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GRAND ROUND
Heart failure

Juvenile-onset multifocal atrial arrhythmias, atrial standstill and compound heterozygosity of genetic variants in *TAF1A*: sentinel event for evolving dilated cardiomyopathy—a case report

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Background Juvenile onset of extensive atrial electromechanical failure, including atrial standstill, is a rare disease entity that may precede ventricular cardiomyopathy. Genetic variants associated with early-onset atrioventricular (AV) cardiomyopathy are increasingly recognized.

Case summary A 16-year-old patient presented with atrial brady- and tachyarrhythmias and concomitant impaired atrial electromechanical function (atrial standstill). The atrial phenotype preceded the development of a predominantly right-sided AV dilated cardiomyopathy with pronounced myocardial fibrosis. A His-bundle pacemaker was installed for high-degree AV conduction block and sinus arrest. Using familial-based whole-exome sequencing, a missense mutation and a copy number variant deletion (compound heterozygosity) of the *TAF1A* gene (involved in ribosomal RNA synthesis) were identified.

Discussion Juvenile onset of severe atrial electromechanical failure with atrial arrhythmias should prompt deep pheno- and genotyping and calls for vigilance for downstream cardiomyopathic deterioration.

Keywords Multifocal atrial arrhythmias • Atrial standstill • Dilated cardiomyopathy • TAF1A • Case report

ESC Curriculum 5.7 Bradycardia • 2.3 Cardiac magnetic resonance • 6.7 Right heart dysfunction • 6.5 Cardiomyopathy

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Learning points

- Juvenile onset of extensive atrial electromechanical failure and atrial arrhythmias should prompt deep pheno- and genotyping and calls for vigilance for downstream cardiomyopathic deterioration.
- Ribosomopathies are inherited diseases of the ribosomal machinery, with extremely variable clinical manifestations but often displaying tissue specificity. Early-onset heart failure may be a manifestation of ribosomopathy.
- Cardiac ribosomopathies are probably rare but may be underdiagnosed with panel-based genetic analyses. Family-based whole-exome sequencing may prove added value.
- In patients with atrial standstill in need of a pacemaker, conduction-system pacing holds promise.

Introduction

Juvenile-onset cardiomyopathy is a rare disorder with an incidence of 1–1.5 cases per 100 000 person-years.[1] In the young, hypertrophic and dilated cardiomyopathies (DCM) are the most common forms. Initial phenotypic expression of DCM may vary widely,[2] ranging from mild cardiac abnormalities to end-stage biventricular dysfunction. The prognosis is worse than in adult DCM patients.[3]

Juvenile cardiomyopathies may arise from genetic mutations, atrial or ventricular tachyarrhythmias, infection, coronary artery abnormalities, toxins, or a combination thereof. A genetic basis of DCM is increasingly identified. Deleterious genetic mutations and/or variants of unknown significance are identified in 53% of the juvenile DCM population using conventional panel-based genetic screening tools.[2] Family-based whole-exome screening (WES), comparing genetic information from all exomes between the parents and their offspring, confers a less biased approach and may be a powerful tool to unravel novel candidate genes. Trio-WES led to a genetic diagnosis in 48% of probands with pediatric DCM that had no genotype–phenotype concordance after panel-based screening.[4] Using this approach, recessive TATA box-binding protein-associated factor RNA polymerase I subunit A (*TAF1A*) gene mutations [involved in ribosomal RNA (rRNA) synthesis] were recently linked to pediatric DCM (i.e. ribosomopathy) that was characterized by extensive fibrosis, gene-specific nucleolar segregation defects in cardiomyocytes, and an early need for heart transplantation.[5]

We describe a case of a 16-year-old patient presenting with atrial brady- and tachyarrhythmias and concomitant impaired atrial electromechanical function (atrial standstill). This atrial phenotype well preceded the development of a predominantly right-sided atrioventricular (AV) DCM and AV conduction disturbances. With trio-WES, both a missense mutation and a copy number variant deletion (compound heterozygosity) in the *TAF1A* gene were identified.

Case presentation

We present a case of a 16-year-old boy who was referred to our hospital because of palpitations triggered by exercise. Besides occasional lightheadedness, he never experienced symptoms such as syncope or angina. He denied using recreational or homeopathic drugs, energy drinks, or dietary supplements. On physical examination, his pulse was irregular with a heart rate of approximately 120 b.p.m., blood pressure of 127/63 mmHg, and oxygen saturation of 100%. Cardiac auscultation was normal and edema was absent.

Electrocardiographically, sinus bradycardia was interrupted by multifocal atrial tachycardias (ATs) with variable ventricular rates (123–240 b.p.m., *Figure 1A*). Sporadic AV block occurred at high rates. *P*-wave amplitudes were strikingly reduced. QRS width and morphology were normal; T waves were inverted in the right precordial leads. Laboratory investigation showed normal electrolytes, high-sensitivity troponin T, thyroid-stimulating hormone, and C-reactive protein. N-terminal pro-brain natriuretic peptide (NT-pro-BNP) levels were slightly elevated, 38.5 (>35) pmol/L. Serology for Borrelia burgdorferi was negative. On transthoracic echocardiography, the left ventricular (LV) ejection fraction (EF) was 55% (fractional shortening 28%) with normal right ventricular (RV) function and no valvular abnormalities. Cardiac magnetic resonance imaging (MRI) (*Figure 2A*) revealed a larger RV than LV volume (98 and 89 mL/m^2, respectively) with a slightly reduced right ventricular ejection fraction (RVEF) of 44%. No late gadolinium enhancement was noted.

The tentative diagnosis of multifocal ATs with variable AV conduction was established. An electrophysiological study (EPS) was conducted after shared decision-making with the patient and his parents. Normal His-ventricular (HV) interval (40 ms) and sinus-node recovery times were noted. Extremely low voltages (<0.15 mV) were observed in a large portion of the right atrium (RA) and the coronary sinus (*Figure 3*). Three focal ATs were targeted in the RA free wall and at the lateral aspect of the tricuspid annulus. Because of the persistent inducibility of different ATs, flecainide (after a negative ajmaline provocation) and verapamil were initiated, successfully suppressing the arrhythmogenic foci. An implantable loop recorder was implanted before discharge. Panel-based screening of genes involved in cardiomyopathy or congenital heart disease, including *SCN5A*, titin (*TTN*), and filamin C (*FLNC*), did not yield a (likely) pathogenic mutation.

Over a 5-year period, a persistent bradycardia of 45 b.p.m. with complete right-bundle branch block, delayed RV activation, and T-wave inversions occurred despite cessation of flecainide (*Figure 1B*). Progressive RA/RV dilatation [right ventricular end-diastolic volume (RV EDV)/body surface area (BSA) 222 mL/m^2], akinesia and hyperenhancement of the basal/mid RV free wall, fatty infiltration, and impaired RV function (EF unchanged with 44% but grade 3–4 tricuspid regurgitation) became apparent on MRI (*Figure 2B*). Aneurysms and shunting were absent. The LV, with LV EDV/BSA 115 mL/m^2 and EF 53%, had delineated mid-wall fibrosis in the basal LV inferolateral segment. RV myocardial biopsies showed hypertrophy with dominant interstitial and replacement fibrosis. Atrial contractions were absent during tissue-Doppler measurements (*Figure 2C*); hence, apixaban was given. Repeat EPS revealed progressive low voltages in the entire RA and failure of capture at physiological thresholds, indicative of atrial standstill. The HV interval was 90 ms with a fragmented His potential (*Figure 3C*). CT excluded anomalous or obstructed coronary arteries. According to the modified arrhythmogenic RV cardiomyopathy/dysplasia (ARVC/D) task force criteria of Marcus *et al.*,[6] these findings were consistent with arrhythmogenic RV cardiomyopathy (ARVC).

The patient developed shortness of breath [New York Heart Association (NYHA) II] and significant fatigue. LVEF on echocardiography was 45%. Volume overload required treatment with bumetanide 2 mg b.i.d. Heart failure medication eplerenone, bisoprolol, and empagliflozine was started. Valsartan/sacubitril at a low dose resulted in symptomatic hypotension without any improvement in dyspnea and fatigue and was stopped. Later that year, the patient experienced syncope during an 8 s arrest recorded on the loop recorder

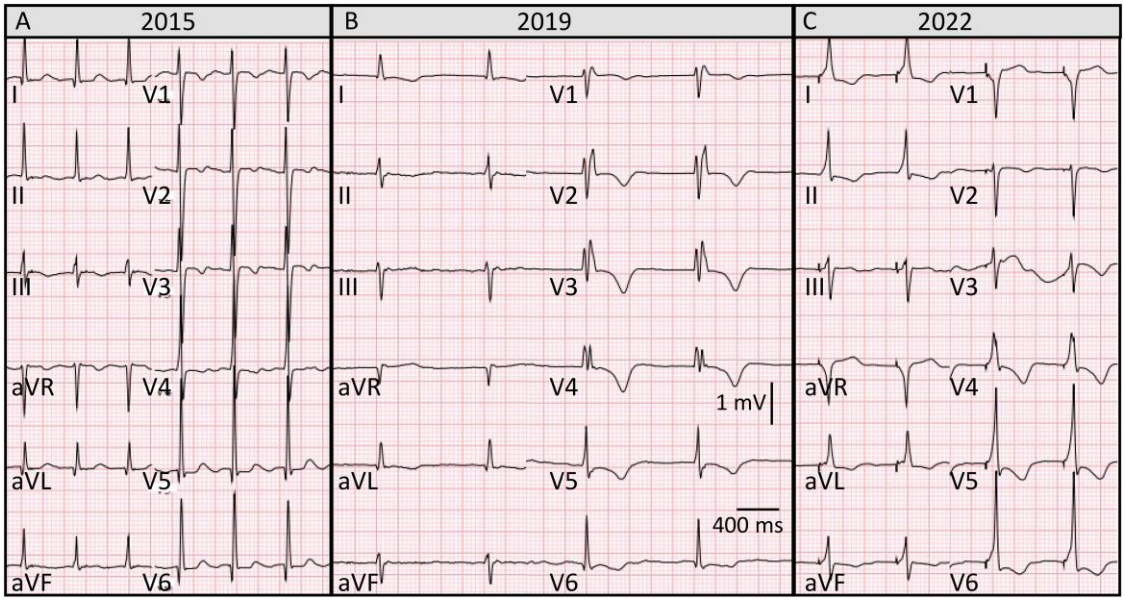

Figure 1 Twelve-lead electrocardiogram of the initial presentation showing atrial tachycardia of 128 b.p.m. (*A*). Bradycardia 45 b.p.m., complete right-bundle branch block with deep inverted T waves (*B*). Twelve-lead electrocardiogram with His-bundle pacing (*C*).

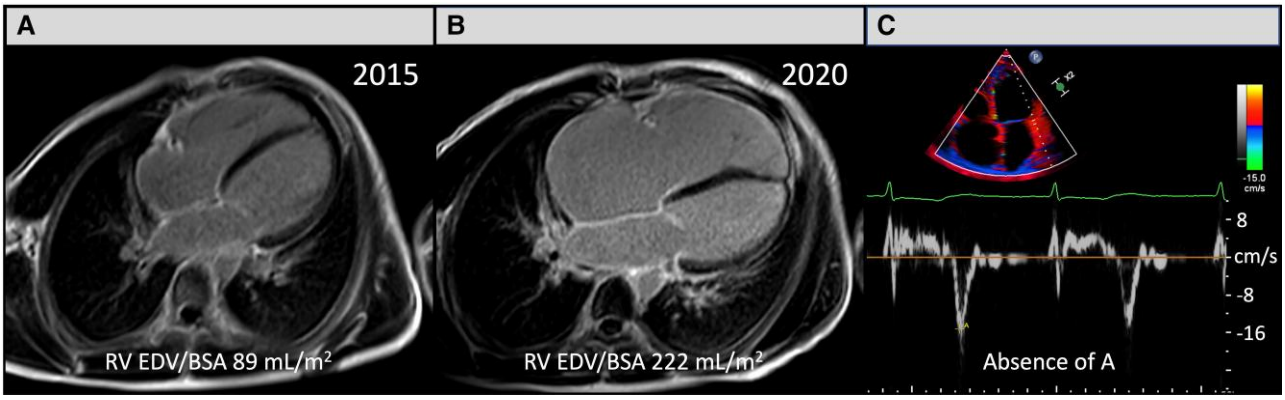

Figure 2 Progression of left ventricular fibrosis and right atrium/right ventricle dilatation over a 5-year time period on cardiac magnetic resonance imaging (*A*,*B*). In (*B*), delayed gadolinium enhancement is present in the basal and mid-regions of the right ventricle free wall and the right atrium. In (*C*), tissue-Doppler velocities of the basal anterolateral wall showing absence of atrial mechanical contractions. RV EDV, right ventricular end-diastolic volume; BSA, body surface area.

(Supplemental *Figure*). A dual-chamber pacemaker implantation was planned, but no adequate atrial position could be found. Acceptable pace/sense thresholds were ultimately obtained with His-bundle pacing (*Figure 1C*). Recently, the general condition is slowly deteriorating, and non-sustained ventricular tachycardias were noted. VO_2 max was 18 mL/min/kg (37% of predicted). Referral for heart transplantation is postponed based on the patient's explicit wish.

Familial WES was performed in the patient and his parents, revealing a hemizygote missense variant [NM_005681.4: c.407T>C, p.(Ile136Thr); variant of unknown significance] in the *TAF1A* gene. This amino acid is strongly conserved across vertebrate species, has not been previously reported in the literature, and was only found once in the 250 710 alleles in gnomAD (http://gnomad.broadinstitute.org/). In addition, a 1.62 Mb sized deletion was identified on chromosomal region 1p36.33, which contains the *TAF1A* gene. This loss-copy number variant was transmitted through the father, whereas the proband inherited the missense variant from his mother (*Figure 4*, both with normal cardiac phenotypes). According to these genotype–phenotype relations, we conclude that this progressive AV electrical, mechanical, and structural cardiomyopathy is based on defective ribosome biogenesis owing to the compound heterozygosity of genetic variants in *TAF1A*.

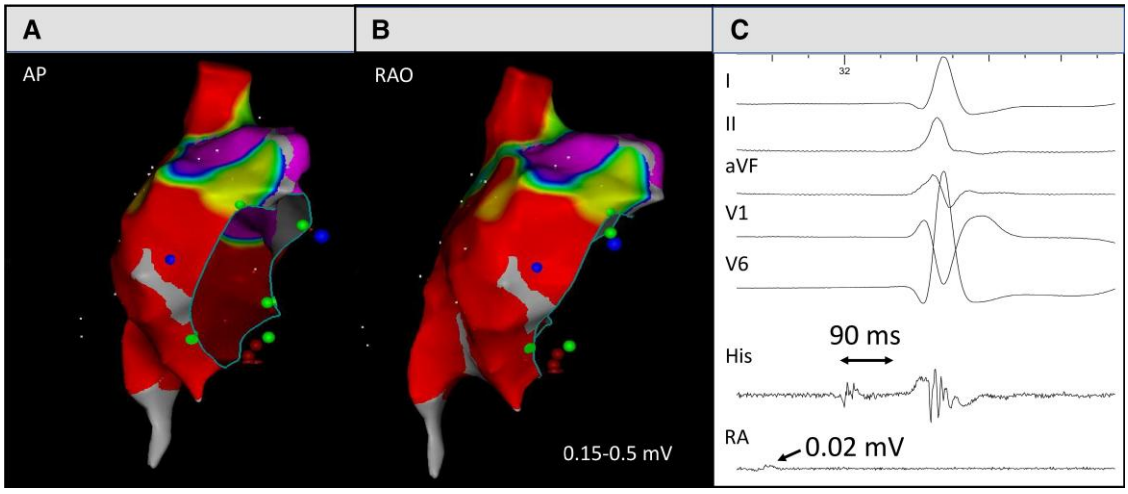

Figure 3 Electroanatomical map of the right atrium in anteroposterior (*A*) and right-anterior oblique (*B*) view demonstrating a large area of low voltage. The superior right atrium is relatively spared. In (*C*), invasive right atrium and His electrograms recorded 4 years after the initial presentation. His-ventricular interval is prolonged, 90 ms. right atrium voltage was well below 0.15 mV. No atrial capture could be obtained at normal stimulation strength, only at very high output.

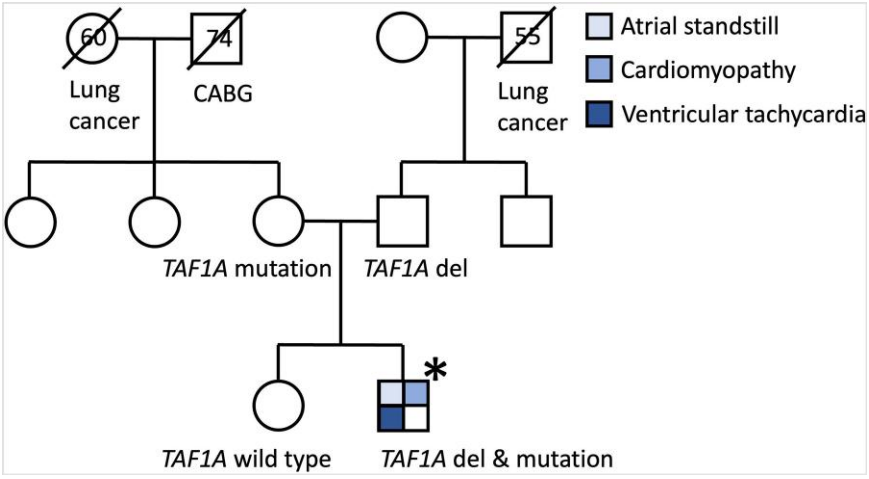

Figure 4 Pedigree of the affected proband (*) carrying both the *TAF1A* missense variant and the deletion due to copy number variant. Both parents with only one affected allele have a normal cardiological phenotype. The sibling, with a *TAF1A* wild type, also has normal cardiac evaluation. CABG, coronary arterial bypass grafting.

Discussion

Juvenile-onset DCM is a rare disease characterized by variable phenotypic expressivity, strong genetic drivers, and often poor cardiovascular outcome. To guide therapeutic strategies and improve outcomes, an in-depth understanding of the pathophysiology is essential. In complex cases, family-based WES with iterative variant filtering may prove valuable to identify (novel) genetic associations. In parallel, thorough clinical phenotyping is crucial for pattern recognition, individualized patient treatment, and tailored monitoring.

We report a patient where premature atrial brady- and tachyarrhythmias and atrial standstill were the presenting clinical features that heralded progressive cardiomyopathic deterioration with AV conduction disturbances. Various inherited diseases have been associated with atrial electromechanical arrest, including loss-of-function *SCN5A* channelopathies, laminopathies, Fabry's disease (alpha-galactosidase A), X-linked and autosomal dominant Emery–Dreifuss muscular dystrophy, and familial Ebstein's anomaly.[7,8] Similar to our patient, atrial involvement is often not exclusive, but merely a sentinel event that should raise alertness for emanating DCM. Besides clinical vigilance, advanced

heart failure therapies should be instigated timely. Anticoagulation to prevent thromboembolic sequelae including stroke is reasonable since atrial standstill is procoagulatory.[9] Not seldomly, symptomatic bradyarrhythmias or ventricular arrhythmias emerge, necessitating a cardiac implantable electronic device potentially with the option of resynchronization (in our case His-bundle pacing) or defibrillation therapies. Severe atrial electromechanical dysfunction may preclude atrial lead placement.

Familial-based WES uncovered the presence of both a missense variant and a copy number variant deletion in the *TAF1A* gene in the patient. The *TAF1A* gene encodes the TATA box-binding protein associated factor 1A that is involved in the recruitment of RNA polymerase I to ribosomal DNA promoters, the essential first step in ribosome biogenesis. Compound heterozygous recessive mutations in *TAF1A* (c.251T>C, p.(Leu84Ser) and c.1021G>A, p.(Gly341Arg)) have recently been associated with pediatric biventricular DCM with marked fibrosis, early cardiac transplantation, stroke, and sudden cardiac death.[5] Histopathology demonstrated gene-specific nucleolar segregation defects in cardiomyocytes, indicating impaired rRNA synthesis.[5] This phenotype was nicely recapitulated in a homozygous knockout zebrafish model by the same group. As ribosomes are essential regulators of growth and metabolism,[10] it is not surprising that the genes involved in the ribosome biogenesis are highly conserved across species[11] and pathogenic mutations were deemed incompatible with life. Indeed, these multicomponent molecular machines synthesize all cellular proteins upon translating messenger RNA (mRNA). Recently, ribosomopathies have been increasingly recognized as inherited diseases with an intriguing tissue-selective expression (despite its omnipresence).[11] They are associated with early-onset disease due to tissue hypoproliferation, haematological defects,[12] and increased oncogenesis in adulthood.[13] Our patient with compound heterozygous *TAF1A* genetic architecture (and the absence of other overt organic defects) portrays a cardiac-specific expressivity with initial atrial standstill and arrhythmias progressing towards an (predominantly right-sided) end-stage DCM. New therapeutic avenues may be available for treating patients with cardiac manifestations of ribosomopathy.[14]

Lead author biography

Dr. Rachel ter Bekke is a clinical–experimental cardiologist–electrophysiologist with a subspecialty in cardiogenetics. She is fascinated by genetics and multimodality image integration to investigate arrhythmia formation and to tailor (non) invasive treatment in the structurally normal and diseased heart.

Supplementary material

Supplementary material is available at *European Heart Journal – Case Reports*.

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Consent: The authors confirm that written consent for publication of this case report, including images and text, has been obtained from the patient in line with COPE guidance.

Conflict of interest: None declared.

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Data availability

The data underlying this article are available in the article and in its online supplementary material.

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