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Coxsackievirus-induced myocarditis

Miocarditis agudas por virus coxsackie

Dear Editor:

Acute myocarditis is a life-threatening myocardial inflammatory disease mainly caused by viral infections. Virus-induced myocarditis can refer to virus-mediated or virus-triggered (immune-mediated) disease; coxsackieviruses may cause virus-mediated myocarditis, as viral replication can cause direct cardiomyocyte injury.[1]

There are critical knowledge gaps regarding the diagnosis, prognosis and treatment of myocarditis. The aim of this report is to describe the clinical presentation of coxsackievirus-induced myocarditis and its outcomes.

Coxsackievirus is one of the most common causative agents of myocarditis in children. In a period of 14 years (April 2007 to September 2021), there were 5 cases of coxsackievirus-induced myocarditis confirmed by polymerase chain reaction (PCR) testing of blood samples out of 55 cases of viral myocarditis, making coxsackievirus the second leading causative agent in the sample following parvovirus B19.

The cases occurred in 4 newborns (median age 16.5 days, range 8–24) and 1 infant aged 10-months. Table 1 presents the demographic and clinical characteristics of the sample.

Certain *Enterovirus* serotypes are associated with particular clinical phenotypes and age groups.[2] In the subset of cases of *Enterovirus* infection in our sample, coxsackievirus was the only detected virus, as it is the predominant type causing myocarditis.[3] Four fifths of the patients with coxsackievirus were newborns, and other viruses were found in older children. As previously described, *Enterovirus* myocarditis and sepsis affect significantly younger children compared to other presentations.[2] A systematic review of severe neonatal enterovirus infections found that 54.7% of the cases of myocarditis occurred in newborns aged less than 7 days.[3] Coxsackievirus–adenovirus-receptor (CAR) is a key element of coxsackievirus-induced myocarditis that also plays a role in cardiac morphogenesis. Its expression peaks in the perinatal period, after which levels decrease with age, thereby decreasing the risk of fatal myocarditis.[4]

The infection may be transmitted vertically, before or after delivery, or horizontally.[3] All cases in our sample involved horizontal transmission, with a history of upper respiratory tract infection preceding heart dysfunction by a median of 4 days (range, 1–7), although the tracheal aspirate PCR test was only positive in 1 patient. While it has been reported that PCR cycle threshold values are considerably lower in faecal samples compared to blood,[2] routine faecal PCR testing in neonates with myocarditis may identify the etiological agent efficiently.

All newborns presented with severe disease in the form of cardiogenic shock, which was consistent with previous studies[2,3] and could be explained by their functionally immature immune system[3] and upregulated expression of CAR in the perinatal period.[4] The infant presented with heart failure. None of the patients had arrhythmia. All patients required admission to the intensive care unit and inotropic support, and all but one (80%) mechanical ventilation. On the other hand, adults usually develop mild symptoms, with only 8.6% presenting with fulminant myocarditis in a retrospective registry.[1]

Electrocardiographic abnormalities were present in 3 patients: ventricular repolarization abnormalities (2/5, 40%) and q waves (2/5, 40%). The initial blood tests showed elevated levels of troponin and creatine kinase. The echocardiographic assessment revealed left ventricular (LV) dysfunction in every patient (median ejection fraction, 30%; IQR, 13%), LV dilatation in 1, left atrial dilatation in 4 and mitral valve regurgitation in 4. Left ventricular hypertrophy was present in 4 patients (80%). Significant right ventricular dysfunction was present in 2 patients.

The clinical diagnosis of myocarditis was confirmed in all but one patient by cardiovascular magnetic resonance imaging (CMR), the primary tool for non-invasive assessment of myocardial inflammation.[5] Table 1 documents the Lake-Louise criteria and the presence of pericardial effusion. The patient that did not undergo CMR in the acute phase presented with cardiogenic shock almost requiring mechanical

Table 1 Clinical presentation and followup of the patients.

Patient	Age	Sex	Initial clinical presentation	Initial ejection fraction (Echo)	Cardiovascular magnetic resonance imaging				Positive PCR	Specific treatment	Outcome	Days to cardiac function recovery
					Lake-Louise criteria			Pericardial effusion				
					T2-weighted images	Early gadolinium enhancement (T1)	Late gadolinium enhancement (T1)					
1	24 days	Male	Cardiogenic shock	29%	High signal intensity	Not performed	Not assessable	Absent	Blood		Complete recovery	65
2	24 days	Male	Cardiogenic shock	30%	High signal intensity	Negative	Positive	Absent	Blood		Complete recovery	58
3	9 days	Male	Cardiogenic shock	42%	Negative	Positive	Not assessable	Present	Blood and CSF		Complete recovery	168
4	10 months	Male	Heart failure	45%	High signal intensity	Positive	Negative	Absent	Blood and TA		Complete recovery	2
5	8 days	Female	Cardiogenic shock	15%					Blood	Interferon beta + corticosteroids	Complete recovery	147

CSF, cerebrospinal fluid; Echo, echocardiography; PCR, polymerase chain reaction; TA, tracheal aspirate.

circulatory support, and coronary involvement was ruled out in the catheterization laboratory. She remained haemodynamically unstable and required inotropic support for 39 days, and was therefore unable to be transported to undergo CMR. Ideally, CMR should be performed within 2–3 weeks of the onset of symptoms.[1]

The previous literature describes a substantial neonatal mortality, of up to 38.6%, in addition to persistent of impaired myocardial function in a large proportion of survivors.[2,3] In contrast, we found complete recovery of cardiac function in 100% of patients in a median of 65 days (IQR, 89).

Per our protocol, implemented since 2015, corticosteroids and interferon beta (IFNß) are administered to patients with severe *Enterovirus* myocarditis (need for extracorporeal membrane oxygenation or severe dysfunction without improvement after 2 weeks). Recent research supports the role of IFNß in effective enterovirus clearance, LV function improvement and survival,[6] as viral replication causes direct cardiomyocyte injury in virus-mediated myocarditis.[1] Our most unstable patient received IFNß leading to successful recovery. Furthermore, immunosuppressive therapy has been proposed if myocardial damage is associated with lymphocytic infiltration,[1] so steroids may also be useful.

In conclusion, in this sample of patients with myocarditis confirmed by CMR, we found a severe clinical presentation, and we believe that newborns presenting with cardiogenic shock should be tested for coxsackievirus. In contrast to previous series, outcomes in our sample were favourable, as 100% of patients survived and achieve complete cardiac recovery. The administration of IFNß and steroids could be useful to improve outcomes, although further multicentre studies are needed.

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Morbidity of uveitis associated with juvenile idiopathic arthritis: The silent disease

Morbilidad de la uveítis asociada a artritis idiopática juvenil: la enfermedad silente

Dear Editor:

Juvenile idiopathic arthritis (JIA) is the most frequent chronic rheumatologic disease in the paediatric age group. It encompasses the spectrum of inflammatory arthritis of unknown aetiology, lasting a minimum of 6 weeks, in patients aged less than 16 years. It is a diagnosis by exclusion and is classified into 7 clinical forms based on its clinical and laboratory characteristics and extra-articular manifestations.[1]

Uveitis refers to the inflammation of the iris, ciliary body and choroid, with potential involvement of the retina.[2] Anterior uveitis, or iridocyclitis, is the most frequent extra-articular manifestation of JIA and may cause significant morbidity,[2,3] including development of cataracts, glaucoma, band keratopathy, synechiae, macular oedema, loss of visual acuity (VA) and blindness.[1–3] Juvenile idiopathic arthritis-associated uveitis (JIA-U) is the most frequent form of secondary anterior uveitis in children and occurs in 11%–30% of patients with JIA.[2]

Chronic anterior uveitis (CAU) is the most frequent type of JIA-U. Unlike acute anterior uveitis (AAU), CAU develops silently, without red eye, ocular pain or photophobia. Therefore, ophthalmological evaluations must be performed at regular intervals.[3]

Given the frequency and morbidity of JIA-U and that uveal inflammatory disease is not well known by paediatricians, we conducted a review of the evidence on the