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Increased Arterial and Venous Thrombotic Events in a Case of High-Oxygen Affinity Hemoglobin

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Abstract

The risk of thrombosis in erythrocytosis not related to myeloproliferative neoplasm is still matter of debate. This is as well true for a subgroup of patients with high oxygen affinity hemoglobins. We present a case with a remarkable history of arterial as well as venous thrombosis and reviewed the literature.

Keywords: Idiopathic erythrocytosis; High oxygen affinity hemoglobin; Hb Frauenfeld; Thrombosis

Case Presentation

We present a case of a 64 year old male patient who had an elevated hemoglobin level with normal thrombocytes (always below 250G/l; normal morphology) since his youth. A polycythemia vera was excluded years ago by bone marrow examination and erythropoietin level. Due to the early occurrence of the erythrocytosis, an inborn error was suspected. A novel- α Globin variant with high oxygen affinity could be diagnosed and was called Hb Frauenfeld [α138 (H21) Ser→Phe, TCC>TTC (α2)] [1]. His brother and sister were also carriers of the mutation in the α2 gene but with a normal hematocrit. The variability of the hemoglobin level was described in other forms of high affinity hemoglobins (HAH) [2]. In September 2011, the patient had an unprovoked episode of thrombophlebitis in his right leg and in January 2013 a muscle vein thrombosis in his left calf was diagnosed. No reduced mobility or obvious venous thrombophilia factors were found (Protein C, -S, AT III, Factor V Leiden, Prothrombin 20210A, Antiphospholipid-Antibody syndrome). In addition in 2012 and 2014 amaurosis fugax occurred in the right eye with no source of emboli in cardiac and carotid sonography. In accordance with these findings, no signs for silent additional ischemic events were seen in a MRI of the brain. In July 2015 athrombotic obstruction of the right arteria iliaca communis, iliaca externa and popliteal artery (P2) with critical ischemia of the leg was diagnosed and an urgent surgical thromboembolectomy was successfully performed followed by oral anticoagulation with Phenprocoumon. As an incidental finding a thrombotic occlusion of one left accessory kidney artery with older small infarction was found. Since then, no other thrombotic event occurred. Well controlled hypertension and smoking quitted in 2008 (20 pack years) were the only arteriosclerotic risk factors with moderate arteriosclerosis in angio-CT and duplex sonography. Hematocrit was always around 50%. Phlebotomies were badly tolerated in the youth of the patient and therefore omitted. In addition, due to the rarity of HAH, no firm recommendation for phlebotomies exists in the literature.

Concerning thromboembolic events, two reports can be found in the literature with HAH and additional thrombophilia factors like Protein S deficiency or Factor V Leiden leading to thrombosis [3,4]. Beside a case with a combination of a thalassemia [5] several cases of HAH are reported to be related to thrombosis in either the arterial or venous system: two cases with Hb Pierre-Benite [6], one case with Hb Radcliffe [7], one case with Hb Ypsilanti [8], one case with Hb Fuchu-II [9] and a case of Hb Montfermeil [10]. They are compiled in Table 1. However in a more general approach, the majority of the small series and case reports on HAH do not report an increased rate of venous and arterial thrombosis either because they have not looked at thrombosis or there are no such events [11-13]. In the Hb Var database (http://globin.bx.psu.edu/hbvar/menu.html) 26 cases are listed when searching for hemoglobin variants in the α1- and the

Table 1:

Type	Additional thrombophilia	Number of cases	Age at occurence	Hematocrit	Reference
Hb Rainier	Protein S deficiency	3	<30y	?	[3]
Hb Milledgeville	Factor V Leiden	2	>50y	47-51%	[4]
Hb Olympia	None	1	25	0.64	[5]
Hb Pierre-Benite	None	2	35 and 45	52-56%	[6]
Hb Radcliffe	None	1	51	53%	[7]
Hb Ypsilanti	None	1	>51	42%	[8]
Hb Fuchu II	None	1 (ventricular)	65	55%	[9]
Hb Motfermeil	None	1	66 (?)	0.56	[10]

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α2-Globin Gene combined with erythrocytosis with no clear picture of increased thrombotic events as far as reported. Studies with a broader spectrum looking at patients with idiopathic erythrocytosis, thrombosis seems to be an unusual event compared to the higher rate of thrombosis in cases of polycythemia vera [14].

Despite the general perception of non-increased thrombosis risk in patient with HAH, conflicting observations as in our case exist. Recommendation of phlebotomies or anticoagulation need to be based on an individualized process influenced by additional personal risk factors and the family history of affected persons. To overcome the lack of firm information, reports about HAH should especially focus on this topic and an effort should be made to collect these data because of the rarity of the disease.

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