Neonatal cerebral venous sinus thrombosis. Diagnosis, management and outcome – a short case series

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ABSTRACT

Background. Cerebral venous sinus thrombosis (CVST) is considered a rare condition in neonates. We present the experience of our unit in the diagnosis and management of inborn patients with CVST, in order to increase awareness of this condition and the chances of early diagnosis and management.

Material and method. We present three cases of patients born in our department between 2019-2022 with CVST. There are reviewed: the history, the symptomatology in the neonatal period, the imaging findings and the treatment in the hospital. In all the cases the diagnosis was suspected after an ultrasound examination and confirmed by MRI. After discharge from the hospital the patients were followed by the pediatric neurologist and were included in an early intervention program for motor and occupational therapy. There are also reviewed the motor, cognitive and language outcomes of the patients.

Results. The first case is represented by the term neonate with seizures at 40 hours of age. The seizures were controlled by levetiracetam. The ultrasound and MRI showed lesions with a venous topography of different ages. The patient developed unilateral motor deficit delayed milestones, and cognitive and language impairment. The second case is an asymptomatic neonate diagnosed at 3 days of life by a routine ultrasound with right-sided intraparenchymal and interhemispheric hematomas and CSVT. The patient developed a head growth deficit and motor delay. The third case is a term LGA neonate with respiratory distress that was diagnosed with a white matter lesion and an old CVST. The patient presented with a mild motor deficit.

Conclusion. The diagnosis of CVST requires a high awareness about the risk factors, the presenting symptoms and ultrasound suggestive findings – this in turn leads to an appropriate indication for MRI confirmation of the lesions and a better prognosis because the appropriate treatment could be provided and the patient could be included in an early intervention program in order to decrease incidence and severity of the long-term neuro-behavioral consequences.

INTRODUCTION

Neonatal cerebral venous sinus thrombosis was considered in the past a rare occurrence in the neonate [1,2]. The incidence is considered to be 0.6-12 /100 000 live births [3]. Probably the disease is under-diagnosed, considering the unspecific symptoms and the difficulty to obtain an MRI and/or MRI venography in the neonate. In premature newborns, where the awareness of cerebral ultrasound findings is greater and the number of ultrasound examinations is bigger, the incidence of the disease is higher (about 4% of the deliveries) [1,4].

The risk factors are similar to those in the perinatal arterial stroke [3]. The maternal factors are represented by maternal preeclampsia, gestational diabetes, fever, or chorioamnionitis [1,3]. Peripartum
factors consist of signs of fetal distress (meconium stained fluid, acidosis, hypoxia, and need for resuscitation at delivery [3], they are present in more than 2/3 of the cases [4]. Neonatal conditions involved are represented by congenital heart disease, dehydration, and infectious condition – sepsis, meningitis [3,4]. Prothrombotic states (factor V Leyden deficiency) are encountered in a minority of mother/child pairs [5].

The thrombosis occurs both in the superficial venous system (superior sagittal sinus, torcular or deep venous system – terminal vein, internal cerebral veins and the vein of Galen. Superior Sagittal sinus was thought to be the most frequent occurrence [3], involving 65% of the cases, though, other studies found higher incidences in the lateral sinus or deep veins [6].

Clinical signs are often non-specific. The patients present with seizures, with the onset around 48 hours of life in 60-70% of the cases [3]. Lethargy is another symptom present [7,8]. Some cases present also with respiratory distress [9], apneic spells, and hypotonia [3]. In case of propagation of the thrombus – 25% of the patients during the first week, progression of the symptoms could occur [7]. There are situations in which the patient is asymptomatic, and the diagnosis is made either by imaging for other indications or later because of the symptoms or motor deficits.

The diagnosis is suggested by clinical signs and specific ultrasound findings – abnormal features in the term neonate. These findings are represented by thalamic hemorrhage or infarctions [5,8], intra-periventricular hemorrhage in a term neonate [10], intraparenchymal hemorrhages – venous topography [3], and lesions suggesting white matter disorders in a term neonate. All these lesions should rise the possibility of a CSVT and should be an indication for an MRI exam that could establish the diagnosis.

The MRI examination and MR venography are the gold standards for the diagnosis of CSVT [3,11,12]. MRI identifies the thrombus and could characterize the parenchymal lesions [3,1112]. It has also a role during the follow-up, to appreciate the evolution of the parenchymal lesions.

After the diagnosis is established, the therapy is mostly symptomatic [3]. The initial condition – sepsis, meningitis, congenital heart disease should be treated. Seizures should be treated and monitored according to the guidelines [15]. The principles of the treatment of stroke apply also in this case – maintenance of oxygenation, homeostasis of the body, blood pressure, and good hydration [3]. Regarding anticoagulant therapy, there is no consensus yet [13]. Although anticoagulation has been shown to be safe [14], there is a wide variation in practice between centers [13], although there are studies that have shown that antiocoagulation is associated with a better prognosis [16].

Anticoagulation is though not recommended in the case of hemorrhages [13,14]. Anticoagulation treatment is represented by low molecular weight heparin [3,13,14].

The prognosis is worse than that for perinatal stroke (although – personal opinion – perinatal stroke has also a poor prognosis as the age for follow-up increases – several complications appear later). Most of the patients have motor impairments – approximately 50%, often bilateral [3,16]. There are also cognitive (10-60%) [3] and language impairments (approximately 50%) [16] and a 29-40% incidence of subsequent seizures and epilepsy [3,16]. The main risk factor for bad outcomes was concurrent neurological morbidity at diagnosis [16].

We present a case series consisting of 3 patients with cerebral venous sinus thrombosis diagnosed in our center and monitored in our follow-up program. There will be reviewed for each case the antenatal history, the symptoms at diagnosis, the imaging studies, the treatment in maternity and the short and long-term outcome.

Case 1. Bilateral lesions of different ages

This is the case of a term male neonate, 40 weeks corrected age, birth weight 3100 grams, head circumference 32.5 cm that presented at 40 hours of life with generalized tonic-clonic seizure. The mother is a heavy smoker and presented with a respiratory tract infection just before delivery.

The patient is admitted to the NICU, and after the stabilization measures a loading dose of phenobarbital is administered and aEEG monitoring is installed. The aEEG monitor showed an unilateral left-sided centro-parietal seizure (figure 1.1a – encircled areas – both raw and aEEG).

The seizures persisted despite a second dose of phenobarbital, so the patient received a loading dose and then a maintenance dose of levetiracetam (figure 1.1b) that stopped the seizures.

The head ultrasound performed just after stabilization showed a cystic image in the frontal lobe, in the external angle of the frontal horn of the right lateral ventricle (figure 1.2a – encircled), and a hyperechogenicity with a venous pattern distribution in the external angle of the frontal horn of the left lateral ventricle (figures 1.2 b coronal section; 1.2 c parasagittal section – encircled).

The MRI examination performed on the day of life 7 showed the same lesions with different ages (cystic on the right and with a fan-shaped distribution with venous topography on the left) (Figure 1.3a-c – encircled – red – rights yellow - left). The examination revealed also bilateral hemorrhages at the level of the caudo-thalamic groove (1.3 d, e - encircled) and a
The coagulation/prothrombotic studies identified a low value of factor V Leyden in the neonate. The baby was discharged at home after 14 days, on treatment with levetiracetam.
During the next 18 months the patient received anticonvulsive treatment with levetiracetam and did not repeat the seizures, the medication was stopped at 18 months.

The child presented with a head growth deficit (figure 1.4) the head circumference being at the 2nd percentile at the age of 2 years. He was included in an early intervention program. Despite intensive physical therapy and rehabilitation, he presented with delayed motor milestones – sitting independently at 9 months and walking at 15 months. He developed a deficit of expressive and receptive language also.

Case 2. Asymptomatic(?) cerebral intraparenchymal hematoma

This is the case of a term neonate, birth weight 3360 grams, head circumference 34 cm, gestational age 389 weeks. From the antenatal history, we noticed an urinary tract infection with *Klebsiella pneumoniae* and a period of decreased fetal movements one week before delivery (not mentioned at admission, but the mother remembered this after the diagnosis, due to a comprehensive anamnesis). On the day of life 3, a head ultrasound was performed (figure 2.1) that noticed the presence of a intraparenchymal hematoma with venous topography. In the coronal sections – fig 2.1 a-c we could notice the intraparenchymal hematoma – black circles; an interhemispheric hematoma could also be noticed – fig 2.1c – red circle.

On the sagittal section (figure 2.1 d) there was seen a huge hematoma in resolution with fronto-parieto-occipital location on the right.

The MRI examination performed the same day confirmed the existence of the two hematomas – intraparenchymal and interhemispheric – locations suggestive of a sagittal sinus thrombosis and confirmed the venous topography of the lesions – figure 2.2. Figure 2.2a shows a sagittal T2 sequence with the hematoma; figure 2.2 b shows an SWI image with the 2 hematomas – intraparenchymal – black circle and interhemispheric – red circle.
The neurologic exam did not notice any abnormal findings, but, after consulting with the neurosurgeon, the decision has been made to keep the patient under observation until the risk of increasing intracerebral pressure is considered low and the hematoma is in resolution.

The coagulation and prothrombotic function tests were within normal limits both in the mother and the child.

The ultrasound performed on the day of life 10 shows the evolution of the hematoma (figure 2.3 a, b, c coronal sections; figure 2.3 d – sagittal section).

The patient was discharged at 10 days of life and was included in an early intervention program for physical and kineto-therapy.

In evolution, the patient presented with a head growth deficit (figure 2.4).

At the 2 months visit, the patient had axial hypotonicity, could not rise the head in ventral decubitus, and presented with asymmetry of the popliteal angle.

**FIGURE 1.4.** The evolution of the head circumference – case 1.
– left 90 degrees/ right 110 degrees. At 4 months she presented with the same neurologic status. At the 6 months visit the patient did not sit independently – “échec en arrière”, there was hypertonicity of the left half of the body – both arm and leg.

The ultrasound at 3 months (figure 2.5 a, b) and the MRI at 4 months (figure 2.6 a, b) showed the resolution of the hematomas, atrophy of the callosal body, but no new lesions.
Case 3. Patient with signs of respiratory distress

This is the case of a 38 weeks male LGA neonate, birth weight 3900 grams, head circumference 36 cm, born by cesarean section, that presented after delivery with signs of respiratory distress. The mother presented during pregnancy with repeated urinary tract infections with *Klebsiella pneumoniae*. Blood cultures were drawn and antibiotic therapy was begun according to the antibiogram of the cultures of the mother. The ultrasound performed as a part of the protocol for patients with respiratory distress revealed bilateral grade 1 periventricular hemorrhages in the caudo-thalamic groove (figure 3.1 – encircled) and cysts in the frontoparietal white matter at the level of the body of the left lateral ventricle (figure 3.2 coronal and figure 3.1b parasagittal views).

The MRI exam performed the same day showed both the periventricular hemorrhages and the white matter lesions and identified old venous thromboses of the central cerebral circulation (figure 3.2 a, b sagittal, c – coronal sections – encircled areas). The coagulation tests were within normal limits, Protein C and Leyden factor V had values lower than normal in the child.

The aEEG monitoring showed an electric seizure on the left channel (C3-P3) without clinical correlates (figure 3.3. – encircled areas). The patient did not repeat seizures afterwards and was not sent home on anti-seizure medication.

The evolution of the patient was a good one, with the resolution of the respiratory symptoms at 3 days, a stop of the antibiotics because of negative blood culture at 5 days and full feedings at 5 days. The patient was discharged from the maternity hospital at 10 days of life. He was included in an early intervention program.

At the follow-up visit, we noted an initial deficit of the head growth, followed by a catch-up after 6 months of life (figure 3.4).

The images in the caudothalamic groove resolved after 2 months; the periventricular images on the left fused with the left lateral ventricle, resulting in a slight ventricular dilatation (figure 3.5 a – 2 months b – 4 months).

In evolution, the patient did not present with abnormalities of the axial tone (head control at 2 months, sitting at 7 months, but developed since the age of one month a passive tone asymmetry (the right side of the body slightly hypertonic than the left – with a scarf sign limited on the left and a popliteal angle around 90 degrees. At present, the patient is 9 months old.

**DISCUSSIONS**

The main reason for the presentation of these cases is to rise the attention to this pathology that is probably still underdiagnosed due to the non-specific mode of presentation and the non-specific history and ultrasound signs, with the aim to provide clues to a more rapid and accurate diagnosis.

The three cases presented show different characteristics of the neonatal CSVT. There are a couple of common features of the cases. Regarding the history, in 2 of the 3 cases, there could be identified an infectious risk factor – a urinary tract infection in the mother with a Gram-negative strain. Also, in all the
cases there were identified abnormalities of the Factor V Leyden, so a couple of factors were present that predisposed the patient to the occurrence of the cerebrovascular event.

Two of the cases were symptomatic in the neonatal period – cases 1 and 3. In case one, the onset consisted of seizures – that were generalized, though the aEEG identified a left-sided focus. In case 3, there were present symptoms of respiratory distress – but the EEG monitoring showed also the presence of seizures – probably asymptomatic. Case 2, despite the severity of the lesion, was considered “asymptomatic” in the neonatal period. In this patient, a good history taken after the diagnosis showed what probably were the signs of the CVST during the fetal life – a period of decreased fetal movements one week before delivery – the age of the lesion estimated by imaging is consistent with this finding.

The imaging findings, both ultrasound and MRI are consistent with the diagnosis. In case 1 there were discovered lesions of different ages, suggesting multiple thromboses. The ultrasound pattern was consistent with a venous infraction topography – the one seen usually in the preterm hemorrhagic periventricular echogenicity after a germinal matrix hemorrhage. The MRI identified also the unusual periventricular hemorrhages in a term neonate, consistent with the same diagnosis and the thrombus. In case 2, the hematoma was both intraparenchymal and interhemispheric, suggestive of a large thrombosis, and in the evolution we noted also other consequences as atrophy of the corpus callosum. In case number 3, an-

**FIGURE 2.4.** Evolution of the head circumference.
other pattern was seen – periventricular white matter lesions – and an old venous thrombosis has been identified on MRI.

The treatment was supportive in all cases. The decision not to use thrombolytic therapy was supported by the following facts. In case 1 the lesions had different ages, so one of the lesions was too old for treatment, and in the other one, the diagnosis was established when the vessel was already permeable. In case 2, the hemorrhagic nature of the lesion was a contraindication for the thrombolytic therapy and in case 3 the thrombosis was shown on the MRI examination to be old, the thrombolysis was not indicated anymore.
Regarding the evolution of the cases, the main symptoms noticed have been a deficit in the head growth – logic after the destruction of a region of the brain because of the infarction and an unilateral motor deficit. The presence of an unilateral motor deficit was in contradiction with the data in the literature that noted that the deficit is usually bilateral. In the case that had a longer follow-up period, the deficiencies were noted also in the cognitive and language domains. The deficits were noted despite the fact all the patients were included in early intervention programs.
FIGURE 3.4. Evolution of the head circumference

FIGURE 3.5 a – coronal section – 2 months; b – coronal section 4 months
CONCLUSIONS

Neonatal CSVT is not such a rare occurrence. A high level of awareness regarding certain history elements (infections in the mother, deficit of factor V Leyden) correlated with neurologic symptoms present in a term neonate, especially seizures or apneic spells, should bring into the differential diagnosis this entity. More than this, certain cerebral ultrasound findings (hemorrhages or infarctions with a venous pattern, germinal matrix hemorrhage in a term neonate or white matter lesion in the same category of patients should rise the suspicion of a CSVT and prompt the indication for an MRI. Once the diagnosis is established, the patient should be managed accordingly and included in an early intervention program because the risk for long-term neurologic deficits is high.

It is our belief that by increasing awareness on this pathology, the number of cases diagnosed in the neonatal period will increase and early intervention will lead to a better prognosis for these patients.

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REFERENCES


