What can a cryptogenic stroke hide in a young patient? Ce poate ascunde un accident vascular cerebral criptogenic la pacientul tânăr?

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Abstract
Introduction: Left ventricular hypertrabeculation is a recently described ventricular phenotype characterized by the alternation of excessive trabeculations with deep intertrabecular recesses that communicate with the left ventricular cavity but not with the coronary circulation.
Case presentation: We report the case of a young patient, recently diagnosed with ischemic stroke, in whom the cardiological assessment revealed the coexistence of left ventricular hypertrabeculation and dilated cardiomyopathy, which pathologies associated with a high risk of embolic events. The treatment administered followed the therapy for chronic heart failure, control of rhythm disorders that might occur, and the prevention of embolic accidents.
Conclusions: The particularity of the case is represented by atypical onset through a complication of the disease in a cardiovascular paucisymptomatic patient. Multimodal imaging corroborated with clinical and anamnestic elements had an essential role in the diagnosis.

Keywords
left ventricular hypertrabeculation, cardiomyopathy, heart failure, ischemic stroke

Rezumat
Introducere: Hipertrabecularea ventriculului stâng reprezintă un fenotip ventricular recent descris, caracterizat prin alternanța de trabeculații excesive cu recesuri intertrabeculare adânci care comunică cu cavitatea ventriculului stâng, dar nu și cu circulația coronariană.
Prezentarea cazului: Prezentăm cazul unui pacient tânăr, recent diagnosticat cu accident vascular cerebral ischemic, la care bilanțul cardiologic a evidențiat coexistența hipertrabeculării de ventricul stâng și a cardimiopatiei dilatative, patologii asociate cu un risc embolic ridicat. Tratamentul administrat a vizat terapia insuficenței cardiace cronice, controlul tulburărilor de ritm care ar putea apărea și prevenirea accidentelor embolice.
Concluzii: Particularitatea cazului prezentat este debutul atipic, printr-o complicație a bolii, la un pacient paucismptomatic din punct de vedere cardiovascular. Imagistica multimodală coroborată cu elementele clinice și anamnestice au avut un rol esențial în diagnostic.

Cuvinte cheie
hipertrabeculare ventriculară stângă, cardiomiopatie, insuficiență cardiacă, accident vascular cerebral

Introduction

According to the European Society of Cardiology, left ventricular (LV) hypertrabeculation, previously known as left ventricular non-compaction, describes a phenotype characterized by the alternation of excessive trabeculations with deep intertrabecular recesses that communicate with the cavity of the LV but not with the coronary circulation.[1,2] The American Heart Association defines LV hypertrabeculation as a form of congenital cardiomyopathy distinguished by the spongy appearance of the left ventricular myocardium (predominantly at the apical level), this being the result of interruption of the normal process of embryogenesis.[3]

Normally, until weeks 5-8 of intrauterine life, the fetal myocardium has a spongy, noncompacted appearance. Subsequently, the process of myocardial compaction begins, progressing from the epicardium to the endocardium and from the base of the heart to the apex. Concurrently, the development of the coronary circulation commences, leading to the involution of the intertrabecular recesses, which are reduced to capillaries.[1,4] Specifically, this defect comprises an epicardial-oriented myocardial layer - compact and an endocardial-oriented myocardial layer - non-compact which contains numerous trabeculae and deep intertrabecular recesses that communicate with the LV cavity.[1] Characteristic is the distribution of trabeculations at the level of the apex, lateral, anterior, and posterior wall but very rarely at the level of the interventricular septum.

The most recent classification of this pathology encompasses primary and congenital forms as well as secondary, acquired forms.[4] Familial forms often exhibit autosomal dominant transmission, with documented mutations in sarcomeric, mitochondrial, or

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cytoskeletal protein synthesis genes. Notably, the Laminin A/C mutation is associated with progression to dilated cardiomyopathy (DCM).[1,4,11] Physiological LV hypertrabeculation can be observed in young athletes or during pregnancy, both resulting secondary to LV remodeling.[2,3,12] The pathological form has been described in neuromuscular and hematological pathologies or as a side effect of the chemotherapy treatment used in malignant hemopathies, such as anthracyclines or mitoxantrone.[1,13]

Case Presentation

We present the case of a 46-year-old male patient, a smoker without a personal pathological history or chronic treatment at home but with a family history of cardiovascular diseases. His father, who had no previously documented cardiovascular pathology, passed away at the age of 47 due to cardiac arrest.

The patient presented at the emergency room with a severe motor deficit in the left hemibody and dysarthria, symptoms that suddenly appeared. The cerebral CT examination revealed an ischemic stroke in the territory of the right middle cerebral artery (MCA) and multiple old cerebral infarctions (Figure 1). Consequently, he was admitted to the Neurology Clinic, where thrombolysis with alteplase was administered approximately three hours after the onset of neurological symptoms. The patient's condition slowly improved, showing a slight regression of the motor deficit but with the persistence of speech disorders.

After the neurological emergency was resolved, the patient was referred to the Cardiology Clinic, experiencing dyspnea during moderate exertion and pronounced fatigue, symptoms that had insidiously started a month ago. The physical examination revealed a conscious, cooperative, time-spatially oriented patient, hemodynamically and respiratory stable and dysarthric with facial asymmetry and motor deficit on the left side of the body. The clinical examination objectified tachycardic heart sounds, a holosystolic murmur of 3/6 at the mitral focus, BP - 105/70 mmHg, HR - 103/min, and slight bilateral leg edema.

The blood examination revealed a discrete inflammatory syndrome (CRP-1.8 mg/dl), GFR - 107 ml/min/kg m2, NTproBNP - 5489 pg/ml, and concerning the lipid profile - total cholesterol 185 mg/dl, LDL-cholesterol 137 mg/dl, HDL-cholesterol 44 mg/dl and triglycerides 97 mg/dl. Considering the slight increase in CRP, urine cultures and blood cultures were collected, both of which yielded negative results. We attributed this slight CRP elevation to the stroke, especially considering the CRP value of 8 mg/dl upon admission to the Neurology Clinic.

The electrocardiogram (Figure 2) showed sinus tachycardia at 110/min, first-degree atrioventricular block, and negative T waves in V5-V6. To rule out a paroxysmal rhythm disorder, Holter ECG monitoring was conducted, revealing sinus rhythm throughout the examination, an average ventricular rate of 82/min, and the presence of rare ventricular and supraventricular extrasystoles, predominantly isolated.

The Doppler ultrasound examination of carotid arteries indicated the presence of small atheroma plaques at the bifurcation of the left common carotid artery and bilaterally on the internal carotid arteries in the initial portion but without hemodynamic impact. Additionally, normal flow was observed in the bilateral vertebral arteries.

Transthoracic echocardiography (TTE) showed a dilated left ventricle (TDDLV-71 mm, TSDLV-60 mm) with a globular appearance and a wall thickness of 8 mm at the IVS level and 10 mm at the LVPW level (Figure 3). Additionally, severe systolic dysfunction with global hypokinesia was indicated by a left ventricular ejection fraction (LVEF) of 25%. Notably, important trabeculations (>3) were observed at the LV apex and along the entire length of the lateral wall with a ratio of trabeculated area/normal myocardium measuring 13 mm/7 mm=1.85 (Figure 4). The examination also identified left atrial dilatation (LA volume – 76 ml) and moderate mitral regurgitation secondary to mitral annulus dilation (Figure 5). The regurgitation jet was centrally oriented, occupying 30% of the LA area with vena contracta measuring 5 mm, effective regurgitant orifice area of 0.28 cm^2, and regurgitant volume of 43 ml/beat. Furthermore, a restrictive diastolic dysfunction - grade 3 was described (E=135 cm/sec, A=60 cm/sec, septal e'=2 cm/sec, septal s'=4 cm/sec, septal a'=10 cm/s, E/A=2,26, E/e' septal=67,5, lateral e'=4 cm/sec, E/e' medium=45) and attributed to hypervolemia, moderate mitral regurgitation, increased pressure in the LA, and severe LV systolic dysfunction. Withal, TTE revealed a trileaflet aortic valve (AV) with a maximum gradient of 8 mmHg (V max 1.4 m/s), an AV annulus diameter of 23 mm, an ascending aorta diameter of 31 mm, and an aortic arch diameter of 29 mm without aortic regurgitations or stenosis. The right heart cavities had normal dimensions with mild tricuspid regurgitation and a transvalvular gradient of 19 mmHg without echocardiographically detectable intracavitary masses or pericardial fluid.

To exclude other causes of stroke, transesophageal echocardiography was performed, revealing the absence of thrombi in the cardiac cavities, intact septa, and a left atrial appendage without echogenic material suggestive for thrombi. Also, the additional images were not suggestive of vegetations or other formations at the level of the heart valves.

The diagnostic hypothesis of LV hypertrabeculation complicated with DCM was supported by three specific echocardiographic criteria (Chin, Jenni, Stollberger). According to the literature, only 30% of patients present all three criteria. The appearance of the divided myocardium into two layers, associated with a ratio of non-compact/compact > 2.1 (measured in telesystole) is highly suggestive of the cardiomyopathy due to LV hypertrabeculation, according to the criteria of Jenni et al.[1,6] The ratio between the diameter of the compacted layer and the sum of the diameters of the non-compacted and compacted myocardium < 0.5, evaluated in diastole, constitutes the criterion developed by Chin et al.; [1, 6] in the case of the presented patient, this ratio had a value of 0.4. The third criterion, elaborated by Stollberger et al. is suggestive of LV hypertrabeculation in the presence of more than 3 trabeculations at the LV level, visible in the same section.[8, 9]

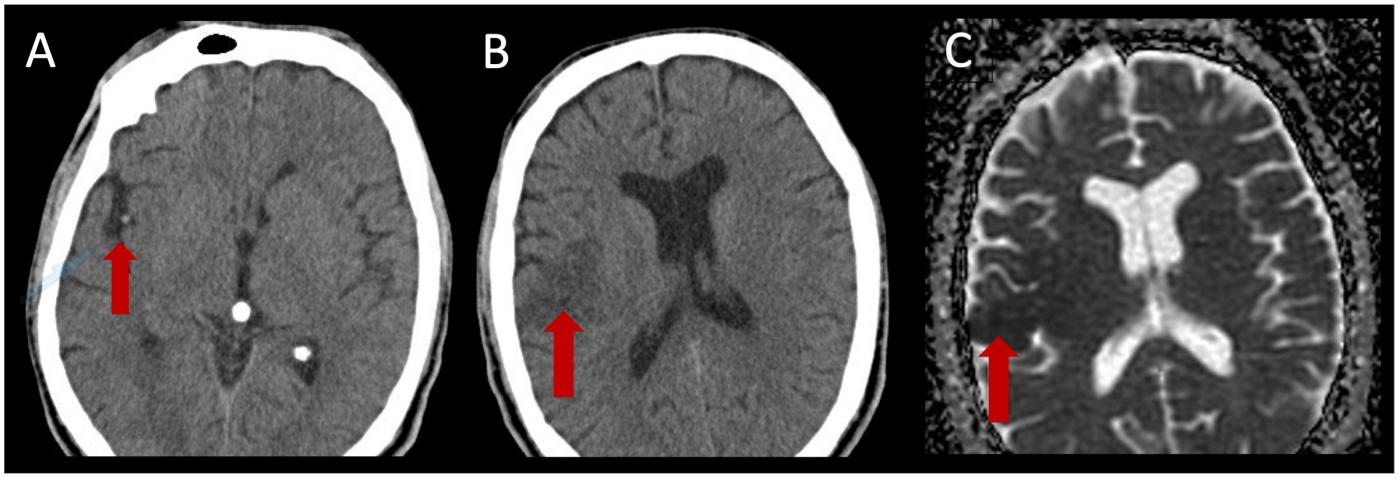


Figure 1. A – Nativ CT cerebral examination: spontaneous hyperdense -aspect of the M3 segment of the right MCA, indicative of acute thrombosis at admission; B - Nativ CT cerebral examination: hypodense area in the right temporo-insular and cortico-subcortical region, which was erasing intergyral grooves and causing loss of differentiation between white and gray matter, consistent with an acute ischemic area in the territory of the right MCA after 24 hours; C – Cranio-cerebral MRI: the diffusion sequence shows hypersignal in the same region, corresponding to hyposignal in the ADC map, characteristic of a recently developed stroke in the territory of the right MCA after 5 days.

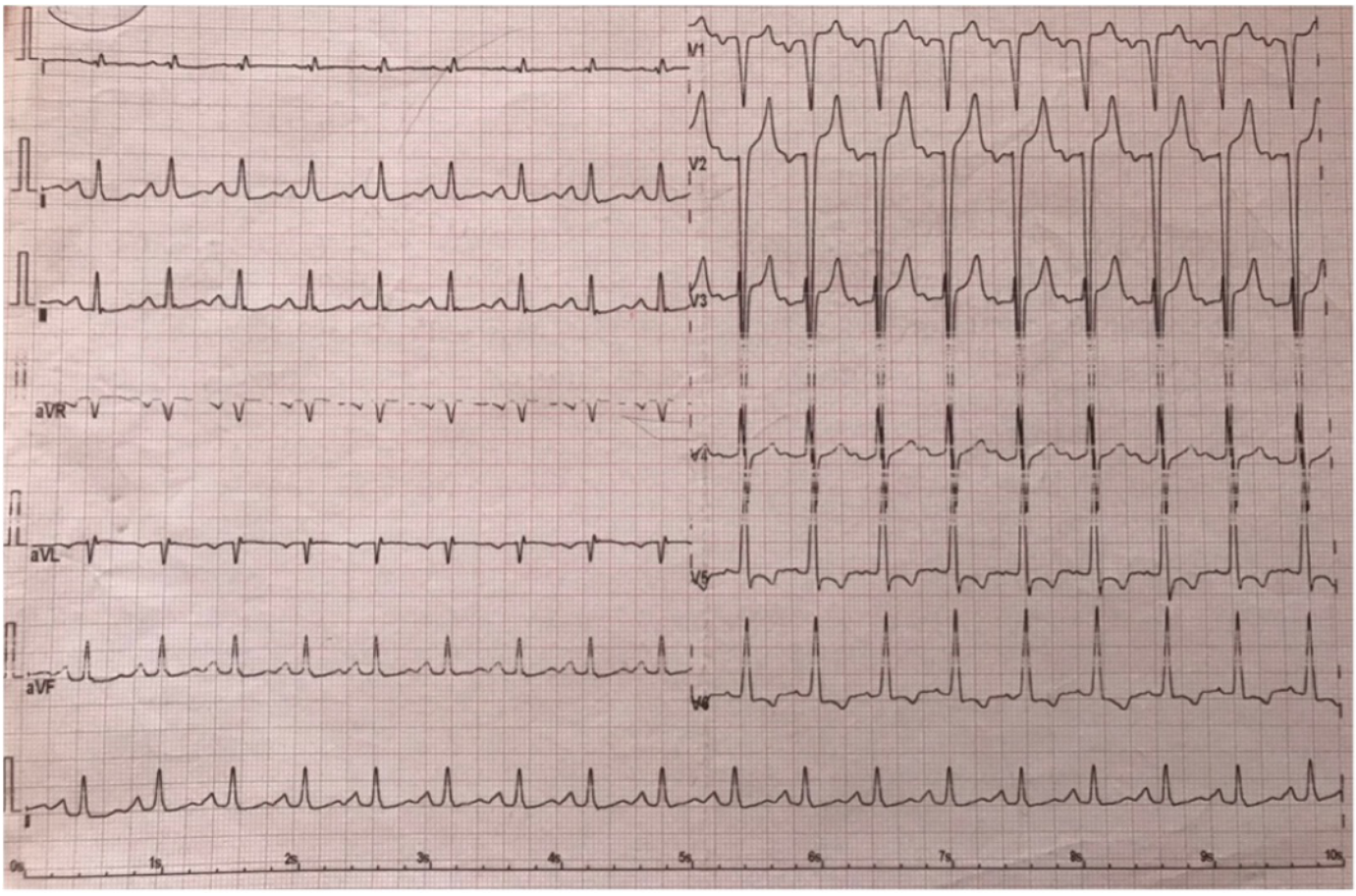


Figure 2 - ECG trace: sinus tachycardia 110/min, left atrial dilatation (evidenced by negative, widened, and deepened P wave in V1), first-degree atrioventricular block, left ventricular hypertrophy (Sokolow-Lyon index-37 mm and left ventricular “strain” pattern).

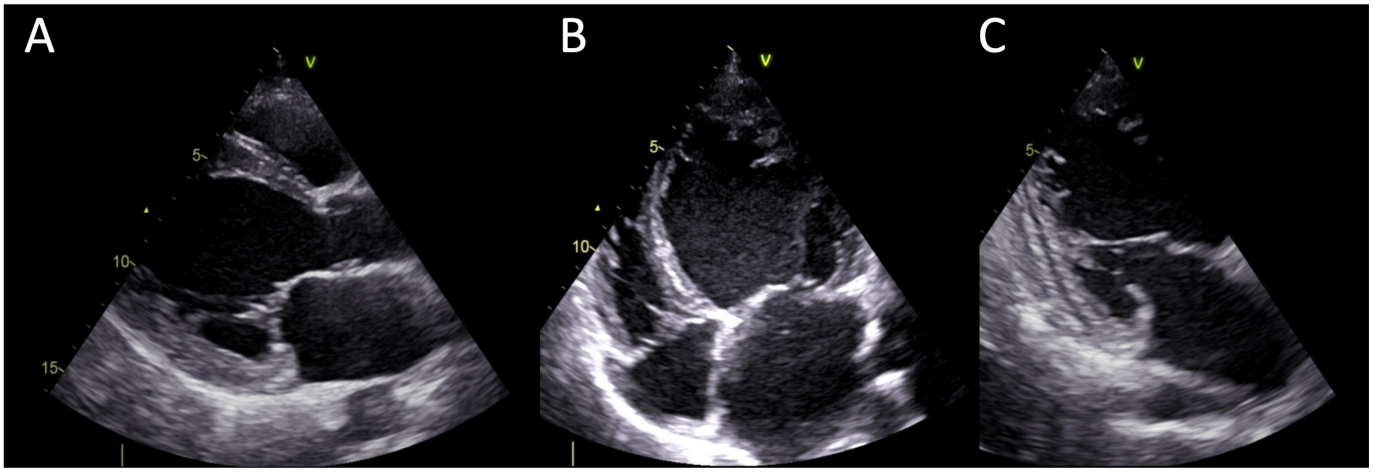


Figure 3 - TTE – A – PLAX – IVS 8 mm and LVPW 10 mm, dilatation of the left atrium and the aortic and mitral valves with normal morphology; B - A4C – dilatation of the left heart cavities and LV hypertrabeculations at the level of the apex and lateral wall; C – A2C –LV hypertrabeculations at the level of the inferior wall and LV apex.

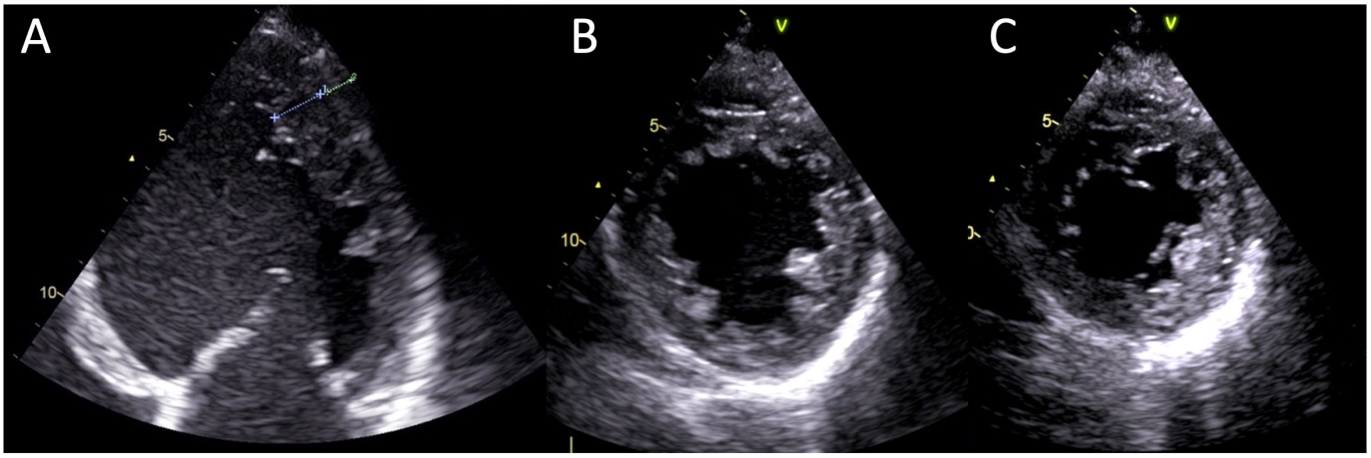


Figure 4 - TTE - A4C - the ratio of trabeculated area/normal myocardium = 1.85; B – Medioventricular SAX – the presence of hypertrabeculation at the level of anterior, lateral, posterior and inferior LV walls; C – Apical SAX – circumferential hypertrabeculation of LV.

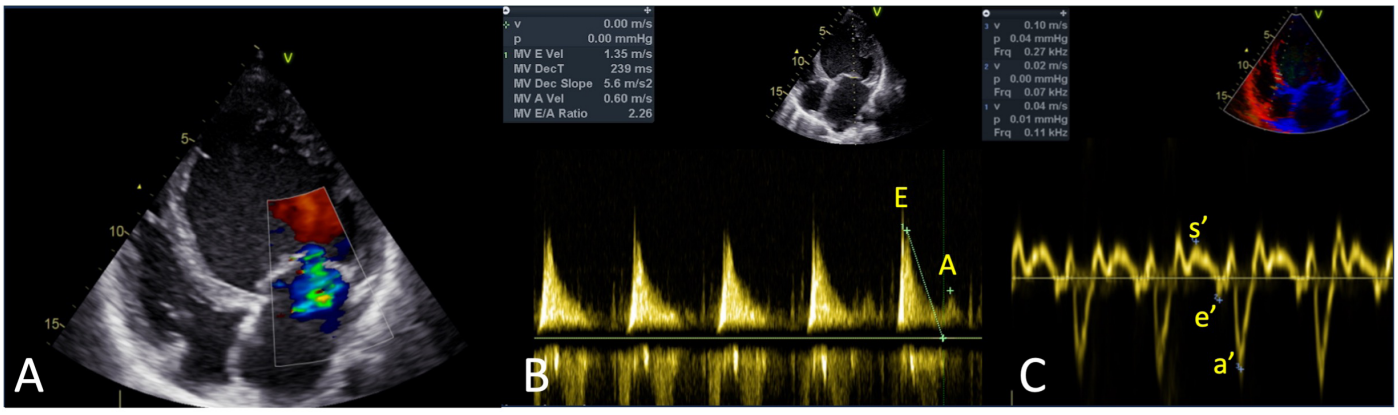


Figure 5 - TTE – A - Colour Doppler A4C – moderate mitral regurgitation secondary to mitral annulus dilatation with the regurgitation jet centrally oriented; B – Mitral PW Doppler A4C- restrictive flow pattern – diastolic dysfunction grade 3 (E=135 cm/sec, A=60 cm/sec, E/A=2,26); C – Septal TDI A4C – restrictive filling pattern (e'=2 cm/s, a'=10 cm/s, s'=1 cm/s, E/e'=67,5).

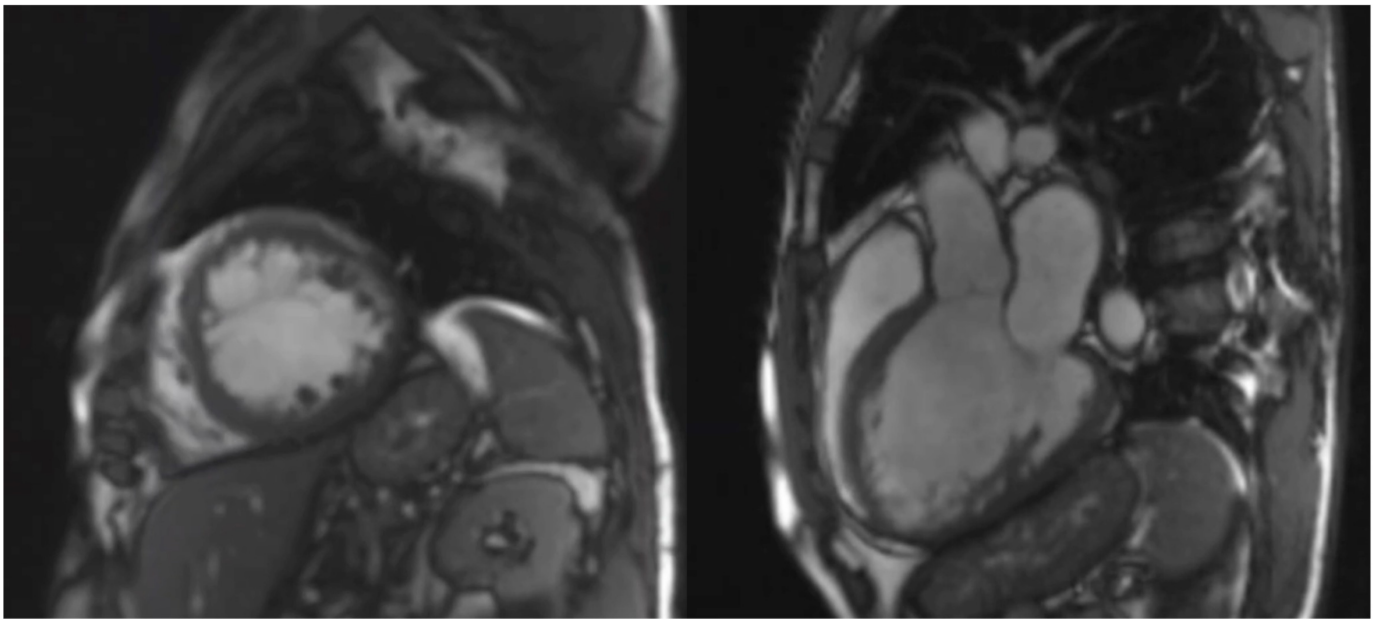


Figure 6 - CMR – A – short axis image of the LV from base to apex at end-diastole, regions of prominent trabeculation at the level of anterior, antero-lateral walls, and infero-laterally in the basal and medio-ventricular segments; B – left ventricular outflow tract section, areas of accentuated trabeculation at the level of apex and lateral wall.

According to the literature data, approximately 29% of patients with LV hypertrabeculation also associate coronary abnormalities.[9] To exclude the ischemic component of DCM, coronary angiography was performed, revealing the following aspects: at the level of the left coronary artery - intact left main stem, the anterior descending and circumflex arteries without atherosclerotic lesions, and the right coronary artery, also without atherosclerotic lesions.

For the optimal characterization of the myocardium in the case of high suspicion of LV hypertrabeculation cardiomyopathy, cardiac magnetic resonance imaging (CMR) with late gadolinium-DTPA capture was performed (Figure 6). The CMR revealed an increased volume of the LV with an LVEF-24.7%, areas of accentuated trabeculation at the anterior, anterolateral, and inferolateral walls in the basal and medio-ventricular segments and circumferentially at the apical segment with a non-compact/compact ratio of 3.04. According to the Petersen criteria, a value of this ratio > 2.3 in diastole is highly suggestive of LV hypertrabeculation.[3]

Another suggestive criterion for the LV hypertrabeculation phenotype, developed by Stacey et al., involves calculating the non-compact/compact ratio at the end of systole, in the parasternal short-axis incidence, which should be at least 2. [1,10] In the presented case, this ratio had a value of 2.7. The mass of trabeculated myocardium, being > 20% of the whole LV mass as illustrated by the criteria developed by Jacquier et al., serves as a sensitive and specific marker for LV hypertrabeculation.[3] In this case, it exceeded 20%. Late gadolinium enhancement (LGE), a marker of myocardial fibrosis, was observed in both the compact and non-compact layers of the myocardium, located at the septal and free ventricular wall levels. This distribution is correlated with an unfavorable prognosis, being associated with an increased risk of major adverse cardiovascular events (MACE).

Therefore, the diagnosis established after the CMR examination was DCM due to LV hypertrabeculation, considering the areas of accentuated trabeculations and the presence of Petersen, Jacquier and Stacey criteria. The distribution of LGE is also highly suggestive for LV hypertrabeculation cardiomyopathy.

It is very important to differentiate between primary forms of LV hypertrabeculation and secondary forms, which can be either pathological or physiological. In the presented case, the imaging differential diagnosis was established by combining the patient's history with clinical and paraclinical data. The entities considered included normal anatomical variants (hypertrabecular LV, aberrant chordae, septomarginal trabeculae), apical hypertrophic cardiomyopathy, apical LV thrombosis, apical cardiac tumors, and apical fibroelastosis.[3]

By collaboratively analyzing the anamnesis, clinical findings, and paraclinical data, the definitive diagnosis for this patient was chronic heart failure (CHF) secondary to DCM with LV hypertrabeculation, a condition that led to multiple ischemic strokes of cardioembolic origin. Currently, there is no specific treatment for cardiomyopathy with LV hypertrabeculation. The therapeutic approach followed the management of CHF, the arrhythmias that may occur in evolution and preventing thromboembolic events. Being a recently diagnosed patient with CHF and reduced LVEF, the pharmacological treatment included the combination of an angiotensin-converting enzyme inhibitor (ACEI), alpha1-beta-blocker, mineralocorticoid receptor antagonist, loop diuretic, and SGLT-2 inhibitor. Considering the increased thrombotic risk, antiplatelet and statin treatment was continued, as recommended by the neurologist in combination with anticoagulant treatment (apixaban).

The clinical and paraclinical progress of the patient was monitored at 1 and 3 months after discharge. Due to the persistence

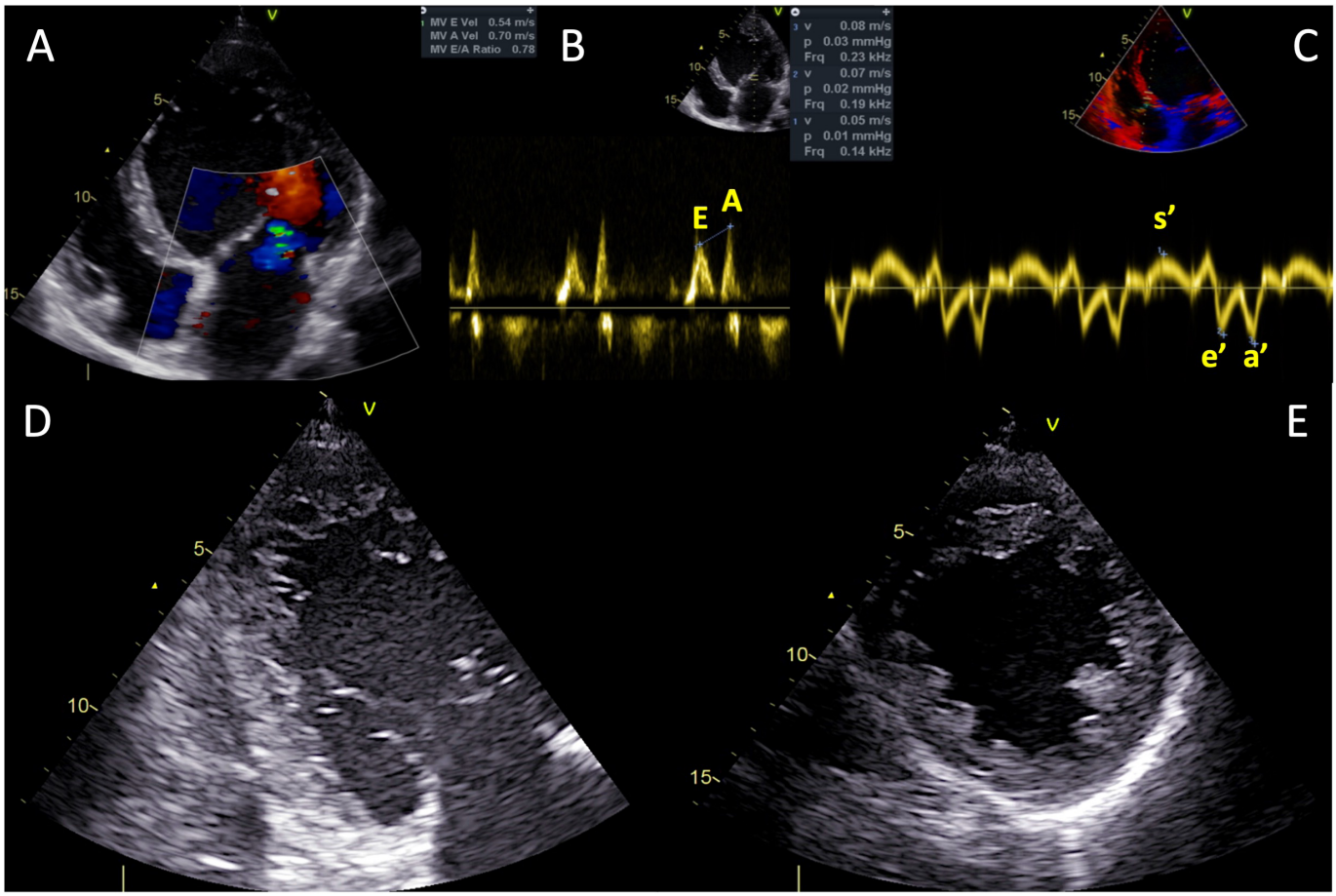


Figure 7 - Follow-up TTE at 3 months – A – Colour Doppler A4C - Dilatation of the left heart cavities is maintained, but mitral regurgitation shows improvement; B – Mitral PW Doppler A4C and C – Septal TDI A4C – diastolic dysfunction grade 1 – impaired relaxation (E=54 cm/sec, A=70 cm/sec, E/A=0.78, septal e'=7cm/sec, septal a'=8 cm/sec, septal s'=5 cm/sec, E/e'=7,7); D – A2C and E – PSAX – trabeculated appearance of LV.

of symptoms, ACEI was replaced with sacubitril/valsartan, and ivabradine was added to the beta-blocker treatment in the maximum tolerated dose by the patient. The subsequent evolution was slightly favorable with the remission of symptoms, increased tolerance for moderate efforts, and a decrease in NTproBNP value (1837 pg/ml). Echocardiography performed at three months revealed the same trabeculated appearance of the LV, improvement of mitral regurgitation and grade 1 diastolic dysfunction (impaired relaxation), and maintenance of LV systolic dysfunction (LVEF - 30%). Additionally, no suggestive images of thrombi or vegetations were observed at the level of the cardiac cavities, and the patient did not experience any thrombotic events during this interval (Figure 7). The ECG performed at 3 months revealed the maintenance of sinus rhythm with a rate of 78/min, first-degree atrioventricular block, and secondary repolarization changes characteristic of left ventricular hypertrabeculation (Figure 8).

Discussion

The first case of LV hypertrabeculation was described in 1932 by Bellet and Gouley after an autopsy performed on a newborn with associated aortic atresia. According to literature data, approximately 4% of patients with LV hypertrabeculation also exhibit aortic valve abnormalities, such as subaortic stenosis and bicuspid aortic valve, highlighting the importance of imaging evaluation for effective management.[14] In the presented case, no congenital defects were observed through the performed imaging studies.

Considering the presence of isolated LV hypertrabeculation, the possibility of a secondary cause of the pathology, such as neuromuscular or hematological diseases (e.g., Cooley's anemia), was considered. According to literature cases, this aspect is found in approximately 30% of patients with Duchenne muscular dystrophy who exhibit dystrophic cardiomyopathy that is secondary to a fragile cytoskeleton leading to a reduction in systolic function.[1,13] However, the absence of facial dysmorphism or clinical signs of myopathy in the patient excluded this hypothesis. Additionally, normal values in the hematological balance ruled out a hemopathy.

In the evolution of this patient group, complications such as worsening LV systolic dysfunction with numerous episodes of CHF decompensation, cardiac arrhythmias due to the fibrotic process and the recurrence of embolic events and sudden cardiac death may occur.

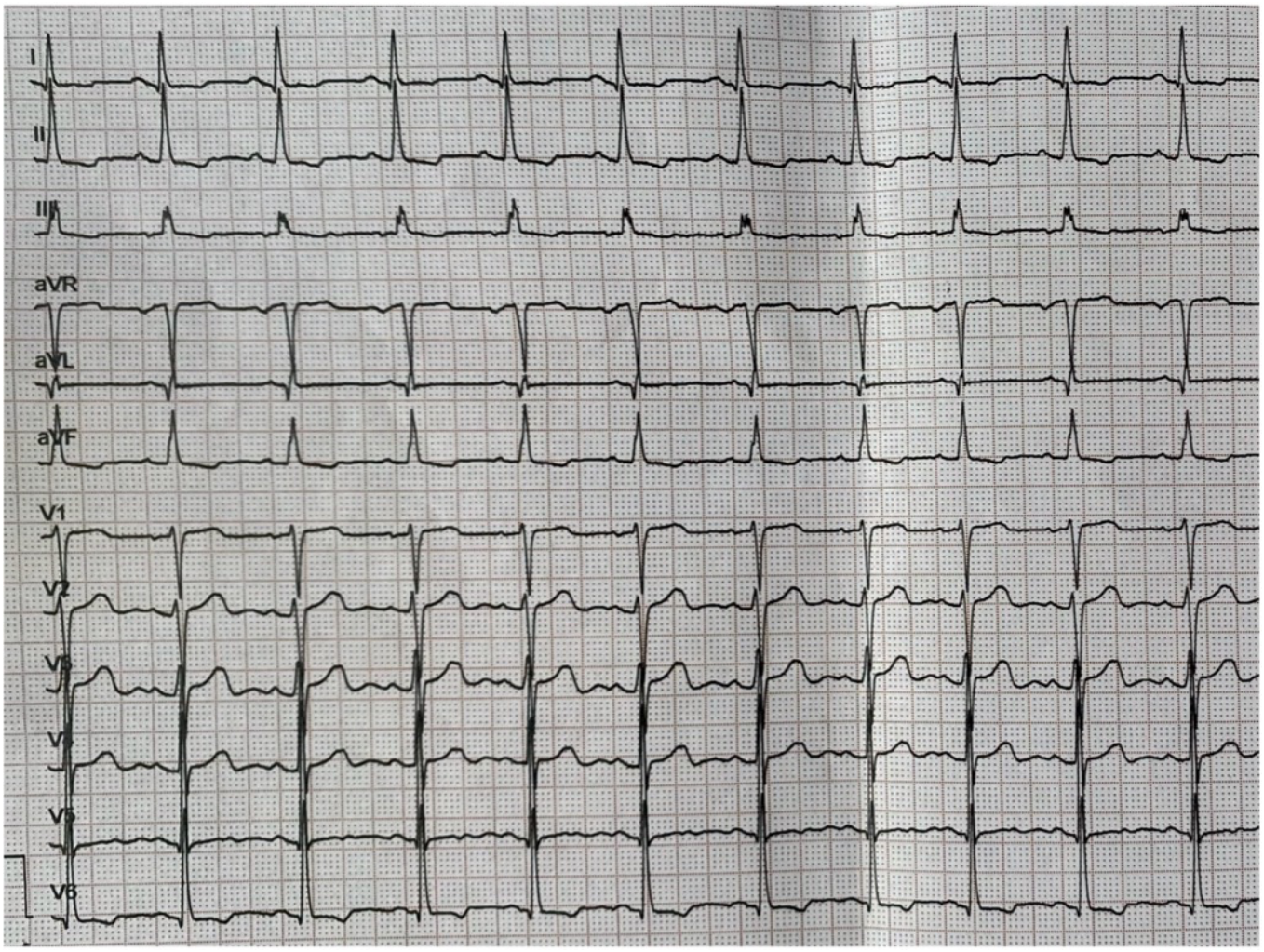


Figure 8 - Follow-up ECG at 3 months: sinus rhythm 78/min, first-degree atrioventricular block (PR 240 msec), left ventricular hypertrophy (Sokolow-Lyon index > 35 mm, and left ventricular "strain" pattern).

According to literature data, LV hypertrabeculation is considered a potentially thrombogenic condition, with the incidence of embolic complications ranging from 5% to 38%. This is attributable to blood clots forming within the lax trabeculated meshwork of the LV, where blood stagnates.[14] There are cited a limited series of cases where the cardiac pathology was unmasked through thromboembolic events in various territories (cerebral, cardiac, splenic, renal, and mesenteric). There are existing controversies about anticoagulant treatment. Given that the patient experienced multiple cerebral embolic events in the context of severe LV systolic dysfunction, we opted for the continuation of anticoagulant treatment in the absence of documented atrial fibrillation.

The particularity of the presented case is the atypical onset through a complication of the disease – ischemic stroke, occurring in a young patient seemingly without thrombotic risk factors and being paucisymptomatic from a cardiovascular standpoint until that moment. In specialized literature, there have been reported a series of cases with LV hypertrabeculation, where over 70% of patients are male and the average age falls within the range of 40-50 years.[15,16] These cases were diagnosed through the same atypical onset, highlighting a notable connection between LV hypertrabeculation and cardioembolic stroke.[15,16]

The prognosis of this patient, in the short term, is favorable due to good therapeutic compliance and lifestyle changes, leading to the improvement of heart failure symptoms. However, in the long term, the prognosis is reserved, burdened by the possibility of complications. Further investigations to be performed include screening the patient's first-degree relatives and genetic testing. The next therapeutic interventions to consider include the implantation of an ICD for the primary prevention of sudden cardiac death (class II A in this patient's case) and enrollment on the heart transplant list.

Conclusions

Although, in the presented case, the patient had a multitude of criteria characteristic of cardiomyopathy due to LV hypertrabeculation, the differentiation between the pathological form of left ventricular hypetrabeculation and the physiological, adaptive forms remains a significant challenge, especially when patients are "borderline" or

asymptomatic. The clinical appearance is often non-specific, making the diagnosis complex. In such cases, a comprehensive diagnostic strategy that includes multimodal imaging, anamnesis, clinical examination, and, if possible, genetic testing is crucial to achieving an accurate diagnosis. The integration of various diagnostic approaches helps in distinguishing between different forms of LV hypertrabeculation and ensures a more precise understanding of the underlying condition.

Conflict of interest

The authors declare no conflict of interest.

REFERENCES

1. Petersen SE, Jensen B, Aung N, Friedrich MG, McMahon CJ, Mohiddin SA, et al. Excessive Trabeculation of the Left Ventricle: JACC: Cardiovascular Imaging Expert Panel Paper. JACC Cardiovascular imaging. 2023 Mar 1 [cited 2023 Mar 14];16(3):408–25.

2. Arbelo E, Protonotarios A, Gimeno JR, Arbustini E, Barriales-Villa R, Basso C, et al. 2023 ESC Guidelines for the management of cardiomyopathies. European Heart Journal. 2023 Aug 25.

2. Albakri A. Left ventricular non-compaction: A review of literature on clinical status and meta-analysis of diagnostic and clinical management methods. Biology, Engineering and Medicine. 2018;3(4).

4. Oechslin E, Jenni R. Left ventricular non-compaction revisited: a distinct phenotype with genetic heterogeneity? European Heart Journal. 2011 Jan 31;32(12):1446–56.

4. Jenni R, Oechslin EN, van der Loo B. Isolated ventricular non-compaction of the myocardium in adults. Heart. 2007 Jan 1;93(1):11–5.

6. Chin TK, Perloff JK, Williams RG, Jue K, Mohrmann R (1990). Isolated noncompaction of left ventricular myocardium. A study of eight cases. Circulation, 82: 507-513.

7. Stollberger C, Finsterer J, Blazek G (2002). Left ventricular hypertrabeculation/noncompaction and association with additional cardiac abnormalities and neuromuscular disorders. Am J Cardiol, 90: 899-902.

8. Stöllberger C, Finsterer J (2004). Left ventricular hypertrabeculation/noncompaction. J Am Soc Echocardiogr., 17: 91-100.

9. Adabifirouzjaei F, Igata S, DeMaria AN. Hypertrabeculation; a phenotype with Heterogeneous etiology. Progress in Cardiovascular Diseases. 2021 Sep;68:60–9.

10. Stacey RB, Andersen MM, St Clair M, Hundley WG, Thohan V. Comparison of systolic and diastolic criteria for isolated LV non-compaction in CMR. J Am Coll Cardiol Img. 2013;699:931–940.

11. Rojanasopondist P, Nesheiwat L, Piombo S, Porter GA, Ren M, Phoon CKL. Genetic Basis of Left Ventricular Noncompaction. Circulation: Genomic and Precision Medicine. 2022 Jun;15(3).

12. Gati S, Rajani R, Carr-White GS, Chambers JB (2014). Adult left ventricular noncompaction: Reappraisal of current diagnostic imaging modalities. JACC Cardiovasc Imaging, 7: 1266-1275.

13. Statile CJ, Taylor MD, Mazur W, et al. Left ventricular noncompaction in Duchenne

muscular dystrophy. J Cardiovasc Magn Reson. 2013;15(1): 67.

14. Abdirahman Ahmed S, Farah Yusuf Mohamud M, Abdullahi Mohamud M. A Young Male Patient with Subaortic Membranous Stenosis and Left Ventricular NonCompaction Cardiomyopathy: A Case Report. Research Reports in Clinical Cardiology. 2021 Nov; Volume 12:53–6.

15. Alrefaee A, Wiseman K, Udongwo N, Sathya B, Demchuk B. Ventricular Noncompaction With Left Ventricular Thrombus: A Case Report. Cureus. 2022 Jun 2.

16. Yacoub HA, Sivakumar K, El-Hunjul M, Cai C, Mehta D. Ischemic Stroke Secondary to Left Ventricular Noncompaction. Journal of Neurology Research. 2019 Jan 1;9(4-5):75–80.