

# Coexistence of Cerebral Sinovenous Thrombosis and Dandy Walker Malformation in Newborn

Snježana Gverić-Ahmetašević<sup>1</sup>, Ana Čolić<sup>1</sup>, Tugomir Gverić<sup>2</sup>, Vesna Elvedi Gašparović<sup>3</sup>, Goran Pavliša<sup>4</sup> and David Ozretić<sup>4</sup>

<sup>1</sup> University of Zagreb, Zagreb University Hospital Center, Neonatal Intensive Care Unit, Department of Obstetrics and Gynecology, Zagreb, Croatia

<sup>2</sup> »Sveti Duh« General Hospital, Zagreb, Croatia

<sup>3</sup> University of Zagreb, Zagreb University Hospital Center, Department of Obstetrics and Gynecology, Zagreb, Croatia

<sup>4</sup> University of Zagreb, Zagreb University Hospital Center, Department of Radiology, Magnetic Resonance Imaging Unit, Zagreb, Croatia

## ABSTRACT

*Cerebral sinovenous thrombosis in neonatal period may cause neurological impairment, epilepsy, and lead to stroke. It is caused primarily by coagulopathy of numerous reasons, occasionally perinatal asphyxia, traumatic delivery and hyperhomocysteinemia. Dandy-Walker malformation is characterized by agenesis or hypoplasia of the cerebellar vermis, cystic dilatation of the fourth ventricle, and enlargement of the posterior fossa. Dandy-Walker malformation, variant, and mega cisterna magna represent a spectrum of developmental anomalies. Insults to developing cerebellar hemispheres and the fourth ventricle are believed to be the cause of malformation. Our patient was born from noncomplicated pregnancy, noncomplicated nontraumatic vaginal delivery at term, excellent Apgar scores, without peculiarities in clinical status. She was breast-fed by the 42<sup>nd</sup> hour of life when she had rightsided seizures during sleep that repeated for five times in next 24 hours. Brain Ultrasound (US) revealed clot in left lateral ventricle, slight dilatation of left ventricle, both sided periventricular echodensity, ischemia, slight enlargement of fourth ventricle and a bit smaller cerebellum. There was no visible flow through left transverse, superior sagittal and straight sinus. Magnetic Resonance (MRI) confirmed the finding and showed thrombosis of left and right transverse venous sinuses and confluence of sinuses. Electroencephalogram (EEG) showed leftsided focal changes. The newborn was treated with phenobarbiton for 8 days and had no convulsions during that period. All coagulation parameters, homocystein, lipoproteins (a) and D-dimers were normal. There were no mutations on FV R506Q, PT 20210A, MTHFR 677C/T. No antiphospholipides were found. Heart US showed no structural anomalies. No other pathology or risk factors were present at the time. Before discharge, US showed hydrocephalus. Flow in affected sinuses was visible with color Doppler. MRI showed recanalization of affected sinuses, also hydrocephalus and presentation of Dandy Walker. On EEG there was borderline finding. Due to progression of hydrocephalus ventriculo-peritoneal shunt was placed. In age of 1 year EEG was slower for age but without focus. Neurological development was normal for age. The question is whether this child had intrauterine insult and inception of Dandy Walker with further postnatal progress of thrombosis and evolution to full picture of Dandy Walker with hydrocephalus OR thrombosis that led to development of hydrocephalus and Dandy Walker malformation in this child were accidental coexistence.*

**Key words:** neonatal cerebral sinovenous thrombosis, Dandy Walker malformation, Dandy Walker variant, neonatal seizures, hydrocephalus, prothrombotic factors, neonatal color Doppler brain ultrasound, brain magnetic resonance imaging

## Introduction

Cerebral sinovenous thrombosis (CVST) is a very rare event during neonatal period with an estimated incidence of 1 per 100 000 per year<sup>1-3</sup>. Although rare it may

leave severe sequels. It can cause neurological impairment, even epilepsy. It can lead to stroke<sup>4,5</sup>. It is most commonly presented by seizures<sup>4,6</sup>.

The diagnosis of neonatal CVST can be presumed with the use of color Doppler Ultrasound (US). Color Doppler is useful in monitoring the newborn with CVST. Confirmatory diagnostic imaging should be Magnetic Resonance (MR) and Magnetic Resonance venography<sup>7,8</sup>.

CVST may be caused by many factors singly or associated. In majority of cases it is caused by some coagulopathy, genetic or acquired due to dehydration, sepsis, meningitis, congenital cardiac malformations. In very occasional cases CVST is caused by perinatal asphyxia and traumatic delivery<sup>9–13</sup>. A clot is formed due to cooperation of the coagulation and fibrinolytic systems.

Dandy-Walker malformation is a rare congenital malformation that involves the cerebellum and fourth ventricle. It is characterized by agenesis or hypoplasia of the cerebellar vermis, cystic dilatation of the fourth ventricle, and enlargement of the posterior fossa with upward displacement of lateral sinuses, tentorium, and torcular herophili. It may be associated with atresia of the foramen of Magendie and the foramen of Luschka<sup>14–16</sup>. Dandy-Walker malformation, Dandy-Walker variant, mega cisterna magna, are classed among posterior fossa cystic malformations and represent a continuum of developmental anomalies on a spectrum that has been termed the Dandy-Walker complex<sup>17–19</sup>. Dandy-Walker variant consists of vermian hypoplasia and cystic dilatation of the fourth ventricle, without enlargement of the posterior fossa. Mega cisterna magna consists of an enlarged posterior fossa secondary to an enlarged cisterna magna, with a normal cerebellar vermis and fourth ventricle. Precise differentiation of the malformations may not be possible using imaging studies.

There are many theories explaining the origin, development, and diffuse manifestations of Dandy-Walker malformation. No single theory has been unanimously accepted.

70–90% of patients have associated supratentorial, which often develops postnatally and should be considered a complication rather than a part of the malformation complex<sup>20,21</sup>. About 80% of patients have normal ventricles at birth and by age of 1 year 80% have ventriculomegaly. Developmental delay appears to be related to the level of control of hydrocephalus. The clinical presentation depends to some extent on the particular combination of developmental anomalies in each infant<sup>22,23</sup>. Difficulty with balance, spasticity, and poor fine motor control are common, rarely respiratory failure. Sometimes seizures occur.

Dandy-Walker malformation is diagnosed with US as initial examination and MRI.

### Case Report

The patient, baby girl, was born by noncomplicated nontraumatic vaginal delivery at 37 weeks of gestational age with excellent Apgar scores. It was second noncomplicated pregnancy of a healthy young mother. Cardiotocography (CTG) during delivery was continuously nor-

mal. Her birth weight and length were within normal range for gestational age. The newborn was without peculiarities in clinical status and behaved normally. She was with her mother and was breast-fed by the 42<sup>nd</sup> hour of life when she had rightsided seizures during sleep. The seizures were in form of jerks of right corner of the mouth, right hand, right shoulder and right leg. The seizures repeated for five times during sleep and awake state during the following 24 hours. Between attacks she was hypotonic but without other symptoms.

### Initial Imaging Findings

Brain Ultrasound (US), including Color Doppler (CD), was performed immediately. The clots in antrum and frontal horn of left lateral ventricle were visualized, with slight dilatation of left ventricle (Figure 1). There were both sided periventricular echogenicity, more pronounced alongside left ventricle that suggested ischemia backed up by CD cerebral flow calculations. There were slight enlargement of forth ventricle and a bit smaller cerebellum. There was no visible flow through left transverse sinus, superior sagittal sinus and straight sinus. Flow through vein of Galen was normal.



Fig. 1. Initial US, Coronal view: Clot in the left ventricle and subependymal, and periventricular echodensities.

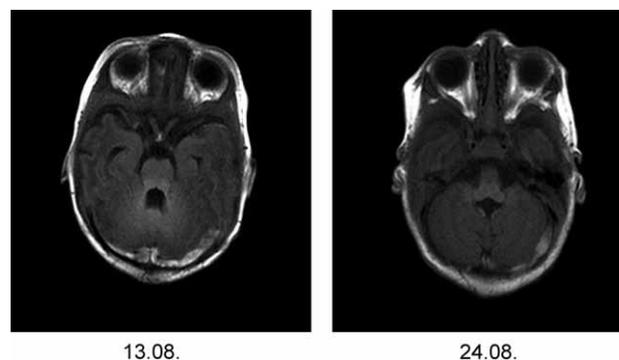


Fig. 2. Axial T1-weighted image: A (13.08): thrombus in both transverse sinuses; B (24.08): regression of thrombosis.



Fig. 3. A: Sagittal T1-weighted image; B: Axial T2-weighted image revealing hydrocephalus and hypoplastic vermis with communication of fourth ventricle and enlarged cisterna magna, corresponding to Dandy-Walker variant; C: Axial T1-weighted image showing normal signal due to restitution of flow in transverse sinuses, without signs of thrombosis; D: Axial T2-weighted image displaying hydrocephalus and subependymal hypointensity as a sign of hemosiderin deposition at the left caudothalamic notch.

Magnetic Resonance (MRI) confirmed the findings. It also showed thrombosis of left transverse venous sinus, confluence of sinuses and in less amount of right transverse sinus. Thrombosis was pronounced in left transverse sinus with minimal edge flow (Figures 2 and 3).

#### Coagulation screening

All coagulation parameters that might have led to thrombosis were examined. PT, APTT were within ranges for newborns. The results for F II, F V, F VIII, F IX, FXII, fibrinogen were normal, as well as for antithrombin III, protein C and protein S. Plasminogen level was also normal. Lipoproteins (a) and homocysteine were normal as well. No antibodies against phospholipids were found. There were no punctual mutations on FV R506Q and PT 20210A. There was no homozygous C677T polymorphism of the MTHFR gene. D-dimers were not found.

#### Other findings

Electroencephalogram (EEG) showed left-sided focal changes in the first week of life. In cerebrospinal liquor there were overmuch of erythrocytes and many macrophages as well as expected increased proteins. Heart US showed no structural abnormalities. No other pathology or risk factors were present at the time. Blood counts were normal.

#### Course

The newborn was treated with phenobarbital for 8 days and had no seizures during that period. Two days after presentation of convulsions the newborn became fe-

brile. The blood parameters did not exhibit inflammation and no bacteria was isolated from bodily fluids and excretions. She was febrile for following 3 days, discontended, with pronounced hypotonus. Although elevated temperature was most likely due to CVST empiric antibiotic treatment was conducted.

#### Discharge

Before discharge, hydrocephalus was seen on US, with normal liquor flow through aqueductus and chambers at the time. CD showed no signs of elevated intracranial pressure. Flow in affected sinuses was visible with CD (Figure 4).

MRI showed recanalization of affected sinuses with remains of smaller thrombus in left transverse sinus with consequently narrower lumen but adequate flow through whole venous system on MRI venography. Previously detected periventricular hyperintensities presenting ischemic lesions were completely regressed. In place of left intraventricular clot an edgy hypodensity remained. Development of hydrocephalus was obvious and presentation of Dandy Walker variant (Figure 3).

EEG finding was borderline with no clear pathology after a month.

The newborn had no convulsions even after withdrawal of phenobarbital therapy. In neurological status there were pronounced hypotonus with »worm-like« movements, without other aberrations.



Fig. 4. US: hydrocephalus with visible flow through transverse sinuses.

#### Follow up

Due to progression of hydrocephalus ventriculo-peritoneal shunt was placed. In age of 1 year EEG was slower for age but without focus. Neurological development was normal for age.

#### Discussion

In case of seizures in healthy term newborn the CVST must be considered and beside obligatory US with possibly CD, MRI and MRI venography must be performed. If CVST is diagnosed, screening for prothrombotic risk factors is highly recommended.

Beside coagulopathy, the other causes are usually more obvious and recognizable, but prothrombotic disorders must be excluded even when other causes are present due to possible coexistence; combination of acquired and genetic risks. Although acquired prothrombotic hemostatic conditions exist in large proportion of newborns with thrombotic stroke while congenital prothrombotic disorders are rare both must be examined<sup>9</sup>. Congenital deficiencies of antithrombin, protein C, protein S, and the presence of activated protein C resistance are predisposing factors for cerebral thrombotic events, especially when an acquired risk factor for thrombosis is present. Protein C resistance increases the risk of thrombosis when imputed to the factor V Leiden mutation or not. Deficiencies in the fibrinolytic system, like congenital deficiency of plasminogen, result in thrombotic complications as well<sup>24–34</sup>. All coagulation parameters including the plasminogen level were normal in our patient. D-dimers were not found.

Significant risk factors for spontaneous CVST in newborns are increased lipoproteins (a) level, presence of antiphospholipid antibodies, FV G1691A mutation, the PT 20210A allele and the homozygous C677T polymorphism of the methylenetetrahydrofolate reductase (MTHFR) gene<sup>9,35–37</sup>. Our patient had no punctual mutations on FV R506Q and PT 20210A. There was no homozygous C677T polymorphism of the MTHFR gene. Lipoproteins (a) and homocysteine were normal. No antibodies against phospholipids were found. Inherited hyperhomocysteinemia may be a cause of thrombotic incident in newborns and the only risk factor that can be treated in attempt to prevent recurrence<sup>38–40</sup>. In very occasional cases CVST is caused by perinatal asphyxia and traumatic delivery<sup>9–13</sup>, but the CTG during delivery was normal. She was born vaginally and had optimal Apgar score. She did not show any sign of hypoxia in the first two days. We did not identify the cause of CVST in our patient but the time of the incidence and further course of pathology remain unrevealed.

There are many theories explaining the origin, development, and diffuse manifestations of Dandy-Walker malformation. The dilatation of the fourth ventricle may originate in a congenital obstruction of the outlets of Luschka and Magendie due to developmental cerebellar defect<sup>41–43</sup>. Some claim that an insult leads to developmental arrest in the formation of the hindbrain, with lack of fusion of the cerebellum in the midline with persistence of the anterior membranous area, which herni-

ates posteriorly. Simultaneous formation of the foramen of Magendie, tentorium, superior longitudinal sinus, straight sinus, torcular herophili, and lateral sinuses helps explain their association with Dandy-Walker malformation. The malformation has not been seen on prenatal US in our patient. First postnatal US of brain showed slightly dilatation of fourth ventricle, intraventricular clot of left lateral ventricle with dilatation of ventricle, without clearly visible Dandy Walker malformation. Hydrocephalus, which often develops postnatally and should be considered a complication rather than part of the malformation complex<sup>20,21</sup>, was developing in our patient also. With developing hydrocephalus, Dandy Walker malformation became more visible, with hypoplasia of cerebellum, dilatation of fourth ventricle and inferior fossa. At the same time, the flow through sinuses became normal.

The question is what is the cause of Dandy Walker malformation in our patient and what is the cause of cerebral sinovenous thrombosis? Is it possible that the full picture of Dandy Walker malformation has developed after birth and if there are some connections between cerebral sinovenous thrombosis and Dandy Walker malformation? The cause of hydrocephalus may be Dandy Walker but the origin could be CSVT as well. Whether this child had intrauterine insult and inception of Dandy Walker with further postnatal progress of thrombosis and evolution to full picture of Dandy Walker with hydrocephalus that usually does develop postnatally OR thrombosis and some possibility of invisible infarction or other cause led to intraventricular haemorrhage with development of hydrocephalus and the picture of Dandy Walker malformation? Or in this child Dandy Walker malformation and cerebral sinovenous thrombosis were accidental coexistence?

No case with such coexistence of pathology has been described so far. It would be interesting to distend research in this area which has not been completely clarified and since there is no single theory that has proven satisfactory or has been widely accepted about Dandy Walker malformation. This case raises question whether picture of Dandy Walker malformation, or better said Dandy Walker like presentation is possible to develop postnatally as described in our case, opposite to embryonic genesis. Discussion and investigation of this problem, origin, development and course with professionals that came across any similar pathology might bring more knowledge and initiate further investigations.

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S. Gverić-Ahmetašević

University of Zagreb, Zagreb University Hospital Center, Department of Obstetrics and Gynecology, Neonatal Intensive Care Unit, Petrova 13, 10 000 Zagreb, Croatia  
e-mail: snjezana1@hi.t-com.hr

## ISTODOBNOST TROMBOZE MOŽDANIH VENSKIH SINUSA I DANDY WALKER MALFORMACIJE U NOVOROĐENČETA

### SAŽETAK

U novorođenačkoj dobi tromboza moždanih venskih sinusa može uzrokovati poremećaje neurološkog razvoja, epilepsiju, te dovesti do razvoja inzulta. Najčešće nastaje uslijed koagulopatije brojnih uzroka, rijetko perinatalne asfiksije, traumatskog poroda, hiperhomocisteinemije<sup>1,2</sup>. Dandy-Walker malformacija je karakterizirana agenezom ili hipoplazijom cerebelarnog vermisa, cističnom dilatacijom četvrte komore i povećanjem stražnje jame. Dandy-Walker malformacija, varijanta, i mega cisterna magna predstavljaju spektar razvojnih anomalija. Inzulti cerebuluma i četvrte komore tijekom razvoja smatraju se uzrokom malformacije<sup>3</sup>. Bolesnica je rođena iz uredne trudnoće nekomplikiranim vaginalnim porodom u terminu, izvršnih Apgara, bez osobitosti u kliničkom statusu. Hranjena je na prsima do dobi od 42 sata kad je imala desnostrane konvulzije u snu a koje su se ponovile u pet navrata tijekom slijedećih 24 sata. Na ultrazvuku (UZV) mozga je viđen ugrušak u lijevoj lateralnoj komori s blagom dilatacijom lijeve komore, obostrana periventrikularna ehogenost, ishemija, te blago povećanje četvrte komore i nešto manji cerebelum, bez vidljivih protoka kroz lijevi transverzalni, gornji sagitalni sinus i sinus rektus. Magnetska rezonanca (MRI) je potvrdila nalaz, te pokazala trombozu lijevog i desnog transverzalnog venskog sinusa i sinusa konfluens. U elektroencefalogramu (EEG) videne su žarišne promjene lijevo. Tijekom 8 dana terapije phenobarbitonom novorođenočica nije imalo konvulzije. Svi koagulacijski parametri, homocistein, lipoproteini (a), D-dimeri bili su normalni. Nije nađeno točkastih mutacija na FV R506Q, PT 20210A, MTHFR 677C/T. Nije nađeno antifosfolipida. Na UZV srca nije viđeno strukturalnih anomalija. Tada nije nađeno druge patologije ili rizičnih faktora. Pred otpust na UZV-u se vidio hidrocefalus, color Dopplerom vidljivi su protoci u zahvaćenim venskim sinusima. Na MRI vidjela se rekanalizacija zahvaćenih sinusa, također hidrocefalus uz znakove Dandy Walkera. U EEG-u graničan nalaz. Zbog progresije hidrocefalusa djetetu je postavljena ventrikulo-peritonealna drenaža. U dobi od jedne godine EEG je bio nešto usporeniji za dob no bez žarišta. Neurološki razvoj je bio primjeren dobi. Pitanje je da li je ovo dijete imalo intrauterini inzult sa začetkom Dandy Walkera te daljnjim napredovanjem tromboze i evolucijom u potpunu sliku Dandy Walkera sa hidrocefalusom ILI je postojanje tromboze koja je dovela do razvoja hidrocefalusa i Dandy Walkera slučajna supojava.

