

# Case report on Ullrich Congenital Muscular Dystrophy-Type VI Collagen Defect

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## Abstract

Congenital muscular dystrophy (CMD) is a heterogeneous group of conditions. Ullrich CMD is due to defect in extra cellular matrix protein- Collagen type VI. It is an autosomal recessive disorder caused by a mutation in 1 of the 3 collagen type VI genes (COL6A1, COL6A2, COL6A3). Clinical features include slow progressive muscle weakness, distal laxity (hand, foot, finger), contracture of proximal joints, early respiratory failure, protruded calcaneum and may never achieve ability to walk. We report a four year old boy with the above features diagnosed to have Ullrich CMD. This case is being reported for its rarity and to highlight the importance of diagnosis of subtype of CMD.

**Key words:** Congenital muscular dystrophy, collagen type VI, Ullrich muscular dystrophy, progressive muscle weakness.

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## Introduction

Congenital muscular dystrophy (CMD) is a group of condition which share early presentation and a common muscle pathology. This heterogeneous condition varies according to severity, associated symptoms, and outcomes. In the last few years a lot of effort has gone into identifying the separate entities and in locating the gene responsible for a number of these forms.

Clinical features are distinctive in Ullrich Congenital Muscular Dystrophy. Ullrich CMD is due to defect in extra cellular matrix protein- Collagen type VI which can be confirmed by muscle biopsy, immunochemistry and molecular genetics. Cases of muscular dystrophy must be researched in detail in order to achieve a breakthrough in therapy.

Ullrich CMD was first described as "congenital atonic sclerotic muscular dystrophy" by Otto Ullrich in 1930 [1]. Other terms in the past include 'congenital hypotonic sclerotic muscular dystrophy' and 'congenital muscular dystrophy with distal laxity'. Since then, more than 20 patients with similar clinical manifestations have been reported worldwide [2], 9 from India [3] and thus recognized as a distinct form of CMD (Online Mendelian Inheritance in Man database no. 254090).

Diagnosis is suspected from history, clinical examination and confirmed by biopsy. We report a four year old boy with the above features diagnosed to have Ullrich CMD. This case is being reported for its rarity and to highlight the importance of diagnosis of subtype of CMD.

## Case Report

A 4 year old boy from West Bengal, born of a second degree consanguineous marriage presented with history of weakness of upper and lower limbs since child was 8 months old. Child learnt to roll over and sit but did not learn to stand or walk. Child had no convulsion or difficulty in respiration. His mental development and speech was normal. There is no family history of similar complaints. He has a normal elder brother and sister. Antenatal, natal and postnatal histories are normal.

On examination, child's weight and length were less than 3rd percentile. Vitals were normal. The boy had low set ears and prominent calcaneum on both feet. Rest of the general examination was normal. On central nervous system examinations, higher functions, cranial nerves, sensory and cerebellar system were normal. Motor system examination showed symmetrical decreased in bulk and hypotonic upper and lower limbs. He had hyper extensible fingers, toes and knees. There were no fasciculation or hypertrophy of any group of muscles. Proximal group of muscles had power of 3/5 and distal 2/5. His reflexes were normal. Examination of other systems was normal. On investigations CPK was 285.9U/L (Normal range: 15-171). EMG showed slow nerve velocity. Muscle biopsy (Fig 2) showed effaced fascicular structure, rounding of myofibres with variation in diameter and atrophied nuclei and angulated fibers. Infiltration of endomysial collagen was present. There was no necrosis, myophagocytosis and regeneration. Enzyme stains showed predominance of type I fibers. Diagnosis of muscular dystrophy was made. Immunocytochemistry and molecular genetics would add value.

Based on clinical presence of hyper extensible limbs, distal wasting (Fig 3) low set ears, prominent Calcaneum, and characteristic muscle biopsy report, a diagnosis of Congenital Muscular Dystrophy – type VI collagen defect -Ullrich muscular dystrophy was made.

**Table 1.** Classification by Muntoni and Voit

1. Extra cellular matrix protein defects:
  - a. Laminin-alpha2-deficient CMD (merosin-deficient congenital muscular dystrophy MDC1A)
  - b. Ullrich CMD (UCMDs 1,2, and 3)
2. Integrin-alpha7 deficiency (ITGA7)
3. Glycosyltransferases (abnormal O-glycosylation of alpha-dystroglycan)
  - a. Walker-Warburg syndrome
  - b. MEB disease
  - c. Fukuyama CMD (FCMD)
  - d. CMD plus secondary laminin deficiency 1
  - e. CMD plus secondary laminin deficiency 2
  - f. CMD with mental retardation and pachygyria
4. Proteins of the endoplasmic reticulum – Rigid-spine syndrome (RSMD1)

## Discussion

In 1908, Howard coined the term congenital muscular dystrophy (CMD) when he described an infant with weakness and an abnormal muscle biopsy at birth. Various clinical patterns with genetic basis emerged and in 2004, Muntoni and Voit suggested scheme of classification for CMD (4) which is followed presently.(Table 1).Ullrich CMD is basically due to defect in extra cellular matrix protein, Collagen type VI. Collagen type VI is expressed in the extracellular matrix of nearly all cell types and is composed of alpha1, alpha2, and alpha3 chains, which intracellularly form a triple helix monomer [5].

This is critical for skeletal muscle stability, regeneration, and muscle cell matrix adhesion (6,7,8). It is an auto-somal recessive (or more rarely dominant) disorder caused by a mutation in 1 of the 3 collagen type VI genes (COL6A1, COL6A2, COL6A3) [9,10,11].

The exact pathogenesis of the disease is unclear .Studies are showing role of mitochondrial dysfunction resulting in muscle loss [12].

International Consortium on CMD (13) included the following clinical features as diagnostic criteria of Ullrich CMD namely, autosomal recessive inheritance, hypotonia, hip dislocation, contractures ,distal laxity(hand, foot, finger) [4], slow progressive muscle weakness, high arched palate, contracture of proximal joints, protruded calcaneum, normal intelligence.

Serum creatine kinase concentration is usually normal or mildly elevated. Muscle biopsy shows dystrophic features with degeneration and regeneration and replacement of muscle with fat and fibrous connective tissue. Immuno-histochemical testing and molecular 4 genetics performed on muscle biopsy can diagnose subtypes of CMD. Collagen VI immunolabeling [15]from endomysium and basal lamina ranges from absent to moderately on markedly reduced.

Genetic testing involves direct sequence and linkage analysis. For families where the muscle biopsy of the proband shows absence of Collagen VI immunolabeling, prenatal diagnosis can be offered even if the causative mutation is not known in the family. No individuals with Ullrich CMD have been known to reproduce.

Immunochemistry and molecular genetics are not done in India. These tests are still only done on a research basis

Management includes physiotherapy, nutrition and respiratory support. Cyclosporine in treatment of these patients is emerging as an option in these patients following research on Col6a1(-/-) mice and reports of an open trial on five patients [16,17]. Muscular dystrophy is often viewed with diagnostic apathy as we can offer no curative treatment at present. This case has been reported to highlight the rarity of the case and the diagnosis of subtype of congenital muscular dystrophy clued by the distinctive clinical features present and muscle biopsy findings

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