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Case Report

Deep Medullary Vein Thrombosis in Newborns: A Case Series and a Comparative Analysis of the Literature

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Abstract

Here in, we present two cases of deep medullary vein (DMV) thrombosis presenting with seizure in previously healthy term neonates. DMV thrombosis is a rare cause of brain damage in both preterm and full-term neonates, with a non-completely understood pathogenesis of damage. Therapeutic approach with anticoagulation is not described in literature. We treated both with enoxaparin with complete resolution of the thrombotic phenomena. Then we followed up until 24 months of age with sequencial neurological evaluations and neuroimaging, assisting to a favourable evolution without neurological sequalae. Our objective was also to conduct a comparative analysis of our data with the body of knowledge regarding neurodevelopmental outcome, therapeutic method, neuroimaging findings, and clinical presentation. In particular, in our experience, anticoagulation was safe and effective leading to a quick clearance of the thrombus without any negative side effects, and the neurodevelopmental outcomes of our cases have been positive.

Keywords: Deep Medullary Vein Thrombosis; Perinatal Stroke; Neuroimaging; Neurodevelopmental Outcomes

Introduction

Perinatal venous stroke has historically been attributed to cerebral Sino-venous thrombosis (CSVT), however recent advance in magnetic resonance imaging (MRI) technique have led to the identification of a new clinical and radiological finding involved in the occurrence of perinatal stroke: the deep medullary vein (DMV) thrombosis. DMV are parts of the deep cerebral venous system [1]. They originate 1-2 cm deep to the pial surface, show a radial configuration in the superior lateral corner of the lateral ventricle and drain into sub ependymal veins, crossing four convergence point in the white matter of the cerebral hemisphere [1]. They are tributaries of the internal cerebral vein, the vein of Galen, and the basal vein of Rosenthal through the sub-ependymal veins, providing drainage to the deep white matter and the deep and periventricular white matter [2]. The pathogenesis of neonatal DMV engorgement is not completely understood. It is hypothesized that it could be due to transient hypo perfusion or cerebral blood flow impairment. In preterm neonates germinative matrix haemorrhages could

determine stasis and medullary vein congestion, with consequent parenchymal damage [3,4].In contrast, in term neonates a fan shape periventricular haemorrhagic venous infarction has seen as a direct sign of DMV thrombosis or an indirect sign of Sino-venous involvement [5,6] .Venous congestion/thrombosis of these thin and subtle radial lines may result in ischemic insults, vasogenic/ cytotoxic edema or cerebral haemorrhage [7]. CSVT and DMV thrombosis can coexist or occur separately. We can speculate that DMV engorgement might have similar risk factor of cerebral Sino-venous thrombosis such as perinatal factors (complicated delivery, maternal preeclampsia, perinatal asphyxia, sepsis/meningitis) and congenital thrombophilia [6]. It is acknowledged that one of the main causes of neurodevelopmental impairments is CSVT, while there is little information available on the cause of neonatal DMV thrombosis, the therapeutic approach and its neurological outcomes [8,9]. We aimed to described two cases of neonatal stroke due to DMV involvement and to compare our data with the existing literature about clinical presentation, neuroimaging findings, therapeutic approach and neurodevelopmental outcome.

Case Presentation

Patient 1

A term male neonate, with no antenatal or perinatal risk factors presented with focal seizure on the 5th day of life. A laboratory workup excluded infections and the cerebrospinal fluid was negative. The video-electroencephalography (v-EEG) showed recurrent focal clonic seizures on the right arm with contralateral central electro genesis. No further seizures since the start of Phenobarbital. The brain magnetic resonance imaging (MRI) was consistent with left thalamic venous infarction involving part of the posterior arm of the internal capsule and thrombosis of the deep medullary veins homolaterally. According to the Benninger et al. scale [9], the global severity score for medullary vein thrombosis resulted to be 15. Anticoagulant therapy with enoxaparin was started at a therapeutical dosage for one month, after that the MRI showed an important reduction of thrombosis. He followed with enoxaparin on prophylactic dosage for two months. Phenobarbital was discontinued after two months. The last EEG was negative. Methylenetetrahydrofolate reductase (MTHFR) homozygosis (A1298C) mutation was found. Genetic analysis for COL4A1, COLA4A2, Notch3 mutations were negative. At 18 months of life the MRI showed glio-malacic evolution with hemosiderin deposits in the left thalamic area, into the white matter of the semi oval centre, of the corona radiata and in the ipsilateral periventricular area. At 6 months of age the Griffiths Mental Developmental scales (GMDS) showed normal neurodevelopment, the ocular electrophysiology tests (ERG) and somatosensorial evoked potentials (SEP) of arms were normal. At 12 months of age the GMDS showed mild delay in locomotor subscale score, corresponding to age 10 months instead of 12 months, while the scores of other subscales (social behaviour and language) were adequate for age. At 22 months of age the GMDS showed adequate scores in all subscales and the EEG was negative.

Patient 2

A term male neonate, with no antenatal or perinatal risk factors presented with focal clonic seizures on the left arm and leg on the 3rd day of life. No further seizures since the start of Phenobarbital. The MRI showed right thrombosis of the medullary veins with secondary parenchymal suffering of the deep white matter of the semi oval centre by cytotoxic oedema; a modest bilaterally haemoventricle coexisted. According to the Benninger et al. scale [9], the global severity score for medullary vein thrombosis resulted to be 11. Anticoagulant therapy with enoxaparin was started at a therapeutical dosage for one month, after that the MRI showed a marked reduction of thrombotic phenomena, furthermore, were no more evident the phenomena of cytotoxic oedema. He followed with enoxaparin on prophylactic dosage for one more month. The EEG was negative after few days of Phenobarbital, so we started decalage and discontinued the therapy after 15 days from the start. The MRI performed at 4 months old showed almost total resolution of thrombotic phenomena in the deep medullary veins in the right semi oval centre, with likely gliotic outcomes. The MRI repeated at the age of 12 months highlighted a nuanced hyper intensity in T2 and FLAIR of the white matter of the semi oval centre and in the anterior periventricular site on the right, in gliotic outcomes, without any signs of recent thrombotic phenomena. The prothrombotic screening found a MTHFR heterozygosis mutation (A1298C). Genetic analysis for COL4A1, COLA4A2, Notch3 mutations were negative. The first neurodevelopmental evaluation at 4 months old highlighted mild motor impairment of the left arm, for which he started physiotherapy. Motor score on the Bayley Scales of Infant and Toddler Development, Third Edition (Bayley-III) at the age of 8 months was only somewhat delayed, but it improved following physiotherapy. The Bayley III evaluation at the age of 12 months showed adequate scores in all subscales. The last neurological evaluation at 21 months with the GMDS confirmed a normal neurodevelopment and the EEG was negative.

Discussion

Clinical picture and risks factor

In the past, thrombosis of DMV was thought to be typical of preterm, with a silent clinical presentation and occasional ultrasound findings. Our cases highlights that it could happen in term new-born presenting with seizures in the first days of life. Our results are consistent with the most recent research; in fact, over half of the instances are now reported to involve previously healthy term new-borns who present with seizures in their first week of

life [7]. Neonates with DMV thrombosis, in literature, as in our experience are predominantly male (68%) [7]. Prematurity and immaturity of the walls of small vessels seemed to be the principal risks factors, but according to the literature, we can speculate that, in reality, the same risks factors involved in cerebral sino-venous thrombosis may be founded in this peculiar form of venous stroke Table 1.

Maternal	Feto-Neonatal
Chorioamnionitis	Neonatal distress or need for resuscitation
Thrombophilia	Sepsis
Autoimmune diseases	Dehydration
Urgent cesarean section	Thrombophilia
Pre-eclampsia or hypertension	Cardiac surgery
Gestational diabetes	Polycythemia

Table 1: Maternal and feto-neonatal risks factors of cerebral venous thrombosis.

In our cases prenatal and perinatal history were silent, with a physiological course of pregnancy but they both have MTHFR mutation. Prothrombotic disorders have been found in 8% of neonates with DMV thrombosis. Therefore, we suggest extended thrombophilia study in these patients aiming to detect all causes of inherited thrombophilia Table 2.

Common inherited causes of thrombophilia • Factor V Leiden mutation • Factor II (prothrombin) mutation • High level of lipoprotein a • Hyperhomocysteinemia • MTHFR mutation (when associated with hyperhomocysteinemia)	Rare inherited causes of thrombophilia • Protein C deficiency • Protein S deficiency • Antithrombin deficiency • Heparin cofactor II deficiency ii • Deletion of angiotensin 1 converting enzyme
Probable inherited causes of thrombophilia • High level of FVIII • High level of FIX • Low level ofFXII	Very rare inherited causes of thrombophilia • Dysfibrinogenaemia • Dys/hypoplasminogenemia • Homozygous for homocystinuria

Table 2: Inherited causes of thrombophilia.

MTHFR mutation is very common in Europe, in fact up to 20% of the European population have 2 MTHFR C677T mutations and up to 12% present another mutation called MTHFR A1298C. In people who are heterozygous for an MTHFR mutation, there is reduced enzyme function ≈65% of normal. In people who are homozygous for MTHFR, there is only 30% of normal enzyme function [10]. MTHFR is involved in the folate metabolism pathway, a defect in that metabolic line has been associated with elevated levels of plasma total homocysteine [11]. Homocysteine may have a thrombogenic effect through inhibition of inactivation of activated factor V (Va) by activated protein C [12]. According to the recent literature in the adult population the MTHFR mutations by themselves, in the absence of elevated homocysteine levels, are not a risk factor for cardiovascular disease or deep vein thrombosis. To date, in fact, in the "Italian recommendations for diagnosis and therapy of neonatal thrombosis" there is disagreement about running the analysis routinely [13] Both our patients had MTHFR mutations with normal level of homocysteine, however precisely by virtue of the para-physiological state of hypercoagulability that characterizes neonatal haemostasis, we cannot exclude that MTHFR mutations have a greater impact in favouring thrombosis phenomena in neonatal age than in adult life.

Neuroimaging

The gold standard for diagnosing DMV thrombosis is brain magnetic resonance imaging (MRI), and recent advancements in technology, including susceptibility-weighted-imaging (SWI), have improved the sensitivity of this technique [3]. Prominent DMV can be recognized with T2 weighted or SWI sequences. The terms brush sign and prominent hypo intense vascular sign have been employed by several authors to characterize the DVM engorgement [14]. On MRI images the restricted diffusion or bleeding might take the form of a fan due to the fan-shaped branching arrangement of the deep medullary veins; this is known as the iris sign [15]. DMV involvement could be associated with parenchymal haemorrhages, cytotoxic oedema, or vasogenic oedema. Over 90% of MRI scans reveal evidence of a haemorrhagic infarction, and up to 75% exhibit localized or widespread oedema, according to the literature [7]. The correlation with intraventricular haemorrhage, as in one of our cases, can be explained by the centripetal drainage of the deep medullary veins [14]. Specific MRI findings of our cases are described in Figure 1 and Figure 2, for patient 1 and 2 respectively.

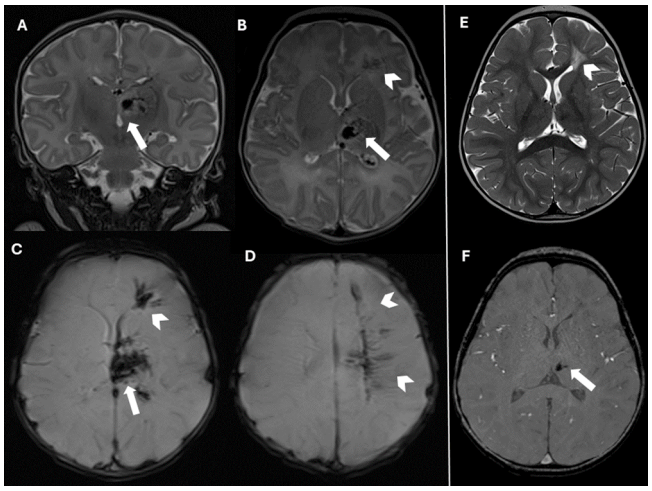

Figure 1: A. Coronal T2 Weighted Images, B. Axial T2 Weighted Images, C. and D. Axial T2 Gradient Echo Weighted Images showing a left thalamic venous infarction (arrows) and homolateral extensive thrombosis of the deep medullary with punctate and linear lesions (arrowhead). E. Axial T2 Weighted Images and F. Axial Susceptibility Weighted Imaging (SWI) follow-up MRI at 18 month of life showing a glio-malacic evolution of the periventricular white matter lesions (E, arrowhead) and punctate hemosiderin deposits in the left thalamus (arrow F).

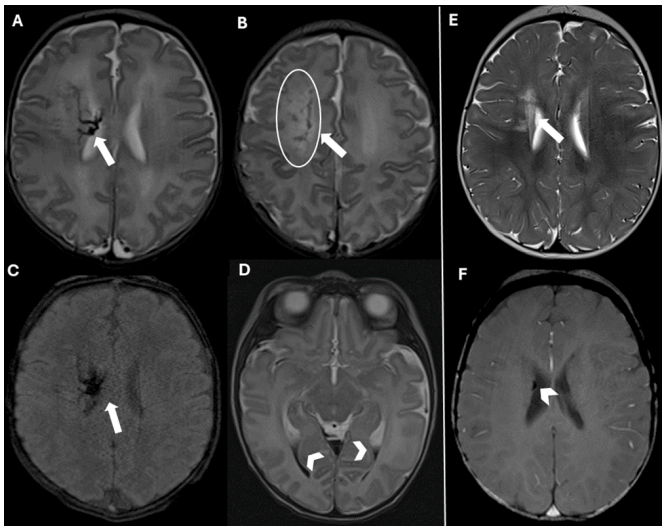

Figure 2: A. B. D. Axial T2 Weighted Images, C. Susceptibility Weighted Imaging (SWI) showing right thrombosis of the medullary veins (arrows in A, B, C) with associated slight loco regional white matter oedema (B, circle) and haemoventricle (D, arrowheads). E. Axial T2 Weighted Images and F. Axial Susceptibility Weighted Imaging (SWI) follow-up MRI at 1 year of life showing glio-malacic evolution of the periventricular white matter lesions (E, arrow) and a small punctate hemosiderin deposit (arrowhead F).

Regarding the timing of the initial MRI and the subsequent imaging, there are no guideline. We performed the first MRI with urgency after the onset of symptoms. We then began anticoagulant therapy, and after one month, we made the decision to repeat the MRI, that show in both cases an important reduction of the thrombosis and the oedema. During the follow up we were able to repeat a second imaging for both patients at 18 months and 12 months respectively (the scheduled MRI follow up at 12 months was missed in one case for poor parental adherence to the follow-up program). In both cases MRI showed gliotic evolution in the areas of previous thrombosis, without any signs of recent thrombotic or ischemic phenomena. Our findings are consistent with published data reporting periventricular leukomalacic-like lesions in the DMW areas without progression or recurrence of ischemic phenomena [3,6]. We borrowed the indications about MRI timing and follow up from the CSVT recommendations. In our experience MRI is the gold standard for the diagnosis and the follow up of DMV thrombosis and associated lesions. We recommend a rigorous imaging follow-up in the early months, especially if therapy has begun. If necessary, we also suggest a MRI evaluation in conjunction with a neurodevelopmental score assessment at the 12-month of age. A score was created by Benninger et al. [9] to evaluate the seriousness of MRI abnormalities. It offers a thorough and impartial categorization of white matter impairment in late preterm and term new-borns following deep vein thrombosis and infarction, and it was independent of gestational age and other antenatal risk factors. The maximum global severity score is 102 points, the max score in Benninger population was 53 (median 11, interquartile range [25th-75th percentile], 5–25) [9]. In our patients the Benninger score at onset of symptoms were 11 and 15 respectively.

Neurodevelopmental outcomes

In general, the prognosis of neonates with perinatal veno-arterial stroke is still poor, with a high incidence of long-term neurological sequelae. However, little is known about the outcome of new-borns with exclusively venous genesis of stroke, particularly those with deep medullary vein involvement. The main data about neurodevelopmental outcome have been published by Benninger et al [16]: they found a quote of neurodevelopmental damage in 37% of patients with neonatal DMV thrombosis. This result is consistent with research on neonates with CSVT, which shows that between 23 and 79% of them experience significant neurological or developmental effects [8]. From the follow up of patients between the ages of 2 and 17, the authors described: movement disorders or cerebral palsy (27%), linguistic impairments (20%), vision and hearing impairment (20%), and intellectual disabilities

and behavioural issues (32% and 22%, respectively) [16]. 18% of patients develop epilepsy, which is consistent with earlier reports about CSVT [8,17]. While there were no differences in gestational age, birth weight, or socioeconomic position between the two groups, patients with severe neurodevelopmental impairment had a higher grade of severity of brain damage; as for CSTV results, that seem to be correlated with the size and bilateral location of the thrombotic infarction [8,16,17]. Additionally, research show that the best cut point to identify children at increased risk for long-term neurodevelopmental impairment is a global severity score of 16 [16]. The infants who have a global severity score greater than 16 ought to be the ones who are most attentively watched for neurodevelopmental delays and, if necessary, referred for early intervention [16]. Given the high rate of morbidity, it is essential to immediately implement strong rehabilitation strategies to exploit the neuroplasticity of this specific population. Therefore, there are published guidelines for stroke rehabilitation that also include the paediatric population [18] Cognitive, intellectual and behavioural disorders can also manifest themselves only many years later, when the deficits become more evident with age [19]. So, neuropsychological testing at school age is recommended to determine whether educational support is needed. Verbal function appears to have an important ability to reorganize itself after perinatal stroke, an early involvement of speech therapy specialists may be helpful for children experiencing speech delays [20,21].

Consequently, it is essential to give the patient thorough an early neuro-rehabilitative therapy and include these patients into a neurological and neurodevelopmental follow-up program in order to promptly detect and intercept any adverse neurological effects. Epilepsy has been associated with worse neurodevelopmental outcomes in children with perinatal stroke, and for this reason the identification and treatment of seizures remains crucial [22].

Therapeutic approach

To date there are no guidelines about the management of DMV thrombosis. Reviewing the literature about DMV we do not found data about treatment of this peculiar type of stroke. We could speculate that the single physicians' clinical expertise dictates the course of treatment, which is typically in compliance with the most recent recommendations for the management of CSVT. According to the results of the "International Pediatric Stroke Study" [23] there is still wide practice variability and uncertainty even about the treatment of perinatal stroke due to CSVT. The American College of Chest Physicians (ACCP) guidelines recommend treatment of neonates with CSVT without significant intracranial haemorrhage, with unfractionated heparin (UFH) or low molecular weight heparin (LMWH)initially, followed by LMWH or vitamin K antagonists for 6–12 weeks. For neonates with CSVT and significant haemorrhage, radiological monitoring is recommended and beginning of anticoagulation therapy, if extension of the thrombus occurs, 5–7 days after the initial haemorrhage [24,25]. More recently anticoagulation has been shown to be safe and well-tolerated in patients with CSVT. If the clinical team decides not to treat a neonate with CSVT with anticoagulation, it is important to repeat imaging at 5 to 7 days to exclude clot propagation that may occur in more than 30% of cases [26,27]. We decided to assimilate DMV thrombosis to CSVT and to treat both patients with anticoagulant therapy, after having excluded intracranial haemorrhages. In both our cases, after one month on enoxaparin at therapeutic dosage, the MRI showed a marked reduction of thrombotic phenomena, without insurgence of haemorrhages.

Conclusions

Deep medullary vein thrombosis represent a quite new type of perinatal venous stroke. It is an uncommon condition, with a non-specific clinical presentation, but it could result in severe neurological consequences. To date, there are many knowledge gaps about the underlying basic mechanisms, risk factors and treatment strategy. We report on two patients that were identified in the first few days of life, treated with anticoagulant medication, and followed up neurologically and radiologically up to 24 months of life. In our experience the use of anticoagulation was safe and effective, resulting in rapid resolution of the thrombus without adverse events. The neurodevelopmental outcomes of our cases have been favourable, mainly due to the prompt diagnosis with the MRI to the rapid start of physiotherapy and the careful clinical and radiological follow up. Larger research are required to look into prevention and treatment measures in particular, as there are currently no international guidelines in this area.

Disclosure

Authors' Contributions: Conceptualization, CM and FC, Methodology, CM and FC; Writing original draft preparation, CM, SR, IB, IS, FC; Writing review and editing, CM, DL, MC, FC, FD, GM Supervision, DL, AD, FC. All authors have read and agreed to the published version of the manuscript.

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