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Case report

Cerebral sinus thrombosis in an infant with Prader-Willi syndrome and literature review

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Abstract

A full-term male neonate from a first pregnancy of two clinical non-consanguineous parents was born at 40 weeks of gestation with cesarean section. He was admitted at 2 hours of life to our III level Neonatal Intensive Care Unit due to generalized hypotonia, presenting at birth. Cerebral ultrasound showed a temporal bilateral aspecific alteration of the parenchimal echogenicity, whereas a magnetic resonance imaging/venography revealed an extensive cerebral sinus thrombus. Extensive diagnostic studies for prothrombotic disorders showed negative results, even if there was an alterated haemostatic screening. Persistency of hypotonia led us to investigate Prader-Willi syndrome among others. Methylation analysis confirmed the diagnosis. This is the third report associating cerebral venous thrombosis and Prader-Willi syndrome, confirming sinus thrombosis as a possible presentation of this syndrome. A review of the literature is provided in order to disclose possible similarities and differences in Prader-Willi syndrome patients with cerebral sinovenus thrombosis.

Keywords

Cerebral sinus thrombosis, Prader-Willi syndrome, hypotonia.

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Introduction

Prader-Willi syndrome (PWS) is a relatively common disorder (1/15,000-1/30,000 births), usually sporadic, with a pattern of dysmorphic features and major neurologic, cognitive, endocrine and behavioral/psychiatric disturbances [1]. PWS results from failure of expression of paternally inherited genes in the region of chromosome 15. PWS can occur by three main mechanisms, which lead to absence of expression of paternally inherited genes in the 15q11.2-q13 region: paternal microdeletion (70-75%), maternal uniparental disomy (UPD; 20-25%), and mutation or other disorder in the imprinting center (< 2%) [2, 3]. Major characteristics in neonates are lethargy and hypotonia causing poor feeding and failure to thrive with occasionally a characteristic facial appearance. Cerebral sinovenous thrombosis (CSVT) is increasingly observed in neonates, with most common sites being superior sagittal sinus, transverse and straight sinus [4, 5]. With estimated incidence at 2.6 per 100,000 half of infants with CSVT have multiple sinuses involved and 40-60% associated parenchymal infarcts (hemorrhagic or ischemic), usually located in frontal and parietal lobes [6-9]. This report is of a neonate with PWS and extensive CSVT, a not so well recognized association [10, 11]. A review of the literature is provided in order to disclose possible similarities and differences in PWS patients with CSVT.

Case presentation

The patient, a term male born at 40 weeks' gestational age from a primigravida 35 year old, was admitted to our hospital at 2 hours after birth for generalized hypotonia. Familial history was unremarkable. Although prenatally there were not decreased fetal movements or polyhydramnios, a need for assisted delivery (ventouse) during caesarian section took place. APGAR score was 2 and 5 at 1 and 5 minutes respectively. Ventilatory resuscitation started with room air, was discontinued when infant's heart rate increased. Birth weight was 2,900 kg (P 9th), length 47 cm (P 3rd) head circumference 32.5 cm (P 2nd) [12]. Examination at admission revealed general severe hypotonia, altered consciousness (lethargy), poor reflexes, characteristic facial dysmorphism with dolichocephaly, narrow bifrontal diameter, epicanthus, bilateral crypsorchidism without signs of dehydration (weight -1%) or systemic illness. The newborn had decreased spontaneous movements, muscle weakness, a weak cry, poor suck and feeding (need for tube feeding). Laboratory investigations and lumbar puncture were normal. A blood culture was performed prior to administration of intravenous broad spectrum antibiotics. Muscle biopsy and fundoscopy were also normal. Additionally, an extensive screening test to detect inherited metabolic diseases was normal. A cranial ultrasound revealed a temporal bilateral aspecific alteration of the parenchimal echogenicity. A brain magnetic resonance imaging/venography (MRI/MRV) revealed an extensive CSVT with a partially occluded lumen of superior sagittal sinus (sparing its anterior portion) extending through torcular herophili to left and right transverse and sigmoid sinuses and no parenchymal brain lesion (**Fig. 1**). Haemostatic screening was within normal range except low INR (0.96; normal values 1.23 ± 0.15), comparatively to small for gestational age infants [13]. Coagulation studies were negative. Low Molecular Weight Heparin (LMWH) was started after MRI on 7th DOL (day of life) at 150 IU/kg/dose twice a day, resulting in therapeutic levels of anti-Xa. Because of persistent hypotonia, the neonate was also tested for PWS and Spinal Muscle Atrophy (SMA) on 13th DOL. Methylation analysis confirmed PWS. FISH analysis excluded a deletion in 15q11-q13 and maternal uniparental disomy (UPD) was confirmed. The patient was discharged on 28th DOL. Electroencephalography (EEG) activity on this day was recorded as normal. On a follow-up examination at 2 months of age, CSVT was evaluated by MRV. MRV showed a significant reduction of thrombosis to superior sagittal (in its

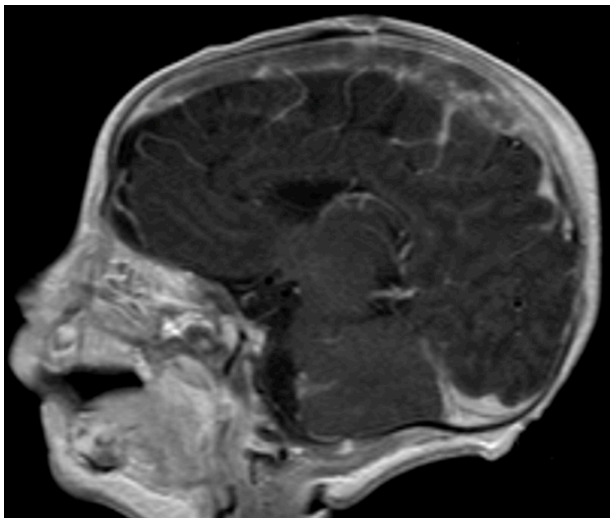

Figure 1. MRI showing signs of superior sagittal thrombosis with no parenchymal brain lesion.

parieto-occipital course), torcular herophili and transverse sinuses (left and right) while other veins appeared normal. During this time period the infant remained hypotonic with a suboptimal score (53/78) in Hammersmith's Infant Neurological Examination (HINE) and developmental delay was observed [14]. Since follow-up MRV showed partial recanalization, anticoagulation therapy was continued for an additional time period of three months (total duration 5 months). At 18 months of life, the child remained hypotonic and could not walk independently. HINE score was still suboptimal (60/78), but improved due to early intervention services.

Discussion

This is the third case report referring to a possible link between PWS and CSVT after MEDLINE was searched using the MeSH terms: Infant, Newborn, PWS and CSVT up to December 2011 [10, 11]. The neonate had a diagnostic testing for PWS since it had profound and persistent hypotonia present at birth, as it is suggested by authors [15].

Beretta et al. published a case report of PWS infant with UPD while Benson et al referred to a case report of a 2.5 year old PWS boy with atonic seizures and 15q11-q13 deletion [10, 11]. Beretta's case genetic disorder with 15q11-q13 deletion is referred similar to our case (maternal uniparental disomy, UPD) while Benson's case had paternal microdeletion (**Tab. 1**). Consequently, the possible association between PWS and CSVT could not be attributed to a specific genetic disorder, but it seems possible that maternally or paternally disorders affecting chromosome 15 are associated with thrombotic states [16].

In our case, coagulation studies (antithrombin [AT] III, factor VIII, factor IX, activated protein C [APC] resistance, PC, PS deficiency, factor V Leiden mutation, prothrombin G20210A mutation, MTHFR mutation, antiphospholipid antibodies [APA]) were negative (**Tab. 1**). Haemostatic screening at Beretta's case report was not as detailed as in our case, while at Benson's et al no hypercoagulation evaluation was pursued. In our case (as in Beretta's case report), haemostatic screening was normal except low INR (compared to small for gestational age infants), indicative of thrombosis [13, 17].

In our case EEG was normal at discharge, while at admission and during hospitalization, no seizures were identified. At Benson's and Beretta's case studies, EEG findings were abnormal. CSVT thrombosis and possible microscarring of the adjacent negative motor areas was anatomically compatible with the epileptic foci. The authors mention the necessity to clarify the association between the specific disorder of PW syndrome and seizure incidence, which has been well recognized from other authors as well [18, 19].

Risk factors for thrombosis of cerebral sinuses are birth asphyxia, infection, hypotension, indwelling catheters, polycythemia, maternal diabetes, dehydration and prothrombotic disorders. Co-morbid risk factors may place these neonates at risk for recurrent thrombosis. It is interesting that in our case cerebral venous thrombosis could not be attributed only to the above common risk factors. Initially, perinatal stress and intrauterine growth retardation were considered as possible risk factors for infant's cerebral sinus thrombosis [5, 20]. Later, PWS

Table 1. Main findings from published case reports.

	History; clinical findings	Genetics	Coagulation studies	Radiologic features (MRI/MRV)	Treatment
Beretta L, et al. (2007)	Newborn PWS female, admitted 28 hrs of life; hypotonia	Maternal uniparental disomy (UPD)	Decreased INR	Thrombosis of vein of Labbé	Rehydration
Benson LA, et al. (2011)	2.5-year-old PWS boy; atonic seizures	Paternal microdeletion in the 15q11.2-q13 region	Not done	Superior sagittal sinus thrombosis extending into the right transverse sinus	Anticonvulsant drug
Case report	Newborn PWS male, admitted 2 hrs of life; hypotonia	Maternal uniparental disomy (UPD)	Decreased INR	Superior sagittal sinus thrombosis extending through torcular herophili	Rehydration, LMWH

diagnosis disclosed a third possible risk factor to cerebral thrombosis.

Cerebral sinus thrombosis probably being present prior to admission, was suggested only by a relatively decreased INR and the abnormal cranial ultrasound. At Benson's case no etiologic association is refereed between PWS and CSVT, while at Beretta's perinatal stress was considered as the most probable cause.

Cranial ultrasonography may be a useful diagnostic method but CT venography and MRI/MRV are the methods of choice in CSVT identification [6, 21]. Cerebral sinuses lack valves and thrombosis is common in neonates due to wall mechanical distortion and/or activation of the coagulation system with subsequent "flow" obstruction [20].

Treatment of neonatal CSVT is controversial. Heparin anticoagulation is recommended for neonates with uncomplicated CSVT which was our case [22]. LMWH was supplied to the infant, in terms of avoiding progression of thrombosis, reestablishment of venous drainage and the presence of multiple thrombosed sinuses [22]. At the other two cases no specific treatment regarding thrombosis was pursued.

Conclusion

More published case reports will probably enhance the hypothesis that a possible link between PWS and CSVT does exist. Based on these case reports, in PWS infants with altered haemostatic screening, it would be prudent to perform a study by MRV for CSTV. CSVT may be considered as a possible finding in PWS infants.

Declaration of interest

The Authors declare that there is no conflict of interest.

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