Magnetic Resonance Imaging Characteristics in Carvajal Syndrome (Variant of Naxos Disease)

Maria Prompona, MD; Rainer Kozlik-Feldmann, MD; Josef Mueller-Hoecker, MD; Maximilian Reiser, MD; Armin Huber, MD

Naxos disease is an autosomal recessively inherited familial syndrome that is characterized by woolly hair, palmoplantar keratoderma, and a cell adhesion cardiomyopathy, specifically an arrhythmogenic right ventricular dysplasia. This cardiocutaneous syndrome was first reported in the Hellenic island of Naxos. Cases also have been reported in other Hellenic islands, as well as in Turkey, Israel, and Saudi Arabia. Apart from a small minority that show woolly hair and a few ECG or echocardiographic abnormalities not fulfilling the criteria for arrhythmogenic right ventricular dysplasia/cardiomyopathy, heterozygotes display normal phenotype. A variant of Naxos disease, reported as Carvajal syndrome, has been described in families from India and Ecuador. Clinically, it presents with the same cutaneous phenotype and predominantly left ventricular involvement.

A 2-bp deletion in the plakoglobin gene has been identified as the cause of Naxos disease. In Carvajal syndrome, 2 different mutations of the desmoplakin gene have been found as causative genes. These mutations in genes encoding desmosomal proteins cause defects in the linking sites of these proteins and consequently can interrupt the contiguous chain of cell adhesion, particularly under conditions of increased mechanical stress or stretch, leading to cell death, progressive loss of myocardium, and fibrofatty replacement.

The affected members of both syndromes have woolly hair at birth, whereas palmoplantar keratoderma appears during the first year of life, when infants start using their extremities. In Naxos disease, the cardiomyopathy clinically manifests in adolescence. Patients may develop progressive heart disease involving the right or both ventricles. Symptoms of right heart failure are found in the final stages when the right or both ventricles are severely affected. In Carvajal syndrome, on the other hand, heart disease becomes clinically apparent earlier during childhood as dilated cardiomyopathy. Fifty percent of affected patients develop heart failure, and most of them die during adolescence.

ECG abnormalities in Naxos disease included inverted T waves in leads V1 through V3 or across the precordial leads, QRS complex prolongation in leads V1 through V3, epsilon waves, and complete or incomplete right bundle-branch block. Low voltage and/or flat T waves in left precordial leads were observed mostly in severe right or biventricular involvement. In the Carvajal syndrome, common ECG findings were low voltage and intraventricular conduction defects. T-wave inversion in V1, V2, or V3, or extended to V5, also was observed.

In Naxos disease, cardiac histology reveals the characteristic loss of the right ventricular myocardium with fibrofatty replacement. Cardiac histology of the Carvajal disease shows areas of extensive myocardial loss and replacement with fibrosis that is very similar to arrhythmogenic right ventricular dysplasia/cardiomyopathy pathology but without the fatty component.

We report the case of a 12-year-old boy who was admitted to our clinic with a known dilative cardiomyopathy and who presented palmoplantar keratosis from 2 years of age and woolly hair from infancy (characteristic triad) (Figures 1 and 2). The patient’s younger brother with the same phenotype also was diagnosed with dilated cardiomyopathy and had died at 6 years of age probably as the result of a cardiac arrhythmic incident. The postmortem cardiac histology revealed multifocal interstitial fibrosis compatible with dilated cardiomyopathy. The remaining living members of the family are healthy and do not present this phenotype. The parents have a second-degree consanguinity (first cousins). The family originates from the city Giresun of Tirebolu near Azerbaijan.

The molecular genetic investigation of the patient’s DNA revealed a homozygote mutation of the desmoplakin gene (2-bp deletion of exon 23). Chest x-ray showed enlargement of the cardiac silhouette with a prominent right or left ventricle contour (Figure 3). The ECG showed sinus rhythm with a heart rate of 77 bpm, right-axis deviation, low voltage in the leads of the extremities, supraventricular and ventricular extrasystoles, and T-wave inversion in leads V2 through V6. No epsilon waves were found. These findings match with the common ECG abnormalities of the Carvajal syndrome (Figure 4). Echocardiographic examination revealed a dilatation of the right and left ventricles with a left ventricular...
ejection fraction of 18% to 20% and biventricular trabecular configuration, predominantly of the left ventricle. Further echocardiographic findings were a grade II tricuspid and mitral valve insufficiency (Figure 5 and online-only Data Supplement Movie IV).

The patient underwent a functional and morphological magnetic resonance imaging (MRI) heart examination. Cine true fast imaging with steady-state precession sequences showed a dilatation of both ventricles and a biventricular trabecular disarray of the myocardium, predominantly left ventricular (Figures 6 through 8 and online-only Data Supplement Movies I through III). An additional finding was hypokinesia of the right and left ventricles. These MRI findings indicate a biventricular noncompaction syndrome. Moreover, the functional MRI showed a reduced left ventricular ejection fraction of 24%. The end-diastolic volume measured 164 mL; the end-systolic volume was 123.5 mL; and the stroke volume was 40.9 mL. Morphological T1-weighted spin-echo images showed a trabecular disarray of both ventricles but no fatty replacement of myocardium (Figure 9). On late-enhancement imaging, a dim contrast enhancement of the interventricular septum was observed, which actually corresponds to a region of fibrosis (Figures 10 and 11). On the basis of the biventricular and predominantly left ventricular involvement of the noncompaction cardiomyopathy and the fibrotic replacement of the myocardium without a fatty component, we assume that the patient is affected by the Carvajal syndrome, a variant of Naxos disease.

Because of the poor clinical condition of the patient, a successful heart transplantation was performed. The histopathological macroscopic analysis of the resected heart showed a prominent trabecular disarray of the myocardium of both ventricles, confirming the morphological MRIs. Microscopic analysis of sections of myocardial tissue showed an increase in interstitial collagen fibers in the myocardium, especially in the interventricular septum, coinciding with the enhancement in the postcontrast MRIs.

This case shows that MRI can contribute to the differential diagnosis of 2 phenotypically similar diseases, Naxos disease and Carvajal syndrome.

**Disclosures**

None.

**References**

Figure 1. Posterior view of the head of our patient with Carvajal syndrome showing the characteristic woolly hair.

Figure 2. Plantar keratoderma of our patient with Carvajal syndrome.

Figure 3. Chest x-ray in posterior-anterior and lateral views showing enlargement of the cardiac silhouette with a prominent right and left ventricle contour and with an automatic implantable cardioverter-defibrillator in the left pectoral area.
Figure 4. ECG showing sinus rhythm, right-axis deviation, low voltage in the leads of the extremities, T-wave inversion in leads V2 to V6, and a single ventricular extrasystole.
Figure 5. Echocardiographic images in the 4-chamber orientation show dilatation of the left and right ventricles and a trabecular disarray predominantly of the left ventricle.
Figure 6. Cine true fast imaging with steady-state precession image in the 4-chamber orientation shows dilatation and a trabecular disarray of both ventricles.

Figure 7. Cine true fast imaging with steady-state precession in the 3-chamber orientation shows a trabecular disarray of the left ventricular myocardium.

Figure 8. Cine true fast imaging with steady-state precession image in the short-axis orientation shows dilatation and a trabecular disarray of both ventricles with the appearance of a noncompaction syndrome.

Figure 9. Short-axis T1-weighted unenhanced spin-echo image shows a trabecular disarray of the myocardium of both ventricles, predominantly of the left ventricle. The absence of hyperintense regions of the myocardium confirms the absence of fatty replacement.
Figure 10. Infrared true fast imaging with steady-state precession image acquired 10 minutes after injection of a gadolinium chelate contrast agent shows a faint enhancement of the interventricular septum (arrow) corresponding to a region of fibrosis.

Figure 11. Representative histological image of the interventricular septum with elastica-van Gieson stain showing the extended fibrosis (red) next to the remaining myocardial tissue.
Magnetic Resonance Imaging Characteristics in Carvajal Syndrome (Variant of Naxos Disease)
Maria Prompona, Rainer Kozlik-Feldmann, Josef Mueller-Hoecker, Maximilian Reiser and Armin Huber

Circulation. 2007;116:e524-e530
doi: 10.1161/CIRCULATIONAHA.107.704742
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2007 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/116/20/e524

Data Supplement (unedited) at:
http://circ.ahajournals.org/content/suppl/2007/11/06/116.20.e524.DC1

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org/subscriptions/