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CONGENITAL CONTRACTURAL ARACHNODACTYLY WITH NEUROGENIC MUSCULAR ATROPHY

Case report

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ABSTRACT - We report the case of a 3-1/2-year-old girl with hypotonia, multiple joint contractures, hip luxation, arachnodactyly, adducted thumbs, dolichostenomelia, and abnormal external ears suggesting the diagnosis of congenital contractural arachnodactyly (CCA). The serum muscle enzimes were normal and the needle electromyography showed active and chronic denervation. The muscle biopsy demonstrated active and chronic denervation compatible with spinal muscular atrophy. Analysis of exons 7 and 8 of survival motor neuron gene through polymerase chain reaction did not show deletions. Neurogenic muscular atrophy is a new abnormality associated with CCA, suggesting that CCA is clinically heterogeneous.

KEY WORDS: congenital contractural arachnodactyly, spinal muscular atrophy, motor neuron disease, survival motor neuron gene.

Aracnodactilia contratural congênita com atrofia muscular espinhal: relato de caso

RESUMO - Relatamos o caso de uma paciente do sexo feminino de 3 anos e 6 meses com hipotonia, contraturas de múltiplas articulações, aracnodactilia, polegares aduzidos, dolicostenomelia e orelhas externas anormais sugerindo o diagnóstico de aracnodactilia contratural congênita (ACC). As enzimas musculares eram normais e a eletromiografia de agulha mostrou desinervação ativa e crônica. A biópsia muscular mostrou desinervação ativa e crônica compatível com atrofia muscular espinhal. A análise dos exons 7 e 8 do gene do *survival motor neuron* por reação em cadeia de polimerase não mostrou deleções. Atrofia muscular neurogênica é uma nova anormalidade associada a ACC, sugerindo a heterogeneidade clínica da ACC.

PALAVRAS-CHAVE: aracnodactilia contratural congênita, atrofia muscular espinhal, doença do neurônio motor, gene do *survival motor neuron.*

First described by Beals and Hecht in 1971[1], congenital contractural arachnodactyly (CCA), also known as Beals syndrome, is an autosomal dominant disorder of the connective tissue characterized by multiple congenital contractures, arachnodactyly, dolichostenomelia, kyphoscholiosis, and abnormal external ears[1-3]. It has been linked to the fibrillin-2 locus on chromosome 5q23-31[4,5] and several mutations have been described[6-10].

There is significant phenotypic variability within and between families and many abnormalities have been associated with CCA.[2] We report a patient with clinical features of CCA and electrophysiological and histopathological features of neurogenic muscular atrophy.

CASE

A 3-1/2-year-old girl presented since birth with hypotonia, hip luxation, and joint contractures. She had delayed motor development and did not achieve deambulation. There was no family history. The parents were healthy and not related. On physical examination, she presented abnormal external ears, epicanthus (Fig 1A), arachnodactyly, adducted thumbs (Fig 1B), long and thin limbs (dolichostenomelia), distal joint hyperextensibility (Fig 1D), dorsal flexion of feet and ilioinguinal, popliteal, and adductors contractures (Fig 1C).

Neurological examination showed muscular atrophy, generalized hypotonia, predominantly proximal muscular weakness, and decreased deep tendon reflexes. Ophthalmological examination was normal. Serum muscular enzimes, urine homocystine, and echocardiography were

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Fig 1. (A) Abnormal external ears, and epicanthus. (B) Arachnodactyly, and adducted thumbs. (C) Dorsal flexion of feet, distal joint hyperextensibility. (D) Distal upper limb joint hyperextensibility.

normal. Motor and sensory nerve conduction velocities were normal. Needle electromyography showed active and chronic denervation in all tested muscles.

Muscle biopsy of quadriceps showed mild proliferation of connective tissue, moderate adipose tissue infiltration, great variability in muscle fiber diameter with angular atrophic fibers, nuclear clumps, rare fibers with necrosis and phagocytosis, basophilic fibers (Fig 2A), type grouping, and atrophy of both type-1 and type-2 fibers (Fig 2B), compatible with active and chronic denervation, and suggestive of spinal muscular atrophy. Analysis of exons 7 and 8 of survival motor neuron gene through polymerase chain reaction did not show deletions. The patient was referred to physical therapy.

DISCUSSION

CCA has four main clinical features including arachnodactyly or dolichostenomelia, kyphoscoliosis, multiple congenital contractures, and abnormalities of the external ears. Other important features are micrognatia, ogival palate, cranial deformities,

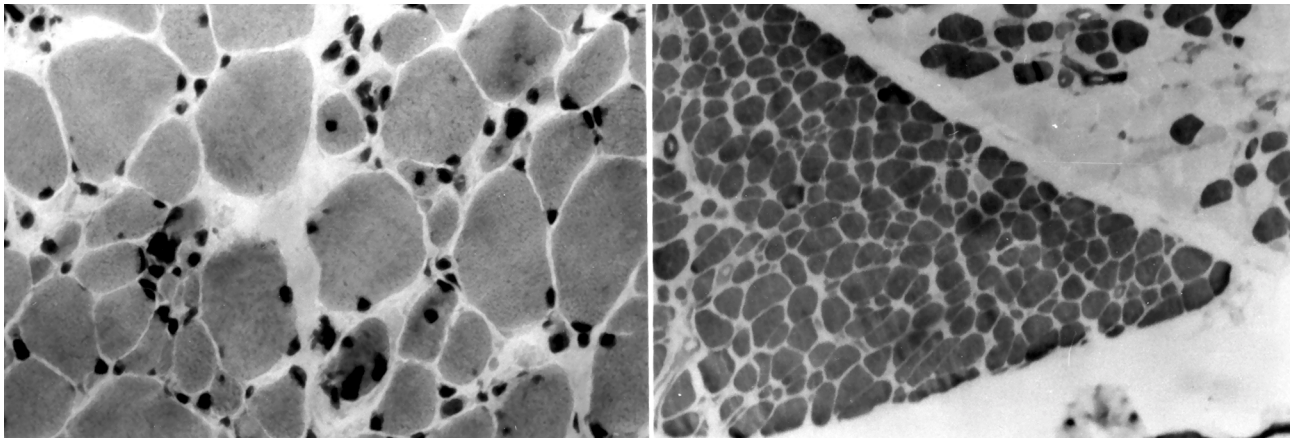

Fig 2. (A) Muscle biopsy stained with hematoxilin-eosin showing great variability in muscle fiber diameter with angular atrophic fibers, and nuclear clumps (400x). (B) Muscle biopsy stained with pH 4.6 ATPase showing type grouping, and atrophy of both type-1 and type-2 fibers (100x).

adducted thumbs, feet deformities, subluxation of patella, muscle hypoplasia, osteopenia, and delayed motor development because of the contractures[1-3]. CCA patients may also manifest cardiac abnormalities, including mitral valve prolapse, atrial sept defect, and aortic hypoplasia[2,11]. There is also an early lethal neonatal CCA phenotype comprising cardiac and aortic arch malformations, duodenal atresia, intestinal malrotation, abnormal facies, restrictive lung disease and skeletal deformities, in addition to external ear malformation, congenital joint contractures, and arachnodactyly[12].

Although muscle hypoplasia was early described as a frequent finding of CCA, we did not find any study showing the electromyographic findings and the pathological features of muscle biopsy in CCA. Because of the electromyographic and histopathological features of our case, a possible diagnosis in our patient was spinal muscular atrophy (SMA). SMA is characterized by degeneration of the anterior horn cells of the spinal cord, leading to symmetrical muscular weakness and atrophy. Three different clinical syndromes can be defined on the basis of severity. The SMA type I (Werdnig-Hoffmann disease) starts with hypotonia and weakness in utero or within the first few months of life. These children are never able to sit unsupported. The majority of these children die within the first three years of life due to recurrent respiratory infection. In the SMA type 2 (Dubowitz disease) onset is usually between 3 and 15 months of age. These children learn to sit without support but never walk unaided. They survive beyond 4 years of age until adolescence or later. The onset of SMA type III (Kugelberg-Welander disease) is after the age of 2 years and is characterized by proximal muscle weakness, predominantly of the lower limbs. These patients manage to stand and walk unsupported, but have problems with running, jumping, and climbing. The long-term survival is usually good, depending on respiratory function.[13] All three types map to chromosome region 5q11.2-q13.3. Lefebvre et al.[14] identified a gene in this region, which is called survival motor neuron gene (SMN). Although the analysis of deletions of exons 7 and 8 of SMN gene has a sensitivity of more than 90% for the diagnosis of SMA, it is not possible to exclude this diagnosis in our patient[13,14].

Other differential diagnosis of CCA include Marfan syndrome, artrogryposis multiplex congenita, homocystinuria, osteogenesis imperfecta, and Achard syndrome.[1,15] Marfan syndrome is also a disease of the connective tissue and is caused by mutations in the gene of fibrillin-1, localized in the chromosome 15. Marfan syndrome and CCA overlap in symptomology and morphology. Autosomal dominant inheritance, arachnodactyly and dolichostenomelia characterize both Marfan syndrome and CCA. On the other hand, Marfan syndrome rarely present joint contractures, and when present the contractures are not congenital and involve the hands and feet rather than the elbows, hips, and knees, and may become worse with time. Cardiovascular complications have been described in 60-93% of patients with Marfan syndrome and are responsible for the poor long-term prognosis of this syndrome. The cardiovascular system is rarely affected in CCA. Ocular abnormalities are frequent in Marfan syndrome but rare in CCA. Artrogryposis multiplex congenita is easily differentiated from CCA by the more rigid congenital contractures, tending to involve more proximal joints. In homocystinuria the skeletal deformities develop after birth and joint contractures are rare. Lens dislocation, mental retardation, and episodes of thromboembolism, frequently seen in homocystinuria, are not features of CCA. The severe osteopenia, blue sclera, and frequent spontaneous fractures of the long bones, so characteristic of osteogenesis imperfecta, are not seen in CCA. Achard syndrome includes arachnodactyly but lacks dolichostenomelia, contractures, and external ear abnormalities[1,15].

Intragenic heterogeneity within the fibrillin-2 gene is likely to be responsible for the wide phenotypic differences in patients with CCA. The clinical expression of the disease can be influenced by the amount of expression of the normal allele. An individual in a family with CCA may be more severely affected if the normal fibrillin-2 production is diminished, whereas an individual with equal amounts of fibrillin-2 production from both the mutant and normal alleles may be less severely affected[6].

Although linkage to fibrillin-2 gene can be achieved through family studies and many mutations have been described,[6-10] diagnosis of sporadic cases of CCA remains clinical. Clinically, our patient has many features of CCA, including abnormal external ears, arachnodactyly, dolichostenomelia, multiple joint contractures, and adducted thumbs. We recognize that the lack of genetic confirmation of the diagnosis of CCA is a limitation of our study, but the great variability in mutations of fibrillin-2 gene makes this study difficult.

The management of patients with CCA is usually supportive and confined to physical therapy in early

childhood to increase joint mobility and lessen the effects of muscle hypoplasia.[2] In the absence of cardiovascular, gastrointestinal, and neurological involvement the prognosis of CCA is good, with progressive improvement of joint contractures. Our report suggests a great variability in the phenotype of CCA and adds neurogenic muscular atrophy as a new manifestation of the disease.[2]

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