

# Paediatric inflammatory multisystem syndrome in a neonate with CHD: case description and current issues in children with CHD

## Brief Report

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### Abstract

We present a case of possible vertical COVID-19 transmission-related paediatric inflammatory multisystem syndrome in a neonate with CHD. Myocarditis and supraventricular tachycardia along with hepatic injury and renal failure were diagnosed on a background of mild aortic valve stenosis; the patient was successfully treated with immunomodulation. Since paediatric inflammatory multisystem syndrome can affect the heart, we could consider neonates with haemodynamically insignificant CHD to be at a higher risk of fatal outcomes. Issues related to early diagnosis and management need to be addressed.

The worldwide COVID-19 pandemic has affected every field of the healthcare system. In contrast to adults, severe paediatric COVID-19 cases remain uncommon.<sup>1</sup> Nevertheless, COVID-19 infection raises new questions regarding disease manifestation in children, especially neonates. The indirect impact of maternal SARS-CoV-2 infection on the neonate is poorly characterised, but should be considered.<sup>2</sup> Herein, we present a case of paediatric inflammatory multisystem syndrome with cardiac involvement in a newborn with a CHD. The paediatric inflammatory multisystem syndrome manifestation in this case was caused by possible vertical transmission of COVID-19.

### Case report

A three-week-old term newborn was admitted to the paediatric ICU due to cardiopulmonary failure after the patient became lethargic and feverish at home. Past medical history included CHD not requiring surgical involvement, that is, bicuspid aortic valve and mild aortic valve stenosis with a peak gradient of 31–33 mmHg.

The patient was admitted in cardiogenic shock, leading to tachycardia, tachypnoea, renal failure, and hepatomegaly. Electrocardiogram showed supraventricular tachycardia of 260–280 beats per minute which was unresponsive to adenosine. Transthoracic echocardiography showed a severely impaired left ventricle with an ejection fraction of 5%. Therefore, inotropic support was started immediately. The patient was intubated, and after successfully synchronised cardioversion, a sinus rhythm was restored.

Laboratory testing revealed highly raised inflammatory markers (ferritin, interleukin-6), 160-fold increased B-type natriuretic peptide, 13-fold elevated troponin, 2-fold higher hepatic enzymes, and a slight elevation in D-dimer levels. In view of this clinical picture and the laboratory findings, there was a strong suspicion of myocarditis with an unknown aetiology.

The mother was known to have COVID-19 infection during pregnancy in the late third trimester. Although the polymerase chain reaction test was negative, the baby had positive antibodies to SARS-CoV-2. These findings, according to the WHO criteria,<sup>1</sup> support the diagnosis of paediatric inflammatory multisystem syndrome temporarily associated with SARS-CoV-2 (PIMS-TS). Therefore, treatment was initiated following the American College of Rheumatology clinical guidance, with intravenous immunoglobulin 2 g/kg (2 days), methylprednisolone 2 mg/kg, non-steroidal inflammatory drugs, and aspirin.<sup>2</sup> There was a dramatic improvement observed within the next few days: no further episodes of arrhythmia were seen, left ventricular function started to recover, and laboratory findings including inflammatory markers and B-type natriuretic peptide decreased. The patient was discharged to the ward on day 5 of hospitalisation.

### Discussion

This case report presents a neonate with prenatal exposure to the SARS-CoV2 virus, leading to fulminant myocarditis, cardiac arrhythmia, acute hepatic injury, and renal failure. The excellent

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response to immunotherapy is consistent with the current definition of multisystem inflammatory syndrome.

Currently, the diagnosis of PIMS-TS is complicated for two main reasons: firstly, there are no unified case definitions casting speculation on reported diagnoses.<sup>3</sup> Secondly, vertical transmission in neonates has been reported, but confirmation is complex. The diagnostic criteria for the confirmation of congenital infection in neonates include clinical features of infection in neonates and mothers with SARS-CoV2 infection or detection of the virus by polymerase chain reaction in umbilical cord blood or neonatal blood collected within the first 12 hours of birth or amniotic fluid collected prior to rupture of the membrane.<sup>4</sup> The case we are presenting does not meet these criteria. However, since there was a known asymptomatic infection diagnosed in the mother in the late third trimester and no other SARS-CoV2-positive contacts were reported, the possibility of vertical transmission in this case still needs to be discussed.

A recent report summarises direct and serological evidence of vertical transmission in more than 40 neonatal cases consistent with the definition criteria for PIMS-TS, mainly presenting with features of severe cardiogenic shock due to structural damage to the myocardium.<sup>5</sup> Given the emerging evidence, the term PIMS-TS is gaining interest amongst researchers and may have future implications, since it reflects immune-mediated effects of previous *in utero* COVID-19 infection, clearly distinguishing the former from postpartum viral transmission. It is important to differentiate the two, since paediatric inflammatory multisystem syndrome may have different time frames and different presentations in cases of SARS-CoV2 exposure *in utero* compared to postpartum exposure.<sup>5,6</sup> According to the British Congenital Cardiac Association recommendations, stable at birth, not requiring surgery, or catheter intervention CHD infants are not estimated to be at a higher risk of cardiac compromise due to COVID-19 infection but have an increased risk for a negative outcome.<sup>7</sup> However, in the context of PIMS-TS, where the majority of affected infants seem to be prone to cardiac dysfunction,<sup>5,6,8</sup> neonates with CHD previously exposed to SARS-CoV2 infection should be monitored with more caution.

The pathogenesis of PIMS-TS is also poorly understood. SARS-CoV-2 infection causes the production of virus-specific antibodies. However, in genetically susceptible individuals, cross-reactive antibodies may form, leading to the activation and secretion of pro-inflammatory cytokines and resulting in the development of PIMS-TS.<sup>9</sup> This explains in part the efficacy of immunomodulation. However, some aspects of susceptibility and prevention are currently unknown.

Although the use of maternal SARS-CoV2 vaccines prior to or during pregnancy has not been systemically evaluated, it may have a role in the prevention of paediatric inflammatory multisystem syndrome. A large case series of PIMS-TS reported that none of the mothers of the ill neonates had been vaccinated.<sup>8</sup> In contrast, preliminary safety reports of vaccinated mothers during pregnancy reported no PIMS-TS cases and no neonatal deaths related to COVID-19 and its mediated syndromes.<sup>10</sup> On the other hand, transplacental transmission of antibodies against SARS-CoV2 may encourage the overdiagnosis of PIMS-TS and miss out on

other neonatal diseases leading to poor outcomes, especially when immunomodulation is considered. Therefore, more longitudinal clinical trials might be helpful to create a unified protocol with new diagnostic aids specific to neonates with CHD.<sup>3</sup>

## Conclusion

We have reported a successfully treated PIMS-TS-related cardiac injury in a neonate with CHD using immunomodulation. We emphasised the important aspects of a unified case definition and the need for a risk assessment for acquiring PIMS-TS in neonates with CHD. Finally, we discussed the need for future directions toward targeted diagnosis and management.

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**Conflict of interest.** None.

**Ethical standards.** Written approval of the mother was obtained prior to publishing the case report.

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