

A unique case of left ventricle apical hypoplasia presenting with a type 1 Brugada ECG pattern and *NEXN* mutation. Are they related?



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Introduction

Left ventricle apical hypoplasia (LVAH) is a rare congenital anomaly characterized by a smaller left ventricle (LV) and a surrounding right ventricle (RV). Only few cases have been described, with quite different clinical presentations. Brugada syndrome (BrS) is, on the other hand, usually assigned at the family of the J-wave syndromes, a spectrum of pathogenic early repolarization predisposing to ventricular arrhythmias. The precise mechanisms of the J-wave syndromes are not entirely clear, but they belong to the biggest group of channelopathies. The electrocardiogram (ECG) is characterized by a right bundle branch block aspect and ST-segment elevation of 2 mm or more (downward-sloping coved-type, followed by a negative T wave for Brugada type 1 pattern or “saddleback” for type 2 and 3) in the anterior precordial leads, classically without evidence of structural heart disease. Only type 1 is diagnostic. ECG can be transient and similar ECG changes can be found in patient without BrS. Controversy remains for the risk stratifications of these patients. Around 20% to 30% of Brugada patients usually carry *SCN5A* mutations responsible for a loss of function of the cardiac sodium (Na) channel alpha subunit ($Na_v1.5$) controlling the I_{Na} (inward Na current). Mutations in the voltage-gated calcium channel are responsible for about another 15% of the cases. Other genes have been associated with BrS, for a total of 18 genes so far.

Case report

A 52-year-old woman presented with a type 1 ECG Brugada pattern (Figure 1A) during clinical assessments for her migraine. Her past medical history included kidney and gall-

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KEY TEACHING POINTS

- Left ventricle apical hypoplasia is a rare congenital heart disease characterized by a spherically truncated left ventricle with the right ventricle wrapped around the deficient apex. Its clinical manifestation can vary significantly.
- The Brugada electrocardiogram (ECG) pattern can also be found in the context of a structural heart disease. Syncopal episodes in patients presenting with a Brugada ECG pattern must be investigated to rule out any significant life-threatening arrhythmias.
- Nexilin has a significant role in plasmatic membrane protein trafficking and T-tubule development in the cardiac cells.
- *NEXN* gene mutations affecting nexilin function seem to have a role in the pathogenesis of some cardiomyopathies and could potentially be involved in ECG alterations, like the Brugada pattern.
- For patients presenting with a Brugada ECG pattern, it might be worth a wider genetics screening, including genes associated with plasmatic membrane development and channel trafficking.

bladder stones. She also mentioned 2 cases of sudden death on her family. Both her father and her paternal grandfather died suddenly in their 60s; neither documentation nor post-mortem evidence was available for either one. She reported few presyncopal episodes, usually related to migraine, and only one syncope, apparently related to an emotional circumstance (husband admitted urgently to a hospital), when she was 24.

An echocardiogram showed a short, spherical LV with normal systolic and diastolic function. The RV was mildly

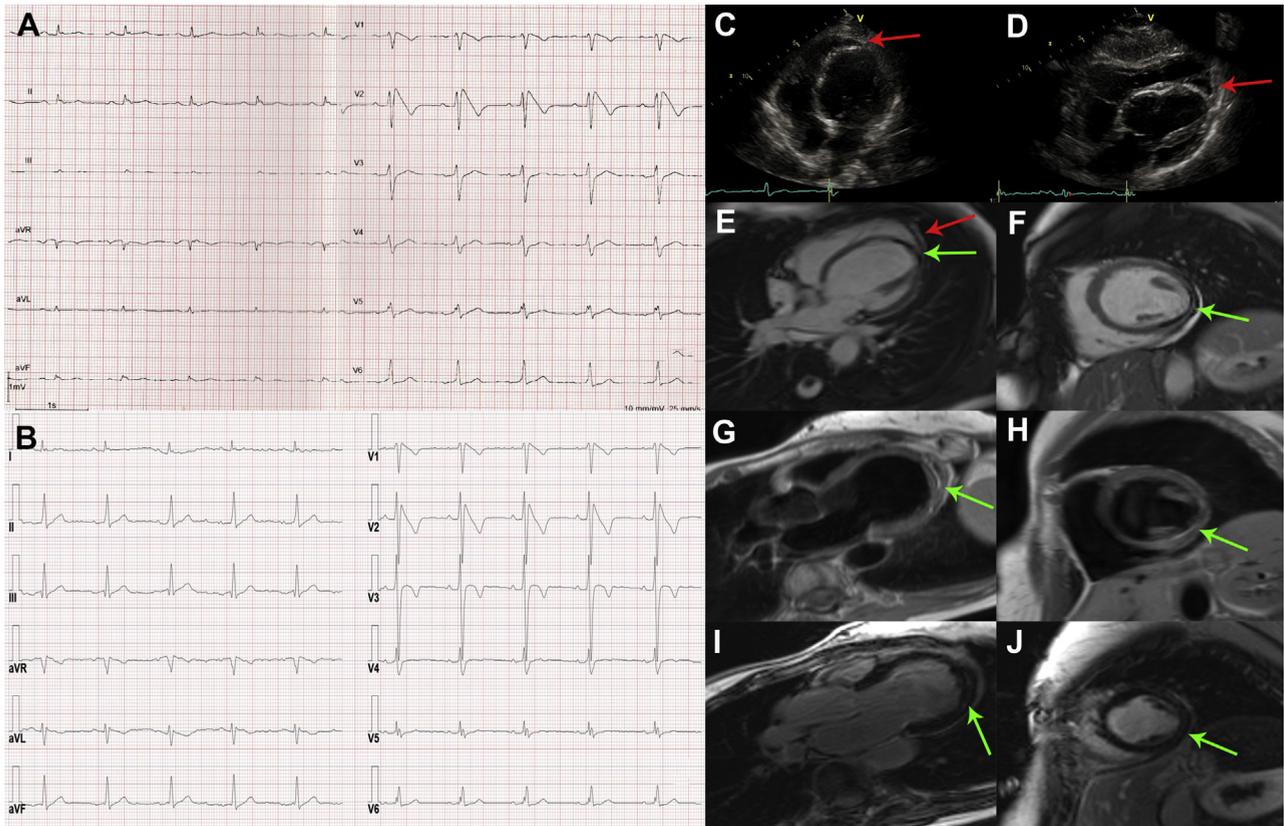


Figure 1 **A:** Electrocardiogram (ECG) on admission showing type 1 Brugada pattern. **B:** ECG after 2 years from first diagnosis. **C,D:** Echocardiogram images showing a mildly dilated, elongated right ventricle (RV) surrounding the left ventricle (LV) apex (red arrows). **E,F:** Long- and short-axis steady-state free precession sequences on cardiovascular magnetic resonance showing a spherical configuration of the LV, with a truncated, thinned apex and rightward bulging of the interventricular septum. The RV was elongated and surrounding the LV apex (red arrow). The “India ink” artifact identified a fat replacement area at the mid-lateral wall and LV apex (green arrows). **G,H:** Long- and short-axis tissue characterization with black-blood T1-weighted sequences showed areas of fatty replacement at mid-lateral wall and LV apex (green arrows). **I-L:** Long- and short-axis late gadolinium enhancement was detected in the same areas of fatty replacement, but with a smaller extension (green arrows).

dilated, elongated, and encompassing the LV, with doubtful focal aneurysms at the free wall (Figure 1C and 1D). Owing to this possible minor diagnostic criterion for arrhythmogenic right ventricular cardiomyopathy (ARVC), a cardiovascular magnetic resonance (CMR) was performed using a 1.5-T scanner (Siemens Avanto, Erlangen, Germany) before and after gadolinium infusion. On ECG-triggered steady-state free precession sequences, CMR confirmed a spherical configuration of the LV, with a truncated, thinned apex; rightward bulging of the interventricular septum; anteroseptal papillary muscle originating from the apex; hypokinesia of LV mid-lateral wall; and akinesia of the apex. The RV showed normal dimensions, kinesis, and function. It was elongated and surrounding the LV apex (Figure 1E and 1F). Tissue characterization with black-blood T1-weighted sequences showed areas of fatty replacement at the mid-lateral wall and apex of the LV (Figure 1G and 1H). Late gadolinium enhancement was detected in the same areas of fatty replacement, but with a smaller extension (Figure 1I and 1L). CMR findings did not support a diagnosis of ARVC or other common cardiomyopathies. These appearances were suggestive for a deficient apical development and supported the

diagnosis of isolated LVAH. A coronary angiogram showed no coronary lesions, ruling out any relevant ischemic issue.

For a better stratification of arrhythmic risk, we performed a 24-hours-ECG Holter monitoring and an exercise test. No ventricular arrhythmias were detected. An invasive electrophysiological study with programmed ventricular stimulation (drive of 600 ms and 400 ms up to 3 extrastimuli from the RV apex and RV outflow tract) did not induce ventricular arrhythmias; it showed slightly prolonged intranodal conduction (AH) with normal His-Purkinje (HV) interval (AH 155 ms, HV 35 ms; Figure 2B). Right and left ventricular endocardial mapping (EnSite Velocity; St. Jude Medical, St. Paul, MN) with unipolar (cut-off for normal voltages 8.3 mV) and bipolar voltage mapping (cut-off for normal voltages 1.5 mV and dense scar below 0.5 mV) showed normal figures at the RV and a small low-voltage area at the LV posterolateral wall, consistent with the CMR findings (Figure 2C and 2D).

Genetic tests for BrS did not detect any of the 18 already known gene mutations, but a new heterozygous mutation in the *NEXN* gene was found (NM_144573.3; c.1582 G>C; p.E528Q).

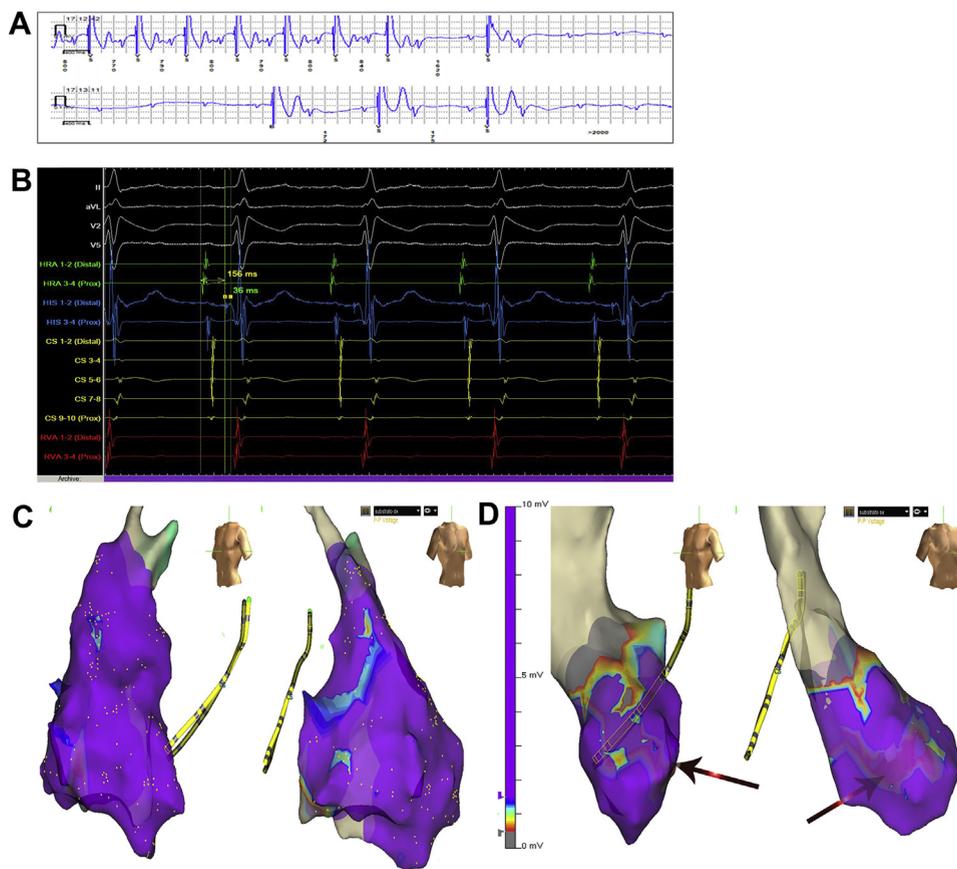


Figure 2 A: Internal loop recorder recording during a syncopal episode showing a high degree of atrioventricular block. B: Invasive electrophysiological study showing AH of 156 ms, HV of 36 ms. C,D: Right (C) and left ventricle voltage map (D), showing a small area of low voltage on the posterolateral wall of the left ventricle (arrows).

We performed ECGs on her relatives (mother, 2 sisters, and one paternal uncle), but no ECG Brugada pattern was noticed. No genetic tests were carried out on them because of patient preference.

An internal loop recorder (ILR) was implanted to assess any arrhythmias. After 30 months, no significant ventricular arrhythmias have been detected; in correspondence with 2 syncopal episodes during abdominal pain owing to new gallbladder stones, transient advanced atrioventricular block (Figure 2A) was detected.

The patient is currently asymptomatic, with no sign of heart failure or evidence of life-threatening arrhythmias. The ECG has varied slightly but the Brugada type 1 pattern remains stable (Figure 1B). The echocardiogram is still comparable, showing no further evolution of her congenital anomaly.

Discussion

A spontaneous type 1 Brugada ECG pattern is considered pathognomonic by itself.

The presence of structural abnormalities is not universally accepted as part of this syndrome. Review of the literature demonstrates scientific evidence that ARVC and Brugada pattern may overlap in some patients. In fact, cases with

structural abnormalities consistent with ARVC and electrocardiographic Brugada pattern were reported.^{1,2} CMR studies led to identification in Brugada patients of some structural features consistent with ARVC, such as larger RV outflow tract area, increased RV end-systolic and inflow tract diameters, occasional fatty infiltration, or RV wall motion abnormalities.^{3,4} In our case, there are not sufficient diagnostic criteria for ARVC⁵; although initially echocardiography seemed to substantiate this hypothesis the CMR findings ruled out the diagnosis.

The peculiar morphology of the patient's LV, with the apex almost replaced by the RV, oriented to a diagnosis of LVAH.

LVAH is a rare isolated congenital abnormality, characterized by a truncated and spherical LV configuration with rightward bulging of the interventricular septum, deficiency of myocardium within the LV apex, adipose tissue infiltration, origin of anteroseptal papillary muscle in the flattened anterior apex, and elongation of the RV wrapping around the deficient LV apex. The etiology is unclear. It was first described in 2004 in a case report.⁶ Only few cases have been reported so far. Clinical presentation varies from absence of symptoms to life-threatening conditions. Initial signs and symptoms of LVAH can be chest discomfort, arrhythmias, murmurs, dyspnea, and heart failure. None of

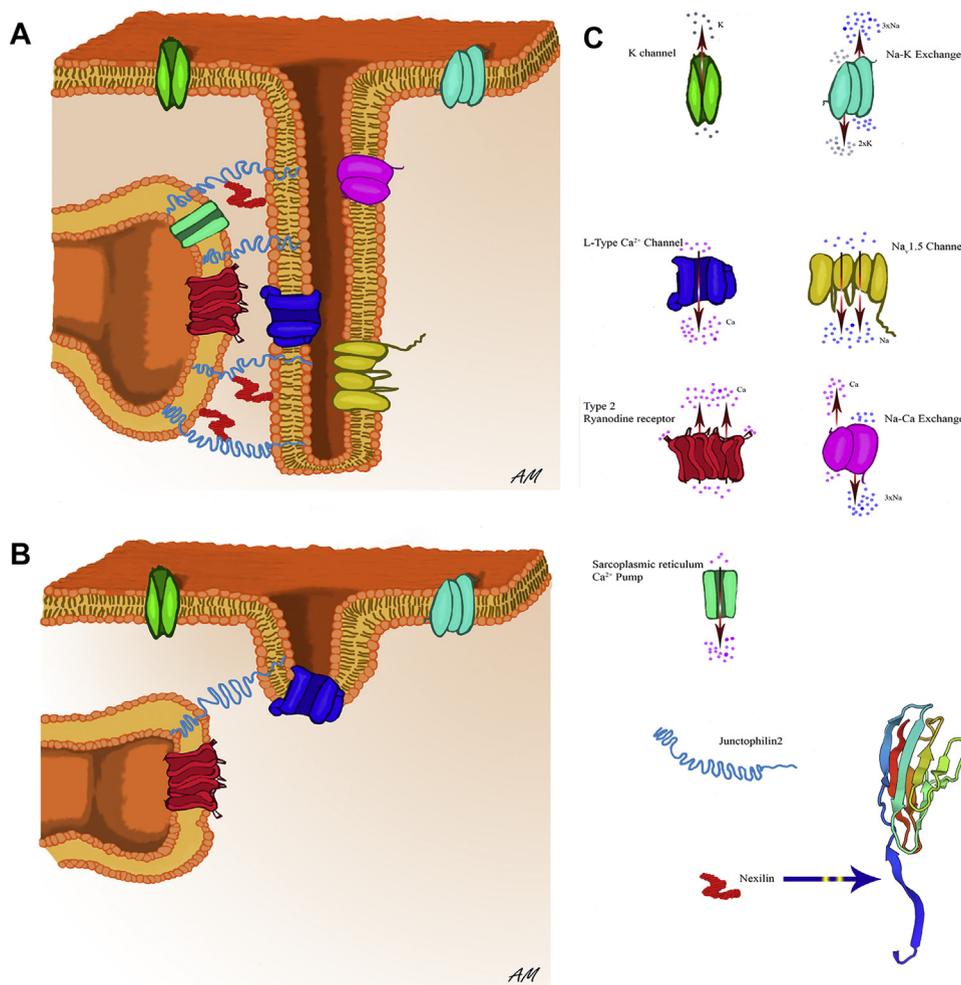


Figure 3 A: Normal T-tubule development in the context of normal nexilin protein function and normal ion channels distribution in the membrane. B: A smaller T-tubule with a reduced distribution of channels when nexilin is absent because of *NEXN* mutation. C: Ion channels involved, their function and the three-dimensional model of nexilin at the bottom.

the cases reported exhibited type 1 Brugada pattern or had evidence of ventricular arrhythmias.

To evaluate the possible risk of sudden cardiac death in our patient, who combines Brugada pattern and LVAH, a careful clinical and electrophysiological evaluation was performed. Both her father and grandfather died in their 60s, but no documentation was available, reducing the strength of these clinical features as predictors of sudden cardiac death. Syncopal episodes were reported, but the ILR did not show any correlation with ventricular arrhythmias. We think that these episodes can be considered vagally mediated (with a strong cardioinhibitory reaction). This unique 30-month follow-up with ILR excluded any form of life-threatening ventricular arrhythmia, suggesting a low arrhythmic risk profile in this patient with LVAH and type 1 Brugada pattern and supporting our decision not to implant an implantable cardioverter-defibrillator to date. The age of the patient and her female sex were considered protective factors, while the negative result of genetic tests for BrS had a neutral value. Regarding the negative predictive value of a normal electrophysiology study, in this clinical setting, there is significant

uncertainty. In fact, the stimulation protocol is still a matter of debate in a nonischemic background (site of ventricular stimulation, number of extrastimuli, etc). Although the predictive value of a negative result is still under discussion, an expert consensus document⁷ reserves implantable cardioverter-defibrillator implant only for asymptomatic patients with life-threatening ventricular arrhythmia induced during this test.

What is remarkable and new in this case is the presence of the *NEXN* mutation. The *NEXN* gene encodes for nexilin, a protein of the junctional membrane complex required for development of cardiac T-tubules.⁸ Transverse-axial tubular system remodeling are well-known features in heart failure. Global and cardiomyocyte-specific loss of *NEXN* in mice resulted in a rapidly progressive dilated cardiomyopathy.⁹ In vivo and in vitro analyses revealed that *NEXN* interaction with junctional sarcoplasmic reticulum proteins, such as junctophilin-2, was essential for optimal calcium transmembrane balance and currents and it was required for initiation of T-tubule invagination and formation. Nexilin is expressed specifically in heart and skeletal muscle and contains 2 N-

terminally located actin-binding domains, a coiled-coil domain, and a C-terminal immunoglobulin superfamily class domain (Figure 3C). One deletion mutation (p.G650 del) and 2 missense mutations (p.P611Y and p.Y652C) in *NEXN* have been found in a large cohort of patients with dilated cardiomyopathy,¹⁰ plus 2 mutations, p.Q131E and p.R279C, have been identified in Chinese patients with hypertrophic cardiomyopathy. The differences in the location of mutations identified in the 2 cohort studies may implicate that the molecular mechanisms underlying the *NEXN*-related pathogenesis for dilated and hypertrophic cardiomyopathy might be different.¹¹

Another study has recently showed a novel *SCN5A* variant (p. Asp197His) in a family with significant segregation in individuals affected with progressive sinus and atrioventricular nodal disease, atrial arrhythmia, dilated cardiomyopathy, and sudden cardiac death. The monozygotic twins of the family also shared a co-occurring *NEXN* mutation (p. Glu757), showing a likely pathogenic trait for the *SCN5A* variant with an additional role for the *NEXN* variant in combination.¹²

Molecular mechanism studies are pending, but looking at the role of the nexilin on T-tubule development, a loss of function can reduce the surface of the plasmatic membrane and impair the proteins and channels trafficking towards the membrane, reducing the ion channel numbers and function and therefore modifying the ion currents (Figure 3A and 3B). This could bring to the phenotype Brugada-like and different forms of cardiomyopathy, as already shown in several studies.

Clearly more research needs to be done to assess a true possible role of *NEXN* mutations, not only as a cause of structural heart disease but also its possible role on the panel of genes responsible for BrS.

To date, 18 genes have been implicated in BrS pathogenicity, but only *SCN5A* shows a significant contribution to the disease. Extreme caution must be used when interpreting rare genetic variants. More than two-thirds of clinically diagnosed Brugada remains elusive, suggesting a high degree of genetic heterogeneity. It is still under discussion whether most of the BrS is a genetically heterogeneous monogenic disorder or a congenital heart defect involving the epicardial right ventricular outflow tract, or even a mixture of monogenic-oligogenic disorders.

Conclusion

To the best of our knowledge, this is the first case reporting at the same time isolated LVAH, Brugada ECG pattern, and *NEXN* mutation. It is also the first attempt to stratify the arrhythmic risk in this unique clinical setting.

Our data are consistent with a low risk profile in this patient. We do think a close follow-up is recommended to detect any sign or symptom of possible clinical deterioration, given the lack of knowledge about this uncommon manifestation.

More and focused studies need to be done to better clarify the possible relationship among these features.

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