Case report of congenital muscular dystrophy with peripheral nerve involvement

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Abstract:
The congenital muscular dystrophies are clinically and genetically heterogeneous group of neuromuscular disorders. Muscle weakness usually presents from birth to early infancy. Affected infants appear floppy with low muscle tone and poor spontaneous movements. Affected persons may present with delay or arrest of gross motor development together with joint or spinal rigidity. Muscle weakness may improve worsen, or stabilize in the short term. With time progressive weakness, spinal deformities, joint contractures and respiratory compromise may affect quality of life and life span. Peripheral neuropathy in patients with congenital muscular dystrophy (CMD) has been sporadically investigated and has been reported. Here we are reporting an interesting case who presented with delayed milestones, early contractures of shoulder, elbow, knee and ankles, electrophysiological evidence of neuropathy and myopathy, elevated creatinine phosphokinase (CPK), biopsy evidence of muscular dystrophy and chronic axonopathy suggestive of CMD with peripheral nerve involvement.

Keyword: Muscular dystrophy, contractures, Merosin, peripheral neuropathy.

Introduction:
The congenital muscular dystrophies (CMDs) are heterogeneous group of inherited muscle Disorders. They are defined by combination of early onset hypotonia, contractures, weakness, variable progression, normal or elevated serum creatine kinase. They may show myopathic changes on electromyogram (EMG) and associated with dystrophic changes on muscle biopsy. There are currently 12 genetically defined forms of CMD. The incidence and prevalence of CMD in populations are not well documented because of limited molecular genetic confirmation of the diagnosis and use of different diagnostic classification systems. Especially Indian incidence and prevalence is not known much. The incidence of all forms of congenital muscular dystrophies has been estimated at 1:21,500 with a prevalence of 1:125,000 in northeastern Italy\(^1\) and an incidence of 1:16,000 in western Sweden.\(^2\)
The point prevalence (i.e., the total number of cases of a specific disease in a given population at a specific point in time) ranges from 0.68 to 2.5/100,000. The failure to diagnose primary muscle disease in individuals with minimal muscle weakness without intellectual disability may continue to result in underestimation of the prevalence of CMD. Peripheral nerve involvement had been documented in merosin negative CMD and fukuyama muscular dystrophy. Here we are reporting a case of congenital muscular dystrophy with peripheral nerve involvement for its rare presentation.

Case vignette:
Our patient Mr. N, 20 years old male, studied upto 10th standard, coming from Chennai, right handed individual presented with complaints of difficulty in using both lower limbs since early childhood.He was born to second degree consanguineous parentage with delayed motor milestones in the form of sitting with support at 1 year, walking without support at 3 years of age. His language and mental development were normal and was immunized fully. When he started to walk he noticed to have weakness of both lower limbs in the form of tripping over toes, buckling of both knees and difficulty in getting up from squatting position, which was insidious in onset and initially very slowly progressive over few years and now it is static in nature. At the same time, patient developed both upper limb weakness in the form of difficulty in holding the objects and difficulty in raising the arm above the shoulder which was also insidious in onset and now static in nature. There was no involvement of trunk, neck or respiratory muscles. History suggestive of flexion deformities of both knees was present. There was no history suggestive of stiffness, flailness, muscle twitching, thinning of limbs, sensory, higher functions, cranial nerves, autonomic involvement. No other family members affected by similar illness.

On examination:
Skeletal deformities in the form of bilateral pes planus, thoracic kyphosis, bilateral clinodactyly of little fingers and little toes with abnormal callosities of both great toes and high arched palate were present. Bilateral contractures of hamstrings, Tendo Achilles, elbow flexors and shoulder abductors were present. There was no nerve thickening. Higher mental functions and cranial nerves were normal. Spinomotor system examination showed bilateral wasting of deltoid, supraspinati, thenar, hypothenar and calf muscles with hypotonia of all four limbs. On power examination proximal muscle weakness was more than distal group in all four limbs. All deep tendon reflexes and bilateral plantar were absent. On sensory examination timed vibration was reduced below knee joints. Investigations revealed normal hemoglobin, complete blood count, total and differential counts, ESR, renal, liver, electrolytes, thyroid, ECG, Echo and chest Xray PA view. Serum creatinine phosphokinase (CPK) was elevated (9311 IU). Nerve conduction study revealed normal bilateral median and ulnar motor conduction. Bilateral tibial and peroneal nerves were not stimulatable. Sensory nerve action potential (SNAP) was not obtained in all 4 limbs. EMG examination showed myopathic pattern. MRI Brain showed cerebellar atrophy. Muscle biopsy taken from right vastus lateralis muscle, and its histopathology showed adipose tissue infiltration, mild creeping fibrosis, rounding and variation of myofibres, internalization of nuclei, splitting, hypertrophy with multiple internal nuclei and moderate numbers of atrophic angulated fibres with clumped and pyknotic nuclei and
negative for merosin staining, suggestive of muscular dystrophy. Right sural nerve biopsy showed significant depletion of myelinated fibres (large fibre predominant) without acute axonal or myelin degeneration or axonal regeneration or inflammation with thickened vessels suggestive of chronic axonopathy.

**Discussion:**
The clinical features in this patient suggested the possibilities of either congenital myopathy, congenital muscular dystrophy, Charcot Marie Tooth disease or mitochondrial disorder. But our patient presented with delayed motor milestones with normal intelligence, early onset weakness, skeletal deformities and contractures. Investigation showed grossly elevated CPK, myopathic pattern in EMG and cerebellar atrophy in MRI Brain. Muscle biopsy showed Muscular dystrophy. These findings are suggestive of congenital muscular dystrophy. Because of such a high CPK Charcot Marie Tooth disease is unlikely. Mitochondrial disorders are usually associated with ptosis, ophthalmoplegia, seizures or cardiac abnormalities which are not present in our case. In congenital myopathies there is usually associated peculiar facies and the CPK value may be normal or slightly elevated and muscle biopsy will show specific pattern of congenital myopathy which is not present in our patient. The congenital muscular dystrophies are usually inherited as autosomal recessive manner with the exception of collagen VI-deficient CMD, which can be inherited as autosomal dominant or autosomal recessive manner. Hypotonia and muscle weakness are present at birth or in infancy. Poor or decreased motor development, delay and/or arrest of motor milestones, and joint or spinal deformities are often the presenting features of CMD.

The age of onset is usually not clearly defined and is more difficult to identify retrospectively. Since delay of motor skill acquisition may be a presenting symptom of CMD, onset of manifestations before age two years may be a reasonable diagnostic criterion.

**Some common types of CMD:**

**Laminin alpha-2 (merosin) deficiency:** It is autosomal recessive and characterized by hypotonia since birth, delayed motor milestones and feeding difficulties. Muscle weakness is absent or very rarely slowly progressive. Most children with laminin alpha-2 deficiency who have complete deficiency of the protein merosin do not acquire independent walking. But in those with partial merosin deficiency with later onset has been ambulant. Brain MRI usually demonstrates diffuse white matter signal abnormalities. Nerve conduction studies may show reduced conduction velocities during disease demonstrating a peripheral neuropathy.

**The collagen VI-deficient CMDs (Ullrich CMD):** It is characterized by congenital muscle weakness and hypotonia and congenital joint and spinal rigidity or deformities, proximal joint contractures and a striking hyperlaxity of the distal joints. Some affected children have acquired the ability to walk independently. Over a period of time disease progression often results in loss of ambulation.

**Fukuyama congenital muscular dystrophy (FCMD) & Walker Warburg syndrome:**
It is characterized by severe muscle weakness since birth, severe mental retardation, frontal leucencies with cobblestone appearance of cortex, absence of grey white lamination in imaging and rarely peripheral nerve involvement. Walker Warburg syndrome (WWS) is a very severe form of CMD characterized by lissencephaly,
cerebellar malformations, and severe retinal and eye malformations (microphthalmia, colobomas, congenital cataracts and glaucoma, corneal opacities, retinal dysplasia, hypoplastic vitreous and optic atrophy) and death usually occurs within 2 years. In peripheral nerve, merosin is expressed in the endoneurium surrounding the Schwann cell/myelin sheath, while the putative merosin receptors dystroglycan and alpha 6 beta 4 integrin are expressed in the outer membrane of Schwann cell/myelin sheath. Together with the well known fact that the deposition of laminin in the basement membrane is essential for Schwann cell myelination, these findings indicate that the interaction of merosin with dystroglycan and/or alpha 6 beta 4 integrin plays an important role in peripheral myelination in merosin deficiency. Matsmura et al in a paper published in neuro muscular journal in 1997, described the CMD with peripheral nerve involvement. Jang DH et al also published in journal of child neurology 2012, a case report of 7 year old child with Fukuyama CMD with peripheral nerve involvement. Jacobus Gilhuis et al in his article published in journal of pediatric neurology, analyzed 12 patients with Merosin negative CMD with peripheral nerve involvement and inferred as both demyelinating and axonal pattern occurred in most of the patients. In our case also, there were clinical features and investigations suggestive of merosin negative CMD (delayed milestones since birth, early contractures, very high CPK, myopathic pattern in EMG, muscular dystrophy in muscle biopsy) with peripheral nerve involvement (absent deep tendon reflexes, electrophysiological evidence of neuropathy and chronic axonopathy in nerve biopsy).

Conclusion:
Peripheral nerve involvement is not that common in congenital muscular dystrophy. This case is presented for its interesting clinical features of Merosin negative CMD and its association with peripheral nerve involvement, which is less frequently reported.

References:


T1 MRI SAGITAL SHOWING CEREBELLAR ATROPHY

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