Author's response to reviews

Title: Pseudo (Platelet-type) von Willebrand disease in pregnancy: a case report

Authors:

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Author's response to reviews: see over
Dear Editor,

We submit a revised manuscript taking into account comments from the Editorial team, and the reviewers as detailed below.

We have made major changes to the Abstract and made many language corrections.

The following indicate the revisions made as a response to the reviewer’s comments:

Reviewer 1.

1) Reviewer Comment: Abstract does not describe the management of the patient during pregnancy.
Response: We have included a brief summary of the management of the patient during pregnancy in the abstract.

2) Reviewer Comment: Background: First line: the Authors should concisely describe what von Willebrand disease is ..........
Response: The whole section on BACKGROUND including the description of von Willebrand disease has been rewritten taken into account all the questions raised by the reviewers.

3) Reviewer Comment: Gly233Val mutation: what do the AA mean with ‘this is common in all affected family members’?
Response: The statement ‘This is common in all affected family members’ has been removed from the manuscript because of its lack of clarity.

4) Reviewer comment: More data is needed on the basal phenotype of the patient: FVIII and VWF level, RIPA, mutation, if any etc.
Response: The diagnosis of Platelet type von Willebrand disease in this patient was made several years ago when the patient was 16 years old in a different hospital. We therefore do not have the results of the basal phenotype of this patient however the diagnosis of Platelet type von Willebrand disease is clearly documented in the patient’s haematology clinic records. Factor VIII levels were checked at 24 and 32 weeks.

5) Reviewer comment: Antenatal care: The Authors claim they decided to assess von Willebrand factor levels at 24 and 32 weeks, but in table 1 only FVIII has been included; PTT should be recorded as ratio to normal plasma....
Response: Factor VIII levels were assessed at 24 and 32 weeks. Von Willebrand factor levels were not assessed during the pregnancy. We have corrected the statement. PTT or APTT is the laborotory measure of the time it takes blood to clot. This is measured in seconds and not as a ratio to normal plasma by our hospital laboratory. We have therefore not changed the Units of APTT (table 1).

6) Reviewer comment: Conclusions: It is correct to state that the disorder should be part of the differential diagnosis..........Thus conclusions should be reshaped.
Response: We have rephrased the conclusions taking into account the reviewer comments.
7)Reviewer comment: Title: von Willebrand, not Willibrand
Response: Spelling corrected.

Reviewer 2.

8)Reviewer comment: The authors should add “region coding for A1 domain” to the following sentence
as follows: “...mutation in the VWF gene (region coding for A1 domain)
located.....
Response: We have rewritten that whole section and corrected the grammar.

9)Reviewer comment: p-VWD should read PT-VWD, please correct throughout the manuscript:
Response: We have corrected this throughout the whole manuscript.

10)Reviewer comment: “...by an abnormally hyper responsive..” should be replaced by “to an
abnormally hyper responsive....”In the same line, please use either “ platelet
glycoprotein Iba (GPIba) or platelet glycoprotein Ib/IV complex. The former is
preferred here
Response: Corrections have been made through the whole of that section. We have rephrased the
whole paragraph.

11)Reviewer comment: “Mutations” instead of “mutation
Response: Mutation is changed to mutations

12) Reviewer comment: results in the haemostatic function of VWF becoming impaired...” should be
modified to “... results in impairment of the haemostatic function of VWF...”
Response: This has been corrected as the whole paragraph has been rephrased.

13) Reviewer comment: What do the authors mean by: “This is common in all affected family
members..”? if it means this mutation is the most common out of the four, please rephrase
Response: Sentence has been deleted because of lack of its clarity.
14) Reviewer comment: The authors state that “Both type 2B vWD and p-vWD are rare disorders and at present no published report of their frequency exits”. This is not true. The recently published report by Hamilton et al., Thromb Haemost 2011; 105: 501–508 represents a worldwide study and provides frequency of type 2B and PT-VWD and percentage of misdiagnosis of PT-VWD among provisionally diagnosed 2B. These facts needs to be stated.
Response: We thank the reviewer for bringing this to our the notice. We have corrected and rephrased the statement and referenced it.

15) Reviewer comment: Vasopressin is the same as desmopressin, please maintain consistency. Also desmopressin is not indicated in type 2B as it worsens the bleeding condition due to increased release of abnormal vWF. Please correct.
Response: We have changed Vasopressin to Desmopressin to maintain the consistency.
Type2B vWD can be treated with Desmopressin but generally avoided as it causes the release of abnormal vVFactor and worsens the bleeding condition therefore treatment with a treated plasma derived vWF/factor VIII concentrates is preferred. This has been stated in the manuscript.

16) Reviewer comment: “A plan for vaginal delivery at term in the absence of any obstetric Contra-indication” please correct grammar sentence is incomplete:
Response: Grammar corrected.

17) Reviewer comment: “…a request for the appropriate platelets…”
Response: Grammar corrected.

18) Reviewer comment: EDTA bottle would better read: EDTA anticoagulated blood sample. Same applies to citrate in the flowing line.
Response: Statement has been rephrased.

19) Reviewer comment: “Umbilical cord blood in a citrate bottle to be taken for Gp1 gene analysis and von Willebrand factor”
Response: Statement has been rephrased.
20) Reviewer comment: Did the authors repeat genetic analysis of exon 28 of VWF ........;
Response: Genetic analysis was not repeated during the pregnancy. They were done prior to pregnancy at the age of 16 years under the haematologist in a different hospital. These results of the genetic analysis and the PT-VWD genetic mutation have not been available to us.

21) Reviewer comment: The authors need to provide better description of the bleeding pattern of this patient prior to pregnancy; eg. was this mild to moderate bleeding, what were the symptoms: epistaxis.. menorrhagia...etc? have these been changed during pregnancy?
Response: The patient had always been asymptomatic with this condition with exception of excessive bleeding at the age of 16 when she underwent a tonsillectomy which prompted investigations following which the diagnosis was made. She remained asymptomatic during the pregnancy.

22) Reviewer comment: Was this the first pregnancy? If there were previous pregnancy what did they look like?
Response: This was her first pregnancy as indicated in the history.

23) Reviewer comment: In table 1: It would be very useful if the VWF :Ag and VWF:RCo levels are added to this table, the follow up of VWF levels as pregnancy advances as this obviously influence bleeding risk and pregnancy outcome.
Response: These test were not performed during the antenatal care of this patient. They are therefore not included in Table 1.

24) Reviewer comment: Post natal information: further description of the baby’s condition is needed: body weight, platelet count..etc
Response: Further description of the baby’s condition has been provided.

25) Reviewer comment: The authors mention that the patient was admitted at 38 weeks gestation for induction of labour and that she had a spontaneous vaginal delivery with minimal blood loss. Two questions: was induction performed or not? If so please provide details. Has the 2 units been administered?
Response: She was booked for induction of labour at 38 weeks. However she went into spontaneous labour on the day of induction and did not require prostaglandin induction.

She received 2 units of platelets on the morning of her labour. Her labour lasted for 8 hours and she had a spontaneous delivery. Total blood loss at delivery was 400mls.

26) Reviewer comment: Her post-partum period was uneventful... for how long was the patient followed up? Was this for the 6 weeks puerperium? When did the platelet count returned to normal? And what was the count?

Response: She was therefore discharged home with the follow up arranged with GP and haematologist at 2 and 6 weeks postpartum. Platelet levels postpartum has been provided.

27) Reviewer comment: The authors state in their conclusion: “…concerns about the wider thrombocytopenia associated with this pregnancy being related to other conditions like: superimposed preeclampsia, gestational thrombocytopenia, idiopathic thrombocytopenia and thrombotic thrombocytopenia and that these conditions were actively excluded”. This is very important but no details were given in this regards earlier in the report. The authors need to detail how they excluded these diagnoses in the case presentation description

Response: Maternal investigations; Full Preeclampsia blood profile was done. FBC, U&E, LFT’s, Urine Prot:Creat, 24 Hour urine protein collection and blood films. The results were all within normal range.

Fetal investigations: Serial Growth scan were also performed. Baby was found to be growing within normal limits.

28) Reviewer comment: It is known that PT-VWD can be also misdiagnosed as ITP so.. I am wondering was bone marrow performed. and what was the results? Was a full preeclampsia testing performed, what was the patient’s blood pressure, kidney function..etc same with TTP? What did the authors perform to exclude this?

Response: Bone Marrow biopsy was not performed in this patient as this investigation was not thought to be necessary during the pregnancy.
Full Pre eclampsia blood profile was done. FBC, U&E, LFTs, Urine PCR, 24 hour Urine protein collection, blood films were done and was found out to be normal. Regular BP monitoring was done which remained within normal limits in all visits.

TTP was excluded on the basis of absence of pentad of features i.e. haemolytic anaemia on blood film, thrombocytopenia, absence of fever, neurological symptoms on clinical examination and normal renal functions.

Reviewer comment: The author mentioned that two other family members: the mother and a sibling were also diagnosed? was this on the basis of VWF levels, including RIPA analysis, has the genetic testing been also done and confirmed the same mutation? Please clarify and add this information.

Response: We do not have results of genetic analysis of the patients mother and sister. We were informed by the haematologist regarding their diagnosis. We do not know the mutations of these family members.

Reviewer comment: Serum creatinine, protein, albumin, liver function and any other available laboratory data would better be also added to table 1. Alternatively, construct two tables: table 1 for general tests and table 2 for haemostatic tests.

Response: We have decided to keep table 1 as it is for clarity and simplicity. We have clearly indicated in the manuscript all other investigations performed and what the results were. The normal range of the results are well known to the readership of this journal. We do not believe that adding these results to Table 1 or creating another table of normal results adds any value to this case report.

Reviewer comment: “Throughout the pregnancy the mother became increasingly thrombocytopenic, but remained asymptomatic and clinically well”. The word “mother” here needs to be replaced by the “patient” and please correct throughout.

Response: The word mother has been changed to patient throughout the manuscript to maintain the consistency.

Sincerely,
On behalf of the authors

Vincent Boama