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ORIGINAL ARTICLE

Parvovirus B19 myocarditis in children: a diagnostic and therapeutic approach

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Abstract

Parvovirus B19 is one of the most frequent causes of pediatric myocarditis, associating high mortality rates or need for cardiac transplantation. The aim of this study is to describe the clinical course of Parvovirus B19 myocarditis in children with emphasis on the role of endomyocardial biopsy and cardiac magnetic resonance, and the use of an innovative therapeutic strategy. Eleven patients and 12 episodes of polymerase chain reaction (PCR)-confirmed Parvovirus B19 myocarditis were prospectively collected for 14 years. Diagnosis was confirmed either histopathologically or by magnetic resonance. A life-threatening clinical presentation is described, similar to previous series, but with 83.3% overall survival without transplantation. We also present a case of recurrent myocarditis, which is extraordinarily rare. Electrocardiographic patterns presented chiefly peaked p waves, low QRS voltages, and negative T waves on inferior or lateral leads. Endomyocardial biopsy is the *gold standard* diagnostic test; alternatively magnetic resonance could be a useful diagnostic tool. A good concordance between myocardial and blood PCRs was observed. Seven patients received treatment with corticosteroids and beta interferon and all underwent a significant cardiac function improvement.

Conclusion: A severe clinical presentation is reported, similar to previous reports but with better outcomes. Endomyocardial biopsy is the *gold standard* diagnostic test; alternatively magnetic resonance may be used. Both blood and myocardium PCR can be used in children to establish the microbiological etiology. Steroids with IFNß could be a useful therapeutic option, although further multicenter studies are needed to confirm these results.

What is Known:
- *Parvovirus B19 is one of the most frequent causes of myocarditis in children. It is associated with a fulminant clinical presentation.*
- *Endomyocardial biopsy is the gold standard diagnostic test but it is an invasive procedure.*

What is New:
- *Myocarditis may recur in pediatrics, even it is extraordinarily rare.*
- *IFNβ with steroids may be a useful therapeutic option to improve the outcomes.*

Keywords Myocarditis · Parvovirus B19 · Endomyocardial biopsy · Cardiac magnetic resonance · Beta interferon · Steroids

Abbreviations

MRI	Magnetic resonance imaging
ECG	Electrocardiogram
ECMO	Extracorporeal membrane oxygenation
IFNß	Beta interferon
IQR	Interquartile range
LV	Left ventricle
PCR	Polymerase chain reaction
RV	Right ventricle
TAPSE	Tricuspid annular plane systolic excursion

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Introduction

Acute myocarditis is an inflammatory disease of the myocardium mainly caused by a viral infection [1]. Its clinical presentation ranges from chest pain to cardiogenic shock, being an important cause of morbimortality [2, 3].

Endomyocardial biopsy is the gold standard diagnostic test. However, since it is an invasive procedure, its use is limited in pediatric patients [4–6]. Cardiac magnetic resonance (MRI) is the main tool for non-invasive assessment of myocardial inflammation [1, 7].

The role of parvovirus B19 in adults with myocarditis or dilated cardiomyopathy is currently under debate. Viral genome has been found in the myocardium of people without cardiac disease, suggesting that these findings could not always imply an active infection [8].

In pediatric patients, it is one of the most frequent causes of myocarditis, with a high mortality rate or need for cardiac transplantation [2, 9]. Nevertheless, evidence in pediatric population is sparse, and large studies are still lacking with only single-case reports and small series in the literature [8, 9].

Our study aims to describe the clinical course of Parvovirus B19 myocarditis in children with special emphasis on the role of endomyocardial biopsy and cardiac MRI in diagnosis and the use of an innovative therapeutic strategy with immunosuppressive treatment and interferon.

Material and methods

Pediatric patients with polymerase chain reaction (PCR)-confirmed Parvovirus B19 myocarditis in a single center were prospectively collected for 14 years (from April 2007 to June 2021).

The clinical-assessed diagnosis of myocarditis was confirmed either histopathologically or by MRI. Parvovirus B19 was considered the causal agent if it was verified by PCR in myocardial or in blood sample.

Cardiac MRI, when performed, it was after initial stabilization, during the first 2 weeks after the onset in those patients who were able to be transferred to the MRI department. Lake-Louise Criteria were used for diagnosis [7]. 1.5 T Magnetom Avanto (Siemens Medical System, Erlangen, Germany) with cardiac synchronization was used. White blood sequences (SSFP) were used to assess ventricular function, and T2-weighted (T2W-STIR) and T1-weighted sequences (TSE) were performed before and after the administration of intravenous gadolinium (0.1–0.2 mmol/kg) and delayed uptake of contrast (PSIR-SSFP).

According to our protocol, biopsy was performed in all patients ≥ 6 months and ≥ 8 kg of weight with a new-onset ventricular dysfunction of unknown origin, who presented with (a) LVEF $< 35\%$ and need of veno-arterial extracorporeal membrane oxygenation (ECMO); (b) LVEF $< 35\%$ with hemodynamic compromise without requiring ECMO but with no echocardiographic improvement after more than 1 week of medical treatment; and (c) hemodynamically stable patients with LVEF $< 35\%$ without any significant improvement after > 2 weeks of medical treatment. Endomyocardial biopsy was performed through jugular access with a 6Fr bioptome, and 6 samples were obtained from the right interventricular septum: 4 were sent to pathology and 2 to microbiology. Hematoxylin–eosin, Mason's trichrome, and immunohistochemical stains for CD45, CD20, CD3, and CD68 were performed. Myocarditis was diagnosed following the Marburg immunohistological criteria of ≥ 14 mononuclear cells with ≥ 7 CD3 lymphocytes per mm^2 [4].

Initial and follow-up echocardiographic studies were evaluated to assess right (RV) and left ventricular (LV) function, hypertrophy, and dilatation. LV function was assessed by M-mode being the ejection fraction by Teicholz considered normal ($> 55\%$), mild dysfunction (45–55%), moderate dysfunction (35–45%), or severe dysfunction ($< 35\%$). LV hypertrophy was considered when interventricular septum or posterior wall thickness z-score was $> +2$ and dilatation when the end-diastolic diameter z-score was $> +2$. RV dysfunction was determined using a tricuspid annular plane systolic excursion (TAPSE) z-score of < -2. Valvular regurgitation was assessed using the color flow area of the regurgitant jet and the extent into the atrium. All electrocardiograms (ECG) were evaluated manually by the same person.

Statistical analysis was performed using SPSS for Windows version 25.0 (Armonk, NY, USA. IBM Corp.). Nominal data were described using proportions and quantitative continuous data with medians and interquartile range (IQR) as the sample did not present a normal distribution.

Results

From April 2007 to February 2021, 53 episodes of acute myocarditis in 52 patients were identified in our center, 22 (41.5%) by endomyocardial biopsy and 31 (58.5%) by cardiac MRI. The main cause was Parvovirus B19 (12/53, 22.6%), followed by Coxsackievirus (5/53, 9.4%). The affected patients were predominantly male (7/12, 58.3%) with a similar age at presentation: median of 21.5 months, range from 7 months to 3 years. Demographic information and clinical presentation are presented in Tables 1 and 2.

The diagnosis of myocarditis was achieved histologically in 9/12 episodes (8 by biopsy and one by necropsy) and by MRI in 3 cases without histology.

Endomyocardial biopsy was performed a median of 22 days (IQR 12–42) after the onset of myocarditis. Specimens demonstrated diffuse interstitial infiltrates of lymphocytes (median of 50 T-lymphocytes per mm^2, IQR 25–70). Edema (7/9, 77.8%), mild fibrosis (3/9, 33.3%), and necrosis (4/9, 44.4%) were also observed, probably describing different phases of the disease. Myocardial hypertrophy or ischemia were not observed (Table 3).

Cardiac MRI was performed in 9 patients, being suggestive of myocarditis in 8/9 patients (88.9%). Lake-Louise

Table 1 Clinical presentation and follow-up of the patients

Episode	Patient	Age (months)	Gender	Initial clinical presentation	Initial ejection fraction	Diagnostic test	Positive PCR for PVB19	Coinfection	Specific treatment	Outcome	Days to cardiac function recovery
1	1	25	Male	Cardiogenic shock	35%	EMB, CMR	Blood and EMB	HHV-6 in blood	Interferon beta + corticosteroids	Complete recovery	922
2	2	11	Female	Cardiogenic shock	22%	CMR	Blood			Complete recovery	360
3	3	16	Male	Heart failure	33%	CMR	Blood			Complete recovery	273
4	4	7	Female	Cardiogenic shock	24%	EMB	EMB			Transplantation	
5	5	26	Male	Heart failure	32%	EMB, CMR	Blood and EMB		Interferon beta + corticosteroids	Complete recovery	245
6	6	36	Female	Cardiogenic shock	30%	EMB, CMR	Blood and EMB		Interferon beta + corticosteroids	Complete recovery	320
7	7	24	Male	Cardiogenic shock	24%	EMB	Blood and EMB			Death	
8	8	9	Male	Cardiogenic shock	30%	EMB	Blood and EMB	HHV-6 in EMB	Interferon beta + corticosteroids	Initial recovery, then recurrence	93
9		21	Male	Cardiogenic shock	31%	EMB, CMR	Blood and EMB	HHV-6 in blood	Interferon beta + corticosteroids	Complete recovery	21
10	9	22	Male	Heart failure	48%	CMR	Blood			Complete recovery	167
11	10	9	Female	Heart failure	23%	EMB, CMR	Blood and EMB		Interferon beta + corticosteroids	Improvement	
12	11	38	Female	Heart failure	25%	EMB, CMR	Blood and EMB		Interferon beta + corticosteroids	Complete recovery	270

PVB19, Parvovirus B19; *EMB*, endomyocardial biopsy; *CMR*, cardiac magnetic resonance; *PCR*, polymerasse chain reaction

Table 2 Demographic information and presentation

Clinical presentation	$n = 12$ episodes (%)
Demographics	
- Male	7 (58.3%)
- Age at presentation: months (median, interquartile range)	21.5 (14.75)
Initial clinical presentation	
- Cardiogenic shock	7 (58.3%)
- Heart failure	5 (41.7%)
- Chest pain	0 (0%)
- Rhythm disturbances	0 (0%)
Severity of illness	
- Intensive care unit admission	12 (100%)
- Mechanical ventilation	8 (66.7%)
- Inotropic agents	12 (100%)
- Mechanical circulatory assist devices	3 (25%)
Echocardiographic assessment	
- Left ventricular dysfunction	
- Mild dysfunction	1 (8.3%)
- Moderate dysfunction	1 (8.3%)
- Severe dysfunction	10 (83.3%)
- Left ventricular dilatation	12 (100%)
- Left ventricle hypertrophy	8 (66.7%)
- Left atrium dilatation	12 (100%)
- Mitral regurgitation (moderate to severe)	7 (58.3%)
- Right ventricular dysfunction	4 (33.3%)
Microbiological confirmation (Parvovirus B19 PCR)	
- Endomyocardial biopsy	9 (75%)
- Blood	11 (91.7%)
- Tracheal aspirate	1 (8.3%)

PCR, polymerase chain reaction

criteria in this sample are presented in Table 3, as well as the presence of pericardial effusion (6/9, 66.7%). Six of these patients also underwent a biopsy, 5 of them after having achieved the diagnosis by MRI. Genetic test was carried out in 5 patients with a negative result.

Parvovirus B19 PCR was positive in myocardium in 9/9 episodes and in blood in 11/12 (91.7%). Myocardium and blood PCR results are concordant (Table 1). It was detected by tracheal aspirate in 1/9 samples (11.1%). Three patients (3/12, 25%) presented coinfection with Human Herpesvirus 6.

Table 2 describes the initial clinical presentation: cardiogenic shock (7/12, 58.3%) and heart failure (5/12, 41.7%). No patient presented initially with chest pain or arrhythmias, although one presented with ventricular tachycardia during hospitalization. A history of upper respiratory tract viral infection was referred in all but one case (11/12, 91.7%), a median of 14 days before (IQR 5.5–21). All patients presented with acute heart failure requiring inotropic support and admission to an intensive care unit, 8/12 (66.7%) required mechanical ventilation and 3/12 (25%) mechanical circulatory support with ECMO. Echocardiography at admission showed LV dysfunction in all the patients; echocardiographic assessment is shown in Table 2.

Patient number 8 (Table 1) presented with cardiogenic shock at 9 months of age, requiring mechanical circulatory assistance and being the diagnosis achieved histologically. A year after complete recovery, he presented again with cardiogenic shock; the diagnosis of myocarditis was also confirmed (MRI and biopsy).

Initial blood tests showed elevated troponin levels in all patients, and creatine kinase was assessed in 8 (median 21.28 µg/L, IQR 7.2–58.98, normal value < 5 µg/L), being elevated in 6 (75%). NT-proBNP (N-terminal pro b-type natriuretic peptide) rose as a heart failure indicator, with a median of 6160 pg/mL (IQR 2157–28,150) (normal value < 100 pg/mL). Inflammation biomarkers such as C-reactive protein (median 0.5 mg/dL, IQR 0.1–3.9) and leukocytes (median 8800 cells/µL, IQR 8512–11,917) were mainly normal.

Table 3 Procedures used to diagnose myocarditis: immunohistological parameters in endomyocardial biopsy and imaging criteria in the cardiac MRI

Episode	Diagnostic procedure	Endomyocardial biopsy						Cardiovascular magnetic resonance			
		Days after presentation	T-lympho-cyte/mm2	Necrosis	Fibrosis	Edema	Hypertrophy	Lake-Louis criteria			Peri-cardial effusion
								T2-weighted images	Early gadolinium enhancement (T1)	Late gadolinium enhancement (T1)	
1	EMB, CMR	42	40	Absent	Mild	Absent	Absent	Negative	Positive	Negative	Absent
2	CMR							High signal intensity	Non-performed	Non-assessable	Yes
3	CMR							High signal intensity	Negative	Negative	Absent
4	EMB	22	15	Mild	Absent	Mild	Absent				
5	EMB, CMR	33	80	Severe	Absent	Mild	Absent	High signal intensity	Negative	Negative	Yes
6	EMB, CMR	79	50	Absent	Mild	Mild	Absent	Negative	Negative	Negative	Absent
7	EMB	8	65	Absent	Absent	Severe	Absent				
8	EMB	12	25	Absent	Mild	Mild	Absent				
9	EMB, CMR	6	15	Absent	Mild	Absent	Absent	High signal intensity	Non-performed	Non-assessable	Yes
10	CMR							High signal intensity	Non-performed	Positive	Yes
11	EMB, CMR	17	70	Mild	Absent	Mild	Absent	High signal intensity	Positive	Positive	Yes
12	EMB, CMR	105	180	Mild	Absent	Mild	Absent	High signal intensity	Negative	Positive	Yes

EMB, endomyocardial biopsy; *CRM*, cardiovascular magnetic resonance

Table 4 Electrocardiographic abnormalities presented at diagnosis

Electrocardiographic abnormalities	$n = 12$ (%)
Electrocardiographic abnormalities	12 (100%)
Atrial abnormalities	
- Peaked p wave	6 (50%)
Interventricular conduction delay (QRS prolongation)	1 (8.3%)
Q waves in lateral and inferior leads	1 (8.3%)
Ventricular repolarization abnormalities	
- T wave inversion in lateral or inferior leads	9 (75%)
- ST segment elevation	0 (0%)
Low voltages	9 (75%)
Abundant ventricular ectopy	1 (8.3%)

ECG abnormalities were present in all patients (Table 4). Ventricular repolarization abnormalities (9/12, 75%) and low voltages (9/12, 75%) were the most common findings. Interestingly, a similar ECG pattern, consisting of peaked p waves, low QRS voltages, and ventricular repolarization abnormalities with negative T waves on inferior or lateral leads (example in Fig. 1), was observed repeatedly (6/12, 50%).

From the whole sample, cardiac function improved in 10 episodes (10/12, 83.3%), 9 of them with a complete recovery after a median of 270 days (IQR 167–320) and one still with mild dysfunction at 1-year follow-up. One patient died and one required transplantation 154 days after presentation.

In 7 occasions, treatment with corticosteroids and beta interferon (IFNß) was administered. One hundred percent underwent a significant cardiac function improvement; the improvement being detected a median of 9 days (IQR 6.5–15) after starting it. Complete recovery was achieved in 6/7 episodes (85.7%).

Discussion

In our experience, Parvovirus B19 is the most common virus causing myocarditis in children. However, literature on pediatric Parvovirus B19 Myocarditis is very scarce, with only two observational studies published [2, 9]. We present our 14-year experience, all cases being confirmed either by endomyocardial biopsy or by cardiac MRI; clinical presentation and follow-up are described, with better outcomes than those previously reported. Also one case of recurrence is reported, which is extraordinarily rare.

The clinical presentation described in this study (cardiogenic shock and heart failure) is similar to previous series, but arrhythmias are reported in the literature among 12–16% of patients [2, 9]. Severity of the episode requiring ICU admission is almost universal but the use of mechanical circulatory assistance in our sample was 25%, less than in other series: 41–47% [2, 9].

We also describe the recurrence of myocarditis in one patient (Table 1), 1 year later and being confirmed in both

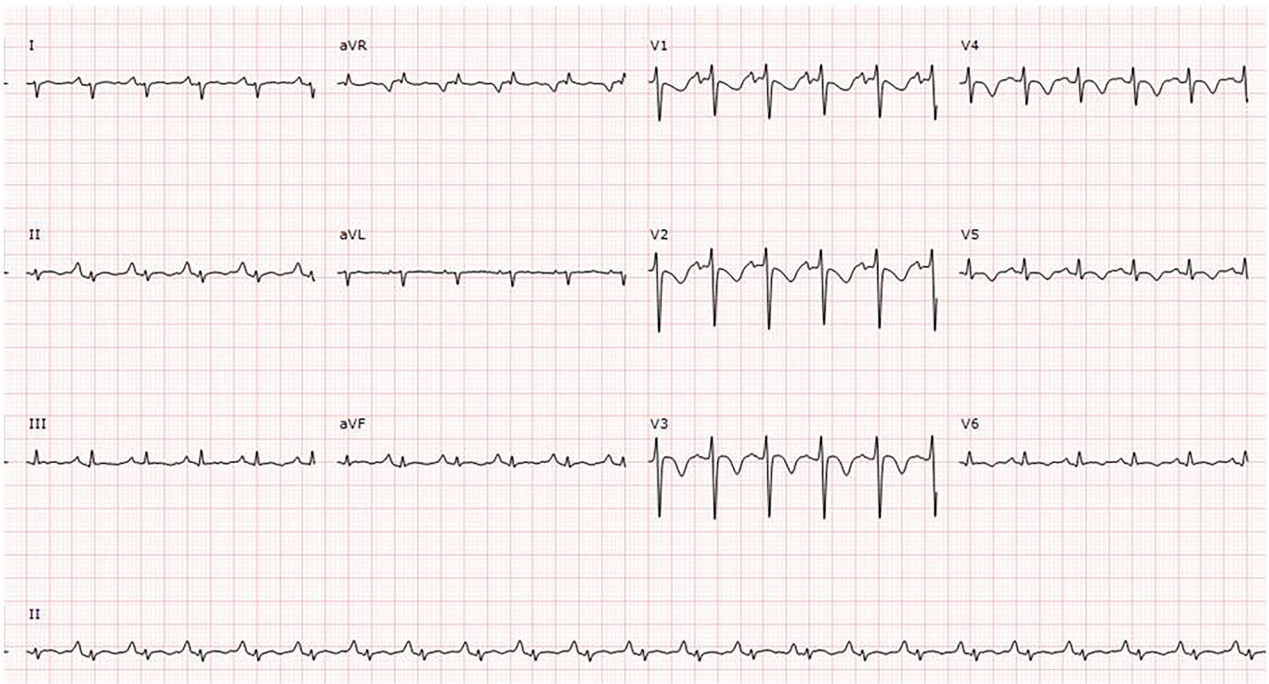

Fig. 1 Electrocardiogram from patient 9. A pattern, consisting of peaked p waves, low QRS voltages, and ventricular repolarization abnormalities with negative T waves on lateral leads, is shown

episodes histologically. Symptoms, LV function, ECG, and blood tests completely normalized between episodes. The recurrence of myocarditis is extraordinarily rare and the vast majority of reported cases involve adults, with only 3 reports in children [10, 11]

To establish the etiological diagnosis, blood and myocardium PCR are useful in children, especially in infants [9, 12] but its usefulness in adults seems less clear as it may be a bystander in the myocardium without causing myocarditis [8, 13, 14]. A good correlation between myocardial and blood PCR results, especially in younger patients, was present in our sample.

As presented in this series, Parvovirus B19 dual infections are mainly with Human Herpesvirus 6. Contrarily to our good outcomes (3/3, 100% improvement), in adults, it usually results in a more severe course because it reactivates latent Parvovirus infection [8].

Endomyocardial biopsy is the *gold standard* test for myocarditis but it is an invasive exam; furthermore, its sensitivity can be low due to the patchy inflammation within the heart and the fact that sampling is usually performed from the less affected right ventricle, to decrease the risk of complications [5, 6, 9]. For this reasons, in our opinion, it should be reserved for the most severe cases and for those with ventricular dysfunction without improvement during follow up, to guide targeted treatment.

Cardiac MRI has become the primary tool for non-invasive assessment of myocardial inflammation [7] with a diagnostic sensitivity in this study (5/6, 83.3%) similar to previous series [15]. The lack of large-scale multicenter data precludes the possibility of establishing the real diagnostic accuracy, being in some studies about 78% when using the 3 tissue markers of the Lake-Louise criteria and 68% when using only late gadolinium enhancement in T1-weighted images [7]. Other studies report a sensitivity of 57% in patients with a cardiomyopathic presentation (LV dysfunction and heart failure) and overall sensitivity of 61.4% [16].

We report a typical ECG pattern in our sample (6/12, 50%), consisting of peaked p waves, low QRS voltages, and ventricular repolarization abnormalities with negative T waves on the inferior or lateral leads. In previous publications in children, T-wave and ST changes were the most common findings on ECG [2, 9, 17], being ST changes associated with worse outcomes [9]. Peaked p waves and low QRS voltages have been less often highlighted.

Since February 2015, as part of our protocol, treatment with steroids and IFNß is used in those patients with severe episodes (need for ECMO or LVEF < 35% without any significant improvement after > 2 weeks).

On the one hand, immunosuppressive treatment is recommended in inflammatory cardiomyopathy when the viral PCR in myocardial tissue is negative, and it has also been proposed in viral myocarditis where an immune-mediated lymphocytic infiltration is the main cause of the myocardial damage [1, 17, 18] and Parvovirus B19 appears to cause both a virus-mediated and virus-triggered immune-mediated myocarditis [1]. So far, steroids have not significantly demonstrated a reduction in the death rate but significant differences in left ventricular systolic function have been demonstrated [17].

On the other hand, IFNß was initially associated to LV function improvement after adenoviral and enteroviral clearance [19]. A mild improvement has also been described in Parvovirus B19 cardiomyopathy after IFNß treatment in adults [20, 21]. IFNß use in pediatric patients with acute myocarditis was initially described in 2016 [22]. The use of immunoglobulin (IVIG) has also been proposed but there is no evidence to support its use [1, 17].

A severe clinical presentation is described, similar to other series [2, 9]. Parvovirus B19 myocarditis often demonstrate persistent and progressive myocardial dysfunction, which may be ischemia related, as persistent parvovirus infection may affect the coronary endothelium [23]. Even so, the clinical outcome is favorable with better outcomes in our sample than those published previously. Particularly noteworthy is the good outcome of the patients who received specific treatment (100% (7/7) cardiac function improvement) although they were the most severely affected.

We highlight two patients who were referred from other centers to evaluate heart transplantation. Upon arrival at our center, an endomyocardial biopsy was performed (79 and 105 days after onset, Tables 1 and 3) and steroids with IFNß were started. The recovery achieved after this treatment, in patients with long-time dysfunction despite heart failure treatment, makes us think that the treatment we propose could be a good option. The fact that no fibrosis was found in the biopsy is consistent with the further recovery.

The overall survival without transplantation represents 83.3% (10/12) of the sample, being higher than in previously published series: 31.6% in the Texas and Arkansas Children's Hospitals (5/19 death, 8/19 transplantation) [2] and 64.7% in the Great Ormond Street Hospital (5/17 death, 1/17 transplantation) [9].

Study limitations

The first limitation is that, since the study began in 2007, a suboptimal method (Teicholz method) has been used to calculate ventricular function; Even so, the same method has been used over time to avoid generating biases.

The main limitation of the study is its single-center design, with a small group of patients as it is a very rare disease; therefore, it is difficult to extrapolate our data to general population. The small sample size does not allow establishing whether the proposed treatment offers an advantage to supportive therapy alone.

In addition, our clinical management has changed over these years, having a different approach before and after February 2015. Larger and multicentric studies would help to achieve stronger conclusions.

Conclusion

Parvovirus B19 is the most frequent cause of acute myocarditis in children, presenting usually with acute heart failure or cardiogenic shock. The recurrence of acute myocarditis is extraordinarily rare; this study includes the 4th pediatric case reported in the literature. Endomyocardial biopsy is the *gold standard* diagnostic test but it is an invasive procedure, and it may be reserved for those patients with the most severe forms of clinical presentation. Cardiac MRI is also a useful diagnostic tool for acute myocarditis. To establish the etiological diagnosis, blood and myocardium PCR can be used in children. Treatment with steroids plus/minus IFNß could be useful to improve the outcomes and our experience supports this attitude, although this ongoing debate still has to be solved and well-designed studies are needed to answer this question.

Authors' contributions All authors contributed to the conception and design of the work. Data collection, analysis, and interpretation were performed by Roger Esmel-Vilomara and Ferran Gran. The first draft was written by Roger Esmel-Vilomara. The draft was read and approved by all the authors.

Availability of data and material Yes.

Declarations

Ethics approval This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of Vall d'Hebron Hospital Campus.

Consent to participate Not applicable.

Consent for publication Informed consent for publication was obtained.

Conflict of interest The authors declare no competing interests.

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