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The Constellation of Centronuclear Myopathy and Craniofacial Dysmorphism

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THE CONSTELLATION OF CENTRONUCLEAR MYOPATHY AND CRANIOFACIAL DYSMORPHISM

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ABSTRACT:
A 20 years old third-year MBBS female student from Dow Medical College in 2008 presented to the Neurology Dept. in Karachi with a short history of rapidly worsening bilateral lower limb weakness for 6 months. There was facial dysmorphism. Motor neuron disease was the suspicion; EMG/NCS study revealed non inflammatory myopathic process involving all limb muscles; Centro nuclear myopathy (CNM) was diagnosed via muscle biopsy. CNM is a group of congenital myopathies, where cell nuclei are abnormally located in skeletal muscle cells. Craniofacial dysmorphism is characterized by abnormal development of facial and skull structures. To the best of the author's knowledge, this is the first case report from Pakistan, though few cases have been published in the international literature.

KEY WORDS: Myopathies, Structural, Congenital, Craniofacial Abnormalities, pathology, electromyography.

INTRODUCTION:

Centro nuclear myopathy (CNM) is a group of congenital myopathies where cell nuclei are abnormally located in skeletal muscle cells. Individuals with CNM show hypotonia, hypoxia-requiring breathing assistance, and scaphocephaly. The X-linked myotubular myopathy form presents at birth. However, some centronuclear myopathies may present later in life. There are three genetic types of CNM. X-linked myotubular myopathy (manifesting in males) have mutations in MTM1. Autosomal abnormalities can either be dominant AD or recessive AR with mutations in DNM2 or BIN1, RYR1, TTN gene respectively.[1]

CASE PRESENTATION

In 2008, 20 years old female medical student from Dow Medical College presented to the Neurology OPD of Patel hospital, with a short history of rapidly worsening bilateral lower limb weakness for 6 months. She stopped driving and on normal routine physical exertion, felt leg fasciculations and tremors with a sensation and H/o repeated falls on ground, bradykinesia, requiring support for walking on uneven grounds, Long distances, climbing stairs. Later on, there was the increased falling frequencies and worsening lower limb weakness during the winter season. During childhood, she started feeling a mild sensation of heaviness while walking mild without hindering in routine activities, which was negligible according to the family. There is a history of birth atonia of mild intensity, but there was no asphyxia or delayed developmental milestones. No intellectual disability and a good upbringing with the siblings. There was no family history of myopathy. She had 4 siblings including one step brother, without any neurologic deficit.

There was a progressive history of bilateral ptosis, for which she underwent blepharoplasty and squint surgeries at 14-15 years of age, which later on recurred, the operation had general anesthesia complication according to patient – post op delay in regaining muscle power; otherwise the pediatric history was unremarkable.

On examination, craniofacial features were dysmorphic, there was squint with ptosis, dental malocclusion, flat long face with a high arched palate, micrognathia, facial asymmetry, hemi facial micro-somia, Plagiocephaly, Deviated nasal septum, High arched palate, Dental malocclusion, Microstomia (Figure 1), Prognathism.There was Lipo-dermatosclerosis as well as mild pedal edema in lower limbs; Sensory system was unremarkable. Hearing Fundoscopy was normal.
Neurologic exam: She was unable to perform squat test; Unable to stand still, get up from chair without support. Gait was uncoordinated.Reduced power in neck, Proximal and distal limb muscles0; lower limb power was 3/5, upper limb power was 4/5, pseudo hypertrophic hypotonic muscles, all the limb reflexes including plantar reflex, were absent.

All blood and serologic tests including Creatine kinase,

vitamin B12 levels, and MRI of the brain (indicated for posterior fossa abnormality) were unremarkable. Work up for myasthenia gravis was negative.

There was bilateral leg pitting edema, Cardiomyopathy was in suspicion; the echo and Ultrasound venography was normal. Pedal edema was likely due to defective muscle functioning.

The sample was taken from the left deltoid via the incisional biopsy at Agha Khan University Hospital: H & E section revealed skeletal muscle fibers exhibiting mild variation in size and shape of fibers. Predominantly, the cells had central nuclei with peri-nuclear halos, both type I and type II fibers appeared affected. On NADH, dark central pale peri-nuclear halos were highlighted. PAS, SDH, Alkaline phosphatase and cytochrome oxidase were unremarkable. No significant muscle inflammation or atrophy was present. Findings were compatible with Centro nuclear myopathy (Figure 2). In 2022, Plain CT scan of para nasal sinuses performed for sinusitis showed Fatty degeneration of posterior cervical muscles (Figure 1).

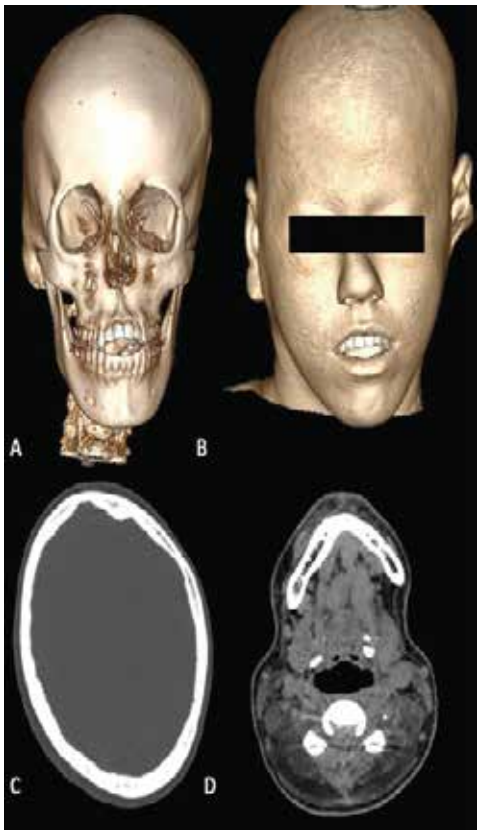

Figure 1: Multiple CT Images of Head; A- 3D skull reformat and B- Volume Rendered image of Face shows features of craniofacial dysmorphism, C- Axial bone window shows dysmorphic shape of skull, D- Axial soft tissue window shows lipomatous degeneration of posterior cervical muscles.

On EMG NCVS interpretation: the skin temperature was 35 degrees. Right median motor nerve showed normal distal latency, low CMAP amplitude and normal conduction velocity along with normal F wave. Right ulnar motor nerve showed normal distal latencies, normal CMAP amplitudes and slow conduction velocities along with normal F wave. Bilateral posterior tibial and paroneal EDB motor nerves showed normal distal latencies, CMAP amplitudes and slow conduction velocities along with normal F wave. Bilateral facial orbicular oculi motor nerves showed prolonged distal latencies and low CMAP amplitudes, bilateral H Reflex study was not recordable. Bilateral sural, superficial paroneal, median (F2) and bilateral ulnar (%) sensory nerves showed prolonged peak latencies, SNAPamplitudes and slow conduction velocities (Figure 3). Conclusion of EMG/NCV study: there was electro-diagnostic evidence of non-irritable myopathic process.

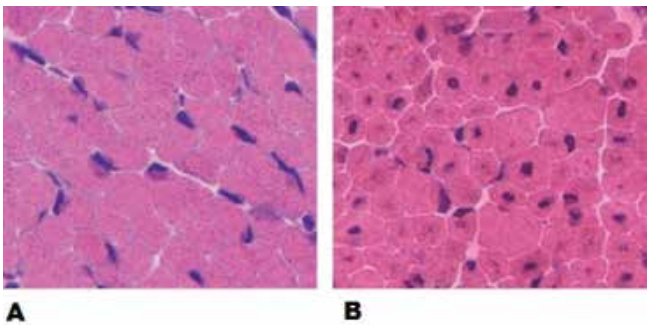

Figure 2: Microscopic analysis of normal muscle fibers- A, where nuclei are arranged at the periphery and Centro nuclear myopathy B – where nuclei are present at the center.

Figure 3: Tabular data of EMG/ NCVS study.

DISCUSSION

There are various kinds of congenital myopathies including central core disease, multi – mini core disease, nemaline myopathy and CNM- the incidence is estimated at around 0.06/1,000 live births; most common is X linked Muscular dystrophy.[2] Only 19 families with CNM

have been identified in world till now.[1]

In 1966, Spiro et al published a Neurology report in at New York of a boy with myopathy, which upon muscle biopsy, showed that the nuclei of the muscle cells were located in the center of the muscle cells.[3] In 1972, a family with muscular dystrophy affecting 16 members over 5 generations was brought into notice. Muscle wasting affected predominantly proximal muscles, but in some cases, facial and distal muscles were also involved. The disease was slowly progressive and compatible with a normal life span.[4]

HC Fan et al reported two male preterm newborns with X-linked Centro nuclear myopathy, which resulted in respiratory failure immediately after birth and progressed to total dependence on the ventilator.[5] The findings of muscle histo-chemistry and electron microscopy are consistent with the diagnosis of Centro-nuclear myopathy. Sustersic B et al reported a 'Long-term survivor' male with a severe disability with congenital X linked myotubular myopathy, presenting at birth, who survived until 2.5 years of life and died from a chest infection.[6]

In this case, genetic testing was lacking; karyotype analysis was normal. Neuro-psychiatric testing was unremarkable. The case was followed for 10 years, she had non-progressive neurologic deficit with weight control diet. Though the house job was difficult because of night fatigability,she completed her primary and specialty medical education from Civil Hospital, working as a Consultant Radiologist (Faculty member) at DUHS/ Ojha Campus, Pakistan and also is the author of this paper. She has grade 1 on ECOG Performance Status Scale- Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work. In 2018, the disability certificate was issued from Aga Khan University Hospital by Neurologist, on request as a proof of her handicap. The PMC grants equal rights to disabled students for Under Graduate and Post Graduate Education. GMC acknowledges the fact that the medical journey is complex, and for the disabled one, it's more complex!The Royal College considers disability as natural diversity. The CPSP provides disability adjustments for Examinations.

CONCLUSION

CNM is a congenital myopathy- a rare irreversible disease manifested in adulthood in this case; like muscular dystrophy, it has no cure/treatment apart from supportive management. It calls for suitable adjustments in education and employment as well as a social awareness in developing countries for disabled people.

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Mahnoor Hafeez; data collection, data analysis, manuscript writing, manuscript review