RELATIONSHIP BETWEEN HERPES SIMPLEX VIRUS TYPE 1 AND EXTENSIVE CEREBRAL SINOVENOUS THROMBOSIS IN A CHILD WITH INHERITED HYPERCOAGULABLE STATES

Monica Luminos¹,², Anca Draganescu¹, Angelica Visan¹,², Magdalena Vasile¹, Cristina Negulescu¹, Madalina Maria Merisescu¹,², Sabina Schiopu¹, Anuta Bilasco¹

¹National Institute for Infectious Diseases "Prof. Dr. Matei Balş", Bucharest, Romania
²Carol Davila University of Medicine and Pharmacy, Bucharest, Romania

Abstract
Cerebral sinovenous thrombosis (CSVT) is a rare, but potentially serious condition among children which requires a multidisciplinary team approach. Clinical manifestations of CSVT include: headache, vomiting, photophobia, blurred vision, focal or generalized seizures, motor deficits, altered mental status and coma.

Objective: Exposure clinical data, laboratory and management in cerebral venous thrombosis in children- a clinical case report.

Material and methods. We present a case of 14 months - old boy, admitted in ICU National Institute for Infectious diseases "Prof. Matei Bals" for: fever, vomiting,focal and generalized seizures, right hemiparesis and coma. The child was diagnosed with acute herpetic gingivostomatitis one week before onset of neurological symptoms.

MRI brain and angiography revealed extensive thrombosis of the straight, transverse and occipital venous sinuses, bilateral thalamic infarction and left haemorrhagic transformation with intraventricular hemorrhage and univentricular obstructive hydrocephalus.

Thrombophilic screening was performed and a heterozygous mutations genes of C677T MTHFR and 4G/5G PAI was detected. He was treated with low molecular weight heparin (enoxaparine) followed by oral anticoagulant (acenocumarol) with good clinical outcome and complete neurological recovery.

Conclusions: CSVT in children can be fully reversible with early diagnosis and a prompt management. Brain MRI with angio MRI remains the gold standard for diagnosing CSVT. Thrombofilic screening should be considered in any child with stroke history and CSVT. Herpes simplex virus associated infections may precipitate thrombosis in individuals with inherited or acquired hypercoagulable states

Key Words: anticoagulant, cerebral venous sinus thrombosis, magnetic resonance angiography, inherited hyper- coagulable state

Introduction
Cerebral sinovenous thrombosis (CSVT) is a rare but potentially serious condition in children, involving a multidisciplinary team approach. CSVT is defined by thrombosis within the superficial (cortical veins, superior sagittal sinus, sigmoid sinus, transverse sinus and jugular vein) or deep (inferior sagittal sinus, straight sinus internal cerebral veins, vein of Galen) venous system. Clinical manifestations of CSVT include: headache, vomiting, photophobia, blurred vision, focal or generalized seizures, motor deficits, altered mental status and coma. CSVT occurs in about one of 100,000 children per year including, neonates and is the most important and frequent cause of pediatric stroke, with a high rate of mortality (8-19%) and severe long-term neurological sequelae, that are reported in 38 up to 48 % of patients.

CSVT in children is a multi - factorial disease, which, in the majority of cases, results from a combination of pro-thrombotic risk factors and underlying clinical conditions, that may consist of infections, anemia, dehydration, cranial trauma, systemic diseases, cardiac or renal diseases, malignancies and their treatment regiments (drugs and/or radiation associated procedures). The diagnosis should be established as soon as possible after the symptoms onset in order to obtain good clinical progressions, with reduced mortality and complete/partial neurological recovery.

Clinical case
We present a case of a 14 months - old boy, admitted to the Pediatric Intensive Care Unit (pICU) at The National Institute for Infectious diseases "Prof. Matei Bals" - Bucharest in November 2014 for: fever, vomiting, focal and generalized seizures, right hemiparesis and coma. The child was diagnosed with acute herpetic gingivo - stomatitis one week before the onset of neurological symptoms. The patient was initially admitted to Curtea de Arges Hospital (Pediatric Compartment) where he received antibiotic therapy, intra-venous fluids therapy, antipyretics with unfavorable clinical and neurological evolution. The child experienced repeated vomiting, irritability and drowsiness, high fever, weakness, partial and generalized
seizures with neurological deterioration and coma. He was transferred to the pICU at the National Institute for Infectious diseases “Prof Dr Matei Bals” - Bucharest. His family medical history revealed: maternal grandfather died of myocardial infarction, maternal grandmother died of stroke and mother has a history of miscarriage at 25 week gestational age.

On admission, the clinical examination revealed: altered general status, normal body temperature, comatose with GCS 10/15, the eye exam revealed pupils equal in diameter, round, reactive to light; anicteric sclera, pale skin, vesicular rash around the mouth, he presented spontaneous breathing, no rales were noted over the lung area, cardiac rhythm was regular, no extra-beats or murmurs were identified during the initial evaluation, heart rate - 120-130 beats/min, blood pressure - 90/58 mmHg; no cyanosis; oxygen saturation measured by pulse oximetry was 97% in room atmosphere, multiple ulcerations on the gums, lips, tongue and oral mucosa were observed, with hyperemia and active hemorrhage of the gums, halitosis; the abdominal exam presented: symmetric, soft and non tender abdomen, no hepatosplenomegaly was discovered; physiological urination present; the neurological exam described: stiff neck, right hemiparesis, with reactivity to nociceptive stimuli.

Laboratory blood tests showed increased leukocyte count, mycroctic - hypochrome anemia, hypo-sideremia, no biological inflammatory syndrome associated, no coagulation disturbance.

Serological tests using Elisa immunosorbent assays (ELISA) came back positive for Herpes Virus for the acute (IgM) antibody subclass (with rising antibody titers - 3 samples collected in dynamics Brain angio-MRI studies revealed extensive thrombosis of the straight, transverse and occipital venous sinuses, bilateral thalamic infarction and left hemorrhagic transformation with intra-ventricular hemorrhage and uni-ventricular obstructive hydrocephalus. (fig 1, 2, 3, 4)

Fig. 1. Brain MRI showed bilateral thalamic infarction and left hemorrhagic transformation with intraventricular hemorrhage and uni-ventricular obstructive left hydrocephalus with transependymal resorption edema by obstruction foramina of Monro with mass effect

Fig. 2 and 3. Brain MRI showed extensive thrombosis (loss of normal signal intensity) of the straight, transverse, superior sagittal and occipital venous sinuses and intra-ventricular hemorrhage

Fig. 4. Magnetic resonance brain angiography showed extensive thrombosis of the transverse, occipital, superior sagittal and straight venous sinuse.
Anticardiolipin antibody, anti-thrombin III, protein S, protein C, lupus anticoagulant were in normal range. Thrombophilic screening was performed and a hetero-zygous mutations of the genes C677T MTHFR and 4G/5G PAI was detected. Due to focal neurological signs and active intraventricular homorhage the lumbar puncture was not performed.

He was treated with Aciclovir i.v, anti-convulsivant drugs in order to control seizures, anti cerebral-edema measures were implied - consisting of intravenous 20% mannitol and dexamethasone, i.v human non- specific immunoglobulins were administered. We decided to delay the initiation of anticoagulant treatment because of signs of active bleeding observed MRI evaluation and para – clinically supported by the constant drop of the hemoglobin and hematocrite values.

The clinical and neurological evolution was good, but subsequent brain angio - IRM reevaluations showed CVST progession to superior sagittal sinus and related cortical veins. Anticoagulant therapy was started with low molecular weight heparin (Enoxaparine) followed by oral anticoagulant regimen (acenocumarol) with good clinical outcome and complete neurological recovery. Controle brain IRM showed repermeabilisation of all venous sinuses. The patient was discharged after 8 weeks, on oral anticoagulants, with the recommendation to weekly monitor the coagulation parameters and was addressed to a pediatric hematology department in order to stratify his residual risk factors and to receive long term recommendation due to his thrombophilic status.

**Discussion:**

We suggest that anticoagulation should be considered in all children with CSVT without active intracranial hemorrhage and that is should be used with caution in the presence of proven intracranial hemorrhage. Early repeated brain angio - IRMs studies in order to screen for CSVT propagation, in children that are treated with a conservatory approach in regard to the anti-coagulation regimen is absolutely necessary for a successful and correct management. Still, it is difficult to affirm whether the herpes virus itself, the inflammatory process itself, the dehydration or the iron deficiency anemia in association with the inherited hypercoagulable states predisposed our young patient to cerebral venous thrombosis. A balanced clinical reasoning in association with brain angio-IRM studies are necessary for an accurate and early diagnosis of CSVT. On the other hand, the herpes virus infection can trigger CSVT in a patient presenting with an underling hypercoagulable states.

**Conclusions:**

1. CSVT in children can be fully reversible with early diagnosis and a prompt management
2. Brain MRI with angio MRI remains the gold standard for diagnosing CSVT.
3. Thrombofilic screening should be considered in any child with strokes and CSVT.
4. Herpes simplex virus may precipitate thrombosis in individuals with inherited or acquired hypercoagulable states

**References**

1. Stroke. 2008; 39: 2644-2691 Management of Stroke in Infants and Children E. Steve Rouch, MD, FAHA. Chair; Meredith R. Golomb, MD, MSc; Robert Adams, MD, MS, FAHA; Jose Biller, MD, FAHA; Stephen Daniels, MD, PhD, FAHA; Gabrielle deVeber, MD; Donna Ferriero, MD

**Correspondence to:**

Monica Luminita Luminos, MD, PhD
Associate Professor
National Institute for Infectious Diseases "Prof. Dr. Matei Balș", Bucharest, Romania
1, Calistrat Grozovici street, Bucharest
E-mail: monicaluminos@yahoo.com.