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CLINICAL CHARACTERISTICS OF THE "HOT PHASE" OF ARRHYTHMOGENIC CARDIOMYOPATHY IN A PEDIATRIC PATIENT

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This article describes a rare clinical manifestation of arrhythmogenic cardiomyopathy in a 13-year-old boy - the "hot phase", characterized by severe chest pain and a significant increase on a level of troponin I. The clinical case demonstrates the difficulties of the differential diagnosis of this disease and an importance of an integrated approach to examination of the patient, including cardiac magnetic resonance imaging and genetic testing.

Key words: arrhythmogenic cardiomyopathy; "hot phase"; myocarditis; children; sudden cardiac death; magnetic resonance imaging; troponin I

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Arrhythmogenic cardiomyopathy (ACMP) is a congenital pathology, the clinical picture of which is very diverse: from asymptomatic course to sudden cardiac death (SCD). It should be noted that the concept of the disease has undergone significant changes in recent years. And if at the beginning of the study of nosology it was assumed to be exclusively a disease of the right ventricle (RV), which was reflected in the name of the disease "arrhythmogenic RV dysplasia", the accumulated data on the involvement of both the left and both ventricles in the pathological process prompted the Heart Rhythm Society working group in 2019 to produce updated recommendations for the diagnosis, risk stratification and treatment of this disease and to form a common term - ACMP [1]. Fainting, palpitations, and signs of chronic heart failure (CHF) are the most common in patients [1]. In addition, the early manifestations of ACMP, especially in pediatric patients, may include the so-called "hot phase" manifested by chest pain and release of myocardial enzymes, especially troponin I [2-5].

The term "hot phase" was first used in 2007 by St. Choudhry et al. when describing the clinical picture of the disease exacerbation [2]. Nevertheless, to date, either isolated cases [6] or small cohorts of patients with these symptoms have been described in the literature [2-5, 7-12]. Data from a systematic review conducted by researchers at the University of Padua in 2022, which included 103 patients with a "hot phase" from 9 studies [3], described the recurrent nature of this phenomenon. Thus, in some patients, chest pain with myocardial enzyme release occurred more than once (a maximum of 6 reported episodes). A systematic review noted the predominance of this condition in male patients [2, 5]. Interestingly, "hot phases" have been described most frequently in younger individuals [4-5, 7]. Martins et al. report that the youngest patient who suffered this phenomenon was only 2 years old [5]. An analysis of the literature suggests

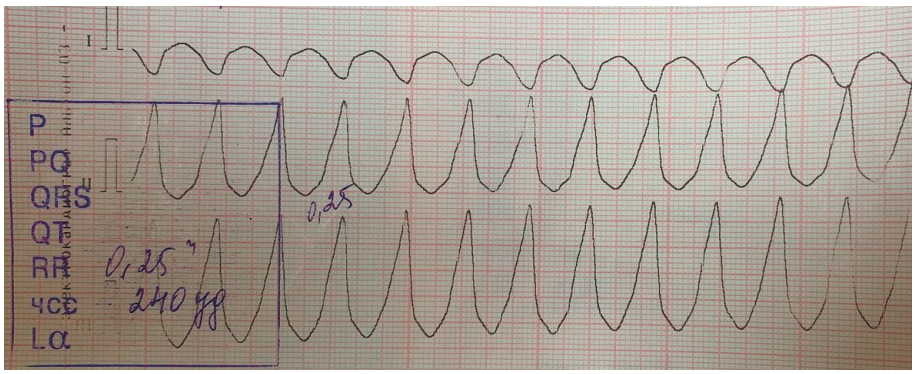

Fig. 1. Electrocardiogram of the patient at the moment of rapid heartbeat attack. Tachycardia with wide QRS complexes with heart rate 240 per min.

that "hot phase" episodes can occur in any ACMP phenotype, but especially in patients with the left dominant form of the disease [5, 7-10]. In addition, the association of this phenomenon with mutations in certain genes was found. Thus, mutations in the DSP gene are the most common in patients with "hot phase" [11, 13]. The literature also presents episodes of this phenomenon in patients with mutations in the PKP2 and DSG2 genes [3, 5, 7].

Often being the debut of the disease, the "hot phase" can complicate the diagnostic search [4]. This article presents a clinical case of ACMP "hot phase" development in a pediatric patient and describes the difficulties of differential diagnosis of the disease in the presence of this phenomenon.

Patient G., 13 years old, was first admitted to the Department of Pediatric Cardiology and Medical Rehabilitation of the Federal State Budget Institution V.A. Almazov Scientific Research Center of the Ministry of Health of the Russian Federation in January 2022 with complaints of palpitations, pain in the heart area, weakness, and one-time syncope. The patient's medical history shows that the patient lost consciousness in August 2021 while riding a bicycle in hot weather. A few days later, the boy complained of palpitations, chest discomfort, and repeated vomiting. An electrocardiogram (ECG) showed tachycardia with wide QRS complexes and heart rate (HR) over 250 beats per minute (Fig. 1). The tachycardia attack was stopped by electric cardioversion with 160 J (4 J/kg).

When the patient was examined at his place of residence, the increased level of NT -proBNP up to 16308 pg/ml (normal < 370.00 pg/ml) was noticed. The ECG showed negative T waves in V1-V4 leads. According to the data of the daily ECG monitoring, a rare ventricular extrasystole was registered, while the echocardiography (EchoCG) showed no pathology. It should be emphasised that the patient had no significant family history of SCD. Antiarrhythmic therapy with propafenone was prescribed at the place of residence and the patient was referred for examination to tthe Federal State Budget Institution V.A. Almazov Scientific Research Center of the Ministry of Health of the Russian Federation.

On admission during physical examination, the patient was bradycardic; otherwise, there was no pathology. Laboratory data showed high levels of NT-proBNP up to 929.70 pg/ml (normal <370.00 pg/ml) and troponin I up to 37.8880 ng/ml (normal up to 0.0340 ng/ml), inflammatory markers were within reference values. Polymerase chain reaction for cardiotropic viruses (Epstein-Barr virus, herpes simplex viruses types 1 and 2, human herpes virus type 6, Parvovirus B19) was negative.

ECG showed sinus rhythm with heart rate 60 per min, PQ interval prolongation up to 200 ms, complete right bundle branch block with QRS 130 ms were recorded. Daily ECG showed rare monomorphic ventricular extrasystole, as well as paroxysms of monomorphic ventricular tachycardia from the RV exit region, which is a low criterion for ACMP according to Task Force Criteria 2010 [14]. The patient had late ventricular potentials, which also belongs to the low criterion (Task Force Criteria 2010) [14].

EchoCG findings in the four-chamber position revealed RV dilatation (end-diastolic size 38.2 mm, Z-score 2.8), as well as short- and long-axis dilatation of the RV outlet (PLAX/BSA=20.8 mm/m2, PSAX prox=20 mm/m2). However, impaired contractility and areas of dyssynchrony, dyskinesia and/or akinesia were not detected (Fig. 2).

During hospitalization, the patient complained of pain in the retrosternal region, accompanied by a marked increase in cardiospecific enzymes, especially troponin I, up to 232.744 ng/mL. On physical examination during pain syndrome, hemodynamics remained stable: BP 115/75 mm Hg, heart rate 60 per minute, tones rhythmic. According to ECG data, no rhythm abnormalities were registered at the time of complaints. Reliable assessment of ischemic changes on ECG was difficult due to the presence of complete right bundle branch block (Fig. 3).

Taking into account the clinical picture of acute coronary syndrome (ACS), selective coronary angiography was performed to exclude coronary artery pathology, which re-

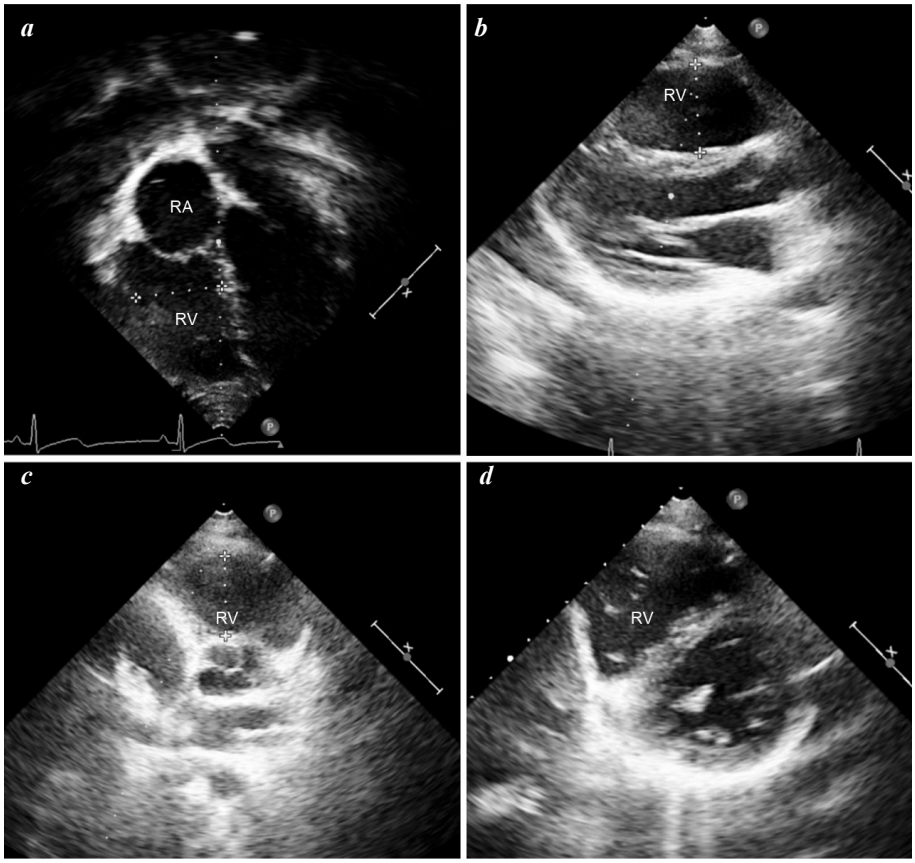

Fig. 2. Echocardiography of a patient: a - four-chamber position, b - parasternal long axis, c - parasternal short axis, d - two-chamber position.

vealed no pathological changes in coronary arteries (Fig. 4). Undoubtedly, this condition required exclusion not only of the ACS. The differential diagnostic circle also included "hot phase" of ACMP, acute myocarditis.

For differential diagnosis, the boy also underwent magnetic resonance imaging (MRI) of the heart with contrast. MR evidence of RV dilatation (65x40 mm, end-diastolic volume 84 ml) as well as decreased contractility and widespread fibrous changes in the RV myocardium were detected. Thus, 1 major MRI criterion was found according to Task Force Criteria 2010 [14] (Fig. 5).

Endomyocardial biopsy has been restricted in children due to the high risk of complications during the procedure. Thus, according to the results of the examinations, there were no convincing data for ACS, acute myocarditis. The presence of 2 minor and major criteria according to Task Force Criteria 2010 allowed to establish a reliable diagnosis of ACMP [14].

To confirm the genetic nature of the disease, the patient underwent genetic examination by next-generation sequencing followed by Sanger validation. A probable-pathogenic mutation in the DSG2 gene (NM_001943.5:p.146G>A) was detected in the patient, confirming the diagnosis of ACMP, and the condition was considered a manifestation of the "hot phase" of ACMP. The patient's pain relief and normalization of troponin I level were observed in the dynamics. However, there were no significant changes according to daily ECG and Echo CG.

Taking into account the patient's age, history of sustained VT, syncope, and decreased RV contractility, absolute indications for cardioverter-defibrillator (ICD) implantation were determined [1, 15]. Sotagexal was prescribed as antiarrhythmic therapy and correction of CHF symptoms with diuretics and ACE inhibitors (Eplerenone and Enalapril) was performed.

To date, the patient has not had any hot phase relapses or ICD triggers. According to daily ECG data, there was no increase in ectopic activity against the background of the therapy. However, EchoCG showed negative dynamics in the form of increasing RV dilatation: end-diastolic size in inflow increased from 38 to 39 mm (Z-score from 2.68 to 2.88), PLAX/BSA from 20.8 to 20.9 mm/m2, PSAX prox from 20 to 22.4 mm/m2 and a slight decrease of TAPSE in dynamics (from 24 to 20 mm). The child continues to receive multicomponent therapy for CHF, as well as antiarrhythmic drugs, and is monitored at our center.

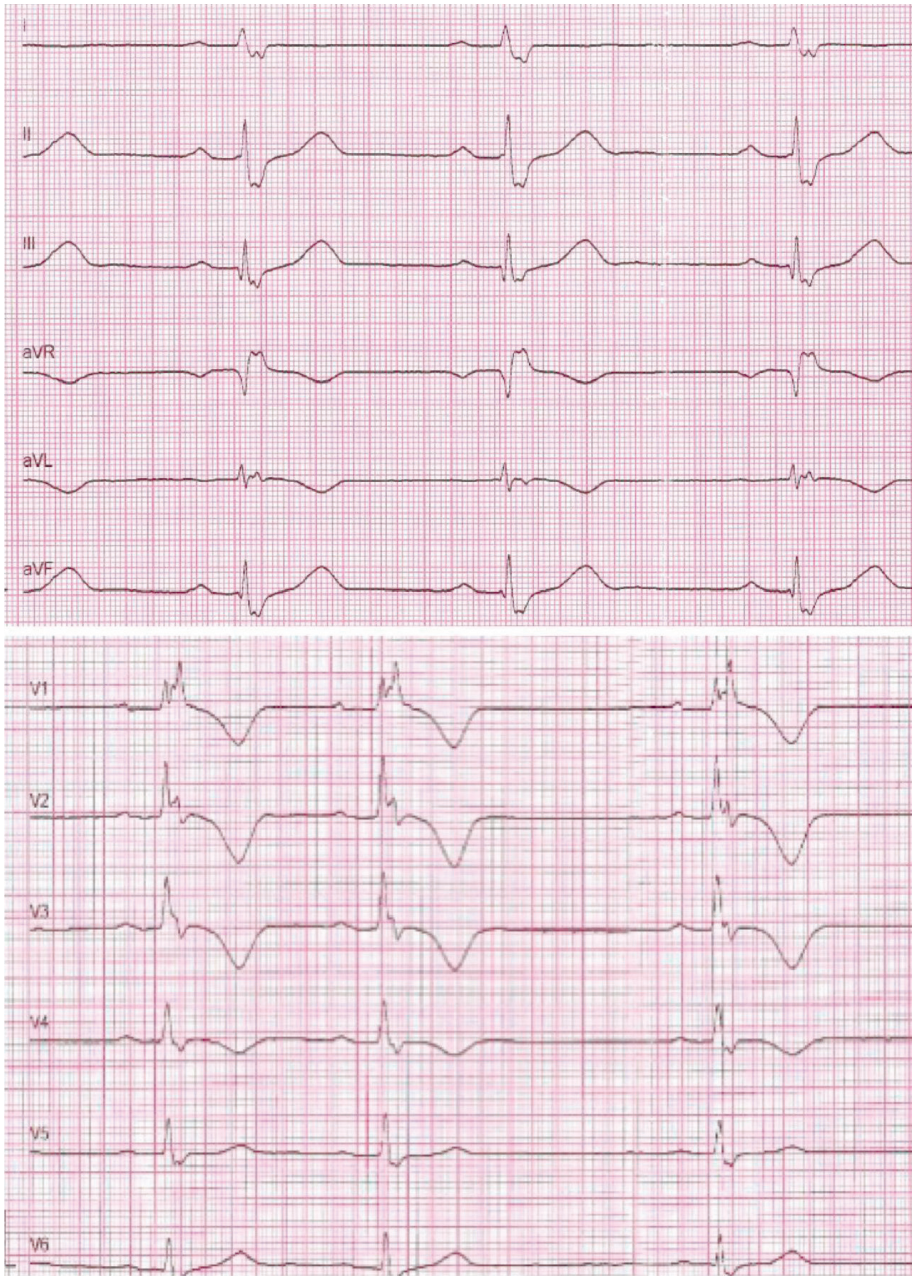

Fig. 3. Electrocardiogram of a patient during an episode of chest pain. Sinus rhythm with heart rate 64 per min. Complete right bundle branch block.

DISCUSSION

The "hot phase" is a very rare manifestation of ACMP [3]. This is probably due to the fact that this phenomenon may be the earliest manifestation of ACMP when patients do not have structural changes in the heart characteristic of this disease and the patient is misdiagnosed. Thus, some patients in the initial report described such pathologies as acute myocarditis, acute myocardial infarction without coronary artery lesions, however, ACMP was subsequently diagnosed [3]. In addition, the pathophysiological interpretation of this clinical manifestation is still unexplored to the end. It should be emphasized that since the first descriptions of the disease,

the role of inflammation in the pathogenesis of ACMP has been thought about. Thus, as early as 1990, some authors suggested that inflammation may be a provoking factor in the development of ACMP [12]. The current opinion is that a defect in the desmosomal gene predisposes to myocyte death. Significant loss of myocytes may be accompanied by an inflammatory response that is exacerbated by a secondary immune response, clinically characterised as the "hot phase", which is the first sign of the disease [2-3]. Importantly, studies in mouse models have confirmed that inflammation in ACMP may precede the appearance of obvious histological and electrical abnormalities [16].

Given the above, it is extremely difficult to distinguish the course of ACMP from acute myocarditis in the early stages of the disease. In our clinical case, there were several aspects to exclude the course of acute myocarditis. First, there was no association of cardiac symptoms and complaints with an acute infection, and there was also a negative polymerase chain reaction for cardiotropic viruses. Second, there was no increase in inflammatory markers. Thirdly, cardiac MRI with contrast revealed no "classical" signs of myocarditis, while MRI signs of ACMP were detected [1, 17-18].

Another acute condition with which we made a differential diagnosis was ACS. It should be noted that in some patients with "hot phase", according to the literature, ECG changes in the form of ST-segment abnormalities were registered [2-3]. However, reliable assessment of ischemic changes in the presented case was difficult due to the presence of the complete right bundle branch block. The absence of coronary artery lesions according to coronary angiography allowed us to exclude ACS.

Given the patient's ACMP phenotype, a genetic study was performed, which revealed a pathogenic mutation in the DSG2 gene. Mutations in this gene have a proven association with the development of ACMP [1]. Nevertheless, there is information about the association of this mutation with the development of the "hot phase" phenomenon [3]. Unfortunately, the role of "hot phase" in disease progression and arrhythmic risk stratification is poorly known to date. Some researchers have noted an increase in electrical instability of myocardium during such episodes, which undoubtedly increases the risk of SCD [3, 17]. In addition, the association of the "hot phase" with the worse prognosis of ACMP has been noted [3]. One year after the "hot phase" episode, our patient did show negative dynamics in the form of CHF progression. Unfortunately, we have not found any studies in the literature on the effect of troponin I elevation on the course of the disease. Our personal experience shows that not all pediatric patients with ACMP have the described phenomenon, but patients with a "hot phase" had an early debut and rapid progression of the disease [6]. Therefore, we still assume that the "hot phase" is another risk factor for CHD and the worse course of ACMP. Of course, further studies are needed to study this clinical phenomenon in patients with ACMP in a large cohort of patients.

CONCLUSION

Thus, this clinical case demonstrates that ACMP in childhood can occur under the mask of other diseases, which complicates the timely detection of hereditary pathology. Of course, a thorough history and examination, including genetic testing, can make the correct diagnosis. Taking into account our clinical experience, in pediatric patients with cardiac pain syndrome accompanied by elevated levels of cardiospecific enzymes, in

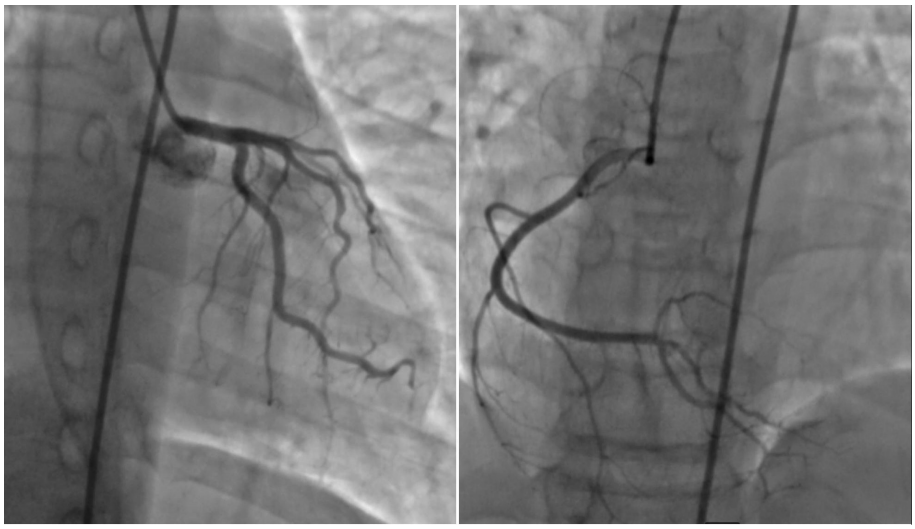

Fig. 4. Coronary angiography of the patient. Coronary arteries without angiographic signs of atherosclerotic lesion, no local stenoses. Blood flow is satisfactory.

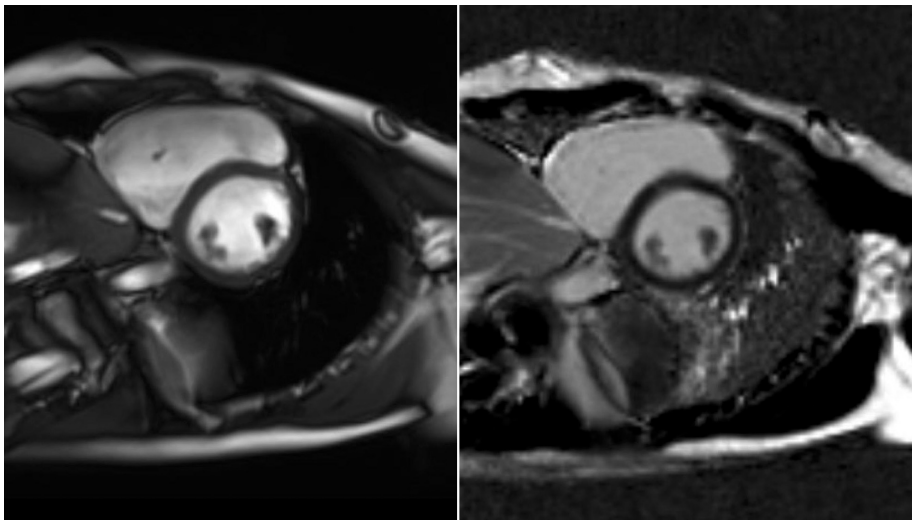

Fig. 5. Results of magnetic resonance imaging of the heart with contrast.

particular troponin I, one should keep in mind such a genetically determined disease with a high risk of SCD as ACMP. Perhaps, in the future, understanding the pathophysiology of the "hot phase" phenomenon in patients with ACMP will broaden the horizons in the therapy of this disease.

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