Review

Naxos Disease: A Comprehensive Review of its Genetic Basis, Pathophysiology and Clinical manifestations

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Abstract

Naxos Disease is a rare and complex genetic disorder inherited in an autosomal recessive pattern, involving major cardiogenetic and dermatologic abnormalities. It was first discovered in the Greek island of Naxos, yet affected families have been also detected in other Aegean islands, Turkey, Israel and Saudi Arabia. Mutations in the plakoglobin and desmoplakin affecting genes lead to defects in desmosomal junctions mainly in tissues that are subject to mechanical stress, such as the myocardium and the epidermis. Organism's compensation to that specific pathophysiology, is a replacement of the damaged heart-muscle cells by fibro-fatty tissue and regarding the cutaneous tissue, a responsive hyperplastic keratin layer with palmoplantar localization. While dermatological symptoms appear from the first year of life, cardiac manifestations appear by adolescence in various symptoms and echo/ECG signs. Unfortunately, the first indication of the disease may be sudden cardiac death and there is a high risk to end up in heart failure. About the diagnostic approach, a conjunction between Task Force ARVC criteria and cardiac magnetic resonance imaging (CMR) should be taken under consideration and finally as for treatment of the condition besides symptomatic cures studies orient on genetic and molecular solutions.

Keywords: Naxos disease, pathophysiology, therapy, clinical manifestations

Introduction

Naxos Disease is an exceptionally rare and intricated genetic disorder that is inherited with an autosomal recessive pattern, which represents a significant cardiogenetic and dermatologic pathology. First discovered in the Greek island of Naxos by Dr Nikos Protonotarios and his team, is described as a special form of Arrhythmogenic right ventricular dysplasia (ARVD) that is characterized with the progressive replacement of the heart muscle cells by fat and fibrous tissue (1,2,3,4). This type of cardiac abnormalities can cause sudden cardiac death, arrythmias and early on set heart failure to affected individuals. As for its dermatological background, patients also present palmoplantar keratoderma and wooly hair. Despite that it is an uncommon condition, the impact of the disease is profound, considering that its complications may vary in severity, but many are life threatening (1,5).

The aim of this review is to examine pathophysiology including its genetic foundation, clinical presentation and as well as the latest diagnostic and management methods.

Materials and Methods

Detailed research was conducted through the published bibliography via PubMed database. The terms used for the search were "Naxos disease". To ensure accuracy and adequacy, information was gathered through a common data extraction form designed for the aforementioned keywords. The research study adhered to the guidelines of PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews), a comprehensive approach for conducting scoping reviews. Specifically, as regards the PRISMA, the records that were initially identified through PubMed search were 80. The final number of screened records was 80, as no filters were used. Based on their titles and abstracts, 68 articles were excluded due to irrelevance to the study. Hence, the specific article is based on the information retrieved from 12 reliable references (Figure 1).

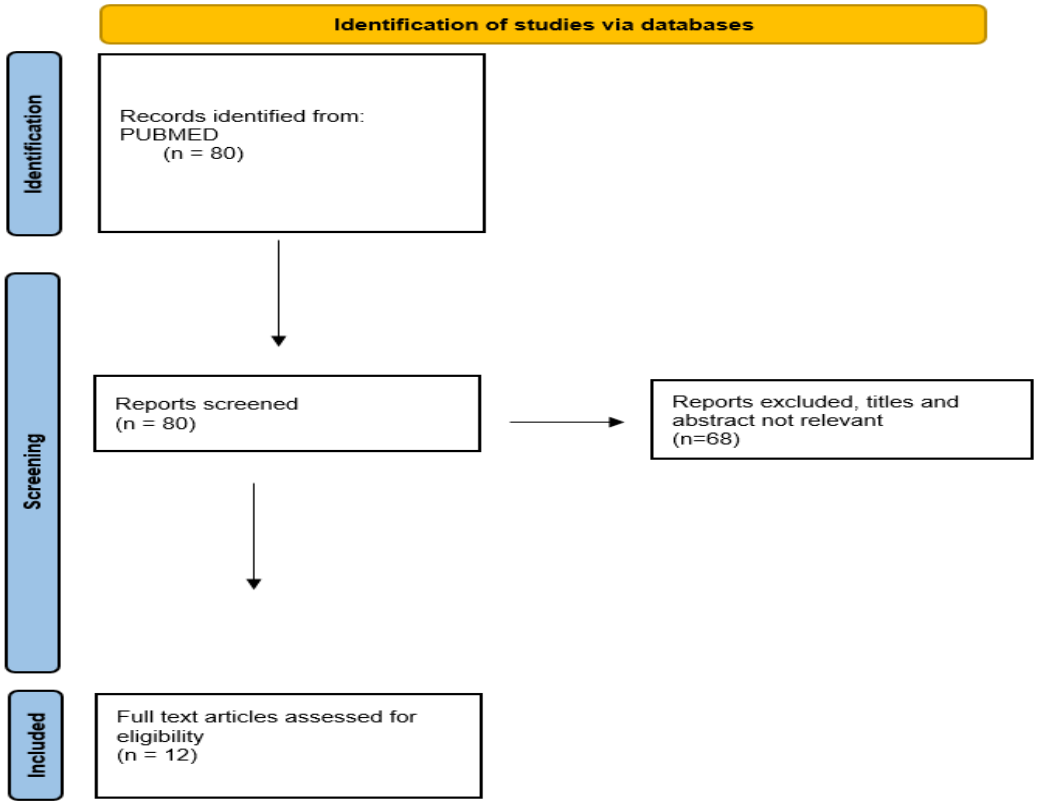

Figure 1: PRISMA 2020 flow diagram for new systematic reviews which included searches of databases, registers and other sources **: title and abstract non relevant

Results

In relation to the epidemiology of the disease, it seems that it reaches 1:1000 in the population of the Greek islands and apart from Naxos, affected families are also discovered in Turkey, Israel, Saudi Arabia. Additionally, there is a rare disorder called Carvajal syndrome, detected in families from India and Ecuador, that appears to be a variation of Naxos disease. It typically manifests in younger ages with left ventricular involvement, with the consequences that will be analyzed below (1,3,4).

As for etiology, and to understand the pathophysiology of the disease, one must first delve into its genetic background. Reference point for the study of the condition was undoubtedly the identification of the Naxos gene by Dr McKenna and his team in 2000, after firstly recognizing and working on a critical zone on chromosome 17, position q21(1,2,4,6,7). The research proved that a mutation Pk2157del2TG, in the gene truncating the C-terminal of the protein Plakoglobin, is the genetic abnormality responsible for Naxos disease, and therefore homozygosity for the gene mutation is followed with Naxos disease and unfavorable prognosis. As for the heterozygous patients, the only findings in a minority of them were small ECG/echocardiographic changes, but not clinically severe characteristics were developed (1,7). Also, beside Plakoglobin, in another protein's gene, Desmoplakin, 2 different mutations have been found, specifically in genes Dsp7901del1G and DspG2375R, that also truncate the C-terminal of the protein (1). These types of genetic abnormalities were discovered in families from Ecuador and India, presented a similar cardiocutaneus syndrome (8).

Additionally, to understand why a mutation that includes plakoglobin's gene is so crucial for the

genesis of Naxos disease, one must also know about the protein's normal function (4,9). In more detail, there are two main reasons to characterize Plakoglobin essential for cardiomyocytes. Firstly, because it provides mechanical integrity to the cells by contributing to the formation of desmosomes, as it facilitates the linking of desmoplakin proteins to the intermediate cytoskeletal filaments and recruits plakophilin 3 to the membrane, where cadherin proteins are concentrated (9). Secondly, because of the protein's important role in cellular communication, with signaling activity to the nucleus and to desmosome structures (4,9). Therefore, readily one understands the major role of the protein in the cell's stability, especially in tissues subject to mechanical strength (4). Plakoglobin is also homologous with the keratin filaments found in cutaneous tissue, reinforcing its involvement in maintaining the strength and resilience of epithelial layers (1). The identification of that genetic association helped to comprehend the clinical characteristics of Naxos disease, that besides the arrhythmogenic dysplasia, also presents dermatological abnormalities. Elaborately, regarding the condition's pathophysiology, flaws in the binding sites of the mentioned homologous proteins can disrupt cytoskeletal networks, resulting, gradually, cell death and loss of the normal tissue foundation (1,3). There is a dualistic response to this harmful process, an organism's counterbalance: the damaged heart-muscle cells loss (appeared mainly in right ventricular myocardium, and mostly in the subepicardial and mediomural layers) are replaced by fibro-fatty tissue, imitating a dilated cardiomyopathy procedure, leading to insufficient contraction and creation of re-entrant ventricular arrhythmia (1,4,8). Arrhythmogenic substrate can also occur due to Plakoglobin mutation- caused reduced connexin-43 levels, that result to myocardial gap junction remodeling (1,3,8). As for the cutaneous tissue, the disruption of the desmosomal ligaments produces a responsive hyperplasia keratin layer that explains the dermatological phenotype (1,2,3,4,8).

A useful categorization for the clinical characteristics of Naxos Disease is the division of them into cardiac and extracardiac manifestations. Regarding the cutaneous phenotype, patients present wooly rough hair from birth and palmoplantar keratoderma which first appeared during the child's first year from birth while it starts using hands and feet (1,3,4,5,8,10). Both epidermolytic and non-epidermolytic histological findings were identified and were not gene specific (8). Regarding cardiac manifestations, until adolescence there was no evidence of the disease, and then ECG and/or echocardiographic abnormalities appeared. The most common anomalies (abnormal ECG in overwhelming majority) were QRS complex prolongation (QRS ≥120 ms) on V1-V3, inverted T waves (V1-V3 or across precordial leads), epsilon waves or the presence of a complete or incomplete right bundle branch block (RBBB) and ventricular extrasystoles of left bundle branch block configuration were also detected (1,2,3). The echocardiographic examination presented right ventricular dilatation and dysfunction, while diffuse hypokinesia was detected as well. Also, 'the triangle of dysplasia' which refers to aneurysms are prominent in the outflow tract, apex, and posterior wall of the right ventricle, along with noticeable impairment of the left ventricle has been recorded. It's crucial to be mentioned that the condition may appear with left or biventricular manifestations. As for the symptomatic clarification, it is usually with syncope and/or sustained ventricular tachycardia of left bundle branch block configuration, especially in young adulthood and unfortunately, the first and catastrophic sign of the disease may be sudden cardiac death (1,2,3,4,6,8,10). During the progress of time, one third of patients present symptoms before they turn thirty years old and in a ten-year follow-up heart failure was developed in ½ of the patients. Finally, as there are no exact criteria for heart participation, established Task Force ARVC criteria are commonly used in association with cardiac magnetic resonance imaging (CMR) that can detect the presence of fibrosis (scar tissue) and fatty infiltration in the heart muscle. Usage of ARVC criteria may present

significantly lower sensitivity, and they shouldn't be taken into consideration as the only method used (1,3,6,10).

Regarding therapeutic management Naxos disease requires multidisciplinary approach, including cardiac care to manage arrhythmias and heart failure and dermatological care for skin issues (1,4). Firstly, for prevention of sudden cardiac death for symptomatic patients with ECG/echocardiographic abnormalities, an implantation of an automatic cardioverter defibrillator should be considered. Also, antiarrhythmic drugs; solatolol and amiodarone are recommended for episodes of VT either alone or in conjunction with b-blockers. Meanwhile in late stages that heart failure is presented, the usual therapeutic approach is indicated, including beta-blockers, ACE inhibitors and diuretics (1,4). Additionally, it's important to mention that genetic counseling and lifestyle modifications, such as exercise restrictions, are also key components of managing the disease (1,4,11). About genetic and molecular mechanisms, latest researches have shown that that's the path that could possibly present an actual therapeutic solution. Specifically, Dr Kessler and team, by experimenting with Zebrafish models and rat cardiomyocytes with induced plakoglobin mutations, discovered that drug SB216763 (SB21) managed to save and partially restore the Arrhythmogenic Cardiomyopathy (ACM) phenotype (1,11). However, this is the only information provided, and more data needs to be discovered in new heart models. Lastly, studies on induced pluripotent stem cells (iPSCs) such as Dr. K Walz and team paper have yielded encouraging outcomes, aiding in the advancement of treatment approaches (1,12).

Conclusion

Naxos Disease constitutes a rare genetic disorder with significant cardiological, and dermatological effects caused by the mutations in Plakoglobin and Desmoplakin genes. Even though there are very few studies especially about its diagnostic criteria, early detection and genetic screening are crucial from preventing disastrous outcomes such us sudden cardiac death. While the disease remains challenging, ongoings studies across the scientific community, especially the ones oriented towards a molecular and cellular background, seem to be closer than ever to present rational answers about a deeper understanding of the disease and therefore the discovery of more specific and effective treatments.

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