Congenital Limb Deficiency Disorders

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KEYWORDS

• Limb deficiency • Split-hand • Split-foot • Ectrodactyly • Hemimelia • Phocomelia

KEY POINTS

- Congenital limb deficiencies are common birth defects, occurring in 1 in 2000 neonates.
- The presence of a limb deficiency should prompt a thorough examination for other skeletal and nonskeletal anomalies, a 3-generation pedigree, assessment of teratogenic exposures during the pregnancy, and often examination of the parents.
- Consultation with a medical geneticist should be sought especially for longitudinal deficiencies.
- Genetic testing is available and helpful for management and genetic counseling in many cases.
- Most families should be promptly referred to a specialized limb deficiency center for ongoing management.
- With appropriate specialized care, most children with isolated limb deficiencies are able to lead productive lives with excellent function.

INTRODUCTION

The limb deficiency disorders (LDDs) are a broad group of congenital anomalies featuring significant hypoplasia or aplasia of one or more bones of the limbs. LDDs of all types occur in approximately 1 in 1300 to 2000 births.[1–6] LDDs can occur in isolation or associated with other anomalies. The nomenclature of limb deficiencies is often confusing with many historical terms that are imprecise (**Table 1**). An international standard nomenclature was adopted in 1989, permitting a more precise description of the specific bones that are hypoplastic or absent in each case.[7–10] The standard nomenclature divides limb deficiencies into 2 basic types, longitudinal and transverse. Longitudinal deficiencies are

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Clin Perinatol 42 (2015) 281–300
http://dx.doi.org/10.1016/j.clp.2015.02.004 **perinatology.theclinics.com**
0095-5108/15/$ – see front matter

Table 1
Descriptive terms for limb deficiencies

Standard terminology	
Transverse deficiency	Absence of limb elements distal to a specified level across the long axis of the limb, eg, the loss of the left distal forearm and hand (see Fig. 1A)
Longitudinal deficiency	Aplasia or hypoplasia of a bone along the long axis of the limb, eg, left radial and thumb aplasia (see Fig. 1B)
Historical terminology	
Amelia	Absence of one or more limbs
Ectrodactyly	Absent digit or digits (often used interchangeably with split-hand/foot)
Hemimelia	Absence or significant hypoplasia of the lower part of one or more limbs (fibular, radial, tibial, or ulnar hemimelia)
Oligodactyly	Fewer than 5 digits
Peromelia	Malformation of one or more limbs
Phocomelia	Absence of the proximal limbs with some preservation of the distal elements (seal limb or flipper-like
Split-hand, split-foot	Absent digit or digits producing a cleft appearance

Data from Prosthetics and orthotics - limb deficiencies- Part 1: Method of describing limb deficiencies present at birth. ISO 8548-1:1989. International Standards Organization; 1989. Available at: http://www.iso.org.

along the long axis of the limb, such as absence of the radius. In contrast, a transverse deficiency is across the long axis of the limb, such as an amputation of the foot (**Fig. 1**, see **Table 1**). It is common to refer to transverse deficiencies as preaxial (radial and tibial side), postaxial (ulnar and fibular side), and central.[6]

The LDDs have traditionally been placed in the skeletal dysostosis group (early developmental disorders that are fixed at birth), as opposed to the skeletal dysplasias (disorders with ongoing abnormalities of skeletal development). However, disorders that have features of both have made this distinction less useful.[11] There is no classification system for the LDDs that is useful for the practicing clinician; only the better-defined LDDs are listed in the International Nosology of Genetic Skeletal Disorders,[11] a catalog of skeletal disorders.

Limb development in tetrapods is complex, involving numerous interconnected regulatory circuits including the wingless family (WNTs), bone morphogenic proteins (BMPs), fibroblast growth factors, hedgehog proteins, homeobox and other transcription factors, and retinoic acid. Despite intense study for decades, many essential components remain to be discovered.[12–14]

Studying the genetics of human limb malformations and dysplasias has led to new understandings of limb development; this has been especially true for the brachydactylies[15] and skeletal dysplasias (reviewed by Krakow elsewhere in this issue). As in the brachydactylies and skeletal dysplasias, the molecular pathways identified to date in the LDDs are diverse; some were predicted based on animal studies, whereas others were unexpected until the defect in humans was identified. Examples of the variety of pathways involved in the LDDs include chromatid adhesion in Roberts SC phocomelia (268300 [numbers in parentheses in this review correspond to Online Mendelian Inheritance in Man (OMIM; www.ncbi.nlm.nih.gov/omim) numbers]); cell adhesion in the ectodermal dysplasia, ectrodactyly, and macular dystrophy syndrome (225280); transcription factors in synpolydactyly 1 (186000), split-hand/foot malformation with