

The assessment of the fetus with a skeletal dysplasia

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Since skeletal dysplasias are uncommon, their prenatal diagnosis is difficult. Acquiring a large experience takes time. This chapter will review the birth prevalence and classification of skeletal dysplasias and provide a frame to approach the diagnoses of conditions identifiable at birth¹.

Social and historical importance

Skeletal anomalies are unique among birth defects. Although many dysplasias are lethal some affected individual survive and lead productive life without the intervention of therapeutics. Therefore, the identification of patients with abnormal skeleton existed since the beginning of history. This is in contrast with many other birth defects. Four thousand years ago, for instance, a child born in Egypt with multicystic kidney disease, posterior urethral valve, transposition of the great vessels or many other conditions would have died and not appeared much different to observers than any other still birth due to a complicated delivery. In contrast, a child with achondroplasia or a conjoined twin could have survived and caused various interest.

This has resulted in a rich documentation in the Arts of individuals with skeletal anomalies, the most common being probably clubfeet and achondroplasia.

The following painting is one of the most famous representations of skeletal dysplasia. It is called "Las Meninas" from Velázquez (1656, Prado museum, Madrid). It represents Velázquez painting the court of king Philip IV and the Queen (Mariana of Austria). The composition is interesting because it is the view the King and Queen, not the view of the painter. The king and Queen are actually visible in the mirror on the back wall. The center person is the infant Margarita and her play maid (meninas). Of course our interest is in Mari-Bárbola. The facial appearance, the square forehead, the short arms and legs and the hands are very typical of achondroplasia. Velázquez had a kind eye for her and for many other people with anomalies (look at his painting of "Prince Baltasar Carlos and Dwarf" Prince Baltasar in the riding school, Sebastián de Morra, El niño de Vallecas, Diego de Acedo "El Primo")



Fig. 1: Las Meninas, Velázquez (1656, Prado museum, Madrid, Spain).

The term “dwarf” is often used in a pejorative connotation, and it is best reserved to cartoons by Walt Disney then to describe fellow human. A more appropriate terminology is to talk about “short-limb dysplasias”. The names of the painting should not be changed though.

Achondroplasts have led important careers in the Arts as movie goers surely know, in specific trades (a team of achondroplasts worked in the maintenance of the wings of the Enola Gay bomber during World War II), and in more conventional functions in the society.

The second figure is a painting from Henry de Toulouse-Lautrec a French painter famous for his painting of the life around Montmartre in Paris. The parents of Henry belonged to an old family who could trace their lineage all the way to Charlemagne. As many french noble families in the last century, their fortune was no longer considerable, and in order to preserve as much as possible it was common to intermarry

within the family. As such the father of Henry (Count Alphonse de Toulouse-Lautrec) was first cousin with his mother (Countess Alèle Tapié de Ceyleran). Henry de Toulouse-Lautrec is considered to have suffered from a disorder called pycknodysostosis^{2,3,4,5,6}. Pycknodysostosis is an autosomal recessive skeletal disorder characterized by short stature, increased bone density, delayed closure of cranial sutures, loss of the mandibular angle, dysplastic clavicles, dissolution of the terminal phalanges of the hands and feet, dental abnormalities and increased bone fragility. The defect links to a narrow region on band 21 of the long arm of chromosome 1.

When Henry was a child (13 and then 14 years old), he broke a femur after a horse fall during a training session with his father (an avid equestrian) and later broke the second femur. Because of the bone disorder it took almost a year for the fracture to heal. Understandably, little Henry was not eager to repeat the experience, and preferred to spend time improving his drawing and painting skills which he developed during his long convalescence. This led to paternal rejection and a sensation that he did not belong to his original aristocratic environment. Like many in this situation, he gravitated towards others rejected by the society and found a more tolerant environment in the artistic and entertainment population around Montmartre.

The painting entitled: “Dance au Moulin Rouge” (a famous establishment at the time) is centered around the visual axis created by the upper middle class woman in pink and the two dancers. Note the contemptuous attitude of the lady in pink towards the dancers and in particular “La Goulue” (the female dancer that raises her left leg). “La Goulue” (the Glutton) was so nicknamed for her habit to go to the tables of the customers, sit on the lap of the gentleman and drink their drinks (thus increasing the consumption in the establishment!). Actually the important personage in the painting, his her dancer partner: “Valentin le Désossé” (the Snakeman in English). Vincent, which appears in other paintings of Toulouse-Lautrec, was a famous contortionist, a skill made easy because of his condition of Ehler-Danlos a connective tissue dysplasia with some similarities with osteogenesis imperfecta.



Fig. 2: “Dance au Moulin Rouge”, Henry de Toulouse-Lautrec 1890 Philadelphia Museum of Art, Philadelphia

Clearly the artistic patrimony of the world has been enlarged by the contribution of Henry de Toulouse-Lautrec, and his art was significantly influenced by his disorder.

Patients with skeletal dysplasia have existed in all societies and we should make effort to allow them to function as normally as possible in the society (fig. 3). One of my friends with achondroplasia was relating her anxiety when taking an elevator once in a big city. When the door closed behind her, there was no button she could reach and she was trapped in the elevator until someone else came in. Fortunately, the passage in the United States of the *American with Disability Act* has contributed to the adaptation of these special people in our society. We can only hope that this will be more widespread around the globe.

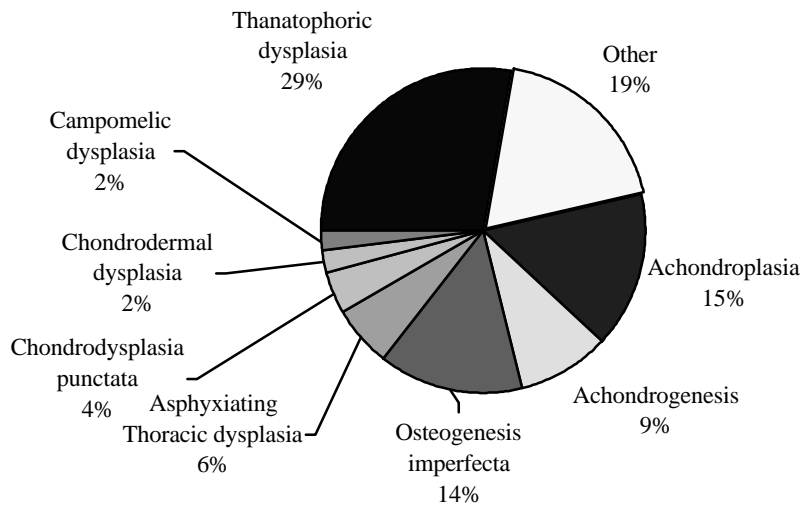


Fig. 3: Our society has to adapt to the needs of patients with short-limb dysplasia (© 1972 Quino “Ia a mi no me grite” Ediciones de la Flor)

Many organizations assist patients with skeletal dysplasia. A vibrant example is the Little People of America (www.lpaonline.org) that assist patients with achondroplasia and similar disorders. Physicians have to be aware of these resources and help their patients take advantage of the support they provide.

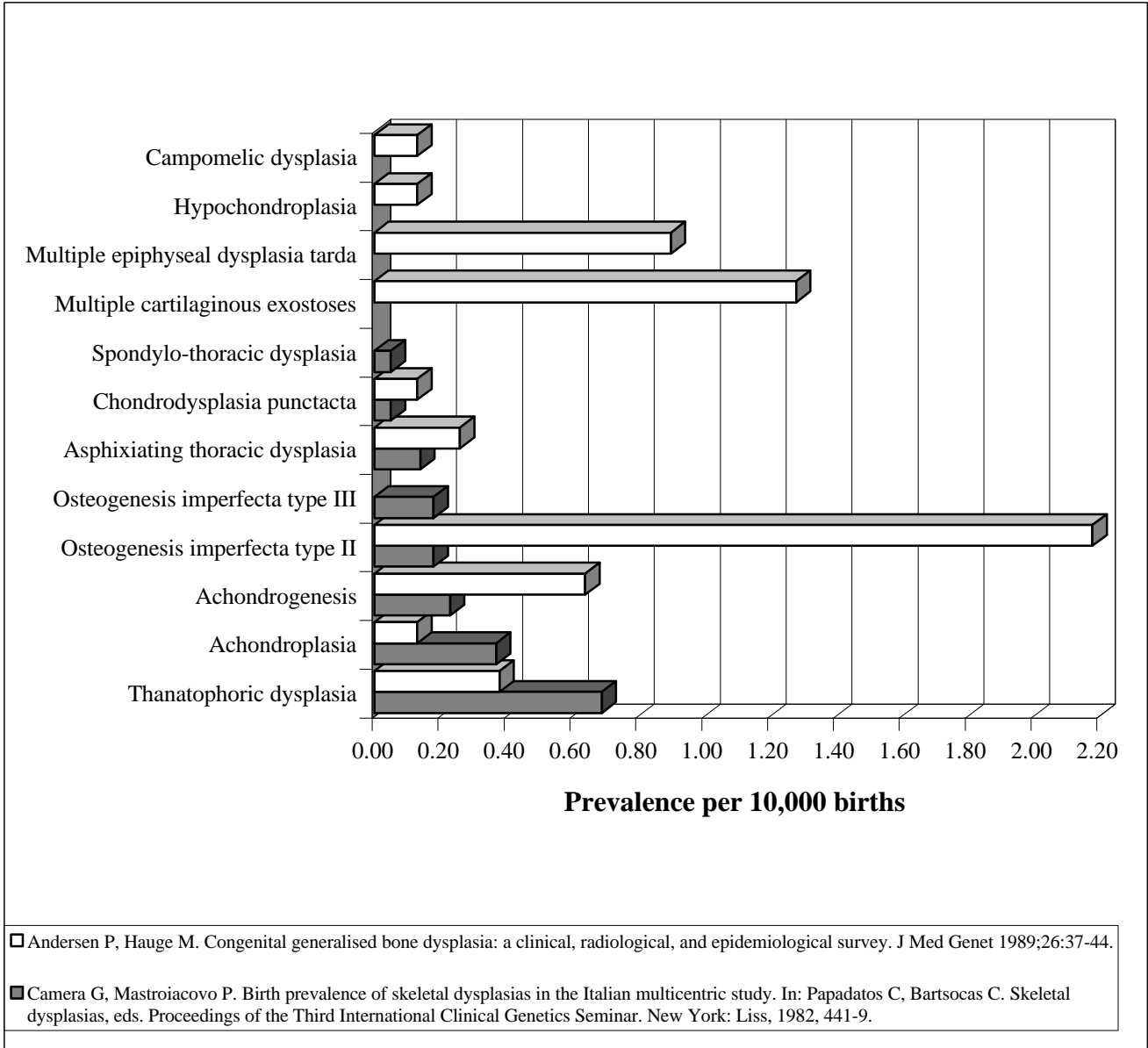
Birth prevalence and contribution to perinatal mortality

The birth prevalence of skeletal dysplasias, excluding the limb amputations, recognizable in the neonatal period has been estimated to be 2.4/10,000 births⁷. In a large series, 23% of affected infants were stillbirths, and 32% died during the first week of life. The overall frequency of skeletal dysplasias among perinatal deaths was 9.1/1,000. The relative frequencies of the different skeletal dysplasias are shown in figure 4.



The four most common skeletal dysplasias found were thanatophoric dysplasia, achondroplasia, osteogenesis imperfecta and achondrogenesis. Thanatophoric dysplasia and achondrogenesis accounted for 62% of all lethal skeletal dysplasias⁸. The most common non-lethal skeletal dysplasia is achondroplasia. In another large series, reporting the prevalence and classification of lethal neonatal skeletal dysplasias in West Scotland, the prevalence was 1.1/10,000 births, and the most frequently diagnosed conditions were thanatophoric dysplasia (0.24:10,000), osteogenesis imperfecta (0.18:10,000), rhizomelic chondrodysplasia punctata (0.12:10,000), campomelic syndrome (0.1/10,000) and achondrogenesis (0.1/10,000)⁹.

The following chart is the prevalence of selected skeletal dysplasias in the studies of Anderson and Camera.



Classification of skeletal dysplasias

Until recently the classification of skeletal dysplasia has been hampered by the rarity of the condition and the lack of understanding of the etiologies. Thus disorders that look the same were assimilated, and then separated under new entities. This lack of understanding resulted in classifications that were mainly descriptive and the technique most likely to identify the findings was predominantly used to categorize the anomalies. Therefore many definitions are based on radiological criteria with a fewer based on histological or clinical criterias. This in turn, further complicated matters because the nomenclature of disorder was then either a description of the clinical outcome (thanatophoric dysplasia = that carries (result in) death), clinical description (diastrophic dysplasia = referred to the twisted joints, cleidocranial dysplasia...), or possible pathogenesis (osteogenesis imperfecta, achondrogenesis). Those disorders too uncertain or with too many features were given eponyms (Ellis-van Creveld syndrome).

In an attempt to bring some order, an *International Nomenclature for Skeletal Dysplasias* was proposed by a group of experts Paris in 1977. This classification was revised in Germany in 1992 and more recently in Los Angeles in 1998. The current version has been renamed "*International Nomenclature of Constitutional Disorders of Bone*" and it is available on line at

<http://www.csmc.edu/genetics/skeldys/nomenclature.html>

The original 5 categories have been enlarged into 32 groups.

The reason for the rapid revision has been the explosion of knowledge brought in by the discoveries of the genetic defect underlying many of the conditions. In 1994, two groups (Le Merrer¹⁰ at the INSERM, Paris, France and Velinov¹¹ in Farmington CT, USA) independently concluded that the gene responsible for achondroplasia was located in the telomeric region of the 16.3 band of the short arm of the chromosome 4. The next year Bellus¹², at John Hopkins, demonstrated that a Glycine to Arginine at codon 380 of the Fibroblast Growth Factor Receptor 3 was responsible for achondroplasia. Fibroblast growth factors regulate cell proliferation, differentiation and migration by a transmembrane tyrosine-kinase receptor called "fibroblast-growth-factor-receptor" (FGFR). These molecules contain transmembrane domains components and an extracellular component composed of 3 immunoglobulin-like domains (fig. 5).

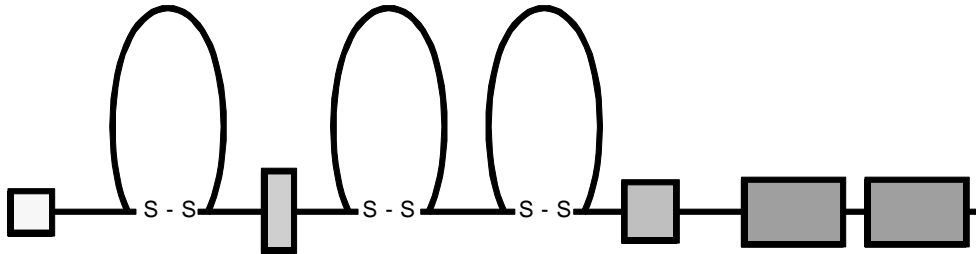


Fig.5: Schematic representation of the Fibroblast Growth Factor Receptor (FGFR). On the left, the molecule starts with a signal peptide. The extracellular component is composed of 3 immunoglobulin-like domains (the 3 arches). On the right side of the molecule are the transmembrane domains.

Over the next few months and years a literal explosion of knowledge occurred with the locus for Pfeiffer, Aperts, Crouzon, Jackson-Weiss, thanatophoric dysplasia, achondroplasia, hypochondroplasia and many other being identified. Several other deficient proteins were subsequently discovered.

Although more than 271 skeletal dysplasias have been described, and more will probably be identified as distinct entities, the number that can be recognized with the use of sonography in the antepartum period is considerably smaller.

Definitions and "what to look for ?" when doing a prenatal examination

Skeletal dysplasias are disorders of bones. They may result from abnormal:

1. Growth: resulting in abnormal shape and size of the skeleton.
2. Number: either decreased or increased
3. Texture: either decreased or increased activity of the remodeling process and mineral deposition.

Shortening of the extremities can involve the entire limb (micromelia), the proximal segment (rhizomelia), the intermediate segment (mesomelia) or the distal segment (acromelia) (fig. 6).

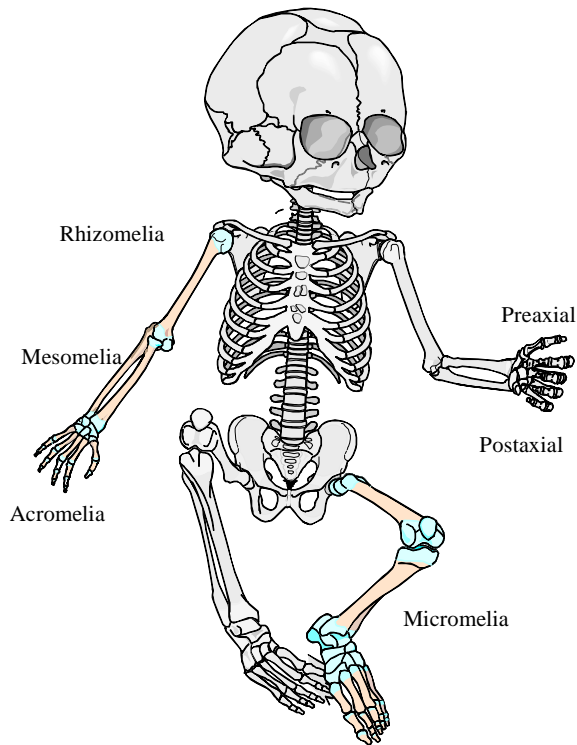


Fig. 6: Shortening of the extremities can involve the entire limb (micromelia), the proximal segment (rhizomelia), the intermediate segment (mesomelia) or the distal segment (acromelia). Extra digits on the ulnar or fibular side are “post-axial” and “pre-axial” if they are located on the radial or tibial side.

The diagnosis of rhizomelia or mesomelia requires the comparison of the dimensions of the bones of the legs and forearm with those of the thigh and arm.

Acromelia may be due to several anomalies of the hands and feet. **Polydactyly** refers to the presence of more than five digits. It is classified as post-axial if the extra digits are on the ulnar or fibular side and pre-axial if they are located on the radial or tibial side (fig. 6). Most commonly the extra digit is a simple skin tag, difficult to see by ultrasound, but occasionally bones may be present too.

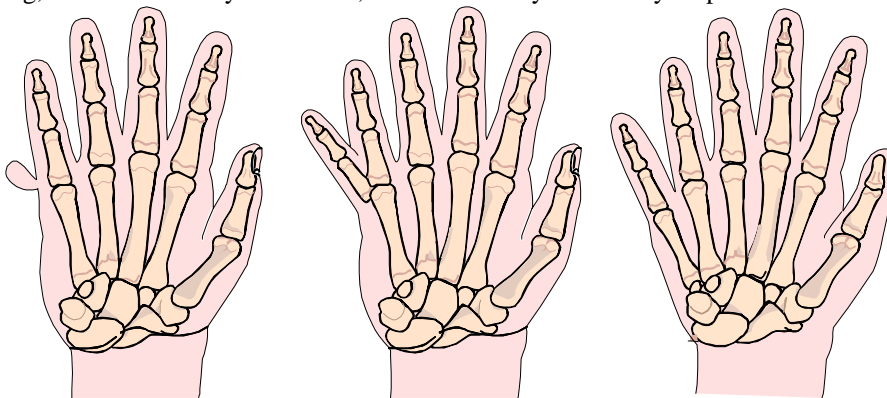


Fig. 7: Polydactyly refers to the presence of extra digits. Most commonly the extra digit is a simple skin tag, difficult to see by ultrasound, but occasionally bones or a completely duplicated but non functional digit may be present too. In this illustration post-axial polydactylies have been represented.

Syndactyly refers to soft tissue or bony fusion of adjacent digits and is difficult to recognize in the less severe forms (fig. 7).

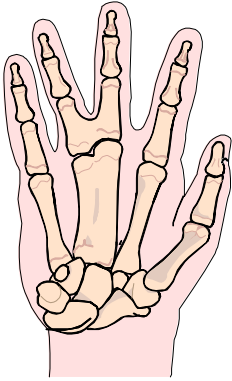


Fig. 7: Bony syndactyly.

Clinodactyly consists of deviation of a finger(s). It may result from an abnormal middle 5th phalanx such as in brachymesophalangia (fig. 8)

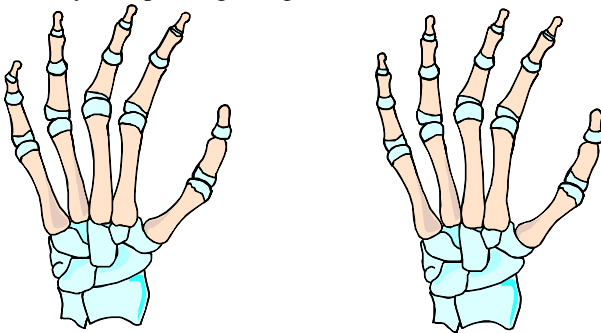


Fig. 8: Left: an abnormal middle 5th phalanx can be responsible for clinodactyly.

Clubbing of the hand is very suggestive of “radial-ray” anomalies. These anomalies range from abnormal thumbs (sometimes triphalangeal as in Holt-Oram syndrome) to hypoplasia or absence of the thumb and sometimes absence of the radius or even the radius and the hand. The three most likely diagnoses include Holt-Oram syndrome, the thrombocytopenia-absent radius (TAR) syndrome and trisomy 18.

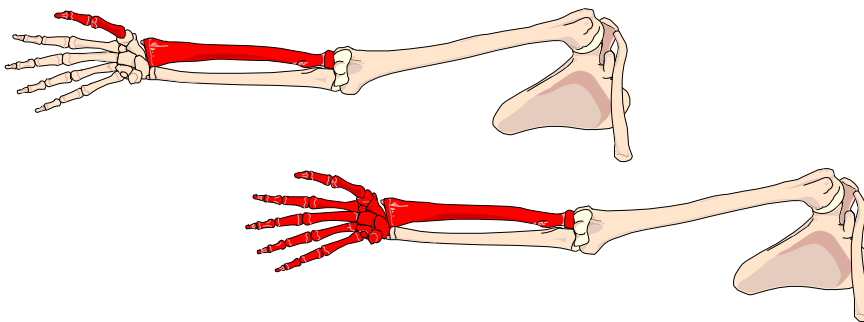


Fig. : “Radial-ray” anomalies range from abnormal thumbs to hypoplasia or absence of the thumb and sometimes absence of the radius or even the radius and the hand.

The foot length is very close to the femoral length and can be used to compare the two^{13,14}. At the level of the feet, a rocker-bottom foot (abnormal vertical position of the talus and calcaneus) or a clubfoot should also be sought.

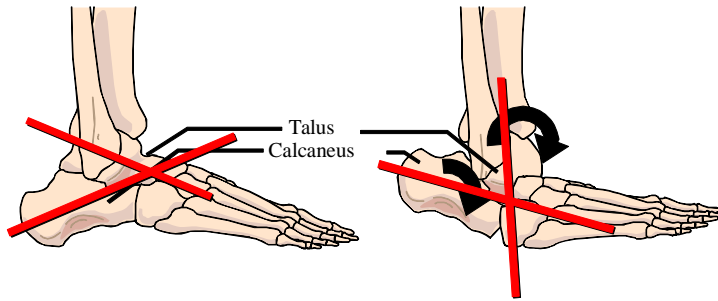


Fig. : An abnormal vertical position of the talus and calcaneus causes a rockerbottom foot.

At the level of the head, deviations from the normal shape of the head should be observed. These include brachycephaly, scaphocephaly and the craniosynostoses.

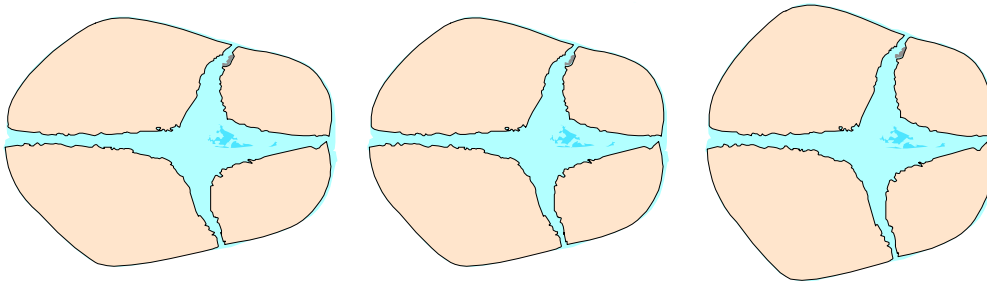


Fig. : Normal appearance of the skull in cross-section (middle image) should be compared to scaphocephaly (the lateral flattening, first image) and brachycephaly (the antero-posterior shortening, right image)

Brachycephaly occurs in many acrocephalopolysyndactylies. Scaphocephaly is more common and is associated with premature rupture of the membranes, growth restriction, in-utero crowding and acromesomelic dysplasia.

Craniosynostoses result from premature fusions of the suture. The expanding brain deforms the adjacent bones resulting in specific anomalies. One of the common one being the clover-leaf shape (or kleeblattschadel) that occurs in the Type II Thanatophoric dysplasia. Other conditions with craniosynostosis are Carpenter's syndrome, hypophosphatasia, acrocephalosyndactyly, Crouzon – Aperts, acrodysostosis, trimethadone sequence and many others.

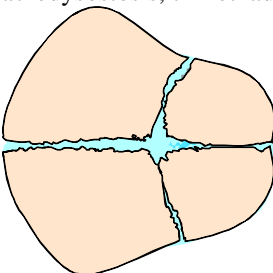


Fig. : Craniosynostosis results from premature fusions of the suture.

Frontal bossing is a deformity of the forehead that may be associated with achondroplasia and the craniosynostosis but also due to increased intracranial size with large hydrocephalus. The diagnosis is often

suspected in a section of the lips of the fetus (the section used to assess the presence of a cleft lip) and made or confirmed in a sagittal facial section. At the same time look for a low nasal bridge

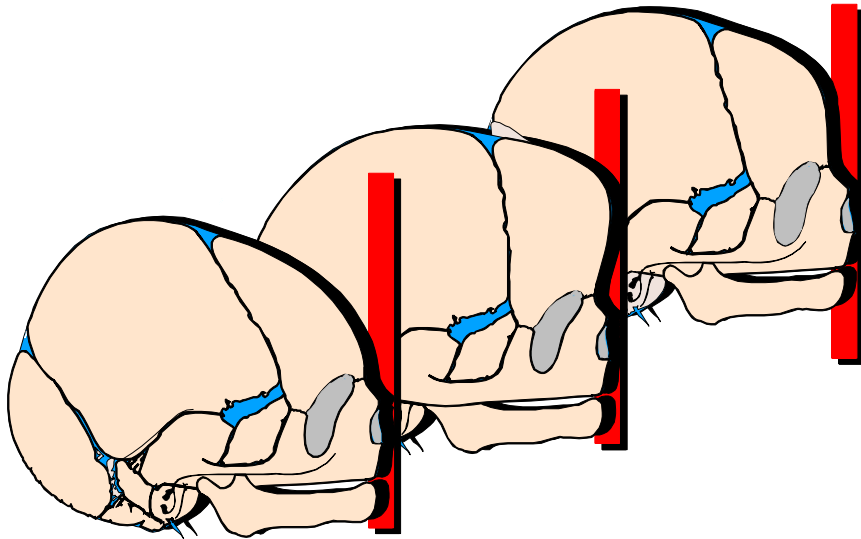


Fig: The section used to assess the presence of a cleft lip is just in front of the forehead (top right). In frontal bossing (middle) the forehead appears in the section, and in frontal slanting(left) it is further away.

Wormian bones are small bones in the fontanelles and they may be associated with cleidocranial dysplasia, osteogenesis imperfecta, trisomy 21, hypothyroidism, pyknodysostosis and progeria.

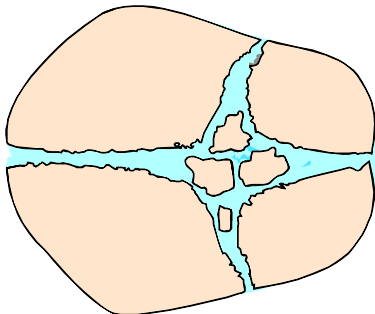


Fig: Wormian bones are small bones in the fontanelles

While looking at the head, note the distance between the eyes. A decreased distance (hypotelorism) or increased (hypertelorism) may also be present in skeletal dysplasias.

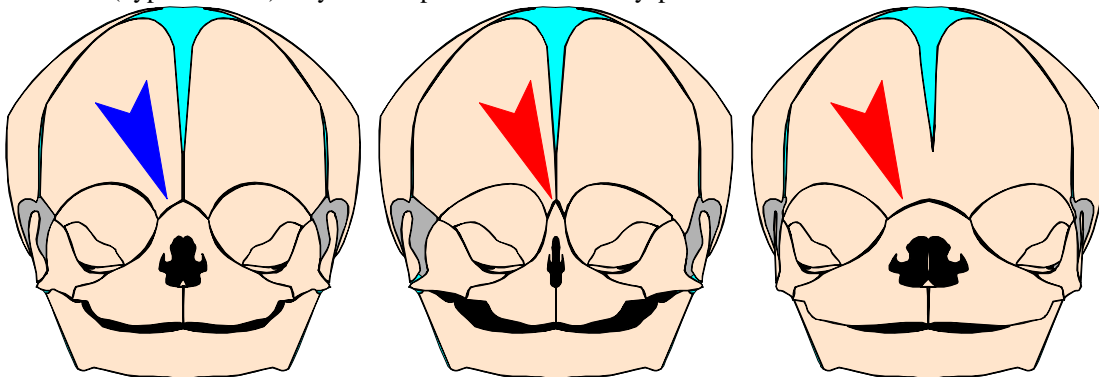


Fig. : The normal distance between the eyes in a cross section of the eyes should be approximately equal to the ocular diameter. Thus the “rule of thirds”: the binocular distance can be divided in almost 3 equal

thirds: one each being an orbit, the third being the distance between the eyes. A decrease of the interocular distance is hypotelorism while an increased represents hypertelorism.

A smaller jaw (micrognathia, which you remember affected Henry de Toulouse-Lautrec) should also be sought at this time of the exam¹⁵.

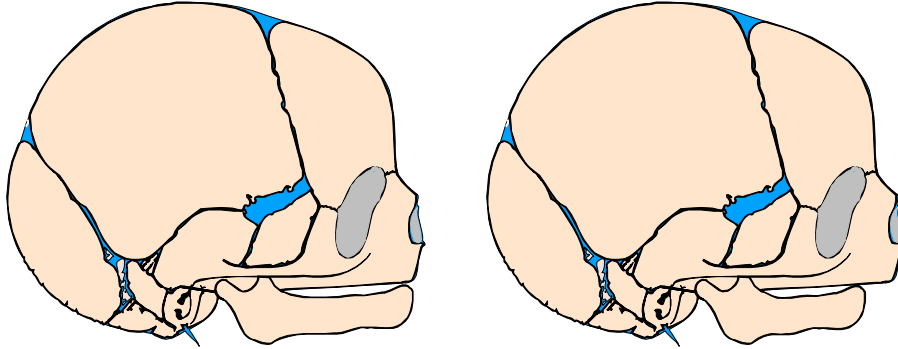


Fig. : Micrognathia is a smaller than normal mandible and is associated with many conditions

At the level of the chest, look for abnormal rib size resulting in a chest that is too narrow. This is a typical finding of most of the lethal skeletal dysplasias (thanatophoric dysplasia, achondrogenesis, hypophosphatasia, camptomelic dysplasia, chondroectodermal dysplasia, osteogenesis imperfecta, short-rib polydactyly...). These conditions are not lethal because the bones are abnormal, but because the ribs are too short and thus prevent the normal growth of the lungs. It is the resulting pulmonary hypoplasia that is lethal. In practice we do not need to measure the chest or the ribs. It is sufficient to know that the chest diameter should be between 80-100% of the abdominal diameter. Lethal skeletal dysplasias will often have chest size around 50%, and thus the anomaly is not subtle.

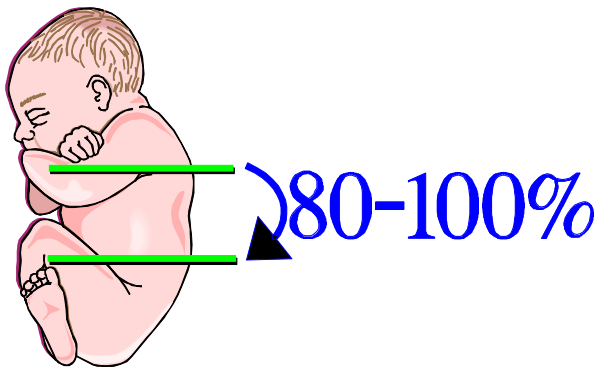


Fig. : The chest diameter should be between 80-100% of the abdominal diameter.

The most common spinal abnormality seen in skeletal dysplasias is platyspondyly, which consists of flattening of the vertebrae. This sign is typical of thanatophoric dysplasia. The prenatal diagnosis of congenital hemivertebra has also been reported¹⁶. Kyphosis and scoliosis can also be identified in utero.

Other findings to investigate

Hypomineralization occurs in hypophosphatasia, achondrogenesis and osteogenesis imperfecta. The typical appearance is that of bones with little posterior shadowing, but the most characteristic is the ability to visualize both corticals (something which is not possible in normal bones).

Absence or aplasia of some bones. This is the case in cleidocranial dysplasia for instance where the clavicle appear too short. The normal clavicle length should match in millimeters the number of weeks of the gestation, so that a 20 week fetus has a clavicle of about 20 mm. The presence of 11 pairs of ribs is another example, and it may occur in camptomelic dysplasia, cleidocranial dysplasia and trisomy 18 and 21.

Bone curvature: this suggests osteogenesis imperfecta, campomelic dysplasia and hypophosphatasia. In OI, an angle (fracture) is often visible instead of a curve.

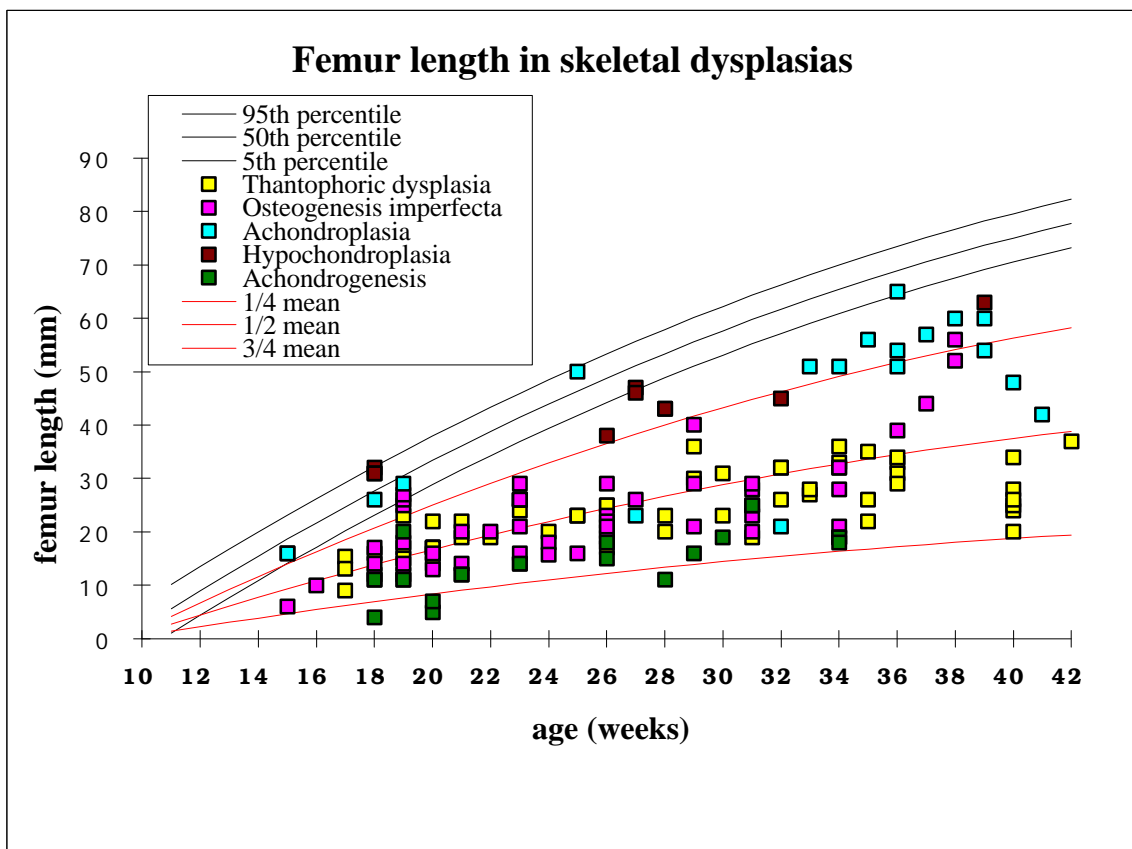
Biometry in the diagnosis of bone dysplasias

Long bone biometry has been used extensively in the prediction of gestational age. Nomograms available for this purpose use the long bone as the independent variable and the estimated fetal age as the dependent variable. However, the type of nomogram required to assess the normality of bone dimensions uses the gestational age as the independent variable and the long bone as the dependent variable. For the proper use of these nomograms, the clinician must accurately know the gestational age of the fetus. Therefore, patients at risk for skeletal dysplasias should be advised to seek prenatal care at an early gestational age to assess all clinical estimators of gestational age. The following table presents nomograms for the assessment of limb biometry for the upper and lower extremities and the clavicle.

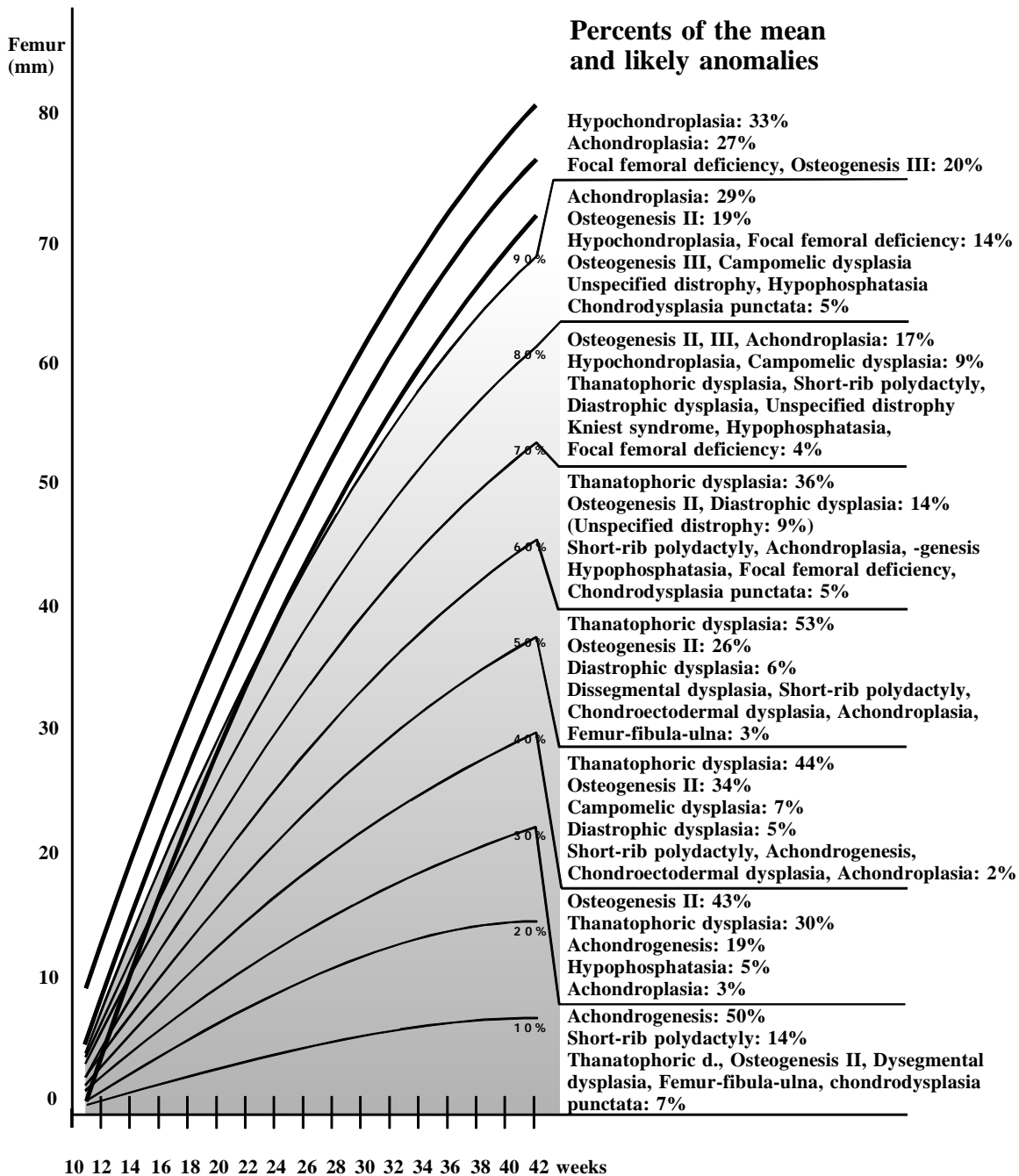
Age	Femur			Humerus			Tibia			Fibula			Ulna			Radius			Clavicle		
	5 th	50 th	95 th	5 th	50 th	95 th	5 th	50 th	95 th	5 th	50 th	95 th	5 th	50 th	95 th	5 th	50 th	95 th	5 th	50 th	95 th
12	4	9	14	5	9	13	3	7	11	5			8			7			8	13	18
13	7	12	17	9	13	17	6	10	14	8			11			10			10	15	20
14	10	15	20	12	16	20	9	13	17	11			9	13	17	13			11	16	21
15	14	19	24	14	18	22	12	16	20	14			12	16	20	6	15	24	12	17	22
16	17	22	27	17	21	25	15	19	23	17			15	19	23	9	18	27	13	18	23
17	20	25	30	20	24	28	18	22	26	8	19	30	17	21	25	11	20	29	14	19	24
18	23	28	33	23	27	31	20	24	28	11	22	33	20	24	28	13	22	31	15	20	25
19	26	31	36	25	29	33	23	27	31	13	24	35	22	26	30	15	24	33	16	21	26
20	28	33	38	28	32	36	25	29	33	16	27	38	25	29	33	18	27	36	17	22	27
21	31	36	41	30	34	38	28	32	36	18	29	40	27	31	35	20	29	38	18	23	28
22	34	39	44	32	36	40	30	34	38	20	31	42	29	33	37	22	31	40	20	25	30
23	36	41	46	34	38	42	32	36	40	22	33	44	31	35	39	23	32	41	21	26	31
24	39	44	49	37	41	45	35	39	43	24	35	46	33	37	41	25	34	43	22	27	32
25	41	46	51	39	43	47	37	41	45	26	37	48	35	39	43	27	36	45	23	28	33
26	44	49	54	41	45	49	39	43	47	28	39	50	37	41	45	28	37	46	24	29	34
27	46	51	56	42	46	50	41	45	49	30	41	52	39	43	47	30	39	48	25	30	35
28	48	53	58	44	48	52	43	47	51	32	43	54	40	44	48	31	40	49	26	31	36
29	51	56	61	46	50	54	45	49	53	34	45	56	42	46	50	33	42	51	27	32	37
30	53	58	63	48	52	56	47	51	55	36	47	58	43	47	51	34	43	52	29	34	39
31	55	60	65	49	53	57	48	52	56	37	48	59	45	49	53	35	44	53	30	35	40
32	57	62	67	51	55	59	50	54	58	39	50	61	46	50	54	36	45	54	31	36	41
33	59	64	69	52	56	60	52	56	60	40	51	62	48	52	56	37	46	55	32	37	42
34	60	65	70	53	57	61	53	57	61	41	52	63	49	53	57	38	47	56	33	38	43
35	62	67	72	54	58	62	55	59	63	43	54	65	50	54	58	39	48	57	34	39	44
36	64	69	74	56	60	64	56	60	64	44	55	66	51	55	59	39	48	57	35	40	45
37	66	71	76	57	61	65	57	61	65	45	56	67	52	56	60	40	49	58	36	41	46
38	67	72	77	57	61	65	58	62	66	46	57	68	53	57	61	40	49	58	37	42	47
39	69	74	79	58	62	66	60	64	68	47	58	69	53	57	61	41	50	59	39	44	49

For those patients presenting with uncertain gestational age, comparisons between limb dimensions and the head perimeter can be used. The head perimeter has the advantage of being shape independent. A limitation of this approach is that it assumes that the cranium is not involved in the dysplastic process, and this may not be the case in some skeletal dysplasias. The table uses the 5% percentile and thus a fair number of normal fetuses will fall outside these boundaries.

The following table¹⁷ illustrates the femoral lengths of several fetuses with skeletal dysplasias (see legends). The 3 upper percentiles are the 95th, 50th and 5th percentiles and the 3 lower red lines are the 3/4, 1/2 and 1/4 of the mean respectively from top to bottom. From this chart it is clear that most short-limb skeletal dysplasias will fall significantly below the 5th percentile. The only exceptions are hypochondroplasia and achondroplasia.



The following graph¹⁷ is useful to suggest what might the differential diagnosis be according to the various lengths. Although this table is based on one of the largest prenatal series, be aware that many skeletal dysplasias are not represented. Simply place a measurement in the graph and see what are the differential diagnoses in that slice. The percentages indicate the percent of the disorder in that category. Of course, when a differential diagnosis is suggested, search for findings to confirm or infirm it.



Clinical presentation

The assessment of skeletal dysplasias will occur either because of a familial history or because of the incidental discovery of an abnormally shaped or too short bone during an examination. When a familial history is present the task is often limited to assessing whether the same findings are present or not. In practice we look at all long bones and measure all that are not obviously within normal limits

After the delivery

Despite all efforts to establish an accurate prenatal diagnosis, a careful study of the newborn will be required in all instances. The evaluation should include a detailed physical examination performed by a

geneticist or an individual with experience in the field of skeletal dysplasias and radiograms of the skeleton. The latter should include: anterior, posterior, lateral and Towne views of the skull and antero- posterior views of the spine and extremities, with separate films of hands and feet. Examination of the skeletal radiographs will permit precise diagnoses in the overwhelming majority of cases, since the classification of skeletal dysplasias is largely based upon radiographic findings. In lethal skeletal dysplasias, histologic examination of the chondro-osseous tissue should be included, as this information may help reach a specific diagnosis. Chromosomal studies should be included, as there is a specific group of constitutional bone disorders associated with cytogenetic abnormalities. Biochemical studies are helpful in rare instances (e.g., hypophosphatasia). DNA restrictions and enzymatic activity assays should be considered in those cases in which the phenotype suggests a metabolic disorder such as a mucopolysaccharidosis.

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