Intracranial hemorrhage in a term newborn with severe von Willebrand disease type 3 associated with sinus venous thrombosis

Intracranial hemorrhage of term neonates with severe von Willebrand disease type 3 and near normal delivery have not been published to date. We report on a term newborn with severe type 3 VWD who suffered a large intracranial bleeding presumably subsequent to sinus venous thrombosis. This case is remarkable in two aspects: i) with respect to the low risk of perinatal intracranial hemorrhage even in neonates with VWD type 3 and ii) since VWD type 3 with factor VIII:C levels < 5 IU/dl does not seem to protect from thromboembolism. Guidelines for the management of hemophilia advise atraumatic delivery of neonates with known or suspected bleeding disorders, however primary caesarean section in the absence of complications is not obligatory. To answer the question whether the presented case could have an impact on the recommended management we carried out a worldwide survey including 24 participating specialized centers. Except a single case from Sweden of a female neonate with VWD type 3 who also had an inhibitor against VWF no further cases were reported to us. We conclude that CNS bleeding in term neonates with severe VWD type 3 is a rare event that requires additional risk factors for manifestation. Therefore, the amendment of current guidelines does not seem to be mandatory.

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Von Willebrand disease (VWD) is a bleeding disorder caused by the quantitative deficiency or dysfunction of von Willebrand factor (VWF). It is the most common inherited bleeding disorder, affecting men and women worldwide, with a prevalence as high as 1 percent in the general population. Severe VWD type 3 however, is very rare with an estimated prevalence of 0.5-3/106.[1] VWF is a large, adhesive, multimeric protein which has two main functions in hemostasis: it mediates adhesion and aggregation of platelets at the site of vascular injury especially under conditions of high shear as in the arterial system and the microvasculature and it forms a noncovalent complex with coagulation factor VIII (FVIII) in plasma, thereby protecting it from inactivation and subsequent clearance.[2] VWF is encoded by a gene spanning 178 kb of genomic DNA on the short arm of chromosome 12, consisting of 52 exons.[3] VWD is very heterogenous disorder. It is classified into three main types being characterized by relative or absolute quantitative deficiency of VWF (type 1 and type 3), and by qualitative defects (type 2).[4] Type 3 with a complete lack of VWF in patients´ plasma and platelets is inherited in an autosomal recessive manner. It is in these rare cases of type 3 disease that clinical symptoms are more frequent and severe, thus manifesting in early childhood through the typical symptoms of mucocutaneous bleeding, and additionally with hemarthrosis and muscular bleedings[5] similar to those in cases of severe hemophilia A due to the associated reduction of FVIII. Patients suffering from type 3 VWD require replacement therapy with FVIII concentrates containing VWF. Thrombotic complications in patients with VWD are rare,[6] and are often, if not always, associated with diverse inherited or acquired prothrombotic risk factors. In these cases the coexistence of such risk factors seems to outweigh the bleeding tendency of the disease. Most respective reports regard those following infusion of FVIII/VWF concentrates in the setting of surgery with high post-treatment levels of factor VIII[7] - an established risk factor for venous thromboembolism[8] - and with additional coexisting risk factors such as high age, previous thrombosis, hormone replacement therapy, immobility or obesity.[7,9,10]

Table 1. Coagulation parameters of the patient at initial presentation and during the further course. Time scale: days after birth. Day 10 is after transfusion of FFP, day 59 is 6 weeks after the last replacement with Humate P. nd = not done, nr normal range.

Parameter	*day 5*	*day 10*	*day 59*
aPTT (s)	67	54	69
FVIII:C (U/dl)	nd	26	5
VWF:Ag (U/dl)	nd	9	< 1
VWF:RCo (U/dl)	nd	< 10	< 10
PFA100 Epi (s)	nd	236	nd
PFA100 ADP (s)	nd	> 259	nd

Case report

The patient is the second child of healthy, non-related, German parents. The family history, including the 4 year old sister, is negative with respect to bleeding symptoms. Delivery took place after an uneventful pregnancy at the 38 week of gestation at the parents' home. The midwife described a rather quick delivery and reported a simple umbilical cord coiling. Child measurements were above the 97th percentile, except for the weight, which was adequate. No vitamin K supplementation was given at day 1. Two days after delivery the child presented with petechiae and an increase of the head circumference. At day 5 seizures and progressive somnolence were observed and the child was referred to the hospital. A markedly elevated anterior fontanel was noted and there was an increase in outer cranial venous filling. The muscular tone was notably decreased, however, the child presented attacks of rowing leg movement and an intermittent ophistotonus. The following cerebral computed tomography revealed a large right temporal subdural hematoma, a large bleeding site in the right posterior cranium and structural abnormalities of the right cerebellum with cystic components, which were held for a malignant tumor. Coagulation test revealed normal values apart from a prolonged activated partial thromboplastin time (aPTT) (Table1). The patient was treated with vitamin K and fresh frozen plasma (FFP). After stabilization the boy was transferred to our hospital with the diagnosis of cerebral bleeding subsequent to a malignant tumor in the cerebellum and brainstem for decompression surgery and implantation of a ventricular drainage system. Further imaging by MRI with phase-contrast angiography, and CNS ultrasound revealed no evidence of a malignant tumor, but bilateral congestion of the sinus transversus (Figure 1). Furthermore, infarction of the a. cerebri media and the a. cerebri posterior basins were seen. Coagulation tests, comprising coagulation factors and VWF parameters were carried out (Table1). A screen for prothrombotic risk factors including Protein C, Protein S, Antithrombin, APC ratio, Lp(a), homocysteine and molecular testing for FV Leiden and the prothrombin mutant G20210A gave negative results and the family history was negative for thromboembolism. Unaware of the previous plasma infusion at the referring hospital, FVIII:C of 26 IU/dl and VWF antigen (VWF:Ag) of 9 IU/dl suggested the diagnosis of VWD, however, these results spoke against severe VWD type 3. Supported by an aberrant VWF multimer pattern (Figure 2) we initially favored the diagnosis of variant VWD type 2A. Because of the unusual clinical presentation, however, we

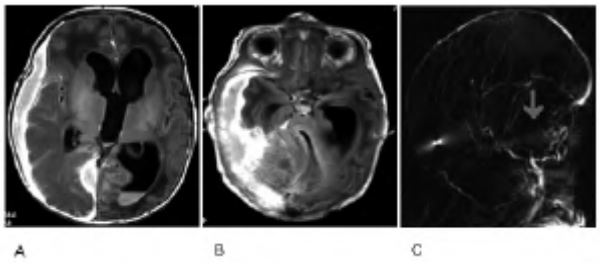

Figure 1. Initial cerebral MRI and phase-contrast angiography. A) large right temporal subdural hematoma compressing the lateral ventricle on the right side, blood penetrating the lateral ventricle on the left side, as well as a slight midline shift to the left side. Tension hydrocephalus is being induced. B) Large, space-consuming bleeding site in the right posterior cranium with fresh hemorrhage and adjacent old hematomas, hinting towards multiple bleeding episodes. The fourth ventricle is being compressed. C) Phase-contrast angiography illustrates sinus transversus occlusion.

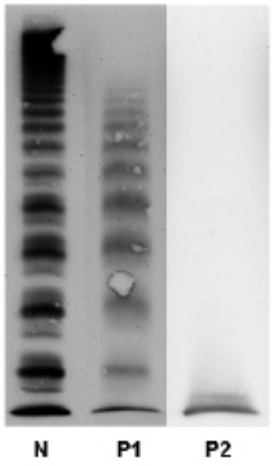

Figure 2. VWF multimers subsequent to transfusion of FFP (P1) and after discontinuation of replacement therapy (P2) compared with a normal control (N). The aberrant multimer pattern of P1 is due to residual VWF from FFP. Almost no VWF is seen in lane P2. Multimer analysis was performed by SDS agarose gel electrophoresis (11) with luminescent visualization (12).

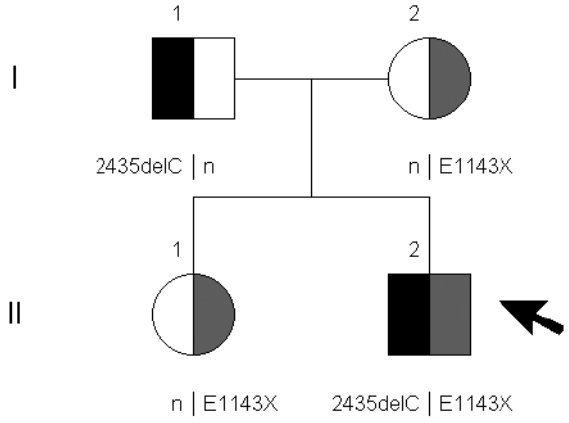

Figure 3. Pedigree of the family and segregation of mutations. The unaffected parents and the sister were each heterozygous carriers.

performed a molecular study which revealed compound heterozygosity for 2435delC in exon 18, the most common molecular defect in VWD type 3 in northern and central Europe[13,14] and the novel nonsense mutation 3427G>T in exon 27 (E1143X) (Figure 3) The diagnosis was subsequently corrected to severe VWD type 3 and the patient was treated with VWF/ FVIII concentrates (Humate P®, ZLB Behring). Follow-up imaging, taken 4 months after the initial event, showed severe hydrocephalus ex vacuo with massive ventricular enlargement. Angiography revealed reperfusion of the left sinus transversus (*not shown*).

Discussion

We report on a term newborn with severe type 3 VWD who developed large intracranial hemorrhage presumably subsequent to sinus venous thrombosis. We performed a survey including 24 specialized centers worldwide on similar cases. A comparable case was not observed. Most specialists never encountered such bleeding complications in type 3 VWD. Furthermore, in the region of Skejby, Denmark, all newborns, mature as well as premature, who have been diagnosed with an intracranial bleeding have been investigated for a possible hemorrhagic disorder, including VWD, since 1986 (birth cohort database of 95.000). No newborn with VWD was amongst these (J. Ingerslev, personal communication). Only one case of a girl in Sweden who suffered from severe VWD and who developed massive thrombocytopenia just after birth was brought to our attention. An inhibitor against VWF was detected (M. Blombäck, personal communication). In accordance to our survey, existing data from large clinical series underline the fact that CNS bleedings in neonates with type 3 VWD are extremely rare events.[5,15] In two other reports an intracranial hemorrhage and subdural hematoma were discovered incidentally at 32 and 22 weeks of gestation, respectively, in two fetuses that were subsequently diagnosed with VWD, one with subtype 2A, the other with unknown subtype.[16,17] In contrast to patients suffering from severe hemophilia, who are at risk of developing spontaneous cerebral hemorrhage, the low but usually detectable levels of FVIII in patients suffering from type 3 VWD, seem to be sufficient to prevent such incidents. Thrombotic complications in patients with VWD are rare, however, the disease does not necessarily protect from sinus venous thrombosis. Blood flow in the newborn is considerably slower than in the older child or the adult, vessel diameter is smaller, hematocrit is higher, blood pressure is lower and the lower, though physiologic levels of coagulation inhibitors may enhance the risk of thrombosis in the newborn. Sinus blood flow is even slower than in the average venous system and there is a predisposition of the development of thrombi at the orifice of bridge veins. Studies investigating the origin of cerebral sinus venous thrombosis in children unraveled multiple predisposing and influencing factors, among these, asphyxia and vascular trauma, both possible implications of the delivery. However, the study also demonstrated that in almost 30% of the 149 examined children no predisposing clinical condition was observed.[18] Even without the existence of additional risk factors, delivery itself might have led to the initial sinus clotting event in the presented case. Although our imaging did not finally illustrate the pathogenic process, we speculate that the formation of sinus venous thrombosis was the initial event, followed by intracerebral bleeding subsequently aggravated by the underlying VWD type 3. According to the guidelines for the management of hemophilia, delivery of infants at risk should be as atraumatic as possible to decrease the probability of bleeding.[19] Vacuum extraction, forceps, fetal scalp electrodes, and fetal scalp blood sampling should be avoided. A caesarean section should be performed for obstetrical indications only (evidence grade II-2C).[20, 21, 22] Since VWD is not considered to be clinically more severe than hemophilia, the same guidelines should be applied.

Conclusion

1. Perinatal intracranial hemorrhage in type3 VWD is very rare: the bleeding episode in our patient was possibly initiated by sinus venous thrombosis and aggravated by severe VWD type 3.

2. Sinus venous thrombosis developed without evident inherited or acquired prothrombotic risk factors except delivery itself.

3. Even severe VWD may not protect against venous thrombosis.

4. The particularity of this case speaks against an amendment of the guidelines.

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Key words von Willebrand disease, intracranial hemorrhage, thrombosis, neonate

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