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# A Preterm Neonate with Coxsackievirus Infection, Supraventricular Arrhythmia and Cerebral Sinus Venous Thrombosis

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## Abstract

We report a preterm infant with coxsackievirus B3 (CVB 3) infection accompanied by supraventricular arrhythmia and cerebral sinus venous thrombosis. CVB 3 belongs to the Picornaviridae family and usually causes mild respiratory and gastrointestinal symptoms. Newborns, especially preterm infants, are at higher risk of severe infection involving the cerebral and cardiovascular system. Our case illustrates that CVB 3 infection can present highly variable and with unusual symptoms. Furthermore we discuss cerebral sinus venous thrombosis as a rare and relevant complication of CVB 3 infection.

## Keywords

Coxsackievirus, Supraventricular arrhythmia, Sinus venous thrombosis

## Case Presentation

After delivery at 33 + 5 weeks of gestational age and regular postnatal adaption on the fourth day of life a Eutrophic male twin developed an unspecific Erythematous macular rash in the gluteal region without any clinical signs for viral or bacterial infection.

On the seventh day of life the newborn became lethargic, showed elevated body temperatures up to 38.6 °C and prolonged capillary refilling time. Despite of monocytosis laboratory findings on the same day were unremarkable and remained normal during the next days. Because of typical symptoms, neonatal sepsis was suspected and antibiotic therapy with ceftazidime and teicoplanin was started. Prior to antibiotic therapy a blood culture was taken. Rapidly the patient deteriorated and finally respiratory failure occurred with the need of mechanical ventilation. A chest radiograph showed normal cardiac size and lungs without any infiltrates. Lumbar puncture was performed on the second day of illness. Cerebrospinal fluid (CSF) showed decreased glucose level (2.31 mmol/l), high protein level (3023 mg/l) and minimal pleocytosis (30 MPt/l).

The patient presented an episode of supraventricular tachycardia that was converted into rhythm by application of adenosine. Because of recurrent supraventricular tachycardia (at least four times in two days), treatment with sotalol (105 mg/m²/d) was started.

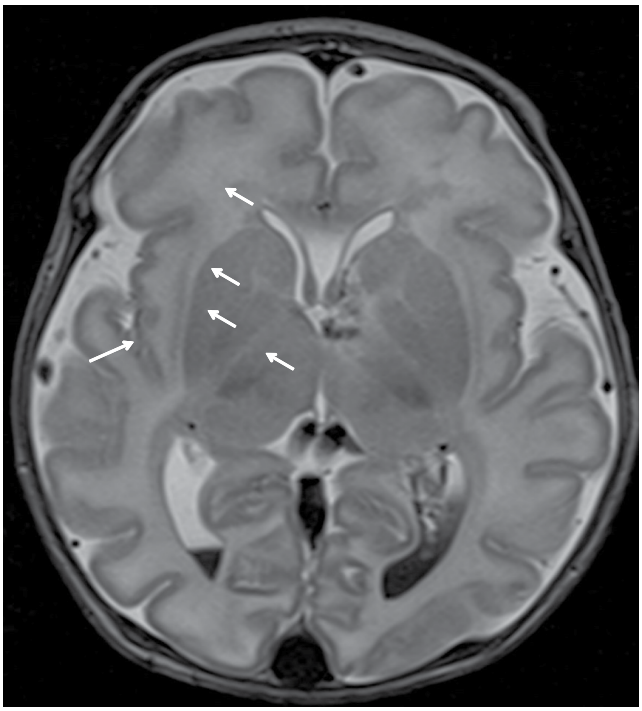

**Figure 1:** The transversal T2-weighted image of the head shows hypointense blood level intraventricular, a hemorrhage in the basal ganglia and a thrombus with low intensity in the superior sagittal sinus, vena galena and venae cerebri internae.

An echocardiogram showed unrestricted cardiac function, good ventricular contractility and no signs of myocardial hypertrophy.

The initial cranial ultrasound was unremarkable. On the tenth day of life an Intraventricular hemorrhage (IVH) grade II on the left side, a bilateral bleeding within the basal ganglia and a thrombosis of the sinus sagittalis superior was found. An MRI scan verified the large intracranial thrombosis including the whole sinus sagittalis superior, confluens, sinus transversus and basal ganglia (Figure 1). Furthermore in homogenous diffusion of frontal white matter was

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seen. Apart from lethargy and muscular hypotonia the neonate remained neurologically healthy, seizures were not observed. Amplitude-Integrated Electroencephalography did not detect pathological electro cortical activity.

Laboratory workup at this time showed elevated D-dimers with 12717 ng/ml. International normalized ratio (INR 1,12), activated partial thromboplastin time (APTT 34 seconds) and platelet count (347 MPt/l) were within range. However, antithrombin III was slightly low at 74% (reference range 79%-131%). After risk-benefit analysis regarding the IVH and the thrombosis a low dose anticoagulation therapy with heparin (480 IU/kg/d) was started. Thrombophilia workup was performed after first year of life and revealed unremarkable parameters including protein S, protein C, apc resistance, prothrombin and factor V leiden.

Because of the sepsis-like presentation of the infant with suspicious CSF-findings and cardiac arrhythmia a viral infection was suspected. Therefore PCR tests of CSF, blood, stool and bronchial secretion were performed and ruled out an infection with varicella zoster-, herpes simplex 1 and 2-, adeno -, human herpes 6 - and parvovirus B19. A nested real-time PCR of CSF showed positive results for CVB 3 [1]. Laboratory testing on the mother was omitted. After four days of mechanical ventilation the boy was extubated successfully. The patient was discharged on the 30th day of life in good condition.

Follow up cranial ultrasound at the age of nine weeks showed complete reperfusion of the sinus sagittalis superior as well as resorption of the intraventricular hemorrhage. As the in homogenous diffusion of the frontal white matter was only seen in MRI scan no evaluation of this finding via ultrasound was feasible.

## Discussion

Taken by itself each of the diseases described (infection, IVH, cerebral sinus venous thrombosis and supraventricular tachycardia) might occur in preterm infants. However, their combination in a single infant has not been described yet. The present report indicates that CVB 3 infections are relevant during the neonatal period and may cause life threatening illness.

CVB 3 is an enterovirus belonging to the Picornaviridae family. Coxsackievirus infections underlie seasonal variation with peak season from June to October. Transmission can occur vertically from the mother or postnatally [2]. Furthermore it seems likely that transmission by breast milk from symptomatic mothers is a possible infective route [3]. Still, usually breast feeding provides a protection against severe enteroviral infection due to the transmission of maternal antibodies. It has been noted that enteroviral infections occur in infants who lack of maternal antibodies for that specific serotype [4]. In the presented case laboratory testing on the mother was omitted, the transmission of the virus therefore cannot be proved.

Epidemiologic surveillance in Germany from 2006 to 2009 showed a predominance of CVB 3 in enterovirus infections during the neonatal period [5]. Especially infections during the first week of life have a greater risk for severe illness [6]. The various clinical symptoms of coxsackievirus infection can be explained by the characteristic tissue tropism of the virus, infecting different target cells such as neurons, cardiomyocytes and epithelial cells. Thus infants can present with aseptic meningitis and meningoencephalitis, myocarditis, respiratory disease or pancreatitis. Differential diagnosis of neonatal enterovirus infection includes herpesvirus infection and bacterial sepsis [7] which could be excluded in our patient.

Despite of severe clinical symptoms, levels of inflammatory indicators in blood can be low [5]. In our patient a viral aetiology of the symptoms is very likely as bacteria culture was taken before antibiotic exposure and was shown to be sterile. Polymerase chain reaction is used for diagnosis of CVB 3 infection and appears to have greater sensitivity than viral culture [8].

We diagnosed CVB 3 infection by PCR analysis from CSF. Supraventricular tachycardia as observed in our patient has been described previously in a few patients [9] as well as in the case of an intrauterine coxsackievirus infection [10]. CVB 3 induced myocarditis is associated with a high mortality [11]. Symptoms include amongst others cardiac arrhythmia [12]. Our patient presented recurrent supraventricular tachycardia without any signs of structural changes of the myocard. We suggest an affection of the cardiac conduction system by CVB 3 and/or heredity transmission.

Additionally to cardiovascular symptoms our patient presented severe viral encephalitis, IVH and sinus venous thrombosis of the sinus sagittalis superior. Though, IVH and periventricular leukomalacia have been described in a newborn boy suffering from a fatal neonatal echovirus 6 infection [13]. It is discussed that enterovirus encephalitis can cause mild to severe white matter lesions [14,15]. Furthermore, seizure activities with pathologic EEG pattern can occur [16]. In our patient mild white matter lesions were found in MRI scan. AEEG pattern showed normal brain activity, clinically seizures were not observed.

To our knowledge this is the first case reporting a cerebral sinus venous thrombosis associated with CVB. The interpretation of plasma-based coagulation in newborns and especially preterm infants is unreliable due to the rapidly developing hemostatic system. There are not evidence-based guidelines for children with inherited thrombophilia and therefore in our patient thrombophilia screening was performed after the first year of life. Normal parameters for protein S and C, apc resistance, prothrombin and factor V leiden were revealed which strengthens the assumption of CVB 3 induced hypercoagulability. The influence of cytomegalovirus (CMV) of the coagulation system is well studied and it is suggested that CMV can enhance platelet adhesion and induce factor X by infecting endothelial cells [17]. There are only few studies investigating the effect of CVB 3 infection and hypercoagulation: The microscopical evaluation of organs in a fetus with CVB 3 infection revealed mononuclear inflammatory infiltrates in the subarachnoid space and both intraluminal obstructive calcifications of meningeal vessels and non-obstructive calcium precipitates within the lumen and on the endothelium [18]. CVB 3 induced elevation of tissue factor (TF) might be another mechanism leading to hypercoagulation since CVB 3 infected mice showed 5-fold increased TF expression in the myocardium leading to elevated plasma activity. Analysis of human myocardial tissue with inflammatory cardiomyopathy revealed a correlation between TF expression and activation of endothelial cells [19].

The mentioned morbidity and mortality caused by CVB 3 infection in the neonatal period strengthens the need for a specific antiviral treatment. In a clinical study Pleconaril - an enterovirus-rhinovirus capsid inhibitor - has been used to treat severe neonatal coxsackievirus infection with multiple organ dysfunctions [20]. The use of intravenous immune globulin in neonatal enterovirus infection was tested in a prospective study. An antiviral effect was seen via modest increase of serum neutralisation titers, but incidence of viremia and viruria was not significantly reduced [21]. Recently gemcitabine was identified as a novel inhibitor of CVB 3 proliferation, and in combination with ribavirin a synergistic antiviral effect was shown [22]. However, results so far are not conclusive and further evaluation is necessary.

In conclusion our case illustrates that CVB 3 infection can present highly variable and with unusual symptoms. Moreover, it can lead to severe neurological impairment. Therefore in newborn infants with sepsis-like symptoms CVB 3 infection should be considered as an important differential diagnosis and should be ruled out by PCR.

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