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Duchenne Muscular Dystrophy: Case Report

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ABSTRACT: Muscular dystrophies are a clinically and heterogeneous group of disorder that all share clinical characteristics of progressive muscular weakness. Duchenne muscular dystrophies the most common x-linked disorder muscular dystrophy in children, presenting in early childhood and characterized by proximal muscle weakness and calf hypertrophy in affected boys. There is usually delay in motor development and eventually wheelchair confinement followed by premature death from cardiac or respiratory complications. Treatment modalities such as corticosteroid therapy and use of intermittent positive pressure ventilation have provided improvement in function, ambulation, quality of life, and life expectancy, although novel therapies still aim to provide a cure for this devastating disorder. Here, we present a case of DMD in a 12-year-old male with remarkable clinical and oral manifestation

1. INTRODUCTION:

Duchenne muscular dystrophy is an atypical inherited musculoskeletal disorder which shows clinical characteristics of progressive muscular weakness at an early stage and pathologic features of fibrosisand fatty replacement,particularly late in the disease course.It is a recessive x-linked disorder occurring 1 in every 3500 live male births and named after a French neurologist Guillaume Benjamin Amand Duchenne in 1860

It is the most common and severe form of muscular dystrophy, beginning at 3-5 year of age and characterized by proximal muscle weakness and calf hypertrophy in affected boys.DMD has a very high mutation rate with distinctive and relentless clinicalpresentation. Patients usually become wheelchair-bound by the age of 12 and dies in their late teens to early twenties. According to Pubmedliterature, approximately 150 cases have been reported till death. Here, we present a rare case of DMD in a 11 year old child. (1)

2. CASE REPORT:

History:

An11-year-old male patient reported to the department with chief complaint of abnormal gait. His parent gave medical history of repeated falls,fatigue,muscle weakness, reduced bulk muscle and inability to climb stairs. There was a history of associated muscular pain in the leg when he tries to walk and climb stairs and pain also in the hand when he tries to lift his hand. Patient's family history revealed that one of his maternal uncles died of the same illness at a young age

Examination finding:

On general physical examination,the child had a lean appearance and presented with difficulty in standing,walking,getting up from sitting position and climbing stairs,proximal

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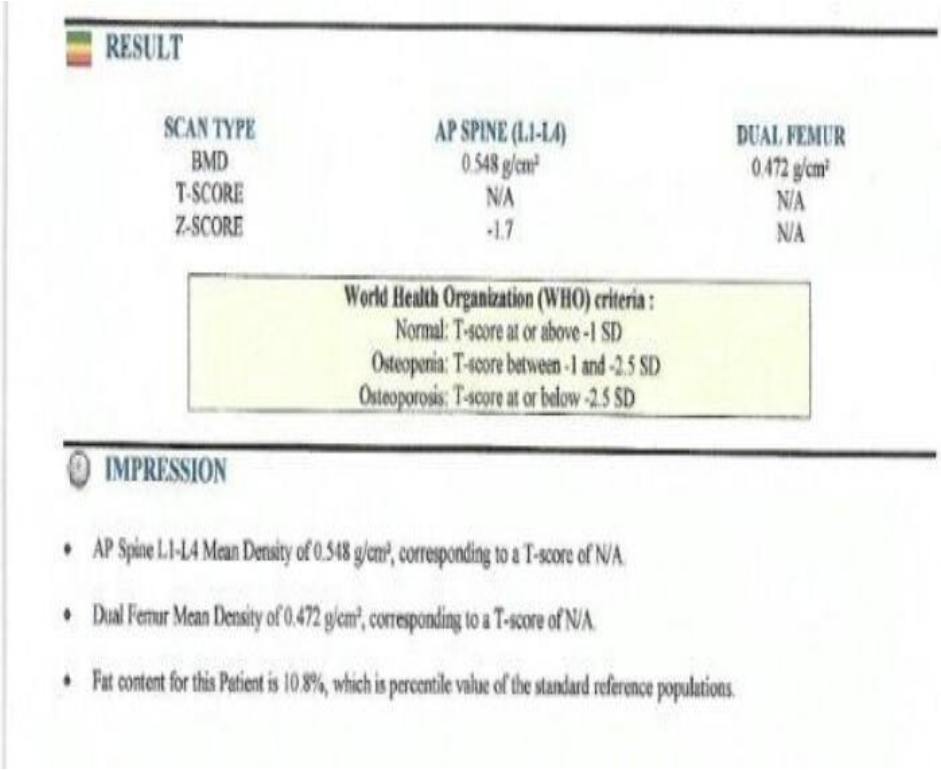
weakness and Gower's sign positive. There was a thinning of muscles, muscle tone and cranial nerve examination was found to be normal.

Investigation:

The patient was subjected to radiological and laboratory investigation. Bone mineral density test (BMB) revealed that AP spine L1-L4 mean density of 0.548 g/cm2 corresponding to a T-score of N/A and dual femur mean density of 0.472 g/cm2 corresponding to T-score of N/A fat content for this patient is 10.8% which is percentile value of the standard reference populations. Echocardiograph evaluation revealed that normal chamber dimension, normal systolic and dysfunction. Mitral valve prolapsed grade 1.no mitral valve regurgitation, no regional wall motion abnormality, nopericardial effusion. Flow pattern through all values are normal. Genetic analysis report showed that deletion of a segment of DMD gene involving exons 3 to 41. Based on the history of clinical examination and investigation, diagnosis of DMD was established.

Figure 1: Bone marrow density test:



RESULT

SCAN TYPE	AP SPINE (L1-L4)	DUAL FEMUR
BMD	0.548 g/cm²	0.472 g/cm²
T-SCORE	N/A	N/A
Z-SCORE	-1.7	N/A

World Health Organization (WHO) criteria :
Normal: T-score at or above -1 SD
Osteopenia: T-score between -1 and -2.5 SD
Osteoporosis: T-score at or below -2.5 SD

IMPRESSION

- AP Spine L1-L4 Mean Density of 0.548 g/cm², corresponding to a T-score of N/A.
- Dual Femur Mean Density of 0.472 g/cm², corresponding to a T-score of N/A.
- Fat content for this Patient is 10.8%, which is percentile value of the standard reference populations.

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Figure 2: Echocardio graphic evaluation:

ECHOCARDIOGRAPHIC EVALUATION

Spectral and Color Doppler:

Flow pattern through all the valves are normal.
Interatrial or interventricular shunt - nil.
Patent ductus arteriosus flow - nil.

Impression:

- Normal chambers dimensions.
- Normal LV systolic and dys function.
- Mitral valve prolapsed Grade I
- No mitral valve regurgitation.
- No regional wall motion abnormality.
- No pericardial effusion.

Figure 3: Genetic Analysis:

Sample-Three ml of EDTA blood; DNA is extracted by salting out method
Gene tested: DMD gene for Duchenne/ Becker Muscular Dystrophy
Deletion analysis carried out by mPCR. **Number of exons studied**-30
Primers sequences are as per Leiden Muscular dystrophy pages (www.dmd.nl).
(DEL) Indicates the absence of exons; (+) indicates the presence of exons

Exon	Result	Exon	Result	Exon	Result	Exon	Result	Exon	Result	Exon	Result
1	+	12	DEL	20	DEL	41	DEL	46	+	51	+
3	DEL	13	DEL	21	DEL	42	+	47	+	52	+
4	DEL	16	DEL	22	DEL	43	+	48	+	53	+
6	DEL	17	DEL	32	DEL	44	+	49	+	55	+
8	DEL	19	DEL	34	DEL	45	+	50	+	60	+

Interpretation

Master Sanjay, clinically diagnosed to have Duchenne Muscular Dystrophy, was tested for mutations in the Dystrophin gene by multiplex PCR. He shows **deletion of a segment of the DMD gene involving exons 3 to 41.** The deletion status of exon 2 is not known. However, the deletion is limited to exon 1 on the 5' end.
Genotype: del "3-41"

Conclusion and Genetic Counseling

Duchenne Muscular Dystrophy is an X-linked recessive disorder. Master Sanjay, a product of non-consanguineous marriage, is an isolated case of DMD in the family. On analysis, he shows deletion of exons 3 to 41 in the DMD gene. This mutation could be a de-novo mutation arising in him or X-linked. The parents are advised to contact the doctor for further clarifications. You could fix an appointment with us for a genetic counseling session.

Note

The above technique analyses 30 exons of Dystrophin gene, covering the hotspot. As the deletion borders for assessing frameshift is not clear by the above analysis, we recommend the technique of MLPA to study all the 79 exons.

Although all precautions are taken and the results are crosschecked during DNA tests, the currently available data indicate that the technical error rate for all such analysis is 1-2% approximately. The results should be interpreted and acted upon in the light of this information.

Treatment plan:

There is no particular treatment. The child was advised to consult a paediatrician regarding his general and physical health status. He was counselled to undergo daily physiotherapy, steroid therapy and regular assessment for progressive muscle and cardiac/ respiratory damage. The patient was kept under periodic recall to prevent any further complication

Management:

Current management of DMD involves physiotherapy and corticosteroid treatment which delay loss of ambulation 1-3 years but doesnot cure the disease which was provided in our case.

Patient progress:

Age progresses disease also progressing. Progression will be till 18 years of age. The patient is undergoing daily physiotherapy, steroid therapy and regular assessment for progressive muscle and cardiac/respiratory damage.

3. CASE DISCUSSION:

DMD is the most common muscle dystrophy in India as well as the world, caused by mutations in dystrophin gene as a result of which the body is unable to synthesize the protein dystrophin required for muscle contraction. Every time the muscle contracts, muscle damage occurs which is repaired but with deficient protein resulting in repaired muscle which is also a damaged one. This continuous succession of damage and repair and eventually replacement of muscle with fibrofatty tissue is responsible for the clinical signs of progressive muscle wasting and degeneration that is usually evident by 3–4 years.(1)

DMD is caused by mutations in the DMD gene encoding a protein called dystrophin, which localizes to the cytoplasmic face of the sarcolemma of the skeletal muscle, forming one component of a large glycoprotein complex (dystrophin‐associated glycoprotein complex). Dystrophin consists of an N‐terminal actin‐binding domain, 24 spectrin‐like repeat units interspersed by four hinge regions, followed by a cysteine‐rich domain and a C‐terminal domain. The cysteine‐rich domain binds to laminin‐2 through alpha and beta‐dystroglycan, and therefore acts as mechanical link between actin in the cytoskeleton and the extracellular matrix. The DMD gene contains 79 exons but accounts for only 0.6% of the gene; the rest made of large introns. The large size of the DMD gene makes it susceptible to mutations, leading to loss of function of dystrophin, resulting in a prematurely truncated, and unstable dystrophin protein. The majority of mutations are intragenic deletions, which account for 65–72% of all DMD patients. The precise mechanism of how dystrophin deficiency leads to degeneration of muscle fibers remains unclear. The absence of dystrophin at the plasma membrane leads to delocalization of dystrophin‐associated proteins from the membrane, disruption of the cytoskeleton with resultant membrane instability and increased susceptibility to mechanical stress. In addition, altered membrane permeability and abnormal calcium homeostasis are thought to play a role, with increased cytosolic calcium concentration leading to activation of proteases such as calpains.(2)

Affected boys clinically present with difficulty in running or getting up from the ground, frequent falls, or toe‐walking. Patients have a waddling gait, calf enlargement, and lumbar lordosis which disappear on sitting. There is weakness of the proximal muscles of the lower limb as in which a patient uses his hands and arms to “walk” up their own body from a squatting position due to lack of hip and thigh muscle strength suggestive of Gower’s sign. In

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this case, the affected child clinically presented with signs of delayed motor development, difficulty in walking and climbing stairs, positive Gower's sign, and muscle weakness. Oral manifestations include wide dental arches, large tongue, delayed eruption, open bite, and retrognathic facial morphology. The development of malocclusion in these patients is linked to the involvement of the orofacial muscles by the disease which was apparent in the present case.(3)

Differential diagnosis:

Polymyositis,kennedydisean,facioscapulohumeraldystrophy,emery-dreifus muscular dystrophy,metabolicmyopathies,spinal muscular atropy,physical medicine and rehibiliton for limb-girdle muscular dystrophy are the differential diagnosis. Based on the bone mineral density test,echocardiogram,genetic analysis and clinical examination(gower's sign positive). Diagnosis is confirmed to be duchenne muscular dystrophy.(4)

Complications:

Common complications associated with DMD includes contractures,scoliosis,breathing difficulties due to the weakness of diaphragm and chest muscles,facial and throat muscles also affected, heart is also a muscle so it can also affected by muscular dystrophy.(5)

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