Clinical and molecular aspects of DYSF mutations in dysferlinopathy: A single centre experience

Gunce Basarir[1], Berk Ozyilmaz[2], Pinar Gencpinar[3], Figen Baydan[4], Nihal Olgac Dundar[3]

[1] University of Health Sciences, Haseki Training and Research Hospital, Department of Paediatric Neurology, Istanbul, Turkiye
[2] University of Health Sciences, Izmir Bayrakli City Hospital, Genetic Diagnosis Center, İzmir, Turkiye
[3] Izmir Katip Celebi University, Faculty of Medicine, Department of Paediatric Neurology, Izmir, Turkiye
[4] University of Health Sciences, Tepecik Training and Research Hospital, Department of Paediatric Neurology, Izmir, Turkiye

INTRODUCTION

Dysferlinopathy encompasses a spectrum of autosomal recessive rare muscle diseases caused by mutations in the *DYSF* gene which is located on chromosome 2p13 and spans a genomic region of over 230 kbp consisting of 55 exons. It encodes the "dysferlin" which is a transmembrane protein critical for muscle membrane repair, cell adhesion, T-tubule formation, and Ca^{+2} signaling.[1] Clinical phenotypes are highly heterogenous and include Miyoshi myopathy, limb-girdle muscular dystrophy type R2 (LGMD-R2), distal myopathy with anterior tibial onset, dysferlin-deficient proximo-distal type, and asymptomatic creatine kinase (CK) elevation. The worldwide prevalence is approximately 5–10 per one million.[2] A total of 416 different disease-causing mutations have been identified in 843 patients worldwide, mostly in Northwest Africa, Israel, Saudi Arabia, Egypt, Iran, India, Japan.[3]

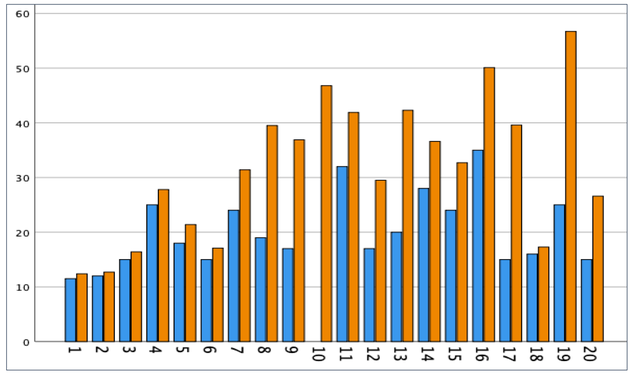
OBJECTIVES

This study aims to contribute to the literature by presenting the demographic, clinical, and genetic characteristics of 20 patients diagnosed with dysferlinopathy, followed by a single centre.

METHODS

This descriptive, retrospective study was conducted on 20 patients who had a genetically confirmed diagnosis of dysferlinopathy between November 2018 and April 2023. Next Generation Sequencing method was performed for identification of DYSF variants. Demographic, genetic, clinical, laboratory findings of the patients were obtained and analyzed using SPSS 28.

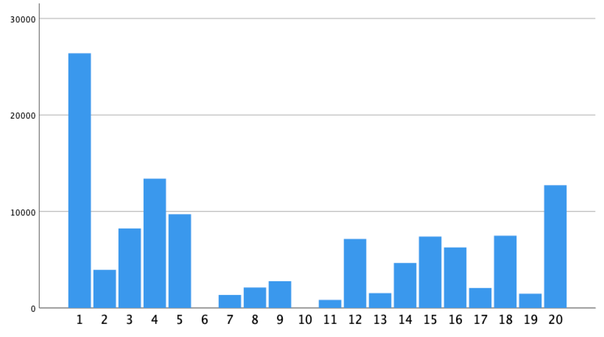
Graphic 1. Age at symptom-onset and diagnosis



RESULTS

Mean age at the time of genetic diagnosis was 31.8±12.8 years (min=12.4; max=56.7), while mean symptom onset age in previously asymptomatic patients was 22.5 (min=14;max=35) years. Female/male ratio was 14/6. Eighty percent of the patients (n=16) had homozygous mutations, whereas three patients had compound heterozygous mutations and one had heterozygous mutation. Missense mutations were the most common type of variants in our case series and 25% of the patients (n=5) had novel mutations. Mean serum CK level of the patients was 6642±6270 (min=834; max=26394) IU/l.. The most common clinical phenotype was LGMD-R2.

Graphic 2. Serum CK levels in study population



CONCLUSIONS

Dysferlinopathy is a clinically heterogeneous group of diseases. Although it is usually asymptomatic in childhood, it can rarely causes symptoms. Given that dysferlinopathy is a slowly progressive disease characterized by a typically long period from symptom onset to diagnosis and the presence of inflammatory changes on biopsy or imaging findings, patients can be followed with different misdiagnoses such as polymyositis.[4] More importantly, they can receive immunosuppressive or immunomodulatory treatments for extended periods. It should be kept in mind in the differential diagnosis in patients with late-onset proximal muscle involvement and high serum CK levels.

SUPPLEMENT

REFERENCES

1) Liu J, et al. Nat Genet. 1998;20(1):31-36
2) Mah JK, et al. Can J Neurol Sci. 2016;43(1):163-177.
3) Universal Mutation Database for Dysferlin (UMD-DYSF). Available at: http://www.umd.be/DYSF/ (Accessed:01/04/24).
4) Contreras-Cubas C, et al. BMC Medical Genomics. 2022;15(1):139.

CONTACT

Gunce Basarir, MD
: guncebasarir@gmail.com. : +905059356330