Distal Arthrogryposis

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Introduction

Congenital multiple joint contractures involving two or more body areas are collectively termed as arthrogryposis. Based on the extent of joint involvement (proximal and/or distal joints), neurological involvement, and involvement of other parts of the body/other organs the etiology and prognosis of arthrogryposis differs.[1] Various etiologies of arthrogryposis include single gene mutations, chromosomal anomalies, and intrauterine environmental factors (e.g. fetal crowding, failed termination of pregnancy).[1,2] Distal arthrogryposis (DA) are a subset of arthrogryposis characterized by congenital joint contractures predominantly affecting joints of the hands and feet (distal joints) with or without associated anomalies.[3] Here we discuss DA – its types, clinical presentation, inheritance and genes, prognosis and genetic counseling.

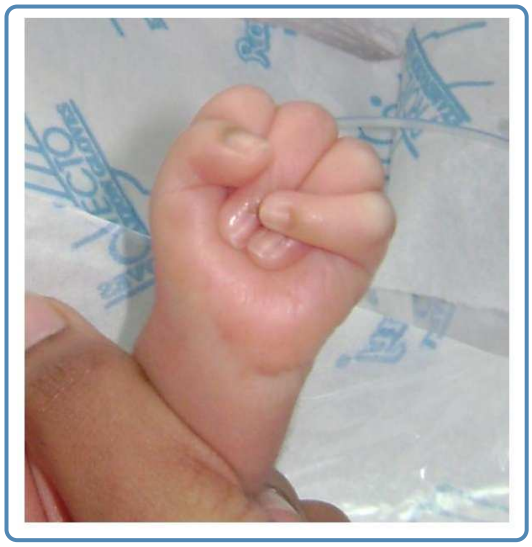

Figure 1 Clenched hand at birth.

Definition and Diagnostic criteria

According to Bamshad et al., DA are defined as disorders predominantly affecting the limbs in the form of congenital joint contractures in two or more body areas without any underlying neurologic and/or muscle pathology.[3]

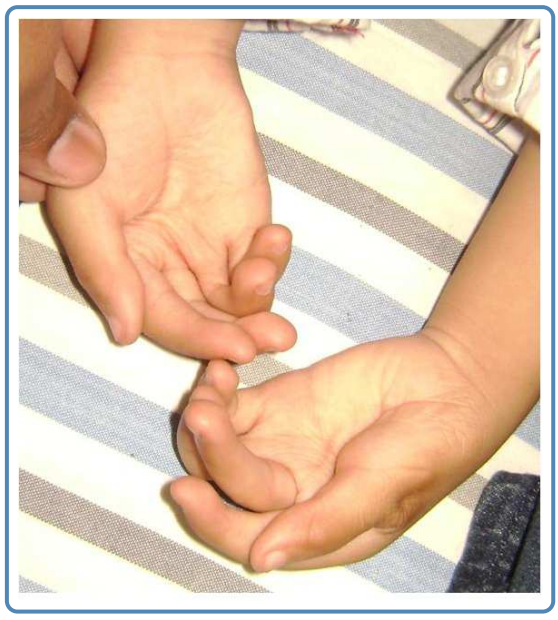

Figure 2 Ulnar deviation of fingers with contractures, faint flexion creases and adducted thumb.

A diagnosis of DA should be considered in any child with predominant involvement of joints of the hands and feet, presenting with upper extremity features of clenched fingers at birth (Fig 1), ulnar deviation of fingers, flexion contractures of fingers (Fig 2), and hypoplastic and/or absent flexion creases, and lower extremity features of clubfoot, calcaneovalgus deformities, metatarsus

varus and/or vertical talus (prominent heels or rocker bottom feet)(Fig 3). There might be variable involvement of proximal joints of both the upper limb and lower limb. Based on the associated anomalies in systems other than skeletal system (face, eye, spine and other organ systems), DAs are further classified into subtypes.[3]

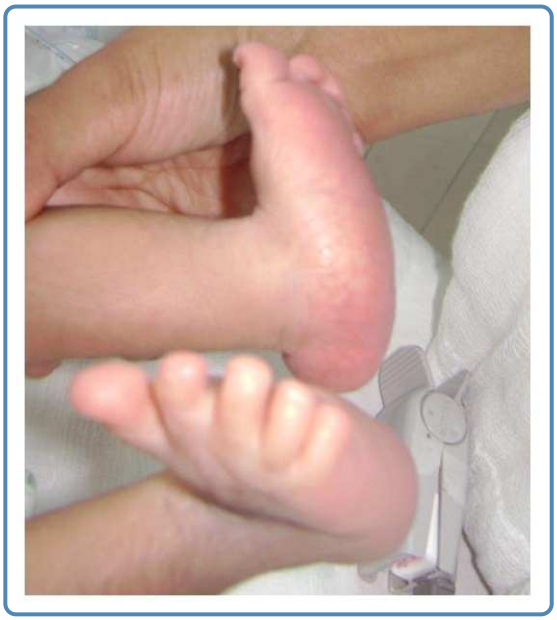

Figure 3 Rocker bottom feet.

The clinical features of DAs show marked interfamilial and intrafamilial variability. In some families a carrier might be completely unaffected or might have mild clinical manifestations like absent palmar flexion creases, toe contractures, mild flexion contractures of fingers noticed at birth etc. As suggested by Bamshad et al. the above mentioned definition/diagnostic criteria (two major diagnostic criteria involving the upper limb and lower limb) of DA should hold true for at least one member of the affected family and for other family members mild clinical features can be considered for the diagnosis. Further, molecular genetic testing might help to confirm the diagnosis in mildly affected individuals and obligate carriers.[3]

Incidence

Incidence of arthrogryposis is around 1 in 3000 births.[1]

Inheritance and Genes

Most of the DAs are inherited as autosomal dominant disorders with both interfamilial and intrafamilial variability.[1,3] Some of the DAs are also inherited as autosomal recessive disorders.[3,4] Most genes causing DA are the ones that code for contractile proteins of fast-twitch muscle fibers.[3]

Classification

Based on the above definition and diagnostic criteria, 10 types of DA have been identified. Table 1 summarizes the clinical features and genetics of different types of DA.

Clinical features

Majority of DAs are inherited as autosomal dominant disorders with variable clinical features.[1,3] DA type 1 is classified into type 1A and 1B based on the chromosomal locus, otherwise clinically they are indistinguishable. In DA type 1, around 98% of the cases have typical manifestations of the hand and 88% have typical manifestations of the feet. The face is normal and there are no associated anomalies.[9] DA type 2 is classified into 2A and 2B, which are differentiated by the facial features. Facial features of DA2A include deep-set downslanting eyes, hypertelorism, small mouth, puckered lips, H-shaped chin dimple, small nose, long philtrum, and mild micrognathia.[10] Some of the other features in DA2A include scoliosis, hip dislocation, strabismus and cryptorchidism. Facial features in DA2B include triangular face, downslanting eyes, prominent nasolabial folds, small mouth and pointed chin. Variable clinical features include proximal joint involvement, short stature and short webbed neck.[9,10] In a recent article by Beck AE et al. mutations in four genes (*TNNI2*, *TPM2*, *TNNT3* and *MYH3*) have been found to cause both DA1 and DA2B; therefore, authors suggest that DA1 and DA2B should be considered as a single disorder representing a spectrum of manifestations. On sequencing of these four genes, mutations were found in 29% of DA1 cases and 40% of DA2B cases.[5]

DA type 3 is characterized by finger contractures and cleft palate. Variable features include hip dislocation, patellar dislocation, talipes equinovarus, hearing impairment, scoliosis and limitation in elbow joint movements.[3,5]

Type of DA	Clinical features	Intelligence	Synonyms	Inheritance	Genes
DA type 1 (1A & 1B)	Typical involvement of hands and feet	Normal	–	AD[#]	*TNNI2*, *TMP2*, *TNNT3*, *MYH3*, *MYBPC1*[5,6]
DA type 2A	Typical involvement of hands and feet, typical facies[*]	Normal	Freeman-Sheldon syndrome	AD	*MYH3*[7]
DA type 2B	Typical involvement of hands and feet, typical facies[*]	Normal	Sheldon-Hall syndrome	AD	*TNNI2*, *TMP2*, *TNNT3*, *MYH3*[5,6]
DA type 3	Finger contractures, cleft palate, talipoequinovarus	May have intellectual disability	Gordon syndrome	AD	–
DA type 4	Finger contractures, scoliosis	May have intellectual disability	–	AD	–
DA type 5	Finger contractures, ophthalmoplegia, ptosis	Normal	–	AD, AR[θ]	*ECEL1* (AR)[4]
DA type 6	Finger contractures, sensorineural hearing loss	Normal	–	AD	–
DA type 7	Trismus, camptodactyly on dorsiflexion of wrist	Normal	Trismus-pseudo-camptodactyly syndrome	AD	*MYH8*[8]
DA type 8	Typical involvement of hands and feet, multiple pterygia, typical facies[*]	Normal	–	AD	–
DA type 9	Finger contractures, arachnodactyly, external ear deformity	Normal	Congenital contractural arachnodactyly (Beals syndrome)	AD	*FBN2*

[*] For facial description see text.
[#] AD – Autosomal dominant.
[θ] Autosomal recessive.
TNNI2 – Troponin I; TMP2 - Tropomyosin 2; TNNT3 – Troponin T3; MYH3 – Myosin heavy chain 3; MYBPC1 – Myosin-binding heavy protein C; MYH8 - Myosin heavy chain 8; FBN2 – Fibrillin 2.

Table 1 Clinical characteristics, inheritance and the known causative genes of different types of DA

DA type 4 manifests with finger contractures and scoliosis. Variable features include intellectual disability and limitation of elbow joint movements.[3,5]

DA type 5 is inherited as both an autosomal dominant and autosomal recessive disorder. Along with finger contractures and feet involvement, eye findings are peculiar to patients with DA5. Variable eye features include ophthalmoplegia, strabismus, ptosis, pigmentary maculopathy, keratoconus and an abnormal electroretinogram. Some cases are known to have pulmonary hypertension secondary to restrictive lung disease.[3,5] Based on the eye and other findings, DA5 has been classified into four subtypes (DA5A-D).[4] DA5D is inherited as an autosomal recessive disorder.

DA type 6 is characterized by distal limb contractures and sensorineural hearing loss.[3,5]

DA type 7 is characterized by inability to open the mouth and flexion of fingers on dorsiflexion of the wrist. Variable clinical features include talipes equinovarus, hip involvement, short leg muscles and short stature.[3,5]

In DA type 8, along with typical manifestations in the hands and feet, patients present with multiple pterygia, scoliosis with vertebral segmentation defects, facial features, short neck and short stature. Facial features include ptosis, downslanting eyes, low set ears, and high arched palate. It is an autosomal dominant disorder, with most cases occurring sporadically due to de novo mutations. The other conditions which present with similar clinical features include autosomal recessive multiple pterygium syndrome (Escobar syndrome), X-linked multiple pterygium syndrome and a lethal form.[3,5]

DA type 9 is characterized by finger contractures and crumpled ears. Variable clinical features include scoliosis, limitation of elbow and hip joint movements, valvular heart disease and talipes equinovarus.[3,5] DA9 is caused by *FBN2* (fibrillin 2) gene mutations, with most of the mutations occuring in exon 23 to exon 34. Some patients with the severe form of DA9 can simulate neonatal Marfan syndrome.[11] Crumpled ear is used as a hallmark to identify patients with DA9.

Management and Genetic counseling

Management of patients with DA should involve various specialties (clinical genetics, orthopedics, neurology, pediatrics and physiotherapy). Joint contractures and skeletal complications (scoliosis) are managed by physical therapy and/or surgery. Patients requiring surgery might face difficult intubation and are at risk of malignant hyperthermia (documented in some of the subtypes). Inheritance is autosomal dominant in most of the cases. Mutations can occur de novo (sporadic), in which case the risk of recurrence in siblings is negligible. If the mutation is inherited from one of the parents, the risk of recurrence is 50% for the siblings. Molecular genetic testing and identification of the causative gene mutation help in providing an accurate risk of recurrence and appropriate genetic counseling. In cases with autosomal recessive inheritance, the risk of recurrence in siblings of an affected individual is 25%.

Prenatal diagnosis can be achieved by ultrasound (less accurate) and molecular genetic testing, if the underlying gene mutation is known (more accurate).

Author suggests readers the recent article on *Arthrogryposis: Diagnostic approach to etiology, classification, genetics and general principles* by Dr Judith G Hall published in *E J Med Genet* (2014) for updated clinical approach and list of genes.

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