



Differences between genetic dilated cardiomyopathy and myocarditis in children presenting with severe cardiac dysfunction

Ferran Gran¹ · Andrea Fidalgo¹ · Paola Dolader¹ · Marta Garrido² · Alexandra Navarro² · Jaume Izquierdo-Blasco³ · Joan Balcells³ · Marta Codina-Sola⁴ · Paula Fernandez-Alvarez⁴ · Anna Sabaté-Rotés¹ · Pedro Betrián¹ · Joaquín Fernández-Doblas⁵ · Raúl Abella⁵ · Ferran Roses-Noguer^{1,6}

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Abstract

Acute myocarditis is an inflammatory disease of the myocardium, and it can present as severe heart failure in children. Differential diagnosis with genetic cardiomyopathy can be difficult. The objective of this study is to identify patterns of clinical presentation and to assess invasive and non-invasive measures to differentiate patients with acute myocarditis from patients with dilated genetic cardiomyopathy. We performed a retrospective descriptive study of all paediatric patients (0–16 years old) that presented with new-onset heart failure with left ventricle ejection fraction < 35% in whom we performed an endomyocardial biopsy (EMB) during the period from April 2007 to December 2020. The patients were classified into two groups: Group 1 included 18 patients with myocarditis. Group 2 included 9 patients with genetic cardiomyopathy. Findings favouring a diagnosis of myocarditis included a fulminant or acute presentation (77.8% vs 33.3%, $p = 0.01$), higher degree of cardiac enzyme elevation ($p = 0.011$), lower left ventricular dimension z-score (2.2 vs 5.4, $p = 0.03$) increase of ventricular wall thickness (88.8% vs 33.3%, $p = 0.03$) and oedema in the EMB. Seven (77.8%) patients with genetic cardiomyopathy had inflammation in the endomyocardial biopsy fulfilling the diagnostic criteria of inflammatory cardiomyopathy.

Conclusion: Differentiating patients with a myocarditis from those with genetic cardiomyopathy can be challenging, even performing an EMB. Some patients with genetic cardiomyopathy fulfil the diagnostic criteria of inflammatory cardiomyopathy. Using invasive and non-invasive measures may be useful to develop a predictive model to differentiate myocarditis from genetic cardiomyopathy.

What is Known:

- Acute myocarditis could present with cardiogenic shock in paediatric patients.
- Parvovirus B19 is the main cause of myocarditis in this population.

What is New:

- Current diagnostic criteria for myocarditis have limited use in paediatric patients presenting with new-onset heart failure.
- Some patients with a genetic cardiomyopathy and a new-onset heart failure fulfill the diagnostic criteria of inflammatory cardiomyopathy.

Keywords Paediatric heart failure · Myocarditis · Cardiomyopathy · Endomyocardial biopsy

Abbreviations

EMB Endomyocardial biopsy
PVB19 Parvovirus B19
PCR Polymerase chain reaction
CMR Cardiac magnetic resonance

ECG Electrocardiogram
ECMO Extracorporeal oxygenation membrane
LVEF Left ventricular ejection fraction
LVEDD Left ventricular end-diastolic diameter

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✉ Ferran Gran
fgran@vhebron.net

Extended author information available on the last page of the article

Introduction

Acute myocarditis is an inflammatory disease of the myocardium that can present with cardiogenic shock requiring mechanical circulatory assistance [1, 2]. In our environment,

the most frequent cause is a viral infection, especially parvovirus B19 (PVB19) [1, 3]. The gold standard diagnostic test is the endomyocardial biopsy (EMB), although since it is an invasive and risky procedure [4, 5], its use is limited in paediatric patients. The Dallas histological diagnostic criteria [6] have shown to have low sensitivity and high inter-observer variability [7]. Therefore, new immunohistochemical criteria (≥ 14 white blood cells/mm² and ≥ 7 CD3 T lymphocytes/mm²) have been proposed [3, 8].

Although most patients with myocarditis have a complete recovery, there are still 20–30% of them that can develop dilated cardiomyopathy [3, 8–10]. It has been reported that 50–60% of adults [8–11] and 46% of children [8, 9] with dilated cardiomyopathy have evidence of inflammation or viral genome in the heart, suggesting previous viral myocarditis. These patients could benefit from immunosuppressive or antiviral treatment [8, 12–14]. Nevertheless, it is known that some patients with genetic cardiomyopathy can present inflammatory infiltrates [10, 15] and the presence of a viral genome in the myocardium has been found in patients without cardiomyopathy [16]. Still, these findings do not always imply an active infection. Differentiation between inflammatory dilated cardiomyopathy secondary to a previous myocarditis versus genetic dilated cardiomyopathy might be very challenging, but it has important implications both for prognosis and to establish the appropriate treatment [17].

The objective of this study is to describe clinical findings and tests results at presentation in a group of children with severe cardiac dysfunction (LVEF < 35%) and identify factors to differentiate patients with acute myocarditis from those with dilated genetic cardiomyopathy.

Material and methods

We performed a retrospective descriptive study including all paediatric patients (0–16 years) that presented with new-onset heart failure, with a left ventricular ejection fraction (LVEF) < 35%, who underwent an EMB during the period from April 2007 to December 2020. The investigation conforms with the principles outlined in the Declaration of Helsinki (Br Med J 1964; ii: 177) and obtained approval by our local ethics committee. The patients were divided retrospectively into two groups: group 1 included all patients with ≥ 14 white blood cells/mm² and ≥ 7 CD3 T lymphocytes/mm² in the EMB, indicating the presence of myocardial inflammation in whom (a) a definitive diagnosis of myocarditis was performed after a typical clinical course or (b) those in whom the genetic study did not find any pathogenic mutation associated with cardiomyopathy; group 2 included all patients in whom a definitive pathogenic genetic mutation associated with dilated cardiomyopathy was found.

Data on personal medical history, clinical outcomes and medical treatment were recorded. Clinical presentation

was defined as acute (symptoms of heart failure were present ≤ 15 days before admission) or subacute (> 15 days). A positive family history was considered when there was history of sudden death or cardiomyopathy in a first-degree relative. We collected histological and immunohistochemical findings in the EMB samples, viral polymerase chain reaction (PCR) in the heart and blood, troponin levels, brain natriuretic peptide and respiratory secretions, 12-lead electrocardiogram (ECG) and transthoracic echocardiogram data. Also, in all haemodynamically stable patients, a cardiac magnetic resonance (CMR) was performed.

Endomyocardial biopsy

According to our protocol, EMB was performed to all patients ≥ 6 months and ≥ 8 kg of weight with a new-onset ventricular dysfunction of unknown origin, who presented with the following: (a) LVEF < 35% and need for extracorporeal membrane oxygenation (ECMO); (b) LVEF < 35% with a haemodynamic compromise without ECMO but with no echocardiographic improvement after more than 1 week of medical treatment; (c) patients with LVEF < 35% that remained hemodynamically stable but without any significant improvement after > 2 weeks of medical treatment.

The EMB was performed through jugular access with a 6 Fr biptome, and 6 samples were obtained from the right interventricular septum. Four were sent to pathology examination and 2 for microbiology. Haematoxylin–eosin and Mason's trichrome stains and immunohistochemical stains for CD45, CD20, CD3 and CD68 were performed. We used immunohistology criteria of ≥ 14 mononuclear cells with ≥ 7 CD3 lymphocytes per mm² for diagnosis of myocarditis.

In those patients < 6 months or < 8 kg, the decision to perform an EMB was made individually.

Cardiac magnetic resonance

CMR studies were performed using a 1.5 T Magnetom Avanto, Siemens Medical System, Erlangen, Germany, with cardiac synchronisation. The sequences used were white blood sequences (SSFP) to assess ventricular function, T2-weighted sequences (T2W-STIR), T1 sequences (TSE) before and after the administration of intravenous contrast and delayed uptake of the contrast (PSIR-SSFP). We used gadolinium as contrast with a dose of 0.1–0.2 mmol/kg. For the diagnosis of acute myocarditis, the Lake-Louise criteria were used [18].

Genetic testing

Genomic DNA was isolated from peripheral blood following standard procedures. Genetic testing was performed on a Mi Seq sequencer using the Tru Sight Cardio Panel, which

includes exonic and flanking intronic regions of 174 genes related to cardiovascular disorders. Variant classification was performed according to the guidelines established by the American College of Medical Genetics and Genomics [19]. In those patients who presented with a typical fulminant course of myocarditis [20] and had a complete recovery, genetic testing was not performed as was thought not to be clinically indicated. Thus, these patients were included in group 1.

Statistical analysis

Statistical analyses were performed with SPSS version 18.0.0 (IBM Corporation, Armonk, NY). Data are presented as count (percentage) and mean \pm SD value or median (range) were appropriate. Categorical data were compared using the Mantel–Haenszel chi-square test ($\times 2$). In case of not complying with its application norms (expected frequency < 5), Fisher's F test was used with the continuity correction. Differences in continuous variables were analysed using independent Student's T-test or Mann–Whitney test when applicable. A level of statistical significance with $p < 0.05$ was considered.

Results

Twenty-seven patients with a median age of 26 months (0–194) and 55.5% (15/27) female gender were included (Table 1). Eighteen patients were included in group 1 (myocarditis) and 9 patients in group 2 (genetic cardiomyopathy). Among those patients with myocarditis, 77.7% had a previous history of viral infection and presented a shorter history of symptoms (Table 2). Viral PCR in blood was positive in 50% (9/18) of myocarditis episodes, but it was also positive in 33% (3/9) of patients with genetic cardiomyopathy ($p = 0.431$). Patients with myocarditis had a higher elevation of troponin levels ($p = 0.011$) with no differences seen between pro-BNP levels. In the echocardiogram, left ventricle trabeculations were seen in 4/9 (44%) of patients with genetic cardiomyopathy, but were also present in 11.1% (2/18, $p = 0.136$) of patients with myocarditis. The LVEDD Z-Score was significantly lower in patients with myocarditis (2.2 vs 5.4, $p = 0.03$), and they had an increased ventricular wall thickness (88.8% vs 33.3%, $p = 0.03$). Amongst patients that underwent a CMR (8 patients in group 1 and 6 in group 2), 37.5% (3/8) in group 1 and 33.3% (2/6) in group 2 fulfilled 2/3 Lake Louis Criteria ($p = 1$). The presence of inflammatory infiltrate was higher in patients with myocarditis (37.5 (8–180) vs 14 (0–24) CD3/mm²), although no significant differences were found ($p = 0.1$). Nine (50%) patients in group 1 met Dallas criteria [6] compared to only 1 (11.1%) in group 2 ($p = 0.09$). Immunohistochemical criteria

of inflammatory cardiomyopathy [8] (≥ 14 white blood cells/mm² and ≥ 7 CD3 T lymphocytes/mm²) were fulfilled by 7/9 (77.7%) of patients in group 2. Oedema was not seen in any patient with genetic cardiomyopathy, whereas in the myocarditis group, oedema was seen in 12 (66.6%) out of 18 patients ($p = 0.01$). Viral PCR was positive in 9 (50%) heart samples of patients with myocarditis and 2 (22.2%) of patients with genetic cardiomyopathy ($p = 0.183$). PVB19, alone or in coinfection with Human Herpesvirus 6 (HHV6), was found in 10/11 samples (90.1%).

Ten (55.5%) patients with myocarditis required ECMO, of which 8/10 (80%) could be weaned and had a complete recovery. Only 1 patient required mechanical circulation assistance with a Berlin-Heart® as a bridge to heart transplant. On the other hand, 3 patients required ECMO and 2 Berlin-Heart® in group 2, and none of them recovered. After a follow-up time of 45 months (2–238), 77.7% of patients with acute myocarditis had a complete recovery, while 3 (16.6%) died in the acute phase. In group 2, there were no deaths, but 7/9 (77.8%) required a heart transplant and none presented a complete recovery (Table 2).

Table 1 describes the most relevant clinical data for each patient. Patient 1 died during the EMB. It was the first case in our centre, and it was performed obtaining the myocardial samples from the right interventricular septum and left ventricle free wall. Since then, all the samples were taken from the right interventricular septum with no further complications. Patient number 5 had diphtheria myocarditis, and he developed a severe cerebral haemorrhage while he was supported with ECMO. Patient 17 was an 11-year-old girl who presented with fulminant myocarditis during a SARS-CoV-2 infection. After 5 days on ECMO, she had a complete recovery.

Discussion

Acute myocarditis can present with new-onset severe left ventricular dysfunction, and differential diagnosis with a genetic dilated cardiomyopathy should be considered. In our study, most patients from group 2 (66.6%) had a subacute clinical presentation (more than 15 days of evolution) whereas most patients from group 1 had a fulminant or acute presentation. Unlike what might be expected, the presence of a family history of genetic cardiomyopathy was infrequent. Troponin values were higher in patients with myocarditis, and left ventricle end-diastolic diameter was significantly lower in this group. These facts may be related to a more acute form of presentation. The presence of trabeculations that met non-compaction criteria was more common in group 2 (44.4%), but it was also seen in 2 patients (11.1%) from group 1 ($p = 0.136$). These 2 patients had a subacute presentation, with a history of

Table 1 Description of patients included in the study including clinical description, infectious results, genetic results, and clinical outcomes. DCM, dilated cardiomyopathy; ND, not done; PCR, polymerase chain reaction; CMV, cytomegalovirus; PVB19, parvovirus B19; HHV6, human herpesvirus 6; RSV, respiratory syncytial virus; LVD, Left ventricular dysfunction; MYBPC3, myosin-binding protein C; DES, desmin; TPM1, tropomyosin 1; TNNT2, troponin T2; TNNI3, troponin I3; MYH7, myosin heavy chain 7; SDHA, succinate dehydrogenase complex flavoprotein subunit A

Case	Diagnosis	Gender	Age (months)	History of recent infection	Clinical presentation	Genetic test	CD3 lymphocyte/mm ²	Heart PCR	Blood PCR	Respiratory tract PCR	Outcome
1	Myocarditis	Female	1	No	Fulminant	ND	35	CMV	CMV	Negative	Died
2	Myocarditis	Male	25	Yes	Acute	Negative	40	PVB19	PVB19+HHV 6	Negative	Recovery
3	Myocarditis	Female	7	Yes	Acute	Negative	15	PVB19	Negative	Negative	Transplant
4	Myocarditis	Male	27	Yes	Acute	Negative	80	PVB19	PVB19	Negative	Recovery
5	Myocarditis	Male	79	Yes	Acute	ND	70	Negative	Difteria	Difteria	Died
6	Myocarditis	Female	36	Yes	Acute	Negative	50	PVB19	PVB19	Negative	Recovery
7	Myocarditis	Male	26	Yes	Acute	Negative	20	Negative	Negative	RSV	Recovery
8	Myocarditis	Male	10	Yes	Acute	Negative	25	PVB19+HHV 6	PVB19	Negative	Recovery
9	Myocarditis	Male	22	No	Acute	Negative	15	PVB19	PVB19+HHV 6	Negative	Recovery
10	Myocarditis	Female	91	Yes	Fulminant	ND	15	Negative	Negative	Influenza A	Recovery
11	Myocarditis	Female	109	Yes	Fulminant	ND	8	Negative	Negative	Influenza A	Recovery
12	Myocarditis	Male	194	No	Subacute	Negative	8	Negative	Negative	Negative	Recovery
13	Myocarditis	Female	0	No	Fulminant	Negative	65	Negative	Negative	Negative	Died
14	Myocarditis	Female	92	Yes	Fulminant	ND	10	Negative	Negative	Influenza B	Recovery
15	Myocarditis	Male	7	Yes	Subacute	Negative	50	Negative	Negative	Negative	Improve
16	Myocarditis	Female	10	Yes	Subacute	Negative	70	PVB19	PVB19	Negative	Improve
17	Myocarditis	Female	39	Yes	Subacute	Negative	180	PVB19	PVB19	Negative	Improve
18	Myocarditis	Female	142	Yes	Fulminant	ND	75	Negative	Negative	SARS-Cov-2	Recovery
15	Genetic DCM	Male	2	No	Acute	MYBPC3 c.721C>T	4	Negative	Negative	Negative	Transplant
16	Genetic DCM	Male	99	Yes	Subacute	DES c.364 T>G	24	Negative	Negative	Negative	Transplant
17	Genetic DCM	Male	6	No	Acute	TPM1 c.40G>A	2	Negative	Negative	Negative	Transplant
18	Genetic DCM	Female	109	No	Subacute	TNNT2 c.629_631del	10	Negative	Negative	Negative	Transplant
19	Genetic DCM	Male	187	Yes	Subacute	MYBPC3 c.1288G>A	15	PVB19	Negative	Negative	Transplant
20	Genetic DCM	Female	11	Yes	Acute	TNNI3 c.204del	11	PVB19	PVB19	Negative	Transplant
21	Genetic DCM	Female	30	No	Subacute	TNNI3 c.292C>T	14	Negative	CMV	Adenovirus	LVD
22	Genetic DCM	Female	26	Yes	Subacute	MYH7 c.2710C>T	18	Negative	Negative	Influenza A	Transplant
23	Genetic DCM	Female	11	No	Subacute	SDHA c.1660C>T c.1549A>G	20	Negative	CMV	Negative	LVD

Table 2 Clinical characteristics of patients with myocarditis compared with patients with genetic cardiomyopathy

	Acute myocarditis 18 cases		Genetic cardiomyopathy 9 cases		Statistical significance
Age (months)	26.5 (0–194)		26 (-2187)		$p = 1$
Male gender	44.4% (8)		55.6% (5)		$p = 0.795$
History of family heart disease	0% (0)		33.3% (3)		$p = 0.021$
History of recent infection	77.7% (14)		44.4% (4)		$p = 0.083$
Clinical presentation	Fulminant	30% (6)	Fulminant	0% (0)	$p = 0.01$
	Acute	44.4% (8)	Acute	33.3% (3)	
	Subacute	22.2% (4)	Subacute	66.7% (6)	
ECMO	55.5% (10)		33.3% (3)		$p = 0.147$
Troponin elevation	60 (1.1–2950)		2.2 (0.25–16)		$p = 0.011$
Pro-BNP	1498 ng/ml (459–53,500)		4221 ng/ml (278–23,804)		$p = 0.315$
Blood PCR	50% (9)		33.3% (3)		$p = 0.431$
Echocardiogram					
LVEF (%)	24.6% (± 6.18)		23.4% (± 6.17)		$p = 0.846$
LVEDDZ-score	+ 2.2DS (0–10)		+ 5.4DS (+ 3.2–10.4)		$p = 0.03$
LV hypertrophy	88.8% (16)		33.3% (3)		$p = 0.03$
Trabeculation	11.1% (2)		44.4% (4)		$p = 0.136$
RV dysfunction	50% (9)		55.5% (5)		$p = 0.35$
ECG					
Low voltages	66.6% (12)		33% (3)		$p = 0.127$
CMR Lake-Louise	37.5% (3/8)		33.3% (2/6)		$p = 1$
EMB					
Dallas Criteria	50% (9)		11.1% (1)		$p = 0.091$
CD3/mm ²	37.5 (8–180)		14 (2–24)		$p = 0.1$
Oedema	66.6% (12)		0% (0)		$p = 0.001$
Necrosis	50% (9)		11.1% (1)		$p = 0.091$
Fibrosis	44% (8)		55.5% (5)		$p = 0.94$
Hypertrophy	5.5% (1)		44.4% (4)		$p = 0.03$
Heart PCR	50% (9)		22.2% (2)		$p = 0.183$
Outcome					
Complete recovery	71.4% (10)		0% (0)		$p = 0.021$
Death/transplant	22.2% (4)		77.8% (7)		

ECMO extracorporeal membrane oxygenation, Pro-BNP pro-brain natriuretic peptide, LVEF left ventricle ejection fraction, LVEDD left ventricle end-diastolic diameter, LV left ventricle, RV right ventricle, CMR cardiac magnetic resonance imaging, PCR polymerase chain reaction

PVB19 infection several weeks before heart failure and PVB19 PCR was positive in blood and heart samples. Genetic test was negative in both, and there was no family history of cardiomyopathy. Thus, LV trabeculations seen in these patients could be the result of a LV remodelling process. Hypertrophy of the septum or posterior wall of the LV was more frequent in patients with myocarditis (88.8% vs 33.3%, $p = 0.03$), and this finding is likely to be associated with myocardial oedema.

In our experience, CMR sensitivity in paediatric patients with myocarditis is low in cardiomyopathic clinical presentation. This fact has been previously described in adult patients [21]. In our study, we could perform a CRM in only 14 patients due to hemodynamic instability

on admission: 8 patients in group 1 and 6 in group 2. In the myocarditis group, 7/8 patients (87.8%) met at least 1 of the Lake Louise criteria, but only 3 patients (37.5%) met 2/3, a necessary condition for making the diagnosis. Interestingly, we also found 2 out of 6 patients in group 2 (33.3%) that underwent a CMR that also met 2/3 Lake Louise criteria for myocarditis. This finding has also been recently described by Martins et al. [22].

The current gold standard test for the diagnosis of myocarditis is the EMB but is a risky technique [4, 5] in paediatric patients and is not widely used. In our experience, the rate of complications is low when performed in patients ≥ 6 months and ≥ 8 kg and the samples are taken from the right ventricular septum.

Suthar et al. [17] published a remarkably interesting study in which they assessed the utility of non-invasive measures to distinguish myocarditis from other forms of dilated cardiomyopathy in paediatric patients. They establish the diagnosis of myocarditis based on Dallas criteria. In our experience, these criteria [6] are of limited use, as only 50% of patients with myocarditis fulfilled them. Despite this, some of our results are similar. In addition, we describe the most common findings in EMB. Current immunohistology criteria [8] have not been validated in the paediatric population. We observed a high rate of false positives, given that 77.8% of the patients with genetic cardiomyopathy presented ≥ 14 mononuclear cells/mm² with ≥ 7 CD3 lymphocytes/mm² in the EMB. One possible explanation for these findings could be that these patients had concurrent acute myocarditis. As previously described [10, 15], an acute myocarditis presentation may be the initial manifestation of arrhythmogenic or dilated cardiomyopathies in children. In our opinion, a more plausible explanation is that myocardial inflammation can be triggered by acute clinical decompensation with severe cardiac dysfunction in individuals with genetic cardiomyopathy. This theory has also been proposed recently by Ammirati et al. [23].

Although the number of lymphocytes/mm² was higher in group 1 (37.5 (8–180) vs 14 (0–24) CD3/mm², $p=0.1$), no significant differences were found. Some patients in group 1 had a minor infiltrate, and this could be due to the patchy nature of the disease. Interestingly, a recent paper from Ukimura et al. reported that myocarditis secondary to influenza viruses could present a clinical picture of fulminant myocarditis with very mild histological changes [24]. In our study, 3 cases had influenza (patients 9, 10 and 13), and all of them had very mild histological changes. If those patients were excluded from the analysis, the number of lymphocytes/mm² would have been significantly higher in the myocarditis group (53 (8–180) CD3/mm² vs 14 (0–24), $p=0.009$). Then, the differences in both groups would become statistically significant. Myocardial oedema in the EMB was observed in 66.6% of patients in group 1 and none of group 2 ($p=0.001$), suggesting that it could be a specific marker of myocarditis. On the other hand, myocyte hypertrophy was more likely in patients with genetic cardiomyopathy (5.5% vs 44.4%, $p=0.03$). The latter, we believe, was an unspecific finding associated with a long-standing clinical picture.

In our patients, PVB19 was the main responsible for acute myocarditis, as has been described before [1, 3]. Despite this, myocardial PCR only had a 50% sensitivity, with a 22.2% rate of false-positive cases. The detection of viral genome in the heart of patients without cardiomyopathy has also been previously described [16]. The usefulness of the blood PCR was greater in younger patients (Table 1), especially in children under 5 years of age.

Mortality during the acute phase of illness was higher in patients from group 1 (16.6% vs 0%, $p=0.021$), and 55.5% required ECMO support on admission. If patients survived the initial stage, the long-term survival was excellent. Thus, 92.8% of cases of myocarditis who survived the initial stage had a complete recovery. On the other hand, patients from group 2 had 0% acute mortality and had a non-fulminant clinical presentation. Still, recovery is rare, and only 22% were free of transplant at the end of follow-up time.

Differential diagnosis between myocarditis and genetic cardiomyopathy can be difficult, and, using invasive and non-invasive test, it would be especially useful to create diagnostic scores to differentiate one patient from another. For this purpose, it would be important to do a multicentre study with a larger number of patients.

Conclusions

Our study suggests that current diagnostic criteria for myocarditis have limited use in paediatric patients presenting with new-onset heart failure and LVEF < 35%. Some patients with genetic cardiomyopathy fulfil diagnostic criteria of inflammatory cardiomyopathy. Thus, familiar and genetic study is recommended in paediatric patients with acute and subacute new onset-heart failure. Acute myocarditis is a suspected diagnosis where no examination, by itself, is sensitive and specific enough. Using invasive and non-invasive measures may be useful to develop a predictive model to differentiate myocarditis from genetic cardiomyopathy. For this purpose, it would be important to do a multicentre study with a larger number of patients.

Study limitations

The main limitation of our study is the small number of patients and its retrospective nature. Despite this, our cohort is one of the published series with a higher number of paediatric patients with myocarditis that underwent EMB. Furthermore, the observed effects should be applied only to patients with a severe form of presentation with LVEF < 35%. We cannot rule out that some of the patients with a genetic mutation might have, at the same time, acute myocarditis.

Another source of potential bias is the requirement for a confirmed genetic mutation for the diagnosis of genetic cardiomyopathy: the yield of genetic testing is low in some cardiomyopathy subtypes, and it is quite possible that some of those patients in the myocarditis group may have in fact have had a genetic cardiomyopathy. In addition, in our study, genetic testing was not performed in those patients with a fulminant presentation.

Supplementary information The online version contains supplementary material available at <https://doi.org/10.1007/s00431-021-04175-z>.

Authors' contributions 1) The following coauthors have participated in the study design: Ferran Gran, Andrea Fidalgo, Paola Dolader, Ferran Rosés-Noguer. 2) Data collection and statistical analysis: Ferran Gran, Andrea Fidalgo, Paola Dolader, Marta Garrido, Alexandra Navarro, Jaume Izquierdo-Blasco, Paula Fernández-Álvarez, Marta Codina-Sola. 3) Manuscript preparation: Ferran Gran, Ferran Rosés-Noguer, Raúl Abella, Joaquín Fernández-Doblas, Anna Sabaté-Rotés, Pedro Betrián, Joan Balcells. 4) Manuscript revision: Ferran Rosés-Noguer, Raúl Abella, Joaquín Fernández-Doblas, Anna Sabaté-Rotés, Pedro Betrián, Joan Balcells. All authors read and approved the final manuscript.

Data availability All data was stored following our Ethics Committee and data files are kept in our Hospitals Servers and are available for further analysis and data transparency.

Code availability Statistical analysis was done with SPSS v 21, and syntax files are available with syntax's code fully auditable.

Declarations

Ethics approval The study complies with the Declaration of Helsinki, the locally appointed ethics committee has approved the research protocol, and informed consent has been obtained from the subjects (or their guardians).

Consent to participate Consent is not required as all the data is anonymized, and the submission does not include images that may identify.

Consent for publication Consent is not required as all the data is anonymized, and the submission does not include images that may identify the person.

Conflict of interest The authors declare no competing interests.


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Authors and Affiliations

Ferran Gran¹  · Andrea Fidalgo¹ · Paola Dolader¹ · Marta Garrido² · Alexandra Navarro² · Jaume Izquierdo-Blasco³ · Joan Balcells³ · Marta Codina-Sola⁴ · Paula Fernandez-Alvarez⁴ · Anna Sabaté-Rotés¹ · Pedro Betrián¹ · Joaquín Fernández-Doblas⁵ · Raúl Abella⁵ · Ferran Roses-Noguer^{1,6}

Andrea Fidalgo
andrea.fidalgo.1989@gmail.com

Paola Dolader
pdoalder@vhebron.net

Marta Garrido
magarrid@vhebron.net

Alexandra Navarro
alenuavar@vhebron.net

Jaume Izquierdo-Blasco
jizquierdo@vhebron.net

Joan Balcells
jbalcell@vhebron.net

Marta Codina-Sola
mcodina@vhebron.net

Paula Fernandez-Alvarez
pauferna@vhebron.net

Anna Sabaté-Rotés
asabate@vhebron.net

Pedro Betrián
pbetrian@vhebron.net

Joaquín Fernández-Doblas
j.fernandez@vhebron.net

Raúl Abella
r.abella33@gmail.com

Ferran Roses-Noguer
froses@vhebron.net

¹ Paediatric Cardiology Unit, Hospital Universitari Vall d'Hebron, Vall d'Hebron Barcelona Hospital Campus, Passeig Vall d'Hebron 119-129, 08035 Barcelona, Spain

² Department of Pathology, Hospital Universitari Vall d'Hebron, Vall d'Hebron Barcelona Hospital Campus, Barcelona, Spain

³ Paediatric Intensive Care Unit, Hospital Universitari Vall d'Hebron, Vall d'Hebron Barcelona Hospital Campus, Barcelona, Spain

⁴ Department of Clinical and Molecular Genetics, Vall d'Hebron University Hospital and Vall d'Hebron Research Institute, Barcelona, Spain

⁵ Department of Paediatric Cardiac Surgery, Hospital Universitari Vall d'Hebron, Vall d'Hebron Barcelona Hospital Campus, Barcelona, Spain

⁶ Department of Paediatric Cardiology, Royal Brompton and Harefield NHS Foundation Trust, London, UK