CASE STUDY

Type 3 VWD and an inhibitor to VWF: Challenges in diagnosis

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Developing an inhibitor to von Willebrand factor (VWF) is extremely uncommon. Consequently, patients with von Willebrand disease (VWD) tend not to be routinely evaluated for inhibitors, leading to the possibility of delay in inhibitor diagnosis. We present such an occurrence to raise awareness, with a view to avoiding such delays. A 1-year-old male with no family history of bleeding disorders or parental consanguinity presented with a tongue bleed lasting three days. Investigations confirmed a diagnosis of Type 3 VWD. Over the next few months, the patient received seven exposures to Humate-P (a plasma derived FVIII containing von Willebrand factor concentrate), but developed an anaphylactic reaction necessitating adrenalin and Benadryl (diphenhydramine). The reaction quickly abated and did not recur with further exposure to Humate-P. In 2013, due to recurrent epistaxis and tonsillar bleeding, the patient was commenced on prophylaxis receiving Humate-P 50 RCo U/kg twice weekly. Despite this regimen, he continued to experience recurrent epistaxis, leading to escalation of prophylaxis to 3/week. In November 2014, he showed persistent tonsillar bleeding, despite having received two doses of Humate-P (each 40 RCo U/kg) in the previous 12 hours. Testing revealed reduced VWF:Ag, VWF:RCo and FVIII:C recoveries. Further testing revealed an anti-VWF antibody (2.6 BU) of unspecified Ig type. Since diagnosis of the inhibitor, he has received 100 RCo U/kg daily for prophylaxis and immune tolerance. He is now bleed-free; however, monthly inhibitor testing shows that his inhibitor persists. Given the limited experience and literature on inhibitors in VWD, the prognosis for such cases is unknown.

Keywords: children, Type 3 von Willebrand disease, VWF inhibitor

Type 3 von Willebrand disease is a rare, severe bleeding disorder requiring the inheritance of two von Willebrand factor gene mutations. As such, it is an autosomal recessive disorder with patients either being homozygous for a VWF mutation (more commonly seen when parents are consanguineous) or being compound heterozygotes [1,7]. The disorder is characterised by a complete quantitative deficiency of von Willebrand factor (VWF) in plasma [1,7]. The incidence of Type 3 VWD is 0.1-5.3 per million and varies by region [2]. The highest prevalence of Type 3 VWD is reported in countries with high rates of consanguineous marriages and in Scandinavia [3]. The lack of plasma VWF in Type 3 VWD results in patients having very low levels of FVIII (1-5%), given that VWF is a carrier protein for FVIII [1]. The lack of VWF results in the rapid clearance of FVIII in the circulation. The combination of severely reduced VWF and FVIII results in a bleeding pattern that can be characterised as a combination of mucosal bleeding seen in VWD and of musculoskeletal bleeding as might be seen in a patient with moderate haemophilia A [3].

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Although inhibitors to FVIII in patients with severe haemophilia A are common (seen in 30-40% of such patients), inhibitors to VWF in patients with Type 3 VWD are much rarer (possibly seen in 5-10% of patients with Type 3 VWD). This, together with the fact that Type 3 VWD is much less common than severe haemophilia A, means that the occurrence of an inhibitor in Type 3 VWD is a very rare event [2]. As a result, few clinicians/centres undertake routine surveillance for inhibitors in Type 3 VWD (unlike in severe haemophilia A, where routine surveillance is standard), seldom diagnose inhibitors in Type 3 VWD and have little experience in managing such patients. Yet the development of inhibitors in Type 3 VWD (as in severe haemophilia A) is

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likely to complicate the management of patients greatly [7].

Case report

The case presented describes events leading up to diagnosing a Type 3 VWD patient with an inhibitor, the challenges in identifying it, and implications for future practice to avoid delay in inhibitor diagnosis.

In 2010, a 1-year-old male presented to the Emergency Department (ED) with a tongue bleed that lasted on and off for three consecutive days. There was no family history of bleeding manifestations or confirmed bleeding disorders. The child's parents were not consanguineous. Laboratory findings demonstrated a prolonged PTT of 60 seconds and a FVIII:C of <1%. The child had a normocytic anaemia (Haemoglobin 102 g/L) with an MCV of 78.3 fL. The platelet count was normal at 539 x 109/L. Blood film was found to be normal.

He received one dose of rFVIII in the ED on the day of presentation, with the assumption of severe haemophilia A, as VWF:Ag and VWF:RCo had been obtained but results were as yet unavailable. The following day, the VWF test results were available and demonstrated a VWF:Ag of 2% with a VWF:RCo of <10%. His diagnosis was then determined to be Type 3 VWD. At that point, he began to receive Humate-P (CSL-Behring, Marburg, Germany). He underwent genetic testing, confirming that he is a compound heterozygote for two different null (non-VWF producing) mutations: deletion 2709delG (exon 21) and nonsense 4666C>T (exon 28) mutations.

Over the next three years, the patient continued to receive on-demand treatment with Humate-P. During the few months following his diagnosis of Type 3 VWD, he received seven exposures to Humate-P. Immediately after the seventh exposure, he developed an anaphylactic reaction requiring adrenalin and Benadryl (diphenhydramine). He made a full recovery from the reaction, which quickly subsided. Following this reaction, he continued to receive Humate-P on demand, but with Benadryl given first. After a total of 22 exposure days, the premedication was discontinued with no further reactions presented.

In 2013, due to recurrent episodes of epistaxis and tonsillar bleeding, the patient was started on prophylactic treatment with Humate-P 50 RCo U/kg administered twice weekly. Despite this change, he continued to have recurrent episodes of epistaxis requiring hospitalization. On one hospitalization event over a holiday period, the boy's PTT was not corrected, despite the fact that he had not received frequent infusions of Humate-P. The failure to correct the PTT was unfortunately not followed up after this episode. Due to ongoing bleeding, his prophylaxis was escalated to three times a week.

In November 2014, the boy (now 5 years old) presented to the ED with persistent tonsillar bleeding, despite receiving two doses of Humate-P each 40 RCo U/kg administered at home in the previous 12 hours. Recovery bloodwork results revealed reduced VWF and FVIII:C levels (VWF:Ag 38%, VWF:RCo 13%, and FVIII:C 10%) (Table 1). These results suggested the presence of an inhibitor. Treatment was increased to Humate-P 100 RCo U/kg every 6 hours and tranexamic acid was added. With these measures, normal PTTs and adequate VWF and FVIII levels were obtained and the bleeding was controlled.

Upon further testing and investigations, an anti-VWF antibody was confirmed and measured at 2.4 Bethesda Units. Lupus anticoagulant testing was negative. Pharmacokinetic testing revealed the clearance of VWF to be extremely rapid: the patient's VWF:RCo half-life was < 1 hour (a normal VWF half-life in children is thought to be a mean 12.2 hours, ranging from 8.4-17.4 hours) [8]. With the detection of the inhibitor, his dose of Humate-P was increased to 100 RCo U/kg three times weekly as a form of both high dose prophylaxis and for immune tolerance.

In December 2014, the patient experienced his first musculoskeletal bleed. He was admitted with a left thigh haematoma and treated with Humate-P 100 RCo U/kg every 6 hours. Ultrasound revealed a distal quadriceps haematoma tracking into the suprapatellar region. Following this bleed, he was discharged on daily Humate-P 100 RCo U/kg for

Table 1: Recovery blood work in November 2014 suggesting the presence of an inhibitor

	Pre-infusion of Humate-P	20 minutes post-infusion of Humate-P 1600 RCo (72 RCo U/kg) 1004 FVIII u (43 FVIII U/kg)	Expected levels 20 minutes post-infusion of Humate-P
PTT (seconds)	70	43	Corrected PTT
FVIII:C (%)	1	20	>60%
VWF:Ag (%)	1	49	>100%
VWF:RCo (%)	13	41	>100%
PFA-100 (Col/Epi) (seconds)	>276	>273	Improved
PFA-100 (Col/ADP) (seconds)	Not available	>221	Improved

8 days, then resumed an every-other-day regimen. Since then, he has been bleed-free; however, monthly inhibitor testing continues to show that his inhibitor is unchanged.

The value of hindsight

There is much to be considered in this case. In retrospect, it was clear that the inhibitor had actually developed when the child received his seventh exposure to Humate-P (at age one) and he had developed an anaphylactic reaction [5]. Even after starting on prophylaxis, the boy continued to bleed, suggesting the presence of an inhibitor resulting in ineffective prophylaxis. Another indicator was that the PTT was not corrected following an infusion of Humate-P. Clearly, these were all clues to the presence of the inhibitor, yet they were not picked up.

There were probably a multitude of reasons why such clues were not picked up and acted upon:

- 'Multiple clinicians following the patient, none of whom were aware of all the "clues"
- 'Failure to undertake routine inhibitor surveillance, most of which arises from the combined rarity of Type 3 VWD and of inhibitor development in Type 3 VWD
- 'Failure to undertake routine pharmacokinetic evaluation of VWF in patients with Type 3 VWD.

The rarity of Type 3 VWD and of inhibitor development in Type 3 VWD is such that a delay in diagnosing inhibitors in this disorder (as occurred in this case) is probably not that unusual. It is for this reason that this particular case has been written up, with the aim of alerting clinicians managing such patients to consider this possibility, "look" for it and recognize the clues suggesting the existence of an inhibitor in this rare disorder.

Despite a paucity of literature on inhibitor development in Type 3 VWD, it is believed that the presence of null mutations increases the risk of inhibitor development in this condition (as it does in severe haemophilia A) [4,7]. With this in mind, it is therefore important to undertake mutation analysis in all patients with Type 3 VWD. In those patients identified with non-missense mutations, vigilance and close monitoring for inhibitor development is imperative to identifying inhibitors in a timely manner. In the case discussed here, the boy's null mutations most likely increased his risk of developing an inhibitor.

Developing an inhibitor complicates treatment and increases the risk of bleeding. At present, the literature and experience available to guide clinicians in how to best manage such patients is limited [7]. In most cases, management is extrapolated (possibly wrongly) from inhibitor management of severe haemophilia A. In retrospect, for the case discussed here, if the inhibitor had been detected 4 years earlier, the boy would have been managed differently, with more intense prophylaxis and more intense management of bleeds. Whether earlier detection of the inhibitor and commencing immune tolerance would have somehow resulted in eradication of the boy's inhibitor is debatable, particularly as he seems to have now failed immune tolerance.

The prognosis for such Type 3 VWD patients with an inhibitor is unknown. Two years after diagnosis of his inhibitor, the boy remains inhibitor positive, despite ongoing and frequent routine exposure to Humate-P. Although the treating team has considered the use of rituximab, as his bleeds are reasonably infrequent, this treatment strategy is currently on hold.

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Disclosures

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