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Arthrogryposis: A Review and Update

By Michael Bamshad, MD, Ann E. Van Heest, MD, and David Pleasure, MD

Congenital contractures can be divided into two groups: isolated contractures and multiple contractures (Fig. 1). Isolated congenital contractures affect only a single area of the body; the most common isolated contracture is congenital clubfoot, which occurs in one of every 500 live births.

The term arthrogryposis is often used as shorthand to describe multiple congenital contractures that affect two or more different areas of the body. Arthrogryposis is not a specific diagnosis, but rather a clinical finding, and it is a characteristic of more than 300 different disorders2-3. The overall prevalence of arthrogryposis is one in 3000 live births4. The inheritance, natural history, treatment guidelines, and outcomes of arthrogryposis vary among disorders, underscoring the importance of making a specific diagnosis in each child5-10. The purpose of this article is to present the current state of knowledge about the classification, etiology, and management of children with various types of arthrogryposis.

Classification of Arthrogryposis

To establish a differential diagnosis, it is important to first decide whether a child has normal neurological function. A normal neurological examination suggests that arthrogryposis is due to amyoplasia, a distal arthrogryposis, a generalized connective tissue disorder, or fetal crowding. In contrast, an abnormal neurological examination indicates that movement in utero was diminished as a result of an abnormality of the central or peripheral nervous system, the motor end plate, or muscle.

Amyoplasia

Amyoplasia (A = no; myo = muscle; plasia = growth) is a distinct form of arthrogryposis with characteristic clinical features as shown in Figure 2: the shoulders are usually internally rotated and adducted, the elbows are extended, the wrists are flexed and ulnarly deviated, the fingers are stiff, and the thumbs are positioned in the palm. In the lower limbs, the hips may be dislocated, the knees are usually extended, and the feet have severe equinovarus contractures. Many patients have a midfacial hemangioma. In one series, 10% of the patients had abdominal abnormalities such as gastroschisis or bowel atresia11. Clinical series12 have shown that 84% of the children have symmetric involvement of the upper and lower limbs; other variations of presentation include upper limb only, lower limb only, or asymmetric patterns of involvement. In Hall’s original description of 135 patients with amyoplasia13, all cases were sporadic. She also noted an increased prevalence in twins and in conditions that would lead to decreased limb movement, such as a bicornuate uterus, oligohydramnios, or intrauterine crowding.

The goals of initial treatment are to mobilize the joints, apply splints for improved position and function, and to provide physical and occupational therapy as well as instructions to the child’s caregivers so that they may provide home therapy. Ongoing therapy services are part of most children’s lives, with 80% of children with amyoplasia receiving therapy services into their teenage years14. Persistent limb deformities that restrict function are common and are often treated surgically. In one series of children with amyoplasia15, orthopaedic surgeries were performed on the feet in 76% of children; on the knees, in 39%; and on the hips, in 18%. The elbows were operated on in 24% of children; the wrists, in 16%; and the hands, in 8%; and 5% required spinal surgery.

The primary long-term goals of treatment of amyoplasia are increased joint mobility and muscle strength and the development of adaptive use patterns that allow for walking and independence with activities of daily living. Surgical intervention in the upper limb16-18 may be recommended for fixed joint contractures that preclude or interfere with upper-limb function. Surgery is rarely needed for shoulder contractures; however, if internal rotation of the shoulder specifically precludes functional positioning of the hand in space, an external humeral rotational osteotomy is indicated. An inability to reach the hand to the mouth due to an elbow extension contracture can be treated with a posterior capsulotomy of the elbow with triceps lengthening19-21. Multiple tendon transfers have been attempted to add active elbow flexion12-19. However, a recent study questioned the long-term result of elbow flexion transfers in this population22, and those authors recommended elbow capsulotomy without tendon transfer23. For the wrist, a dorsal carpal wedge osteotomy with a possible flexor carpi ulnaris tendon transfer to preserve the arc of motion but re-
position the wrist in extension and neutral deviation has been reported\(^1\). Surgical correction of the thumb-in-palm deformity may improve thumb position for pincer function.

In summary, children with amyoplasia typically exhibit severe joint contractures with weakness of the muscles that are present. With multiple orthopaedic and rehabilitation interventions, the ability to walk and perform activities of daily living has been reported to be as high as 85\(^\%\)\(^{10}\). Nevertheless, children with amyoplasia usually require more surgical interventions than do children with any other type of arthrogryposis and, in adult life, the majority of individuals need assistance with activities of daily living\(^5\).

Distal Arthrogryposes

Distal arthrogryposes are a group of autosomal dominant disorders that mainly involve the distal parts of the limbs. Characterization of the genetic and molecular basis of the distal arthrogryposis syndromes has served as a valuable framework to identify genetic risk factors for congenital contractures.

The distal arthrogryposes are characterized by congenital contractures of two or more different body areas without a primary neurological and/or muscle disease\(^2\). Features shared among all distal arthrogryposes include a consistent pattern of hand and foot involvement, limited involvement of proximal joints, and variable expressivity. Ten different distal arthrogryposes have been described to date\(^{22-24}\) and are classified hierarchically according to the proportion of features they share with one another (Table I). For example, there is more overlap between the phenotypes of distal arthrogryposis type 1 (DA1) and distal arthrogryposis type 2 (DA2) than there is between DA1 and distal arthrogryposis type 3 (DA3).

Major diagnostic criteria are used to make the diagnosis of a specific distal arthrogryposis. For the upper limb, major diagnostic criteria include camptodactyly or pseudocamptodactyly (limited passive proximal interphalangeal joint extension with hyperextension of the wrist), hypoplastic and/or absent flexion creases, overriding fingers, and ulnar deviation at the wrist. For the lower limb, major diagnostic criteria are talipes equinovarus, calcaneovalgus deformities, vertical talus, and/or metatarsus varus. To be considered affected, an individual must exhibit two or more of these major criteria, but when a first-degree family member (i.e., a parent or a sibling) meets these diagnostic criteria, other family members with at least one major diagnostic criterion are considered affected. Salient features of several distal arthrogryposes are described below. (For conditions referenced in this paper, the reader is encouraged to go to the human genetic database Online Mendelian Inheritance in Man [OMIM] at http://www.ncbi.nlm.nih.gov/sites/entrez?db=omim and enter the OMIM six-digit identifier number in the search field.)

Distal Arthrogryposis Type 1 (DA1)

The prototypic distal arthrogryposis is distal arthrogryposis type 1 (DA1, OMIM 108120).\(^3\) DA1 is characterized largely by camptodactyly and clubfoot. Hypoplasia and/or absence of some interphalangeal creases is common. The shoulders and hips are less frequently affected. While the pattern of affected joints is consistent, the degree to which the joints are affected is highly variable, with equinovarus deformities ranging from mild to severe and hand involvement ranging from isolated hypoplasia of the distal interphalangeal crease of the fifth digit to severely clenched fists and ulnar deviation of the wrist. With
the mildest form of DA1, affected individuals have only hy-
poplasia of the gastrocnemius—although ascertainment of such
cases requires that a family member meet the diagnostic criteria
for distal arthrogryposis.

Distal Arthrogryposis Type 2 (DA2)
DA2 is phenotypically similar to a condition called Freeman-
Sheldon syndrome (FSS or DA2A, OMIM 193700). In addi-
tion to contractures of the hands and feet, FSS is characterized
by oropharyngeal abnormalities, scoliosis, and a distinctive
face (Fig. 3) that includes a very small oral orifice (often only
a few millimeters in diameter at birth), puckered lips, and an
H-shaped dimple of the chin; hence, FSS has also been called
“whistling-face syndrome.” Individuals with DA1 and FSS may
have such similar limb phenotypes that they can only be dis-
tinguished by the differences in their facial morphology. Reports
of extended families in which some individuals were diagnosed
with DA1 while others were diagnosed with FSS led to the
delineation of a distinct disorder with overlapping phenotypes
between DA1 and FSS. The congenital contractures in this
distinct condition were similar to those observed in DA1, but
affected individuals tended to have more prominent nasolabial
folds, downslanting palpebral fissures, and a small mouth. This
disorder is now called DA2B or Sheldon-Hall syndrome (SHS,
OMIM 601680), whereas FSS is considered as DA2A. Sheldon-
Hall syndrome is probably the most common of the distal
arthrogryposis disorders.

Distal Arthrogryposis Type 5 (DA5)
DA5 (OMIM 108145) is unique among distal arthrogryposes
because, in addition to contractures of the skeletal muscles,
affected individuals have ocular abnormalities. These typically
include ptosis, restricted movement of the extraocular muscles,
and/or strabismus, findings that suggest that the extraocular
as well as the skeletal muscles are involved in the pathogenesis
of DA5. Recently, several unrelated individuals with DA5 have
been reported as having pulmonary hypertension as a result of
restrictive lung disease. This is consistent with earlier anec-
dotal observations of abnormal chest-wall muscles in adults
with DA5.

Distal Arthrogryposis Type 7 (DA7)
DA7, or trismus-pseudocamptodactyly syndrome (TPS, OMIM
158300), is an uncommon distal arthrogryposis characterized
by an inability to fully open the mouth (trismus) and pseudo-
camptodactyly. Additional reported features of TPS include
shortened hamstring muscles and short stature. The clinical
characteristics of TPS vary widely within families, and no
single feature, including either trismus or pseudocampto-
dactyly, is present in all affected individuals.

Distal Arthrogryposis Types 3, 4, and 6 (DA3, DA4, and DA6)
DA3, DA4, and DA6 are very rare. DA3, or Gordon syndrome
(OMIM 114300), is distinguished from other distal arthro-
gryposes by short stature and cleft palate. However, the ma-
jority of individuals who are considered as being affected have
neither of these defects but have been ascertained from large,
multiplex families in which the index individual had a cleft
palate in addition to congenital contractures.

The Molecular Basis of Distal Arthrogryposis Syndromes
Mutations in at least five genes (TNNI2, TNNT3, TPM2,
MYH3, and MYH8) that encode components of the contractile
apparatus of fast-twitch myofibers can cause distal arthro-
gryposis. FSS and SHS are caused by mutations in MYH3,
a gene that encodes embryonic myosin. Mutations in MYH3
explain approximately 90% of the cases of FSS and approxi-
mately 40% of the cases of SHS, making MYH3 mutation the
most common known cause of distal arthrogryposis. No
mutations overlap between those that cause FSS and SHS,
suggesting an unambiguous genotype-phenotype relationship.
SHS can also be caused by mutations in either of the genes that
encode troponin I (TNNI2) or troponin T (TNNT3). More
recently, in families with SHS, mutations have been found in
TPM2, a gene that encodes tropomyosin 2 (Bamshad, unpublished data). This is of interest because mutations in TPM2 were first identified in families with DA1. Moreover, mutations in TNNI2 and TNNT3 have also recently been found in individuals with DA1. Thus, mutations in TNNI2, TNNT3, and TPM2 can be found in individuals diagnosed with DA1 or SHS. These results suggest that DA1 and SHS represent variable expressivity of the same syndrome. Mutation analysis of these genes is not available for clinical service as of yet but is commonly performed in research laboratories.

Two DA5 families have been found to have mutations in MYH2 and MYH13, both of which are expressed in the skeletal muscles of the limbs and the extraocular muscles. Each of these mutations is a missense mutation that is predicted to cause substitution of highly conserved amino acid residues. No other DA5 families were found to have mutations in either gene. Accordingly, mutation of either MYH2 or MYH13 appears to be a rare cause of DA5. In each of approximately a dozen families studied to date, DA7 is caused by a single missense mutation in MYH8 that is predicted to cause an arginine-to-glutamine substitution in perinatal myosin.

The mechanism by which mutations in these genes cause contractures is unclear. TnI, TnT, β-tropomyosin, and myosins are part of the multimeric troponin-tropomyosin-myosin complex of the sarcomere. Mutations in genes that encode sarcomeric proteins in cardiac muscle cause defects in force production that can result in either hypocontractility or hypercontractility. Similarly, the results from in vitro contractility studies in which recombinant mutant TnI and β-tropomyosin molecules were used suggest that distal arthrogryposis syndromes are, in some cases, caused by increased myofiber contractility. However, the mechanism by which contractility is altered is not yet clear. In contrast, direct measurement of the contractile properties of chemically skinned single muscle fibers sampled from affected muscles in individuals with MYH3 mutations suggests that maximal force normalized to fiber cross-sectional area is less than that observed in myofibers from unaffected individuals (Bamshad and Beck, unpublished data). These results suggest that there might be multiple mechanisms by which contractility can be altered to cause contractures. Understanding these mechanisms could provide a model to explore the pathogenesis of more common con-

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*OMIM = Online Mendelian Inheritance in Man.

Fig. 3
Child with distal arthrogryposis type 2A (Freeman-Sheldon syndrome).
Arthrogryposis in Children Who Have Abnormal Results on Neurological Examination

This section will be restricted to central nervous system and neuromuscular diseases. These are thought to be a common cause of arthrogryposis and the most common cause of severe arthrogryposis.

Central Nervous System Causes of Arthrogryposis

Developmental abnormalities affecting the forebrain (e.g., hydranencephaly, microcephaly, or forebrain neuronal migration disorders), whether due to primarily genetic factors or as a consequence of fetal central nervous system infection, are sometimes associated with arthrogryposis. In most such cases, joint contractures are probably due to diminished corticospinal tract activation of spinal cord motor neurons. Sometimes, however, the underlying disease also directly injures spinal cord motor neurons, contributing to fetal hypomotility. Such disorders can be suspected on clinical examination if hyperreflexia, unilateral arthrogryposis, or cognitive deficits are present and can be anatomically localized by magnetic resonance imaging of the brain.

Chromosomal deletions or rearrangements are an occasional cause of arthrogryposis. Developmental loss of facial and other brainstem motor neurons (e.g., Moebius syndrome) is also sometimes associated with arthrogryposis. It is not known whether the deficient limb movement in these children is due to impaired corticospinal input to spinal cord motor neurons or because development of spinal cord motor neurons is also impaired. Arthrogryposis is a frequent feature of X-linked spinal muscular atrophy, a progressive motor neuron disease caused by mutations of the ubiquitin proteasome system gene, UBE1, and it also occurs in fetuses with spinal cord anterior horn atrophy owing to mutation of ERBB3, which encodes a protein that modulates the phosphatidylinositol-3-kinase/Akt pathway. Arthrogryposis also occasionally occurs in the much more common, recessively inherited, infantile spinal muscular atrophy (Werdnig-Hoffmann disease), which is seen in infants with inactivating mutations of both copies of SMN1 who lack more than two copies of SMN2.

Neuromuscular Causes of Arthrogryposis

Genetic peripheral neuropathies with an onset during fetal life have been described, but they are a rare cause of arthrogryposis. Neuromuscular junction blockade in fetuses carried by mothers with myasthenia gravis and autoantibodies that recognize fetal acetylcholine receptors can result in arthrogryposis. Measures that suppress autoantibody formation, including maternal thymectomy prior to pregnancy, or intravenous gamma globulin administration during pregnancy, are likely to reduce the risk of arthrogryposis in such pregnancies. Repeated administration of botulinum toxin to pregnant women has the theoretical potential to inhibit acetylcholine release at neuromuscular junctions in the fetus and hence cause fetal hypomotility, but children with arthrogryposis arising from this etiology have not been reported. Arthrogryposis also occurs in infants with inherited mutations in genes that encode skeletal muscle acetylcholine receptor proteins, or proteins associated with these receptors (e.g., rapsyn [Rapsn]).

Congenital myopathies that are sometimes associated with arthrogryposis can be caused by mutations of genes that encode fetal skeletal-muscle myosin heavy chains, skeletal-muscle thin filament proteins, and the ryanodine receptor protein. Congenital myotonic dystrophy causes arthrogryposis because of the toxicity of RNA encoded by a triplet repeat expansion in the 3′-untranslated region of the dystrophin myotonia protein kinase (DMPK) gene. Congenital muscular dystrophies caused by mutations of the LMNA gene, which encodes A-type lamin, or of several genes that participate in the glycosylation of alpha-dystroglycan, can cause congenital muscle disease that progresses after birth (congenital muscular dystrophy) and joint contractures that increase in severity after birth. Congenital neuropathy associated with LMNA mutations may also contribute to the genesis of joint contractures.

Electromyography is useful in detecting and anatomically localizing neuromuscular disorders that have caused fetal immobility and led to arthrogryposis. Evidences of denervation (e.g., fibrillations, giant motor unit potentials, and diminished numbers of motor units) would indicate the presence of skeletal muscle denervation, as would occur with spinal cord motor neuronopathy or axonal neuropathy. Abnormal skeletal muscle responses to repetitive motor-nerve stimulation are helpful in diagnosing neuromuscular transmission disorders. Profoundly slowed nerve conduction velocities indicate the presence of a dysmyelinating neuropathy, whereas electrically inexcitable nerves suggest an axonal neuropathy. Studies helpful in diagnosing neuromuscular causes for arthrogryposis include assays for acetylcholine receptor antibodies and creatine kinase. Because DNA diagnostic tests to distinguish the various congenital myopathies and/or dystrophies are not yet readily available to the clinician, skeletal muscle biopsy is sometimes useful. However, care should be taken in the choice of anesthesia for this procedure in order to minimize the risk of malignant hyperthermia.

Conclusions

Congenital contractures are a common birth defect and are associated with substantial morbidity and economic burden. Attempts to identify the etiology and understand the pathogenesis of congenital contractures are an important area of pediatric health-care research.

Arthrogryposis describes the multiple congenital contractures that are part of more than 300 different disorders. Amyoplasia and the distal arthrogryposis syndromes, of which there are at least ten different types, are common causes of arthrogryposis when the results of neurological examination are normal. Amyoplasia is a sporadic disorder, whereas the distal arthrogryposes are autosomal dominant disorders. Central nervous system abnormalities, peripheral nervous system defects, or intrinsic muscle diseases can also cause arthrogryposis. These can be due to genetic or environmental factors.
Any factor that diminishes fetal movement can, in principle, cause congenital contractures, so identifying these factors would seem to be relatively straightforward. Indeed, some environmental factors (e.g., uterine crowding) and genetic factors (e.g., trisomy 18) that cause congenital contractures have been relatively easy to find. However, the underlying etiology of most congenital contractures remains an active area of investigation.

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