Chapter

Naxos Disease: Current Knowledge and Future Advances

Marianna Leopoulou, Gustav Mattsson, Ida Kåks and Peter Magnusson

Abstract

Naxos disease is a genetic cardiocutaneous syndrome manifesting with a cardiomyopathy that belongs in the arrhythmogenic right ventricular cardiomyopathy (ARVC) spectrum and follows an autosomal recessive pattern. It manifests with wooly hair, keratosis of the extremities and right ventricular dysfunction. It is accompanied by risk of arrhythmias as well as sudden cardiac death (SCD), even at a young age. Furthermore, the disease often progresses to right ventricular heart failure, but can also affect the left ventricle. Patient management follows current guidelines on ARVC and principles for heart failure management. Bioengineering and research about pluripotent stem cells seem to have potential to improve future management of the disease. This chapter covers current knowledge on Naxos disease regarding clinical features, epidemiology, pathogenesis, guidelines on patient management and provides insights in research frontlines.

Keywords: arrhythmias, cardiomyopathy, genetics, heart failure, Naxos disease, sudden cardiac death

1. Introduction

Naxos disease is an arrhythmogenic cardiomyopathy, considered to represent a form of ARVC [1]. It is of genetic origin and two main proteins have been associated with the disease. The clinical manifestations include wooly hair, keratosis of the extremities, and right ventricular dysfunction. Albeit rare, the disease can cause advanced heart failure and life-threatening arrhythmias, even in the young [2]. Data on Naxos disease are limited, and current patient management follows the guidelines for heart failure and ARVC. In recent years, research has focused on the field of bioengineering, illuminating some of the aspects of the disease and cultivating future perspectives regarding its management. In this chapter we present current knowledge regarding the clinical presentation, epidemiology, genetic substrate, pathophysiology, current guidelines for patient management, and future paths for Naxos disease.

2. Clinical presentation of Naxos disease

Naxos disease manifests with a typical phenotype including both cardiac and extracardiac characteristics. The extracardiac manifestation of the disease involves

tight, wooly and rough hair, commonly present from birth [3]. In addition, Naxos patients exhibit diffuse palmoplantar non-epidermolytic keratosis, with clear borders, manifesting as soon as the child starts using hands and feet [3, 4]. Small arms and hands, short fingers, curved nails and hypo/oligodontia have also been reported in some cases [5, 6]. Notably, heterozygous carriers do not display certain aspects of the disease, such as palmoplantar keratoderma but wooly hair may manifest [7].

Regarding the cardiac characteristics, the disease resembles the ARVC phenotype. Echocardiography frequently portrays right ventricular dysfunction. In more detail, prominent dilation is often present along with hypokinesia and aneurysms that affect mainly the outflow tract, apex, and inferior wall of the right ventricle [3, 7]. In a quarter of the cases, the left ventricle is also affected, exhibiting the same characteristics as seen in dilated cardiomyopathy [4]. The term 'triangle of dysplasia' has been suggested in Naxos disease, which refers to aneurysms of the outflow tract, apex, and posterior wall of the right ventricle [8]. The disease prognosis is generally adverse [8]. The annual cardiac mortality reaches 3.0% [7].

While the extra-cardiac manifestations are prominent from a young age, symptoms suggestive of cardiac involvement usually occur in adolescence and in young adulthood. Heart failure and life-threatening ventricular arrhythmias may occur in adolescence [4]. Palpitations, syncope, and atrial arrhythmias are frequently encountered [5]. Arrhythmic events involve a wide range of patterns, from numerous premature ventricular complexes to sustained ventricular tachycardia (VT) and are present in half of the patients [7]. Events of VT, most commonly of a left bundle branch block (LBBB) pattern suggestive of right ventricular origin [9], have been documented in Naxos disease, even being drug-refractory in some cases [5]. Symptomatic patients tend to exhibit inducible VT in electrophysiology studies [3].

Symptoms suggestive of right ventricular dysfunction occur in advanced heart failure [8], while heart failure, either right- or bi-ventricular affects half of the patients after 10-year follow-up after diagnosis [7]. When severe hypokinesia is present in the context of progression of heart failure, intra-cardiac thrombi may occur [10]. Heterozygous carriers do not display ventricular arrhythmias or late potentials on signal-averaged electrocardiography (ECG), but atypical ECG or echocardiographic discrepancies may occur [7]. Similarly, they did not display symptoms or echocardiographic abnormalities in follow-up, in a paper by Protonotarios et al. [7].

3. Epidemiology and genetic substrate

Naxos disease has been identified as a form of ARVC inherited in an autosomal recessive pattern by the World Health Organization since 1995 [11]. However, the disease was first described in 1986, when Protonotarios and associates first documented the disease manifestations and clinical course [5]. The name "Naxos" originates from this original description of the disease; nine patients, aged 7 to 41 years, from four families of Naxos island in Greece, were presented. All these patients had wooly hair and palmoplantar keratosis as well as a range of arrhythmic events, including VT. Interestingly, all patients had echocardiographic signs of right ventricular (RV) dysfunction, while in some the left ventricle (LV) was also affected [5]. Since then, more patients have been found not only in Greece, but in Israel, Saudi Arabia, Italy, and Turkey [12]. Sporadic cases of the disease have also been identified in Bangladesh and in Canada [13, 14]. The prevalence of the disease in the Greek islands has been calculated to 1:1000 [3]. Officially, the disease was first named "Naxos disease" in a 1994 abstract [15]. Of interest, since ARVC and its clinical spectrum has been found to manifest with biventricular or mainly LV

dysfunction, the term arrhythmogenic cardiomyopathy (ACM) has been proposed as more accurate [1]. Prevalence of heterozygous carriers is up to 5% in the Naxos population [8].

The proposed recessive hereditary pattern and the resemblance of the disease to ARVC [5, 16], was confirmed in 1998, when its locus was identified in chromosome 17 in position q21 [17], and in 2000 when plakoglobin was identified as the mutated protein attributed to the disease [18]. Since then, research has concluded that the causative mutation (Pk2157del2TG) is in the gene truncating the C-terminal of the protein plakoglobin [3, 12]. In addition, another mutation, the homozygous 2-bp deletion (c.2157delTG) (also in the protein plakoglobin) has been associated with the disease [18]. Furthermore, mutations of the protein desmoplakin have been identified to cause cardiocutaneous ARVC [19, 20]. Early data suggested that Naxos disease was a more severe form of ARVC [12], while a more recent comparison between the two entities indicates a similar cardiac phenotype, easily identified through non-invasive screening [2, 21]. In 2017, a novel homozygous mutation was discovered to cause Naxos disease, in unrelated patients of French-Canadian families. This is a mutation of the exon 5 of the JUP gene (p.Glu301 Gly) [14]. Two mutations of the desmoplakin gene have been implicated; Dsp7901del1G and DspG2375R [19, 20]. All aforementioned mutations follow an autosomal recessive pattern [2]. However, in 2011 a mutation (c.1790 C > T, p.Ser597Leu) was reported to be causative of the disease associated with hypo/oligodontia, that follows an autosomal dominant pattern [6].

A syndrome resembling Naxos disease, known as Carvajal syndrome, has been described in families from Ecuador and India as well as in Arab-Palestinian families [8, 22, 23]. Truncated proteins of desmoplakin, plakoglobin and desmocollin-2 have been implemented in the genetic substrate [23]. This syndrome was first described by Carvajal-Huerta [22]. Patients present with epidermolytic keratoderma while the disease usually manifests at a younger age and the LV is commonly affected [3, 8]. Notably, the replacement of the myocytes by fatty tissue is not apparent in Carvajal syndrome [24].

4. Pathophysiology and diagnostic criteria

Both plakoglobin (γ-catenin) and desmoplakin, that are linked with Naxos disease are associated with myocardial cell adhesion [3, 25]. Plakoglobin has a two-fold role in both mechanical contraction and electrical signal conduction; it is a component of the desmosomes, interconnecting with the intermediate filaments of desmin, and constitutes a component of the adherens junctions where it is connected to the actin skeleton [3, 26]. Similarly, desmoplakin is a cytoplasmic protein that links plakoglobin to the intermediate filaments of desmin [3]. The defective cell adhesion in the case of the truncated plakoglobin protein, also causes a reduction in the connexin-43 levels, a major gap junction protein. The associated myocardial gap-junction remodeling, creates a substrate for arrhythmogenic events [27]. Furthermore, the defective cell adhesion of the cardiomyocytes leads to their apoptosis which is then followed by fibrofatty replacement in the affected ventricles [18]. The associated conduction disturbances created can induce arrhythmogenic events and sustain re-entry circuits [3].

In the landmark paper Protonotarios et al., all patients were reported to have signs of intra-ventricular conduction delay ECG as well as echocardiographic findings of right- or bi-ventricular dysfunction. In more detail, the ECG abnormalities that were reported include a wide QRS ≥120 ms and abnormal T-wave inversions in seven out of nine patients [5]. The most common abnormalities documented

Category	Criteria
Global or regional dysfunction and structural alterations	**Major** By 2-D echocardiography: • Regional RV akinesia, dyskinesia, or aneurysm • and 1 of the following (measured in end diastole): ○ PLAX RVOT ≥32 mm (corrected for body size PLAX/BSA ≥19 mm/m2) ○ PSAX RVOT ≥36 mm (corrected for body size PSAX/BSA ≥21 mm/m2) ○ or fractional area change ≤33% By CMR: • Regional RV akinesia, dyskinesia or dyssynchronous RV contraction • and 1 of the following: ○ Ratio of RV end-diastolic volume to BSA ≥110 mL/m2 (male) or ≥100 mL/m2 (female) ○ or RV ejection fraction ≤40% By RV angiography: • Regional RV akinesia, dyskinesia or aneurysm **Minor** By 2-D echocardiography: • Regional RV akinesia or dyskinesia • and 1 of the following (measured in end diastole): ○ PLAX RVOT ≥29 to <32 mm (corrected for body size PLAX/BSA ≥ 16 to <19 mm/m2) ○ PSAX RVOT 32 to 36 mm (corrected for body size PSAX/BSA ≥18 to <21 mm/m2) ○ or fractional area change 33–40% By CMR: • Regional RV akinesia or dyskinesia or dyssynchronous RV contraction • and 1 of the following: ○ Ratio of RV end-diastolic volume to BSA ≥100 to <110 mL/m2 (male) or ≥ 90 to <100 mL/m2 (female) ○ or RV ejection fraction >40% to ≤45%
Wall tissue characterization	**Major** Residual myocytes <60% by morphometric analysis (or < 50% if estimated), with fibrous replacement of the RV free wall myocardium in ≥1 sample, with or without fatty replacement of tissue on endomyocardial biopsy **Minor** Residual myocytes 60–75% by morphometric analysis (or 50–65% if estimated), with fibrous replacement of the RV free wall myocardium in ≥1 sample, with or without fatty replacement of tissue on endomyocardial biopsy
Repolarization abnormalities	**Major** Inverted T waves in right precordial leads (V1, V2, and V3), or beyond in individuals >14 years old (in the absence of complete RBBB ≥QRS 120 ms) **Minor** • Inverted T waves in leads V1 and V2 in individuals >14 years old (in the absence of complete RBBB) or in V4, V5 or V6 • Inverted T waves in leads V1, V2, V3, and V4 in individuals >14 years old in the presence of complete RBBB

Category	Criteria
Depolarization/ conduction abnormalities	**Major** Epsilon wave (reproducible low-amplitude signals between end of QRS complex to onset of the T wave) in the right precordial leads (V1 to V3) **Minor** • Late potentials by SAECG in ≥1 of 3 parameters in the absence of QRS ≥110 ms on the standard ECG • Filtered QRS duration (fQRS) ≥114 ms • Duration of terminal QRS <40 μV (low-amplitude signal duration) ≥38 ms • Root-mean-square voltage of terminal 40 ms ≤20 μV • Terminal activation duration of QRS ≥55 ms measured from the nadir of the S wave to the end of the QRS, including R', in V1, V2, or V3, in the absence of complete RBBB
Arrhythmias	**Major** Nonsustained or sustained ventricular tachycardia of LBBB morphology with superior axis (negative or indeterminate QRS in leads II, III, and aVF and positive in lead aVL) **Minor** • Nonsustained or sustained ventricular tachycardia of RV outflow configuration, LBBB morphology with inferior axis (positive QRS in leads II, III, and aVF and negative in lead aVL) or of unknown axis • >500 ventricular extrasystoles per 24 hours (Holter monitoring)
Family history	**Major** • ARVC confirmed in a first-degree relative who meets current Task Force criteria • ARVC confirmed pathologically at autopsy or surgery in a first degree relative • Identification of a pathogenic mutation categorized as associated or probably associated with ARVC in the patient under evaluation **Minor** • History of ARVC in a first-degree relative in whom it is not possible or practical to determine whether the family member meets current Task Force criteria • Premature sudden death (<35 years of age) due to suspected ARVC in a first-degree relative • ARVC confirmed pathologically or by current Task Force Criteria in a second-degree relative

Required for definite diagnosis: 2 major or 1 major and 2 minor criteria or 4 minor from different categories; borderline: 1 major and 1 minor or 3 minor criteria from different categories
Possible diagnosis: 1 major or 2 minor criteria from different categories.
ARVC, arrhythmogenic right ventricular cardiomyopathy; BSA, body surface area; CMR, cardiac magnetic resonance imaging; LBBB, left bundle branch block; PLAX, parasternal long-axis view; PSAX, parasternal short-axis view; RBBB, right bundle branch block; RV, right ventricular; RVOT, RV outflow tract; SAEG, signal averaged ECG.
Adapted from Marcus et al. [31].

Table 1.
Revised task force criteria for arrhythmogenic right ventricular cardiomyopathy.

in Naxos patients are wide QRS and inverted T-waves in V1-V3 or in all precordial leads, while epsilon waves may also be present [3]. An incomplete right bundle branch block may also be apparent, while the extrasystoles tend to manifest with an LBBB morphology [7]. Flattened T-waves appear in the case of biventricular involvement [3]. Late potentials in Naxos disease are more often abnormal than in

other forms of cardiomyopathies [28]. In echocardiography, dysfunction, hypokinesia and aneurysms are prominent [3, 7]. In histological specimens fibrofatty patterns are prominent, while focal myocarditis has also been reported in follow-up histology specimens [4]. Both the subepicardial and the mediomural myocardium of the involved ventricles is replaced by fibrofatty tissue, while healthy myocytes are surrounded by fatty tissue [3, 29]. In immunohistochemical specimens the signal of plakoglobin and connexin-43 in the intracellular junctions is diminished [24, 27].

Since the disease belongs in the ARVC spectrum and there are currently no specific diagnostic criteria for the cardiac manifestations of Naxos disease, the diagnostic criteria of ARVC are widely used [30, 31]. However, while the specificity of the revised task force criteria is high, sensitivity has been shown to be as low as 13–20% [32]. Since then, progress has been made regarding tissue characterization through cardiac magnetic resonance (CMR), possibly providing a tool of higher diagnostic accuracy, high specificity and high sensitivity [32, 33]. The revised task force criteria for ARVC are depicted in **Table 1**. In November 2020 the Padua criteria for the diagnosis of ACM was published. The Padua diagnostic criteria introduce tissue characterization by contrast enhanced cardiac magnetic resonance for detection of fibro-fatty myocardial replacement of both ventricles. It also adds new ECG criteria, including depolarization/ repolarization abnormalities and ventricular arrhythmias, specific for the LV involvement [34]. The proposed Padua diagnostic criteria need to be validated by further clinical studies in large cohorts of patients.

5. Therapeutic management

5.1 Heart failure

Naxos disease is predominantly a condition affecting the right ventricle, causing right ventricular failure. Unlike for LV failure, less is known regarding the optimal pharmacological therapy. However, the expert consensus regarding the management of ACMs suggests that when treating left or right ventricular dysfunction, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers, beta-blockers, mineralocorticoid receptor antagonists, and diuretics, in the case of fluid overload, should be considered [35]. Despite the lack of Naxos-specific guidelines, ACE inhibitors, betablockers, and diuretics are reasonable prescribing choices [2]. Dapagliflozine and empagliflozine have been introduced in the treatment of heart failure, even in non-diabetic patients [36, 37], while sacubitril/valsartan is indicated for patients with left ventricular ejection fraction (EF) ≤35% [38]. Anticoagulation treatment is indicated in the case of atrial fibrillation/flutter, in the event of intra-cardiac thrombi and can also be considered in patients with ventricular aneurysms, either left or right [35, 39]. In the case of advanced heart failure, patients may benefit from devices such as cardiac resynchronization therapy (CRT), often combined with an implantable cardioverter-defibrillator (ICD), left ventricular assist devices (LVAD) and assist devices for the right ventricle (RVAD or BiVAD) in the setting of an LVAD implantation and considered as bridge to transplant [38].

5.2 Arrhythmias and sudden cardiac death

The prognosis of the disease is adverse, especially in the young and annual SCD mortality is 2.3% [7, 8]. As risk factors for SCD, the following have been identified: history of syncope, onset of symptoms before the age of 35, structural progression

before the age of 35, and left-ventricular involvement [7]. However, risk stratification of SCD constitutes a challenge. ARVC guidelines and position papers on ICD implantation, guide the same decisions in the management of Naxos disease [35, 40]. Criteria for risk stratification for SCD is presented in **Table 2**. A clear indication for an ICD implantation is aborted SCD and VT with haemodynamic instability, while in the case of VT without haemodynamic compromise it should also be considered [35, 40]. An ICD protects from SCD in ARVC either in secondary prevention or is justified as primary prevention based on careful judgment of risk factors [40–42]. However, the clinical presentation should play a major part in the decision making; unexplained syncope, risk markers associated with medical history, family history and severity of clinical presentation and deterioration should be considered [40]. An ICD is indicated for ACM patients with low ejection fraction ≤35% and New York Heart Association (NYHA) class II or III, provided that the patient's estimated survival exceeds one year [35]. The same guidelines apply for Naxos patients. The first implantation of an ICD in a Naxos patient was reported in 2000 [43]. Naxos-specific guidelines are rare. Among those, an ICD is indicated for patients who are symptomatic or present structural progression especially before the age of 35 [8, 44]. Naxos patients, like ARVC patients, should abstain from competitive sports as myocardial stress can exacerbate the dysplasia [40]. Regarding drug therapy, beta-blockers (Class I), and possibly amiodarone (Class IIb) and sotalol (Class IIb) in special cases have been suggested for patients with ACMs for the control of arrhythmias and the reduction of ICD shocks [35, 45]. Specifically for Naxos patients with recurrent sustained VTs, anti-arrhythmic drugs should be prescribed as per the general guidelines of arrhythmias, while amiodarone or sotalol alone or in combination with beta-blockers have been suggested [8, 40, 45]. As far as catheter ablation is concerned, it should be considered in ACM cases with amiodarone-refractory recurrent monomorphic VT, recurrent symptomatic drug-refractory

Estimated Risk	Parameters
High risk (>10% / year)	*Major arrhythmic events*
	• Cardiac arrest due to ventricular arrhythmia
	• Sustained ventricular tachycardia
Intermediate risk (1–10% / year)	*Major risk factors*
	• Non-sustained ventricular tachycardia
	• Unexplained syncope
	• Severe right or left ventricular dysfunction
	Minor risk factors
	• Male sex, proband
	• Frequent ectopic beats (≥1000 premature ventricular beats per day)
	• Extent of negative T-waves (beyond V3)
	• Inducibility on electrophysiological study
	• Extent of right ventricular fibrofatty scarring
	• Multiple associated desmosomal mutations
Low risk (<1% / year)	*No events/no risk factor*
	• Healthy gene carriers
	• Patients with definite ARVC

Adapted from Corrado et al. [46].

Table 2.
Risk stratification for sudden cardiac death in ARVC.

sustained VT, symptomatic nonsustained VT or a high ectopic burden (≥1000 premature ventricular contractions/day) refractory to beta-blockers [35]. Beta-blockers are also recommended for patients without an ICD (Class IIa) [35].

5.3 Bioengineering

On the front of cellular and molecular engineering, advances have been made that may create a substrate with therapeutic potentials in the future. The pharmaceutical substance SB216763 (SB21) (an inhibitor of the glycogen synthase kinase GSK-3β) prevented heart failure and reduced mortality when administered early on to zebrafish models with induced plakoglobin mutations that resulted in Naxos disease. The effect could possibly be attributed to the prevention of the formation of an arrhythmic substrate on the intercalated disk level [47]. Further data on mammalian models are, however, needed [2, 48].

On the front of induced pluripotent stem cells (iPSCs) that enable the in-vitro study of human genetic disorders like ARVC through the induction of mutant cardiomyocytes, albeit a challenging field, promising results have been reported [49–51]. Researchers have been able to re-create the ARVC phenotype using adult-like metabolic energetics, proving that adultlike metabolism plays a crucial role in establishing ARVC models through iPSCs [49]. Furthermore, cultured ARVC cardiomyocytes manifest with adipogenic phenotype and reduced cell surface localization of desmosomal proteins, characteristic features of ARVC [50]. Also Naxos-ARVC has been created in mice models through a homozygous mutation of the plakoglobin gene [52] and of the desmoplakin gene, the latter causing human-like cardiac arrhythmias, palmoplantar keratosis, and alopecia [53]. Interestingly, cardiac function was restored in mice through the normalization of Naxos plakoglobin levels, indicating that it is the downregulation of the protein that causes the cardiac dysfunction, rather than the mutation itself [54]. This conclusion, if further supported, could have clinical applications in Naxos disease [2]. The article suggests that an approach to this would be to use antisense technology to specifically block nonsense-mediated decay of mutant plakoglobin mRNA, enabling the expression of the truncated protein at increased levels [54, 55].

6. Conclusion

In this chapter key aspects of Naxos disease are presented. Due to its rarity, the condition follows the general guidelines for arrhythmias and heart failure, as disease-specific criteria is lacking. However, due to its uniqueness, larger Naxos registries are needed, as they would illuminate the individual characteristics of the disease as well as guide the way to designated guidelines for the management of Naxos patients. Possibly, the thorough study of the origins of the disease, the genetic substrate and pathogenesis, can offer insights with therapeutic potential.

Conflict of interest

IK and ML reports no conflicts of interest. GM has received speaker's fee from Alnylam, MSD, and Internetmedicin. PM is on the advisory board of Coala Life and has received speaker's fees or grants from Abbott, Alnylam, Amicus Therapeutics, AstraZeneca, Bayer, Boehringer-Ingelheim, Internetmedicin, Lilly, MSD, Novo Nordisk, Octopus Medical, OrionPharma, Pfizer, Vifor Pharma, and Zoll.

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Acronyms and abbreviations

ACE	angiotensin-converting enzyme
ACM	arrhythmogenic cardiomyopathy
ARVC	arrhythmogenic right ventricular cardiomyopathy
CMR	cardiac magnetic resonance
CRT	cardiac resynchronization therapy
ECG	electrocardiography
iPSC	induced pluripotent stem cell
ICD	implantable cardioverter-defibrillator
LBBB	left bundle branch block
LV	left ventricle
LVAD	left ventricular assist device
NYHA	New York Heart Association
SCD	sudden cardiac death
VT	ventricular tachycardia

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