IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 22, Issue 9 Ser.5 (September. 2023), PP 59-61
www.iosrjournals.org

Study Of Clinical And Laboratory Profile Of Dystrophinopathies In A Tertiary Center In Andhra Pradesh

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Date of Submission: 14-09-2023 Date of acceptance: 24-09-2023

I. INTRODUCTION

Genetic variations in the X-linked dystrophin gene results in a spectrum of milder

phenotypes of BMD to severe phenotype of DMD. Dystrophinopathies can present as hyperCKemia, cramps, rhabdomyolysis, dilated cardiomyopathy, cognitive decline, attention deficit hyperactivity disorder and learning disability. The incidence of DMD in live male births is 1 in 3500 to 1 in 5000. BMD is much less common with a prevalence of 1 in 17,500 to 1 in 50,000. The prevalence of DMD is lower than BMD mainly because of the reduced survival.

The dystrophin gene is one of the largest genes in the human genome comprising 2.3 megabases in which 79 exons are present. The dystrophin gene encodes a 427 kD skeletal muscle protein which is abundantly expressed in skeletal, cardiac, and smooth muscle cells and brain. The dystrophin protein joins the extracellular matrix to the contractile apparatus.

Affected boys have motor delay, Gowers sign, enlarged CK values, elevated CPK values (100-200 ULN)[1]. Variations include deletions (50% to 60%; in frame or out of frame), sequence alterations (20% to 35%), duplications (5% to 10%).

II. AIMS AND OBJECTIVES

To study the clinical, laboratory profile of patients with dystrophinopathy and to perform targeted genetic analyses.

III. MATERIALS AND METHODS

This is Prospective hospital-based observational study in which patients with limb girdle syndrome admitted in King George Hospital from July 2021 to June 2023 are included. Patients presenting with chronic progressive(>1yr) proximal weakness of both upper limbs/lower limbs/both along with genetically confirmed Dystrophinopathy are included. A total of 18 patients are studied. Thorough history taking and clinical examination was done. Laboratory investigations like CBC, Creatinine, RBS, CPK, Thyroid profile, Serum Calcium, Vit-D levels were performed along with cardiac evaluation with an ECG and 2D-ECHO.Targeted genetic testing is performed.

IV. RESULTS

A total number of 18 cases are included in the study. Mean age of onset among the patients is 5.27yrs. All the patients are males. Mean duration of illness among the cases is 3.61yrs +/-1.99. Two of them are non-ambulatory. Two of the 18 cases showed consanguinity. Two of the 18 cases showed positive family history.

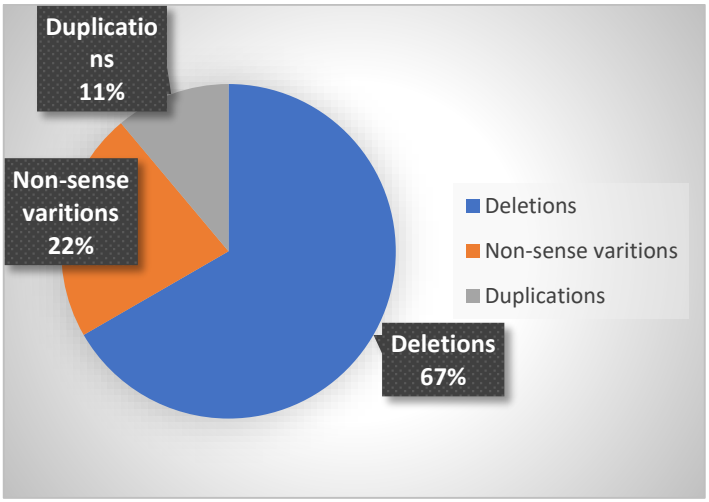
While eight of the 18 cases showed developmental delay, eight of the 18 cases showed calf hypertrophy. 4 cases displayed a waddling gait while walking. Four cases showed preserved deltoid and two cases showed deltoid atrophy. Two cases showed winging of scapula. Two patients had lumbar lordosis.

CLINICAL FEATURE	**No of patients**
Developmental delay	8/18
Calf hypertrophy	4/18

Waddling gait	4/18
Contractures	4/18
Preserved deltoid	4/18
Deltoid atrophy	2/18
Hip abductor sparing	0
Winging of scapula	2/18
Lumbar lordosis	2/18

Mean CPK of DMD is 3681 +/- 1565 U/L.
All the patients showed myopathic pattern on EMG.
Targeted gene panels showed mutation in dystrophin gene.

V. TYPES OF GENETIC MUTATIONS AMONG DMD PATIENTS



VI. DISCUSSION

In Swaminathan et al[57] study, a total of 101 DMD patients were enrolled. Mean age of onset (years) was 3.1 +/- 1.44 while the mean age at presentation (years) 8.0 +/- 3.1.

In the present study, the mean age at onset is 5.27yrs +/- 2.72. Mean age at presentation is 8.75yrs +/- 2.43 yrs.

In the Swaminathan et al study, Consanguinity was found in 19/101 (18.8%) patients. While Delayed motor milestones was reported in 63 of 101 patients (62.37%), family history in sibling(s)] was present in 21 of 101 patients (20.8%).

In the present study, consanguinity is present in four of the 18 patients (11.11%). Family history in sibling(s)] was present in four of the 18 patients (11.11%) and delayed motor milestones was reported in 8 of 18 patients (44.44%) which are similar to Swaminathan study.

In the Swaminathan et al study, progressive lower limb weakness was present in all the 101 patients (100%). Calf hypertrophy was found in 91 of 101 patients (90.1%) whereas ankle contractures were present in 89 of 101 patients (88.11%). Toe walking was reported in 45 of 101 patients (44.55%)

In the present study, progressive lower limb weakness is present in all the 18 patients (100%). Ankle contractures are present in 4 of 18 patients (22.22%) which is different from that of Swaminathan study. Toe walking is present in 6 of 18 patients (33.33%) which is similar to Swaminathan study.

In the Swaminathan et al study, Hypertrophy of Deltoid was found in 34 of 101 patients (33.6%). And hypertrophy of Calf was present in 91 of 101 patients (90.1%).

In the present study, while deltoid preservation is found in 4 of nin18 patients (22.22%), calf hypertrophy is present in 8 of 18 patients (44.44%).

In the Swaminathan et al study, all the 101 patients had neck flexor weakness. In the present study, all the 18 patients had neck flexion weakness.

In the Swaminathan et al study, the mean CpK (units/L) 11822.6 +/- 8206.9. In the present study, mean CPK among the nine DMD patients is 3681 +/- 1565 U/L.

In the Swaminathan et al study, while Electrocardiography revealed Abnormal q-waves 23 of 101 patients (22.7%) and Right ventricular dominance 24 in 101 patients (23.7%), 2D- Echocardiography was abnormal in only two patients- one with Bicuspid aortic valve and the other with Dilated cardiomyopathy.

In the present study, Electrocardiography and Echocardiography is normal in all the patients which may be due to the small sample size.

In the Swaminathan et al study, Electromyography in all the patients revealed myopathic changes. In the present study, all the eighteen DMD patients revealed myopathic changes.

In the Swaminathan et al study, Distal hotspot including Exons 45, 47, 49 and 50 were common deletions. In the present study, deletion hotspot is within exons 49,50,52 in ten of the 18 patients patients.

VII. COMPARISON OF SWAMINATHAN ET AL STUDY VS PRESENT STUDY IN DMD PATIENTS

		Swaminathan study (n=101)	Present study(n=9)
Mean age of onset (yrs)		3.1 +/- 1.44	5.27 +/- 2.72
Consanguinity		19/101 (18.8%)	2/18 (11.11%)
Family history		21/101 (20.8%).	2/18 (11.11%)
Motor delay		63 /101 (62.37%),	8/18 (44.44%)
Progressive lower limb weakness		101/101(100%)	18/18 (100%)
Calf hypertrophy		91/101 (90.1%)	8/18 (44.44%)
Deltoid hypertrophy		34 of 101 (33.6%)	4/18 (22.22%)
Ankle contractures		89 of 101 (88.11%)	4/18 (22.22%)
Toe walking		45/101 (44.55%)	6/18 (33.33%)
Neck flexor weakness		101/101(100%)	18/18 (100%)
CPK mean+/-SD (U/L)		11822.6 +/- 8206.9	3681 +/- 1565 U/L
Echocardiogram	Normal	99	18/18
	Abnormal	2	0
Deletion hotspot		Exons 45, 47, 49 and 50	Exon 49,50,52

VIII. CONCLUSION

- The diagnosis of muscular dystrophies is based on clinical, biochemical and histopathologic studies and further confirmed by molecular analysis.
- These distinct clinical phenotypes and newly identified genotypes of patients –promote a comprehensive understanding of the phenotype – genotype correlation and help improve the diagnosis and treatment of these diseases, as well as reproductive counselling

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