Author's response to reviews

Title: Life-threatening hypersplenism due to idiopathic portal hypertension in early childhood: Case report and review of the literature

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Author's response to reviews: see over
Dear Mrs Neilan,

Please find enclosed the revised version of the above mentioned manuscript for consideration for publication in the BMC Gastroenterology. All listed authors on the manuscript has seen and approved the revised version of the manuscript and take full responsibility for the manuscript. All authors report no financial support and/or conflicts of interest. The manuscript has not been published and is not under consideration for publication elsewhere. The work will not be submitted to any other journal while under consideration by the BMC Gastroenterology.

We have addressed the comments in the revised manuscript and provide a point-by-point response to the concerns below. We have also highlighted all changes made when revising the manuscript.

Yours sincerely

Dr Jan Däbritz
- On behalf of the authors -
POINT-BY-POINT RESPONSE

Referee 1: I find the language of the report difficult to read. It would be helpful to have a native English speaking editor review it and make appropriate changes.

Response: The manuscript has been edited by a native English speaking colleague.

Referee 1: I am unclear exactly what the point of this report is. It is simply the presentation of IPH in a young infant (which is rare and of interest in itself) or description of novel pathologic and laboratory findings suggestive of NO mediated disease (which is poor data but interesting). A hypothesis, even for a case report, would be helpful to direct the authors.

Response: We report the first case of uncontrolled splenic hyperperfusion and enlargement with subsequent hypersplenism leading to life-threatening complications of IPH in infancy and show that disease remission after splenectomy in early childhood points to the spleen as the main organ underlying pathogenesis and progression of IPH. We provide a hypothesis as requested: The primary defect in the regulation of splenic blood flow seems to be crucial for the development of IPH. This view of the pathophysiology is supported by the fact that i) liver function abnormalities do not occur in IPH, ii) the abnormal expression of eNOS and VCAM-1 was only seen in splenic but not hepatic tissue, iii) the signs of portal hypertension resolved in our patient after splenectomy, and iv) both the adult patients reported before and our young patient have not developed recurrent signs of portal hypertension, liver pathologies or complications after splenectomy. Thus, splenectomy needs to be considered as being the radical and complete treatment for IPH. Our paper describes a case of IPH in early infancy for the first time, provides an up-to-date review of similar cases in the field, and illustrates novel pathologic and laboratory findings suggestive of a NO mediated disease. The article type of our manuscript has been changed from “Original Work” to “Case Report” by the BMC Editorial office. Therefore, we were requested to format our manuscript as a Case report. However, a comprehensive literature review is provided.

Referee 1: The abstract is too wordy, long, and unclear. Again the lack of hypothesis shows in the structure of the abstract.

Response: According to the suggestion of the reviewer we have shortened and restructured the abstract of our revised manuscript.
**Referee 1:** I think the description of IPH is not directed appropriately, with many causes other than parenchymal atrophy of the liver. In children, the emphasis should be on portal vein thrombosis and non-thrombotic causes. Discussion along the lines such as in Sarin and Kapoor, *J of Gastro and Hepatology, 17:526-534, 2002*, which more clearly summarize the known etiology and classification of IPH would be helpful.

**Response:** Following the suggestion of the reviewer we have discussed the etiology and classification of IPH in more detail in our manuscript (Background section). Changes are highlighted in red.

**Referee 1:** To follow-up, I would disagree that most references point to "increased splenic and portal vein blood flow." In contrast, most suggest either presinusoidal or extrahepatic vasculopathy which lead to portal hypertension.

**Response:** The information was included in the “Background” section.

**Referee 1:** The case presentation is too long and again, not directed. For example, the first paragraph on patients is almost itself not required, as this could be included in the case summary. What were the findings of the open liver biopsy at 13 months? Most of the clinical background is not necessary, but this is a key data point that needs to be described.

**Response:** The case presentation has been shortened according to the suggestions of the reviewer. The liver biopsy showed no signs of storage disease and, depart from signs of mild secondary hepatitis, no specific abnormalities. This information has been included in the case presentation.

**Referee 1:** Splenomegaly, not hepatosplenomegaly, is the hallmark clinical finding of IPH, along with variceal bleeding. Therefore, the diagnosis of IPH of extrahepatic origin is not clearly made.

**Response:** This information has been corrected – we observed a progressive splenomegaly in our otherwise healthy 8 months-old infant during a pediatric routine examination.

**Referee 1:** I am not sure what sonogram findings of "highly normal blood flow" mean, as this is not common language.
Response: The portal vein blood flow was markedly increased, suggestive of a hyperdynamic circulatory state. The term “highly normal” has been replaced by “markedly increased”.

Referee 1: Shorter, but clearer, description of the clinical problem of hypersplenism needs to be done. What was the "hemorrhagic diathesis." Pathologic findings should be separate section. What is meant by "splenadenoma?"

Response: The case presentation has been shortened and focused on the clinical problems of hypersplenism. Pathologic findings are summarized in a separate section. Hemorrhagic diathesis was caused by a prolonged bleeding time (> 6 min). This information has been added. Splenadenoma is a term used by our pathologists to describe a hyperplasia of the lymphatic tissue within the white pulp of the spleen. This information has been added.

Referee 1: The rationale for choice of immunologic staining should be done. Why eNOS, VCAM-1, etc.

Response: Is has been reported that the expression of VCAM-1 and ET-1 may be involved in splenic and portal hyperperfusion. These molecules have been suggested to influence the development of IPH by causing hypercirculation and thereby hypertension in the portal venous system (ET-1) or by enhanced adhesion and migration of lymphocytes into the wall of the portal tracts followed by fibrosis (VCAM-1). Although the stimulus leading to augmented production in the enlarged spleen remains unknown, the circulating soluble isoforms of these factors may be elevated in the serum of IPH patients. Furthermore, is has been reported that sinus lining cells of IPH spleens showed diffuse and strong expression of inducible and endothelial nitric oxide synthetase (iNOS and eNOS). In contrast, ET-1 was detectable in only a few mononuclear leukocytes in the red pulp of IPH spleens. These results suggest that NO liberated in spleen in the presence of low ET-1, is responsible for the dilatation of splenic sinuses, leading to splenomegaly and thereby contributing to portal hypertension in IPH. This is intriguing, since our case represents the first case in which pathology underlying IPH was studied at such young age, making secondary phenomena less likely than in older patients with long-standing portal hypertension. In this concept, VCAM-1 overexpression would not be a prime mechanism propagating portal hypertension but rather a secondary event likely related to chronic vascular stress, inflammation, and phagocyte migration leading to nuclear factor kappaB (NF-kB) activation. VCAM-1 expression may be induced in proliferating cells of myeloid origin in the spleen, which can either be a sign of extramedullary hematopoiesis or of phagocytic activation. While an increase of adhesion molecules is a common
phenomenon in cases of endothelial activation, the underlying pathophysiology of IPH seems to be different from arterial pulmonary hypertension of portopulmonary hypertension, in which and increased ET-1 expression and reduced NO lead to vasoconstriction.

**Referee 1:** “Splenectomy in IPH” too wordy. Is point of section simply to tell of previous case reports of splenectomy (which is standard care for IPH), reports of children, or association of autoimmune disease (which is well described)?

**Response:** The section “Splenectomy in IPH” together with Figure 2 provides an up-to-date review of similar cases in the field and makes clear that similar cases in children have not been reported so far. Since our case represents the first case in which pathology underlying IPH was studied at such young age, making secondary phenomena less likely than in older patients with long-standing portal hypertension. We have changed the subhead of our manuscript to “Case report and review”. The section “Splenectomy in IPH” has been shortened.

**Referee 1:** “Role of Spleen in IPH pathogenesis” too wordy and unclear what the point of this section is. The previous reports of overexpression of VCAM-1 and ET-1 are quite interesting, but I am not sure what the authors are trying to argue in terms of underlying pathogenesis of IPH.

**Response:** The section “Role of Spleen in IPH pathogenesis” has been shortened. This section points out that the spleen seems to play a major role in the pathogenesis of IPH as disease remission can be observed after splenectomy in adults. It is conceivable that the primary cause of IPH is not related to hepatic abnormalities but rather to abnormal splenic perfusion.

The overexpression of VCAM-1 and ET-1 may be involved in splenic and portal hyperperfusion/-circulation leading to hypertension in the portal venous system and by enhanced adhesion and migration of lymphocytes into the wall of the portal tracts followed by fibrosis. Circulating soluble isoforms of these factors are elevated in the serum of IPH patients. It has been reported that sinus lining cells of IPH spleens showed diffuse and strong expression of iNOS and eNOS. In contrast, ET-1 was detectable in only a few mononuclear leukocytes in the red pulp of IPH spleens. These results suggest that NO liberated in spleen in the presence of low ET-1, is responsible for the dilatation of splenic sinuses, leading to splenomegaly and thereby contributing to portal hypertension in IPH. In this concept, VCAM-1 overexpression would not be a prime mechanism propagating portal hypertension but rather a secondary event likely related to chronic vascular stress, inflammation, and phagocyte migration leading to nuclear factor kappaB (NF-kB) activation. VCAM-1 expression may be induced in
proliferating cells of myeloid origin in the spleen, which can either be a sign of extramedullary hematopoiesis or of phagocytic activation. Our results suggest that splenic NO and VCAM-1, rather than ET-1, has a significant impact on the development of IPH already at a very early stage of disease.

Referee 1: “Conclusions” too wordy and poorly organized. Again a hypothesis would help organize this discussion. In terms of treatment, there should be a notation of options other than splenectomy, including splenic embolization, etc.

Response: The “Conclusions” section has been shorted, restructured and other treatment options (splenic embolization, percutaneous transhepatic obliteration or transjugular intrahepatic portosystemic shunt procedure) have been mentioned.

Referee 1: Figure 1 clear, but as only one MRI, cannot state "progressive" enlargement. Not sure what "highly normal" portal vein flow means. Figure 3 does not contribute to the report and should be deleted. Table 1 needs legend. Most of this information is in the text, and can probably be deleted in either the text or remove the table. Table 2 needs legend.

Response: The term “progressive” has been deleted. The term “highly normal” has been replaced by “markedly increased”. Table 1 and 2 has been revised (incl. legend). Information given in Table 1 was deleted in the text. Figure 3 has been deleted.

Referee 2: With the primary diagnosis in this child being idiopathic portal hypertension, it is a requisite to demonstrate that there was an increase in portal pressure: there is in fact no evidence at all in the paper that portal pressure was high. A grade 1 gastropathy is - per se and in the critical condition of the child - not indicative of portal hypertension, when all other facts do not support the latter hypothesis. The authors refers to the size of portal vein (that is within the normal range for age!) and hyperdynamic state as a sign of portal hypertension when in fact they write also "absence of formally abnormal portal vein flow on Doppler Ultrasound". The authors cannot prove that portal hypertension was present and this is major weakness in discussing the case as presented; they may have faced a condition with a primary disorder of the spleen caused secondary hypersplenism and abdominal compression, and of course a resolution of the symptoms after splenectomy.

Response: The portal vein of our Turkish patient was relatively prominent with a width of at least 10 mm. Standards values of portal vein size in infants and children are limited, to some extent conflicting or controversially discussed. However, according to
more recently published data of portal venous diameter in children (Soyupak S et al. Portal venous diameter in children: Normal limits according to age, weight and height. Eur J Radiol. 2009 Apr 29. Epub ahead of print) the size of the portal vein in our patient was not within the normal range for age (4.0-8.38 mm, 2.5-97.5 percentiles) and/or height (4.0-8.0 mm, 2.5-97.5 percentiles). Further evidence for a hyperdynamic situation is a clear asymmetry of the renal veins (left>right) suggesting a portorenal shunt. Furthermore, we could detect the left V. gastrica sinistra by keyhole angiography, which also suggests an increased portal vein pressure. Although, invasive measurements of portal vein pressure were not feasible in our critically ill infant patient, these findings are strongly indicative of portal hypertension.

Referee 2: *Splenomegaly per se is not a sign of portal hypertension, as is not Hepatomegaly.*

**Response:** We thank the reviewer for this excellent and thoughtful comment. Indeed, the existing splenomegaly in our case report is per se not a sign of portal hypertension. However, patients with IPH (i.e. non-cirrhotic portal fibrosis) often present with long-standing mass in the left upper quadrant (splenomegaly) and consequences of hypersplenism. Of all the causes of portal hypertension, a massive and disproportionately large spleen is most commonly seen in non-cirrhotic portal fibrosis (Sarin and Kapoor, J of Gastro and Hepatology, 17:526-534, 2002). Thus, splenomegaly is the hallmark clinical finding of IPH.

Referee 2: *In the worse condition of portal hypertension, splenomegaly develops moderately with time and never causes such rapidly progressing organomegaly in children; the latter rapid development suggests rather a malformative growth. Vascular malformations and angiomas typically grow rapidly during early childhood and some can be associated with major thrombopenia and coagulation disorders causing hemorrhagic diathesis. Even the results of immunochemistry would be consistent within the latter context.*

**Response:** The splenomegaly developed moderately. There were no signs of vascular malformations or angiomas on histology of the whole spleen specimen.

Referee 2: *The terminology "Banti syndrome", a term mostly used in the past to describe any condition with splenomegaly of uncertain origin, has been quasi abandoned in literature and nearly disappeared from papers a decade ago. It is nowadays accepted that in most cases portal hypertension had a specific, but unrecognised, cause.*
Response: The term "Banti syndrome" has been deleted/replaced.

Referee 3: The author's have made no mention of the well-described observation that splenectomy or even splenic transposition may be an effective treatment of portal hypertension alone, and the reduction in the degree of flow thru the spleen into the portal circulation would be expected to enhance liver function and reduce portal pressures post-splenectomy independent of any causality of the spleen and IPH.

Response: According to the suggestion of the reviewer we have mentioned this information in our revised manuscript ("The role of the spleen in IPH pathogenesis").

Referee 3: eNOS, VCAM-1, and ET-1 may play a role in the pathogenesis of IPH, but it is equally plausible that the author's are reporting a secondary benefit of splenectomy in portal hypertension reducing portal pressures. This requires elaboration in the manuscript.

Response: It is not clear how splenectomy would reduce portal pressure in cases were a primary hepatic problem would be causative. Following the suggestion of the reviewer, we however discuss this point in the revised discussion.

Referee 3: The author's have made no mention of the possible role of partial splenectomy in this IPH disease management. This would have the benefit of treating the high-flow portal state yet salvaging portion of the spleen for protecting the infant form blood post-splenectomy infections.

Response: According to the suggestion of the reviewer we have mentioned the possible role of partial splenectomy in IPH disease management in our “Conclusions”.

Referee 3: A series of spelling and grammatical errors require correction.

Response: The spelling and grammatical errors have been corrected.