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Osteochondral Diseases and Fibrodysplasia Ossificans Progressiva

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Abstract

Osteochondrodysplasias like thanatophoric dysplasia, osteogenesis imperfecta, achondroplasia, and other genetic skeletal disorders like fibrodysplasia ossificans progressiva are infrequently seen in clinical practice. In cases of sporadic achondroplasia as well as in fibrodysplasia ossificans progressiva, there is a strong association with paternal age, a relationship that is less evident in other genetic osteochondral diseases. No other constitutional or environmental factor has proven to be associated with these disorders. The use of prenatal ultrasonography as a routine component of prenatal care is crucial in the early suspicion of osteochondrodysplasias whereas definitive diagnosis is usually obtained by pre-natal molecular analysis. In the case of fibrodysplasia ossificans progressiva, recognition of congenital great toe malformations associated with rapidly–appearing soft tissue swelling is sufficient to make the proper clinical diagnosis, which can be confirmed by genetic testing. Large regional centres will improve diagnosis performance, provide accurate genetic counselling, and ensure an integral assistance for these often severe and incapacitating conditions.

Keywords

Constitutional disorders of bone; Osteochondrodysplasias; Fibrodysplasia ossificans progressiva; Paternal age effect; Prenatal ultrasound; Pre-natal molecular analysis; Early clinical and radiological detection; Genetic counseling

19.1 Scope and Definitions

The complexity of the skeleton, the diverse origin of its components, and the heterogeneity of its physiology provides a basis for understanding the broad diversity of ways in which bone, cartilage and related tissues may become damaged. Historically, skeletal disorders are often described eponymously, descriptively or pathologically.

In an attempt to develop an operative and universally accepted classification, a group of experts met in 1970 and proposed an International Nomenclature called “Constitutional (or Intrinsic) Disorders of Bone” [24]. This classification was subsequently revised. The latest

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revision incorporates recognized disorders and reflects new molecular and pathogenetic concepts [36]. Three hundred seventy-two different conditions were included and placed in 37 groups defined by molecular, biochemical and/or radiographic criteria. Of these conditions, 215 were associated with one or more of 140 different genes.

A comprehensive description of the epidemiology of these diseases, many of which lack consistent data, is beyond the aim of this chapter. Epidemiological studies based on total populations are expensive and difficult to perform. The scant reports available on skeletal dysplasias are heterogeneous and incomplete, so that critical data are missing or are not comparable. In addition, many of these disorders are difficult to diagnose and thus often misclassified. Moreover, they might remain undiagnosed, especially in stillborn babies and in children dying shortly after delivery. As a consequence, here we briefly review the data on the disorders usually recognizable at birth that cause the most relevant clinical involvement, and on which there is reliable information about frequency, determinants and consequences. We will address separately the osteochondrodysplasias from fibrodysplasia ossificans progressiva, a genetic disorder of ectopic skeletogenesis.

19.2 Epidemiology of Osteochondrodysplasias

Osteochondrodysplasias are a heterogeneous group of more than 200 disorders characterized by abnormalities of cartilage and bone growth and development resulting in abnormal shape and size of the skeleton and disproportion of the long bones, spine, and head [34]. Classically, this concept includes: achondrogenesis, achondroplasia, chondrodysplasia punctata, camptomelic dysplasia, congenital lethal hypophosphatasia, perinatal, lethal type of osteogenesis imperfecta, thanatophoric dysplasia, and short-rib polydactyly syndromes, among other important disorders [24, 34].

19.2.1 Frequency Measurements, Gender, Parental Age, and Familial Occurrence

Table 19.1 summarizes data of the major epidemiological studies on osteochondrodysplasias [1-3, 6, 7, 10, 16, 25, 27, 30, 35]. In these studies the point prevalence rates (at delivery) vary from 1.1 [7] to 9.46 [1], per 10,000 births. Although ethnic and geographic variations can not be discounted, differences in case ascertainment, definition, and classification criteria account for the largest part of this variation. The highest prevalence rate corresponds to the most recent survey, performed in an area with high risk of inbreeding [1]. The second highest point prevalence – 7.6 per 10,000 births – corresponds to the only study performed on generalized bone dysplasias including cases detected in both the neonatal period and later in life [3]. The majority of these studies include cases detected in the perinatal period, which probably underestimates the true rate of osteochondrodysplasias. Milder cases are seldom recognizable in this period because they do not manifest until short stature, joint symptoms, or other skeletal complications arise during childhood. Importantly, incomplete investigation of the cases could mask the true frequency at birth. This fact could lead one to underestimate the true prevalence of bone dysplasias, especially when the diagnosis is retrospective.

One of the most controversial issues in this field is the association between parental age and the occurrence of osteochondrodysplasias. Some general studies report that a higher paternal age exists in sporadic achondroplasia [25, 35], consistent with that of other previous [23]

and subsequent work [39]. In contrast, Al Gazali did not observe statistical differences between the ages of fathers and mothers of the newborns with either sporadic achondroplasia or thanatophoric dysplasia, compared to the controls [1]. In one study specifically designed to address this aspect, paternal ages of nonfamilial cases of achondroplasia, thanatophoric dysplasia, and osteogenesis imperfecta from both an Italian and a South American series, were compared with matched controls [26]. The degree of paternal age effect on the origin of these dominant mutations differed among the three conditions. Thus, in achondroplasia mean paternal age was elevated in both the Italian (36.30 ± 6.74 years) and Latino American (37.19 ± 10.53) series. In thanatophoric dysplasia, mean paternal age was also elevated in both series, although less consistently. In osteogenesis imperfecta, paternal age was only slightly elevated in the South American cases whereas in Italian cases paternal age did not differ from controls. Increased maternal age or "birth order" in these conditions disappeared when corrected for paternal age. Approximately 50% of achondroplasia and thanatophoric dysplasia cases and only 30% of osteogenesis imperfecta cases were born to fathers above age 35 years. For achondroplasia and thanatophoric dysplasia, the increase in relative incidence with paternal age fit an exponential curve. Taken together, these data suggest a strong relationship between an older paternal age and the appearance of sporadic achondroplasia, an association that is less evident in other genetic osteochondral diseases.

The frequency of parental consanguinity, which also was rarely addressed in depth, ranges widely between 4% [25] and 72% [1], reflecting variations in ascertainment as well as in methods of study. Family history was occasionally reported, being remarkable in isolated cases of proven achondroplasia [25], ostopetrosis [35] and osteogenesis imperfecta [27]. No indications of geographical cluster were communicated.

Only six studies have a sample size large enough to allow a reliable disclosure between subtypes of osteochondrodysplasias [1, 3, 6, 25, 27, 35] (Table 19.2). However, it should be noted that setting, design, and research methods were quite different between these studies (Table 19.1), making their results heterogeneous and difficult to compare. In addition, in the pre- and peri-natal period, the differentiation between bone dysplasias is often difficult and in most instances a sensible proportion of cases, reported from 16% [27] to 42% [25], did not fit into a specific diagnostic category. Although these limitations oblige caution, it is possible to make some general observations. Four conditions appear to predominate: Thanatophoric dysplasia, osteogenesis imperfecta, achodroplasia and achondrogenesis (Table 19.2). One exception is the report of Orioli et al. [25], a multicenter hospital based study performed in 20 cities of nine South American countries, in which thanatophoric dysplasia shows a frequency that is unusually low. The other confounding data are that of Al Gazali et al. [1], which report on a population with a huge proportion of consanguinity and, therefore, prone to develop autosomal recessive disorders.

The birth prevalence of sporadic achondroplasia shows a wide variation ranging from 0.13 [3] to 0.78 [1]. However, most authors provide values near to the lower limit (0.46 [25, 35], 0.37 [6], 0.24 [27]), well below the expected prevalence. Consequently, there is an agreement that this represents the recognised tendency to over-register achondroplasia,

mostly due to the misdiagnosis of cases of thanatophoric dysplasia and achondrogenesis [3, 8, 25].

Apart from these general studies, few investigations have ascertained the prevalence of specific osteochondrodysplasias. In a population based study on achondroplasia and thanatophoric dysplasia performed in selected regions of the US the prevalence of achondroplasia ranged from 0.36 to 0.60 per 10,000 live-births (1/27,780–1/16,670 livebirths) and the prevalence of thanatophoric dysplasia ranged from 0.21 to 0.30 per 10,000 livebirths (1/33,330–1/47,620 livebirths) [39]. These results were consistent with previously reported general studies on osteochodrodysplasias [1, 3, 6, 25, 27, 35] (Table 19.2).

19.2.2 Early Detection and Specific Diagnosis

The increasing use of prenatal ultrasound is changing the surveillance of skeletal dysplasias [27, 35]. Although, diagnostic specificity is difficult with this procedure, a high proportion of chondrodysplasias can be suspected early in gestation with its appropriate use. From an epidemiologic viewpoint, prenatal diagnosis may prevent the delivery of a stillborn infant or of an infant destined for early death, but does not appear to change the frequency of delivery of liveborns likely to survive more than a month [27].

The increasing trend of prenatal diagnosis has altered the birth status of cases of osteochondrodysplasias which, with a growing frequency, are the products of pregnancy terminations after ultrasonographic identification. As a consequence, making an accurate diagnosis by traditional clinical means could be difficult, and in some cases impossible. In spite of this, clinical manifestations and radiological investigations remain a cornerstone in the diagnosis of generalised bone dysplasias. As a rule, the radiological findings in these disorders are so characteristic that an exact diagnosis can be made, even after destructive pregnancy termination procedures [27]. Nevertheless, with the increasing use of ultrasonography, the role of biochemical and molecular techniques in diagnosis of some osteochondrodysplasias appears to be crucial, especially in order to provide appropriate genetic counselling [4, 5, 11, 29, 31, 37]. Their implementation has the potential for assisting in the specific diagnosis of cases of osteochondrodysplasias, and could allow for earlier and more accurate prenatal diagnosis in future pregnancies [27]. This is important because, even in cases where the therapeutic possibilities are few or non-existent, a correct diagnosis is crucial for valid genetic counselling and evaluation of clinical prognosis.

19.2.3 Temporal Trends

In diverse geographical areas, an increasing temporal trend has been reported in the occurrence of generalised bone dysplasias [1, 16]. Thus, the birth prevalence of osteochondrodysplasias in the United Arab Emirates seems to have doubled in the last 2 years of the 5-year observation period (6.74/10,000 in 1996 vs. 12.86/10,000 in 1999, and 13.45/10,000 in 2000). Although such tendency could be explained by changes in ascertainment methods [16], it is not possible to rule-out increased parental exposure to either environmental or domestic teratogenic agents [1].

19.2.4 Mortality Rates

With the exception of achondroplasia, there is a paucity of data about mortality in osteochondroysplasias. In the few general studies in which this aspect is mentioned, the data are scant and fragmentary. Thus, in one of these studies, the overall frequency of skeletal dysplasias among peri-natal deaths was 9.1 per 1,000 [6]. In Orioli's series, the peri-natal mortality rate for skeletal dysplasias was as high as 44% (with no deaths among the 16 proven achondroplasia cases), and rated at 40% for the osteogenesis imperfecta cases [25].

An additional difficulty concerns the low quantity and poor quality of available information on this topic. Further, it is important to analyse mortality data attributable to osteochodrosysplasias in the context of general causes of death in children. Results from a Canadian study showed that infant deaths caused by major congenital anomalies have decreased substantially from 3.11 per 1,000 live births in 1981 to 1.89 per 1,000 live births in 1995 [40]. Because the decrease in major congenital anomaly-attributed infant mortality paralleled the decrease in infant mortality due to other causes, the percentage of infant deaths attributable to major congenital anomalies remained constant at about 30% during the 15 years of study. Reductions varied according to specific forms of anomalies. Cause-specific infant mortality rates (per 1,000 live births) for musculoskeletal anomalies and multiple congenital anomalies were of 0.22 and 0.13 respectively, in 1981–1983, whereas corresponding rates were 0.12 and 0.06 in 1993–1995. By contrast, during the same time period, there were only moderate non-significant decreases or even a tendency to an increase in infant deaths due to urinary system, respiratory system, and chromosomal anomalies. This substantial decrease in infant mortality related to certain congenital anomalies, particularly in skeletal dysplasias and multiple congenital anomalies, seems to be the result of increased prenatal diagnosis [40].

The only exception to the scarcity of mortality data on specific osteochondrodysplasias is achondroplasia, perhaps because premature death, particularly in young adults, has been a big concern [13]. Studies performed on large cohorts of proven cases revealed that the overall mortality and age-specific mortality at all ages remained significantly increased [13, 41]. Moreover, rates of death were similar across all 42 years of follow-up suggesting that higher death rates were still occurring in the contemporary achondroplasia population. Overall survival and the average life expectancy for this population were decreased by 10 years. Compared to the general population, accidental, neurological, and heart disease related deaths were increased in adults with achondroplasia. Specifically, heart disease-related mortality, between ages 25 and 35, was more than 10 times higher than the general population. These results demonstrate that despite advances in the knowledge of the natural history of achondroplasia and improvements in health care, mortality remains increased in this disease. The high rate of heart disease related deaths illustrates the need to identify specific risk factors and, accordingly, develop treatment interventions.

19.3 Epidemiology of Fibrodysplasia Ossificans Progressiva

Fibrodysplasia ossificans progressiva, the most severe and disabling disorder of extraskeletal ossification in humans, is a genetic condition characterised by congenital malformation of

the big toe and progressive heterotopic ossification following specific anatomic patterns [9, 20]. The worldwide prevalence is, approximately, one in two million of individuals [9, 20].

There appears to be no ethnic, racial, gender, or geographic predisposition [18, 19, 32]. Most cases arise as a result of a spontaneous new mutation and a paternal age effect has been reported [28]. Fewer than ten small multigenerational families are known [32]. When inherited, the pattern of transmission is autosomal dominant. The condition can be inherited from either mothers or fathers [17, 32]. Maternal mosaicism has been described [15].

Phenotypic heterogeneity has been observed in fibrodysplasia ossificans progressiva [14, 38] and, both, genetic and environmental factors affect the phenotype of the disease. A study of three pairs of monozygotic twins found that within each pair, congenital toe malformations were identical. However, postnatal heterotopic ossification varied greatly depending on life history and environmental exposure to viral illnesses and to soft tissue trauma. Genetic determinants strongly influence disease phenotype during prenatal development while environmental factors strongly influence postnatal progression of heterotopic ossification [12].

Diagnostic errors are common in fibrodysplasia ossificans progressiva [9, 20, 21]. Most patients are misdiagnosed before the appearance of heterotopic ossification and undergo unnecessary diagnostic and therapeutic procedures that alter the natural history of the disease, causing permanent harm [21, 22]. However, an accurate diagnosis of the disease can be made early in life on the basis of the clinical findings of tumor-like swellings in association with characteristic malformed great toes [22].

The recent identification of the genetic cause of fibrodysplasia ossificans progressiva represents a real hope for a better control of this disorder [33]. After identifying linkage of fibrodysplasia ossificans progressiva to chromosomal region 2q23–24, a recurrent mutation in the gene encoding activin A receptor, type I (ACVR1), a BMP type I receptor, was demonstrated as the cause of all classically-occurring inherited and sporadic cases [33]. The identification of this gene, also known as activin like kinase 2 (ALK2), allows a reliable confirmatory diagnoses before ectopic ossification appears [20, 22]. Recognition of highly specific diagnostic features of the disease – particularly congenital great toe malformations associated with rapidly–appearing soft tissue swelling, should prompt early genetic consultation and testing. Such proper diagnosis can avoid harmful diagnostic and therapeutic procedures. The identification of fibrodysplasia ossificans progressiva provides a specific target for the development of therapeutic agents that block overactive ACVR1/ALK2 signaling, and thus may eventually prevent the progression of the disease [20, 22].

19.4 Implications of Epidemiological Findings: Conclusions and Recommendations

Generalized bone dysplasias are more frequent than generally assumed, with thanatophoric dysplasia, osteogenesis imperfecta, achondroplasia and achondrogenesis, accounting for the majority of cases. True Achondroplasia is less common than expected, perhaps because

many bone dysplasias are often erroneously classified as achondroplasia. Thus, it is important to emphasize correct diagnosis for prognosis, treatment, and genetic counselling.

In sporadic achondroplasia as well as in fibrodysplasia ossificans progressiva, there is a strong association with paternal age, a relationship that is less evident in other genetic osteochondral diseases. No other constitutional characteristic has proven to be associated with generalised skeletal dysplasias. Similarly, no environmental agents, either chemical or biological, have been demonstrated, although more research should be done to determine the possible role of these exposures in the etiology of osteochondrodysplasias. Environmental agents, by increasing the rate of mutation, might explain the increasing occurrence observed in different countries, although changes in ascertainment methods can not be excluded.

Clinical and radiographic features are crucial for diagnosis of osteochondral diseases and fibrodysplasia ossificans progressiva since radiological findings are often definitive. In suspected cases of skeletal abnormalities and dwarfism, it is important to obtain skeletal surveys as soon as possible in order to secure the correct diagnosis. In the case of fibrodysplasia ossificans progressiva, recognition of congenital great toe malformations associated with rapidly–appearing soft tissue swelling early in childhood is sufficient to make the proper diagnosis, which can be confirmed by genetic testing. Such proper diagnosis can avoid substantial iatrogenic harm.

The use of prenatal ultrasonography as a routine component of prenatal care can aid in the suspicion of osteochondrodysplasias earlier in pregnancy. However, as a specific diagnosis is required for the counselling of families, additional methods are needed. Definitive diagnosis is most often achieved by pre-natal molecular analysis.

Although osteochondrodysplasias and other genetic skeletal disorders are relatively frequent in general practice, individually they are rare. As a consequence, it is difficult for most hospital and primary care services to obtain experience in managing these disorders. These facts emphasize the need for large regional centres which will improve diagnosis performance and provide the integral assistance for these often severe and incapacitating conditions.

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Table 19.1

Summary of main epidemiological studies on osteo-condral diseases (in chronological order)

References (year) [Area; country]	Setting Years of study	Population targeted and period of ascertainment	No. of cases (female/male)	Rate per 10.000 deliveries (95%CI, when provided)
Gustavson [10] (1975) Uppsala (Sweden)	Hospital-based Feb 1970–Aug 1974	Osteochondrodysplasias in newborns	7 (4/ 3)	4.7
Camera [6] (1982) Italy (90' hospitals)	Hospital-based (multicenter)	Osteochondrodysplasias in newborns (first 7 days)	53	2.4 (1.8–3.2)
Connor [7] (1985) West Scotland	Population-based 1970–1983	Lethal neonatal Osteochondrodysplasias	38	1.1
Orioli [25] (1986) [20 cities; 9 South American countries]	Hospital-based (multicenter) 1978–1983	Osteochondrodysplasias in newborns (first 3 days)	80 (47/ 32) (+ 1 intersex)	2.3
Stoll [35] (1989) [Strasbourg; France]	Population-based Jan 1979–Dec 1986	Osteochondrodysplasias in newborns (first 8 days)	34 (18/16)	3.22
Andersen [2] (1989) [Fyn; Denmark]	Population-based Jan 1970–Dec 1983	Lethal Osteochondrodysplasias	12	1.5
Andersen [3] (1989) [Fyn; Denmark]	Population-based Apr 1973–Dec 1983	Generalized bone dysplasias (any age)	59	7.6 (5.9–9.3)
Sánchez [30] (1991) [Ciudad Bolívar; Venezuela]	Hospital-based (monitoring system) Apr 1978–Aug 1990 in newborns	Osteochondrodysplasias	25	3.5
Källén [16] (1993) [International]	Monitoring systems: • 3 hospital-based • 4 population-based	Osteochondrodysplasias (age no specified)	1,500	1.6
Rasmussen [27] (1996) [Boston , USA]	Hospital-based	Neonatal Osteochondrodysplasias (first 5 days)	27 (14/11) [+ 2 undetermined]	2.14
Al-Gazali [1] (2003) [United Arab Emirates]	Hospital-based (multicenter) Jan 1996–Dec 2000	Osteochondrodysplasias in newborns (first 7 days)	36 (23/13)	9.46

Table 19.2

Relative frequency (point prevalence at birth/10,000) of osteochondrodysplasias (outsiders values are in bold)

Condition	Author (References)					
	Camera [6]	**Orioli [25]**	**Stoll [35]**	**Andersen [3]**	**Rasmussen [27]**	**Al-Gazali [1]**
I. Usually frequent (in order of frequency)						
Thanatophoric dysplasia	0.69	**0.09**	0.28	0.38	0.40	0.78
Osteogenesis imperfecta	0.36	0.43	0.64	**2.2**	0.40	0.78
Achondroplasia[a]	0.37	0.46	0.46	**0.13**	0.24	1.04[b]
Achondrogenesis	0.23	**0.03**	0.28	0.64	–	–
II. Usually rare (in alphabetical order)						
Achondrogenesis or Thanatophoric dysplasia	–	0.11	–	–	–	–
Asphyxiating thoracic dysplasia (Jeune)	0.14	–	0.09	0.26	–	0.26
Campomelic dysplasia	0.05	0.09	0.09	0.13	0.16	0.26
Cereebro-costo-mandibular Dysplasia	–	–	–	–	–	0.26
Chondrodysplasia punctata (all types)	0.09	0.06	0.27	0.13	–	**1.04**
Chondroectodermal dysplasia	0.05	0.06	0.09	–	–	–
Cleidocraneal dysplasia	–	0.03	–	–	–	–
Desbusquois syndrome	–	–	–	–	0.08	–
Diastrophic dysplasia	–	0.03	0.09	–	–	–
Ellis van Creveld syndrome	–	–	0.09	–	–	**0.52**
Engelman disease	–	–	0.09	–	–	–
Fibrochondrogenesis	–	–	–	–	–	**1.05**
Fibrous dysplasia	–	0.03	0.09	–	–	–
Hypochondroplasia	–	–	–	0.13	–	–
Hypophosphatasia	–	0.03	–	–	–	–
Larsen syndrome	0.05	–	–	–	0.08	–
Melnick-Needles (Ostodysplasty)	–	–	–	–	0.08	–
Metaphyseal chondrodysplasia (Schmid type)	–	–	–	0.13	–	–
Micromelic dysplasia with Cloverleaf skull	–	–	–	0.26	–	0.26
Multiple cartilaginous exostoses	–	–	0.18	1.28	–	–
Multiple epiphyseal dysplasia (tarda)	–	–	–	0.9	–	–

Condition	Author (References)					
	Camera [6]	Orioli [25]	Stoll [35]	Andersen [3]	Rasmussen [27]	Al-Gazali [1]
Osteopetrosis	–	–	0.18	**0.51**	–	0.26
Schneckenbecken dysplasia	–	–	–	–	–	0.26
Schwartz-Jampel syndrome	–	–	–	–	–	0.52
Short rib polydactyly (any type)	–	–	–	–	0.16	0.52
Spondyloepiphyseal dysplasia	–	–	–	0.26	0.24	–
Stickler syndrome	–	–	–	–	–	**0.52**
Without specific diagnosis	0.23	0.37	No specified	0.26	0.32	No specified

[a] Only “true” cases of Achondroplasia are considered; some authors’ added some “questionable” cases.

[b] Original data are presented disaggregated by pattern of inheritance. The frequency of achondroplasia was 0.78 for sporadic cases and 0.26 for inherited ones. As per osteogenesis imperfecta, sporadic cases represent 0.52 whereas inherited cases account for the remaining 0.26.