Epidemiology, etiology, and genetic aspects of reduction deficiencies of the lower limb

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Abstract Although the majority of lower limb deficiencies are of sporadic occurrence and of unknown etiology, genetic factors are involved in a significant number, with variable modes of inheritance. A better-informed public is demanding advice concerning cause and recurrence. Careful scrutiny of the medical history and family tree and attention to phenotypic details may help to delineate entities. At times, specific chromosomal tests are important, mainly when there is bilateral or multiorgan involvement or when limb deficiency is associated with developmental delay and/or mental retardation. This paper is intended to refamiliarize the orthopaedic community with basic genetic aspects regulating reduction deficiencies of the lower limbs, and to emphasize on the importance and indications of genetic counseling.

Keywords Congenital anomalies · Lower limbs · Genetics in orthopaedics

Epidemiology

The majority of limb deficiencies seen in childhood are congenital in origin. This is followed at a distant second by trauma, and lastly as a result of tumors. There is little information on the incidence of congenital limb deficiency in the population, and what is reported varies widely from 1 per 15,000, to 3 per 100, depending on whether all anomalies are counted including the mildest.

Fibular deficiency is the most common long-bone deficiency. The incidence varies between 1 and 2 per 100,000 live births. The prevalence of tibial deficiencies is far lower, and is reported to be approximately 1 per 1,000,000 live births. The incidence of congenital femoral deficiencies (CFD) ranges from 1 in 50,000 to 200,000 live births [1–4]. Although this is a more common anomaly than fibular deficiency, the explanation lies in the difficulty in separating congenital short femur associated with fibular deficiency from true CFD.

Although such figures, if available, would be of use to health planning agencies, the fact for the orthopaedic surgeon is that the child with a limb deficiency will not be a common problem.

Etiology

Although the vast majority of congenital limb deficiencies are sporadic and not transmissible, a small number are, and this is something parents often desire to know. In order to insure a better care of the child and his or her family, the physician should be aware of the possible existence of other problems and the natural history of the syndrome.

There are at least four ways in which limb deficiencies can be caused: intrauterine amputation from amniotic bands, disruption of the developing arterial supply, environmental factors, and errors in the genetic control of limb development.

The oldest and most commonly held etiology for congenital amputation in the past was amniotic bands. There is evidence that amniotic bands can form a constriction around the developing limb that interferes with the growth of the limb, resulting in any degree of damage, from a minor constriction band around a limb that is otherwise normal, to a complete transverse amputation [5].

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The disruption of the developing arterial supply may cause a severe ischemic aggression to the limb bud, thus producing the anomaly with variable degrees of severity and associated lesions [6].

Environmental causes have been identified in approximately 10% of malformations: maternal infections or disease, uterine constraint, and exposure of the embryo to recognized drugs, chemicals, irradiation or hyperthermia [1, 7].

Modern genetics have shown that the development of the limb is a complex phenomenon that requires the precise interaction of a large number of genes and their effects. The opportunity for errors in this system is great, and animal experimentation has identified the probable mechanism in several limb anomalies. The chapter of genetically determined congenital anomalies is increasing with the new advances in the field of genetics. An example (one of a million) of an advance in this field is the one related to Escobar syndrome that has been recently recognized as a prenatal myasthenia caused by disruption of the acetylcholine receptor fetal γ subunit [8]. A simple example such as polydactyly is now known to belong to more than 119 different syndromes with over 39 identified mutations [9]. Hip dislocation may not be postural or developmental but is demonstrated to be more and more syndromic [10–11].

A genetic cause is suspected when the congenital anomaly is bilateral and/or symmetrical, and when there are other associated anomalies. Exploration of the genealogic tree may be helpful in confirming the genetic etiology of the anomaly.

It is not possible in this brief report to catalog every literature-cited disorder in which there are limb deficiencies of familial or genetic origin. The purpose of this review is to provide orthopaedic specialists with simple but sufficient scientific and useful genetic information for a better understanding and work-up of genetic syndromes of orthopaedic importance in everyday practice.

Genetic aspects of congenital anomalies of lower limb deficiency

A short reminder of terms most commonly used in genetics will help in a better understanding of the genetic aspects of the most frequent congenital deficiencies of the lower limbs. Selected entities will then be used to illustrate points in recurrence risk counseling.

Genetic diseases may be recognized at birth or much later in life. The term congenital means that a particular disease or somatic abnormality is present at birth. Such

conditions may be the result of environmental factors, genetic factors, or a combination of both.

The term familial indicates that certain disorders occur more frequently in a given family than chance alone would predict. The etiology could be either environmental, genetic or both [12].

The term hereditary is generally used to refer to those disorders that are related to traits determined largely by genes or chromosomes [13].

Autosomal dominant traits are characterized by a 50% transmission risk and are widely variable in their clinical presentation. Failure to recognize this characteristic can result in erroneous counseling [14]. Penetrance refers to whether the trait is expressed at all, that is, the percentage of patients with the gene who show some manifestation of it [15]. When an individual has the gene and fails to express it, the trait is said to exhibit reduced penetrance. Clinically, this can be the basis of a skipped generation. Many autosomal dominant traits are the result of new point mutations. In such instances, entirely normal parents have a child affected by an autosomal dominant trait who has 50% chance of transmitting the trait to any offspring he or she might produce one day. This is more commonly associated with old paternal age at conception [16].

Autosomal recessive traits are often associated with a high degree of consanguinity of the parents. Parents of a child with an autosomal recessive trait have 25% risk of having another affected child [17].

A trait transmitted as an X-linked disorder is expressed by all males who carry the gene. When a female carries the mutant X-linked gene, she is said to be a carrier. Half of her sons are at risk to be affected, and half of her daughters are at risk to be carriers. The affected male will have all carrier daughters because he can transmit only a mutant X. His sons will be unaffected [18].

Polygenic conditions are attributed to the interaction of two or more genes of small effect that, in themselves, are not deleterious [19]. Because the genes are contributed by both parents and are thought to interact with a variety of environmental agents, the disorders can be considered multifactorial in etiology.

In the clinical setting in which a patient presents for evaluation of a limb deficiency, it is crucial to observe the proband and other family members carefully for all abnormalities. When widespread defects or anomalies are noted, syndrome identification should be attempted. When mental retardation is also present, chromosomal analysis should be performed before final genetic counseling is provided.

Genetic aspects of the most common congenital deficiencies of the lower limbs will be briefly presented and discussed.

Coxa vara

The familial tendency of coxa vara as an isolated anomaly has long been observed. This disorder has been reported in three generations of a Cypriot family and is compatible with autosomal dominant inheritance [20]. Coxa vara can also occur as one manifestation of a number of generalized disorders, some of them with autosomal recessive inheritance. A thorough medical and family history as well as a physical examination can allow differential diagnosis and recognition of specific conditions.

Absence defects of the lower limbs

They are usually partial, and are likely to be part of a more widespread multiple malformation complex. Total absence of hands and feet has been reported in multiple members of Brazilian families of Portuguese background in an autosomal recessive mode [21].

Congenital femoral deficiency

Also known as proximal focal femoral deficiency (PFFD), it is characterized by its clinical heterogeneity. It is often unilateral and sporadic, but may also be part of a more complex syndrome [22]. Although there is a slightly greater tendency towards autosomal dominant transmission, all modes of inheritance have been reported in the literature.

Fibular deficiency

It is more often sporadic and of unknown etiology. It is predominantly unilateral. As part of a widespread skeletal disorder or multisystem entity, fibular deficiency is found in a variety of conditions, the inheritance mode of which is more often autosomal recessive. However, new point mutations as well as X-linked inherited cases have been described [23].

Tibial deficiency

This is a rare abnormality. It is sporadic in the majority of instances and highly variable in severity. Most cases are part of a systemic syndrome. Although both autosomal dominant and autosomal recessive modes of inheritance have been reported, there seems to be a greater tendency towards autosomal dominant mode with variable penetrance [24].

Split hand/split foot deformity

It is heterogeneous and may occur as an isolated malformation or as part of a syndrome [25]. A wide variety of

syndromes with this anomaly have been reported with a mode of inheritance until recently much more often autosomal dominant, with variable penetrance and frequent new mutations.

Summary

Although the majority of lower limb deficiencies are of sporadic occurrence and of unknown etiology, genetic factors are involved in a significant number, with variable modes of inheritance. A better-informed public is demanding advice concerning cause and recurrence. Careful scrutiny of the medical history and family tree and attention to phenotypic details may help delineate entities. At times, specific chromosomal tests are important, mainly when there is bilateral or multiorgan involvement or when limb deficiency is associated with developmental delay and/or mental retardation.

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