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A New Distal Arthrogryposis Syndrome Characterized by Plantar Flexion Contractures

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Abstract

The distal arthrogryposis (DA) syndromes are a distinct group of disorders characterized by contractures of two or more different body areas. More than a decade ago, we revised the classification of DAs and distinguished several new syndromes. This revision has facilitated the identification of five genes (i.e., *TNNI2*, *TNNT3*, *MYH3*, *MYH8*, and *TPM2*) that encode components of the contractile apparatus of fast-twitch myofibers and cause DA syndromes. We now report the phenotypic features of a novel DA disorder characterized primarily by plantar flexion contractures in a large five-generation Utah family. Contractures of hips, elbows, wrists, and fingers were much milder though they varied in severity among affected individuals. All affected individuals had normal neurological examinations; electromyography and creatinine kinase levels were normal on selected individuals. We have tentatively labeled this condition distal arthrogryposis type 10 (DA10).

Keywords

distal arthrogryposis; new syndrome; autosomal dominant; contractures; Achilles; plantar flexion; toe-walking

INTRODUCTION

Arthrogryposis is a general term used to describe individuals with non-progressive congenital contractures of two or more different body areas. Arthrogryposis has been described as a feature of more than 150 different syndromes [Hall 1992]. The distal arthrogryposes (DA) are a subset of such syndromes that are characterized by frequent involvement of the hands and feet, limited proximal joint involvement, autosomal dominant inheritance, reduced penetrance, and variable expressivity. To date, 10 different DA syndromes have been characterized and classified [Bamshad et al., 1996; Hall et al., 1982]. This classification has facilitated the development of diagnostic criteria for DA syndromes,

improved the understanding of differences in the natural history of DA disorders, and led to the identification of several genes that cause congenital contractures.

Most of the genes identified to date to cause DA disorders (i.e., *TNNI2*, *TNNT3*, *MYH8*, *MYH3*, and *TPM2*) encode components of the contractile apparatus of fast-twitch myofibers [Sung et al., 2003a; Sung et al., 2003b; Veugelers et al., 2004; Toydemir et al., 2006]. These discoveries suggest that DA disorders are novel myopathies in which affected individuals demonstrate neither hypotonia nor weakness. Accordingly, phenotypic and molecular characterization of DA syndromes is providing novel insights about the mechanism by which prenatal defects of contractility can cause congenital contractures.

We report the phenotypic characteristics of a large five-generation Utah family in which multiple affected individuals primarily exhibit plantar flexion contractures and transmit this trait in an autosomal dominant pattern. This disorder meets the diagnostic criteria for a DA syndrome [Bamshad et al. 1996] and yet it is distinct from all other DA syndromes and appears, to our knowledge, to be unique.

CLINICAL REPORTS

The proband (IV-9) is a 26 year-old man who presented with a history of bilateral plantar flexion contractures that had been surgically corrected in early childhood. His physical examination revealed residual plantar flexion contractures and modest flexion contractures of the elbows and fingers, diminished extension of the wrists, and modestly reduced supination. He also had decreased flexibility of the hamstring muscles with normal flexibility of his lower spine. Strength testing in both the upper and lower limbs was normal. He had well-developed muscle bulk in all limbs with particular attention to the gastrocnemius, soleus, and extensor digitorum brevis muscles. An electromyogram showed normal sural sensory response, normal peroneal and tibial motor responses, and excellent recruitment of motor units of selected muscles of the right lower limb including the tibialis anterior, peroneus longus, medial gastrocnemius, extensor digitorum brevis, and flexor hallucis brevis. A detailed family history revealed multiple family members with apparently similar contractures that were transmitted in an autosomal dominant pattern (Fig. 1).

After obtaining informed consent, physical examinations and medical histories were obtained on 15 affected and 10 unaffected family members from this large 5-generation Utah pedigree. Medical histories and phenotypic status on additional members (Fig. 1) were obtained via phone interview in circumstances where in person examination was not possible. For several individuals who were deceased, phenotypic status was assigned by reviewing medical histories obtained via interviews with living family members.

Each affected individual had bilateral plantar flexion contractures although the severity varied widely among cases (Fig. 2). In the majority of affected individuals, contractures were not evident at birth but became apparent to family members in early childhood, typically with the onset of ambulation. Indeed, the plantar flexion contractures commonly manifested as “toe-walking.” In most cases (i.e., 8) surgical palliation (i.e., tendon lengthening) was required to improve ambulation. Contractures of other joints were not as consistently observed as the plantar flexion contractures but when present, typically involved the elbows and wrists (Fig. 3). No affected individual had clubfeet, calcaneovalgus deformities, hip dislocation, camptodactyly or abnormal flexion creases. No individual had contractures of the oral orifice. All affected individuals had normal neurological and ocular exams. Serum creatine phosphokinase levels were normal in the seven affected individuals who were available for testing. Electrocardiograms on selected individuals were normal. Plain radiographs of the ankle were obtained on one individual (IV-5) and no structural abnormalities of the bones were reported.

Magnetic resonance imaging was performed on a 1.5 Tesla GE Lightspeed magnet utilizing a combination of T1, T2 with fat saturation, and STIR sequences of the elbow and right leg in selected affected individuals. Magnetic resonance imaging of the elbows of two affected individuals demonstrated normal nerve, tendon, and bone morphology and placement. In one individual there was slightly increased T2 signal at the distal biceps tendon with adjacent edema reaction in the radial tuberosity. In the absence of muscle signal abnormalities or joint abnormalities these tendon findings were thought to reflect mild bicep tendinosis and enthesopathy. Magnetic resonance imaging of the right leg with separate acquisitions for the proximal and distal halves was obtained on two affected individuals. These images demonstrated normal nerve and bone morphology and post surgical changes of Achilles' tendon lengthening in the postoperative individuals. All other tendons appeared normal in signal and morphology. However, there was increased intrafascicular fat with low-grade edema in the muscles of the posterior compartment of the legs (Fig. 4). Intrafascicular fatty replacement of muscle is present in a wide variety of myopathies from both intrinsic [De Kerviler et al. 1996, Kobayashi 1996, Lossos et al. 2005] and extrinsic causes [Notzli 2005, Schabitz et al. 2003, Russo 1997]. These findings are nonspecific with respect to etiology, but they are very sensitive to the presence of chronic neuromuscular pathology.

Stature and intelligence was normal in all affected individuals except for one child (V-3) who was evaluated as an infant for mild developmental delay, short stature, and minor facial anomalies. His developmental delay subsequently improved with only mild speech delay at 2 years of age. He developed "toe-walking" when he began to ambulate. Surgery to lengthen his plantar tendons was scheduled at the time of this report. Other findings in affected individuals included a constricted urethra that required surgical intervention (IV-6), a Chiari malformation that required surgical intervention (IV-11), and kyphosis (II-13, IV-11). Otherwise, the medical histories were unremarkable in the remainder of the affected individuals.

The severity of the contractures of the hips, elbows, wrists, and fingers varied among affected individuals (Table I). In several individuals the contractures were mild and subtle to detect by physical exam. Identification of contractures in such cases was facilitated by the observation that affected individuals experienced difficulty when actively stretching or exercising. Several individuals noted that it was difficult to sit upright with their legs flexed and crossed over one another in front of them. In some instances, parents reported having difficulty putting diapers on affected individuals because of the reduced flexibility of the lower back with flexion of the legs towards the upper torso. Despite the presence of contractures, no affected individuals reported an inability to perform routine tasks.

DISCUSSION

Affected individuals in this family meet the general diagnostic criteria of a distal arthrogryposis syndrome [Bamshad et al. 1996] and the wide intra-familial phenotypic variability, the absence of neurological abnormalities, and the transmission of this disorder in an autosomal dominant pattern are consistent with the characteristics of the distal arthrogryposis syndromes. Nevertheless, the pattern of contractures observed in this family distinguishes it from all other distal arthrogryposis syndromes defined to date. Therefore, we conclude that the pattern of contractures observed in this family represents a novel distal arthrogryposis syndrome that we have labeled as distal arthrogryposis type 10 (DA10).

Toe walking in childhood can be observed in many conditions, but the etiology is often not known. Stricker and Angulo [1998] retrospectively reviewed 80 children with idiopathic toe walking. They suggested a potential genetic contribution as 32% reported a family history of toe walking. Some individuals had normal passive ankle dorsiflexion indicating the absence

of an actual contracture, which is not consistent with our family [Stricker and Angulo, 1998].

The clinical characteristics of DA10 appear to be similar to those described by Hall et al. [1967] as congenital short tendo calcaneus or congenital short Achilles tendon described in 33 individuals including 3 familial cases. Levine [1973] described similar findings in five affected family members in two generations in which a short tendo calcaneus was transmitted in an autosomal dominant pattern. In all of these reported cases, each affected individuals had a normal neurological exam and normal muscle bulk. Additionally, muscle biopsies performed in several of these individuals were also normal. Unlike the individuals in our family, involvement of additional joints was not found in any of the cases reported by Hall et al. [1967] and Levine [1973]. It is possible that some individuals with congenital short tendo calcaneus have contractures of other joints that were not appreciated, although in our family, two affected individuals presented with only plantar flexion contractures.

Plantar flexion contractures are a feature of other distal arthrogryposis syndromes (e.g., DA5) and can be observed in a variety of muscular dystrophies and myopathies. For example, both Emery-Dreifuss muscular dystrophy [Helbling-Leclerc et al., 2002] and Bethlem myopathy [Jobsis et al., 1999] are characterized by contractures similar to those observed in DA10 although they do not typically present congenitally. However, both of these disorders are associated with diminished muscle bulk and weakness—neither of which was found in individuals with DA10.

Historically, the term arthrogryposis has been reserved as a description of conditions in which contractures were congenital and non-progressive. In many individuals in the family with DA10, contractures were not noted at birth by other care providers but were apparent to family members shortly thereafter. With subsequent motor development the contractures in these cases eventually became identifiable by care providers as well. This observation raises the question as to whether the contractures were present at birth or were progressive in nature or both. In most affected individuals in this family, the contractures were notable at birth by care providers and other family members alike, and did not worsen with age. Accordingly, we suspect that in these cases in which the contractures were not identifiable at birth, that the contractures were mild enough as to not be detected by general care providers but became symptomatic with age and increasing functional requirements. Confirmation of this supposition will require evaluation by specialists of additional affected individuals in the newborn period and by sequential exam of affected individuals. Similar to our findings, two individuals with congenital short tendo calcaneus reported by Levine [1973] were not recognized at birth, and in another study only 6/80 individuals with idiopathic toe-walking were reported to have tight heel cords at birth [Stricker and Angulo, 1998].

DA1, DA2A, DA2B, and DA7 are caused by mutations in genes that encode proteins of the contractile apparatus of the fast-twitch myofibers including *TNNI2*, *TNNT3*, *MYH8*, *MYH3*, and *TPM2* [Sung et al., 2003a; Sung et al., 2003b; Veugelers et al., 2004; Toydemir et al., 2006]. Because the phenotypic overlap of DA10 with these DAs, we hypothesize that DA10 is also caused by mutations in genes that encode proteins that interact with those of the contractile apparatus. Testing of this hypothesis will depend, in part, on the identification of additional individuals with DA10. Identification of additional DA10 cases will also facilitate the development of diagnostic criteria and promote a better understanding of the natural history of this disorder, both of which should ultimately improve the care provided to affected individuals.

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Fig. 1.
Pedigree of family with DA10. Filled symbols represent affected individuals and open symbols indicate unaffected individuals. Individuals examined by one or more of the authors are denoted with an asterisk.

Fig. 2.
In individuals affected with DA10, the maximum degree of plantar flexion is moderately to severely limited as demonstrated in both A and B.

Fig. 3.
Contractures of the elbows that limit full extension of the upper limb are also frequently found in individuals with DA10.

Fig. 4.

A- Coronal T1-weighted image of a 25 year-old affected male (IV-9) showing uniform intermediate muscle signal intensity. B- Coronal T1-weighted image of an affected 24 year-old female (IV-2) with abnormal fatty infiltration of the superficial posterior compartment (arrow), and more normal muscle signal within the muscles of the deep posterior compartment of the leg (arrowhead). C- Axial STIR sequence in the same leg in B showing elevated fluid signal and atrophy of the medial gastrocnemius (arrow). Note the decrease in muscle mass compared to the adjacent lateral gastrocnemius muscle (arrowhead).

Table I

Contractures in Affected Individuals Examined

Patient	Age	Plantar	Elbow	Wrist	Finger	Hamstring
II-12	76yr	++	+	+	-	-
II-13	74yr	+++	+++	+++	++	+
III-15	49yr	+++ [*]	++	++	++	+
III-18	51yr	++ [*]	+++	++	+	+
III-25	34yr	+	+	+	-	-
IV-21	3.5yr	+	+	-	-	-
IV-22	5yr	+ [*]	+	+	-	-
IV-2	23yr	++ [*]	++	+	-	+
IV-5	18yr	++ [*]	++	+	+	+ [*]
IV-6	15yr	++ [*]	+	+	+	+
IV-9	26yr	++ [*]	+	++	+	+
IV-11	24yr	++	-	-	-	-
IV-14	14yr	+ [*]	++	-	+	+
V-3	2.5yr	++	-	-	-	-

^{*} status post surgical lengthening of the plantar tendons

(- = no contracture; + = mild contracture; ++ = moderate contracture; +++ = severe contracture)