# Isolated Internal Cerebral Venous Thrombosis in a Neonate with Increased Lipoprotein (a) Level: Diagnostic and Therapeutic Considerations

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#### Abstract

**Background:** Internal cerebral venous thrombosis is a lifethreatening condition, which requires immediate therapy. Being infrequent in childhood, internal venous thrombosis is very rare in the neonate and has never been observed without concomitant occlusion of further dural sinuses.

Case Description: We report a neonate born at term, who developed seizures on the third day of life after normal pregnancy and uneventful delivery. Ultrasound and CT disclosed bilateral intraventricular and intracerebral hemorrhage with an unusual distribution for germinal matrix hemorrhage. MRI disclosed thrombotic occlusion of the straight sinus and the internal cerebral veins with concomitant bleeding into the ventricles, the basal ganglia, thalamus and the periventricular hemispheres. The other sinuses were not affected. The clinical condition of the child improved after initiation of a low-dose heparin treatment with subsequent partial recanalization of the occluded vessels. The screening for risk factors disclosed an elevated lipoprotein (a) level, also present in both parents.

**Conclusion:** Internal cerebral venous thrombosis may be encountered in neonates and must be included in the list of differential diagnosis of perinatal intraventricular and intracerebral bleeding. MRI allows the diagnosis even in the absence of widespread dural sinus occlusion. Low dose heparin may be a therapeutic option in these cases. This is the first report of neonatal internal venous thrombosis due to hereditary lipoprotein (a) level elevation, which must be included in the list of possible predisposing conditions.

#### **Key words**

MRI · neonatal · CVT · lipoprotein (a) · treatment

## Introduction

Internal cerebral venous thrombosis is a potentially life-threatening condition, which mostly occurs in the course of extensive dural sinus thrombosis. The prognosis used to be grave but has improved considerably after the introduction of anticoagulatory treatment [2,4]. However, rapid and reliable diagnosis of CVT as well as of internal cerebral venous thrombosis still may pose a problem. Because the clinical signs are often non-specific, imaging has to be employed to demonstrate, or rule out, venous thrombosis [2]. Because CT is not always diagnostic in CVT, MRI is frequently used for the definite confirmation of the diagnosis as well as for the evaluation of the extent of the venous occlusion and the demonstration of damage to the cerebral parenchyma. Intra-arterial angiography is no longer justified in the majority of cases. Doppler ultrasound is not used to monitor intracranial venous blood flow after closure of the fontanel but is a useful method to rule out jugular vein thrombosis as a possible cause of intracranial venous congestion.

We report CT and MRI findings in a case of internal venous thrombosis in a neonate with increased lipoprotein (a) level. Furthermore, we were able to demonstrate internal cerebral venous occlusion with colour-coded duplex ultrasound. Previous reports on this topic had focused on the thrombosis of the sagittal sinus [3].

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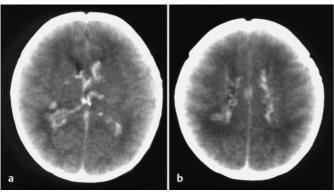


Fig. 1a and b a CT scan on the 5th day of life one day after the onset of symptoms. There is intraventricular hemorrhage in both lateral ventricles as well as in the 3rd ventricle. An intracerebral hematoma can be seen in the left thalamus and in the white matter of the right hemisphere. The internal cerebral veins are abnormally dense, the sinuses are not. **b** This CT at a more apical level shows bilateral hemorrhage into the periventricular brain parenchyma.

# **Case Report**

# **Clinical findings**

This child of a healthy 32-year-old mother was born at 42 weeks gestation by an uneventful spontaneous vaginal delivery (body weight 3500 g, head circumference 36 cm, Apgar score 8 after one minute, 10 after 5 and 10 minutes). There was no family history of stroke or hypercoagulability. A few hours after discharge from the maternity ward on the 2nd day of life brief left-sided jerks were observed at home. On day five the child was referred to a regional children's hospital under suspicion of a generalised epileptic seizure. Clinical and neurological findings were normal except for intermittent horizontal nystagmus.

Electroencephalography showed repetitive spikes and rhythmic theta activity predominantly in the right temporo-occipital region. CSF protein was elevated (276 mg/dl). Ultrasound examination revealed intracranial hemorrhage. CT scan on the same day revealed bilateral hemorrhage into the lateral ventricles with extension into the third ventricle. Parenchymal bleeding could be seen in the left thalamus and in the periventricular white matter bilaterally. The region of the germinal matrix was largely spared. There was a very prominent hyperdensity of the internal cerebral veins (Fig. 1a). The dural sinuses did not seem to be involved. Anticonvulsive, antibiotic and antiviral therapy was initiated and after two days the child was transferred to a neonatal unit.

On admission, clinical and neurological examinations were normal. Ultrasound scan of the brain showed hyper- and hypoechoic areas in both thalami predominantly on the right side; colorcoded duplex sonography of the basal cerebral arteries was normal, intracranial veins were not examined.

MRI of the brain was performed subsequently on a 1.5 T unit (Magnetom Vision, Siemens, Germany). A pathologic hyperintensity of the internal cerebral veins suggestive of thrombosis was detectable on the sagittal T<sub>1</sub>-weighted survey image (Fig. 2a). A phase-contrast MR angiography with a maximum sensitivity to flow at 10 cm/s did not show flow in the internal

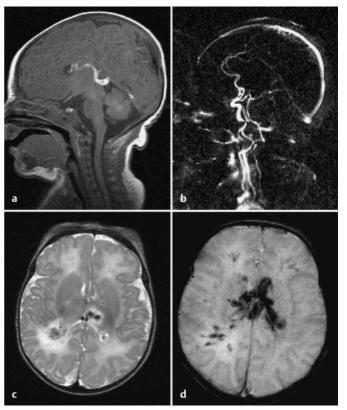


Fig. 2a to d MRI on the 6th day of life at 1.5 T. a This T<sub>1</sub>-weighted spin-echo image in the sagittal plain shows pathological hyperintensity of the internal cerebral veins and part of the straight sinus. The sagittal sinus has a normal appearance and signal intensity. **b** Phase-contrast MR angiography. The superior sagittal sinus has a normal flow signal whereas the internal cerebral veins and the straight sinus do not show venous flow. **c** T<sub>2</sub>-weighted turbo-spin-echo image in the transverse plain at the level of the basal ganglia. The hemorrhage into the left thalamus and adjacent to the right occipital horn of the lateral ventricle are hypointense. The perifocal edema is visible in the left thalamus and right occipital white matter. The internal cerebral veins are dark due to an intraluminal thrombus. **d** This T<sub>2</sub>\*-weighted gradient echo image in transverse orientation shows bilateral intracerebral hemorrhage.

cerebral venous system including the straight sinus (Fig. 2b). Further transverse T<sub>2</sub>-, T<sub>2</sub>\*- and T<sub>1</sub>-weighted sequences confirmed the presence of intracerebral blood as suggested by CT and ultrasound (Fig 2c,d). These hemorrhages were located in the draining areas of the internal cerebral veins, the thalamostriate veins and the basal vein of Rosenthal. The subarachnoid extension of the hemorrhage, clearly visible on CT, was not apparent on MRI. Normal flow could be demonstrated in both transverse sinuses with a time-of-flight MR phlebography, thereby proving an isolated internal venous thrombosis. Diffusionweighted sequences did not demonstrate a diffusion abnormality (not shown).

The following laboratory findings were normal: blood count, serum electrolytes, glucose, creatinine, liver enzymes, lipid profile. In the patient and in both parents the following coagulation tests were normal: prothrombin time, activated partial thromboplastin time, fibrinogen, antithrombin III, protein C and S, APC-resistance, factor V G1691 A-mutation. Anti-cardiolipin antibodies were negative.

When the diagnosis of an internal cerebral venous thrombosis was established, antibiotic and antiviral therapy was terminated and heparin therapy was begun. Initial infusion therapy of heparin (10 IU/kg/h) was increased up to 36 IU/kg/h. As there was no sufficient effect on activated partial thromboplastin time (PTT), therapy with low-molecular heparin (3 mg/kg body weight/24 h) was established. Anti-factor Xa was kept within a range of 0.3 – 0.6 U/ml. After 1 week partial revascularization of the left internal cerebral vein was seen on color duplex sonography which was confirmed on MRI one week later. After 4 weeks, the straight sinus and the vein of Galen were reopened on MRI and partial recanalization of the cerebral veins could be diagnosed. Therefore, therapy was switched to low-dose low-molecular

Throughout the complete time of hospitalization, the infant revealed no neurologic abnormalities. When the child was discharged after 5 weeks, the parents were instructed to continue administration of low-molecular heparin.

heparin (1.5 mg/kg body weight/24 h).

Three months after onset of the thrombosis MRI was repeated and a color duplex scan of the intracranial veins was performed. MR phlebography showed an asymmetric, faint flow signal in the internal cerebral veins, more pronounced on the left side, while on color duplex scan both internal veins were normally perfused. The neurological examination of the infant again was normal. Because of incomplete recanalization of the internal veins on MR phlebography low-molecular heparin therapy was continued.

After six months, supplementary examinations revealed that lipoprotein (a) was elevated in the patient (52.0 mg/dl), as well as in his mother (82.0 mg/dl) and his father (36.7 mg/dl; normal lipoprotein (a) levels are below 30 mg/dl in children and adults, and < 20 mg/dl in neonates). Prothrombin G20210 A-mutation, methylenetetrahydrofolate reductase (MTHFR) C677 T-mutation, plasminogen activator inhibitor-1 promoter 4 G/5 G genotype were normal in the patient and in both parents. Low-molecular heparin therapy was discontinued one month later. Presently, at the age of 8 months, clinical and neurological findings in the child are normal; the motor development is appropriate for age. Color duplex sonography through the large fontanel revealed patent internal cerebral veins on both sides; the B-scan image of the brain was normal. EEG is normal.

## Discussion

Dural sinus thrombosis is thought to be less frequent in children than in adults [11]. The incidence in the pediatric age group has been estimated to be 0.07 per 10,000 as opposed to 2.5-5% in adults [1]. Neonatal dural sinus thrombosis is a very rare event. No more than 30 cases have been reported in the literature [11,17,19].

It is well established that the hemostatic system of children is different from adults [1]. Furthermore, risk factors such as smoking and oral contraceptives are absent in the pediatric age group. Predisposing disorders in children are among others lupus erythematodes [22], mastoiditis [5,20], trauma [21], leukemia [12]. However, till recently the reason for pathologic clotting re-

mained unclear in the majority of children. In the series of Shevell et al [19] a predisposing condition could only be identified in 3/17 cases. A prospective study on neonatal thrombosis [18] found as predisposing factors venous catheters and general infection, however other prevailing reasons could not be detected.

Using molecular techniques, many clotting abnormalities have been identified in affected patients within the last years. Prothrombotic risk factors such as genetic recombinations of FV G1691 A or PT G20210 A with deficiencies of protein C, S [14,15] were discovered and factor V [16] and MTHFR mutations [8] could be identified in children with cerebral venous thrombosis. The cause of venous occlusion in our patient is thought to be a lipoprotein (a) elevation in the blood of the child. LP (a) elevation has been demonstrated to be a predisposing factor for embolic infarctions and venous thrombosis in the pediatric age group [13,15], but not yet in a newborn baby.

Shevell et al [19] found seizures as initial symptom of venous thrombosis in 15 of 17 children, Rivkin et al [17] in three of seven patients. The clinical presentation of our patient was also dominated by seizures. This occurs mostly within the first week of life, presumably indicating the onset of cerebral damage by increased venous pressure. However, asymptomatic widespread venous thrombosis as an incidental finding on screening ultrasound has been reported recently [16].

Internal venous thrombosis mostly ensues from propagation of dural sinus thrombosis to the straight sinus and the internal cerebral veins and is the most severe form of impaired venous drainage of the brain. The true incidence of internal cerebral venous involvement in dural venous thrombosis in newborns is not clear. Most cases reported so far with MRI demonstration of internal venous involvement [11,16,17] had an extensive occlusion of the superior sagittal sinus. In contrast, the patient reported here suffered from an isolated thrombotic occlusion of the straight sinus and internal cerebral veins, a very rare event [7,10,23].

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Like the patient of Lasjaunias [11], our patient presented with hemorrhage into the ventricles, basal ganglia, thalamus and cerebral hemispheres. Intraventricular bleeding due to venous thrombosis seems to be a feature more common in neonates than in adults, even though larger studies on this topic are lacking.

If the large sinuses are not involved, the diagnosis of venous thrombotic occlusion is particularly difficult on CT without intravenously administered contrast agent [19]. In the patient presented here, only the hyperintensity of the internal cerebral veins and the straight sinus were indicative of venous thrombosis

Instead of contrast-enhanced CT, MRI was performed in our patient to further investigate the cause of the atypical intraventricular hemorrhage. MR phlebography with a phase-contrast sequence revealed absent flow in the internal cerebral veins and straight sinus. The clot itself was hyperintense on the T<sub>1</sub>-weighted images and hypointense on the T<sub>2</sub>-weighted slices. This indicates intracellular methemoglobin [6] with a presumed age

of 2-4 days. Hence, T<sub>2</sub>-weighted images were not able to demonstrate the clot because the signal did not differ from the normal flow-related signal void in the internal cerebral veins. In contrast to other reports [9], diffusion-weighted images were normal in our patient.

In adults, dural sinus thrombosis is treated with heparin [2,4] even in the presence of intracerebral hemorrhage. Thereafter, anticoagulation is advocated for several months. Treatment for venous thrombosis in neonates is not based on prospective studies. However, in the largest report on this topic most patients received heparin and the overall outcome was not bad with 82% surviving the hospital discharge [18].

While the study cited above comprises patients with neonatal thrombosis in many locations, the authors of the study on neonatal dural sinus thrombosis also report a good clinical course of most patients [19]. Of the patients without asphyxia, 11/12 had no neurodevelopmental deficits in a follow-up period up to six years. The seizures, the initial symptom in 15/17 patients, did not extend beyond the neonatal period in 12 patients. Because most patients were not treated with heparin, it may be concluded that in the neonatal age the natural history of dural sinus thrombosis is more favorable than in adults. However, there is no indication in the study of Shevell et al [19] as to how many of these patients had internal cerebral venous occlusion, which is particularly dangerous. This statement may be corroborated by a recent case report [16]. The patient reported by Ramenghi et al did not develop neurological symptoms without any treatment although MRI disclosed straight sinus and internal cerebral venous occlusion.

Our patient was put on low-dose heparin and also made a good clinical recovery with resorption of the intracranial hematomas and partial recanalization of the occluded venous vessels, as documented by follow-up MRI. No relapse of hemorrhage was encountered.

In conclusion, intraventricular hemorrhage may be caused by internal venous occlusion, which is most reliably demonstrated by MRI. It remains unresolved whether anticoagulatory treatment with heparin has a beneficial influence on the clinical course of neonatal dural sinus thrombosis, of which lipoprotein (a) elevation, among others, seems to be a predisposing factor.

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