Inherited Heart Disease as a Clinical Marker of Neurogenetic Syndromes

EDER ALENCAR MOURA[1]; BRUNO MOREIRA SANTOS; BRUNO DE OLIVEIRA STEPHAN[1]; BIANCA DOMIT WERNER LINNENKAMP[1]; GIOVANNA NAPOLITANO PEREIRA[1]; LUCAS VIEIRA LACERDA PIRES[1]; ATMIS MEDEIROS HAIDAR[1]; KELVIN HENRIQUE VILALVA[1]; BRUNO AUGUSTO ESTEVES[1]; MARIANA LOMBARDI PERES DE CARVALHO[1]; EMANUELLE MARQUES[1]; JOSÉ EDUARDO KRIEGER[1,2]; GRUPO DE PESQUISADORES MAPA GENOMA BRASIL[1,2]

1. CardioGen – Center of Precision Medicine in Cardiology, Laboratory of Genetics and Molecular Cardiology, Heart Institute, Medical School, University of São Paulo, São Paulo, Brazil.
2. Beneficiência Portuguesa, São Paulo, Brazil.

INTRODUCTION

Cardiac involvement in neurogenetic disorders presents a diagnostic and therapeutic challenge. In many cases, cardiac abnormalities may be the earliest or most prominent clinical sign of an underlying genetic condition, particularly in disorders with neuromuscular or neurodegenerative manifestations.

OBJECTIVES

To characterize the molecular and clinical profiles of patients with cardiac disease harboring pathogenic variants in genes primarily associated with neurological phenotypes, highlighting the role of cardiac manifestations as potential clinical markers for neurogenetic syndromes.

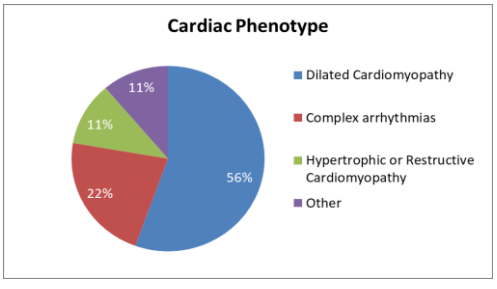
METHODS

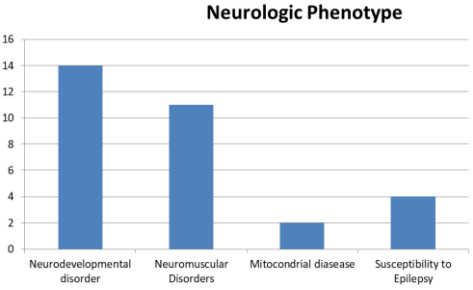
This retrospective study included patients initially referred for cardiological evaluation at a national reference center and subsequently underwent molecular testing (whole-exome or whole-genome sequencing). We selected individuals carrying pathogenic, likely pathogenic, or variants of uncertain significance (VUS) in genes known to be associated with neurological disorders.

RESULTS AND DISCUSSION

Among 3,865 probands analyzed in the MAPA Genoma Brasil project, 36 individuals met inclusion criteria (58% were male; mean age was 29.7 years). The most common cardiac phenotypes were dilated cardiomyopathy (55.5%), followed by complex arrhythmias (22.2%) and hypertrophic or restrictive cardiomyopathy (11.1%). Frequently implicated genes included *DMD*, *LMNA*, *SCN5A*, *RYR1*, and *CACNA1A*, all previously associated with neurological conditions such as hypotonia, motor delay, peripheral neuropathy, or muscular dystrophy.

Variants in *LMNA* were strongly associated with dilated cardiomyopathy and are known to confer risk for neuromuscular phenotypes such as muscular dystrophy. Notably, *DMD* variants were identified in patients whose initial presentation was cardiac, preceding any diagnosed skeletal muscle involvement. Importantly, none of the *DMD* variants in this cohort would have been detected by MLPA, commonly used for Duchenne muscular dystrophy diagnosis, underscoring the need for complementary sequencing technologies such as next-generation sequencing (NGS).
Overall, 78% of variants were classified as pathogenic or likely pathogenic, while 22% were VUS, reinforcing the need for ongoing clinical monitoring and genetic reassessment.





CONCLUSIONS

Cardiac manifestations may precede or coincide with neurological symptoms in patients with underlying neurogenetic diseases. Integrating cardiological evaluation with comprehensive molecular testing enables early diagnosis, prevention of severe outcomes such as sudden cardiac death, and more effective genetic counseling. This approach is critical for appropriate management of both cardiac and neurological components of these complex disorders..

REFERENCES

Hershberger RE, Jordan E. LMNA-Related Dilated Cardiomyopathy. 2008 Jun 12 [updated 2022 Mar 17]. In: Adam MP, Feldman J, Mirzaa GM, Pagon RA, Wallace SE, Amemiya A, editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993–2025. PMID: 20301717.
Johnson R, et al. DMD-Associated Dilated Cardiomyopathy: Genotypes, Phenotypes, and Phenocopies. Circ Genom Precis Med. 2023 Oct;16(5):421-430. doi: 10.1161/CIRCGEN.123.004221. Epub 2023 Sep 6. PMID: 37671549; PMCID: PMC10592075.