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# ARRHYTHMOGENIC CARDIOMYOPATHY IN CHILDREN: GENETIC BASIS AND PHENOTYPIC MANIFESTATIONS. A SINGLE CENTER EXPERIENCE

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**Aim.** To investigate clinical manifestations, phenotypic variants, genetic features, and outcomes in children with arrhythmogenic cardiomyopathy (ACM).

**Methods.** The study group consisted of 24 patients (< 18 years of age) with ACM, who were under observation from 2011 to 2024. The median age at ACM diagnosis was 13 years [12-15]. The following data were analyzed: complaints and medical history, laboratory parameters (biochemical markers of inflammation and serum myocardial damage markers, NT-proBNP levels), electrocardiogram, Holter monitoring, echocardiography results, cardiac magnetic resonance imaging, selective coronary angiography, histological and molecular genetic studies. The median follow-up duration for ACM patients was 27 months [16.5-38].

**Results.** All patients were unrelated probands. All children presented with asymptomatic ventricular arrhythmias (VA) as the initial manifestation of the disease, 23 (95.8%) patients had complaints: palpitations in 21 (87.5%) children, syncope in 14 (58.3%) children, heart failure symptoms in 12 (50.0%), and isolated chest pain in 4 (16.7%) patients. 5 (20.8%) children had a "hot" phase. Analysis of arrhythmic data revealed several features of ACM in childhood: VAs were polymorphic, daily VA density was less than 20% at the time of diagnosis, presence of late ventricular potentials in most patients, and several criteria from the «repolarization abnormalities» group had low informativeness. During follow-up, 9 (37.5%) children had the right-dominant ACM, 7 (29.9%) had ACM with left ventricle involvement, and 8 (33.3%) had biventricular form. Desmosomal mutations were found in 16 children (66.7%), non-desmosomal gene variants in 8 patients (33.3%).

**Conclusion.** It has been shown that ACM can manifest at an early age and is associated with the development of arrhythmic events and/or severe heart failure. Increasing awareness among physicians about the early onset of ACM is crucial for timely treatment of heart failure, prevention of sudden cardiac death, and family screening.

**Key words:** arrhythmogenic cardiomyopathy; children; sudden cardiac disease; ventricle arrhythmias; heart failure; genetic cardiomyopathy

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Arrhythmogenic cardiomyopathy (ACM) is a rare hereditary cardiomyopathy characterised by fibro-fatty replacement of the myocardium in both ventricles [1-3]. According to current estimates, the prevalence of ACM among adults ranges from 1 in 1,000 to 1 in 5,000 [4].

Although ACM is relatively uncommon, its clinical significance is extremely high due to the elevated risk of life-threatening complications, including ventricular arrhythmias (VAs), heart failure (HF), and sudden cardiac death (SCD) [1-3]. Published data indicate that ACM accounts for up to 25% of SCD cases among children and adolescents [5].

Despite the severity of the condition, awareness of ACM in paediatric practice remains insufficient, for several reasons.

First, for many years ACM was considered a disease predominantly affecting individuals over the age of 30 to 40 and was thought to be extremely rare in children [1-3,

***Table 1.***

***Data on the age of disease onset in children across different age groups according to the classification of childhood periods by I.M. Vorontsov and A.V. Mazurin (2009)***

| Age group | Total, n (%) |
|---|---|
| 1-3 y.o. | 0 |
| 4-6 y.o. | 3 (12.5) |
| 7-11 y.o. | 6 (25.0) |
| >12 y.o. | 15 (62.5) |

6-7]. To date, only a limited number of international studies have described small paediatric cohorts with ACM, and follow-up periods in these studies have generally been short [8-14]. In the Russian literature, we found only isolated case reports of ACM in children [15-17].

Second, prior to 2019, ACM was regarded exclusively as a disorder affecting the right ventricle (RV) [2]. However, subsequent research confirmed that the left ventricle (LV) can also be involved, leading to the recognition of new disease phenotypes, namely the left-dominant and biventricular forms [2, 18-20]. It is important to note that the 2010 Task Force Criteria (TFC 2010) were designed to identify only the classic RV phenotype, which substantially limited the detection of other forms of the disease [18-21]. To address this limitation, the Padua Criteria were introduced in 2020, incorporating diagnostic parameters for evaluating involvement of both ventricles and thereby expanding diagnostic capabilities [18, 22].

Third, existing diagnostic criteria are not adapted for use in children [23-24]. For instance, certain ACM criteria require cardiac magnetic resonance imaging (MRI) with contrast or endomyocardial biopsy, both of which may be difficult to perform in children due to age-related restrictions and the high risk of complications. Additionally, electrocardiographic criteria such as T-wave inversion in the right precordial leads (V1-V3) are considered normal in children younger than 14-16 years, and epsilon waves are rarely seen in paediatric populations, as they tend to appear at later stages of the disease [23-25]. Moreover, the manifestations of ACM, including ventricular arrhythmias and morphofunctional myocardial changes, lack specificity and require careful differential diagnosis with other similar conditions.

Fourth, ACM in children often presents without symptoms or with only minimal clinical signs, making early diagnosis and treatment challenging. In some cases, SCD in children may be the first and only manifestation of the disease [2, 8-9].

Taken together, these factors underscore the need for increased attention to ACM in the paediatric population and the implementation of measures aimed at improving the effectiveness of early diagnosis in order to reduce paediatric mortality. Several key issues remain unresolved, including the natural history of ACM in childhood, the absence of validated paediatric diagnostic criteria, and challenges in differential diagnosis.

The aim of the present study was to describe the clinical features, phenotypic variants, genetic characteristics, and outcomes of ACM in the largest paediatric cohort of patients with this condition in the Russian Federation.

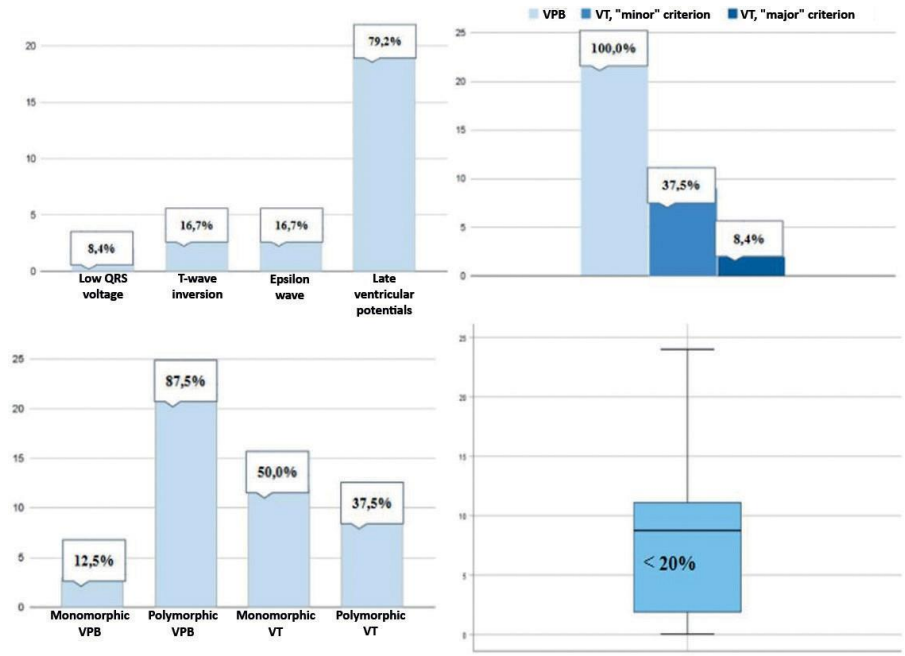


***Fig. 1. Electrocardiographic and arrhythmic criteria of arrhythmogenic cardiomyopathy in paediatric patients, where a - repolarisation and depolarisation criteria, b - arrhythmic criteria, c - characteristics of ventricular arrhythmias, d - burden of ventricular arrhythmia at the time of diagnosis., VPB - ventricular premature beats, VT - ventricular tachycardia.***

***Table 2.***

***Histological findings in paediatric patients with arrhythmogenic cardiomyopathy***

| № | Genotype | Conditions | Residual CMCs, % | Fibrosis | Lipomatosis | Inflammation |
|---|---|---|---|---|---|---|
| 1 | *PKP2/PKP2* | NH | 0-30 | + | - | + |
| 2 | *PKP2* | EMB | 37 | + | + | - |
| 3 | *MYH7* | NH | 5-10 | + | + | + |
| 4 | *FLNC* | EMB | - | + | - | - |
| 5 | *SYNE1* | EMB | 38 | + | - | - |
| 6 | *PKP2* | NH | <40 | + | + | + |

Note: CMCs - cardiomyocytes; NH - native heart; EMB - endomyocardial biopsy.

## METHODS

Between 2011 and 2024, 24 patients under the age of 18 were followed as part of the paediatric ACM registry (database registration certificate No. 2022621121, dated 04 May 2022). The diagnosis of ACM was established according to the 2010 Task Force Criteria and the Padua criteria [21-22].

The median age at diagnosis was 13 years (interquartile range, 12 to 15). Among the patients, 15 (62.5%) were boys and 9 (37.5%) were girls. The median follow-up duration was 27 months (interquartile range, 16.5 to 38).

Comprehensive clinical evaluation included history and symptom review, laboratory testing (inflammatory biochemical markers, serum cardiac injury

biomarkers, NT-proBNP), and cardiovascular instrumental assessment. This included electrocardiography (ECG), 24-hour Holter ECG monitoring, transthoracic echocardiography (Echo), contrast-enhanced cardiac MRI, selective coronary angiography (if indicated), histological examination (if indicated), and molecular genetic analysis.

Electrocardiographic and Holter monitoring focused on identifying ACM-specific ECG criteria, including depolarisation and repolarisation abnormalities (age-specific assessment of repolarisation in precordial leads, presence of epsilon wave, QRS voltage in limb leads; low voltage defined as <0.5 mV). In the presence of ventricular rhythm disturbances, their burden, morphology, and origin were assessed.

Echocardiography included measurements of cardiac chamber size, biventricular systolic function, and wall motion abnormalities. Criteria for RV and/or LV dilation or dysfunction were as follows: RV dilation >2 z-score, RV FAC <35%, RVOT PLAX/BSA ≥16 mm/m², RVOT PSAX/BSA ≥18 mm/m²; LV dilation >2 z-score, LVEF <50%, and regional wall motion abnormalities in the LV or RV. RV z-scores were calculated using the Koestenberger calculator, and LV z-scores using the Boston Children's Hospital (BCH) Z-score calculator.

Cardiac MRI with contrast included evaluation of chamber dimensions, biventricular contractility, and myocardial fibrosis. LV dilation and/or dysfunction were defined by end-diastolic volume ≥120 mL/m² and LVEF <50%; RV dysfunction was defined by RVEF <40% and RVEDV ≥120 mL/m² in males or ≥110 mL/m² in females, with associated wall motion abnormalities.

Histological assessment (performed via endomyocardial biopsy of the right heart chambers or native heart tissue after transplantation) included haematoxylin and eosin staining, and Van Gieson staining. Immunohistochemistry using antibodies against CD3, CD68, and HLA-DR was performed to exclude myocarditis. Morphometric analysis of residual cardiomyocyte area and inflammatory infiltrates was conducted using the Image Scope Color M image analyser (Russia).

Genotyping was performed using targeted next-generation sequencing with a panel of 172 genes most commonly associated with cardiomyopathy. Variant pathogenicity was classified according to the 2015 ACMG criteria [26].

Following diagnosis, patients received antiarrhythmic and heart failure therapy, as well as interventional treatments including radiofrequency ablation of arrhythmogenic foci and implantation of implantable cardioverter-defibrillators (ICDs), in accordance with current clinical guidelines at the time of decision-making. In cases of end-stage heart failure, patients were placed on the heart transplant waiting list (HTWL) and subsequently underwent orthotopic heart transplantation using the bicaval technique with cardiopulmonary bypass and pharmacohypothermic cardioplegia.

This study was conducted in accordance with the Declaration of Helsinki (1964) and approved by the Ethics Committee of the Almazov National Medical Research Centre (Protocol No. 01-23, dated 23 January 2023). Written informed consent was obtained from all legal guardians prior to inclusion in the study.

**Statistical Analysis**

Statistical analysis was performed using IBM SPSS Statistics version 26 (IBM Corporation, USA). Both parametric and non-parametric methods were applied. Due to the sample size, the Shapiro-Wilk test was used to assess normality of distribution.

Categorical variables were presented as absolute values and percentages. Continuous variables were expressed as mean ± standard deviation for normally distributed data, or as medians with interquartile ranges (50 [25, 75]) for non-normally distributed data. Comparisons between categorical variables were made using Pearson's chi-squared test or Fisher's exact test, as appropriate. A p-value <0.05 was considered statistically significant.

Survival analysis without arrhythmic events was performed using the Kaplan-Meier method.

## RESULTS

All patients were unrelated probands. A review of the medical records revealed that in all children, the disease onset manifested as asymptomatic ventricular arrhythmias (VAs), with one-third of patients experiencing VA before the age of 12 years (Table 1). In 7 children (29.2%), ventricular rhythm disturbances were detected during routine screening, while in 17 children (70.8%) they were identified by a paediatrician following intercurrent illnesses. The analysis showed that, in most cases, the initial presentation was isolated, infrequent ventricular ectopy (VEs), observed in 22 patients (91.7%). Only 2 patients (8.3%) presented with sustained monomorphic VT as the first manifestation. Clinical symptoms and morphofunctional changes were observed later. The median age at onset of symptoms and morphofunctional abnormalities was 12 years [10.5-15] and 12 years [11-15], respectively. The median age at diagnosis of ACM was 13 years [12-15].

**Clinical Picture and Family History**

Symptoms were reported in 23 patients (95.8%), while one child (4.2%) remained asymptomatic. Palpitations were reported in 21 children (87.5%), syncope in 14 (58.3%), and HF symptoms, such as dyspnoea

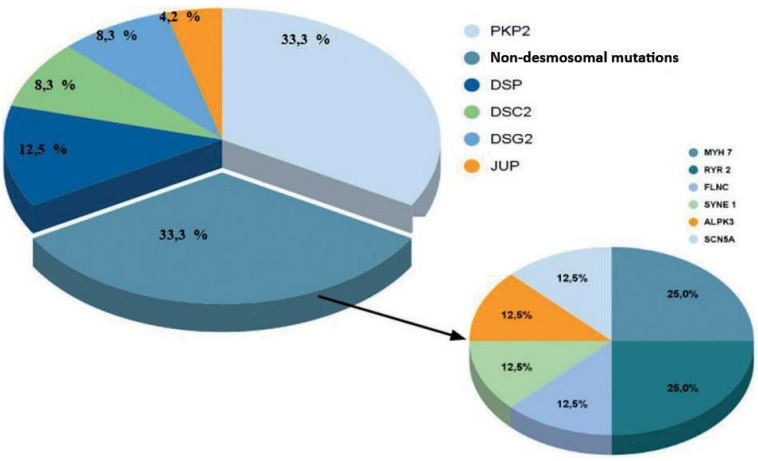


***Fig. 2. Genetic spectrum of arrhythmogenic cardiomyopathy in children.***

and reduced exercise tolerance, in 12 (50.0%). Chest pain was observed in 4 children (16.7%). Five patients (20.8%) presented with a distinct and rare manifestation - a symptom complex involving chest pain and elevated troponin I, consistent with an "inflammatory phase". This manifestation was independent of ACM phenotype and was more common in patients with desmosomal mutations. Disease progression was noted in all children following this "hot" phase. Myocarditis and acute coronary syndrome were ruled out in all such cases due to similar clinical and laboratory features. None of the patients experienced sudden cardiac arrest. However, 4 patients (16.7%) had a positive family history of SCD, all involving first- or second-degree relatives. No patient had a known family history of ACM.

***Table 3.***
***Outcomes in children with arrhythmogenic cardiomyopathy***

| Outcomes | Quantity |
|---|---|
| Syncope, n (%) | 14 (58.3) |
| Sustained VT, n (%) | 8 (33.3) |
| ICD activation, n (%) | 5 (20.8) |
| HTWL / HTx, n (%) | 5 (20.8) |

Note: VT - ventricular tachycardia; ICD - implantable cardioverter-defibrillator; HTWL - heart transplant waiting list; HTx - heart transplantation.

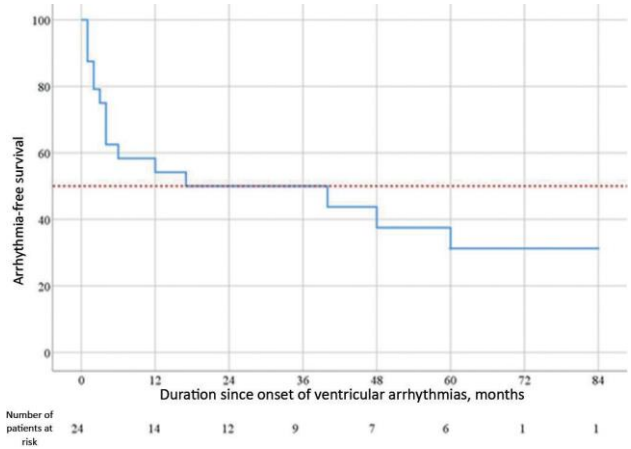


***Fig. 3. Kaplan-Meier curve illustrating event-free survival from arrhythmic events.***

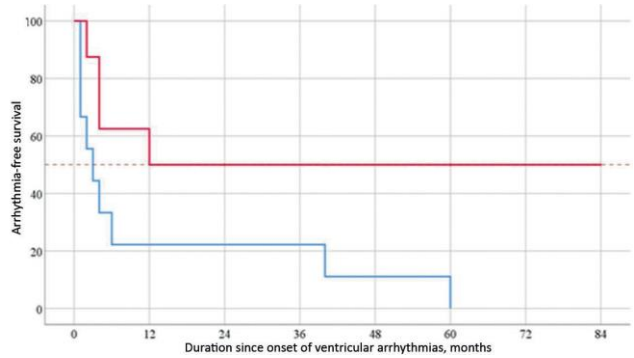


***Fig. 4. Kaplan-Meier curves illustrating event-free survival from arrhythmic events: the red line represents patients with a PKP2 mutation, and the blue line represents patients with a non-plakophilin genotype.***

**Electrocardiographic and Arrhythmic Findings**

All paediatric patients had more than 500 VEs per day. Sustained VT was recorded in 16 patients (66.7%). Monomorphic VEs were observed in only 3 patients (12.5%), while the remaining 21 (87.5%) exhibited polymorphic VEs (2 to 4 morphologies). Among those with VT, 12 (50.0%) had monomorphic VT, and 9 (37.5%) had polymorphic VT. Four children (16.7%) presented exclusively with polymorphic VT. Before antiarrhythmic treatment, the median daily burden of ventricular arrhythmias was 8.75% [1.9-11.1], based on 24-hour Holter monitoring.

The "minor" ECG criterion of T-wave inversion in leads V1-V4 with complete right bundle branch block, as defined by the 2010 TFC, was observed in only one patient (4.2%) with RV involvement at age 17. Two children (8.3%) with LV involvement at age 16 had negative T-waves in leads V4-V6, consistent with the "minor" Padua criterion. One patient (4.2%) with biventricular ACM had T-wave inversions in leads V1-V4 at age 17, meeting the "major" Padua criterion. Epsilon waves (a "major" criterion per TFC 2010 and "minor" by Padua) were identified in only 4 patients (16.7%) with biventricular disease, and only in the late stages, after 4 to 5 years of follow-up. Late ventricular potentials were found in 19 cases (79.2%).

In summary, analysis of ECG and arrhythmic data revealed several distinct features of paediatric ACM: polymorphic VAs, VA burden less than 20% at diagnosis, predominance of RV involvement, and low diagnostic value of repolarisation abnormality criteria (Figure 1).

**Morphofunctional and Structural Features**

At the time of diagnosis, 11 children (45.8%) had a right-dominant form of ACM, 9 (37.5%) had LV involvement, and 4 (16.7%) had biventricular disease. During follow-up, several patients with initial univentricular involvement progressed to a biventricular phenotype. Specifically, 2 patients each (8.3%) with initial LV or RV involvement developed biventricular disease.

Aneurysm formation was documented in 7 children (29.2%) during follow-up: 5 (20.8%) had RV aneurysms, 1 (4.2%) had an LV aneurysm, and 2 (8.3%) developed aneurysms in both ventricles.

Myocardial fibrosis, characteristic of the disease, was detected in all 22 patients (91.7%) who underwent contrast-enhanced cardiac MRI. Two children (8.3%) did not undergo MRI due to severe arrhythmias.

**Histological Analysis**

Histological evaluation was performed in 6 patients (25.0%, Table 2). Three patients (12.5%) underwent histological analysis of the explanted native heart after heart transplantation (HTx), and three others had endomyocardial biopsy during radiofrequency ablation procedures. In all cases, ACM diagnosis was confirmed by the presence of fibrotic myocardial changes (a "major" Padua criterion), and cardiomyocyte residual area was below 40% (a "major" criterion per TFC 2010). In 3 cases (12.5%), lipomatous changes were also found, consistent with the disease's typical features.

**Genetic Analysis and Family Screening**

Desmosomal mutations were identified in 16 children (66.7%), including PKP2 variants in 8, DSP in 3, DSC2 and DSG2 in 2 each, and JUP in 1 patient. Three patients

had compound heterozygosity involving two PKP2 variants, and one child had two DSP variants, consistent with Carvajal syndrome. Non-desmosomal gene variants were detected in 8 patients (33.3%), including FLNC, MYH7/FKTN, RYR2, ALPK3, SCN5A, and SYNE1 (Figure 2). Two patients (8.3%) had digenic mutations - MYH7/FKTN and PKP2/CDH2. Homozygous mutations in DSC2 were found in 2 patients (8.3%), while all other variants were heterozygous. Non-desmosomal mutations were significantly more common in LV-dominant forms of ACM ($p<0.05$).

All families were offered cardiovascular and genetic cascade screening. Cardiological screening was completed for all families, and all parents and siblings were asymptomatic at the time. Genetic testing was successful in 3 families with early disease onset, severe phenotype, and compound genotypes. In these three families, one or both parents carried a single PKP2 variant, although they remained asymptomatic at the time of clinical evaluation.

**Disease Course and Outcomes**

The median follow-up duration was 27 months [16.5-38]. Adverse outcomes included arrhythmic events (syncope, sustained VT, implantable cardioverter-defibrillator [ICD] discharges) and inclusion on the HTx waiting list (Table 3).

Arrhythmic events occurred in 15 children (62.5%). Importantly, there were no cases of SCD or death. ICD shocks were recorded in 5 patients (20.8%), with multiple shocks (3 to 8 discharges) in 4 of these cases.

Kaplan-Meier analysis demonstrated that the median time to the first arrhythmic event was 17 months from VA onset (95% CI: 0.00-63.64). Arrhythmic events were defined as the first occurrence of sustained VT/ventricular fibrillation, syncope, or ICD discharge following VA onset. Hence, by 17 months from disease onset, at least 50% of children with ACM experienced an arrhythmic event (Figure 3). The median time to the arrhythmic event in our cohort was 4 months [2-12].

Since PKP2 mutations were the most frequent in this cohort, survival without arrhythmic events was analysed in patients with PKP2 variants versus other genotypes. The difference in arrhythmia-free survival based on genotype was statistically significant ($p=0.025$). The median time to arrhythmic event was not reached in the PKP2 group, whereas in patients with other mutations, it was 3.0 months (95% CI: 0.078-5.92) (Figure 4).

Five children (20.8%) had severe chronic HF. Their genotypes were characterised as follows: 3 (12.5%) had pathogenic compound heterozygous desmosomal mutations, 2 (8.3%) had digenic mutations involving both desmosomal and non-desmosomal genes, and 1 (4.2%) had a homozygous mutation (Table 4).

Clinical manifestations of NYHA class III-IV HF developed within 12 months [12-26] of follow-up. The median age at inclusion on the HTx waiting list was 12 years [11-14]. At the time of writing, 3 children (12.5%) had undergone heart transplantation.

## DISCUSSION

This study presents the clinical and genetic characteristics of a paediatric cohort diagnosed with ACM. Historically, ACM was considered a condition primarily affecting adults, with peak incidence reported in the third and fourth decades of life [1-3, 6-7, 18-20]. However, contemporary evidence indicates that disease onset may occur much earlier, including in infancy [27-28]. In our study, three children (12.5%) presented with initial manifestations in the form of VAs as early as four years of age. One of these patients had Carvajal syndrome, which is known for early phenotypic expression. One-third of the children exhibited disease onset before the age of 12 years.

Recent studies demonstrate that the risk of life-threatening VAs, sudden SCD, and advanced heart failure is higher in paediatric ACM than in adult cases. L. Daliento reported a higher incidence of SCD among young patients compared to adults with ACM [8]. Similarly, A. Te Riele found SCD to be a hallmark complication of paediatric forms of ACM [10]. Literature data also indicate that end-stage HF requiring heart transplantation (HTx) is increasingly observed in ACM, including in paediatric patients. According to K. Chen, the frequency of HTx and HF-related mortality in ACM ranges from 2% to 22% [29].

In our cohort, arrhythmic events were recorded in 50% of patients, with a median time from VA onset to the first event of 4 months. Kaplan-Meier analysis revealed a median time to arrhythmic event of 17 months from VA onset (95% CI: 0.00-63.64). Advanced HF (NYHA class III-IV) was diagnosed in 20% of patients.

These findings underscore the critical importance of early ACM diagnosis in paediatric practice, primarily to prevent SCD and to ensure timely inclusion on the heart transplant waiting list. Nevertheless, diagnosing ACM in children remains particularly challenging. In early stages, the disease may be asymptomatic, making detection during routine evaluations difficult [29, 30]. In our study, 100% of patients presented with infrequent asymptomatic VAs as

***Table 4.***

***Phenotype-genotype characteristics in patients with severe heart failure due to arrhythmogenic cardiomyopathy***

| № | 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|---|
| Sex | f | f | m | f | m |
| Age at HTx / inclusion on HTWL, years | 11 | 16 | 8 | 12 | 16 |
| Primary involvement | RV | RV | LV | RV | RV |
| Phenotype | BiV | BiV | BiV | BiV | BiV |
| Genotype | PKP2/ CDH2 L/P/VUS | MYH7/ FKTN P\| VUS | DSP/ DSP P/LP | PKP2/ PKP2 P/LP | DSC2 L/P |
| HTx | + | + | HTWL | + | HTWL |

Note: BiV - biventricular; LV - left ventricle; HTWL - heart transplant waiting list; RV - right ventricle; HTx - heart transplantation.

the initial manifestation, discovered incidentally. Similar findings were reported by M. Cicenia et al. in an Italian paediatric cohort, describing an asymptomatic disease onset with minor ventricular rhythm disturbances identified by chance [13].

One possible reason for delayed ACM diagnosis may be that VAs go unnoticed due to their rarity and lack of subjective symptoms. Furthermore, clinical manifestations of ACM may resemble other cardiovascular disorders [2], complicating differential diagnosis. This is particularly true for recurrent episodes of substernal chest pain accompanied by elevated troponin I, referred to as the "hot phase" [28, 32]. Unlike in adults, this symptom complex is more frequently observed in children and may constitute the first disease manifestation, requiring careful differentiation from acute coronary syndrome and acute myocarditis [28, 32].

According to published data, paediatric ACM is often diagnosed through cascade family screening of adult relatives with the condition [8-13]. The absence of a positive family history may hinder diagnostic evaluation in children. In our cohort, only 4 patients (16.7%) had a family history of sudden cardiac death (SCD), and none had relatives with a confirmed ACM diagnosis. This is not always attributable to de novo mutations; it may also result from late phenotypic expression among carriers, diagnostic limitations in previous generations, or reduced gene penetrance [33-35].

Electrocardiographic (ECG) markers of repolarisation and depolarisation abnormalities often precede morphological myocardial remodelling and can serve as early indicators of ACM [2]. In our study, T-wave inversions (repolarisation abnormalities) had diagnostic value in only 4 of 24 cases (16.7%) due to age-related limitations. Epsilon waves were detected at a similar frequency (16.7%). These findings are consistent with international studies that demonstrate the low diagnostic yield of repolarisation abnormalities and epsilon waves in paediatric populations [23-25, 36].

Our findings confirm the high prevalence of arrhythmic manifestations in paediatric ACM, with all patients exhibiting VAs However, only 2 patients (8.3%) met the "major" arrhythmic criterion of the 2010 TFC, which includes sustained ventricular tachycardia with left bundle branch block morphology and superior axis. The remainder presented with VTs of different morphologies, including polymorphic forms, at disease onset. These data highlight the potential limitations of applying arrhythmic criteria to paediatric populations and support the hypothesis by R. Shriprasad et al. that any VT in children may serve as a marker of ACM [37].

Another major diagnostic challenge in paediatric ACM lies in identifying lv involvement in left-dominant and biventricular forms. In our cohort, more than half of the patients exhibited non-classical phenotypes (left-dominant or biventricular), which initially led to misdiagnoses such as dilated cardiomyopathy, tachycardia-induced cardiomyopathy, or myocarditis. Cardiac MRI with contrast, genetic testing, and in some cases, histological examination played critical roles in confirming these "non-classical" ACM phenotypes [11].

All patients in our cohort had pathogenic variants. In 66.7% (16/24), desmosomal mutations were identified, most frequently involving PKP2, followed by DSP, DSG2, DSC2, and JUP (associated with Carvajal syndrome) [15]. Among non-desmosomal genes, mutations were found in FLNC, RYR2, MYH7, SCN5A, ALPK3, and SYNE1. Notably, we observed a clear association between non-desmosomal mutations and LV involvement. Additionally, some patients carried pathogenic variants in genes associated with other hereditary cardiac disorders, such as MYH7, SCN5A, FLNC, and RYR2 [2]. This suggests possible differences in the underlying molecular mechanisms and emphasises the importance of long-term follow-up to better understand phenotypic expression.

Rare ACM genotypes were identified in our cohort, including MYH7 and ALPK3 mutations associated with biventricular phenotypes. Only a few such cases have been described in the literature, and they appear to carry a high risk of arrhythmic complications [29, 38-39]. One patient harboured a SYNE1 mutation, which had not previously been reported as causative of ACM. However, the phenotypic profile, including histological findings, met ACM diagnostic criteria.

Genetic testing has both diagnostic and prognostic value. Patients with advanced heart failure (HF) frequently carried either compound heterozygous or homozygous mutations, or digenic mutations. These findings align with existing literature. Furthermore, we observed that patients with PKP2 variants experienced significantly fewer arrhythmic events (syncope, sustained VT/ventricular fibrillation, ICD activation) compared with children with mutations in other genes. These results support international evidence indicating a higher arrhythmogenic risk associated with ALPK3, DSP, and FLNC mutations [2, 38-39].

In summary, increased clinical suspicion of ACM, comprehensive cardiovascular assessment including contrast-enhanced cardiac MRI and genetic screening, and close longitudinal follow-up are essential for early detection of the disease, even in the presence of minimal symptoms. These measures facilitate risk stratification for life-threatening complications and allow for the development of personalised treatment and monitoring strategies.

**Study limitations**

This study has several limitations. First, the small cohort size reflects the rarity of ACM in the paediatric population. Second, incomplete clinical data may have impacted diagnostic verification; for instance, contrast-enhanced cardiac MRI was performed in 91.7% of patients (22 out of 24), while histological confirmation was available in only 25% (6 out of 24), which could influence the accuracy of diagnosis in certain cases. Another important limitation is the lack of parental genetic testing in most families. This precluded determination of whether the identified mutations were de novo or inherited, thus limiting the assessment of gene penetrance and familial risk.

## CONCLUSION

This study presents the first comprehensive description of a paediatric cohort of patients with ACM in Russian clinical practice. Our findings contribute to a broader understanding of the clinical course and outcomes of ACM in

children. It has been demonstrated that ACM may present at an early age and is associated with the development of arrhythmic events and/or severe heart failure. Enhancing clinician awareness of early-onset ACM, as well as implementing modern diagnostic approaches, is essential for the timely management of heart failure, prevention of sudden cardiac death, and initiation of familial screening - measures that may significantly improve clinical outcomes.

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