

SWISS SOCIETY OF NEONATOLOGY

Extracorporeal membrane
oxygenation support for
neonatal enteroviral
myocarditis

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The incidence of viral infections in young children is very high and seasonal epidemics cause a considerable burden on health care systems (1, 2). Respiratory syncytial virus (RSV), influenza and parainfluenza viruses cause epidemics occurring in winter, whereas enteroviruses and adenoviruses are commonly detected during the summer months. In the NICU, morbidity and mortality of bacterial infections usually outweigh the impact of viral infections, and severe viral infections are seen only rarely (3-5). A Dutch study reported that 1% of NICU patients were diagnosed with a viral infection, and of these 39% were due to enteroviruses (3).

We present two cases of neonatal enteroviral myocarditis requiring support with extracorporeal membrane oxygenation (ECMO) and review the literature on neonatal myocarditis.

A baby girl was vaginally delivered at 36 4/7 weeks gestational age weighing 2610 g. Postnatal adaptation was unremarkable with an arterial cord blood pH of 7.33 and Apgar scores of 5, 9 and 10 at 1, 5 and 10 minutes, respectively. On day eight, feeding difficulties, intermittent cyanosis and short apneas requiring stimulation were noted. Physical examination showed tachycardia, tachypnea and a prolonged capillary refill time. No heart murmur was audible, and pre- and postductal saturations were 98% while breathing room air. Laboratory examinations revealed a low C-reactive protein (5 mg/l), a leukocyte count of 10.4

INTRODUCTION

CASE REPORT 1

G/I with 19% bands and an I:T ratio of 0.32, and a platelet count of 220 G/l. Cerebrospinal fluid (CSF) examination showed a predominantly mononuclear pleocytosis of 330 cells/ μ l. Bacterial cultures and urine examination were negative. A venous blood gas analysis showed a pH of 7.33, pCO₂ 55.5 mmHg, HCO₃⁻ 29 mmol/l, base excess 1.3 mmol/l, and lactate 1.1 mmol/l. EEG showed a reduced baseline activity with multifocal epileptic potentials consistent with encephalitis. Suspecting late-onset sepsis with meningitis, a fluid bolus was given and empirical treatment with amoxicillin, gentamycin and acyclovir was initiated together with a phenobarbital load.

On day ten of life, the patient required urgent intubation and mechanical ventilation due to rapid deterioration with tachycardia, poor peripheral perfusion, arterial hypotension and increased work of breathing. On the chest X-ray, cardiomegaly with pulmonary congestion and pulmonary effusions were noted (Fig. 1). The baby was transferred to the neonatal and pediatric intensive care unit. Physical examination revealed hepatomegaly and a gallop rhythm with a split second heart sound. On an ECG, ST-segment depressions were noted in leads V1 to V4 (Fig. 2). Cardiac enzymes were elevated with a troponin I of 10.2 μ g/l (< 0.04), creatine kinase of 377 U/l (< 262), CK-MB 104 μ g/l (< 7), LDH 478 U/l (< 388) and lactate was 5 mmol/l. Echocardiography revealed normal anatomy but a severely reduced left ventricular contractility with an ejection

fraction of 20% and systemic pulmonary hypertension. The coronary anatomy was normal and the pulmonary veins could be visualized with unobstructed entry into the left atrium. Enteroviral cultures were negative but polymerase chain reaction (PCR) testing of CSF, nasopharyngeal aspirates and stool were positive for Coxsackie B3 virus. The diagnosis of Coxsackie B3 myocarditis was made. Intravenous immunoglobulin was given and treatment with dobutamine and milrinone was started.

Over the subsequent 48 hours recurrent ventricular tachyarrhythmias were recorded (Fig. 3). These episodes were refractory to treatment with amiodarone and refractory to electroconversion, leading to arterial hypotension, pulmonary edema, and renal failure. ECMO was thus considered as a bridge to recovery and agreed upon by the parents. Veno-arterial ECMO was initiated by cannulation of the right atrium and the ascending aorta. ECMO treatment was continued for 3 weeks with adequately decompressed heart chambers, and without major bleeding or infectious complications. However, despite significantly improved rhythm control, left ventricular function did not recover at all, and treatment was therefore withdrawn and the baby died.

Postmortem examination of the heart showed typical diffuse inflammatory infiltrates of lymphocytes between the myocardiocytes and extensive necroses which were partly

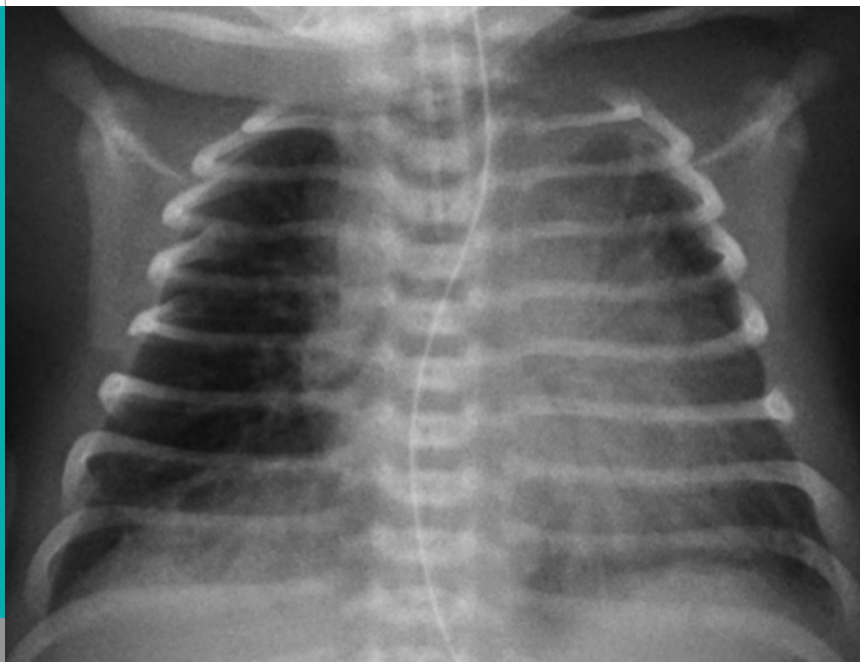
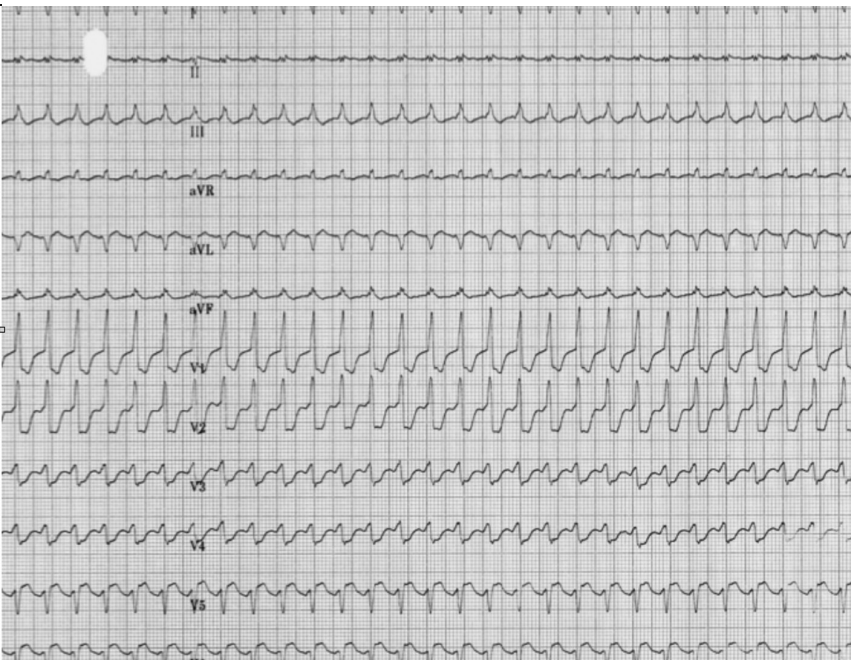


Fig. 1

Chest X-ray showing cardiomegaly, pulmonary edema and small pulmonary effusions.

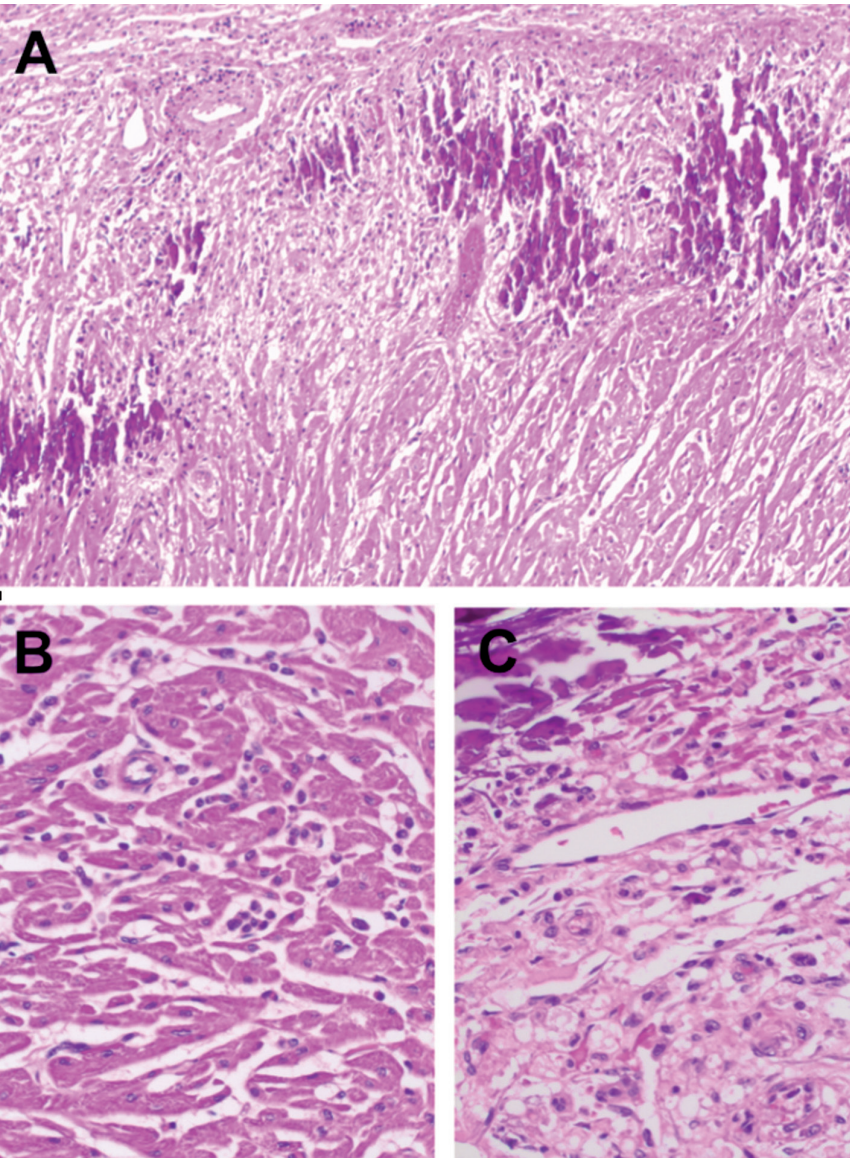
**Fig. 2**

ECG showing tachycardia and ST segment depression in leads V1 to V4.



ECG showing sustained runs of polymorphic ventricular tachycardia.

Fig. 3

**Fig. 4**

Histopathology of the myocardium: low power view: A) areas of necroses; high power views: B) diffuse lymphocytic inflammatory infiltration, C) calcified necroses and necroses in ongoing organization.

CASE REPORT 2

A boy born at 38 0/7 weeks with a birth weight of 3680 g developed temperature instability and tachypnea on the third day of life. Pregnancy had been uneventful and perinatal adaptation was unremarkable with Apgar scores of 9 and 10 at 1 and 5 minutes, respectively. However, maternal fever had been noted during labor and delivery. Pre-ductal oxygen saturations were 88% in room air and the child was placed on oxygen. Suspecting neonatal sepsis, antibiotic treatment with amoxicillin and gentamycin was commenced.

On the seventh day of life, the baby deteriorated with lethargy, and an increasing oxygen requirement. A petechial rash was noted. The child was intubated and retrieved to the tertiary neonatal intensive care unit. Laboratory examination on admission showed a C-reactive protein of 22 mg/l, leukocytes of 6.8 G/l with 9% bands, and a platelet count of 5 G/l. A platelet transfusion was given. The cerebrospinal fluid tap was bloody. The chest X-ray indicated pulmonary edema. Echocardiography showed a dilated left ventricle and left atrium with severe global dysfunction (fractional shortening 5 to 10%). No structural cardiac anomaly was discovered and coronary anatomy was normal. Enterovirus PCR in CSF was positive. Troponin I was 4.3 µg/L (<0.04) and brain natriuretic peptide (BNP) was 3080 pg/ml (< 100). A diagnosis of enteroviral myocarditis was made.

Inotropic support with dobutamine and milrinone was started and intravenous immunoglobulins were given. After a transient stabilization, the patient became progressively tachycardic and hypotensive. Repeated runs of supraventricular tachycardia occurred. Signs of insufficient organ perfusion became evident with rising lactate levels and anuria. The decision to support the child with ECMO was made and veno-arterial ECMO was initiated through a neck incision with cannulation of the right carotid artery and the right internal jugular vein. A balloon atrial septostomy was performed to optimize decompression of the left-sided cardiac structures. A loading dose of levosimendan was given. After six days on ECMO, cardiac function started to improve and the patient was successfully decannulated three days later. Treatment with captopril was started to enhance afterload reduction and inotropes were successfully weaned. The patient went to the ward one week after decannulation from ECMO.

At the age of six weeks, the boy collapsed on the ward requiring short cardiopulmonary resuscitation. Enterococcus species grew from the blood cultures. The collapse was attributed to bacterial sepsis with a reduced capacity for cardiocirculatory compensatory mechanisms given the underlying myocardial dysfunction. Subsequent echocardiographic assessments showed a gradual improvement of cardiac function and the patient could be discharged home at the age of nine weeks. At the age of seven months, cardiac

function on echocardiography had normalized, and neurdevelopmental follow-up assessment was normal.

DISCUSSION

Enteroviruses are a leading cause of viral infections in humans, with epidemics occurring during the summer and autumn months (6). The incidence of neonatal enterovirus infections may reach up to 12% during epidemics (7). Approximately 75% of infected infants remain asymptomatic, and less than 5% of infants require hospitalization. Human enteroviruses belong to the family of picornaviridae and were previously classified into echoviruses, Coxsackie viruses A and B, polioviruses and the „numerated“ enteroviruses. A more recent classification system distinguishes four species (A, B, C, D) of non-polio enteroviruses (6).

The majority of enteroviral infections are mild and self-limiting with non-specific manifestations such as febrile illness, mild upper respiratory tract infection or gastroenteritis. Conjunctivitis and a fine blanching, or occasionally a petechial rash may be observed. However, progression to severe disease such as a viral sepsis syndrome, myocarditis, hepatitis and meningoencephalitis may occur. A U.S. enteroviral surveillance study recorded six deaths during a two-year-period. All deaths were observed in neonates, and all were caused by Coxsackie virus type B, with myocarditis diagnosed in three (8). The first report of enteroviral myocarditis dates back to 1958, when a term-born girl developed cyanosis on the ninth day of

life followed by rapid deterioration and death within six hours (9). Autopsy revealed myocarditis and Coxsackie virus B3 could be isolated from heart muscle. Apart from enteroviruses, adenoviruses are the most frequent pathogens isolated in myocarditis, but parvovirus B19, influenza virus, RSV and herpes viruses have all been reported to cause myocarditis (10, 11). Neonates may acquire enteroviral infections either vertically during maternal viremia, during delivery through contact with infected maternal blood, stool or vaginal secretions, or postnatally by close contact to infected mothers, visitors or health care workers. Neonatal enteroviral myocarditis can mimic bacterial sepsis and pulmonary edema may be mistaken for pneumonia – it is thus imperative not to delay empirical intravenous antibiotic treatment (12). Poor perfusion, tachycardia, lactic acidosis, and an enlarged liver are commonly noted. The ECG usually shows tachycardia, low voltage with flattened or negative T-waves and ST-segment changes. Increased ectopic beats and atrial or ventricular arrhythmias are frequent findings and can be followed by rapid clinical deterioration and collapse (13). Shock, multi-organ failure and sudden death may ensue.

Diagnosis of enteroviral infection has traditionally been made using virus isolation based on immunofluorescence or culture techniques, and cultures obtained on stool and (naso-)pharyngeal swab specimens have the highest diagnostic yield (6). The sensitivity of serologic tests is only moderate. In recent years, PCR testing of

CSF, blood, stool, nasopharyngeal aspirate or even dried blood spots from newborn screening cards has become the preferred diagnostic method, given its excellent sensitivity of > 90%.

The optimal treatment for neonates with myocarditis is poorly studied (14). While inotropic agents improve contractility, they may increase myocardial oxygen consumption and exacerbate arrhythmias. Afterload reduction is one of the mainstays of treatment and can be achieved with milrinone or dobutamine. Levosimendan, a calcium sensitizer with a long half-life, is being increasingly used given its action combining inotropy, lusitropy (improved diastolic function) and afterload reduction. Shekerdemian et al. published a series of pediatric patients with chronic heart failure successfully managed with an cycling regimen alternating milrinone, dobutamine and levosimendan (15). Finally, positive-pressure ventilation (invasive or non-invasive) may reduce left ventricular afterload and work of breathing and should be considered early. Systemic anticoagulation is often advocated to minimize the risk of intracardiac thrombus formation, but evidence is very limited (14). Treatment with intravenous immunoglobulins has been advocated in the past, assuming that neutralizing antibodies could enhance virus clearance and attenuate the detrimental inflammatory response in the early phase of myocarditis (16). However, several pediatric and adult studies reported conflicting results, and so far, no pediatric randomized

controlled trial has been performed. Two meta-analyses concluded that there is insufficient evidence to justify the use of intravenous immunoglobulins in the treatment of myocarditis in children (16, 17).

Pleconaril to date represents the main antiviral agent available against enteroviral infections (12). The drug integrates into the viral capsid and thereby prevents replication. A randomized, controlled double-blind phase II trial studying the virologic efficacy of pleconaril in the treatment of neonates with enteroviral sepsis was launched in 2001, and recruitment has now stopped, but the results of the trial have not been published yet (<http://clinicaltrials.gov/ct2/show/NCT00031512>). At present stage, pleconaril cannot be recommended for the treatment of enteroviral myocarditis.

The prognosis of enteroviral myocarditis in neonates is poor with a mortality in the range of 30 to 83%, but it is unknown how many cases with mild myocarditis remain undiagnosed (6, 9, 18-24). Initially, children with viral myocarditis may appear relatively well. However, the rapid deterioration of ventricular function caused by myocarditis can lead to sudden instability and collapse. In these cases, mortality without ECMO is likely to approach 100%. Therefore, patients showing rapid clinical and echocardiographic deterioration despite adequate inotropic support should be considered early for ECMO (25). The Extracorporeal Life Support Organization (ELSO) registry reported 24 patients receiving

ECMO for neonatal enteroviral myocarditis between 2000 and 2008, of which only 8 (33%) survived to hospital discharge (24). The median duration of ECMO was 10.6 days (range 1.4-33.3). The presence of multi-system organ dysfunction, renal failure prior to ECMO cannulation, and the number of complications while on ECMO were associated with fatal outcome in this study.

Neonatal heart transplantation represents the only available treatment for children failing to improve on ECMO. However, given the problems with organ availability, neonatal heart transplantation is not considered in many countries. A case report from Great Ormond Street Hospital has reported successful outcome in a neonate transplanted at the age of 23 days for fulminant enteroviral myocarditis (22).

In conclusion, enteroviral infections in neonates often present with unspecific findings, and are likely to be mistaken for bacterial infection. Given the severe complications of enteroviral infections, clinicians should look for signs of myocarditis, hepatitis or meningoencephalitis. The presented cases illustrate that cardiovascular collapse may develop rapidly in neonatal myocarditis. ECMO is a valuable therapeutic option in neonates with myocarditis progressing to cardiac failure, and transfer to a pediatric ECMO center should be considered early.

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