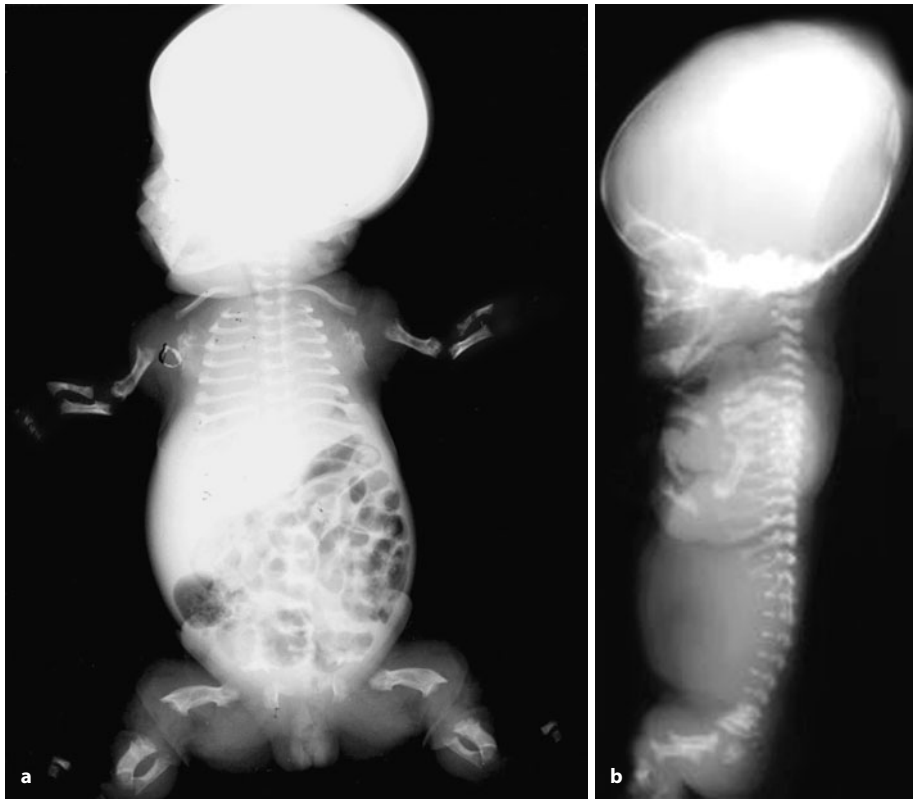

Fig. 3.1 ***Thanatophoric dysplasia I.*** Newborn, 37 weeks gestation: **a** Prominent features are narrow thorax; flat vertebral bodies; squared iliac wings with wide, horizontal inferior margins; short and broad tubular bones, curved femora with radiolucent upper ends. **b** The vertebral bodies are flattened; the posterior elements are well developed

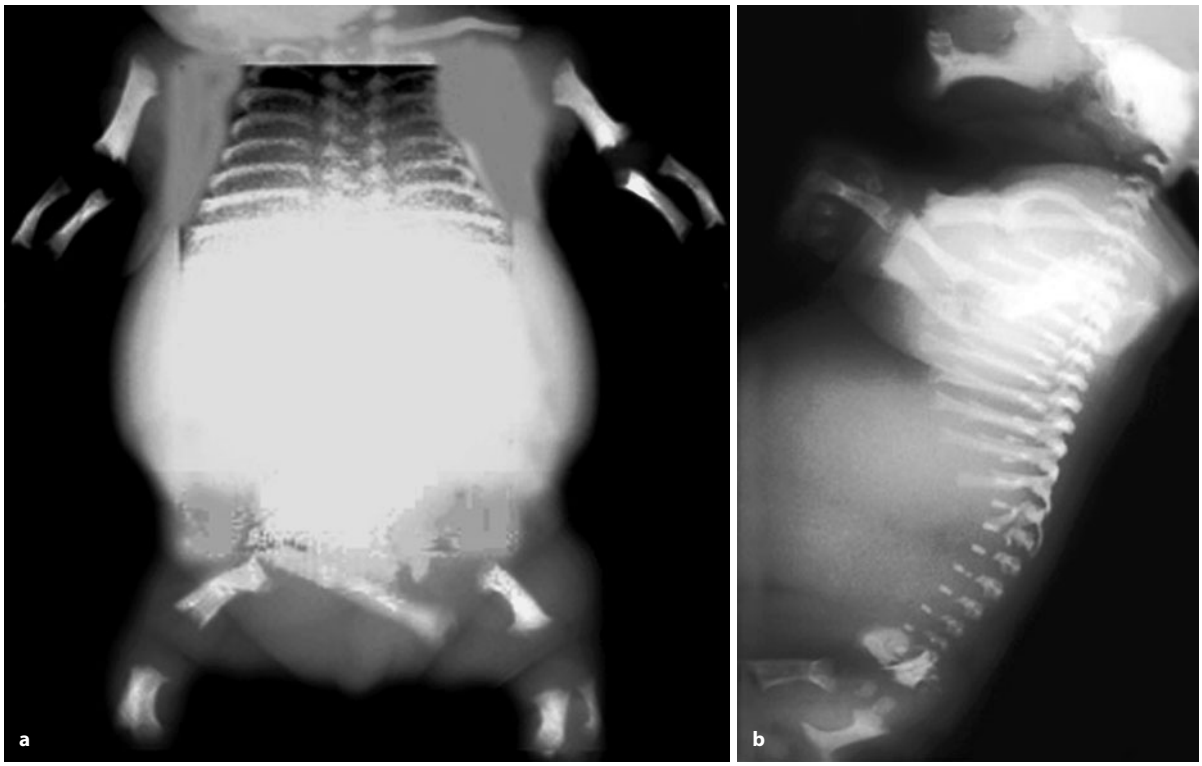

Fig. 3.2 ***Thanatophoric dysplasia I, San Diego variant.*** Newborn, 38 weeks gestation. **a** Compared to Fig. 1 the tubular bones are also short and broad, but the femora are only minimally bowed. **b** The vertebral bodies are wafer-thin. The patient did not have a cloverleaf

severe mental and motor deficiency due to structural brain abnormalities and prolonged dependency on ventilator assistance.

Remarks: The San Diego variant characterized by wafer-thin vertebral bodies, less severely bowed long tubular bones with ragged metaphyseal margins and absence of the gland-like radiolucency of the upper femoral end was formerly thought to represent a distinct entity. It has been shown to be caused be the same mutations as thanatophoric dysplasia I.

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Thanatophoric Dysplasia II MIM 187601

Synonym: Thanatophoric Dysplasia with Kleeblattschädel (cloverleaf).

Major Radiographic Features:

- Often craniosynostosis with cloverleaf formation.
- Narrow thorax due to short ribs
- Flattened vertebral bodies with irregular upper and lower end plates
- Hypoplastic ilia with horizontal inferior margins, often medially extending radiolucent band or multiple ossification centers in inferio-lateral aspects of ilia, narrow sacrosciatic notches, unossified pubic bones
- Short, broad and straight tubular bones with flared metaphyses
- Rounded, radiolucent appearance of proximal femoral end in most cases, squared proximal end with ragged metaphyseal margin in San Diego variant
- Very short and broad tubular bones of hands and feet

Mode of Inheritance: Autosomal dominant.

Molecular Basis: Specific Lys650Glu mutation of the *FGFR* gene encoding the fibroblast growth factor receptor protein.

Prenatal Diagnosis: By ultrasound in 2nd trimester. Confirmation by mutation analysis of *FGFR3* in cultured amniotic cells or cord blood cells.

Differential Diagnosis: *Thanatophoric dysplasia I* differs by the less frequent presence of a Kleeblattschädel and bowing of the long tubular bones. Otherwise same differential diagnosis as thanatophoric dysplasia I.

Prognosis: No long-term survivors with this form of thanatophoric dysplasia have been reported.

Remarks: A mutation in the same FGFR3 codon as the thanatophoric dysplasia II mutation (Lys650Met) is compatible with survival into adulthood leading to severe achondroplasia with developmental delay and acanthosis nigricans (SADDAN).

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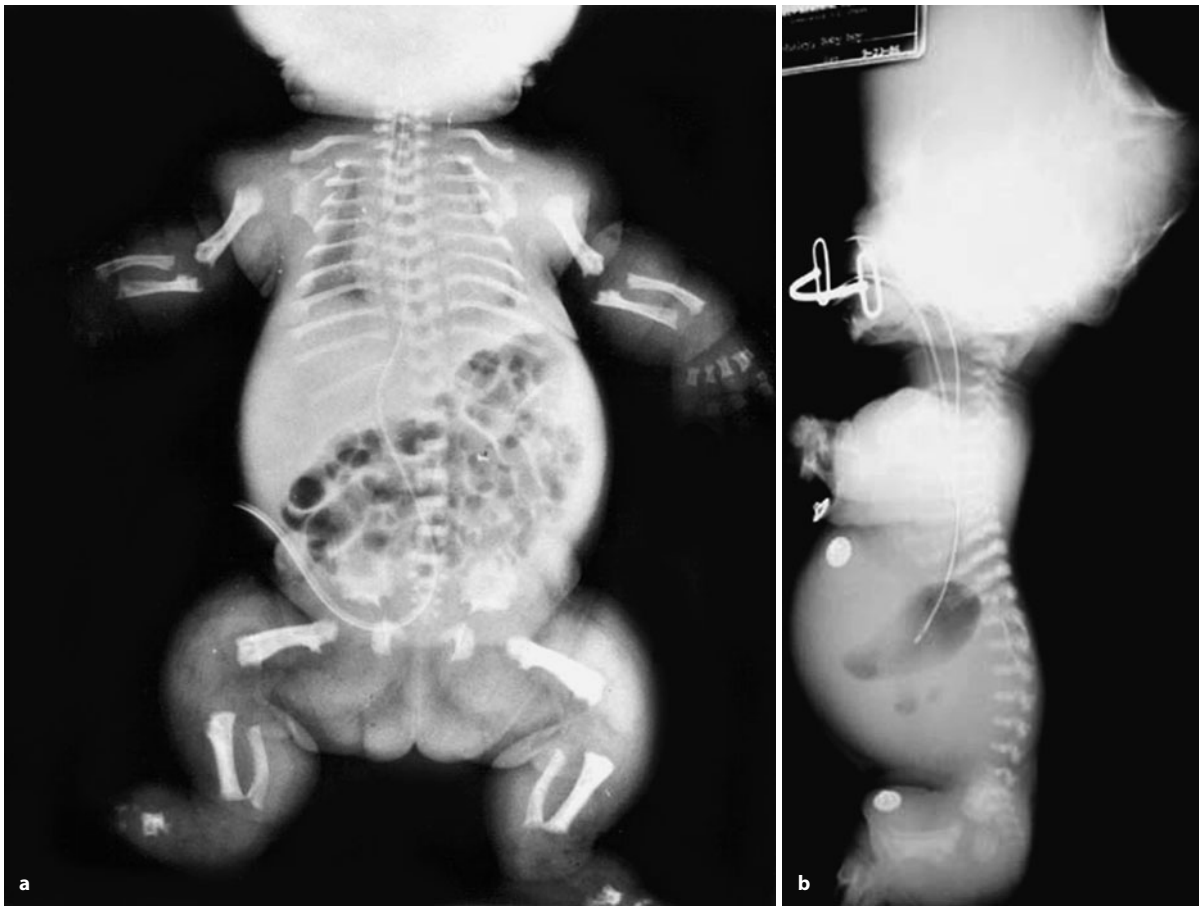

Fig. 3.3. ***Thanatophoric dysplasia II.*** **a** The findings are similar to those in thanatophoric dysplasia I except for the femora which are straight. **b** The lateral view of the skull shows the upper and posterior bulge of the trilobar Kleeblattschädel. The vertebral bodies are not as severely flattened as in thanatophoric dysplasia I

Achondroplasia MIM 100800

Synonym: Chondrodystrophia fetalis, Chondrodysplasia fetalis; Chondrodystrophic dwarfism.

Major Radiographic Features:

- Large neurocranium, short skull base, small occipital foramen
- Decrease of the interpediculate distance from upper to lower spine; short pedicles on lateral view
- Squared iliac bones with horizontal acetabular margins and small sacrosciatic notches
- Shortened tubular bones; oval radiolucent area in the proximal femur

Mode of Inheritance: Autosomal dominant. Parental gonadal mosaicism has been observed raising the recurrence risk of achondroplasia in sibs of unaffected parents to approximately 0.02%.

Molecular Basis: Most commonly point mutation at nucleotide 1138 of the cDNA of the *FGFR3* gene resulting in the substitution of an argine residue for a glycine in the fibroblast growth factor receptor 3. Mutations at other sites have been described.

Prenatal Diagnosis: Short femora have been detected after 20 weeks gestation by ultrasound. A shortened base of the skull and depressed nasal bridge have also been detected. The specificity of short limbs is less than 0.25. Diagnostic ambiguity and errors are common. If one of the parents is affected, *FGFR3* can be determined in chorionic villi, fetal blood cells obtained by cordocentesis or cultured fibroblasts from amniotic fluid.

Differential Diagnosis: The *thanatophoric dysplasias* and *homozygous achondroplasia* differ by the more severe flattening of the vertebral bodies and the more severe shortening of the tubular bones. The femora are bowed in thanatophoric dysplasia I and cranial deformity due craniosynostosis is often present in thanatophoric dysplasia II. Another relatively common neonatal dysplasia with short limbs is *spondyloepiphyseal dysplasia congenita*. Ovoid vertebral bodies and absent ossification of the pubic bones characterize that dysplasia. Other neonatally manifest skeletal dysplasias are differentiated by characteristics described in the appropriate chapters.

Prognosis: Achondroplasia is not lethal. With proper care the patients survive the neonatal period and have a normal life expectancy.

Remarks: If both parents have achondroplasia, the risk of homozygous achondroplasia is 25%. Phenotypically it resembles thanatophoric dysplasia I. SADDAN dysplasia is a acronym for **s**evere **a**chondroplasia with **d**evelopmental **d**elay and **a**canthosis **n**igricans. This extremely rare disorder is caused by a lys650 peculiar mutation at the nucleotide adjacent to the TD-II locus of the *FGFR3* gene (Bellus et al 1999).

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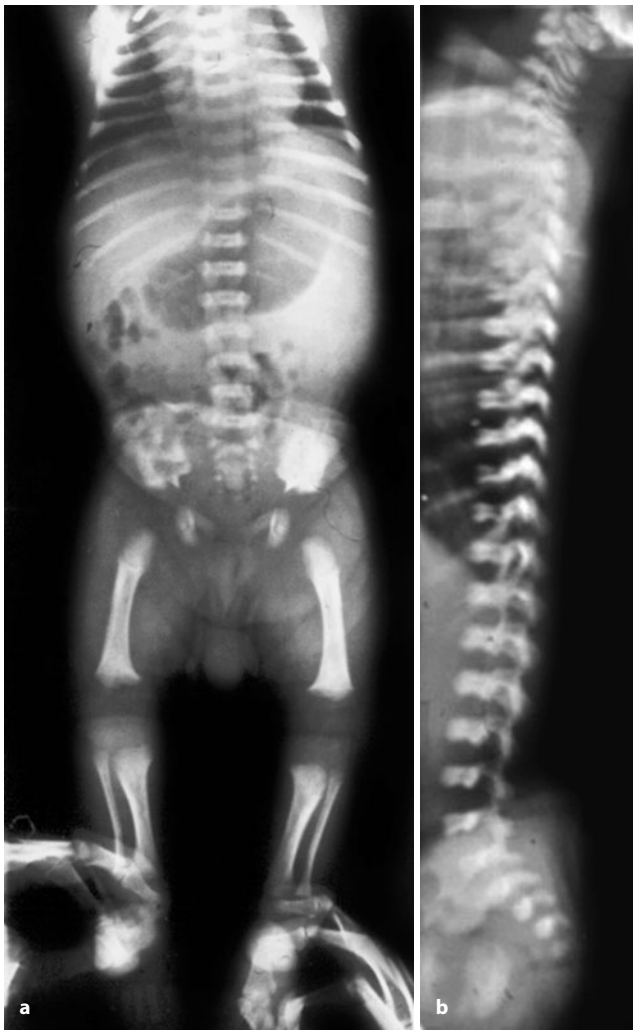

Fig. 3.4. ***Achondroplasia***, newborn. **a** The vertebral bodies are slightly flat. The interpediculate distances decreases from the upper to the lower lumbar spine. The ilia are squared with narrow sciatic notches and spurs extending downward from the medial ends of the horizontal acetabular roofs. The tubular bones are mildly shortened and curved. Note characteristic oval-shaped lucent appearance of the proximal femora. **b** The vertebral bodies are slightly flat with remnants of coronal clefts appearing as central indentations of the upper and lower plates

Metatropic Dysplasia MIM 156530, 250600

Synonym: Includes 'Lethal metatropic dysplasia'.

Major Radiographic Features:
- Small, flattened, often diamond-shaped vertebral bodies
- Narrow thorax
- Hypoplasia of the lower ilia with crescent-shaped iliac crests and low-set anteriosuperior iliac spines
- Shortened tubular bones with marked metaphyseal flare

Mode of Inheritance: Autosomal dominant. Affeceted sibs born to unaffected parents have been observed suggesting parental gonadal mosaicism.

Molecular Basis: Metatropic dysplasia is caused by mutations in *TRPV4*. encoding the calcium-permeable ion channel

Prenatal Diagnosis: Short limbs have been detected at 20 weeks gestation.

Differential Diagnosis: Severe mushrooming of the long tubular bones characterizes lethal metatropic dysplasia. Less severe metaphyseal expansion is present in milder cases of metatropic dysplasia, in *fibrochondrogenesis* and *Schneckenbecken dysplasia* Anterior pointing of the vertebral bodies is more common in metatropic dysplasia than in the fibrogenesis and Schneckenbecken dysplasia but reliable differentiation of these disorders requires molecular analysis.

Prognosis: The prognosis must be individually assessed on the basis of the bone changes. Infants with severely shortened and mushroomed tubular bones are stillborn or do not survive early infancy. Less severely affected infants may survive to adulthood and have children, but early mortality is increased due to respiratory failure secondary to reduced thoracic volume. Their intellectual development is normal.

Remarks: Mutations of the TRPV4 gene also cause the Kozlowski type of spondylometaphyseal dysplasia wich shows similar spinal, but less severe epiphyseal abnormalities. Intermediate phenotypes exist.

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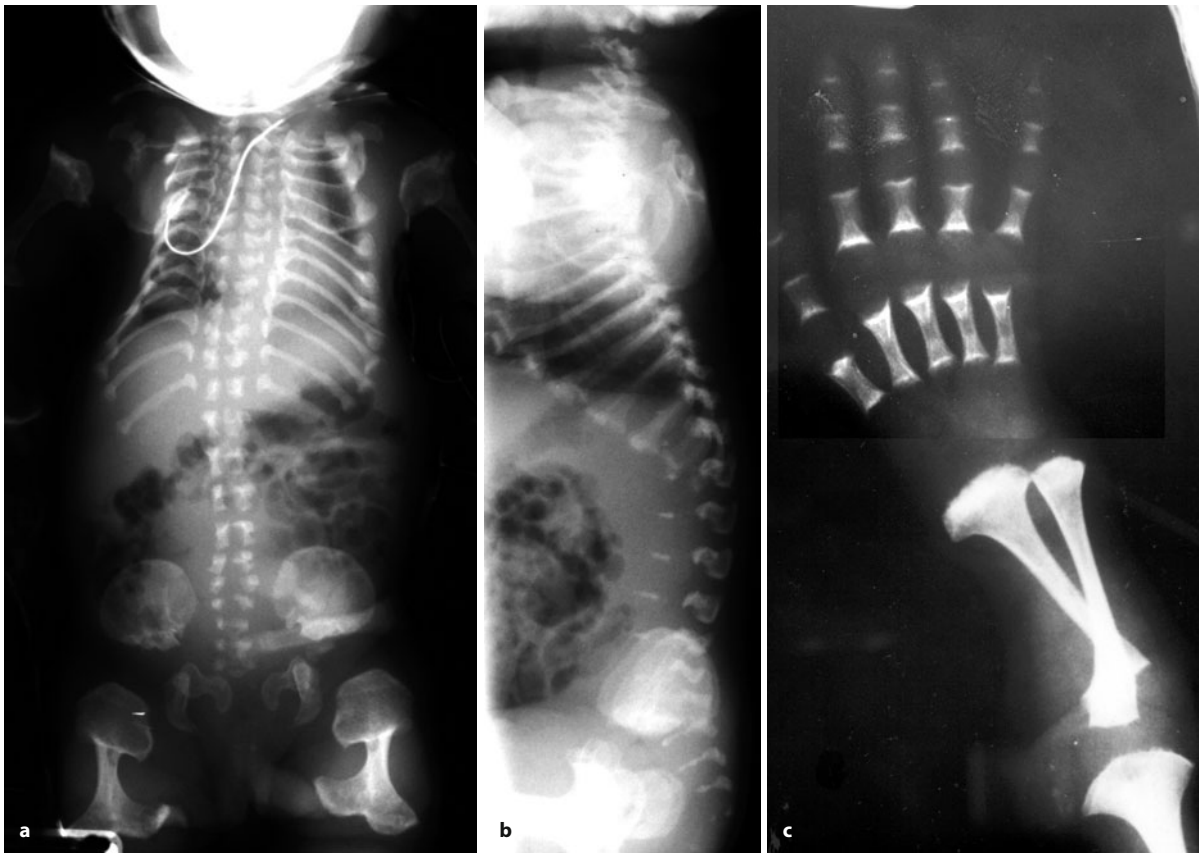

Fig. 3.5. ***Severe metatropic dysplasia.*** **a** The thorax is narrow**. The lower portions of the ilia are not developed.** The tubular bones are short and dumbbell-shaped with very broad, mushroomed ends. **b** The vertebral bodies are severely underossified presenting as thin wafer-like structures. **c** Radius and ulna are shortened with grossly flared ends and konvex metaphyseal margins. The ends of the short tubular bones are slightly wide with scalloped proximal and distal margins

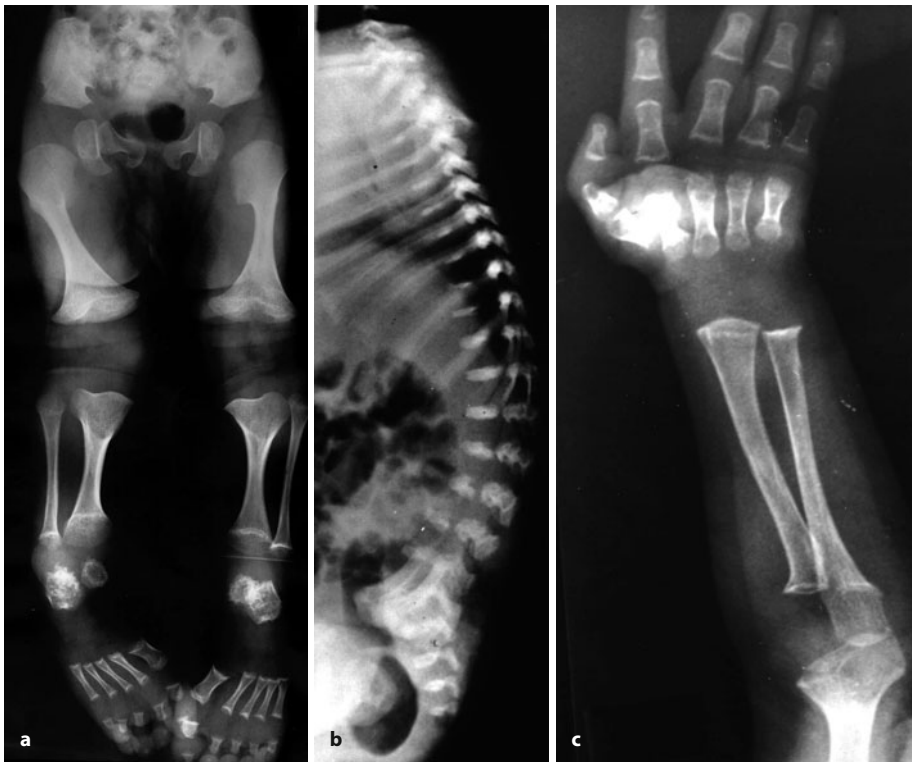

Fig. 3.6. ***Milder form of metatropic dysplasia***. **a** The basilar portions of the ilia are broad with horizontal lower margins.. The femora are short with broad, hyperplastic ends. **b** Flattened vertebral bodies and wide intervertebral spaces are seen. **c** The phalanges are relatively broad with dense contours

Fibrochondrogenesis MIM 228520

Major Radiographic Features:

- Defective ossification of the posterior parts of the vetebral bodies
- Short ribs with splayed ends
- Small ilia with spurs extending caudally from the acetabular roof
- Short tubular bones with bulbous ends

Mode of Inheritance: Autosomal recessive.

Molecular Basis: Unknown.

Prenatal Diagnosis: Short limbs and deficient ossification of the vertebral bodies may be detected by ultrasound in the 2nd trimester.

Differential Diagnosis: *Schneckenbecken dysplasia* is radiologically similar and may be etiopathogenetically related. The tubular shortening is usually less severe in Schneckenbecken dysplasia. The skeletal abnormalities in lethal metatropic dysplasia are also similar, but more severe than in fibrochondrogenesis.

Prognosis: All published patients died at or after birth.

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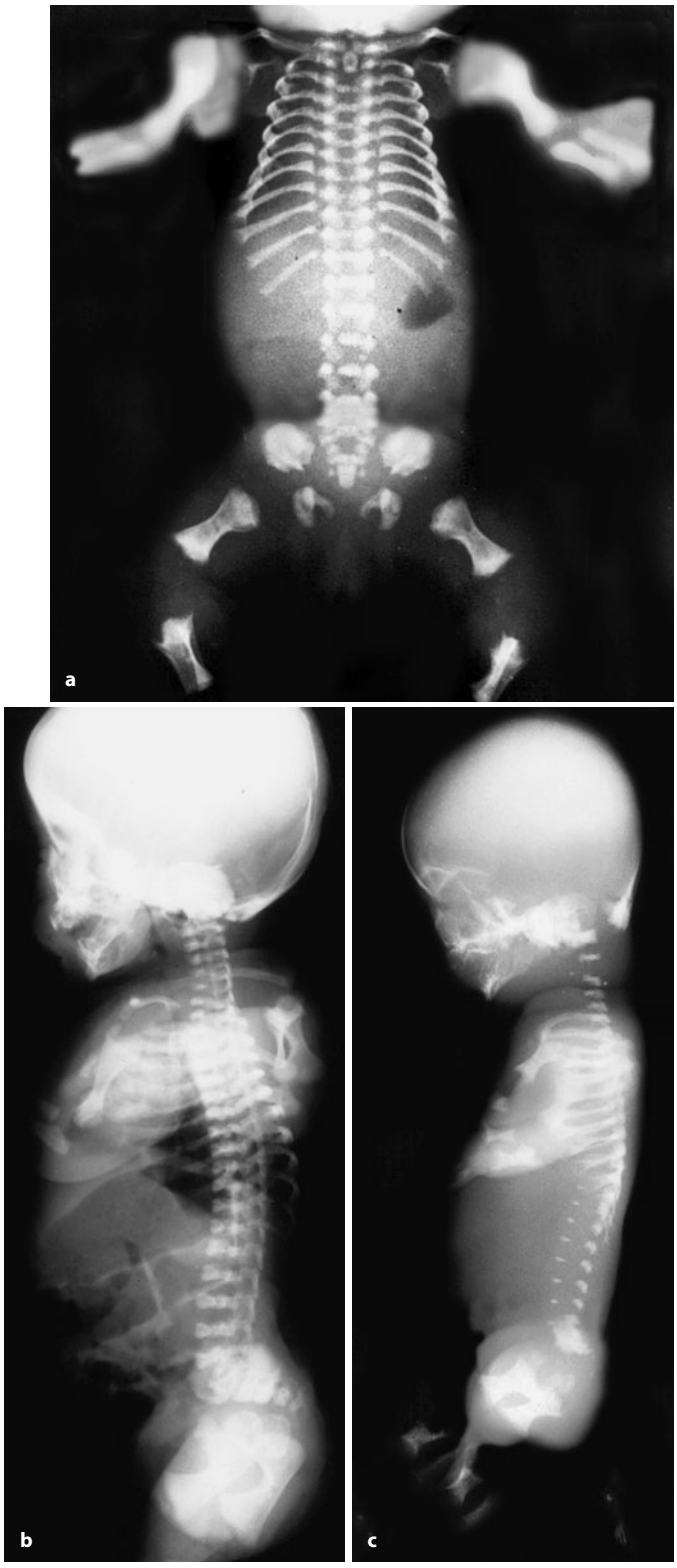

Fig. 3.7. ***Fibrochondrogenesis.*** Newborn, 23 weeks gestation. **a** The anterior ends of the ribs are splayed. The vertebral bodies are flat with increased intervertebral spaces. The iliac bones are small with horizontal inferior margins and osseous spurs extending downward from their medial ends. The tubular bones are short with bulbous ends. **b** Coronal clefts separate diamond-shaped anterior portions of the vertebral bodies from small dorsal ossification centers. **c** In this 23 week old fetus ossification of the vertebral bodies is reduced to thin, wafer-like structures. The cervical and upper thoracic vertebral bodies are not ossified at all

Schneckenbecken Dysplasia MIM 269250

Major Radiographic Features:
- Hypoplastic vertebral bodies.
- Short ribs with splayed ends
- Small ilia with medial projection from the inner margins (snail-like appearance)
- Shortened, dumbbell-shaped tubular bones

Mode of Inheritance: Autosomal recessive.

Molecular Basis: *SLC35D1* gene encoding the SLC35D1 nucleotide transporter

Prenatal Diagnosis: Short limbs were detected by ultrasound at 16 weeks gestation.

Differential Diagnosis: Compared to *fibrochondrogenesis* the medial protrusion of the ilia is more pronounced and the ends of the tubular bones are less bulbous in Schneckenbecken dysplasia. In *severe metatropic* dysplasia the ends of the tubular bones are more severely expanded with convex joint surfaces.

Prognosis: All reported patients were stillborn or died shortly after birth.

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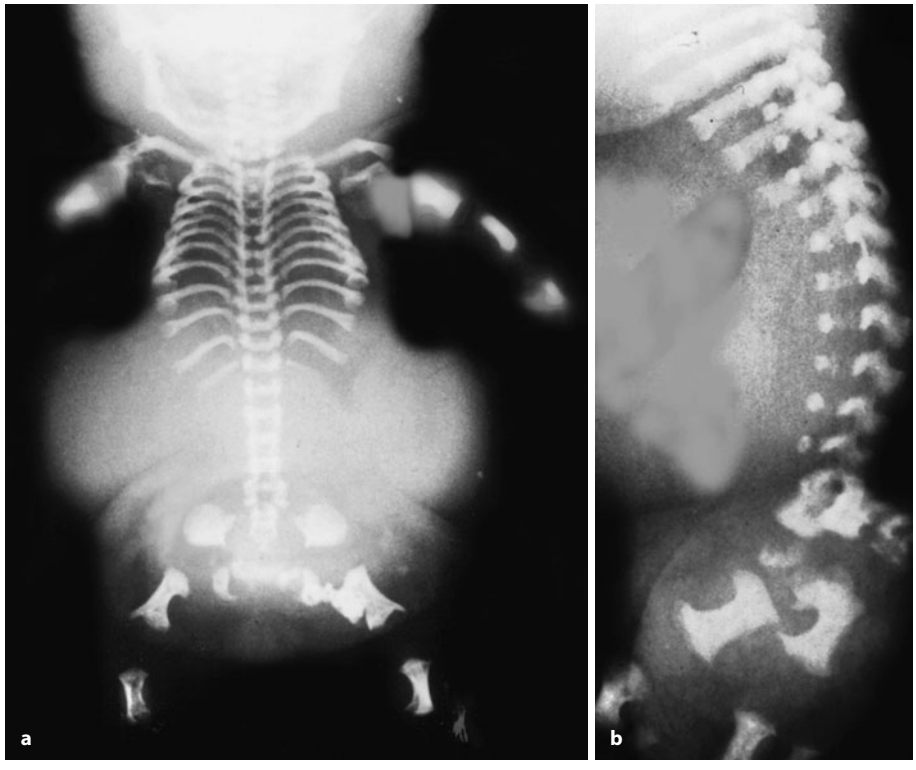

Fig. 3.8. ***Schneckenbecken dysplasia***. **a** Stillborn. The ribs are short with splayed anterior ends. The vertebral bodies are small. The iliac bones are small, round, with a medial osseous projection producing a snail-like configuration. The tubular bones are short and dumbbell-shaped with slightly convex margins of the proximal femora and irregular metaphyseal margins of the distal femora and proximal humeri. **b** Newborn, 34 weeks gestation. Small, round ossification centers are seen in the anterior portions of the vertebral bodies. Both infants are hydropic

Lethal Metaphyseal Chondrodysplasia, Sedaghatian Type MIM 250220

Synonym: Lethal metaphyseal chondrodysplasia, Shiraz type.

Major Radiographic Features:
- Small thorax
- Mild platyspondyly
- Flat and broad iliac wings
- Shortened tubular bones with metaphyseal cupping and irregularity

Mode of Inheritance: Autosomal recessive

Molecular Basis: Unknown.

Prenatal Diagnosis: Short limbs have been detected by ultrasound at 31 weeks gestation.

Differential Diagnosis: *Thanatophoric dysplasia* and *other lethal chondrodysplasias* differ by more severe flattening of the vertebral bodies and more severe shortening of the tubular bones. In *hypochondrogenesis* and *spondyloepiphyseal dysplasia congenita* the pubic bones are characteristically unossified. *Jansen metaphyseal dysplasia* is differentiated by the associated undermineralization.

Prognosis: Most patients are stillborn or die within the first days of life of cardiorespiratory failure. A single patient has been kept alive with respiratory assistance for 161 days.

Remarks: Myocardial necrosis, porencephaly, lissencephaly and absent corpus callosum have been described in some patients.

References

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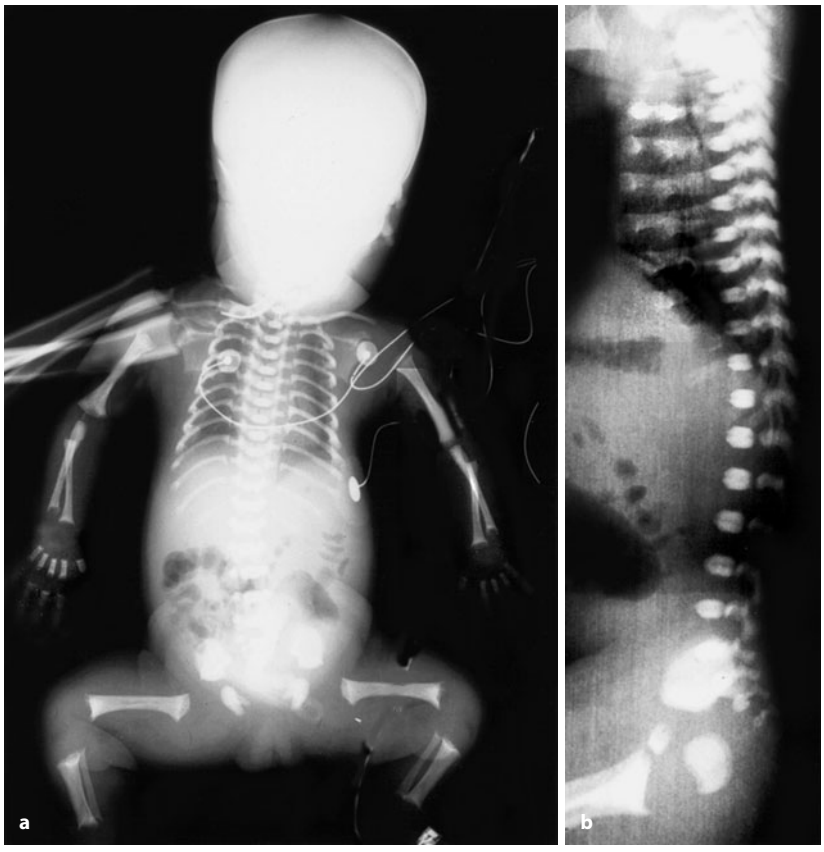

Fig. 3.9. ***Lethal metaphyseal chondrodysplasia, Sedaghatian type***. **a** The ribs are short with splayed posterior ends. The scapulae are reduced in height. The acetabular roofs are broad and horizontal. A lacey appearance of the iliac crest is found in some patients but not well seen here. The tubular bones are mildly shortened but straight and well modeled. The fibulae are relatively long in comparison to the tibiae. Metaphyseal cupping and irregularity are present in the distal femora, tibiae, distal radius and ulna. **b** The vertebral bodies are slightly flattened. Note cupped anterior rib ends (Courtesy Dr. G. Hammersen, Nürnberg)

Achondrogenesis 1A MIM 200600

Synonym: Houston-Harris type of Achondrogenesis.

Major Radiographic Features:
- Poorly ossified skull
- Unossified vertebral bodies
- Short ribs with multiple fractures
- Hypoplastic ilia with horizontal, arched lower margins
- Short, misshapen, often stellate tubular bones with minimal tubulation

Mode of Inheritance: Autosomal recessive.

Molecular Basis: *GMAP-210* encoding a Golgi-microtubule-associated protein.

Prenatal Diagnosis: In the second trimester short limbs are detectable by ultrasound. Hydramnion and Hydrops may be found.

Differential Diagnosis: In *achondrogenesis IB* there are no rib fractures and tubulation of the long bones is completely absent. *Achondrogenesis II* differs by the retained longitudinal axis of the tubular bones and better ossified vertebral bodies. *Hypophosphatasia* does not show the stellate, globular appearance of the tubular bones.

Prognosis: All known patients have been stillborn or died shortly after birth.

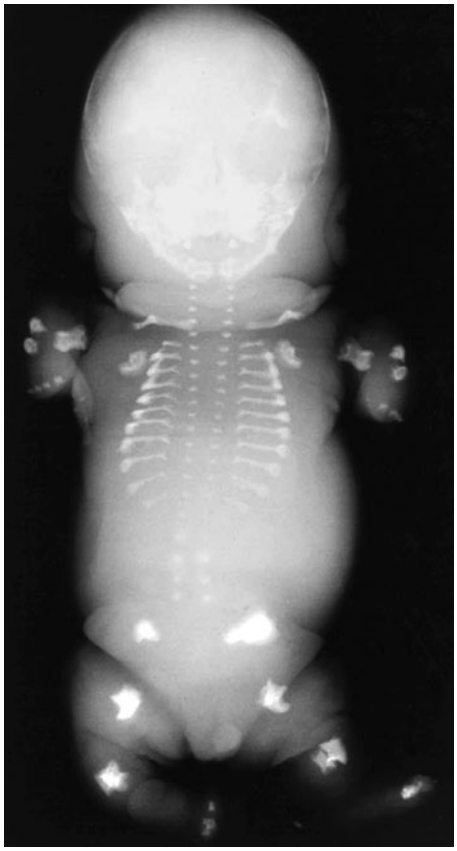

Fig. 3.10. ***Achondrogenesis 1-A*** Stillborn infant , 30 weeks gestation. The calvaria is insufficiently ossified. The ribs are short with splayed ends. Slightly irregular contours in the left 6th and 7th ribs are compatible with multiple fractures that are frequently found in this condition. Vertebral bodies, ischial and pubic bones are not ossified. The lower ilia are not developed. The tubular bones strikingly short, with concave ends, sometimes accentuated by longitudinal spurs extending from their ends. Radius and ulna are seen as small, round bone islands. Ossification of the short tubular bones is severely deficient

References

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Achondrogenesis 1B MIM 600972

Synonym: Achondrogenesis, Fraccaro-(Parenti) type.

Major Radiographic Features:
- Poorly ossified calvaria
- Unossified vertebral bodies
- Short ribs without fractures
- Small ilia with concave medial and inferior margins; unossified pubic and ischial bones
- Globular or stellate long tubular bones lacking axial alignment

Mode of Inheritance: Autosomal recessive.

Molecular Basis: Mutations in the *DTDST* gene encoding the cellular sulfate transporter. Allelic mutations cause atelosteogenesis type II, diastrophic dysplasia and autosomal recessive epiphyseal dysplasia.

Prenatal diagnosis: Sonographic recognition is possible in the second trimster on the basis of short limbs, reduced echogenicity of spine and head, narrow thorax, protuberant abdomen, hydramnios. If the mutation is known from a previously affected sibling, mutational analysis of the *DTDST* gene is possible in fetal cells.

Differential Diagnosis: In *achondrogenesis 1A* longitudinal orientation of the tubular bones is partially preserved and the ribs show multiple fractures. Other differential diagnoses see achondrogenesis IA, p. 112.

Prognosis: Death in utero or within hours after birth.

References

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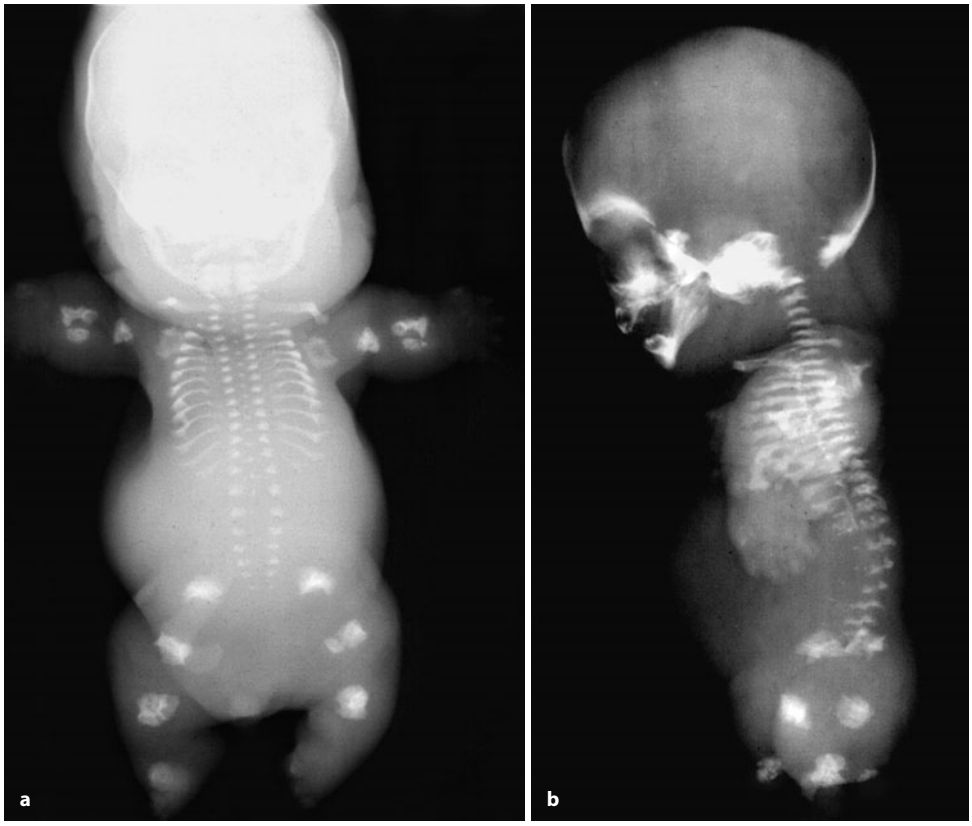

Fig. 3.11. ***Achondrogenesis 1B***, 30 weeks gestation. **a, b** The calvaria is poorly ossified. The ribs are short splayed anterior ends. The scapulae are misshapen. Thin, wafer-like ossification centers are seen in some vertebral bodies of the thoracic spine; the pedicles are well ossified. Only the superior portions of the ilia are mineralized; pubic and ischial bones are not ossified. The long bones are not tubulated and appear as stellate, ragged or nondescript structures

Achondrogenesis Type 2/Hypochondrogenesis MIM 200610

Synonym: Achondrogenesis, Langer-Saldino type.

Major Radiographic Features:

- Absent ossification of the cervical vertebral bodies, severely retarded ossification of the vertebral bodies of the thoracic and lumbar spine; absent ossification of the sacrum
- Barrel-shaped thorax with short ribs
- Small iliac bones with crescent-shaped inner and inferior margins; absent or severely delayed ossification of the pubic and ischial bones
- Very short tubular bones with metaphyseal flare and cupping

Mode of Inheritance: Autosomal dominant.

Molecular Basis: Mutations of the *COL2A1* gene encoding type II collagen molecules.

Prenatal Diagnosis: Short limbs and frequently hydrops are recognized by ultrasound in the second trimester of pregnancy. If the mutation is known from an affected parent, mutation analysis of the *COL2A1* gene can be performed in fetal cells.

Differential Diagnosis: In *achondrogensis 1A* the ribs are thinner, with evidence of multiple fractures, the vertebral bodies are not ossified and the tubular bones are more severely shortened and misshapen. In *achondrogenesis 1B* the vertebral bodies are not ossified and the tubular bones are not longitudinally oriented. *Kniest dysplasia* and *spondyloepiphyseal dysplasia congenita* show slightly better ossification of the vertebral bodies and pelvic bones. The long bones are better tubulated and not as short.

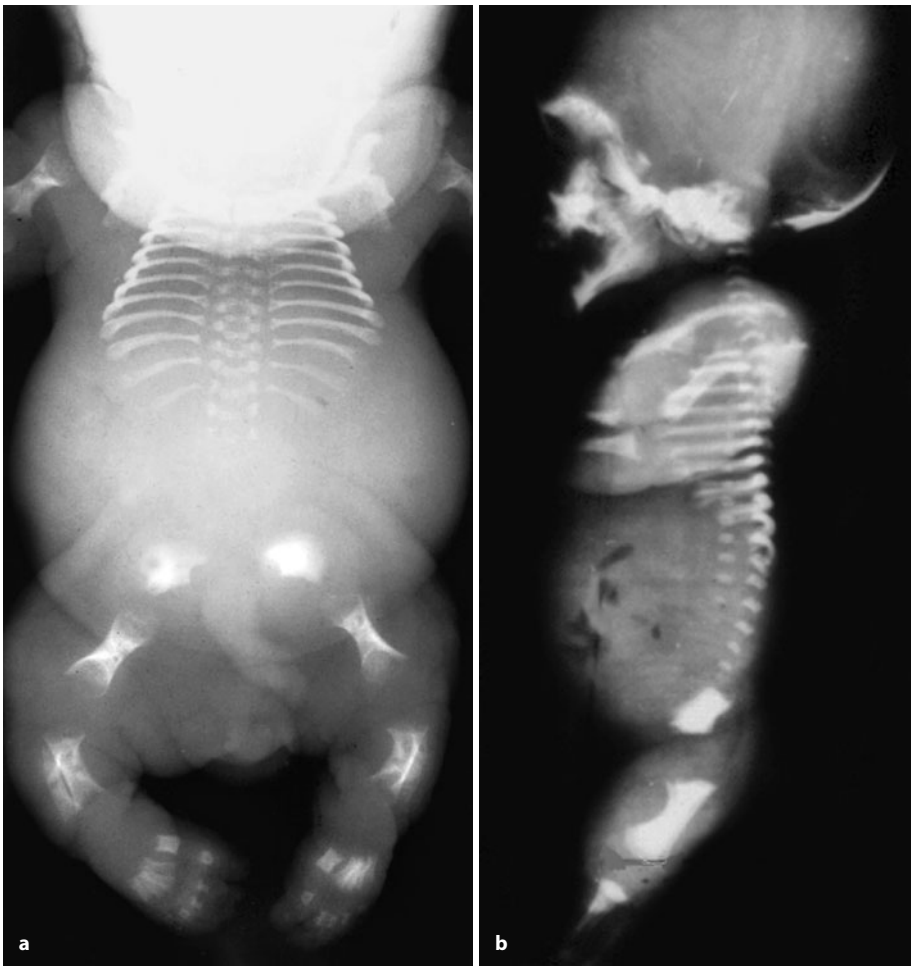

Fig. 3.12. ***Achondrogenesis 2***. **a** The ribs are short and horizontally oriented. Except for the bodies of the thoracic vertebrae and the neural arches of the lower cervical, thoracic and upper lumbar spine the spine is not ossified. There is no ossification of the sacrum, pubic and ischial bones. The ilia are vertically short with concave lower and medial borders. The tubular bones are short and broad with concave metaphyseal margins. **b** Note short ribs and deficient ossification of the vertebrae in the cervical and lumbar spine

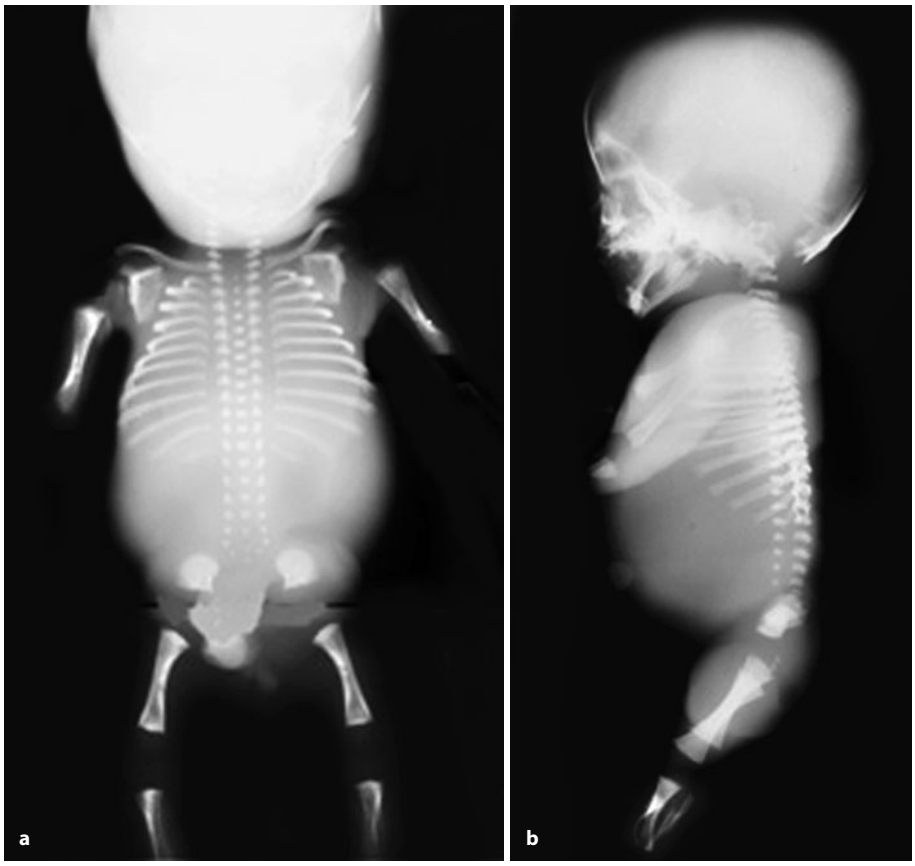

Fig. 3.13. ***Hypochondrogenesis***, 38 weeks gestation. **a, b** The chest is small and broad. Ossification of the truncal skeleton is severely retarded with small ossification centers in the thoracic and lumbar vertebral bodies but absent ossification of the cervical vertebral bodies, sacrum, pubic bones, ischial bones and lower portions of the ilia. The long tubular bones are shortened but well modeled

Prognosis: Affected individuals are usually delivered prematurely. Patients with achondrogenesis II are stillborn or die within a few hours. Children with hypochondrogenesis are usually born alive and may survive with the aid of supportive measures. Depending on the intensity of life support they die within the first days to months from cardiorespiratory failure

Remarks: Achondrogenesis II, hypochondrogenesis, Torrance dysplasia, Kniest dysplasia and spondyloepiphyseal dysplasia congenita are caused by allelic mutations of the same gene encoding type 2 collagen. Although phenotypically they form a continuous spectrum, the nosologic distinction of different entities within the type 2 collagenopathies is justified because of their different prognosis.

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Platyspondylic Dysplasia, Torrance-Luton Type MIM 151210

Major Radiographic Features:
- Varying platyspondyly
- Hypoplasia of the lower ilia, short and broad ischial and pubic bones
- Short and broad tubular bones with splayed and cupped metaphyses

Mode of Inheritance: Autosomal dominant.

Molecular Basis: Mutations in the globular domaine of the COL2A1 gene encoding type 2 collagen

Prenatal Diagnosis: Sonography reveals short limbs and retarded ossification of vertebral bodies.

Differential Diagnosis: In the *thanatophoric dysplasias* the tubular bones are more severely shortened. The femora are bowed in thanatophoric dysplasia I. Cranial abnormalities are common in thanatophoric dysplasia II, less frequent in thanatophoric dysplasia I and have not been described in the Torrance-Luton type of platyspondylic dysplasia. *Achondroplasia* must be differentiated because of its good prognosis. It differs by the milder flattening of the vertebral bodies and the gland-like radiolucent aspect of the upper femoral ends.

Prognosis: Neonatal mortality is increased but at least two females have survived into adulthood and gave birth to two affected children. Their adult height was 127 cm.

Remarks: The original description of the Torrance type of lethal platyspondylic dysplasias showed radiographic overlap with the San Diego type. Later observations showed milder manifestations. The spectrum of manifestations includes the milder Luton variant of lethal chondrodysplasias (Winter et al. 1982) and the nonlethal spondyloperipheral dysplasia. Although the mortality is increased, it is not a lethal disease sensu strictu.

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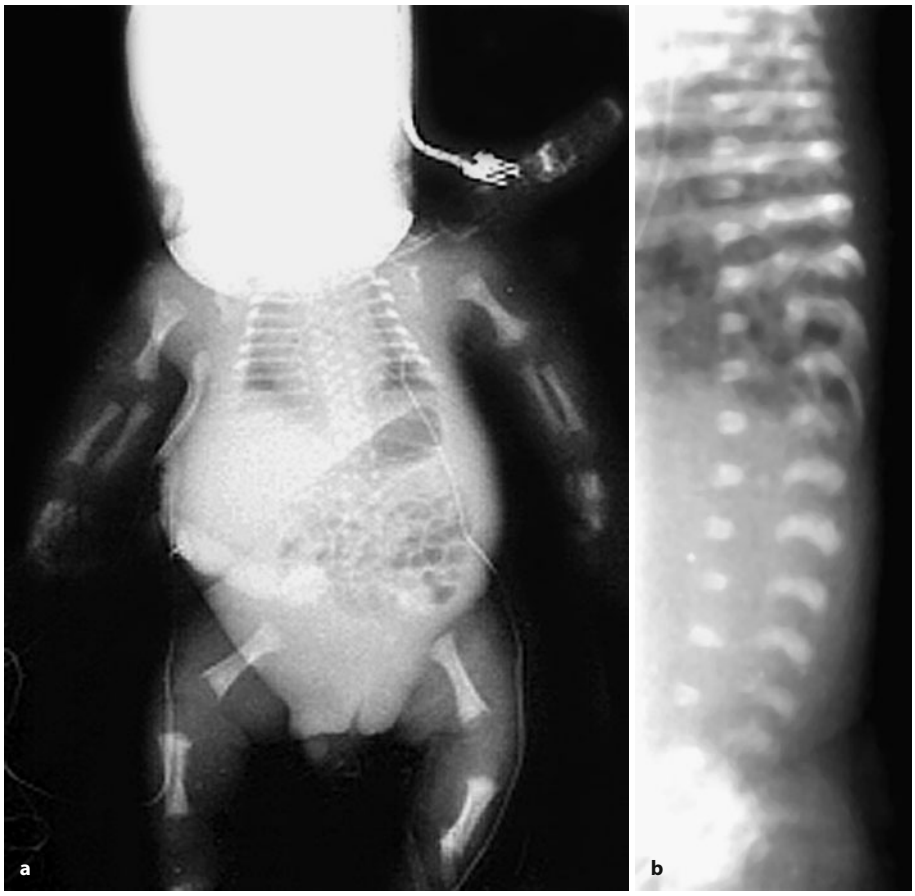

Fig. 3.14. ***Torrance type platyspondylic dysplasia***. Full term newborn. **a** Major abnormalities are the small vertebral bodies, small ilia with horizontal acetabula and downward pointing spurs extending from their medial ends, short and broad tubular bones with slightly concave metaphyseal margins of the distal femora. **b** The vertebral bodies are insufficiently developed with small ossification centers in their anterior portions

Kniest Dysplasia/Spondyloepiphyseal Dysplasia Congenita MIM 156550/183900

Synonym: SED congenita

Major Radiographic Features:
- Flattened, ovoid vertebral bodies, sometimes with coronal clefts
- Small ilia due to hypoplasia of the inferior portions
- Absent ossification of the pubic bones
- Shortened tubular bones; more severe in Kniest dysplasia than in SED congenita
- Dumbbell-shaped femora in Kniest dysplasia

Mode of Inheritance: Autosomal dominant.

Molecular Basis: Mutations of the gene encoding type 2 collagen (Col2A1). Single base mutations, deletion or duplication of part the gene causes SED congenita. In-frame deletions or exon skipping lead to the Kniest phenotype.

Prenatal Diagnosis: Short limbs are detected by sonography. If the mutation is known from an affected parent, mutation analysis of the COL2A1 gene is possible in chorionic villi or amnion cells.

Differential Diagnosis: In *achondrogenesis 2* and *hypochondrogenesis* ossification of the spine and pelvis is more severely retarded, the tubular bones are more severely shortened.

Prognosis: In contrast to newborns with achondrogenesis 2 or hypochondrogenesis survival chances of patients with SED congenita and of most patients with Kniest dysplasia are good.

Remarks: Mutations of the *COL11A2* gene encoding a strand of the trimeric type 11 collagen cause otospondy-

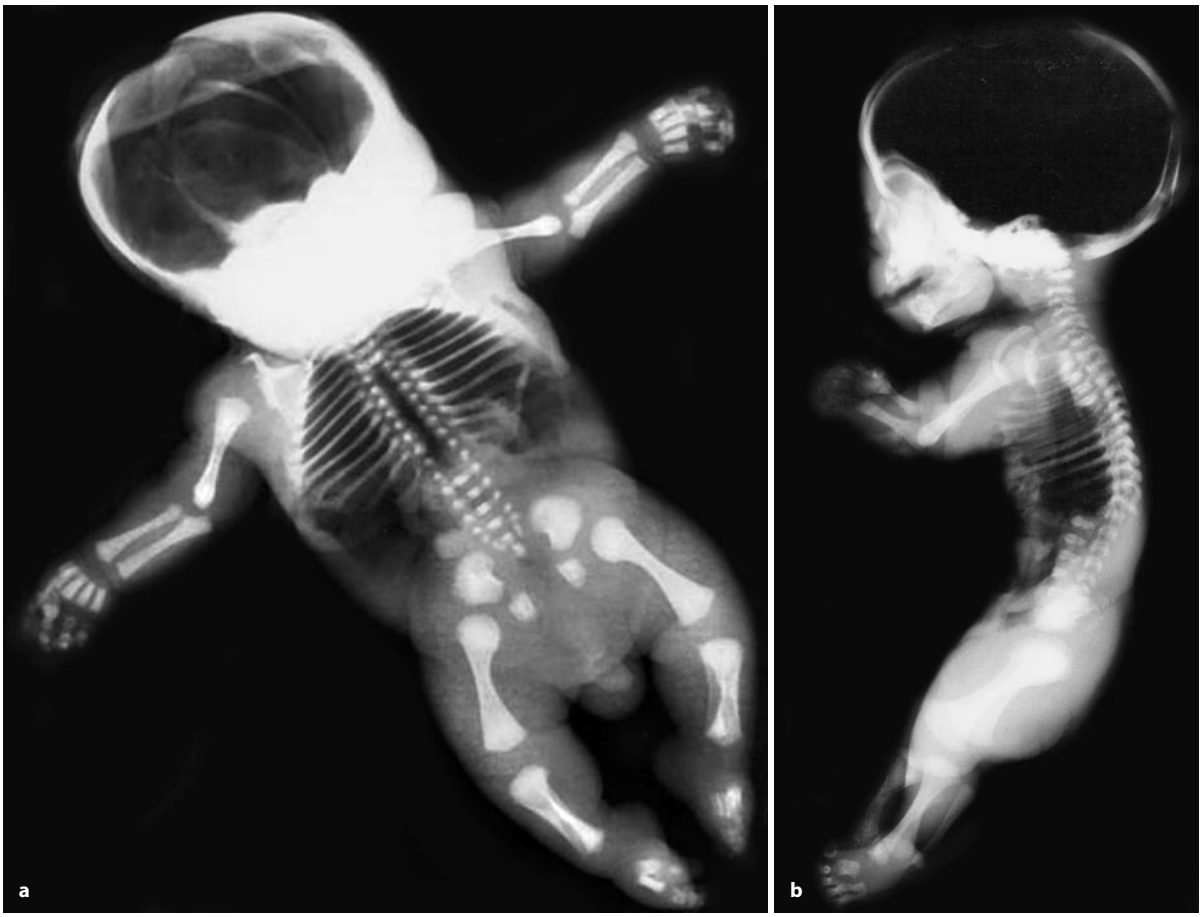

Fig. 3.15. ***Kniest dysplasia***. Stillborn **a** The thorax is short and broad. The lumbar vertebral bodies are flat; the thoracic vertebrae have been removed at autopsy. The pubic bones are not ossified, the ischial bones are short and broad. The tubular bones are short with flared ends. **b** Note coronal clefts of the vertebral bodies. The cervical bodies are not ossified

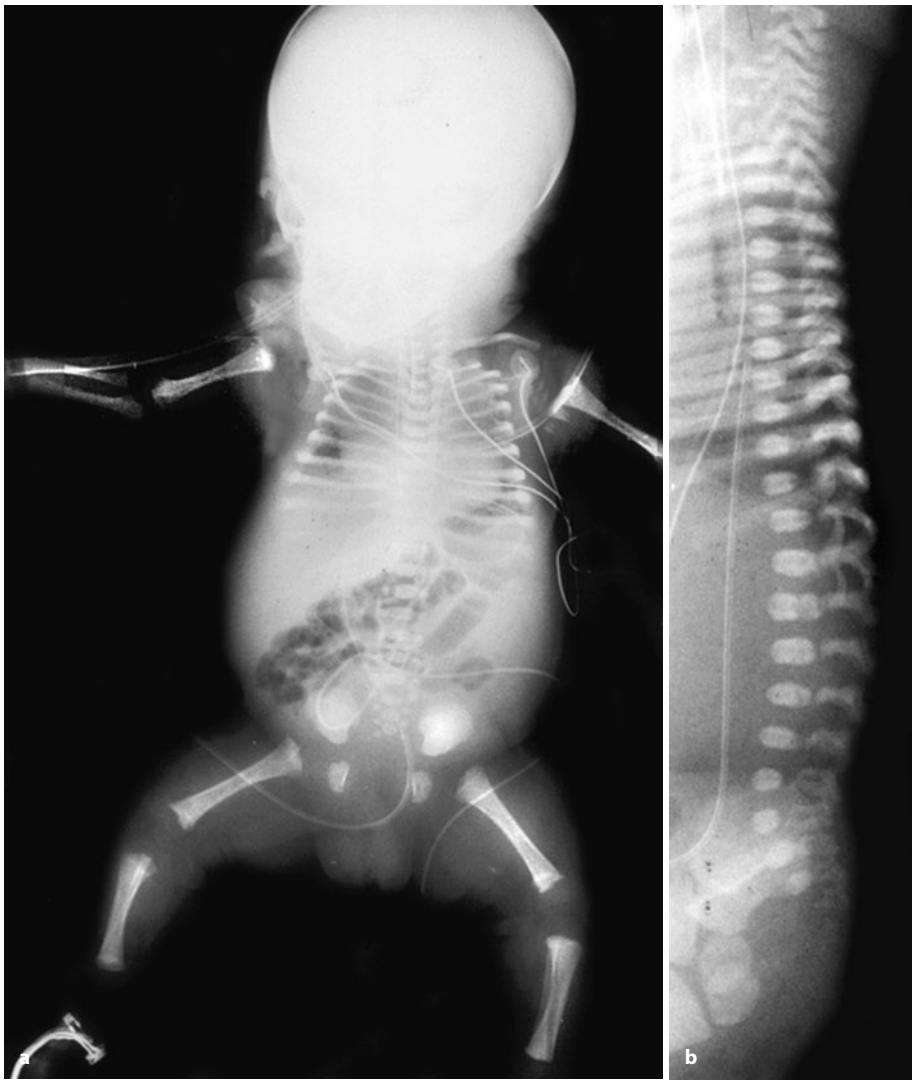

Fig. 3.16 ***Spondyloepiphyseal dysplasia congenita***. **a, b** The chest is small, the vertebral bodies are flat and ovoid. A coronal cleft is seen in L2. There is no ossification of the pubic bones and the tubular bones are shorter than normal. These changes are similar to those in hypochondrogenesis (Fig. 3–14) but less severe

lomegaepiphyseal dysplasia (OSMED) which in the neonate is almost indistinguishable from Kniest dysplasia. Differentiation of the two disorders requires molecular analysis. The nosology of the type 2 collagenopathies is discussed in the chapter on achondrogenesis 2/hypochondrogenesis.

References

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B. Skeletal Dysplasias with Congenital Bowing and Normal Bone Density

Dyssegmental Dysplasia (MIM 224400)

Includes Silverman-Handmaker type, Rolland-Desbuquois type.

Major Radiographic Features:

- Irregularly sized and formed vertebral bodies with single or multiple ossification centers, more severe in the Silverman-Handmaker than in the Rolland-Desbuquois phenotype.
- Small iliac bones; short and thick pubic and ischial bones.
- Shortened, wide, often angulated long tubular bones.

Mode of Inheritance: Autosomal recessive.

Molecular Basis: Severe cases with the Silverman-Handmaker phenotype have been shown to be the expression of a null mutation of the perlecan gene *HSPG2* located on chromosome 1p36.1.–35. Cases with the Rolland-Desbuquois phenotype are allelic variants.

Prenatal Diagnosis: Short, bowed limbs and grossly disorganized vertebral bodies have been recognized at 20 weeks gestation.

Differential Diagnosis: The main feature differentiating the Rolland-Desbuquois phenotype from severe cases with *Kniest dysplasia* is the defective ossification ot the pubic bones in the latter. The skeletal abnormalities in the *Schwartz-Jampel syndrome* are similar but less severe than in dyssegmental dysplasia. Other forms of *congenital bowing of the long bones* are not associated with vertebral segmentation defects.

Prognosis: The prognosis varies with the severity of the bone lesions. Severely affected newborns with the Silverman-Handmaker phenotype are stillborn or die within the first days of life. A single patient has been reported who survived to 8 months of age with marked deficiency, defective hearing and unexplained episodes of hyper-

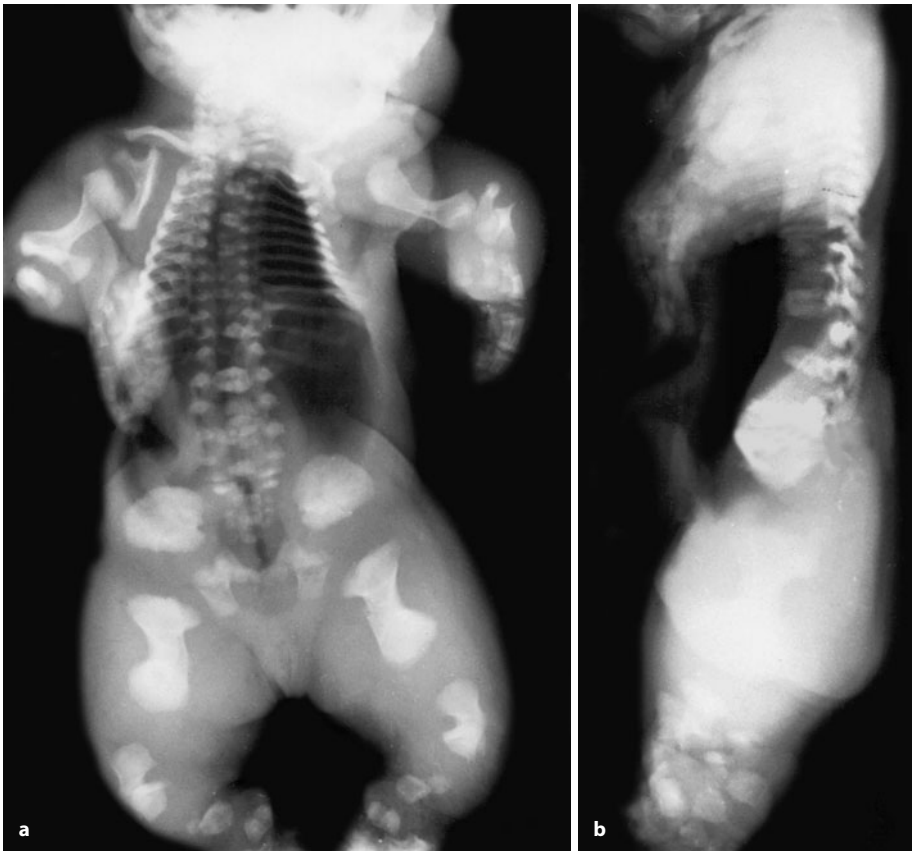

Fig. 3.17. ***Dyssegmenmtal dysplasia****, Silverman-Handmaker type.* **a, b** The vertebral bodies vary in size and shape. Multiple ossification centers are seen in some; other vertebral bodies are not ossified at all. The lower portions of the ilia are not developed; the pubic and ischial bones are broad. The long tubular bones are short and bowed with wide ends

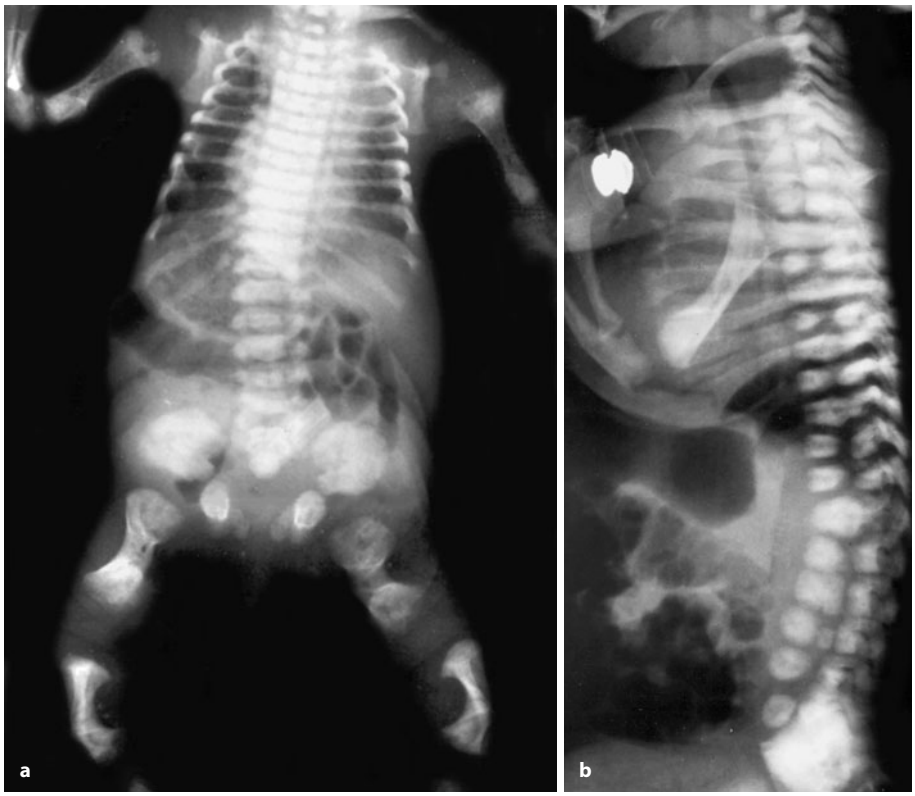

Fig. 3.18 ***Dyssegmental dysplasia****, Rolland-Desbuquois type.* **a, b** The bone changes in this patient are similar but less severe than in the Silverman-Handmaker type (Fig. 3–17). Characteristics seen in both phenotypes are the irregular size and shape of the vertebral bodies, small ilia with wide pubic and ischial bones and the distorted dumbbell shape of the femora. In other patients, femoral and tibial bowing may be less pronounced

thermia. Patients with the less severe Rolland-Desbuquois phenotype may survive to childhood and possibly later.

Remarks: Phenotypically, the Silverman-Handmaker and the Rolland-Desbuquois phenotypes are part of a continuous spectrum.

References

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Schwartz-Jampel Syndrome MIM 255800

Synonym: Myotonic chondrodysplasia, Catel-Hempel syndrome.

Major Radiographic Features:
- Mildly flattened vertebral bodies: coronal clefts
- Flared iliac wings with supra-acetabular lateral notches and wide ischial bones
- Short and bowed femora and tibiae with wide ends

Mode of Inheritance: Autosomal recessive.

Molecular Basis: Mutations of the gene encoding perlecan (HSPG2) on chromosome 1p34-p36.1.

Prenatal Diagnosis: Short and bowed femora may be detected by ultrasound.

Differential Diagnosis: *Kniest dysplasia* may present with coronal clefts of the vertebral bodies and short femora but differs by the retarded ossification of the pubic bones, absence of the supra-acetabular notch and absence of femoral bowing. Grossly irregular ossification of the vertebral bodies is seen in *dyssegmental dysplasia* but not in the Schwartz-Jampel syndrome.

Prognosis: In severely affected infants early feeding and respiratory difficulties have been reported and their prognosis is guarded. Prolonged ventilatory assistance may be needed. Myotonia usually manifests in childhood. Bowing of the long bones (kyphomelia) may persist to an older age and some of the affected children have been misdiagnosed as 'kyphomelic dysplasia'.

Remarks: Dyssegmental dysplasia and Schwartz-Jampel syndrome are part of a continuous spectrum of clinical disorders caused by allelic mutations of the perlecan gene.

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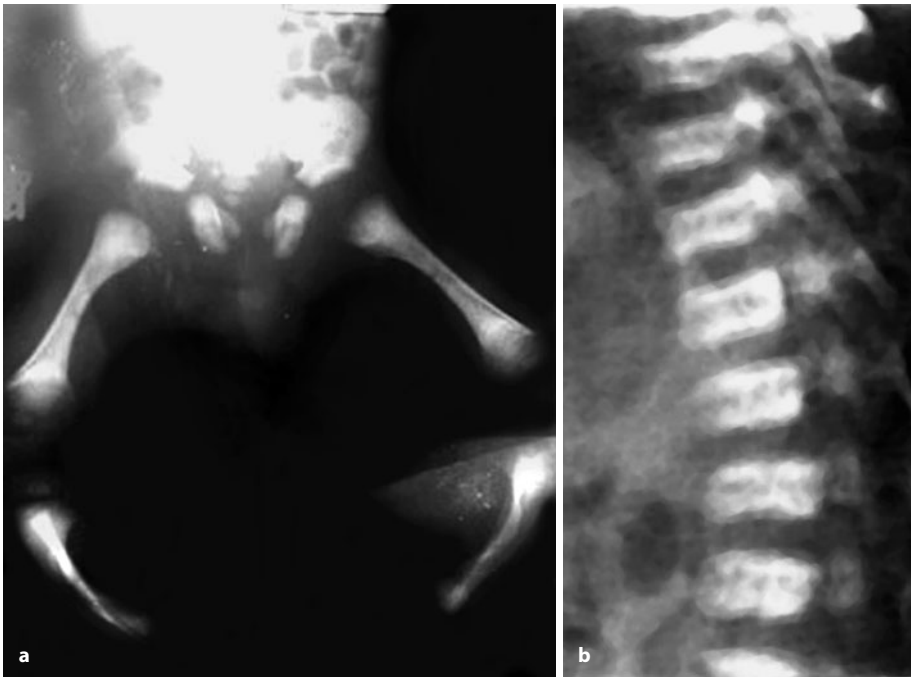

Fig. 3.19. ***Schwartz-Jampel syndrome***. Full term newborn. **a** The iliac bodies are hypoplastic. A lateral supra-acetabular notch is best seen on the right side. The tubular bones are short with wide ends. There is mild bowing of the femora and distinct bowing of the tibiae. **b** The thoracic vertebral bodies are slightly flat. Remnants of coronal clefts are seen in the lower bodies

Cartilage-Hair Hypoplasia MIM 250250

Synonym: Metaphyseal chondrodysplasia, McKusick type, Round femoral inferior epiphysis dysplasia.

Major Radiographic Features:
- Shortened long tubular bones.
- Curved femora, occasionally with well ossified, round distal femoral epiphyses.
- Sometimes short ribs and anterior angulation of the sternum.

Mode of Inheritance: Autosomal recessive.

Molecular Basis: Mutations of the *RMRP* gene located on 9p13 encoding the RNA component of a ribonucleoprotein endoribonuclease.

Prenatal Diagnosis: In late pregnancy short and bowed femora may be detected by ultrasound. If the mutation is known from a sibling, molecular analysis of the *RMRP* gene can be attempted.

Differential Diagnosis: *Campomelic dysplasia* differs by hypoplastic scapulae, hypoplastic thoracic vertebral pedicles and narrow iliac bone. Radio-humeral synostosis and craniosynostosis are present in the *Antley-Bixler* syndrome but not in cartilage-hair-hypoplasia. The *Schwartz-Jampel syndrome* is differentiated by the presence of vertebral anomalies. Bone density and bone thickness are normal in cartilage-hair-hypoplasia and decreased in other forms of *congenital bowing* of the femora.

Prognosis: Neonatal and early development is usually normal. Later complications include impaired immunity, Hirschsprung disease and a higher rate of malignancy. Adult height ranges between 111 cm and 151 cm in males, and between 104 cm and 137 cm in females.

Remarks: Some patients with persistent bowing of the femora have been misnamed 'kyphomelic dysplasia'. Patients with prominent round distal femoral epiphyses have been called 'Glasgow variant".

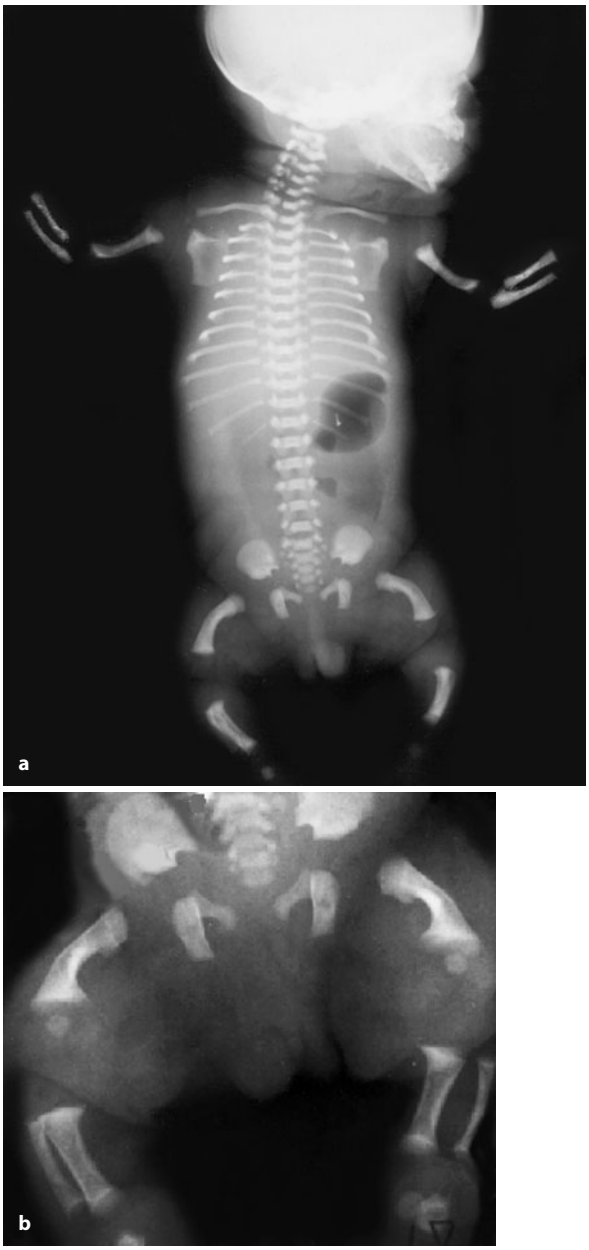

Fig. 3.20. ***Cartilage-hair hypoplasia***. **a** The iliac bones are short and round due to hypoplasia of the iliac bodies. The tubular bones are short with bowing of the femora and, less conspicuously, the other long bones. **b** Large, round distal femoral epiphyses are seen in this full term newborn

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Campomelic Dysplasia MIM 211990, 114290

Synonym: Campomelic syndrome, camptomelic dysplasia. Includes acampomelic campomelic dysplasia.

Major Radiographic Features:

- Hypoplastic scapulae
- Small, bell-shaped chest with eleven pairs of ribs
- Abnormal cervical vertebrae
- Nonmineralized mid-thoracic vertebral pedicles
- Vertically narrow iliac wings, widely spaced vertical ischia, hypoplastic pubic bones
- Dislocated hips
- Bowed femora and tibiae
- Hypoplastic fibulae
- Dislocated radial heads
- Short first metacarpals; short middle phalanges of 2nd through 5th fingers

Mode of Inheritance: Autosomal dominant.

Molecular Basis: Mutations of the *SOX9* gene on chromosome 17p24.3-q25.1 or chromosomal rearrangements outside the coding region. The *SOX9* encoded protein acts as transcription factor regulating chondrogenesis via *COL2A1* and sex determination via *SRY* in early embryogenesis.

Prenatal Diagnosis: Shortened and/or bowed femora and tibiae have been detected at 17 weeks gestation. This finding is nonspecific and, in addition to campomelic dysplasia, occurs in osteogenesis imperfecta, hypophosphatasia, dyssegmental dysplasia, Schwartz-Jampel syndrome, Antley-Bixler syndrome and others. Straight femora due not rule out campomelic syndrome. Hypoplastic scapulae are more specific for campomelic dysplasia.

Differential Diagnosis: Hypoplastic scapulae and ilia are seen in Cousin syndrome and in Kosenow syndrome (Lausch et al 2008). Radiological differentiation of these disorders is difficult in the newborn, and molecular analysis may be needed. Craniosynostosis and humeroradial synostosis characterize the *Antley-Bixler syndrome*. Other disorders with *congenital bowing* and normal bone density do not exhibit hypoplastic scapulae and vertebrae characterizing campomelic dysplasia. Undermineralized bone structure differentiates bent-bone disorders due to congenital osteopenia such as *osteogenesis imperfecta, hypophosphatasia, Stüve-Wiedemann syndrome. Intrauterine hypomobility* with or without *arthrogryposis* is associated with thin, slender bone shafts.

Prognosis: Infantile mortality is increased due to cardiorespiratory insufficiency. Survivors may develop progressive kyphoscoliosis. Mild tibial bowing, hypoplastic scapulae and fibulae have been observed in the mother of a severely affected child with campomelic dysplasia (Lynch et al 1993). Some survivors have been mentally retarded. Patients with a chromosomal rearrangement involving 17q23.3-q25.1 have often a milder phenotype. The degree of femoral bowing is not related to the outcome. Renal anomalies and absent olfactory bulbs and tracts have been found at autopsy.

Remarks: Defective expression of *SRY* causes sex reversal or ambiguous genitalia in approximately three-quarters of chromosomal males with campomelic dysplasia.

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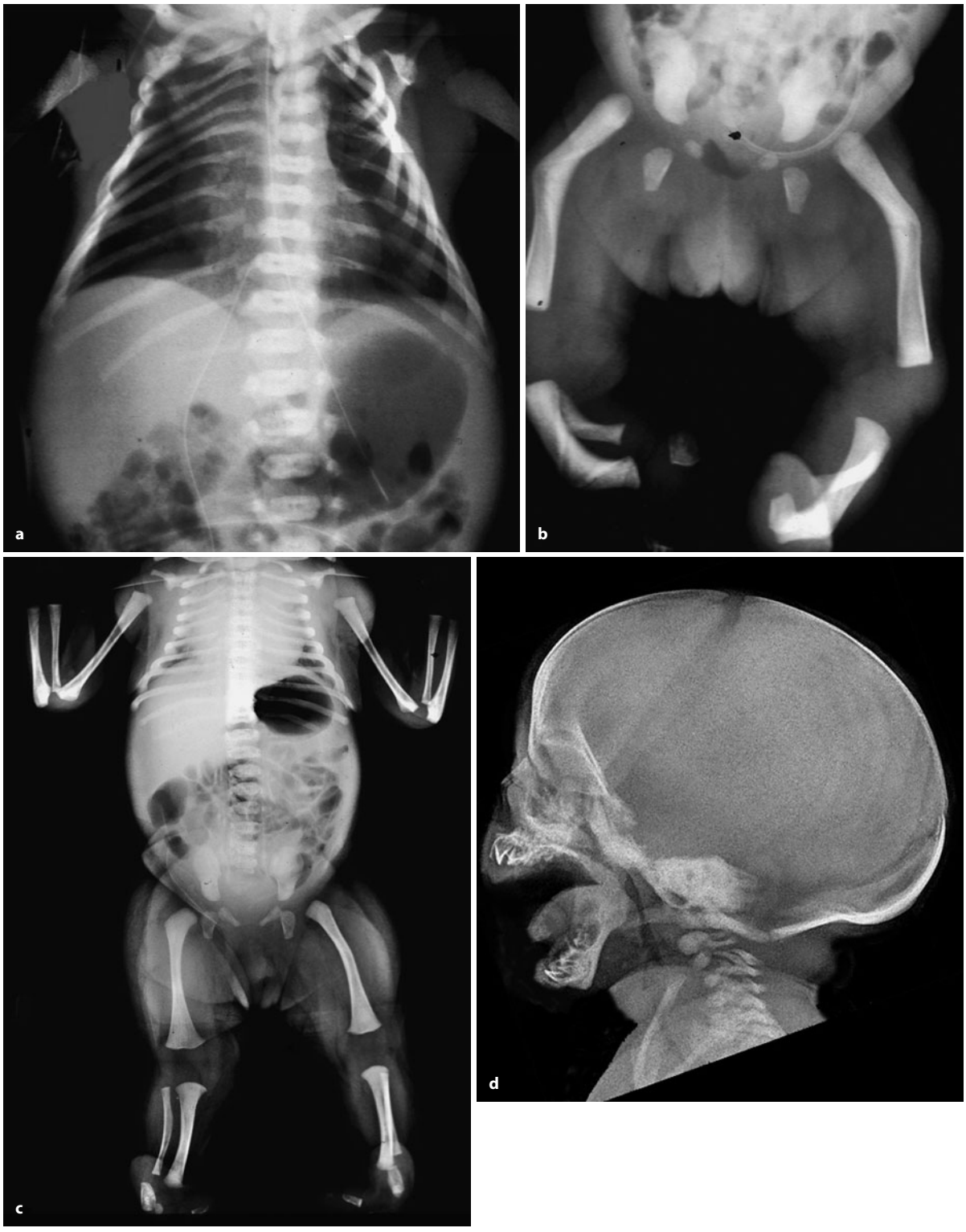


Fig. 3.21. ***Campomelic dysplasia***. **a** The thoracic inlet is small and the chest bell-shaped. Ossification of the ribs is irregular. There are 11 pairs of ribs. A small scapula is seen on the left side, but not on the right. The thoracic vertebral pedicles are not visualized. **b** The iliac wings are narrow, the acetabula poorly ossified, the pubic bones small and the hips dislocated. The femora, tibiae and fibulae are short and bowed; the fibulae are hypoplastic. **c** *Acampomelic campomelic dysplasia*. The bone changes are similar to those in A and B except for the long bones which are not or only slightly bowed. **d** The skull is large and elongated. The cervical vertebral bodies are hypoplastic with ensuing cervical kyphosis

C. Skeletal Dysplasia with Decreased Bone Density, with or without Bowing

Antley-Bixler Syndrome MIM 207410

Synonym: Multple synostosic osteodysgenesis, acrocephalosynankie

Major Radiographic Features:
- Femoral bowing
- Humeroradial synostosis
- Neonatal fractures
- Hypoplastic scapulae
- Craniosynostosis

Mode of Inheritance: Heterogeneous. Autosomal dominant (FGFR3 mutations); Autosomal recessive (POR mutations).

Molecular Basis: Heterozygous mutations of fibroblast growth factor receptor 2 in patients with osseous abnormalities only. Homozygous mutations in P450 Oxidoreductase in patients with osseous abnormalities and signs of defective steroidogenesis.

Prenatal Diagnosis: Bowing of long bones, immobility at the elbows, humeroradial synostosis have been detected by ultrasound in the 17th week of gestation.

Differential Diagnosis: *Campomelic dysplasia* differs by the presence of hypoplastic thoracic pedicles and cervical vertebrae and the absence of neonatal fractures, radiohumeral synostosis and craniosynostosis. Differentiation of the two conditions may be difficult and require molecular analysis of *SOX*9. Hypoplastic scapulae are also found in Cousin syndrome and Kosenow syndrome but not in *other bowing syndromes*. Craniosynostosis, humeroradial synostosis and symphalangism has been observed after longterm use of *fluconazole* in pregnancy. For further differentiation see campomelic dysplasia.

Prognosis: Neonatal mortality is increased, mostly due to respiratory insufficiency associated with choanal stenosis. With intensive medical care, the patients may survive and grow up with normal intellectual development.

Remarks: The term "Antley Bixler syndrome" sensu strictu refers to patients with multiple synostoses only. The disorder combining the Antley-Bixler phenotype with signs of defective steroidogenesis could be called "Antley-Bixler plus syndrome". It is caused by mutations of the electron donor enzyme P450 Oxidoreductase (POR)

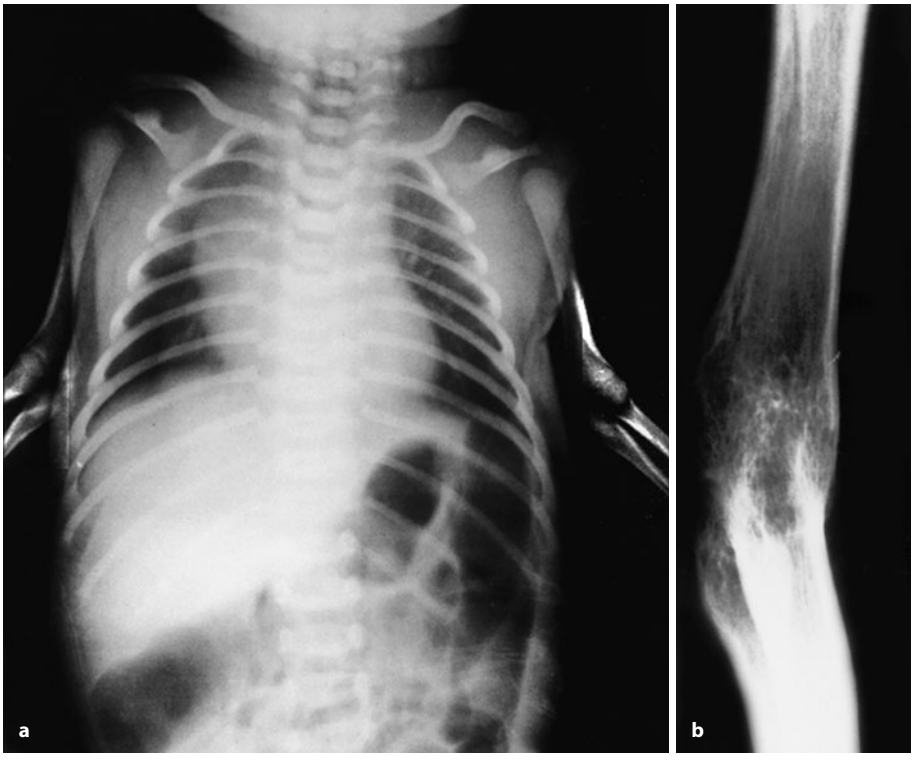
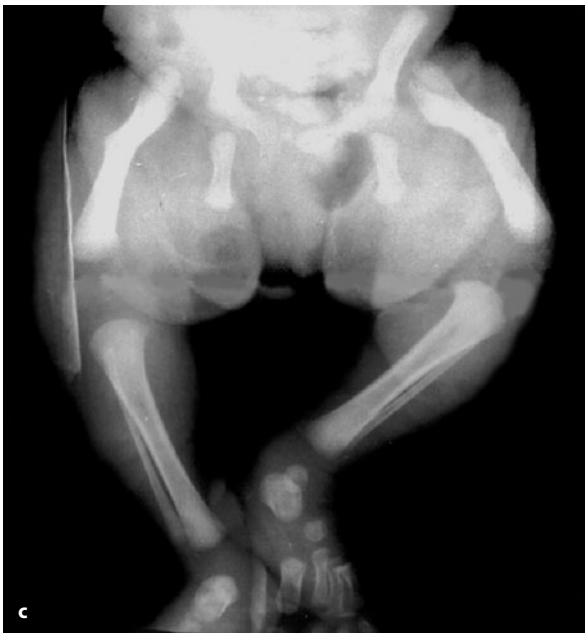
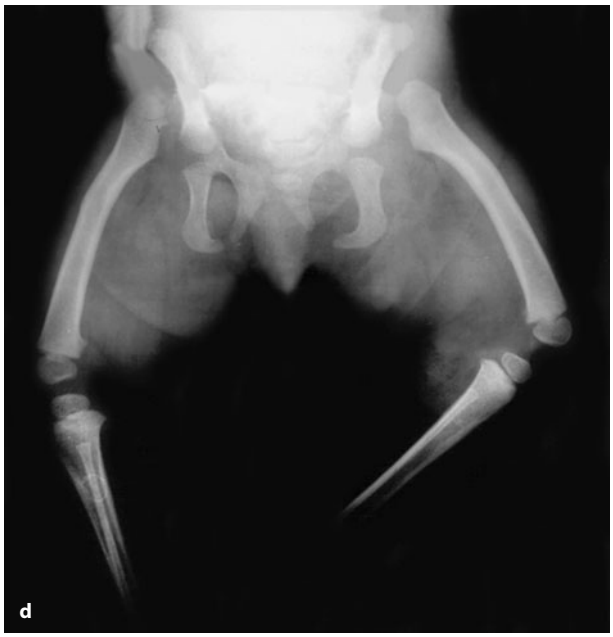


Fig. 3.22. ***Antley-Bixler syndrome***. **a** Newborn. Hypoplastic scapulae are seen. The elbow joints are not well visualized. **b** Same patient, 5 years. Distal humerus, proximal radius and ulna are completely fused





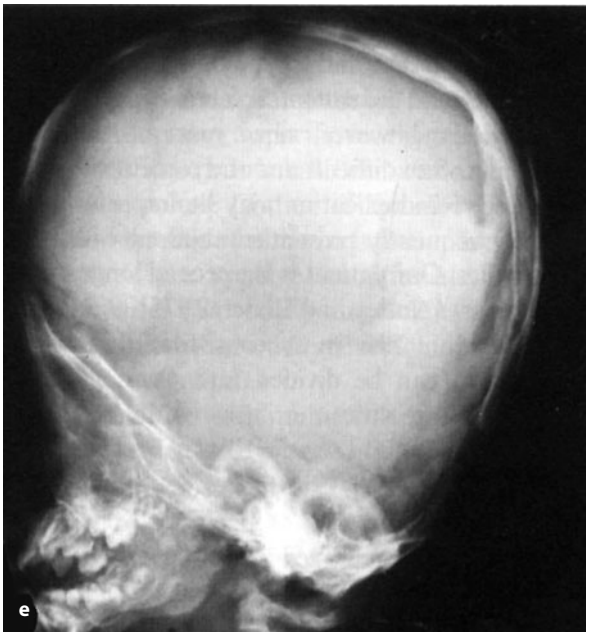


Fig. 3.22. c Newborn The femora are bowed. There are no ossification centers in the knee epiphyses. The hips are dislocated. **d** Same patient, 4 months. Within the first 4 months of life, the femora have spontaneously straightened. The ilia are long and narrow without acetabular fossae. The pubic and ischial bones are well ossified but narrow. **e** Newborn: Brachcephaly due to premature closure of the coronal suture; steep anterior cranial base. (From Escobar et al. Am. J. Med Genet 29: 833, Fig. 3B, by permission of author and John Wiley and sons inc.)

and manifests clinically with ambiguous genitalia such as hypoplastic labia, enlarged clitoris, micropenis. These signs may occur with or without osseous abnormalities. Mildly affected patients may have polcystic ovaries or infertility as the only manifestations. Steroid profiles are abnormal. Glucocorticoid deficiency may occur and require corticoid substitution.

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Osteogenesis Imperfecta MIM 166210, 259420

Major Radiographic Features:

Type 1 Bone Changes
- Deficient calvarial ossification, sometimes Wormian bones
- Generalized osteopenia
- Often thin ribs
- Straight or mildly bowed long bones with occasional fractures

Type 2 Bone Changes
- Deficient calvarial ossification, Wormian bones
- Generalized osteopenia
- Thick appearing ribs with continuous fractures in type II
- Short, thick, crumbled bones

Type 3 Bone Changes
- Deficient calvarial ossification, often without Wormian bones
- Generalized osteopenia
- Thin ribs with discontinuous fractures
- Bowing of the long tubular bones

Mode of Inheritance: Depending on molecular defect autosomal dominant or autosomal recessive (table).

Molecular Basis: Structural defects of type I collagen fibers resulting from mutations of various genes (table)

Prenatal Diagnosis: Ultrasonography in the second trimester shows short, often bowed limbs, fractures and increased nuchal translucency. Biochemical studies may show altered mobility of defective type I procollagen obtained from chorionic villi

Differential Diagnosis: Reduced bone density is nonspecific and, together with bowing of the long tubular bones, occurs many conditions. The *Bruck syndrome* resembles mild forms of osteogenesis imperfecta but is characterized by the presence of neonat joint contractures. Tongue-like metaphyseal ossification are found in *hypophosphatasia* and wide, translucent shafts of the long bones in the *Stüve-Wiedemann syndrome. Geroderma osteodysplastica*, a rare disorder manifesting at birth with osteopenia, fractures and wormian bones, is differentiated by the presence of wrinkled skin, sagging cheeks and dislocated hips. Neonatal fractures also occur in disorders with *thin diaphyses* including the various forms of *arthrogryposis.*, Preserved mineralization and the presence of joint contractures allow to differentiate these disorder. The normal bone structure also differentiates other forms of *congenital bowing* including *campomelic dysplasia, cartilage hair hypoplasia, dyssegmental dysplasias, Schwartz-Jampel syndrome, Antley-Bixler syndrome.*

Prognosis: Most patients with the more severe type 2 (thick bone type) are stillborn or die within a few weeks after birth. Early mortality is also increased patients with type 3 bone changes, but less severely affected patients may survive to adulthood. To some extent the individual prognosis can be predicted from a score based on the type and severity of bone changes (Spranger et al 1982).

Remarks: The classification of the radiographic abnormalities into three categories parallels, but is not identical with the clinical/molecular typology in table 23.1. Type 2 bone changes are seen in type II osteogenesis imperfecta, whereas type 1 and 3 bone changes are variably found in the other clinically and/or molecularly defined disorders of table 23.1. Due to continuing fractures after birth, the appearance of the long bones can change within the first months of life from the thin, bowed diaphyses in type 3 to the thick tubular bones seen in newborns with type 2 bone changes.

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Table 3.1. Clinical/molecular classification of osteogenesis imperfecta

I	AD	*COL1A1/A2*	Type 1 collagen	Type 1 bone changes with neonatal fractures, osteopenia, Wormian bones bowing of long bones
II	AD	*COL1A1/A2*	Type 1 collagen	Type 2 bone changes with numerous fractures, beaded ribs, crumpled long bones, Wormian bones, mostly lethal
III	AD	*COL1A1A2*	Type 1 collagen	Type 3 bone changes with fractures, thin, deformed long bones, discontinuous rib fractures, Wormian bones
IV	AD	*COL1A1/A2*	Type 1 collagen	Varying type 1 or type 3 changes
V	AD	*?*		Mostly type 1 bone changes
VI	?	*?*		Type 1 bone changes
VII	AR	*CRTPAP*	Cartilage-associated protein	Mostly type 3 bone changes, sometimes mild
VIII	AR	*LEPRE1*	Prolyl-3-hydroxylase	Mostly type3 bone changes
IX	AR	*PBIB*	Peptidyl-prolyl-isomerase	Mostly type 3 bone changes

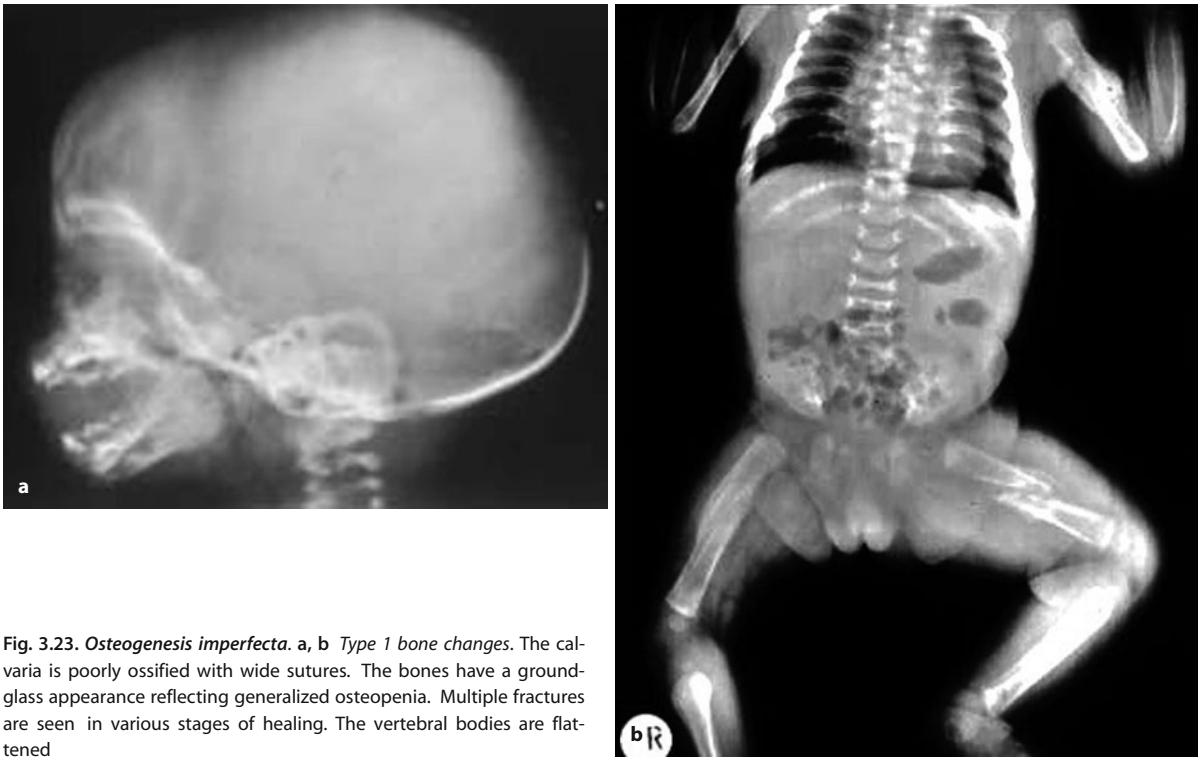

Fig. 3.23. ***Osteogenesis imperfecta***. **a, b** *Type 1 bone changes*. The calvaria is poorly ossified with wide sutures. The bones have a ground-glass appearance reflecting generalized osteopenia. Multiple fractures are seen in various stages of healing. The vertebral bodies are flattened

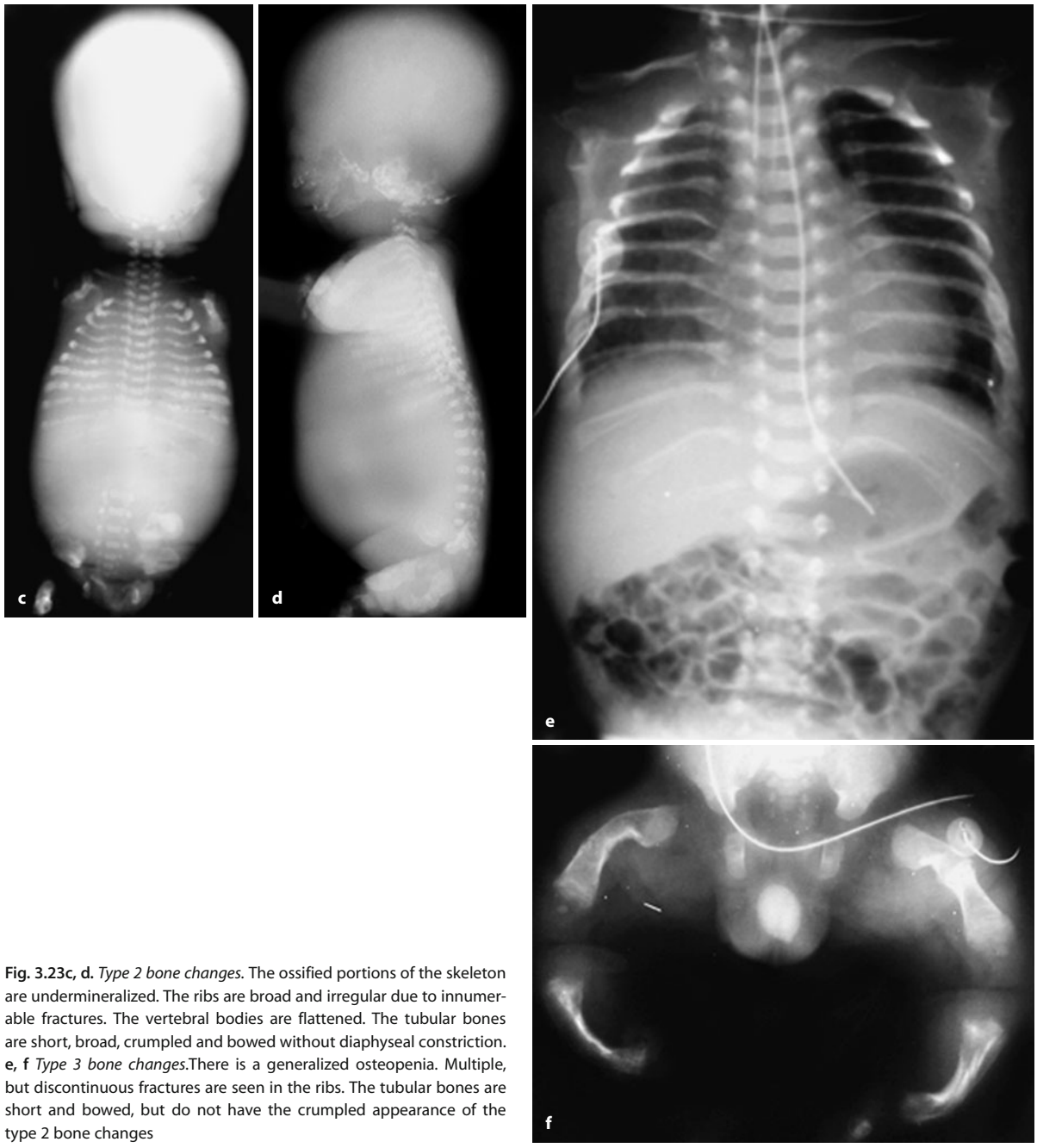

Fig. 3.23c, d. *Type 2 bone changes.* The ossified portions of the skeleton are undermineralized. The ribs are broad and irregular due to innumerable fractures. The vertebral bodies are flattened. The tubular bones are short, broad, crumpled and bowed without diaphyseal constriction. **e, f** *Type 3 bone changes.*There is a generalized osteopenia. Multiple, but discontinuous fractures are seen in the ribs. The tubular bones are short and bowed, but do not have the crumpled appearance of the type 2 bone changes

Infantile Hypophosphatasia MIM 241500, 171760

Major Radiographic Features:

- Absent ossification of major portions of the skull
- Poor ossification of the vertebrae; small scapulae and pelvic bones
- Short, thin ribs and tubular bones; absent ossification of whole bones
- Metaphyseal ossification defects reaching far into the diaphyses
- Occasionally bone spurs extending from the midshafts of long tubular bones (Bowdler spurs)

Mode of Inheritance: Autosomal recessive.

Molecular Basis: Mutations of the *TNSALP* gene located on chromosome 1p36.1-p34 encoding the tissue-nonspecific alkaline phosphatase. Compound heterozygocity or homozygocity of mutated *TNSALP* genes results in infantile hypophosphatasia. Mutations of the *TNSALP* gene may express in the heterozygous state and lead to the milder manifestations of childhood or adult hypophosphatasia, with autosomal dominant inheritance.

Prenatal Diagnosis: Ultrasonography may reveal absent ossification of the calvaria, bowed legs and increased nuchal translucency at 12 to 14 weeks gestation. An affected fetus may be identified by determination of alkaline phosphatase activity in chorionic villi, culture amniotic cells or fetal blood obtained by chordocentesis. If the TNSALP mutation is known from a previous affected child, mutational analysis in chorionic villi is possible.

Differential Diagnosis: *Osteogenesis imperfecta* differs by the presence of rib fractures and absence of metaphyseal lesions. Various forms of *achondrogenesis* are differentiated by the aspect of the tubular bones which are short and thick, rather than thin. The metaphyseal lesions in the *Sedaghatian type of lethal chondrodysplasias* are not associated with the severe demineralization characterizing hypophosphatasia. Bowing of the long bones, Bowdler spurs and low alkaline phosphatase have been observed in *cleidocranial dysplasia.* However, the clavicles are hypoplastic and undermineralization is less severe in cleidocranial dysplasia than in infantile hypophosphatasia.

Prognosis: Severe infantile hypophosphatasia is lethal, mostly due to respiratory compromise, failure to thrive and other signs of hypercalcemia; sometimes convulsions. Spontaneous pre- and postnatal improvement has been reported (Stevenson), as well as postnatal improvement after engraftment of donor bone fragments , cultured osteoblasts and allogeneic mesenchymal stem cells (Cahill).

Remarks: Diagnostic aids in newborns with suggested hypophosphatasia are the low activity of serum alkaline phosphatase, elevated urinary excretion of phosphoethanolamine and elevated pasma concentration of pyridoxal 5' phosphate. Serum alkaline phosphatase activity may be low in the parents.

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(Fig. 3.24 see p. 132)

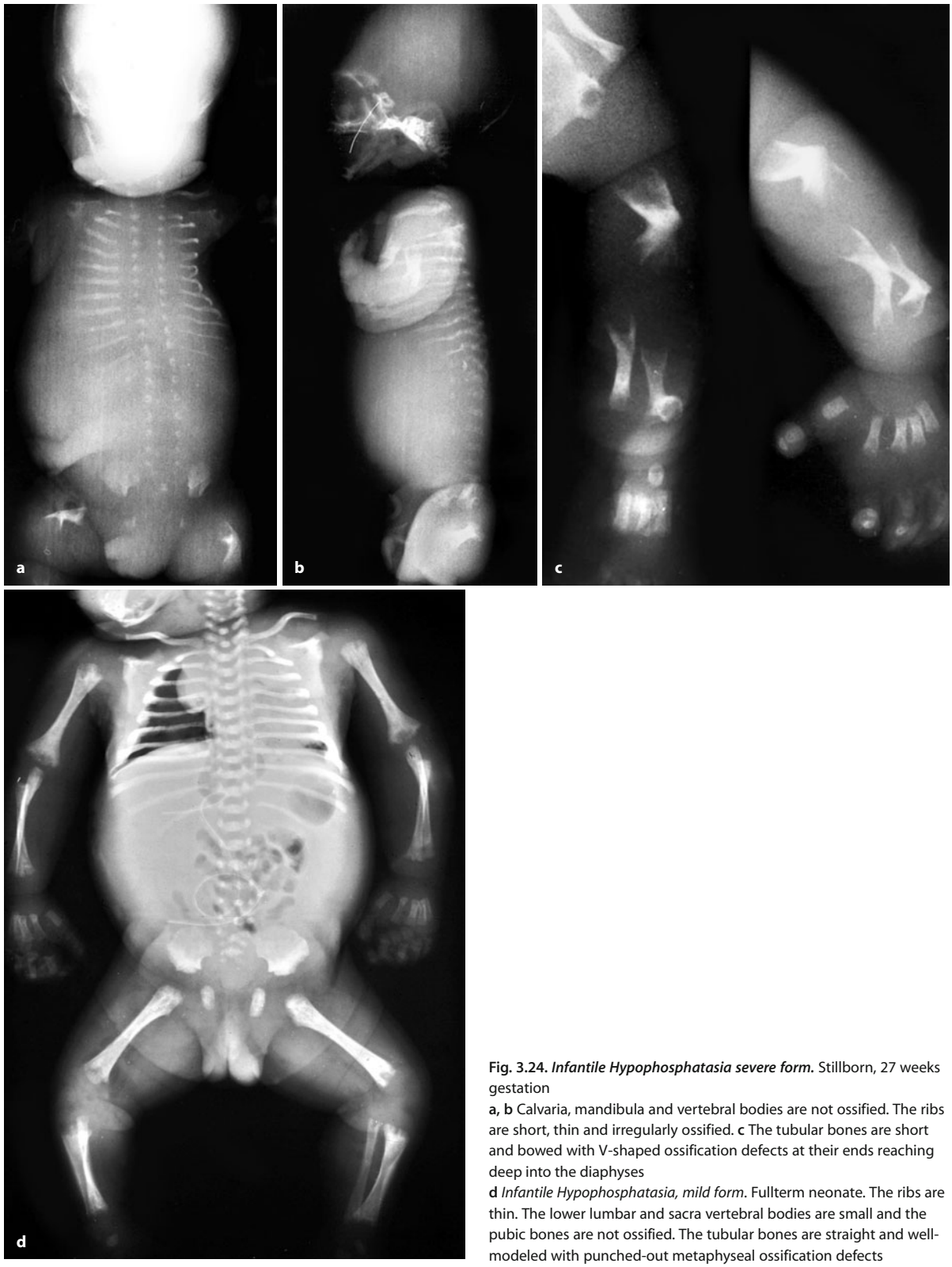

Fig. 3.24. ***Infantile Hypophosphatasia severe form.*** Stillborn, 27 weeks gestation
a, b Calvaria, mandibula and vertebral bodies are not ossified. The ribs are short, thin and irregularly ossified. **c** The tubular bones are short and bowed with V-shaped ossification defects at their ends reaching deep into the diaphyses
d *Infantile Hypophosphatasia, mild form*. Fullterm neonate. The ribs are thin. The lower lumbar and sacra vertebral bodies are small and the pubic bones are not ossified. The tubular bones are straight and well-modeled with punched-out metaphyseal ossification defects

Jansen Metaphyseal Dysplasia MIM 156400

Synonym: Metaphyseal chondrodysplasia, Murk Jansen type.

Major Radiographic Features:
- Generalized demineralization, occasionally fractures
- Splayed ribs ends
- Metaphyseal cupping and fraying of tubular bones

Mode of Inheritance: Autosomal dominant.

Molecular Basis: Mutations of *PTHR1* gene located on chromosome 3p22-p22.1 resulting in a constitutive activation of the receptor for the parathyroid hormone/parathyroid–hormone-related protein (PTHR1).

Prenatal Diagnosis: Affected children may be normal at birth and not be recognized by fetal ultrasound. Short limbs and defective calvarial ossification may be seen in others. In familial cases, molecular analysis may be attempted.

Differential Diagnosis: In *hypophosphatasia* the metaphyseal defects are more regular and the undermineralization is usually more severe. *Infantile rickets* are excluded by low calcium and elevated alkaline phosphatase. Cortical erosion, increased subperiosteal bone formation and metaphyseal irregularities occur in isolated *neonatal hyperparathyroidism* and in hyperparathyroidism associated with *mucolipidosis II*. Biochemical tests may be needed to rule out these conditions. In *Sedaghatian metaphyseal dysplasia* bone mineralization is not defective.

Prognosis: Life expectancy and mental development are normal.

Remarks: Absence of a functional receptor for PTH/PTHR1 receptor results in Blomstrand dysplasia.

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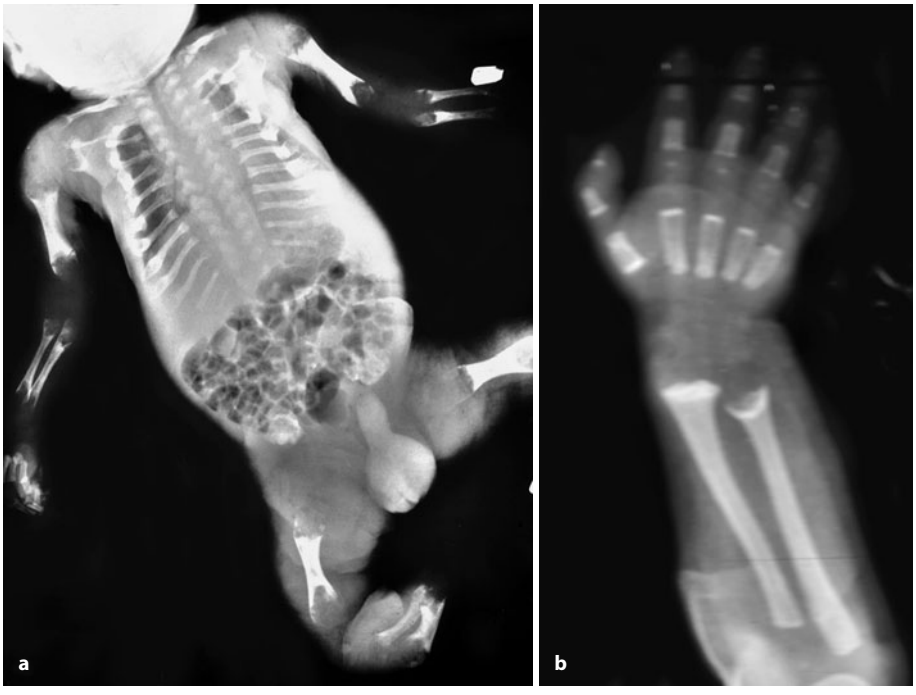

Fig. 3.25. ***Jansen type of metaphyseal dysplasia, 36 weeks gestation***
a, b The tubular bones and ribs are short with large, relatively uniform hollowed-out metaphyseal lesions. Pubic and ischial bones are not ossified. Ossification of the vertebral bodies is defective. Cortical bone erosion and excessive subperiosteal bone formation are not present in this patient

Stüve-Wiedemann Syndrome MIM 601559

Synonym: Schwartz-Jampel syndrome, type 2

Major Radiographic Features:
- Bowing of the long tubular bones with internal cortical thickening
- Generalized rarefaction
- Enlarged, radiolucent metaphyses

Mode of Inheritance: Autosomal recessive.

Molecular basis: Mutations of *LIFR* encoding the leukemia inhibitory factor receptor.

Prenatal Diagnosis: (Nonspecific) bowing of the long bones has been detected by ultrasound in the 22nd week of gestation.

Differential Diagnosis: Bowing of the long bones is nonspecific. One of the bowing disorders without osteopenia (see *campomelic dysplasia*) is the *Schwartz-Jampel syndrome* which is clinically and radiologically similar to the Stüve-Wiedemann syndrome but, in addition to the more normal bone structure, differs by the presence of flattened vertebral bodies. The various forms of *osteogenesis imperfecta* are associated with defectivee calvarial ossification, rib fractures and fractures of the tubular bones. Severely deficient ossification and punched-out metaphyseal lesions characterize *hypophosphatasia*.

Prognosis: Most patients die in infancy failing to thrive and exhibiting recurrent episodes of unexplained fever. Patients have been described to survive into mid-childhood with progressing bowing, spinal deformities and neurological symptoms including temperature instability, reduced pain sensation, absent corneal and patellar reflexes. Mentality was normal.

Remarks: In spite of some clinical and osseous similarities, the Schwartz-Jampel syndrome and Stüve-Wiedemann syndrome are distinct genetic disorders.

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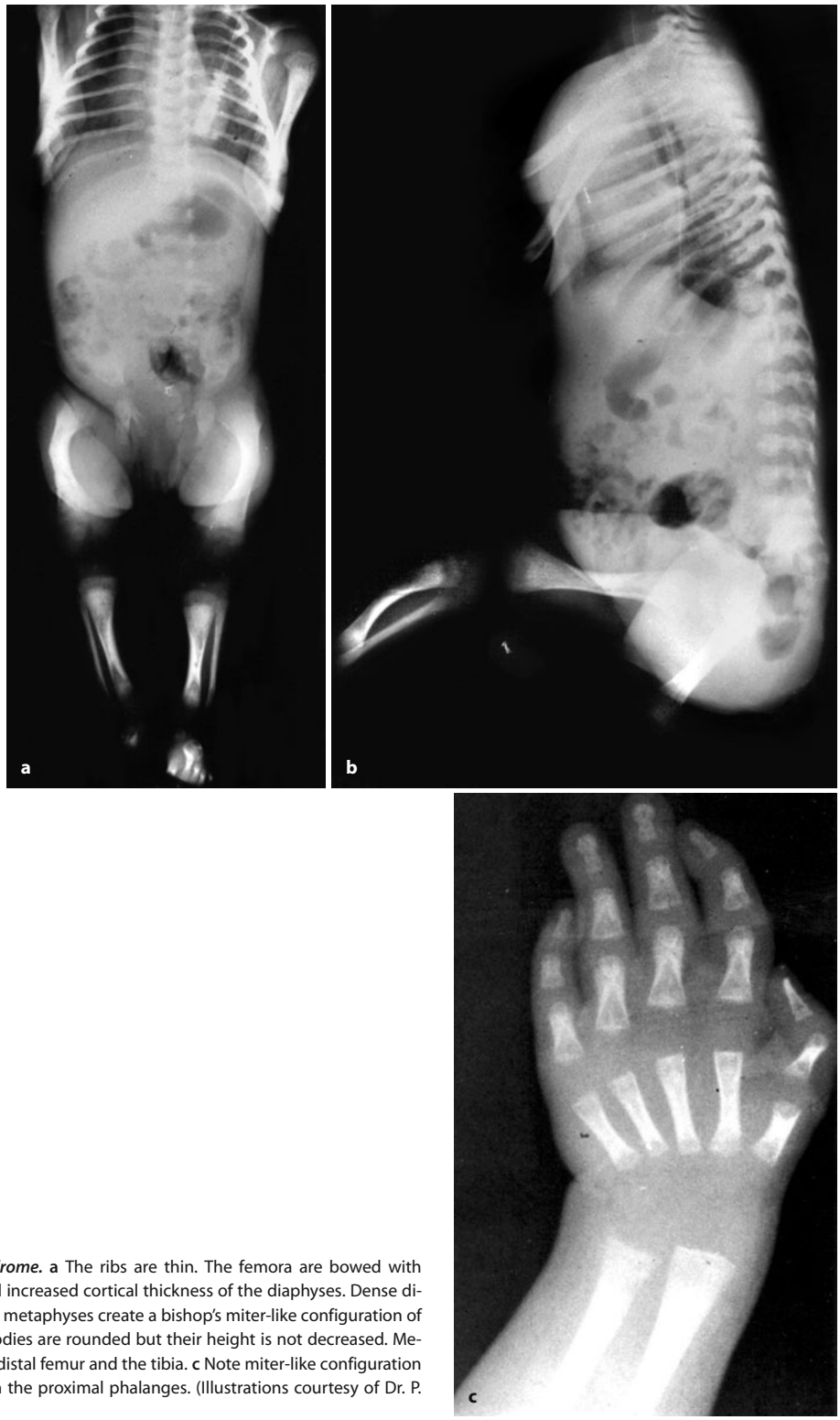

Fig. 3.26. ***Stüve-Wiedemann syndrome.*** **a** The ribs are thin. The femora are bowed with wide, radiolucent metaphyses and increased cortical thickness of the diaphyses. Dense diaphyses and widened, radiolucent metaphyses create a bishop's miter-like configuration of the bone ends. **b** The vertebral bodies are rounded but their height is not decreased. Metaphyseal widening is seen in the distal femur and the tibia. **c** Note miter-like configuration of the tubular bones, best seen in the proximal phalanges. (Illustrations courtesy of Dr. P. Meinecke, Hamburg)

Oto-palato-digital Syndrome Type II MIM 304120

Synonym: OPD-II; Cranio-oro-digital syndrome.

Major Radiographic Features:
- Poorly ossified calvaria with dense skull base and prominent supraorbital ridges
- Thin, sinuous ribs
- Bowed long tubular bones; sometimes fibula a/hypoplasia
- Short, squared, irregularly formed short tubular bones; often a/hypoplasia of the first and second digits

Mode of Inheritance: X-linked dominant, with severe expression in males, mostly mild or minimal in females.

Molecular Basis: Gain of function mutations of *FLNA* encoding filamin A, a protein regulating the actin cytoskeleton.

Prenatal Diagnosis: Bowed tubular bones, small chest and/or boy wall defects are found by sonography.

Differential Diagnosis: OPD-II shows considerable overlap with *OPD-I* and *Melnick-Needles syndrome* but differs by the more severe bone changes and early lethality (see remarks). Multiple dislocations are more common in the *Larsen syndrome* than in OPD-II. OPD is X-linked, the Larsen syndrome autosomal dominant. In the *Yunis-Varon syndrome* the tubular bones are thin but not bowed and the clavicles are hypoplastic or absent. Broad, squared metacarpals and phalanges are seen in mile expressions of *atelosteogenesis*, which differ by the distal hypoplasia of the femora and humeri and the absence of bowing deformities. *Campomelic dysplasia* and *other bowing syndromes without osteopenia* are differentiated by their milder manifestations, notably their more normal ribs and short tubular bones.

Prognosis: The prognosis varies depending on the severity of the clinical manifestations. Lethality is increased due to respiratory insufficiency and associated rare malformations including tracheal stenosis, hydrocephaly, cardiac, ventral wall or neural tube defects.

Remarks: OPD-II is at the severe end of a clinical spectrum including OPD-I, the Melnick-Needles syndrome and frontometaphyseal dysplasia, all of which are caused by allelic mutations of the *FNLA* gene leading to varying degrees of up-regulation of filamin and ensuing abnormalities of the cytoskeleton.

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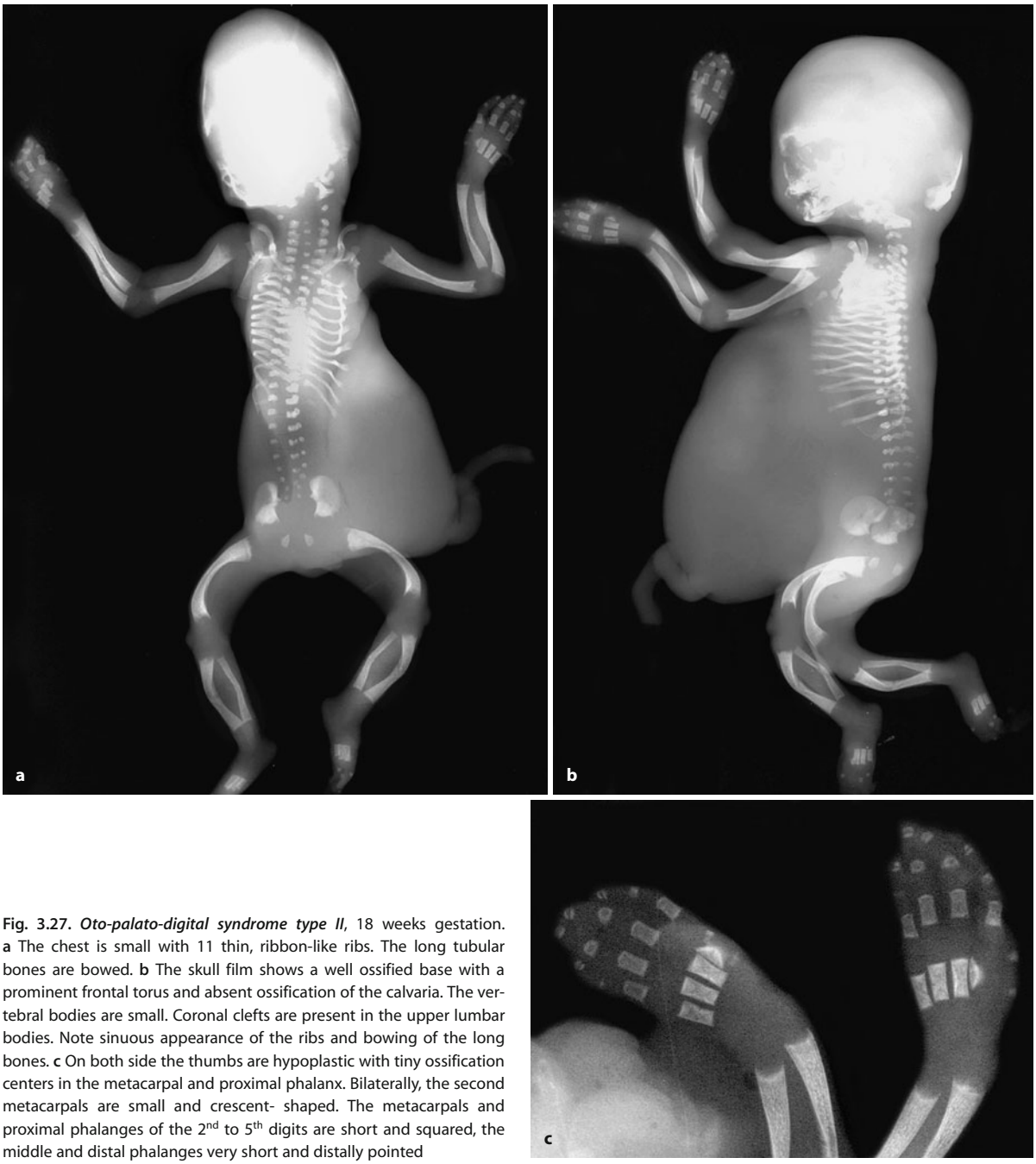

Fig. 3.27. ***Oto-palato-digital syndrome type II***, 18 weeks gestation. **a** The chest is small with 11 thin, ribbon-like ribs. The long tubular bones are bowed. **b** The skull film shows a well ossified base with a prominent frontal torus and absent ossification of the calvaria. The vertebral bodies are small. Coronal clefts are present in the upper lumbar bodies. Note sinuous appearance of the ribs and bowing of the long bones. **c** On both side the thumbs are hypoplastic with tiny ossification centers in the metacarpal and proximal phalanx. Bilaterally, the second metacarpals are small and crescent- shaped. The metacarpals and proximal phalanges of the 2nd to 5th digits are short and squared, the middle and distal phalanges very short and distally pointed

D. Skeletal Dysplasias with Slender Tubular Bones

Fetal a/Hypokinesia Sequence MI 208150, 300073

Synonyms: Includes Pena-Shokeir syndrome, arthrogryposes.

Major Radiographic Features:

- Thin ribs
- Thin tubular bones without metaphyseal enlargement
- Often fractures

Etiopathogenesis: Intrauterine mobility of the fetus may be impeded by numerous genetic and nongenetic factors. Causes limiting fetal mobility fall into six categories (modified from Hall 2002):

1. Neuropathic processes, central or peripheral.
2. Myopathic processes including congenital myopathies.
3. Intrauterine exposure to immobilizing substances including curare, haloperidol.
4. Maternal illness including infections and compromise of blood supply to the fetus.
5. Connective tissue or skin diseases restricting joint mobility.
6. External limitation of space including oligohydramnios, twinning, abnormal uterus.

Restriction of fetal movement for extended periods results in a nonspecific clinical phenotype encompassing multiple joint contractures, pterygia, micrognathia, pulmonary hypoplasia, short umbilical cord and growth retardation. If the hypomobility is caused by decreased fetal muscle activity (categories 1–4), bone modeling and periosteal bone apposition are decreased, and ribs and tubular bones remain thin. If the intrauterine muscle stress remains normal (categories 5,6), such as in the Potter sequence and other disorders associated with oligohydramnios, the ribs and tubular bones develop normally.

Prenatal Diagnosis: Decreased intrauterine mobility may be detected in the 2nd trimester by real-time ultrasound. Depending on the specific condition, associated malformations may be detected.

Differential Diagnosis: The fetal akinesia sequence is a secondary deformation syndrome requiring a primary diagnosis. '*Osteocraniostenosis*' *differs by the abrupt metaphyseal flare of the thin tubular bones. In microcephalic osteodysplasic primordial dwarfism* the tubular bones are slender but not as thin as in fetal akinesia and not associated with fractures.

Prognosis: Depending on the primary cause. Thin tubular bones and ribs point to long-standing intrauterine hypomobility implying a guarded prognosis.

Remarks: The term 'arthrogryposis' refers nonspecifically to multiple joint contractures associated with intrauterine a/hypokinesia. The distinction of different forms of arthrogryposis and their association with specific morphological abnormalities help elucidating the underlying cause. Associated with the sequelae of intrauterine hypomobility may be morphologic manifestations of the primary disorder such as cerebral, eye, cardiac or renal defects.

The 'Pena-Shokair syndrome, type I' is the hypokinesia sequence caused by a hereditary motor neuropathy. The term 'Pena-Shokair syndrome type II' refers to a cerebro-ocular disorder leading to intrauterine hypokinesia and its ensuing deformation sequence.

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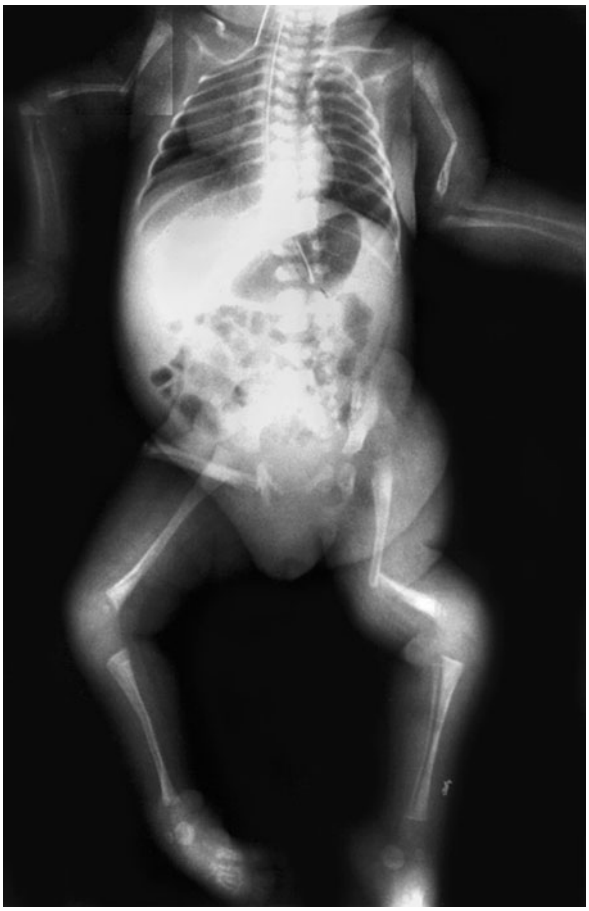

Fig. 3.28. ***Fetal a/hypokinesia sequence***. Newborn, 36 weeks gestation, with lissencephaly, severe intrauterine hypotonia, multiple joint contractures, micrognathia, pulmonary hypoplasia. Ribs and clavicles are thin; the vertebral bodies are well developed. The long tubular bones are thin, poorly modeled but not bowed. Multiple fractures are present

Osteocraniostenosis MIM 602361

Major Radiographic Features:

- Cloverleaf, acrocephalic or brachycephalic skull configuration. Deficient calvarial ossification
- Very thin tubular bones with abrupt metaphyseal flare
- Hypoplasia of the distal phalanges

Mode of Inheritance: Unknown. Possibly autosomal recessive

Molecular Basis: Unknown.

Prenatal Diagnosis: Thin tubular bones with or without fractures and cranial abnormalities are prenatally detected by ultrasound.

Differential Diagnosis: Patients with the *a/hypokinesia sequence* lack the abrupt metaphyseal flare of the tubular bones and usually have associated joint contractures and other manifestations of intrauterine hypomobility. Chondro-osseous histology is normal in fetal a/hypokinesia and abnormal in osteocraniostenosis. In *gracile bone dysplasia* bone density is decreased, abrupt metaphyseal widening of the tubular bones is absent and there are no cranial deformities.

Prognosis: Affected infants were stillborn or died shortly after birth. It is not clear if more mildly affected infants with prolonged survival constitute a variant of osteocraniostenosis or a separate entity (Verloes 2005).

Remarks: Gracile bone dysplasia and osteocraniostenosis have been lumped as one entity (MIM 602361). However the two conditions differ sufficiently to consider them as separate entities. Osteocraniostenosis is characterized by an abnormal cranium, a/hyposplenia, abrupt metaphyseal flare and abnormalities of the endochondral bone formation. Gracile bone dysplasia is characterized by a small, underossified but otherwise normal cranium, stick-like tubular bones with little or no metaphyseal flare, ischial hypoplasia and overgrowth of cortical bone. In both conditions the osseous abnormalities appear to be primary manifestations of genetic mutations, i.e. dysplasias, whereas in the fetal a/hypokinesia sequence they are secondary deformations. Osteocraniostenosis can be associated with nonimmune hydrops (Elliot 2006).

References

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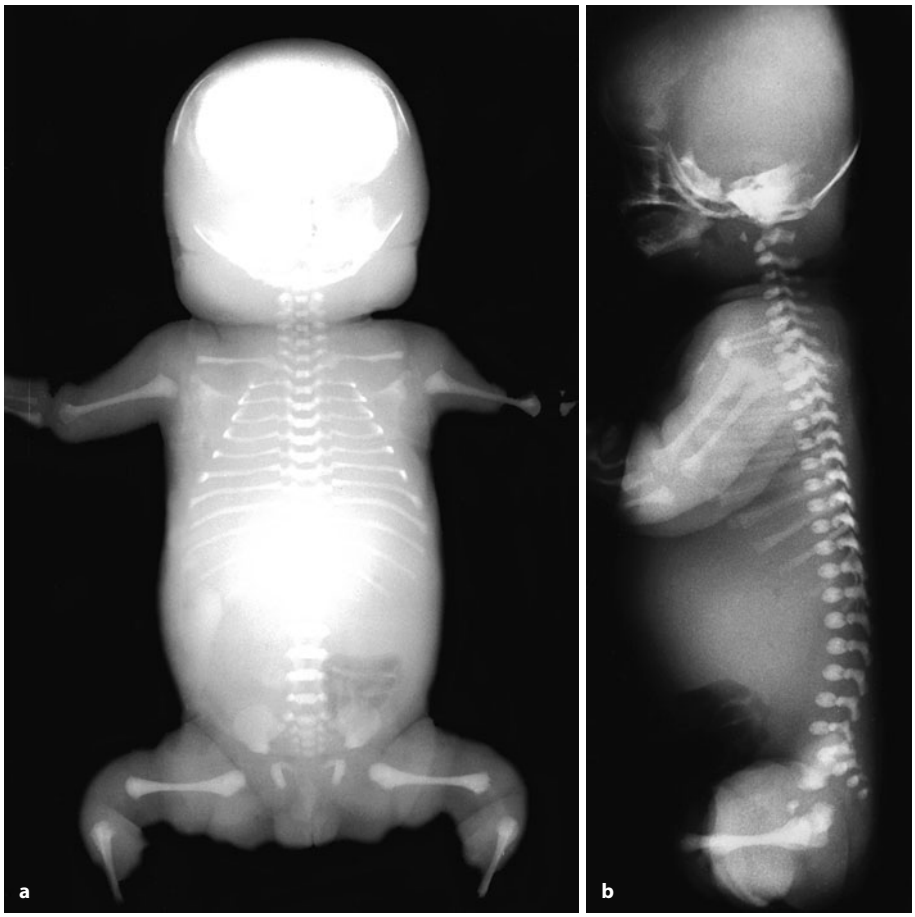

Fig. 3.29. ***Osteocraniostenosis***, 38 weeks gestation. **a, b** There is a cloverleaf deformity of the skull. The ribs are thin and slightly irregular. The shafts of the long tubular bones are thin with a characteristically abrupt metaphyseal flare. Note normally developed vertebral bodies and normal bone density. (Courtesy Dr. K. Runge, Wuppertal)

Gracile Bone Dysplasia MIM 602361

Major Radiographic Features:

- Thin ribs and clavicles
- Deficient ossification of pubic and ischial bones
- Short and slender, stick-like tubular bones with lack of cortical demarcation

Mode of Inheritance: Unknown. Autosomal dominant inheritance with maternal mosaicism has been suggested on the basis of one family (Costa).

Molecular Basis: Unknown.

Prenatal Diagnosis: Short limbs are detected by sonography.

Differential Diagnosis: Joint contractures and other manifestations of intrauterine hypomobility are conspicuous in *fetal a/hypokinesia sequence*. Tubular bone modeling is better preserved and chondro-osseous histology is normal in that condition. The stick-like appearance of the tubular bones and absence of gross cranial deformities differentiates gracile bone dysplasia from *osteocraniostenosis*.

Prognosis: All infants were stillborn or died shortly after birth due to respiratory insufficiency.

Remarks: Osteocraniostenosis and gracile bone dysplasia have been lumped as one condition (MIM 602361). However, radiographic and histologic differences allow their separation as distinct entities (see osteocraniostenosis). The term "gracile bone dysplasias" has also been used as a generic term to denote all neonatal disorders with slender bones, including those caused by heterogeneic a/hypokinesia (Kozlowski et al. Pediatr Radiol 32:629, 2002). There appears to be a familial gracile bone condition associated with normal intrauterine activity and nonimmune hydrops (Abboy 2008).

References

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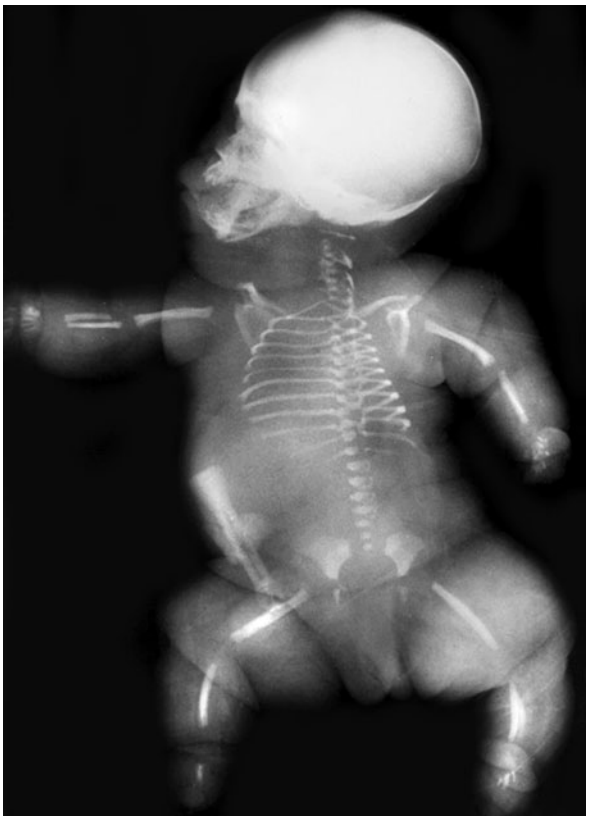

Fig. 3.30 ***Gracile bone dysplasia.*** Full-term newborn. The chest is small and the ribs are thin. Note the well ossified calvaria and clavicles. The lower portions of the ilia and the ischial bones are hypoplastic and the pubic bones are not ossified. The tubular bones are shortened and gracile but with relatively wide mid-portions and lack of metaphyseal flare

Microcephalic Osteodysplastic Primordial Dwarfism, Type 1 MIM 210710

Synonym: MOPD-1 Osteodysplastic primordial dwarfism, type 1, Taybi-Linder syndrome, cephaloskeletal dysplasia, brachymelic primordial dwarfism. Includes microcephalic osteodysplastic primordial dwarfism, type 3.

Major Radiographic Features:

- Microcephaly with sloping forehead
- Short, broad ilia
- Shortened, slender tubular bones with preserved modeling

Mode of Inheritance: Autosomal recessive.

Molecular basis: Unknown.

Prenatal Diagnosis: Short limbs may be detected by ultrasound.

Differential Diagnosis: In the fetal *hypokinesia sequence, osteocraniostenosis* and *gracile bone dysplasia* the tubular bones are thinner (fishbone-like) than in MOPD-1. In contrast to *other forms of primordial dwarfism*, the head is small in relation to length with a sloping forehead. The *Kenny-Caffey syndrome* is differentiated by the increased cortical thickness, medullary stenosis and hypocalcemia. It is rarely manifested at birth.

Prognosis: Early mortality is increased. Surviving infants suffer from recurrent apneas, seizures and psychomotor retardation. The patients fail to develop both physically and mentally. Death usually occurs before one year of age, mostly from intercurrent infections.

Remarks: The bone changes in MOPD-1 are nonspecific and occur also in other forms of primordial dwarfism, including MOPD-2, Silver-Russel-syndrome, 3 M syndrome and others. The prognosis is much better in most of these disorders and the connatal dwarfism is proportionate. The absence of microcephaly with a receding forehead cautions against a diagnosis of MOPD-1.

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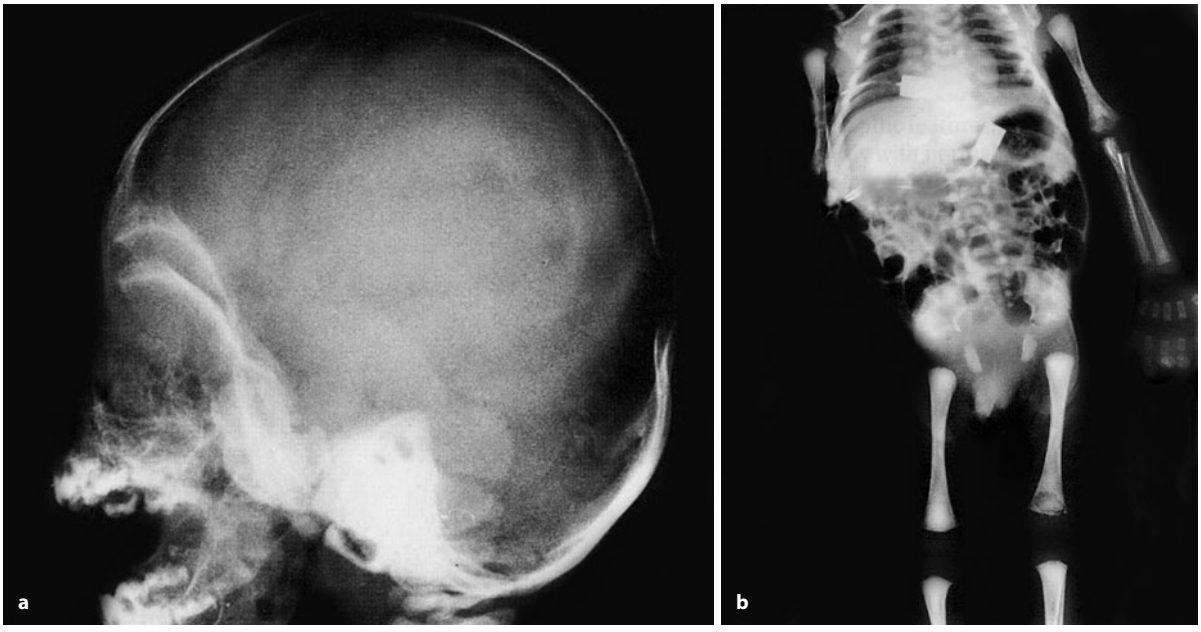

Fig. 3.31. ***Microcephalic osteodysplastic primordial dwarfism, type 1.*** **a** The skull is small and brachycephalic with a receding forehead, steep base and almost closed anterior fontanel. **b** The ilia are short due to hypoplasia of the lower portions. The pubic bones are not ossified. The long bones are short and slender but well modeled

Microcephalic Osteodysplastic Primordial Dwarfism, Type 2 MIM 210720

Synonym: MOPD-2. Osteodysplastic primordial dwarfism type 2.

Major Radiographic Features:
- Small, but well-proportioned skeleton with normally formed bones
- Occasionally mild overtubulation of long bones
- Normocephaly (in proportion to reduced body length)

Mode of Inheritance: Autosomal recessive.

Molecular basis: Mutations of *PCNT2* encoding Pericentrin.

Prenatal Diagnosis: Intrauterine growth retardation is detected by ultrasound.

Differential Diagnosis: Specific skeletal anomalies differentiate *other types of primordial dwarfism.* Differentiation from *MOPD- 1* is difficult on radiographic grounds. Clinical and molecular analysis is required. In the fetal *hypokinesia sequence, osteocraniostenosis* and *gracile bone dysplasia* the tubular bones are thinner (fishbone-like) than in MOPD-2.

Prognosis: Neonatal problems include hypoglycemia, respiratory distress related to small trachea and larynx, and failure to thrive. Growth remains severely deficient.

Remarks: The absence of major bone changes in a newborn with severe growth deficiency may raise the diagnostic possibility of MOPD-2. A proportionately normal head size without a receding forehead supports the diagnosis and justifies molecular studies.

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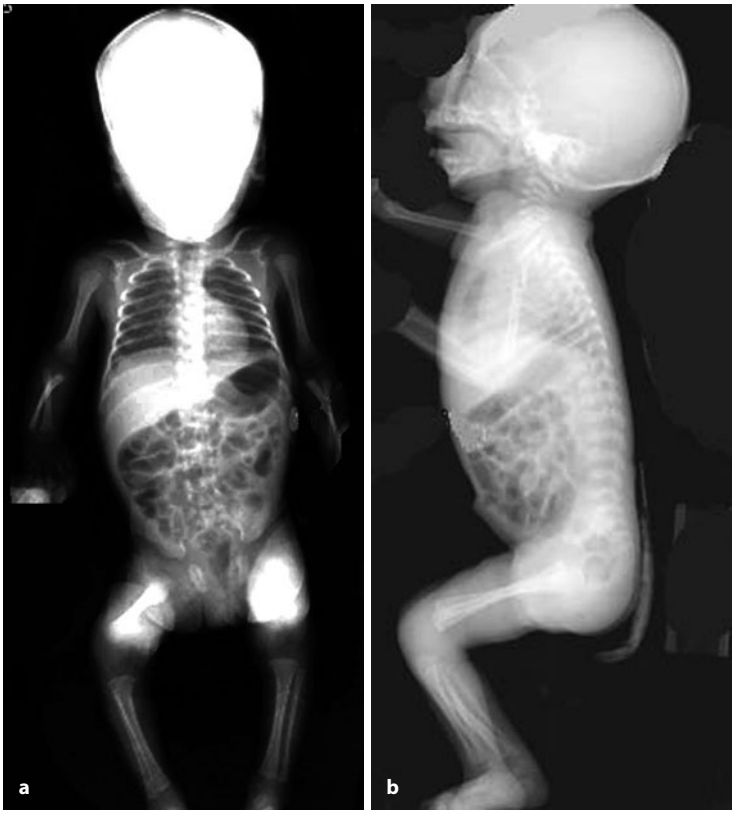

Fig. 3.32 a, b ***Microcephalic osteodysplastic primordial dwarfism, type 2.*** Newborn after 32 weeks of gestation. The bones are normal in form and structure. Apparent femoral shortness is positional

E. Skeletal Dysplasias with Thick Tubular Bones

Mucolipidosis II MIM 252500

Synonym: I-cell-disease; Leroy disease.

Major Radiographic Features:
- Decreased bone mineralization
- Foreshortened vertebral bodies, sometimes butterfly vertebrae
- Metaphyseal cupping and fraying of the tubular bones
- Excessive periosteal new bone formation and diaphyseal expansion of the long tubular bones
- Pelvic dysplasia
- Occasionally punctate calcifications and bone defects

Mode of Inheritance: Autosomal recessive.

Molecular Basis: Mutations of *GNPTAB* encoding GlcNac-1-phosphotransferase.

Prenatal Diagnosis: Once the diagnosis is suspected on the basis of an older affected sibling, the disorder can be diagnosed in the 2nd trimester by demonstrating decreased activity of multiple lysosomal enzymes in chorionic cells or cultured amniotic cells. Lysosomal enzymes are increased in amniotic fluid. Fetal hydrops is often present.

Differential diagnosis: The skeletal abnormalities in *GM_1 gangliosidosis* are very similar to those in mucolipidosis II, and the two disorders are differentiated by biochemical analysis showing isolated deficiency of β-galactosidase in the former and deficient activity of multiple lysosomal enzymes in the latter. Fetal hydrops is a nonspecific manifestation of multiple *lysosomal storage diseases* including mucopolysaccharidoses types I, VII, infantile sialidosis, galactosialidosis and infantile free sialic acid storage disease. In these disorders the neonatal bone changes are those of comparatively mild dysostosis multiplex, without periosteal cloaking, metaphyseal fraying and cupping. The tubular bone abnormalities often suggest a diagnosis of *neonatal rickets* or neonatal *hyperparathyroidism*. Wide ribs and pelvic dysplasia are not seen in these disorders and lysosomal enzyme activities are normal.

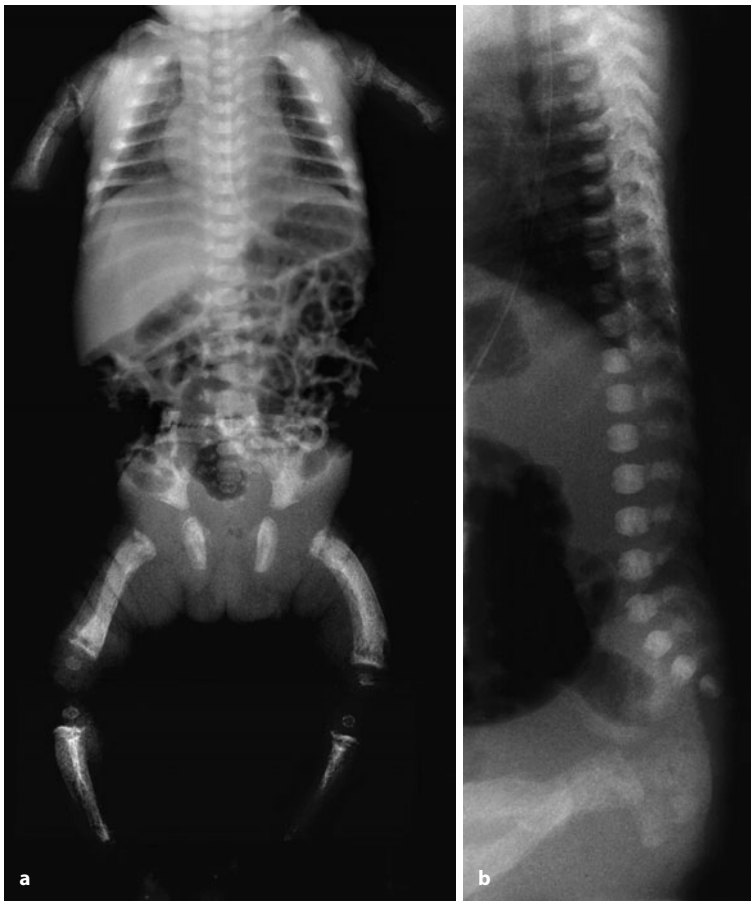

Fig. 3.33. ***Mucolipidosis II,*** full-term newborn. **a** The femora are thick and bowed with a coarsely woven bone structure and periosteal cloaking. These changes are reminiscent of those in neonatal hyperparathyroidism. The lower ilia are hypoplastic with a wide iliac angle. **b** The vertebral bodies are foreshortened

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Infantile Cortical Hyperostosis MIM 114000

Synonyms: Caffey-Silverman disease; Caffey disease; Roske-Caffey disease.

Major Radiographic Features:
- Cortical hyperostosis of single or multiple bones
- In severe cases short and bowed tubular bones

Mode of Inheritance: Autosomal dominant. One parent may have had the disorder in infancy with complete resolution making proper genetic counseling difficult.

Molecular basis: Specific mutations of the *COL1A1* gene encoding type 1 procollagen.

Prenatal Diagnosis: In severe cases, short, bowed limbs with thickened, irregularly echodense diaphyses may be detected by ultrasound. Fetal hydrops and polyhydramnios may be present.

Differential Diagnosis: Other *bowing disorders* including osteogenesis imperfecta and hypophosphatasia do not show the dense, irregularly widened diaphyses. *Mucolipidosis II* is differentiated by the generalized osteopenia, pelvic dysplasia and abnormal vertebral bodies. *Secondary hyperostoses* occur in conjunction with infections, in scurvy, rickets, after prostaglandin E administration and cardiopulmonary disorders but are not present perinatally.

Prognosis: Severely affected cases may be stillborn or die at birth of respiratory failure. The prognosis is good in mildly affected patients with isolated lesions, mostly in clavicles, mandible, ulna ribs or scapulae. In most of these cases complete clinical and radiographic recovery can be expected within weeks or months.

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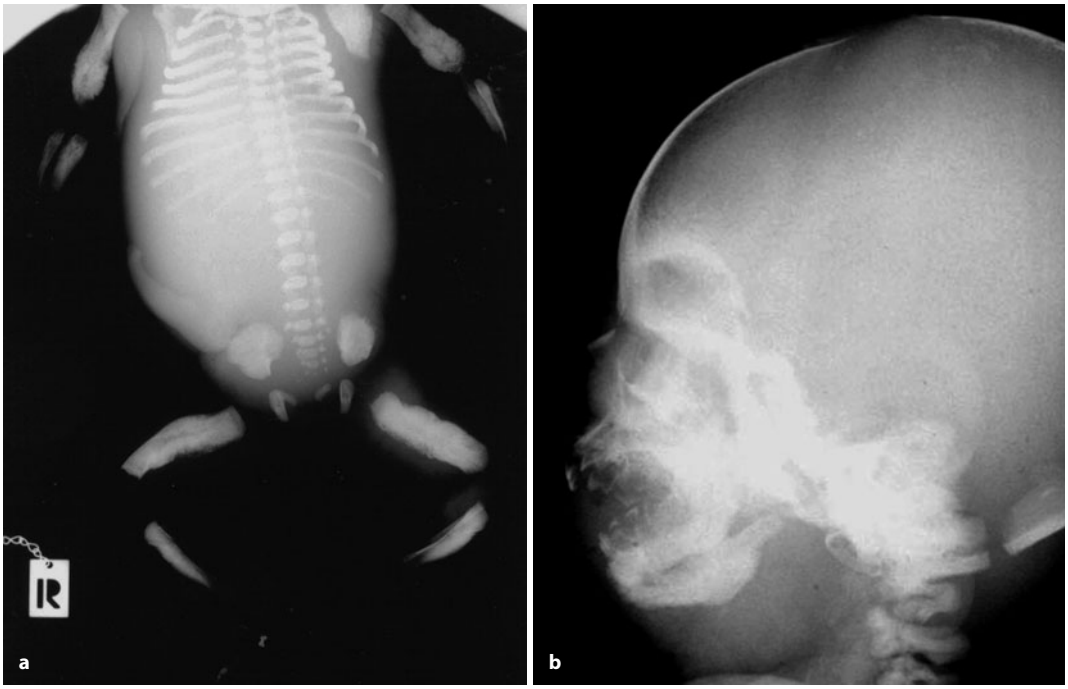

Fig. 3.34. ***Infantile cortical hyperostosis***; 23 weeks gestation. **a** The long tubular bones are shortened and thickened due to excessive masses of cortical bone. There is mild anterior bosing of the tibiae. **b** Cortical hyperostosis is seen in the mandible

F. Skeletal Dysplasias with Short Ribs, with or without Polydactyly

Short Rib (-Polydactyly) Syndrome, Saldino-Noonan/Verma-Naumoff Type MIM 263530, 263510

Synonym: Includes short rib (-polydactyly) type I (Saldino-Noonan) and Short rib-polydactlyly syndrome III (Verma Naumoff); SRPS-I and SRPS-III.

Major Radiographic Features:
- Short, horizontally oriented ribs
- Small iliac bones with horizontal acetabular roofs
- Shortness of tubular bones with a pointed (torpedo-like) or ragged (banana-peel-like) appearance
- Postaxial polydactyly in most cases

Mode of Inheritance: Autosomal recessive.

Molecular basis: Mutations of *DYN C2H1* coding for a cytoplasmic dynein involved in the retrograde transport in cilia.

Prenatal Diagnosis: Sonography shows short tubular bones and short ribs, sometimes paancreatic cysts.

Differential Diagnosis: In the *Beemer-Langer* and *Majewski types* of short rib (-polydactyly) syndrome the pelvis has a more normal appearance and the ends of the tubular bones are smooth. In *asphyxiating thoracic dysplasia* the long bones are less severely affected. Patients with *chondroectodermal dysplasia* (Ellis-van Creveld syndrome) have a more normal thorax and progressive proximal-distal shortening of the extremities.

Prognosis: The patients are stillborn or die shortly after birth from cardiorespiratory insufficiency.

Remarks: The long bone changes in the Saldino-Noonan type are slightly more severe than in the Verma-Naumoff-Type. However, torpedo-like and banana-peel-like lesions can occur in the same patient and are probably the expression of allelic mutations. Mutations of *DYNC2H1* may also cause asphyxiating thoracic dystrophy.

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(Fig. 3.35 see p. 148)

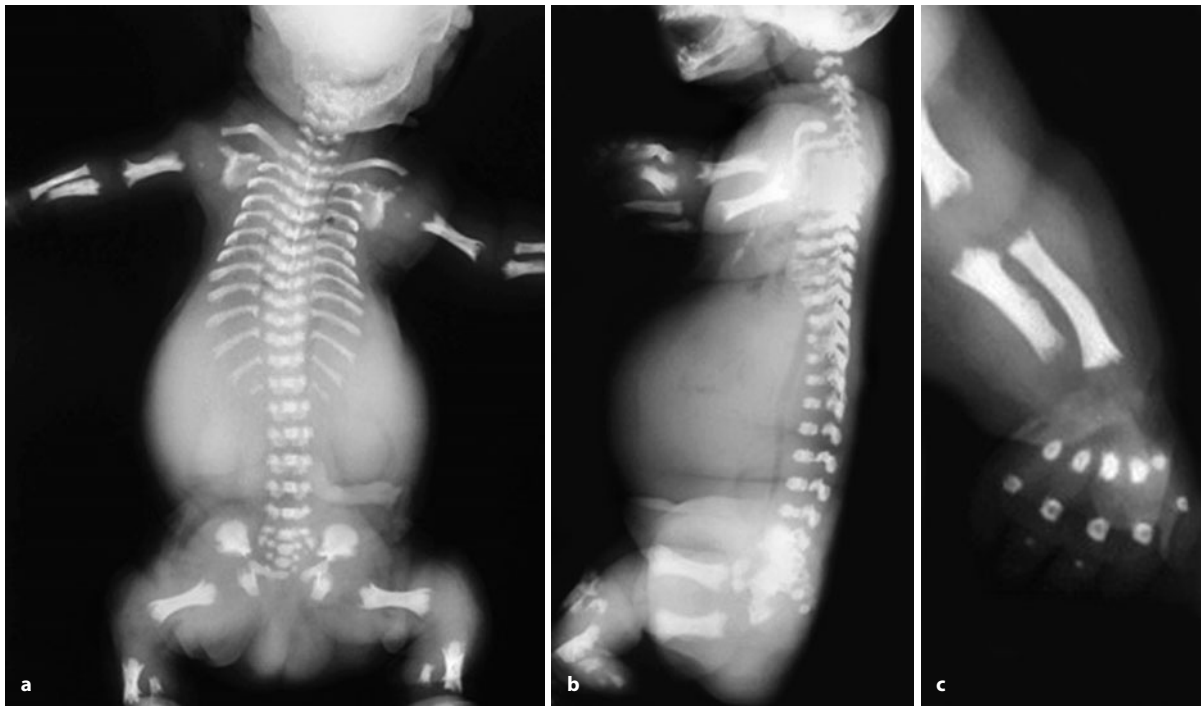

Fig. 3.35. ***Short rib (-polydactyly), Saldino-Noonan/Verma-Naumoff type***, 35 weeks gestation. **a** There is a\ striking restriction of the thoracic cage caused by very short and horizontally oriented ribs. The scapulae are small with irregular margins. The ilia are small with horizontal inferior margins. Small triangular ossification defects are seen above their lateral aspects. The tubular bones are short with spurs of none extending longitudinally from the medial and lateral aspects of the metaphyses resulting in a banana-peel appearance. **b** The vertebral bodies are small with irregular upper and lower margins and absent ossification in the cervical spine. **c** Metacarpals and proximal phalanges are very small; the middle and distal phalanges are not ossified except for two tiny ossification centers in the middle phalanges of digits 3 and 4. Note short radius and ulna with longitudinal spurs extending from the lateral and medial aspects of the bone ends

Short Rib (-Polydactyly) Syndrome, Beemer-Langer Type MIM 269860

Synonym: Short rib syndrome, Beemer-Langer type; Beemer-Langer syndrome; Short rib (-polydactyly) syndrome, type IV; SRPS IV.

Major Radiographic Features:
- Short, horizontally oriented ribs
- Small iliac bones
- Shortened tubular bones with smooth ends
- Tibia not essentially shorter than fibula
- Bowed radius and ulna
- Polydactyly in some patients

Mode of Inheritance: Autosomal recessive

Prenatal Diagnosis: Sonography shows short tubular bones and short ribs.

Differential Diagnosis: The metaphyseal margins are irregular in the *Saldino-Noonan/Verma-Naumoff type*. In the *Majewski type* of short rib (-polydactayly) syndrome the tibiae is shorter than the fibula. In *asphyxiating thoracic dysplasia* the long bones are less severely affected. Patients with *Chondroectodermal dysp*lasia (Ellis-van Creveld syndrome) have a more normal thorax and progressive proximal-distal shortening of the extremities.

Prognosis: The patients are stillborn or die shortly after birth from cardiorespiratory insufficiency.

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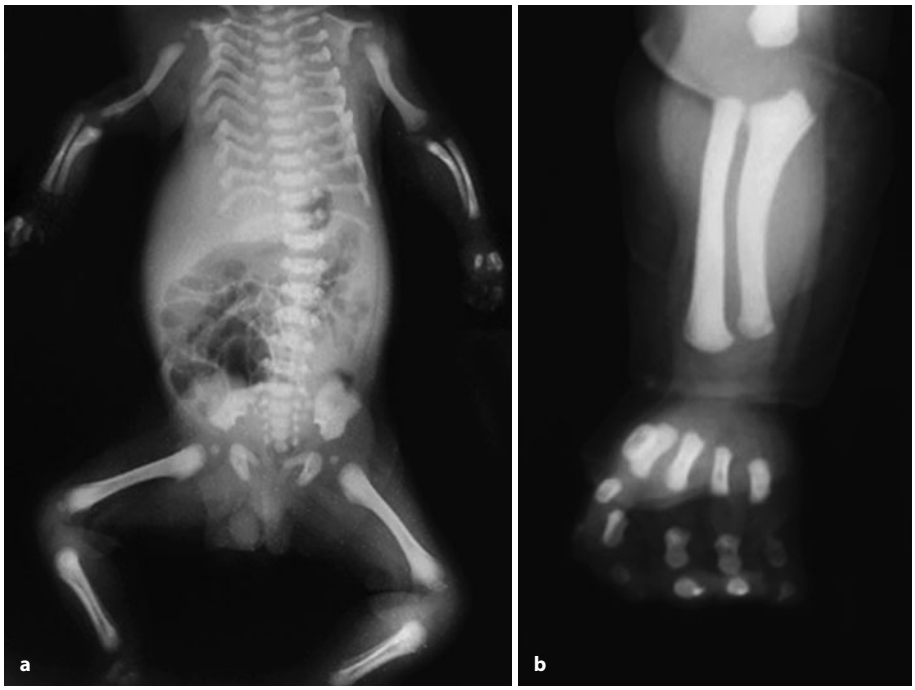

Fig. 3.36. ***Short rib (-polydactyly), Beemer-Langer type***, 38 weeks gestation. **a** The chest is narrow due to shortened, horizontally oriented ribs. The ilia are well formed. Premature ossification center of the capital femoral epiphyses are seen. The leg bones are mildly short but well modeled with round ends. The humeri, ulnae and radii are bowed. **b** Metacarpals and proximal phalanges are short but well formed; the middle and distal phalanges are small. Compare to hand bones in the Saldino-Noonan/Verma-Naumoff type of the short rib(-polydactyly) syndrome

Asphyxiating Thoracic Dysplasia MIM 208500

Synonym: Jeune syndrome; asphyxiating thoracic dystrophy; thoracic-pelvic-phalangeal dystrophy.

Major Radiographic Features:

- Small thorax with short, often horizontally oriented ribs
- Small iliac bones with spur-like downward projection at the medial and lateral aspects of the acetabular roofs; premature ossification of the capital femoral heads.
- Mildly shortened long tubular bones with round ends
- Short middle and distal phalanges
- Occasionally postaxial polydactyly

Mode of Inheritance: Autosomal recessive.

Molecular basis: Asphyxiating thoracic dysplasia is heterogeneous and may be caused by mutations

I) of an unidentified gene on chromosome 15q13,
II) of *IFT80* on chromosome 3q24-q26 encoding an intraflagellar transport protein
III) of mutations of *DYN C2H1* on chromosome 11q13.5 encoding a cytoplasmic dynein.

Prenatal Diagnosis: Sonography shows low thoracic circumference, increased nuchal translucency, sometimes short tubular bones. Hydrops may be present. The disorder has been detected at 14 weeks gestation.

Differential Diagnosis: In the *Saldino-Noonan/Verma-Naumoff* and *Beemer-Langer* types of short-rib(-polydactyly) syndromes the tubular bones are more severely shortened. The *Majewski* type differs by the disproportionately short tibia. *Chondroectodermal dysplasia* differs by the more normal thorax and the presence of cardiac defects and gingival frenula. A narrow thorax may also be found in other bone dysplasias including *thanatophoric dysplasia*, *metatropic dysplasia* and the *Shwachman-Bodian-Diamond syndrome*. These disorders are differentiated by their spinal, pelvic and long bone changes. A narrow thorax without long bone changes may rise the possibility of dominant *Barnes syndrome* (thoracolaryngopelvic syndrome) or of *UPD14* (unipaternal disomy 14) (Fig. 3.37C).

Prognosis: Neonatal mortality is increased due to cardiorespiratory compromise. With appropriate intensive care even severely affected infants may survive, become respiratory-independent and subsequently develop normally. Mildly affected patients have a good a priori prognosis.

Remarks: Asphyxiating thoracic dysplasia and short rib-(-polydactyly) type Saldino-Noonan/Verma-Naumoff are ciliopathies manifesting in a continuous phenotypic spectrum. Other short-rib syndromes may belong to the same pathogenetic family of disorders.

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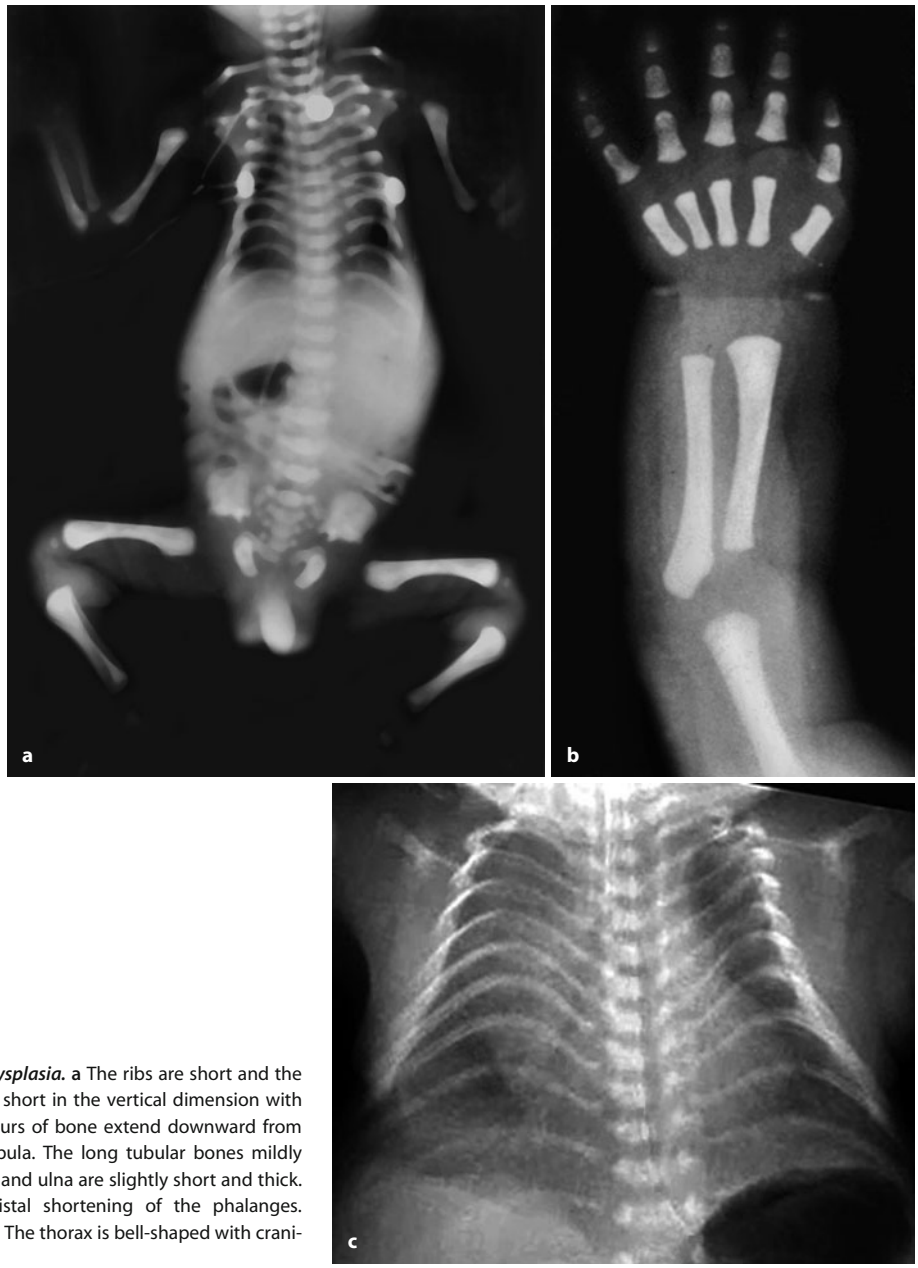

Fig. 3.37. ***Asphyxiating thoracic dysplasia.*** **a** The ribs are short and the clavicles are elevated. The ilia are short in the vertical dimension with horizontal acetabular margins. Spurs of bone extend downward from the medial margins of the acetabula. The long tubular bones mildly short and well modeled. **b** Radius and ulna are slightly short and thick. There is progressive proximal-distal shortening of the phalanges. **c** ***Unipaternal disomy 14 (UPD 14).*** The thorax is bell-shaped with cranial bowing of the posterior ribs

Short Rib (-Polydactyly) Syndrome, Majewski Type MIM 263520

Synonym: Short rib syndrome, Majewski type; Majewski syndrome; Short rib (-polydactyly) syndrome, type II; SRPS II.

Major Radiographic Features:

- Narrow chest with short, horizontally oriented ribs
- Normal pelvis
- Shortened tubular bones with smooth ends
- Tibia ovoid and shorter than fibula
- Pre- and/or postaxial polydactyly

Mode of Inheritance: Autosomal recessive.

Prenatal Diagnosis: Sonography shows narrow thorax and short tibiae. The fetus may be hydropic. Oligohydramnios has been observed in conjunction with glomerulocystic disease.

Differential diagnosis: In the Saldino-Noonan/Verma-Naumoff type of short rib (-polydactyly) the metaphyseal margins are irregular and the fibulae are as short as the tibiae. In *asphyxiating thoracic dysplasia* and *chondroectodermal dysp*lasia (Ellis-van Creveld syndrome) the tibiae are less severely shortened and the pelvis is abnormal with characteristic spurs.

Prognosis: The patients die shortly after birth from cardiorespiratory insufficiency.

Remarks: The Majewski syndrome may be part of a continuous spectrum of disorders that includes patients with the oro-facio-digital syndromes II and IV. Short tibiae, but not short ribs have been observed in the oro-facio-digital syndromes. Disproportionately short tibiae have also been described in an X-linked recessive condition without short ribs but otherwise resembling the oro-facio-digital syndrome II [Edwards M et al. (1988) Clin Genet 34:325].

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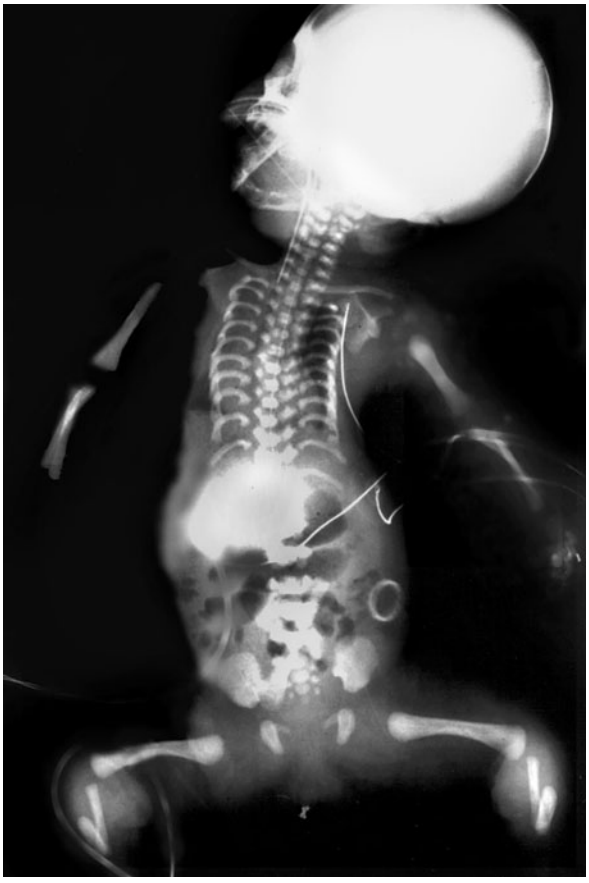

Fig. 3.38. ***Short rib- (polydactyly) syndrome, Majewski type.*** The ribs are short and horizontal. The pelvic appearance is normal. The tibiae are considerably shorter than the fibulae and their contours are rounded

Ellis-van Creveld Syndrome MIM 255500

Synonym: Chondroectodermal dysplasia; Mesoectodermal dysplasia.

Major Radiographic Features:
- Pelvic dysplasia with low ilia; hook-like downward protrusion of the medial and frequently also of the lateral aspects of the acetabulum; often premature ossification of the capital femoral epiphyses
- Mild shortness of the long tubular bones
- Progressive proximal-distal shortening of the tubular bones of hands and feet
- Some times narrow thorax

Mode of Inheritance: Autosomal recessive.

Molecular Basis: The Ellis-van Creveld syndrome is caused by mutations of either the EvC1 gene or the EvC2 gene, both located in the same region on chromosome 4p16. They encode proteins in the basal bodies of primary cilia.

Prenatal Diagnosis: Short limbs, polydactyly, narrow thorax and ventricular septal defect have been prenatally recognized by ultrasound.

Differential Diagnosis: *Asphyxiating thoracic dysplasia* (ATD) closely resembles the Ellis-van Creveld syndrome (EvC). The ribs usually shorter in ATD and polydactyly is less common. Heart defects and gingival frenula are characteristics of EvC but not of ATD. In *short rib(-polydactyly), Majewski type* the pelvic appearance is normal and the tibia is shorter than the fibula.

Prognosis: Infantile mortality is elevated due to pulmonary and cardiac complications. However, most patients survive and their prognosis quoad vitam is good.

Remarks: Heterozygous parents may be asymptomatic or have dental anomalies, postaxial polydactyly and nail dysplasia (Weyers syndrome). Together with other short rib dysplasias EvC syndrome, is a ciliopathy.

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(Fig. 3.39 see p. 154)

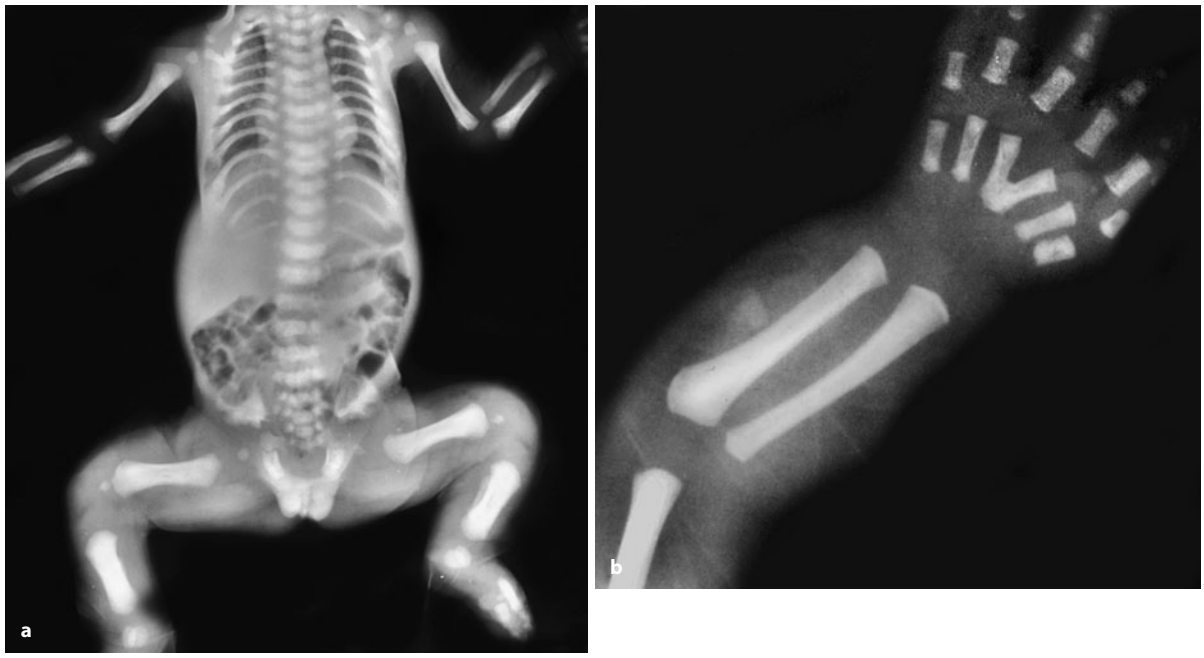

Fig. 3.39. ***Ellis van Creveld Syndrome.*** **a** The ribs are slightly short. The ilia are vertically short, and their inferior margins are horizontal with a downward-pointing hook at their medial ends. Femora and tibiae are short and broad. There is premature ossification of the capital femoral epiphyses. **b** The proximal end of the ulna and the distal end of the radius are wide; both bones are shorter than normal. Intercalary hexadactyly and proximal-distal shortening of the tubular of the hands are noted

G. Chondrodysplasia Punctata Group

Greenberg Dysplasia MIM 215140

Synonyms: Hydrops-ectopic calcification – moth-eaten skeletal dysplasia; HEM/Greenberg skeletal dysplasia. Includes dappled diaphysis dysplasia.

Major Radiographic Features:
- Defective ossification of the calvaria
- Disruption of the facial bones, axial and appendicular skeleton into small islands of ossification

Mode of Inheritance: Autosomal recessive.

Molecular Basis: Mutations of the *LMB* gene on chromosome1q42.1 encoding Lamin B receptor, a sterol delta(14)-reductase. The defective sterol reductase interferes with cholesterol biosynthesis as demonstrated by elevated levels of cholesta-8,14-dien-3beta-ol in cultured fibroblasts.

Prenatal Diagnosis: Fetal sonography in the second trimester shows hydrops fetalis, severe micromelia, and irregular hyperechogenic foci in the ribs and long bones.

Differential Diagnosis: *X-linked dominant chondrodysplasia punctata* differs by the asymmetric, scattered appearance of punctate calcifications. In *autosomal recessive chondrodysplasia punctata*, the vertebral bodies are better ossified and the tubular bones are not as severely disrupted as in Greenberg dysplasia

Prognosis: The fetuses are hydropic and none of the published cases has survived to the end of gestation.

Remarks: In dappled diaphysis dysplasia the shafts of the tubular bones are even more severely fragmented than in some cases of Greenberg dysplasia (Carty et al. (1989) Fortschr Röntgenstr. 150:228). The two disorders are most probably allelic.

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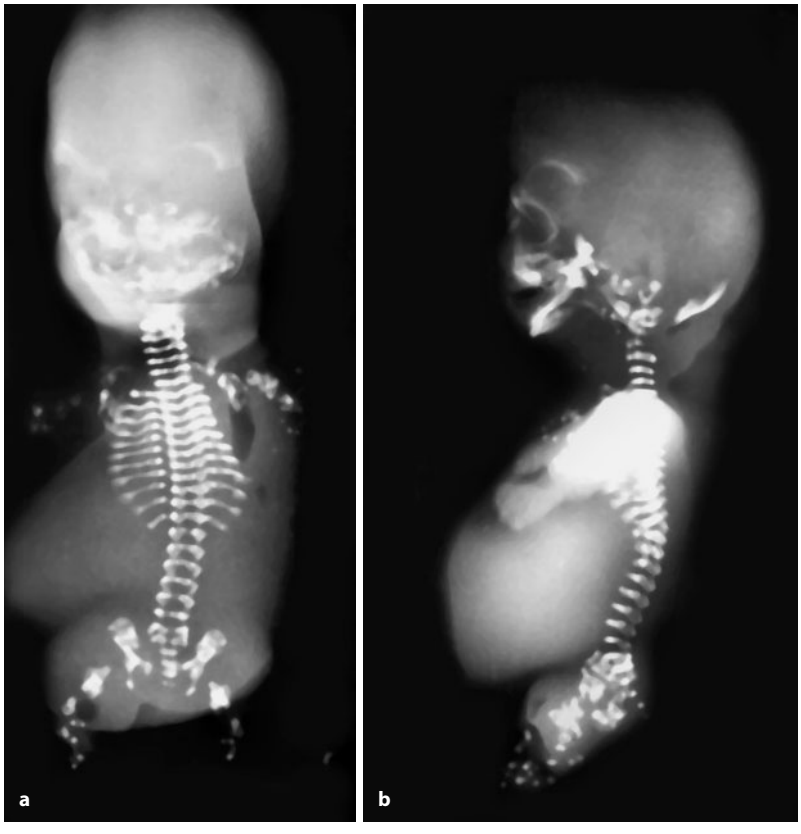

Fig. 3.40. ***Greenberg dysplasia***. **a, b** The calvaria is unossified. The rest of the skeleton, with the exception of the irregularly ossified ribs and vertebral arches, is disrupted into a multitude of radiodensities. The contours of the flattened vertebral bodies are still discernible

Chondrodysplasia Punctata, X-Linked Dominant Type MIM 302960

Synonyms: Conradi-Hünermann syndrome; Conradi-Hünermann-Happle syndrome, Happle syndrome, CDPX2, CPXD.

Major Radiographic Features:
- Punctate calcifications mostly of long bone ends, carpal and tarsal regions, spindous and transvers processes, sometimes laryngeal cartilage
- Irregular shapes of the vertebral bodies
- Sometimes asymmetric shortness of the long bones

Mode of Inheritance: X-linked dominant, lethal in hemizygous males.

Molecular Basis: Mutations in the *EBP* (emopamil) gene located on Xp11.23-p11.22 encoding β-hydroxysteroid Δ^8, Δ^7-isomerase. Allelic mutations and skewed X-inactivation are responsible for typical and atypical forms of X-linked dominant chondrodysplasia punctata including some cases with the CHILD syndrome.

Prenatal Diagnosis: Sonography in the 2nd trimester has revealed asymmetric limb shortening.

Differential Diagnosis: In *autosomal recessive (rhizomelic) chondrodysplasia punctata* marked shortness of the humeri and femora and coronal clefts are noted. The CHILD syndrome is characterized by unilateral ichyosiform erythroderma with ipsilateral limb defects and stippling (see Fig. 3.42). *X-linked -recessive chondrodysplasia punctata* is differentiated by the presence of exquisitely short distal phalanges (see Fig. 3.43).

Prognosis: With few exceptions the disorder is lethal in males. Most affected females survive the neonatal period and develop normally except for localized growth disturbance in stippled bone areas, ichthyosiform skin changes and partial alopecia.

Remarks: Punctate calcifications are nonspecific and occur in numerous conditions including the Zellweger syndrome, Smith-Lemli-Opitz syndrome, after exposure to warfarin, anticonvulsants, alcohol, and maternal vitamin K deficiency. Congenital hemidysplasia with ichthyosiform erythroderma and limb defects (CHILD syndrome, Fig. 3.42) is genetically heterogeneous and can also be caused by mutations of the NSDHL gene at Xq28. Chondrodysplasia punctata, tibia-metacarpal type, is the term used for a phenotype with prominent involvement of the tibiae and metacarpals.

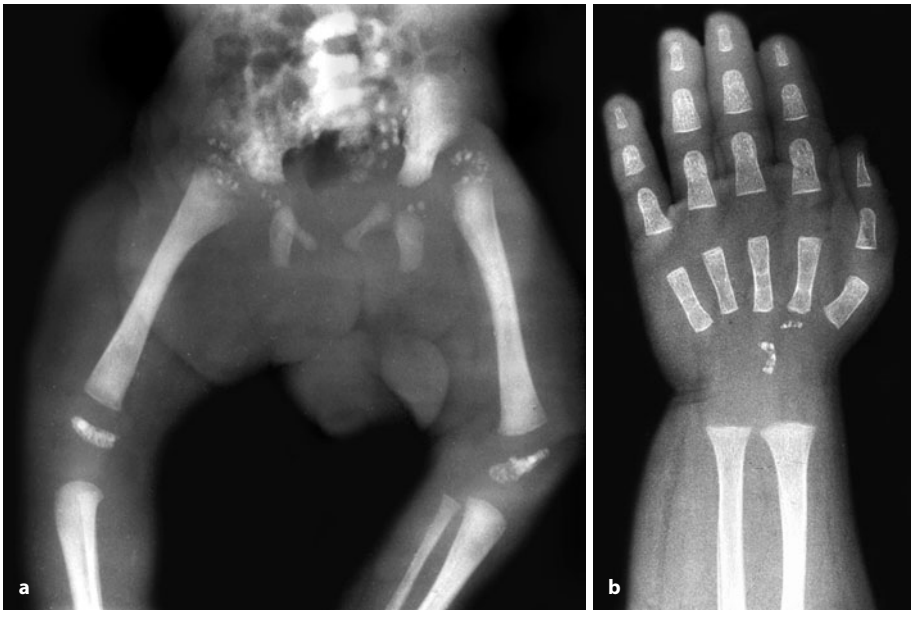

Fig. 3.41. ***Chondrodysplasia punctata X-linked dominant*****; a, b** Punctate calcifications are seen in the pelvis, in the proximal epiphyses of the femora, the knees and the carpal bones

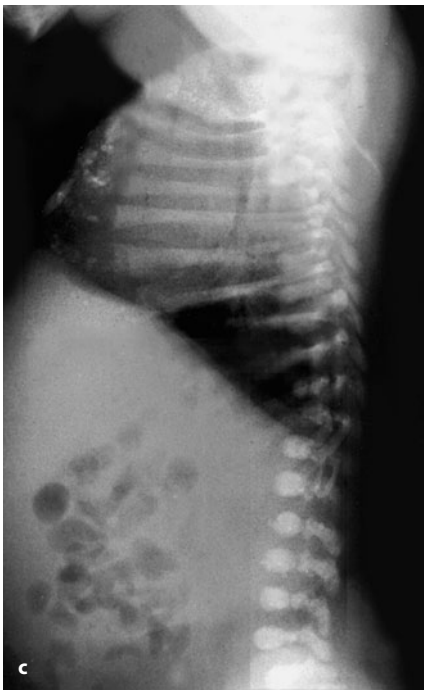

Fig. 3.41c. The form of the vertebral bodies is slightly irregular. There are puncta in the sternum and in the arches of the upper lumbar vertebrae

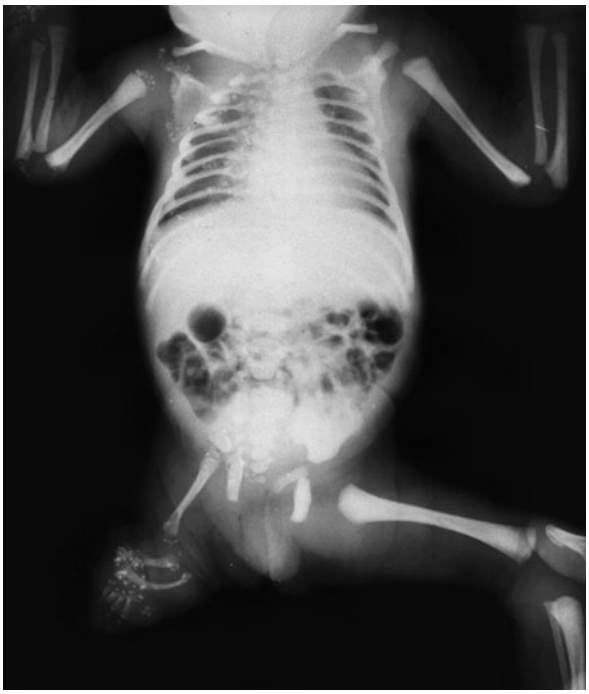

Fig. 3.42. ***CHILD syndrome.*** The bones of the right leg are small and misshapen. Extensive punctate calcifications are present in the right foot. The rest of the skeleton is normal

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Chondrodysplasia Punctata, X-Linked Recessive Type MIM 302950

Synonyms: Chondrodysplasia punctata, brachytelephalangic type, CDPX1, CPXR

Major radiographic features:
- Short, proximally tapered distal phalanges
- Stippling, notably of the spine and calcaneus
- Anterior hypoplasia of cervical vertebral bodies
- Calcification of hyoid bone and trachea

Mode of inheritance: X-linked recessive.

Molecular basis: Mutations of *ARSE* encoding arylsulfatase E.

Prenatal diagnosis: Sonographic examination may show polyhydramnion, defective cervical vertebral bodies and depressed nasal bridge in later pregnancy.

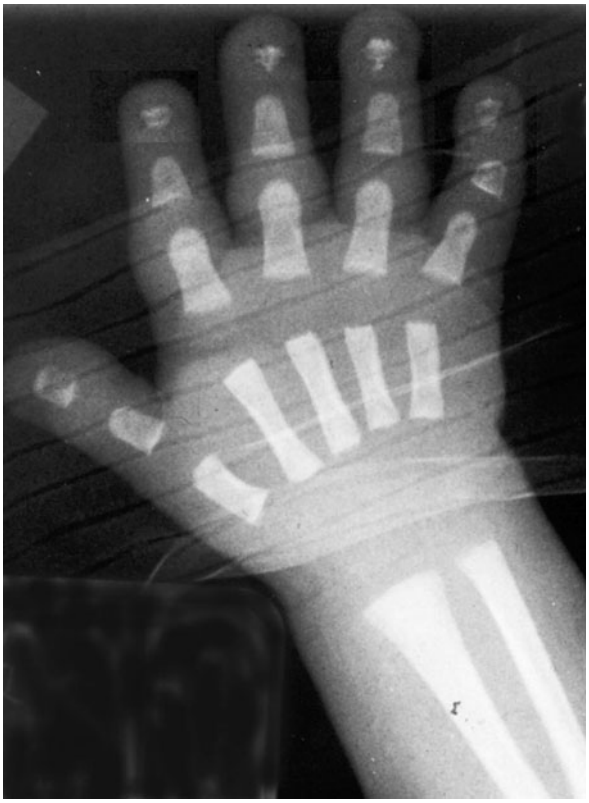

Fig. 3.43. ***X-linked recessive chondrodysplasia punctata*** *(brachytelephalangic type of chondrodysplasia punctata*). The distal phalanges are short and irregularly ossified

Differential diagnosis: Maternal vitamin K deficiency and *maternal lupus erythematodes* may cause the same phenotype and explain CPX1 cases without *ARSE* mutations. The distinctive shortness of the distal phalanges differentiates the CPX from *other types of chondrodysplasia punctata* which frequently also have uni- or bilaterally shortened limbs. Stippling is nonspecific (see Conradi-Hünermann syndrome).

Prognosis: In the neonatal period tracheal stenosis may cause respiratory difficulties. Cervical cord compression caused by insufficient ossification and hypermobility of the cervical spine has been repeatedly observed. Infantile mortality is approximately 15%.

Remarks: There is marked variability of expression and some patients have only very mild clinical and radiographic anomalies.

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Chondrodysplasia Punctata, Rhizomelic Type (MIM 215100)

Synonyms: Rhizomelic chondrodysplasia punctata, autosomal recessive chondrodysplasia punctata, RCDP.

Major radiological features:

- Coronal clefts composed of cartilage separating anterior and posterior ossification centers of vertebral bodies. These clefts are best seen in infancy and may no longer be apparent in the older child as the cartilage ossifies
- Very short humeri and relatively short femora with some metaphyseal splaying
- Punctate epiphyses at the ends of the long bones which disappear after1–3 years

Genetic transmission: Autosomal recessive. There is genetic heterogeneity (see molecular pathology).

Molecular Basis:

- RCDP, type 1: Mutation in the *PEX7* gene located at 6q22-q24 encoding the receptor for peroxisomal matrix proteins with the type 2 peroxisome targeting signal.. The defect interferes with peroxisome biogenesis and leads to multiple defects in peroxisome function.
- RCDP, type 2:Mutation of the *DHAPAT* gene located on chromosome 1 encoding the peroxisomal enzyme acyl-CoA: dihydroxyacetonephosphate acyltransferase. This enzyme is essential for the formation of ether phospholipids.
- RCDP, type 3: Mutations in the *AGPS* gene located on 2q31 encoding alkyldihydroxyacetone phosphate synthase. DHAP synthase is required for a single step in the biosynthesis for plasmalogens.

Prenatal Diagnosis: Severe rhizomelic limb shortening, premature ossification and stippling of multiple epiphyses have been detected by fetal sonography. Knowledge of the specific mutation from a previously affected child will allow for molecular analysis in chorionic villi.

Prognosis: The prognosis is poor. Affected infants fail to thrive, are severely retarded in their psychomotor development and usually die in infancy from repeated infections. Some patients survive into childhood; the oldest reported lived to 16 years. Survivors have severe psychomotor retardation, spastic tetraplegia, and thermoregulatory instability.

Major differential diagnoses: The asymmetric distribution of punctate calcifications and irregular abnormalities of the vertebral bodies differentiate *X-linked dominant chondrodysplasia punctata* from the rhizomelic type. The *Zellweger syndrome*, also a peroxisomal disorder, has puncta in the patellar area and usually does not have coronal clefts. Isolated puncta occur in *many acquired and genetic conditions* and frequently involve only the tarsal bones.

Remarks: The various types of RCDP cannot be differentiated on clinical or radiographic grounds; their differentiation requires biochemical or molecular analysis. RCDP type 1 is by far the most common type. Varying severity of clinical manifestations within type 1 RCDP is explained by allelic mutations leading to varying residual activity of the mutant protein.

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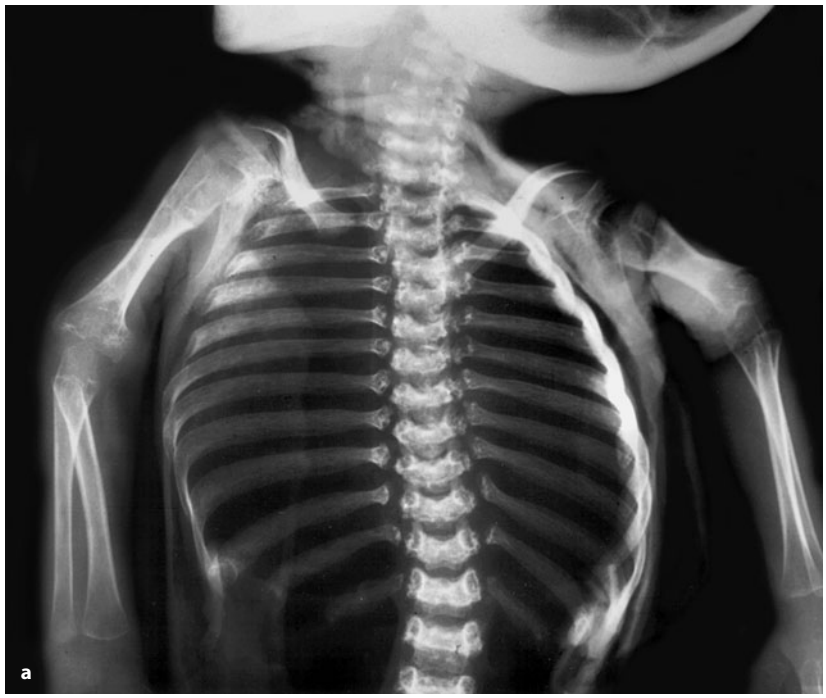
(Fig. 3.44 see p. 160)



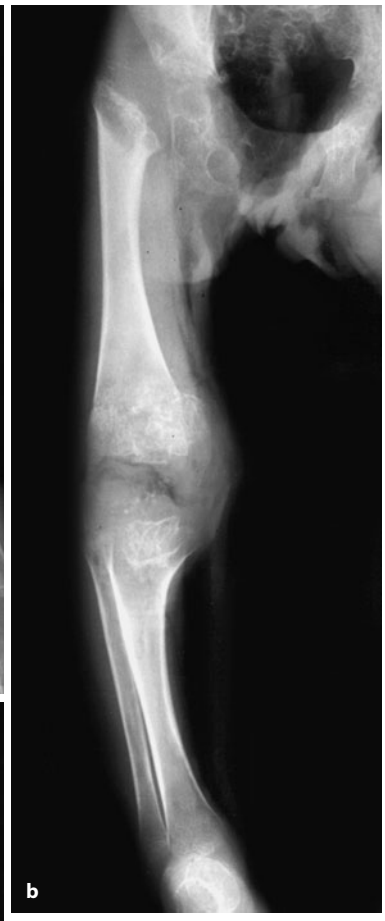


Fig. 3.44a, b. ***Chondrodysplasia punctata, rhizomelic type***. The humeri and femora are short with a 'sawed-off' appearance of the ends the humeri and femur. The ribs are broad with irregularly calcified proximal ends. There is less marked shortness of the tibia. Note the normal appearance of the bones of the forearm. Areas of irregular calcification are not seen in this patient but may be present in others

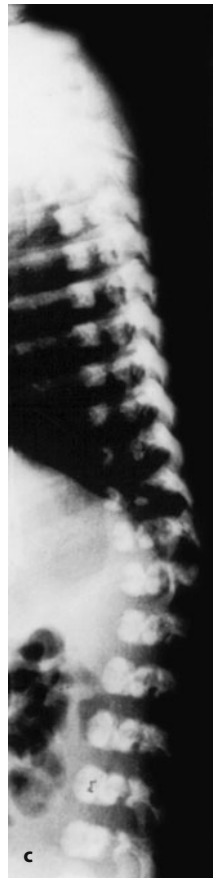


Fig. 3.44c. There are coronal clefts in the lumbar vertebral bodies

H. Skeletal Dysplasias with Multiple Dislocations

Larsen Syndrome MIM 150250, 245600,245650

Major Radiographic Features:

- Multiple dislocations, most notably in the hips, knees and elbows
- Often disproportionately large cranium
- Occasionally hypoplasia of the distal humerus

Mode of Inheritance: Autosomal dominant.

Molecular Basis: Mutations of the *FNLB* gene encoding the actin-binding domain of filamin B.

Prenatal Diagnosis: The disorder has been detected prenatally by ultrasound showing abnormal position of the knee joints and clubfeet. However, abnormally positioned limbs in a fetus are nonspecific and do not allow a diagnosis of Larsen syndrome.

Differential Diagnosis: Hypoplastic distal humeri are seen in *Omodysplasia*, which differs by the associated distal femoral hypoplasia and absence of dislocated hips. The *Desbuquois syndrome* is differentiated by the presence of coronal clefts of the vertebral bodies and the abnormal position and form of finger bones, if present. Dislocated hips and elbows sometimes occur in the *otopalatodigital syndrome I*. Differentiation is possible by molecular analysis showing a mutated *FNLA* gene in OPD.

Prognosis: Most patients survive to adulthood. Early death due to pulmonary hypoplasia has been reported.

Remarks: The Larsen syndrome is part of a continuous phenotypic spectrum encompassing atelosteogenesis types I, III and boomerang dysplasia. There is a phenotypic overlap with the type A filaminopathies, i.e. the otopalatodigital syndromes. The so-called autosomal recessive form of the Larsen syndrome (also called 'Ile de la Reúnion variant of Larsen syndrome', 'Spondyloepiphyseal dysplasia, Omani type', 'Humerospinal dysostosis') is caused by carbohydrate sulfotransferase 3 deficiency. In addition to multiple dislocations it is characterized by markedly short stature and the frequent presence of radio-ulnar synostosis (Hermanns P et al. (2008) Am J Hum Genet 82: 1368–1374).

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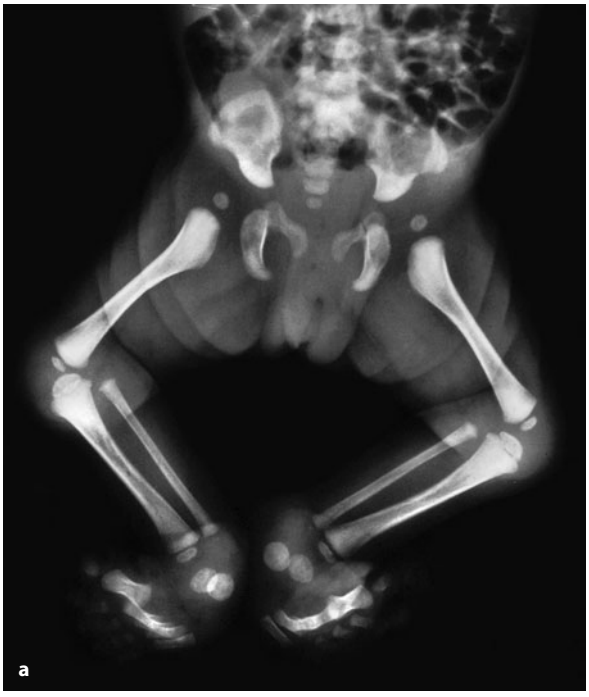
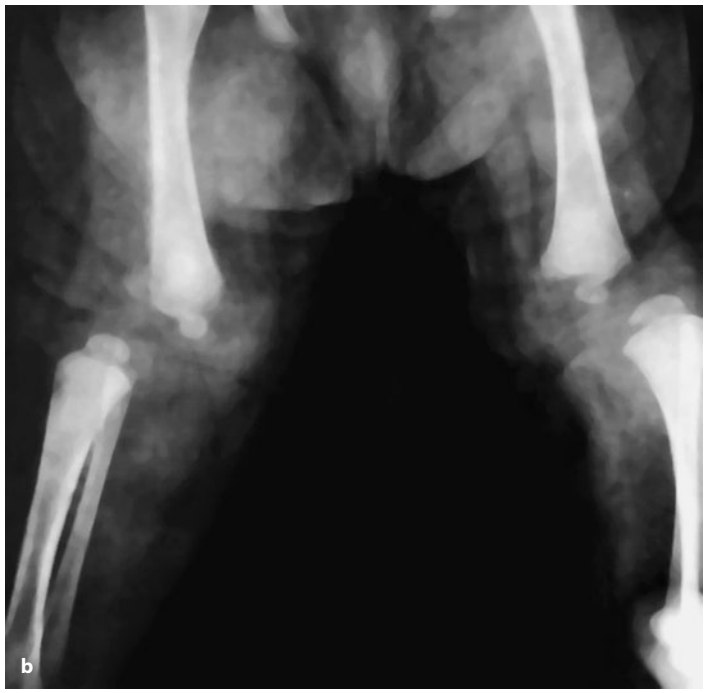
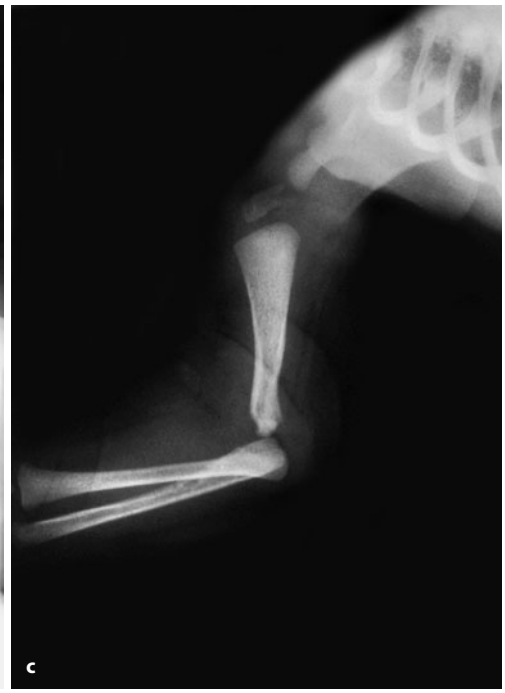


Fig. 3.45a–d ***Larsen syndrome.*** **a** 3 months. The acetabular fossae are underdeveloped due to congenitally dislocated hips

(Fig. 3.45b–d see p. 162)





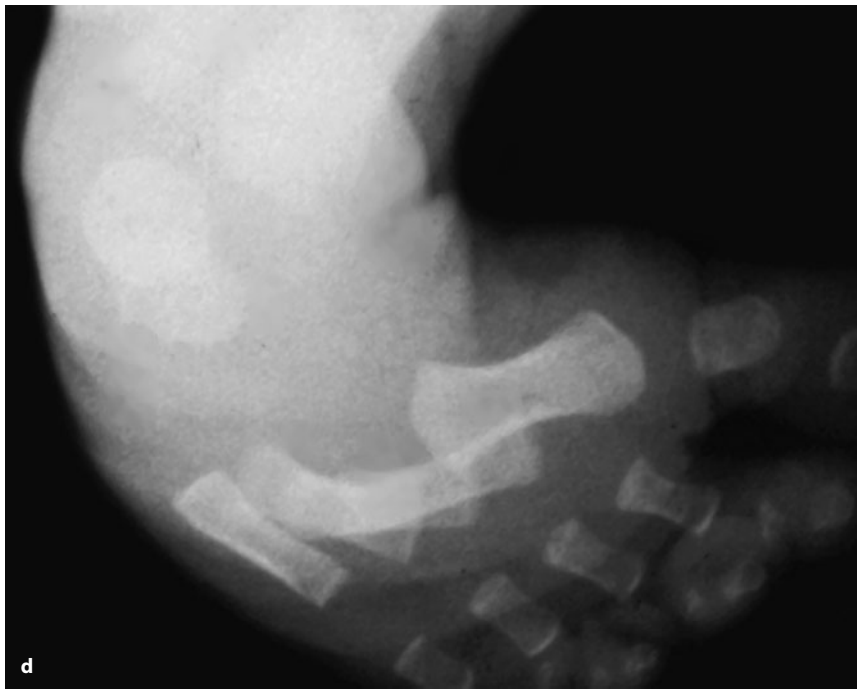


Fig. 45b Newborn. Both knees are dislocated anteriorly and laterally. **c** Newborn. The humerus is short and distally tapered. Lateral dislocation of the radial head is not demonstrated in this view. **d** Newborn. There is a marked equinovarus deformity of the foot

Atelosteogenesis MIM 112310, 108720, 109721

Synonym: Includes Boomerang dysplasia, Piepkorn type of lethal osteochondrodysplasia, Atelosteogenesis I, Atelosteogenesis III

Major Radiographic Features:

- Shortened, misshapen, in severe cases unossified long tubular bones
- Short, misshapen, in severe cases unossified tubular bones of the hands and feet
- Coronal clefts of the vertebral bodies. In severe cases unossified vertebral bodies

Mode of Inheritance: Autosomal dominant.

Molecular basis: Mutations of the *FLNB* gene encoding filamin B.

Prenatal Diagnosis: Short, partially unossified tubular bones are detected by sonography. Polyhydramnios is commonly present.

Differential Diagnosis: The bone changes, notably the short, distally hypoplastic humeri and femora, as well as the wide and irregularly shaped short tubular bones differentiate atelosteogenesis from the milder *Larsen syndrome*. Mild cases of atelosteogenesis (type III) resemble *severe diastrophic dysplasia (De la Chapelle dysplasia)*, which differs by the preserved metaphyseal flare, irregular diaphyseal contours of the long tubular bones and mutated DTDST gene.

Prognosis: Patients with severe atelosteogenesis are stillborn or die shortly after birth. Patients with mild (type III) atelosteogenesis may survive into adulthood.

Remarks: Boomerang dysplasia, atelosteogenesis I and III form a continuous spectrum of disorders. In this chapter they are presented as one entity. They are lethal conditions in contrast to the Larsen syndrome, which carries a good life prognosis. Phenotypic overlap of atelosteogenesis with the X-linked otopalatodigital syndrome II and lethal male Melnick-Needles syndrome is explained by the closely related functions of filamins A and B.

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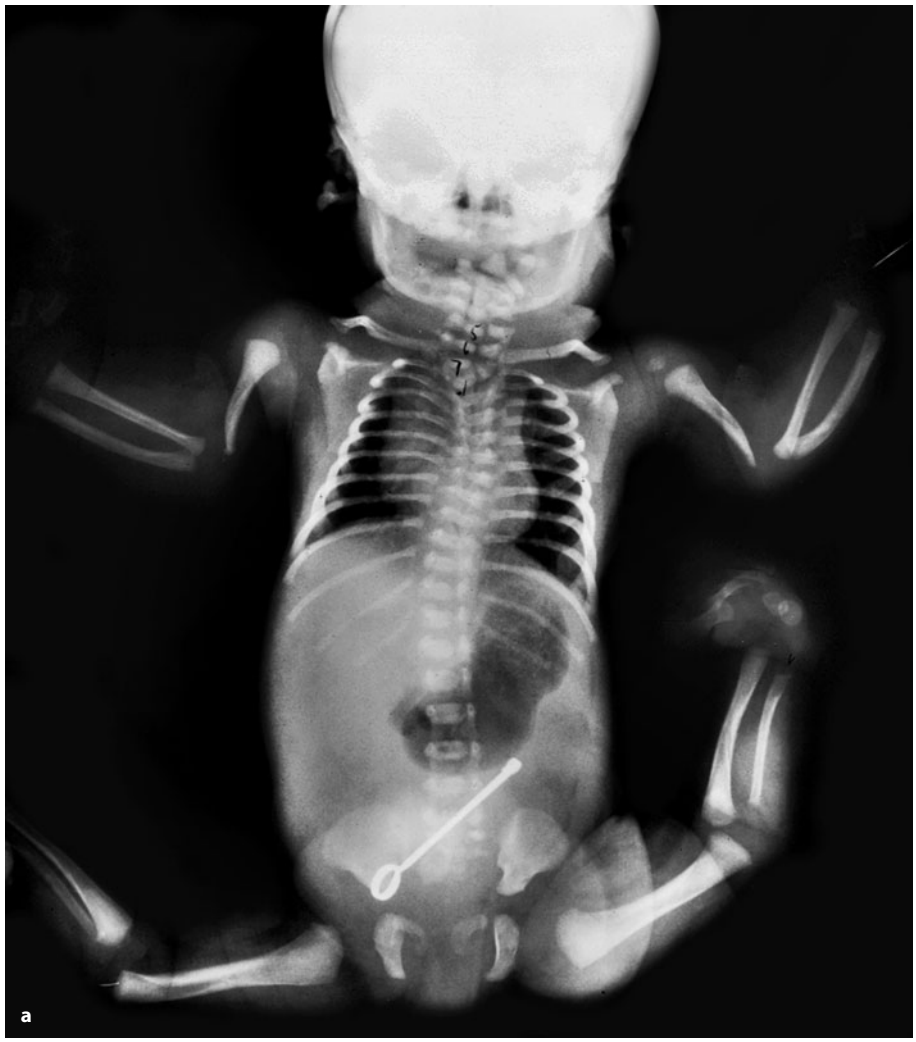
(Fig. 3.46 see p. 164)



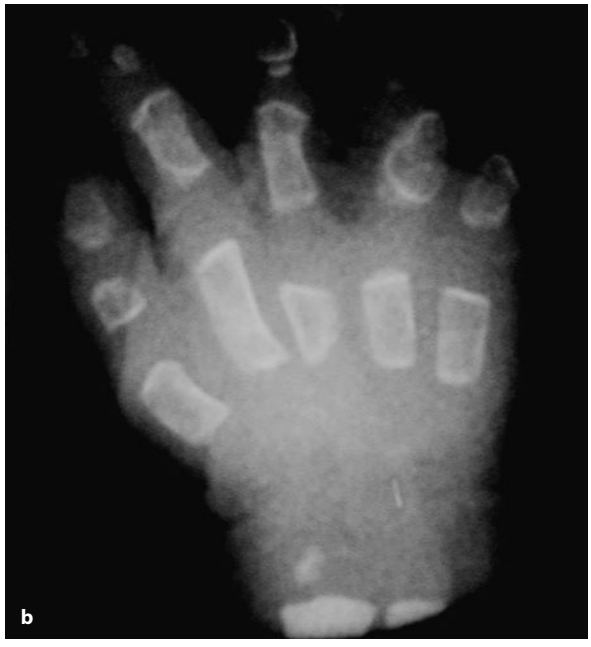


Fig. 3.46a. ***Atelosteogenesis I.*** Ossification of the vertebrae at the cervico-thoracic junction is irregular. The distal humeri are hypoplastic. The basilar portions of the ilia are narrow and the distal portions of the femora are mildly hypoplastic. **b** *Atelosteogenesis III*. The metacarpal bones and proximal phalanges are short and squared except metacarpal III and the proximal phalanx IV, which are grossly misshaped. There is an irregular ossification center at the distal radius

Desbuquois Dysplasia MIM 251450

Synonym: Micromelic dwarfism with vertebral and metaphyseal abnormalities and advanced carpotarsal ossification.

Major Radiographic Features:
- Coronal clefts of vertebral bodies
- Hypoplastic lower ilia
- Short femoral necks
- Dislocated hips and knees in severe cases
- Advanced carpotarsal ossification
- Short first metacarpal bone
- Extra ossicles between metacarpals and proximal phalanges of the first and second fingers

Mode of Inheritance: Autosomal recessive.

Molecular Basis: Mutations of *CANT1* encoding a soluble nucleotidase.

Prenatal Diagnosis: Prenatal diagnosis has to this date not been reported but should be possible on the basis of short limbs and abnormal limb posture in severely affected patients.

Differential Diagnosis: In the *Larsen syndrome*, dislocated joints and coronal clefts of the vertebral bodies are more prominent. *Diastrophic dysplasia* differs by the absence of an extra ossification center distal to metacarpal 2 and the absence of coronal vertebral clefts. Severe cases of the *oto-palato-digital syndrome* show more irregular, bowed long tubular bones. Molecular analysis may be necessary to rule out these conditions. Hand changes similar to those in Desbuquois dysplasia are seen in the *Catel-Manzke syndrome*, which differs by the absence of other skeletal defects.

Prognosis: Neonatal and early infantile mortality is increased due to respiratory failure but more than 70% of the patients survive.

Remarks: The Desbuquois syndrome is heterogeneous. *CANT1* mutations have been found in patients with typical hand changes (type 1). The chromosomal region containing the *CANT1* gene has been exlucded as the locus causing Desbuquois syndrome (type 2) characterized by relatively normal short tubular bones.

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(Fig. 3.47 see p. 166)

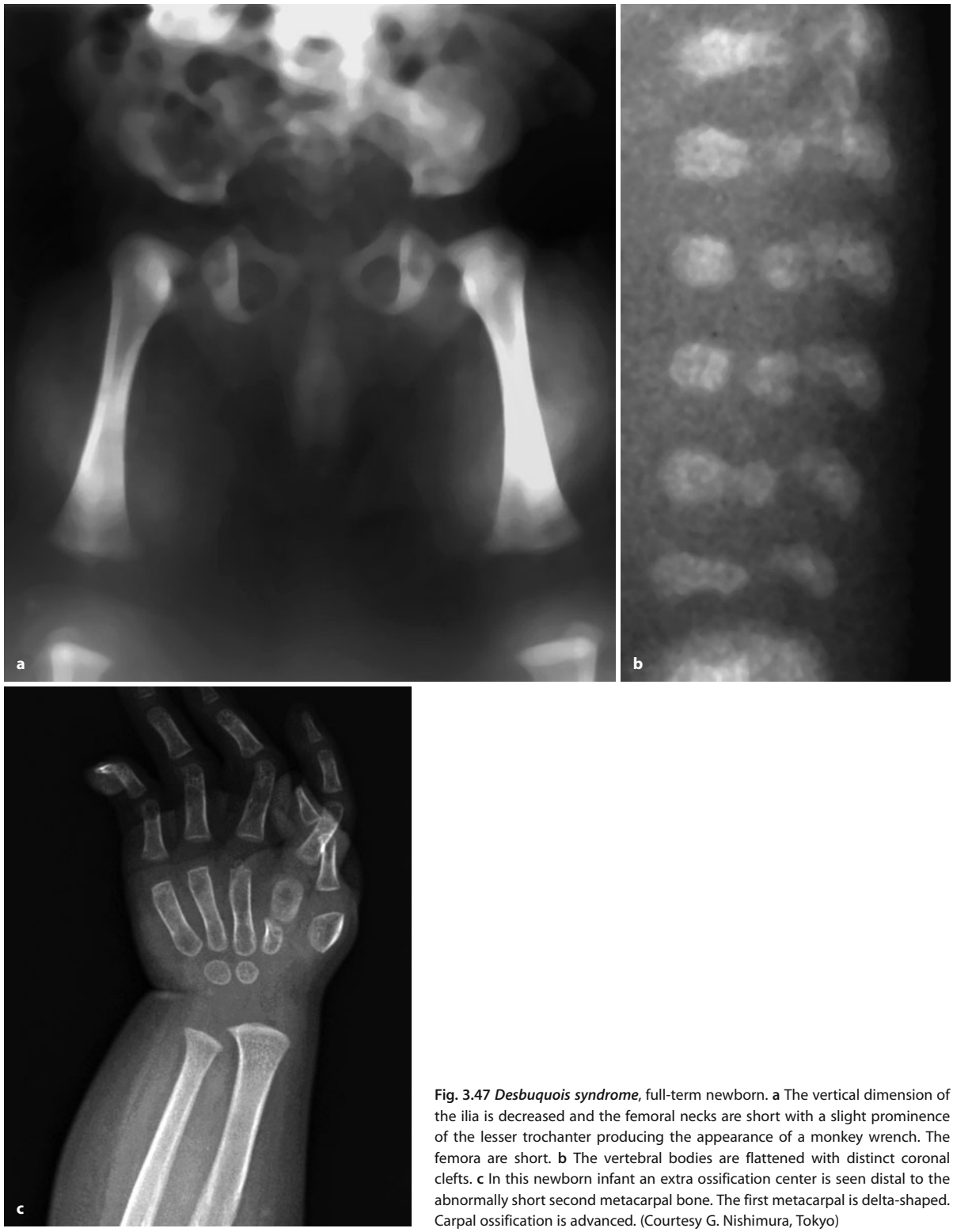

Fig. 3.47 ***Desbuquois syndrome***, full-term newborn. **a** The vertical dimension of the ilia is decreased and the femoral necks are short with a slight prominence of the lesser trochanter producing the appearance of a monkey wrench. The femora are short. **b** The vertebral bodies are flattened with distinct coronal clefts. **c** In this newborn infant an extra ossification center is seen distal to the abnormally short second metacarpal bone. The first metacarpal is delta-shaped. Carpal ossification is advanced. (Courtesy G. Nishimura, Tokyo)

I. Skeletal Dysplasias with Prominent Involvement of the Humeri or Clavicles

De la Chapelle Dysplasia MIM 256050

Synonym: Atelosteogenesis II

Major Radiographic Features:
- Shortened tubular bones with flared ends
- Distal tapering of humeri
- Shortened, sometimes triangular ulna and fibula; less severely shortened, bowed radius and tibia
- Shortened, misshapen tubular bones of the hands and feet; globular appearance of metacarpal I and metatarsal I

Mode of Inheritance: Autosomal recessive.

Molecular Basis: Mutations of the diastrophic dysplasia sulfate transporter gene DTDST.

Prenatal Diagnosis: Short limbs have been detected by ultrasound at 21 weeks of gestation. In familial cases prenatal diagnosis may be achieved by molecular analysis.

Differential Diagnosis: The tubular bones in *atelosteogenesis I/III* show less metaphyseal flare and the tubular bones of the hands are more plump. In *achondrogenesis IB* ossification of the spine and limbs is more defective. Irregular short tubular bones and a rounded metacarpal I are found in *diastrophic dysplasia* which differs by the more normal appearing long tubular bones.

Prognosis: Most patients are stillborn or die shortly after birth. There is overlap with diastrophic dysplasia which has a good prognosis.

Remarks: The clinical spectrum of DTDST mutations encompasses achondrogenesis IB, De la Chapelle dysplasia, diastrophic dysplasia and a relatively mild, late-manifesting form of multiple epiphyseal dysplasia. In spite of their common molecular basis, these disorders are listed as separate diseases because of their different clinical manifestations and course. The name atelosteogenesis II had been chosen because of the phenotypic similarity with atelosteogenesis I/III, which, however, has a different molecular basis.

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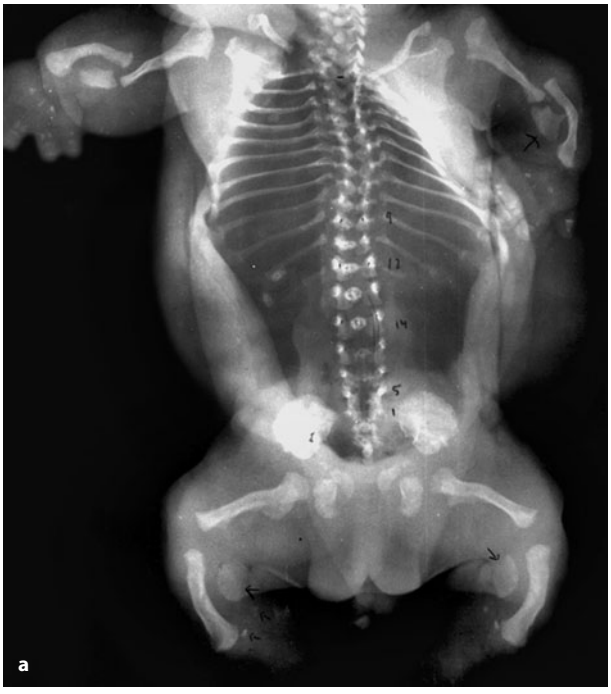

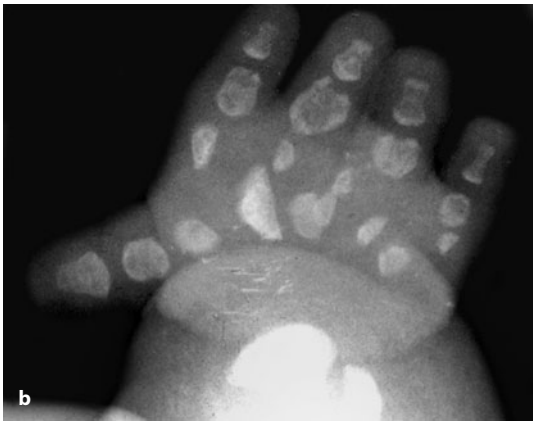

Fig. 3.48 ***De la Chapelle dysplasia***, **a** 38 weeks gestation. The upper thorax is narrow with overconstriction of the mid-thoracic vertebrae Note distal tapering of the d-humeri, very short, triangular ulnae and relatively long, bowed radii. Metacarpals and phalanges are seen as small, irregular bone islands. Femora and tibiae are bowed with wide ends. The fibulae are very short and halberd-shaped. **b** 40 weeks gestation. Metacarpals and phalanges are grossly irregular in size and shape with an extra bone in the basis of the third digit

Diastrophic Dysplasia MIM 222600

Major Radiographic Features:
- Shortened tubular bones with wide ends
- Disproportionate shortness of the first metacarpal
- Club feet

Mode of Inheritance: Autosomal recessive.

Molecular Basis: Mutations of the *DTDST* gene impede the function of a transmembrane protein that transports sulfate into chondrocytes. Lack of intracellular sulfate results in undersulfated proteoglycans.

Prenatal Diagnosis: Short limbs and, short, abducted thumbs and great toes have been detected at 20 weeks gestation by ultrasound. By transvaginal sonography the diagnosis has been suspected at 13 weeks gestation. If the mutation is known, molecular analysis should be possible in chorionic tissue and cultured amnion cells.

Differential Diagnosis: The long bone changes of diastrophic dysplasia are milder than those in *de la Chapelle dysplasia* and *achondrogenesis IB.* The vertebral bodies are normal in diastrophic dysplasia. Coronal clefts are found in *Desbuquois syndrome* which otherwise may resemble diastrophic dysplasia and often needs to be excluded by molecular analysis. *Pseudodiastrophic dysplasia* also resembles diastrophic dysplasia but differs by the presence of multiple interphalangeal joint dislocations. *Omodysplasia* is differentiated by the more marked distal hypoplasia of the humeri and femora as well as the normal hand bones.

Prognosis: Perinatal and early infant mortality is increased, but once stabilized, the infants grow up with a normal life expectancy.

Remarks: Achondrogenesis I B, de la Chapelle dysplasia, diastrophic dysplasia and autosomal recessive epiphyseal dysplasia are members of an etiopathogenic family caused by allelic mutations of the *DTDST* gene. More severe phenotypes result from a more defective sulfate transport and mild phenotypes from partial defects.

References

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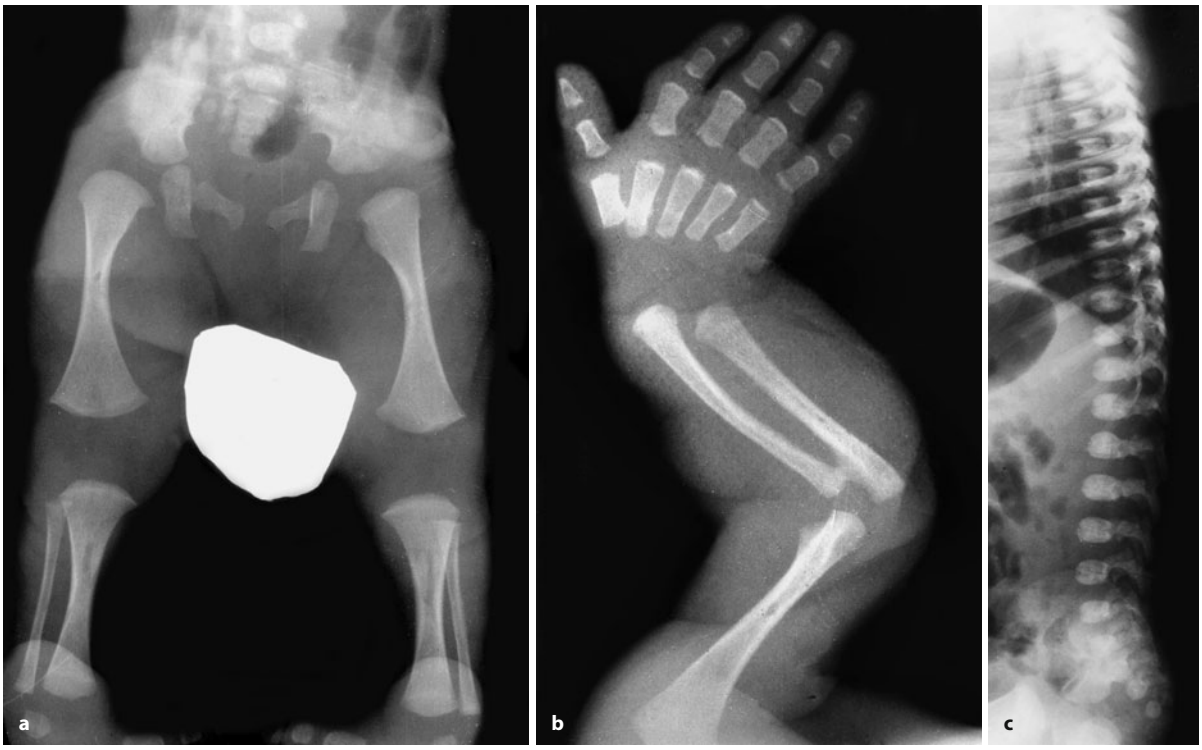

Fig. 3.49. ***Diastrophic Dysplasia.*** Newborn, 38 weeks gestation. **a** The tubular bones are short with wide metaphyses. The knee epiphyses are not ossified. **b** The distal humerus is slightly tapered. The phalanges are short and squared. **c** A lateral spine films shows no major abnormalities

Omodysplasia MIM 258315, 251455, 268250

Major Radiographic Features:
- Shortened arm and leg bones
- Club-shaped, distally tapered humerus and femur
- Dislocated radial heads
- Short first metacarpal in autosomal dominant cases

Mode of Inheritance: Heterogeneous. Autosomal recessive inheritance has been found in more severe cases, autosomal dominant inheritance in slightly milder cases.

Molecular basis: Autosomal recessive omodysplasia is caused by mutations of GPC6 encoding glypican 6, a heparan sulfate proteoglycan stimulating chondrodyte proliferation in growth plates. The molecular basis of dominant omodysplasia is not yet known.

Prenatal Diagnosis: Short arms and legs have been detected by sonography at 17 weeks gestation.

Differential Diagnosis: *Diastrophic dysplasia* differs clinically by the presence of cleft palate, club feet, cystic masses of the external ears and radiologically by the irregularly shortened and dysplastic metacarpals and phalanges. Distally tapered humeri and femora are found in *atelosteogenesis*, which differs by the characteristic abnormalities of the bones of the hands and feet. Mesomelic dysplasia in *Robinow syndrome* is not associated with the humero-femoral abnormalities characterizing omodysplasia.

Prognosis: Except for physical shortness and restricted mobility of the elbows, development is normal.

Remarks: Marked phenotypic overlap between the dominant and recessive forms of omodysplasia suggests common pathogenetic mechanisms.

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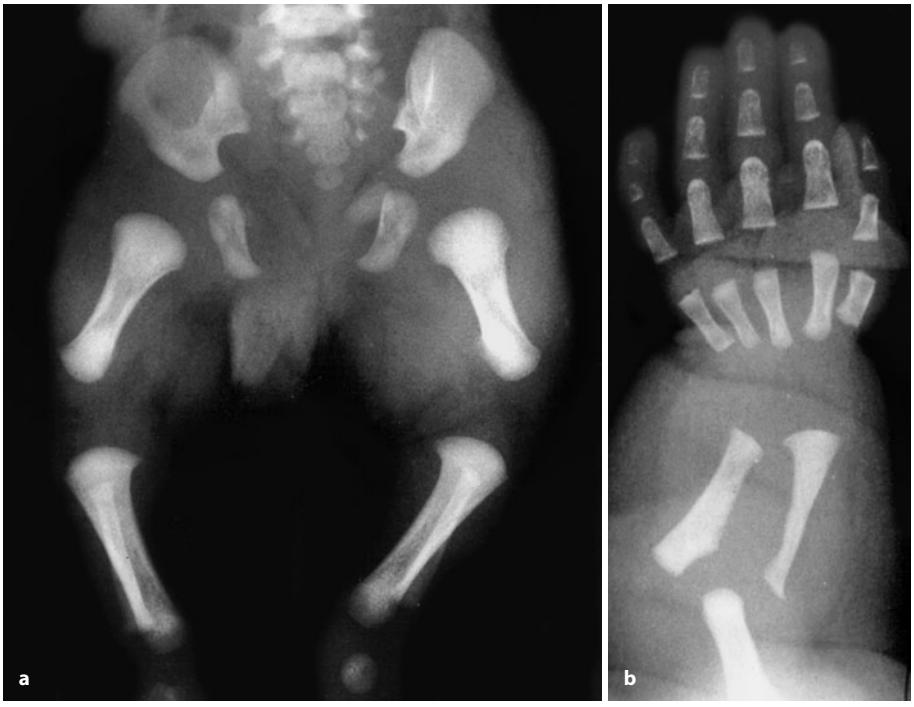

Fig. 3.50. ***Omodysplasia, autosomal recessive***. Newborn. **a** The femora are short with rounded, proximally wide and distally tapered ends producing a club-like appearance. The tibiae and fibulae are short. **b** Note short radius and ulna with dislocated radius. In this patient with recessive omodysplasia the hand bones are normal

Cleidocranial Dysplasia MIM 119600

Synonym: Cleidocranial dysostosis; Pelvico-cleido-cranial dysostosis; Cleido-cranio-digital dysostosis; Osseodental dysplasia; Marie-Sainton disease; Scheuthauer-Marie-Sainton syndrome.

Major Radiographic Features:

- Retarded ossification of the calvaria and skull base
- Partial or total, uni-or bilateral absence of the clavicles
- Absent ossification of the pubic bones
- Short distal phalanges
- In severe cases decreased mineralization with mild bowing of lower limbs

Mode of Inheritance: Autosomal dominant.

Molecular Basis: Mutations of the transcription factor *CBFA1* on chromosome 6p21.

Prenatal Diagnosis: Cleidocranial dysplasia has been diagnosed at 14 weeks gestation on the basis of hypoplastic clavicles and underossified skull bones. In familial cases, molecular analysis may be attempted.

Differential Diagnosis: Abnormal clavicles are present in numerous conditions which are differentiated by analysis of the rest of the skeleton. No other skeletal abnormalities are present in *congenital pseudarthrosis* of the clavicle. *Pyknodysostosis* differs by the increased bone density. The *Yunis-Varon syndrome* is characterized by the presence of distal reduction defects, notably a/hypoplasia of thumbs and great toes. The *Crane-Heise syndrome* shows cleft palate, micrognathia and defective ossification of cervical vertebral bodies. Hypoplastic clavicles have also be reported in *cytogenetic abnormalities* including duplicaton of chromosome 8p22, partial trisomy 11q, partial trisomy 11q/22q and trisomy 20p.

Prognosis: Life expectancy and mental development are normal. Dental, auditory and respiratory problems may require medical attention in later life

Remarks: Phenotypic variability is caused by allelic mutations of the *CBFA1* gene that result in a spectrum extending from severe, classic, mild manifestations to isolated primary dental anomalies. Parental mosaicism may result in mild somatic manifestations and may be responsible for the rare recurrence of the disorder in children of unaffected parents.

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(Fig. 3.51 see p. 172)

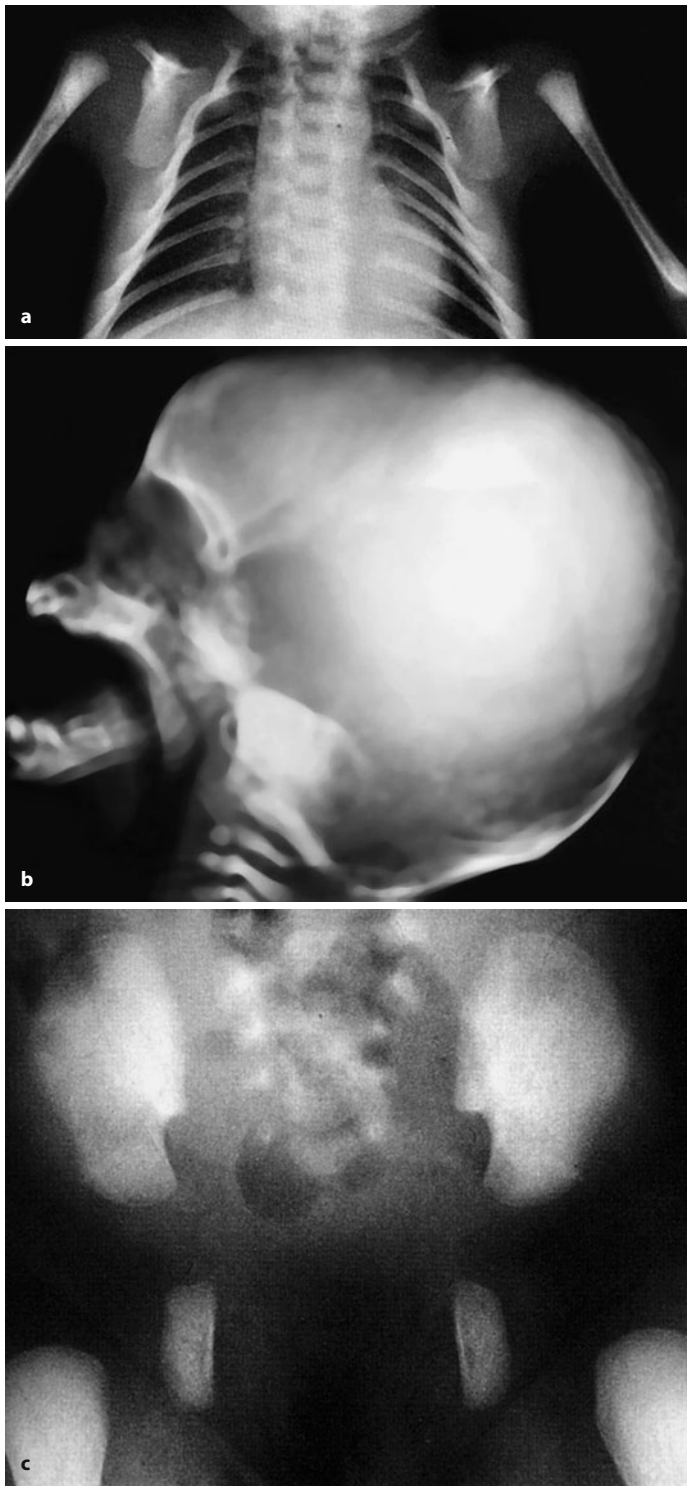

Fig. 3.51. ***Cleidocranial dysplasia.*** Full term newborn. **a** The clavicle is absent on the right side and hypoplastic on the left. **b** Ossification of the calvaria is deficient. Numerous Wormian bones are present in the occipital and parietal bones. **c** The pubic bones are not ossified and the space between the os sacrum and iliac bones is wide

K. Dysplasias with Prominent Involvement of the Mesial and Acral Skeleton

Mesomelic Dysplasia, Langer Type MIM 249700

Synonyms: Mesomelic dysplasia, Langer type; Mesomelic dwarfism of the hypoplastic ulna, fibula, and mandible type; homozygous dyschondrosteosis.

Major Radiographic Features:

- Disproportionate shortness of the mesial segments of the extremities
- Distal hypoplasia of the ulna; radial bowing of the radius
- Short tibia; hyopoplasia of the proximal fibula

Mode of Inheritance: Autosomal recessive. Parents have Madelung deformity and short stature (Dyschondrosteosis).

Molecular Basis: Deletion or mutation of the *SHOX* gene in the pseudoautosomal region of the X and Y chromosomes.

Prenatal Diagnosis: Short extremities are detected by ultrasound. Madelung deformity in both parents should alert to a 25% risk of Langer mesomelic dysplasia in the fetus.

Differential Diagnosis: *Dyschondrosteosis* is a milder condition without excessive shortness of the fibula. Numerous *other mesomelic dysplasias* are differentiated on the basis of associated features including tibio/talar fusion (Kantaputra dysplasia), short metacarpal/metatarsal bones (Ferraz dysplasia), short phalanges (Robinow syndrome, Osebold dysplasia) and others (see Spranger et al. 2002).

Prognosis: Intellectual and motor development are normal, adult height is reduced.

Remarks: Langer mesomelic dysplasia is the homozygous form of Leri-Weill dyschondrosteosis.

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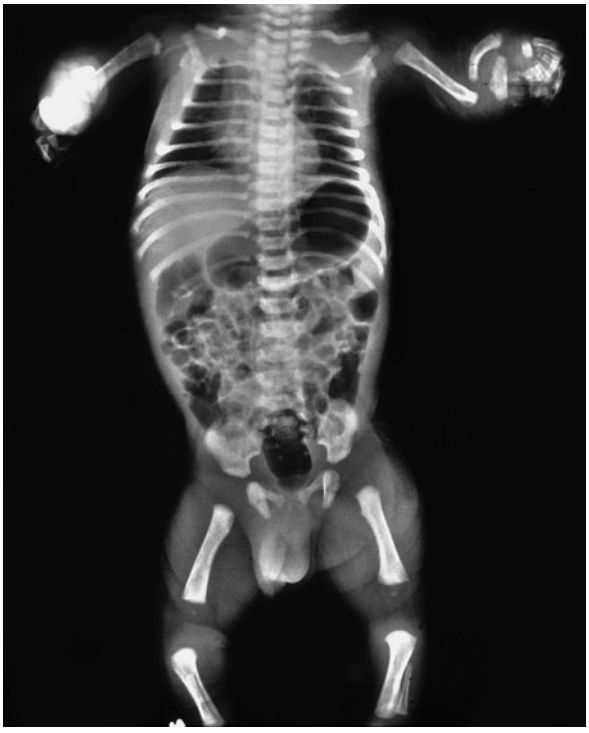

Fig. 3.52 ***Langer mesomelic dysplasia.*** Full term newborn. Abnormalities of the upper extremity are best seen on the left side, which shows a short, thick ulna, proximal hypoplasia and bowing of the radius. Absence of the proximal third of the fibula is noted. The tibiae are short

Robinow Syndrome MIM 180700, 268310

Synonym: Fetal face syndrome.

Major Radiographic Features:
- Short ulna and radius; dislocation of the radial head in severe cases
- Occasionally bifid phalanges
- Short tibia and fibula
- Frequently hemivertebrae and fusion of vertebral bodies in severe cases

Mode of Inheritance: Autosomal recessive and autosomal dominant.

Molecular Basis: Autosomal recessive Robinow syndrome is caused by homozygous loss-of function mutations of the *ROR2* gene located on chromosome 9q22. The protein product of this gene is a cell membrane receptor involved in extracellular protein interactions and intracellular signaling pathways. Autosomal dominant Robinow syndrome is caused by mutations of *WNT5A*, a protooncogene attaching to the ROR2 receptor.

Prenatal Diagnosis: In a severely affected fetus sonography disclosed short extremities and increased nuchal translucency in the 12th week of gestation. Molecular analysis can be attempted in familial, autosomal recessive cases with known mutations.

Differential Diagnosis: In *Langer mesomelic dysplasia*, ulna and fibula are more severely shortened than radius and tibia. *Omodysplasia* differs by the distally tapered, short humerus and femur. *Other mesomelic dysplasias* are ruled out by the different aspect of the bones of the shanks and forearms, associated acral abnormalities and clinical features.

Prognosis: Mortality is approximately 10% in autosomal recessive cases and not elevated in the dominant variety. Affected individuals are short and may have associated anomalies including genital hypoplasia, renal and cardiac defects. Intelligence is usually normal.

Remarks: Autosomal recessive Robinow syndrome tends to be more severe than the autosomal dominant variety with more severe mesomelic shortening, more frequent vertebral anomalies, and 10% mortality (probably due to associated defects), but there is considerable overlap between the two forms. Rib fusions have only been described in the recessive form. Heterozygotes with the mutated *ROR2* gene may have short or absent middle and distal phalanges (brachydactyly B).

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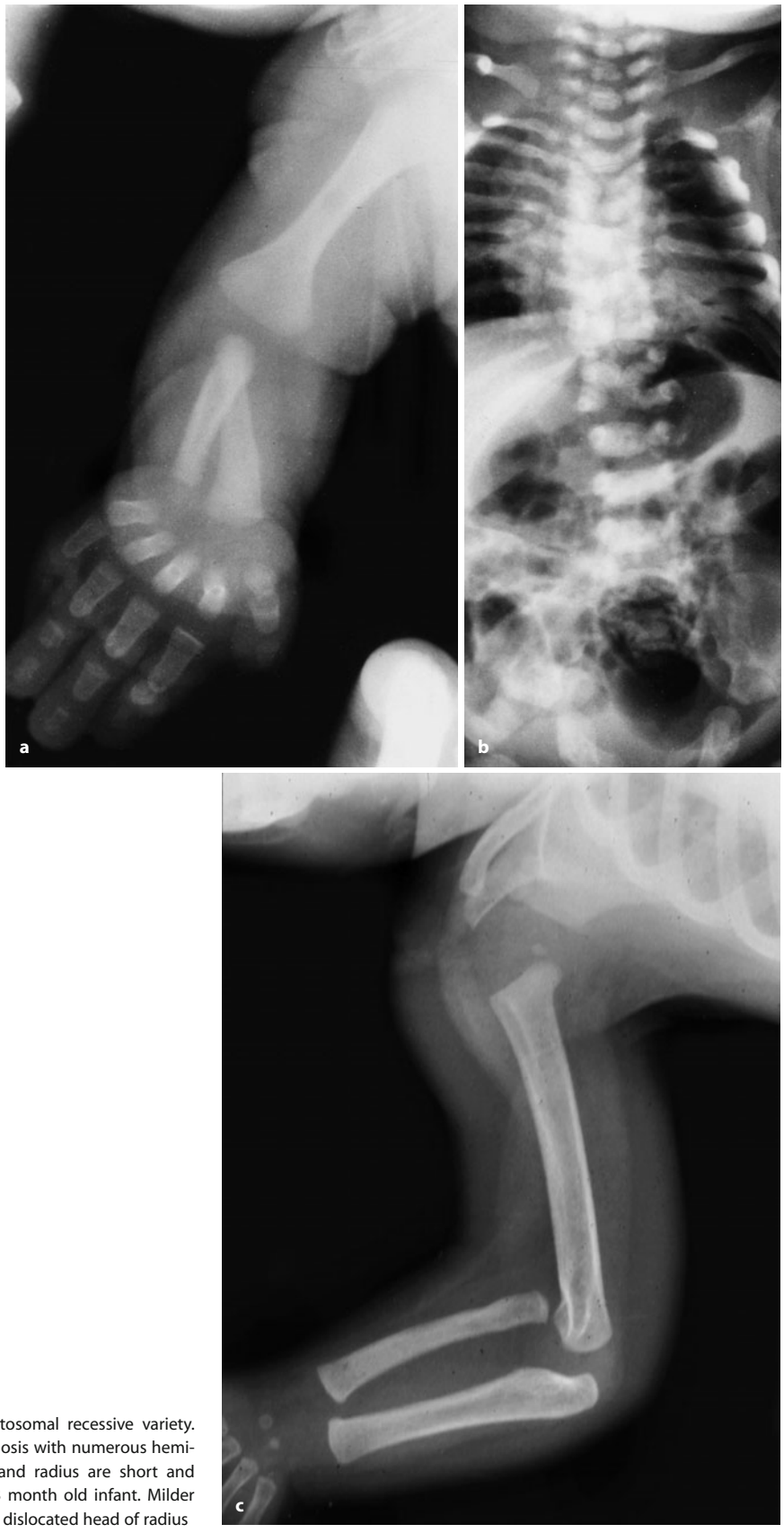

Fig. 3.53 ***Robinow syndrome.*** **a, b** Autosomal recessive variety. Full-term newborn. There is dysspondylosis with numerous hemivertebrae and fused vertebrae. Ulna and radius are short and thick. **c** Autosomal dominant variety, 3 month old infant. Milder shortening of ulna and radius than in B; dislocated head of radius

Nievergelt Syndrome MIM 163400

Major Radiographic Features:

- Very short, triangular or rhomboid tibiae; sometimes similar abnormality of the radii
- Less marked shortening of the fibulae and ulnae

Mode of Inheritance: Autosomal dominant.

Prenatal Diagnosis: Short mesial segments of the extremities can be detected by sonography.

Differential Diagnosis: In *Langer mesomelic dysplasia* the fibula and ulna are more severely affected than the tibia and radius. A short tibia and radius are found in *other mesomelic dysplasias* (for ref see Spranger et al. 2002).

Prognosis: Normal development and life expectancy.

Remarks: There is considerable intrafamilial variability of expression.

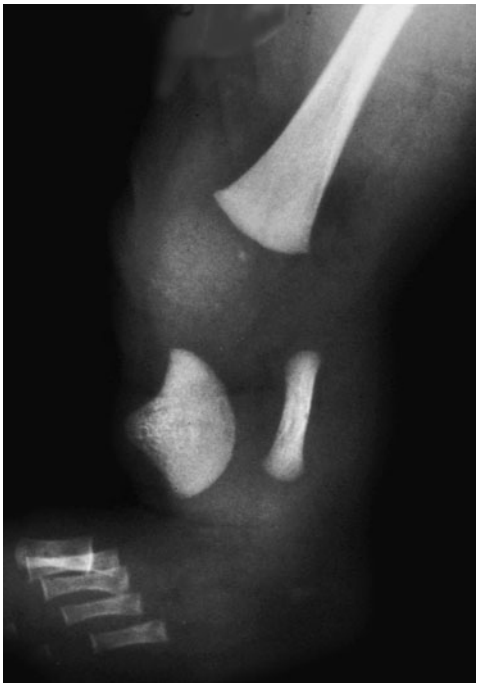

Fig. 3.54 ***Nievergelt syndrome***; full term newborn. The tibia is very short and halberd-shaped. The fibula is less markedly shortened and straight

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Grebe Dysplasia MIM 200700, 201250, 228900

Synonym: Brazilian achondrogenesis. Includes Hunter-Thompson syndrome, Du Pan syndrome; CDMP1 dysplasia (Grebe- Hunter-Thompson- DuPan- types).

Major Radiographic Features:

- Variable shortness of femur and humerus
- Short ulna, bowed radius, radioulnar dislocation in severe (Grebe) and moderately severe (Hunter-Thompson) subtypes, almost normal radius and ulna in mild (Du Pan) subtype
- Short, misshapen metacarpals and metatarsals; hypoplastic, misshaped or absent phalanges
- Short and broad tibiae
- Fibular a/hypoplasia
- Normal craniofacial and axial skeleton

Mode of Inheritance: Autosomal recessive.

Molecular Basis: Grebe dysplasia is caused by mutations of the *CDMP1* gene located on chromosome 20q11.2 coding for cartilage-derived morphogenetic protein-1, a signaling molecule involved in the patterning of the appendicualr skeleton, chondrogenesis and longitudinal bone growth.

Prenatal Diagnosis: Short limbs and fingers are detectable by ultrasound. Molecular analysis of fetal cells is possible in families with a known mutation.

Differential Diagnosis: *Langer mesomelic dysplasia, Nievergelt dysplasia* and *other mesomelic bone dysplasias* differ by the more normal aspect of the hands and feet.

Prognosis: The patients' major handicap is short stature. Their psychomotor and intellectual development is normal.

Remarks: Allelic mutations of the CDMP1 gene lead to a wide spectrum of disorders formerly thought to represent different entities (i.e. Grebe, Hunter-Thompson and

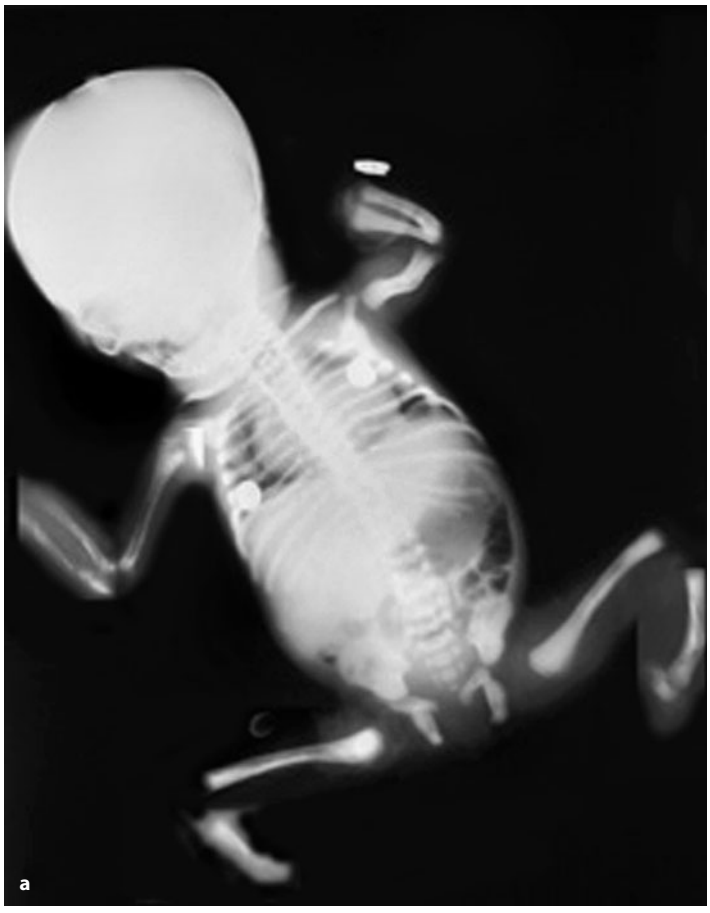

Fig. 3.55 ***DuPan variety of CDMP1 dysplasia***. 38 weeks gestation. **a** The humeri are short and bowed on the left but not on the right side. The tibiae are short and anteriorly bowed with complete absence of the fibulae

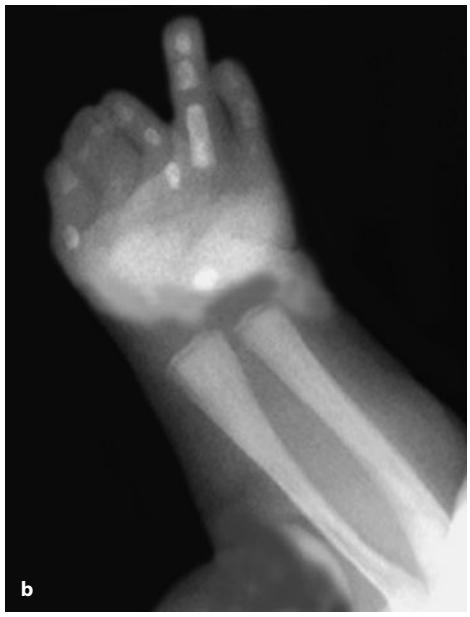

Fig. 3.55b. The metacarpals are not ossified. Three phalanges are seen in the index finger; those in the other fingers are small, misshaped or not ossified. There is an extra bone in the carpal region

Du Pan dysplasia). These three disorders differ mostly by the degree of involvement of the long tubular bones. Heterozygote carriers of the *CDMP1* mutation may have brachydactyly C (short middle phalanges, misshaped extraphalangeal ossification centers).

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L. Skeletal Dysplasias with Increased Bone Density

Infantile Osteopetrosis MIM 259700, 611490, 259720

Synonym: Infantile malignant osteopetrosis. Includes lethal osteopetrosis

Major Radiographic Features:
- Generalized increased bone density
- Metaphyseal undermodeling
- Radiolucent bands at the long bone metaphyses

Mode of Inheritance: Autosomal recessive. There is nonallelic heterogeneity.

Molecular Basis:
A) *TCIRG1* located on chromosome 11q13.4–13.5 encoding T-cell-immune regulator 1 .
B) *CLC7* located on chromosome 16p13 encoding chloride channel protein 7.
C) *OSTN1* located on chromosome 6q21 encoding osteopetrosis-associated transmembrane protein 1.

Prenatal Diagnosis: Prenatal diagnosis has been achieved by radiographic evaluation. If the mutation is known from previous siblings, molecular diagnosis is possible.

Differential Diagnosis: The bone changes in *Raine syndrome*, which is caused by mutations of the FAM20C gene located on chromosome 7p22 resemble those in infantile osteopetrosis. The disorder differs by the craniofacial appearance with bulging fontanels, proptosis, hypoplastic nose and micrognathia. In contrast to infantile osteopetrosis the outer contours of the long bones are irregular due to excessive subperiosteal bone formation (Fig. 56F). *Desmosterolosis*, caused by deficient dehydrocholesterol reductase, may manifest with an almost identical phenotype [Fitzpatric DR et al (1998) J Am Med Ass 75:145–152]. *Other forms of osteopetrosis* including autosomal dominant and autosomal recessive late types, *carboanhydrase deficiency, pycnodysostosis*, *osteomesopycnosis* or *dysosteosclerosis* may manifest in the neonate with comparatively mild sclerosis. They are rarely recognized in fetal life or the neonatal period.

Prognosis: Neonatal mortality is increased. Surviving infants may reach adulthood after bone marrow transplantation in early childhood.

Remarks: Hematopoietic stem cell transplantation is the therapy of choice in severe infantile forms of osteopetrosis.

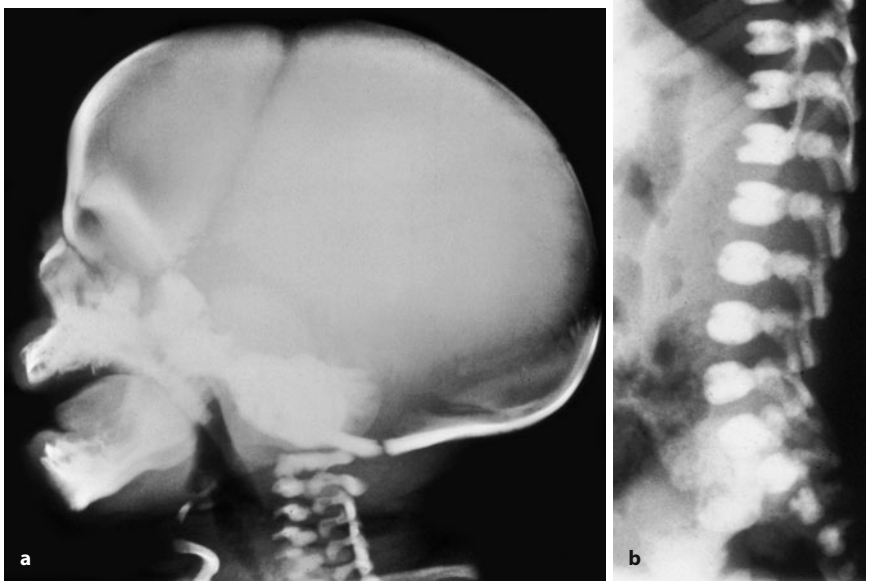
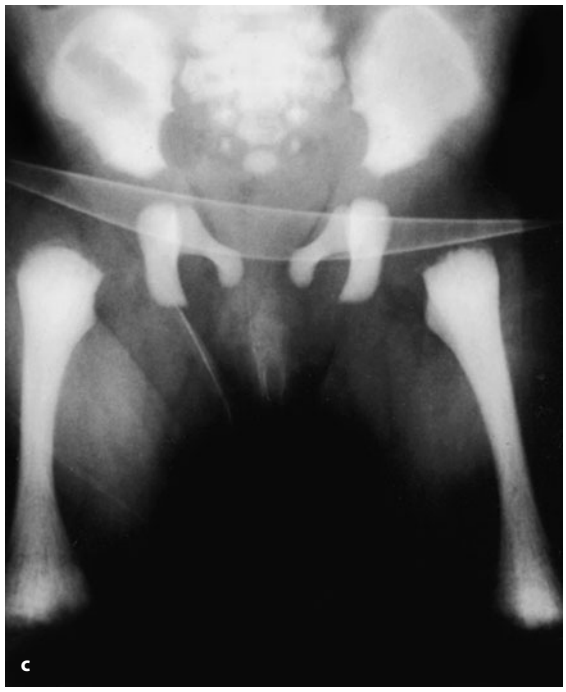
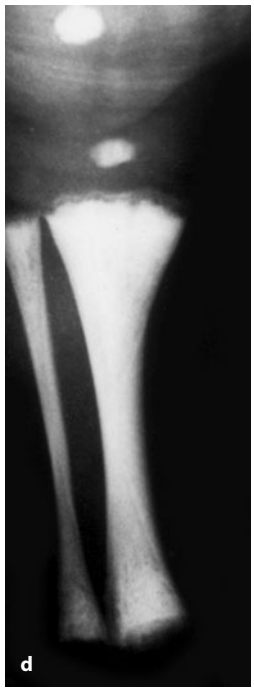
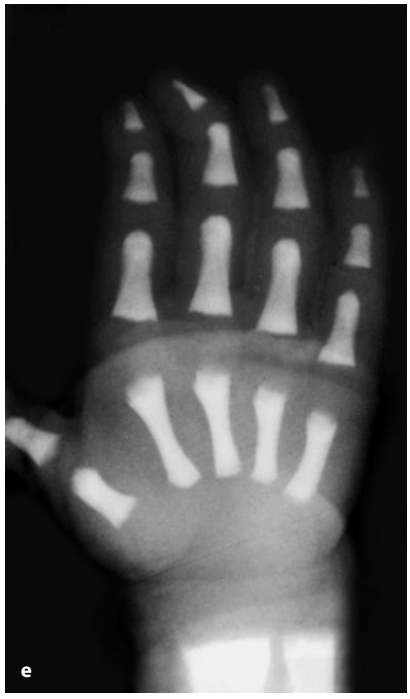


Fig. 3.56. ***Infantile osteopetrosis***, full-term newborn. **a** The base of the skull, facial bones and part of the calvaria are sclerotic. **b** The vertebrae are normally formed and dense







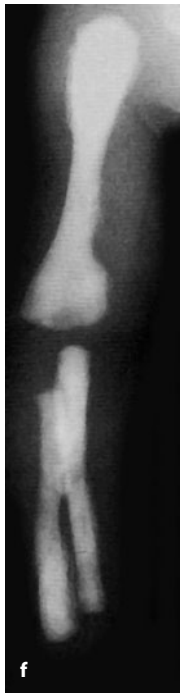


Fig 3.56c, d Pelvis and long tubular bones are homogeneously sclerotic with absent cortico-medullary demarcation and lack of normal metaphyseal modeling. Note slightly irregular appearance of the proximal tibial metaphysis, which later may develop into 'osteopetrorickets'. **e** The short tubular bones are normally shaped and dense. **f** *Raine Syndrome* Bone density is increased as in infantile osteopetrosis, but, in addition, the contours of the long bones are irregular due to excessive subperiosteal bone formation (Courtesy Dr. K. Kozlowski, Sidney)

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Blomstrand Syndrome MIM 215045

Major Radiographic Features:
- Generalized sclerosis
- Small facial bone
- Short and broad ribs
- Tubular bones with mushroomed ends and very short, sometimes bowed or kinked diaphyses
- Advanced bone maturation

Mode of Inheritance: Autosomal recessive.

Molecular Basis: Mutations of the *PTHR1* gene located on chromosome 3p22-p21.1 encoding a receptor for both parathyroid hormone and parathyroid hormone-related protein. The mutations result in the inactivation of the PTH receptor.

Prenatal Diagnosis: Fetal sonography showed polyhydramnion and very short limbs at 19 weeks gestation. In familial cases, molecular diagnosis should be possible.

Differential Diagnosis: In infantile *osteopetrosis* the tubular bones are straight with less severe metaphyseal widening.

Prognosis: All known patients were stillborn or died shortly after birth.

Remarks: Pathogenetically, Jansen and Blomstrand dysplasia are mirror images. Lack of function of the parathyroid hormone receptor causes Blomstrand dysplasia, its constitutive activation Jansen metaphyseal dysplasia. *PTHR1* mutations have also been detected in some patients with Olllier/Maffucci enchondromatosis [Couvineau A et al (2008) Hum Mol Genet 17:2766–2775] and in a family with Eiken syndrome.

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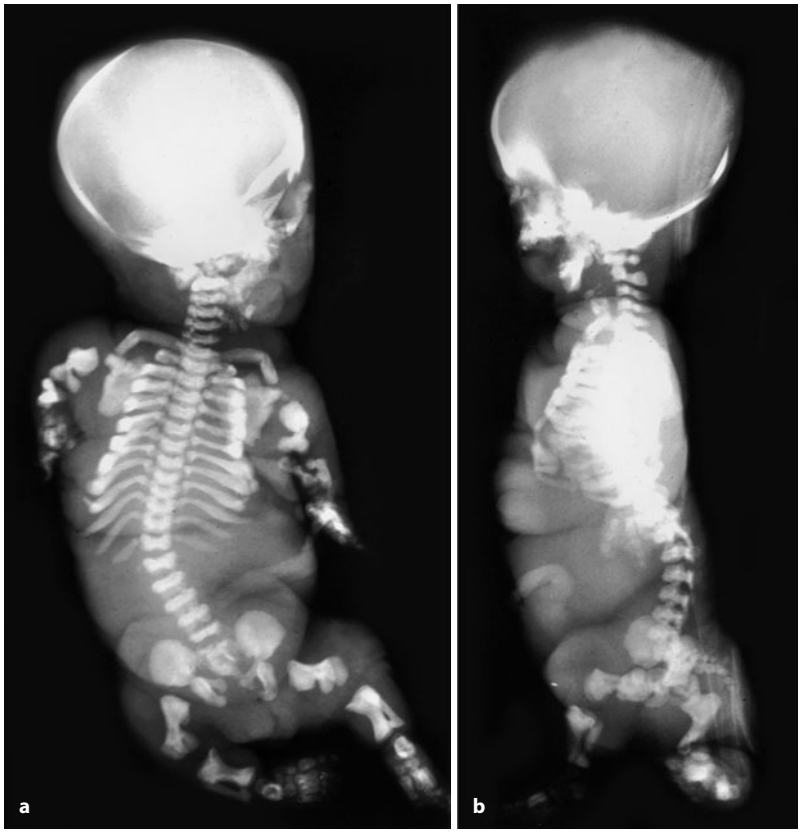

Fig. 3.57 ***Blomstrand Dysplasia***, 32 weeks gestation. **a, b** The skeleton is sclerotic. The viscerocranium is disproportionately small. The chest is small with thick clavicles and ribs. The tubular bones are very short with bowed or kinked diaphyses and wide ends. Advanced bone maturation is best appreciated in the tarsus

Lenz-Majewski Hyperostotic Dysplasia MIM 151050

Synonym: Lenz-Majewski syndrome; Lenz-Majewski hyperostotic dwarfism.

Major Radiographic Features:
- Hyperdensity of the cranial base and facial bones
- Mild hyperostosis of the clavicles and ribs
- Mild hyperostosis of the tubular bones
- Irregular shortening of the metacarpals, defective ossification and fusion of the proximal and middle phalanges especially on the ulnar side

Mode of Inheritance: Uncertain, possibly autosomal dominant.

Molecular Basis: Unknown.

Prenatal Diagnosis: Uncertain.

Differential Diagnosis: The *physiologic skeletal hyperdensity* of the premature infant is less severe and disappears during the first weeks of life. More severe sclerosis and tubular undermodeling are found *in infantile osteopetrosis* and *Blomstrand dysplasia*. The aberrant metacarpal and phalangeal ossification in the Lenz-Majewski syndrome assists in its differentiation from the former and from disorders with mildly increased bone density such as *pycnodysostosis, osteopetrosis with renal tubular acidosis* (carboanhydrases deficiency) or *dysosteosclerosis*.

Prognosis: Neonatal mortality is increased. Survivors have been followed up to adulthood with mental retardation and short stature.

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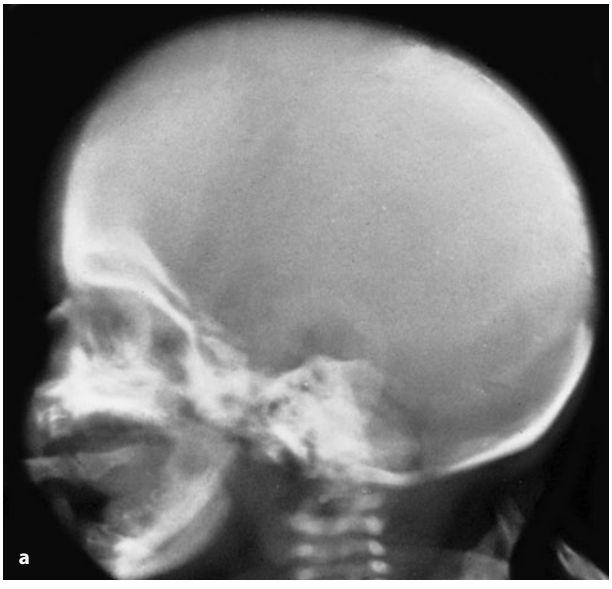

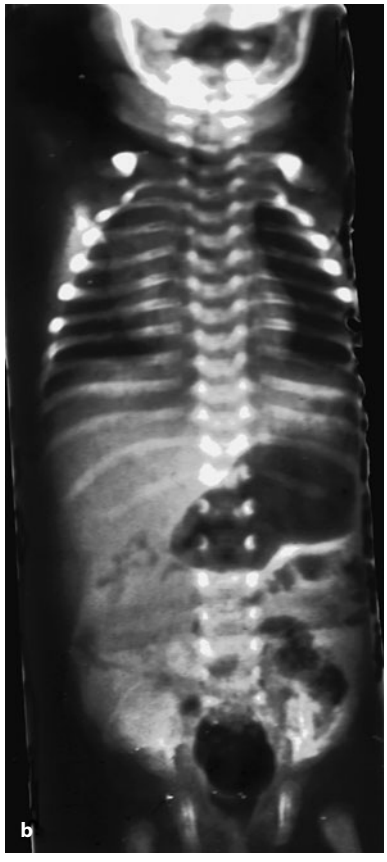

Fig. 3.58a, b. ***Lenz-Majewski Syndrome.*** Full-term newborn. **a** There is mild hyperdensity of the cranial base, facial bones and part of the cranial vault. **b** The bone density is increased in the clavicles, ribs and pedicles

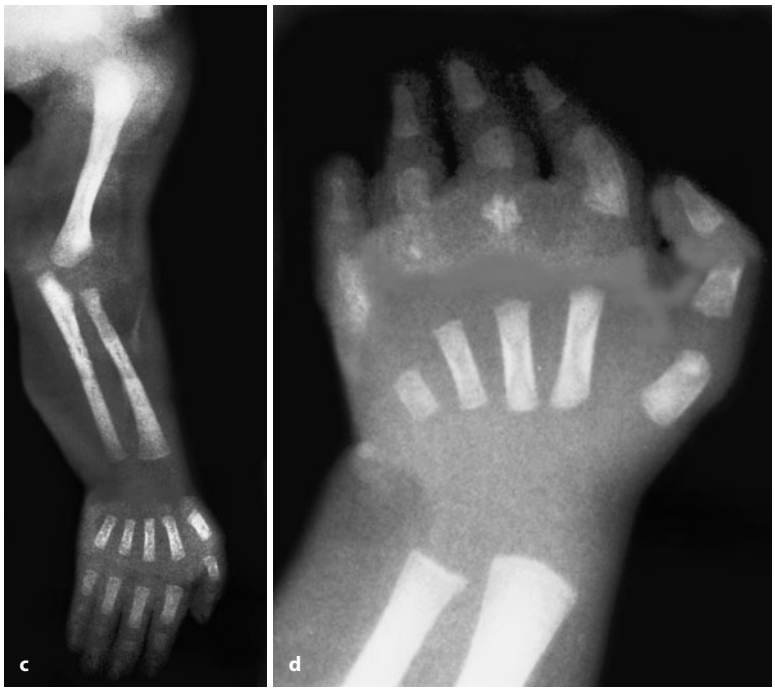

Fig. 3.58c. Patchy hyperdensities are present in the long tubular bones. **d** The first and fifth metacarpals are short. There is erratic ossification and partial fusion of the proximal and middle phalanges of the 2nd to 5th fingers. Fusion of the proximal and middle phalanx of the index finger is complete

Amelia – Amputation – Phocomelia

Diagnosis	Skull	Spine	Humerus
Acrofacial dysostosis, type Rodriguez			x
Amelia, autosomal recessive			x
Amniotic band disruption sequence; ADAM Limb body wall complex	x	x	
Diabetic embryopathy		x	
Disorganisation-like syndrome	x	x	x
DK phocomelia Phocomelia-encephalocele-thromobocytopenia-urogenital malformation von Voss-Cherstvoy sindrome	x		x
Femur-fibula-ulna complex			x
Limb/pelvis hypoplasia/aplasia syndrome. Includes Schinzel phocomelia, AL-Awadi/ Raas-Rothschild syndrome, Fuhrmann		x	
Oromandibula-limb hypogenesis syndromes incl. Hanhart syndrome			
Roberts (pseudothalodomide) syndrome	x		x
Schinzel-Giedion syndrome	x		
Sirenomelia		x	
Splenogonadal fusion – limb defects	x	x	
Tetraamelia with multiple malformations	x	x	
Thalidomide embryopathy			x
Thrombocytopenia-absent radius (TAR) Syndrome (severe form)[			x
VACTERL association		x	

Radius and/or Thumb Aplasia, Hypoplasia

Diagnosis	Skull	Spine	Humerus
Aase syndrome Blackfan-Diamond syndrome			
Acrofacial dysostosis, type Rodriguez			x
Amniootic band disruption sequence; ADAM Limb body wall complex	x	x	
Baller-Gerold Syndrome	x		
Brachmann-de Lange Syndrome			
Cerebro-cardio-radio-rectal community	x		x
Chromosome abnormality Trisomy 18 (Edward Syndrome)	x	x	
Chromosome 13 q- syndrome			
Duane			
Fanconi pancytopenia TAR			
Fetal valproate syndrome	x		

Radius	Ulna	Femur	Tibia	Fibula	Hands/Feet	Others
x	x			x	x	Hypoplastic scapula
x	x	x	x	x	x	
		x			x	
		x	x		x	cardiac defects, anal atresia
x	x	x	x	x	x	Asymmetry
x	x				x	genitourinary and cardiac anomalies
	x	x		x		Synostosis around the elbow
x	x	x	x	x	x	hypoplastic pelvis
					x	Microglossia, transverse limb reduction
x	x	x	x	x	x	Cystic hygroma
x	x		x	x		bowing of long bones
x		x	x	x	x	anal atresia
					x	micrognathia, transverse limb reduction
						nearly totally absent limbs
x	x	x	x	x		defects mostly proximal
x	x				x	present thumb
x			x	x	x	intestinal atresias

Radius	Ulna	Femur	Tibia	Fibula	Hands/Feet	Others
x	x					
x	x			x	x	hypoplastic scapula
x					x	ventral wall defect
x					x	
x	x				x	
x	x				x	
x			x		x	
					x	growth retardation
x					x	TAR: present thumbs
x					x	

Diagnosis	Skull	Spine	Humerus
Fibrodysplasia ossificans progressiva			
Fryns syndrome – acral defects			
Goldenhar syndrome	x	x	
Holt-Oram (cardiomelic) syndrome			x
Mesomelic dysplasias			
MURCS association		x	
Nager acrofacial dysostosis	x		
OPD II (oto-palato-digital syndrome II)		x	x
Poland syndrome		x	
Roberts (pseudothalodomide) syndrome	x		x
Sirenomelia		x	
VACTERL-Association		x	
XK-aprosencephaly	x		

Radio-ulnar Synostosis

Diagnosis	Skull	Spine	Humerus
Aase syndrome Blackfan-Diamond syndrome			
Antley-Bixler syndrome	x		
Cenani-Lenz syndrome		x	
Cloverleaf skull – limb anomaly, type Holtermüller-Wiedemann	x		
Chromosome abnormality Trisomy 18 (Edward Syndrome)	x	x	
Chromosome abnormality Klinefelter syndrome			
Duane anomaly – radial defects		x	
Ectrodactyly AD, AR			
Fetal alcohol syndrome		(x)	
Genitopatellar syndrome			
Holt-Oram (cardiomelic) syndrome			x
Larsen syndrome			
Nager acrofacial dysostosis	x		
Radio-ulnar synostosis, autosomal dominant			
XK-aprosencephaly	x		

Radius	Ulna	Femur	Tibia	Fibula	Hands/Feet	Others
					x	
x					x	diaphragmatic hernia
x						
x	x				x	heart lesions (ASD, VSD)
x	x		x	x	x	See p. 173
x					x	
x	x					
x	x	x	x	x	x	narrow pelvis see p. 96
		x			x	aplasia of pectoralis muscle
x	x	x	x	x	x	cystic hygroma
x		x	x	x	x	anal atresia
x			x	x	x	intestinal atresias
x	x					

Radius	Ulna	Femur	Tibia	Fibula	Hands/Feet	Others
x	x					
x						See p. 126
x	x				x	
x	x					
x	x		x		x	
x	x					
x					x	
x	x				x	
x	x				x	growth retardation
x	x				x	dislocation of hip
x	x				x	Heart lesions (ASD, VSD)
x	x					See p. 161
x	x					
x	x					
x	x					

Ulna, aplasia , hypoplasia

Diagnosis	Skull	Spine	Humerus
Acrofacial dysostosis with post-axial defects	x		
Acrofacial dysostosis, type Rodriguez			x
Brachmann-de Lange Syndrome			
Femur-fibula-ulna complex			x
Fetal alcohol syndrome		(x)	
Grebe syndrome			x
Holt-Oram (cardiomelic) syndrome			x
Humero-radial synostosis-ulnar defects			x
Leri-Weill dyschondrosteosis			
Mesomelic dysplasias			
Mietens-Weber syndrome			
Neu-Laxova syndrome	x		
Neurofibromatosis 1			
Odontotrichomelic syndrome			
Pfeiffer Absent ulna/fibula with oligodactyly			
Roberts (pseudothalodomide) syndrome	x		x
Thrombocytopenia-absent radius (TAR) syndrome			
Ulnar-mammary syndrome type Pallister			
Weyers syndrome			

Humerus, aplasia, hypoplasia

Diagnosis	Skull	Spine	Humerus
Acrofacial dysostosis, type Rodriguez			x
Atelosteogenesis and related OCDs		x	x
Brachmann-de Lange Syndrome			
CHILD syndrome			x
Chondrodysplasia punctata, rhizomelic type		x	x
Chondrodysplasia punctata, tibia-metacarpal type			x
DK phocomelia Phocomelia-encephalocele-thromobocytopenia-urogenital malformation von Voss-Cherstvoy sindrome	x		x
Femur-fibula-ulna complex			x
Fetal thalidomide			x
Fetal valproate syndrome	x		x
Holt-Oram (cardiomelic) syndrome			x
Omodysplasia			x
Oromandibula-limb hypogenesis syndromes incl. Hanhart syndrome			x
Thrombocytopenia-absent radius (TAR) Syndrome (severe form)[			x
Thrombocytopenia-absent radius (TAR) Syndrome (severe form)[			x
Ulnar-mammary syndrome type Pallister			x

Radius	Ulna	Femur	Tibia	Fibula	Hands/Feet	Others
	x				x	
x	x			x	x	Hypoplastic scapula
x	x				x	
	x	x		x		Synostosis around the elbow
	x				x	growth retardation
x	x	x	x	x	x	
x	x				x	Heart lesions (ASD, VSD)
x	x			x		
x	x		x	x		
x	x		x	x	x	See p. 173 ff
x	x			x		Hip dislocation
x	x				x	
x	x	x	x			Pseudarthrosis
					x	
			x	x	x	
x	x	x	x	x	x	Cystic hygroma
x	x					Present thumb
	x				x	Anal atresia
	x			x	x	

Radius	Ulna	Femur	Tibia	Fibula	Hands/Feet	Others
x	x			x	x	Hypoplastic scapula
x	x	x		x	x	See p. 163
x	x				x	
x	x	x	x	x		unilateral
		x				
		x	x		x	
x	x				x	genitourinary and cardiac anomalies
	x	x		x		Synostosis around the elbow
x	x	x	x	x		Defects mostly proximal
x					x	
x	x				x	Heart lesions (ASD, VSD)
x	x	x	x	x		See p. 170
					x	Microglossia, transverse limb reduction
x	x				x	Present thumb
x	x				x	Present thumb
	x				x	Anal atresia

Tibia, aplasia, hypoplasia

Diagnosis	Skull	Spine	Humerus
Acro-renal-mandibular syndrome	x	x	
Amniotic band disruption sequence; ADAM Limb body wall complex	x	x	
Chondrodysplasia punctata, tibia-metacarpal type			
Chromosome abnormality Trisomy 18 (Edward Syndrome)	x	x	
Grebe syndrome			x
Mesomelic dysplasias			
Mesomelic dwarfism of hypoplastic tibia-radius type			
Neurofibromatosis 1			
Split hands/foot, tibial defect			
Tibial hemimelia			
Tibial hypoplasia, polydactyly and triphalangeal thumb (Werner)			
VACTERL-Association		x	

Fibula, aplasia, hypoplasia

Diagnosis	Skull	Spine	Humerus
Acrofacial dysostosis, type Rodriguez			x
Atelosteogenesis and related OCDs		x	x
Campomelic dysplasia		x	x
Chondroectodermal dysplasia Ellis-van Creveld			
De la Chapelle dysplasia		x	x
Du Pan brachydactyly, fibular aplasia			
Ectrodactyly-fibular aplasia			
Femur-fibula-ulna complex			x
Femoral hypoplasia, unusual facies syndrome	x		
Fibular aplasia/hypoplasia			
Limb/pelvis hypoplasia/aplasia syndrome. Includes Schinzel phocomelia, AL-Awadi/ Raas-Rothschild syndrome, Fuhrmann		x	
Mesomelic dysplasias			
Seckel syndrome	x		
VACTERL-Association		x	

Radius	Ulna	Femur	Tibia	Fibula	Hands/Feet	Others
x					x	
			x		x	ventral wall defect, transverse reductions
		x	x		x	
x			x		x	
x	x	x	x	x	x	
x	x		x	x	x	See p. 173 ff
x			x			
x	x	x	x			Pseudarthrosis
	x	x	x		x	
			x		x	
x	x		x		x	Mesomelic dysplasia
x			x	x	x	intestinal atresias

Radius	Ulna	Femur	Tibia	Fibula	Hands/Feet	Others
x	x			x	x	Hypoplastic scapula
x	x	x		x	x	See p. 163
x	x	x	x	x	x	pear-shaped ilia
		x	x	x	x	See p. 124
		x	x	x	x	See p. 153
				x	x	dislocation of great joint
	x			x	x	
	x	x		x		Synostosis around the elbow
		x	x	x	x	micrognathia
				x		
x	x	x	x	x	x	hypoplastic pelvis
x	x		x	x	x	See p. 173
				x		Severe growth retardation
x			x	x	x	intestinal atresias

Femur, aplasia, hypoplasia

Diagnosis	Skull	Spine	Humerus
Atelosteogenesis and related OCDs		x	x
Diabetic embryopathy		x	
Ectrodactyly-tibial hypoplasia			
Femoral hypoplasia, unusual facies syndrome	x		
Femur-fibula-ulna complex			x
Limb body wall complex		x	
Limb/pelvis hypoplasia/aplasia syndrome		x	
Omodysplasia			x
Proximal focal femoral deficiency			

Stippled epiphyses – stippled ossification of cartilage

Diagnosis	Skull	Spine	Humerus
Chromosome abnormality Triploidy		x	
Chromosome abnormality Trisomy 13	x	x	
Chromosome abnormality Trisomy 18 (Edward Syndrome)	x	x	
Chromosome abnormality Trisomy 21		x	
Chromosome abnormality Turner syndrome			
Fetal alcohol syndrome		(x)	
Hydantoin embryopathy	x		
Smith-Lemli-Opitz syndrome	x		
Warfarin embryopathy	x		
Zellweger syndrome	x		

Absent hands/feet

Diagnosis	Skull	Spine	Humerus
Acheiropodia			
Adams-Oliver syndrome	x		
Amniotic band disruption sequence; ADAM Limb body wall complex	x	x	
Brachmann-de Lange Syndrome			
Femur-fibula-ulna complex			x
Holoprosencephaly-transverse limb defect			
Oromandibula-limb hypogenesis syndromes incl. Hanhart syndrome			

Radius	Ulna	Femur	Tibia	Fibula	Hands/Feet	Others
x	x	x		x	x	See p. 163
		x	x		x	cardiac defects, anal atresia
		x	x		x	
		x	x	x	x	micrognathia
	x	x		x		Synostosis around the elbow
x		x			x	Bladder extrophy
x	x	x	x	x	x	hypoplastic pelvis
x	x	x	x	x		See p. 170
		x				

Radius	Ulna	Femur	Tibia	Fibula	Hands/Feet	Others
						Severe growth retardation
					x	Omphalocele
x			x		x	
					x	
					x	Hygroma
	x				x	growth retardation
					x	stippled epiphyses
					x	Growth retardation
					x	Stippled calcifications
						Stippled calcifications around the pelvis

Radius	Ulna	Femur	Tibia	Fibula	Hands/Feet	Others
x	x		x	x	x	
					x	
		x			x	
x	x				x	
	x	x		x	x	Synostosis around the elbow
					x	
					x	Microglossia, transverse limb reduction

Split/cleft/ectrodactyly of hands and/or feet

Diagnosis	Skull	Spine	Humerus
Acro-renal-mandibular syndrome	x	x	
Brachmann-de Lange Syndrome			
Chromosome abnormality Trisomy 13	x	x	
Chromosome abnormality Trisomy 18 (Edward Syndrome)	x	x	
Cleft palate-cardiac defect-genital anomalies and ectrodactyly	x		
DK phocomelia Phocomelia-encephalocele-thromobocytopenia-urogenital malformation von Voss-Cherstvoy sindrome	x		x
Ectrodactyly-Ectodermal dysplasia-Clefting syndrome	x		
Ectrodactyly-fibular aplasia			
Ectrodactyly, isolated			
Ectrodactyly-tibial hypoplasia			
Femur-fibula-ulna complex			x
Holoprosencephaly-hypertelorism-ectrodactyly syndrome	x		
Monodactylous ectrodactyly and bifid femur Wolfgang-Gollop syndrome		x	
Oromandibula-limb hypogenesis syndromes incl. Hanhart syndrome			

Preaxial polydactyly of hands and/or feet

Diagnosis	Skull	Spine	Humerus
Aase syndrome Diamond-Blackfan syndrome Anemia and triphalangeal thumbs			
Acrocallosal syndrome	x		
Carpenter syndrome Acrocephalopolysyndactyly, type 2	x		
Chromosome abnormalities			
Diabetic embryopathy		x	
Greig cephalopolysyndactyly	x		
Holt-Oram (cardiomelic) syndrome			x
Hydrolethalus syndrome	x		
Isolated defect			
Laurin-Sandrow syndrome			
Orofacial digital syndromes	x		
Pfeiffer syndrome Acrocephalosyndaktyly V	x		
Pseudo-trisomy 13 syndrome	x	x	
Short rib-polydactyly syndromes, different types		x	x
Townes-Brocks syndrome			
VACTERL-Association VATER-Association		x	
VATER-Association with hydrocephalus	x	x	

Radius	Ulna	Femur	Tibia	Fibula	Hands/Feet	Others
x			x		x	Severe hypoplasia of mandibula
x	x				x	
					x	Omphalocele
x			x		x	
					x	
x	x				x	genitourinary and cardiac anomalies
					x	cleft lip/palate, renal dysplasia
	x			x	x	
					x	
		x	x		x	
	x	x		x		Synostosis around the elbow
x	x				x	cleft lip,
xx	xx	xx	x	x	x	
					x	Microglossia, transverse limb reduction

Radius	Ulna	Femur	Tibia	Fibula	Hands/Feet	Others
					x	
					x	Macrosomy at birth
					x	
		x	x		x	cardiac defects, anal atresia
					x	
x	x				x	Heart lesions (ASD, VSD)
					x	micrognathia
					x	
x	x		x	x	x	
			x		x	
					x	
x	x				x	Omphalocele
x	x	x	x	x	x	See p. 147 ff Very short ribs
					x	anal atresia
x			x	x	x	intestinal atresias
x			x	x	x	intestinal atresias

Postaxial polydactyly of hands and/or feet

Diagnosis	Skull	Spine	Humerus
Acrocallosal syndrome	x		
Asphyxiyting thoracic dystrophy, Jeune syndrome			
Acrocephalopolydactyly II (Carpenter)	x		
Chromosome abnormality Trisomy 13	x	x	
Chromosome abnormality, other			
Elejalde syndrome	x		x
Ellis-van Creveld syndrome Chondroectodermal dysplasia			
Focal dermal hypoplasia Goltz syndrome			
Grebe syndrome			x
Greig cephalopolysyndactyly	x		
Hydrolethalus syndrome	x		
Isolated defect			
Laurin-Sandrow syndrome			
McKusick-Kaufman syndrome			
Meckel-Gruber syndrome	x		
Orofacial digital syndromes	x		
Pallister-Hall syndrome			
Pseudo-trisomy 13 syndrome	x	x	
Short rib-polydactyly syndrome, different types		x	x
Simpson-Golabi-Behmel syndrome	x	x	
Smith-Lemli-Opitz syndrome	x		
Synpolydactyly			

Premature cranial synostosis/cloverleaf skull

Diagnosis	Skull	Spine	Humerus
Acrocephalosyndaktyly I (Apert) Acrocephalosyndaktyly V (Pfeiffer) Acrocephalopolydactyly II (Carpenter)	x		
Amniotic band/disruption sequence; ADAM Limb body wall complex	x	x	
Antley-Bixler syndrome	x		x
Baller-Gerold Syndrome	x		
Cloverleaf skull – limb anomaly, type Holtermüller-Wiedemann	x		
M. Crouzon	x		
Osteocraniostenosis	x		x
Osteoglophonic dysplasia	x	x	x
Seckel syndrome	x		
Short rib-polydactyly, Beemer-Langer type	x	x	x
Thanatophoric dysplasia II	x		

Radius	Ulna	Femur	Tibia	Fibula	Hands/Feet	Others
					x	Macrosomy at birth
					x	See p. 150 Narrow thorax
					x	
					x	Omphalocele
					x	
x	x	x	x	x	x	Cystic hygroma
		x	x		x	See p. 153
					x	Clavicular hypoplasia
x	x	x	x	x	x	
					x	
					x	micrognathia
					x	
x	x		x	x	x	
					x	
					x	Growth retardation
			x		x	
					x	Anal atresia
x	x				x	Omphalocele
x	x	x	x	x	x	See p. 147 ff Very short ribs
					x	Hydrops fetalis
					x	Growth retardation
					x	

Radius	Ulna	Femur	Tibia	Fibula	Hands/Feet	Others
					x	
		x			x	
x						fractures
x					x	
x	x					
x	x	x	x	x		Fractures see p. 140
		x			x	
				x		Severe growth retardation
x	x	x	x	x	x	See p. 149 Very short ribs
						See p. 102

Un-/hypo-ossified calvaria

Diagnosis	Skull	Spine	Humerus
Acalvaria	x		
Aminopterin/methotrexate fetopathy	x		
Angiotensin inverting enzyme (ACE) inhibitor fetopathy	x		
Chromosome abnormality Trisomy 13	x	x	
Chromosome abnormality Trisomy 18 (Edward Syndrome)	x	x	
Hyperparathyroidism, neonatal familial	x		x
Hypophosphatasia, infantile form	x	x	x
Mucolipidosis type II (I-cell disease)			x
Osteocraniostenosis	x		x
Osteogenesis imperfecta II	x		x

Encephalocele

Diagnosis	Skull	Spine	Humerus
Amniotic band disruption sequence; ADAM Limb body wall complex	x	x	
DK phocomelia Phocomelia-encephalocele-thromobocytopenia-urogenital malformation von Voss-Cherstvoy sindrome	x		x
Dyssegmental dysplasia Silverman-Handmaker type Rolland-Desbuquois type	x	x	
Fukuyama congenital muscular dystropy	x		
Isolated finding	x	x	
Iniencephaly	x	x	x
Joubert syndroem	x		
Knobloch syndrome	x		
Laryngeal atresia, encephalocele and limb anomalies	x		
Meckel-Gruber syndrome	x		
Roberts (pseudothalodomide) syndrome	x		x
Sakoda complex	x		
VATER-Association with hydrocephalus	x	x	
Walker-Warburg syndrome	x		
Warfarin embryopathy	x		

Radius	Ulna	Femur	Tibia	Fibula	Hands/Feet	Others
						Spina bifida, omphalocele
x	x					growth retardation
						growth retardation
					x	Omphalocele
x			x		x	
x	x	x	x	x		subperiosteal bone resorption, metaphysela fractures
x	x	x	x	x	x	
x	x	x	x			Decreased bone mineralization, diaphyseal cloaking
x	x	x	x	x		Fractures
x	x	x	x	x		Multiple fractures incl. ribs

Radius	Ulna	Femur	Tibia	Fibula	Hands/Feet	Others
		x			x	
x	x				x	genitourinary and cardiac anomalies
x	x	x	x	x		See p. 120
						No other radiologic findings
						Omphalocele
			x		x	Fetal hydrops
x					x	Growth retardation
x	x	x	x	x	x	Cystic hygroma
					x	
x			x	x	x	intestinal atresias
					x	Stippled calcifications

Anencephaly/myelomeningocele/spina bifida

Diagnosis	Skull	Spine	Humerus
Amniotic band disruption sequence; ADAM Limb body wall complex	x	x	
CHILD syndrome			x
Chromosome abnormality Trisomy 18 (Edward Syndrome)	x	x	
Diabetic embryopathy		x	
Fetal aminopterin syndrome Folate antagonist chemotherapeutic agents	x		
Fetal valproate syndrome	x		
Isolated defect with or without rachischisis	x	x	
Laterality sequence		x	
Meckel-Gruber syndrome	x		
Omphalocele-Exstrophy of the bladder-Imperforate anus-Spinal defects (OEIS) complex		x	
Pentalogy of Cantrell Thoracoabdominal syndrome			
Short-rib polydactyly syndrome, type II		x	x

Vertebral segmentation defects/hemivertebrae/vertebral fusion

Diagnosis	Skull	Spine	Humerus
Acro-renal-mandibular syndrome	x	x	
Aicardi syndrome	x		
Alagille syndrome		x	
Butterfly vertebrae, isolated		x	
Campomelic dysplasia		x	x
Chromosome abnormality Trisomy 13	x	x	
Chromosome abnormality Chromosome 13 q-syndrome		x	
Chromosome abnormality Trisomy 18 (Edward Syndrome)	x	x	
Chromosome abnormality Triploidy		x	
Diabetic embryopathy		x	
Dyssegmental dysplasia Silverman-Handmaker type Rolland-Desbuquois type		x	
Fetal alcohol syndrome		x	
Goldenhar syndrome	x	x	
(Klippel-Feil syndrome)		x	
Limb/pelvis hypoplasia/aplasia syndrome Al-Awadi/Raas-Rothschild syndrome Schinzel phocomelia		x	

Radius	Ulna	Femur	Tibia	Fibula	Hands/Feet	Others
		x			x	
x	x	x	x	x		unilateral
x			x		x	
		x	x		x	cardiac defects, anal atresia
					x	
x					x	
						visceral heterotaxy
					x	Growth retardation
					x	anal atresia, wide pubic distance
						Sternal defect, ventral wall defect
x	x	x	x	x	x	See p. 147 ff

Radius	Ulna	Femur	Tibia	Fibula	Hands/Feet	Others
x			x		x	Severe hypoplasia of mandibula
						Rib anomalies
						Rib anomalies, butterfly vertebrae
x	x	x	x		x	pear-shaped ilia
					x	Omphalocele
					x	growth retardation
x			x		x	
						Severe growth retardation
		x	x		x	cardiac defects, anal atresia
x	x	x	x	x		See p. 120
	x				x	growth retardation
x						
						cervico-thoracic vertebral fusion
x	x	x	x	x	x	hypoplastic pelvis

Diagnosis	Skull	Spine	Humerus
Jarcho-Levin syndrome see: Spondylocostal dysostosis,		x	
Lethal multiple pterygium syndrome X-linked lethal multiple pterygium syndrome		x	
Microphthalmia-esophageal atresia Anopthalmia-esophageal-genital syndrome	x	x	
MURCS association		x	
Omphalocele-exstrophy of the bladder-imperforate anus-spinal defects (OEIS) complex		x	
Robinow syndrome Costovertebral segmentation defect	x	x	
Simpson-Golabi-Behmel syndrome	x	x	
Spinal dysraphism	x	x	
Spondylocostal dysostosis 1–3		x	
Spondylothoracic dysostosis		x	
Sprengel deformity		c	
Urorectal septum malformation sequence		x	
VACTERL-Association		x	
VATER-Association with hydrocephalus	x	x	

Pelvic-sacral abnormalities

Diagnosis	Skull	Spine	Humerus
Achondrogenesis, type II Hypochondrogenesis Lethal type II collagenopathies	x	x	x
Boomerang dysplasia	x	x	x
Campomelic dysplasia		x	x
Cleidocranial dysostosis	x		
Currarino triad		x	
Diabetic embryopathy		x	
Axial mesodermal dysplasia spectrum	x	x	
Isolated defect		x	
Limb body wall complex	x	x	
Limb/pelvis hypoplasia/aplasia syndrome Al-Awadi/Raas-Rothschild syndrome		x	
Omphalocele-Exstrophy of the bladder-Imperforate anus-Spinal defects (OEIS) complex		x	
Opsismodysplasia		x	
Sacral defect with anterior meningocele		x	
Sirenomelia		x	
Spondyloepiphyseal dysplasia congenita (SEDc)			
Spondylometepiphyseal dysplasia (Strudwick)			
Urorectal septum malformation sequence		x	
VACTERL-Association		x	
X-linked visceral heterotaxy syndrome		x	

Radius	Ulna	Femur	Tibia	Fibula	Hands/Feet	Others
						Rib synostosis, defective
					x	Cystic hygroma
						Fusion of ribs
x					x	
					x	anal atresia, wide pubic distance
					x	Fusion of ribs
					x	Hydrops fetalis
						Hydrocephalus
						Rib anomalies
						Short trunk, crab-like ribs
						Clavicular anomalies
x					x	Prune belly, narrow symphysis
x			x	x	x	intestinal atresias
x			x	x	x	intestinal atresias

Radius	Ulna	Femur	Tibia	Fibula	Hands/Feet	Others
x	x	x	x	x	x	See p. 114
x	x	x	x	x	x	See p. 163
x	x	x	x		x	pear-shaped ilia
						Clavicles and pubic bones unossified
						asymmetric sacral defect
		x	x		x	cardiac defects, anal atresia
					x	
		x	x	x		
		x			x	
x	x	x	x	x	x	Hypoplastic pelvis
					x	anal atresia, wide pubic distance
					x	retarded skeletal maturation
						Urinatry tract obstruction
x		x	x	x	x	Anal atresia
						See charter 3, unossified pubic bone
						Like SEDc.
x					x	Prune belly, narrow symphysis
x			x	x	x	intestinal atresias
						Gatrointestinal atresias

Coronal clefts of vertebral bodies

Diagnosis	Skull	Spine	Humerus
Atelosteogenesis and related OCDs		x	x
Chondrodysplasia punctata, rhizomelic type		x	x
Chondrodysplasia punctata, tibia-metacarpal type		x	
Chromosome abnormality Trisomy 13	x	x	
Chromosome abnormality Trisomy 18 (Edward Syndrome)	x	x	
Chromosome abnormality Trisomy 21		x	
Chromosome abnormality Triploidy		x	
CODAS		x	
De la Chapelle dysplasia		x	x
Desbuquois syndrome		x	x
Fibrochondrogenesis		x	x
Larsen syndrome			
Lethal Kniest-like dysplasia	x	x	x
OPD II (oto-palato-digital syndrome II)		x	x
Oto-spondylo-megaepiphyseal dysplasia (OSMED)		x	x
Short rib-polydactyly syndrome Type I (Saldino-Noonan)		x	x
Weissenbacher-Zweimüller syndrome		x	x

Ectopia cordis

Diagnosis	Skull	Spine	Humerus
Amniotic band disruption sequence; ADAM Limb body wall complex	x	x	
Pentalogy of Cantrell Thoracoabdominal syndrome			
Sternal malformation-vascular dysplasia association Sternal clefts-telangiectasia/hemangiomas Hemangiomas, cavernous of face and supraumbilical midline raphe	x		

Radius	Ulna	Femur	Tibia	Fibula	Hands/Feet	Others
x	x	x		x	x	See p. 163
		x				See p. 154
		x	x		x	
					x	Omphalocele
x			x		x	
					x	
						Severe growth retardation
						Hip dislocation
		x	x	x	x	See p. 167
x	x	x	x	x	x	dislocations
x	x	x	x	x		See p. 108
x	x					See p. 161
x	x	x	x	x		very wide metaphyses
x	x	x	x	x	x	narrow pelvis see p. 136
		x			x	See p. 118
x	x	x	x	x	x	See p. 147 Very short ribs
		x				

Radius	Ulna	Femur	Tibia	Fibula	Hands/Feet	Others
		x			x	
						Sternal defect, ventral wall defect
						Hypoplastic clavicles

Ventral wall defects/omphalocele/gastroschisis

Diagnosis	Skull	Spine	Humerus
Amniotic band disruption sequence; ADAM Limb body wall complex	x	x	
Arthrogryposis multiplex congenita			
Beckwith-Wiedemann syndrome			
Boomerang dysplasia	x	x	x
Chromosome abnormality Trisomy 13	x	x	
Chromosome abnormality Trisomy 18 (Edward Syndrome)	x	x	
Donnai-Barrow syndome	x		
Elejalde syndrome	x		x
Fryns syndrome	x		
Melnick-Needles osteodysplasty Oto-palato-digital syndrome, type 2	x	x	
Omphalocele-Exstrophy of the bladder-Imperforate anus-Spinal defects (OEIS) complex		x	
Osteopathia striata with cranial sclerosis	x		
Pseudo-trisomy 13 syndrome	x	x	
Short rib-polydactyly, Beemer-Langer type		x	x
Tetra-amelia	x		x
Thoracoabdominal syndrome Pentalogy of Cantrell			

Radius	Ulna	Femur	Tibia	Fibula	Hands/Feet	Others
		x			x	
						Gastroschisis, slender long bones
						Macrosomia
x	x	x	x	x	x	See p. 163
					x	Omphalocele
x			x		x	
x	x	x	x	x		Cystic hygroma
					x	Thin, wavy ribs, wavy contour of long bones
					x	anal atresia, wide pubic distance
				x		
x	x				x	Omphalocele
x	x	x	x	x	x	See p. 149 Very short ribs
x	x	x	x	x	x	
						Sternal defect, ventral wall defect

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