FUNDACIÓN VIOELIA
NIÑOS CONTRA LA DISTROFIA MUSCULAR CONGÉNITA POR DÉFICIT DE COLÁGENO VI

Congenital muscular dystrophies (CMD) are, under the clinical and genetic point of view, a quiet heterogeneous group of diseases inside **the neuromuscular pathologies.**

CMD can be classified according to the protein function affected, as a result of mutations in various genes involved (the genes are those that are encoding proteins), their location and their function.

Collagen VI is a major structural protein of the extracellular matrix of skeletal muscle and other tissues such as skin, tendons and ligaments. Collagen VI provides form, strength and flexibility to the tissues. Its function it is important because alterations in tendons and ligaments are associated with other manifestations of the disease as well as hyper mobility, retractions and healing problems.

In the CMD caused by deficit in collagen VI there is an alteration of the extracellular matrix in tissues where it is expressed, not only in skeletal muscle. **There are three genes involved** in the synthesis of collagen VI **(COL6A1, COL6A2 and COL6A3)**, pathogenic mutations in any of the three genes, are severe degenerative consequences.

Clinically, depending on the phenotype, **are described 2 kinds of diseases**, and both are due to a mutation in any of the 3 genes responsible for the synthesis of collagen VI: **DMC Ullrich DMC Bethlem and intermediate forms called collagen VI related myopathies (COL6-RM).**

Initially these pathologies are described separately and differentiated by the severity of presentation and the mode of inheritance:

- **The DMC Ullrich**, is more severe and with autosomal recessive or dominant inheritance. Often mutations are **"de novo"**, it means that neither of their parents nor their grandparents have this genetic alteration and it is the result of a new mutation in a parent germ cell (egg or sperm) or zygote.
- **The DMC Bethlem**, is mainly dominant and less severe clinically speaking, though rarely, found a pattern of autosomal recessive inheritance.
- We are currently seeing **intermediate** forms too.

Clinically present from birth with hypotonia and hypermobility associated with distal to proximal contractures (knees, elbows). There may be kyphoscoliosis or congenital torticollis, protuyente calcaneus and hip dislocation. Contractures tend to improve at the beginning and then can progress again. From the motor point of view, most patients acquire the ability to walk and holds up at the end of the first decade. Accompanying the loss of ability to walk there is a nocturnal respiratory failure that emerges progressively, but that fact may precede the loss of mobility. Follicular hyperkeratosis is also characteristic as well as keloid scarring. The intellectual level is normal.

The Ullrich congenital muscular dystrophy

(UCMD, its acronym in English**) is characterized by** early onset, generalized muscle weakness and slow progression, multiple proximal joint contractures, marked hypermobility of the distal joints and normal intelligence. Among the neonatal findings may be weakness of the facial muscles, arched palate, dislocation congenital hip prominent calcaneus, torticollis, transient kyphotic deformity, contractures (which particularly affect elbows and knees) and distal laxity (which affects hands, feet and fingers).

There is a delay at different stages of motor development. The distal joints of the hands, ankles, feet, toes and fingers have hyperextensibility for life, but with the age, the distal laxity can cause lasting strong flexion contractures of the fingers and important tension in the Achilles tendon. Developmental delay is common.

At an early stage of the disease course, most contractures are released spontaneously but they reappear later. While the disease progresses, spinal rigidity and scoliosis usually develops (in the first or second decade of life).

UCMD patients usually have dry soft skin and follicular hyperkeratosis on the extensor surfaces of the extremities.

Early respiratory failure is a common complication and potential cause of death.

The diagnosis is based on patient history, recognition of typical clinical features and findings reduction of collagen VI in muscle biopsy and / or skin fibroblasts. The diagnosis should be confirmed genetically. It is important to know the mutation and its mode of inheritance. If the mutations are **"de novo"**, the chances of having another child with this affection are very low. There is the possibility of offering prenatal diagnosis for these cases.

Currently there **is no curative therapy**, but supportive treatment can improve the quality of life of patients with UCMD.

The main **forms of palliative treatment** are physiotherapy, early mobilization, home extension and splinting. Typically, in the first or second decade of life respiratory support is required with nocturnal ventilation. Prophylaxis of chest infections and the use of antibiotics is necessary. Nasogastric feeding tube may be needed as well as surgical release of contractures and surgery to prevent progression of scoliosis.

The UCMD is a serious progressive disease. Most patients can not walk or can only do so for a short period of time, usually before puberty. Children can stand and walk with help of leg ferules.

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The Bethlem congenital muscular dystrophy

It is a progressive muscular dystrophy, mainly caused by dominant mutations, though rarely a pattern of recessive inheritance has been found. It usually appears in the 1st decade with significant joint contractures of elbows and interphalangeals, it also progresses to muscle weakness that affects mainly proximal muscles and flexors.

There is often significant respiratory impairment but this functional impairment is variable.

Research

In recent years a great progress in the development of congenital muscular dystrophies treatments has been achieved as well as in other pathologies related with neuromuscular conditions, and as a result, the number of clinical trials has been grown recently.

The deficiencies of collagen VI are designated as rare diseases. So investment in research in this area is in decline comparing to other areas, and the continuation of all the work done till today is in danger due to the lack of interest and that's our main objective, to provide funds to research in this field.