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CASE REPORT

Do Fibrinogen Levels Serve as Indicator of Hepatic Iron Overload in Patients with High Transfusion Regimes Due to a Hematologic Disease?

P Fecher*, V Wiegering and Paul-Gerhardt S

University of Children's Hospital Würzburg, Germany

***Corresponding author:** P Fecher, University of Children's Hospital Würzburg, Germany, Tel: +49 931 201-27728, E-mail: fecher_p@ukw.de

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Abstract

Despite some major improvements in treating beta thalassemia in the past, it remains a challenge to avoid the various complications which go along with iron overload. We retrospectively analyzed data from 17 patients with transfusion-dependent anemia. In this group we consistently noticed reduced fibrinogen levels in nearly all of the study members. Therefore, we addressed the question whether fibrinogen could become a useful parameter to indicate iron overload. This thesis is supported by the impression that fibrinogen is especially low in periods of elevated ferritin. The correlation of fibrinogen and ferritin is emphasized by the investigation of patients with inherited blood disorders who don´t match the criteria for frequent red blood cell transfusion and who don't suffer from iron overload. This patient's fibrinogen values better match the physiological distribution. With our data we hope to contribute to a comprehensive understanding and surveillance of patients with secondary haemochromatosis.

Keywords: Beta-Thallasemia; Iron Overload; Ferritin; Fibrinogen; Anemia; Transfusion

Introduction

Thalassemia is an inherited disorder of hemoglobin which leads to reduced or absent globin synthesis. In beta-thalassemia patients lack beta-globin chains and present with unbalanced accumulation of alpha-globin chains [1]. The excess of these unstable alpha-globin chains is harmful to erythroid precursor cells and causes permanent hemoglobin degradation, which requires frequent red blood cell transfusions and subsequently iron chelation therapy as supportive care to treat iron overload [2]. The accumulation of iron is known to cause several complications such as cardiomyopathy, liver dysfunction and multiple hormone disorders like diabetes mellitus, pubertas tarda or hypothyreosis [3]. In this context, exclusive measuring of serum ferritin levels seems to be insufficient to predict chronic organ damage caused by iron overload [4]. Besides invasive measurement, hepatic and cardiac iron overload are best quantified using MRI-based techniques [5]. However, these investigations can only reveal information at a single time point, which shows the necessity of further laboratory parameters for permanent surveillance of secondary haemochromatosis in addition to serum ferritin, particularly because the potential of measured ferritin to determine total body iron in patients with secondary iron overload seems to be limited [6]. The liver is known to sustain damage from secondary haemochromatosis very easily [7]. To assess liver function, the serum levels of cholinesterase and sensitive coagulation parameters such as factor V or fibrinogen are routinely utilized in clinical practice. In our patients with transfusion-dependent hematological diseases, we incidentally noticed that this group consistently seems to have reduced fibrinogen values. This correlation has been described earlier in some publications [8]. Therefore, we also addressed the question whether reduced fibrinogen levels are constantly prevalent in this specific group of patients and in addition to former publications we intended to clarify if low fibrinogen can be correlated with secondary iron overload due to transfusions expressed by ferritin and MRI-based iron measurements.

Results

Patients (age)	**Diagnosis (age when diagnosed)**	**Treatment details (age when therapy began)**	**Average ferritin (min./max.) (normal: < 150 µg/l)**	**Average fibrinogen (min./max.) (normal: 2,1-4,0 g/dl)**	**Average GPT (min/max.) (normal: 7-44 U/l)**	**Average Cholinesterase (min./max.) (normal: 5.320-12.920 U/l)**	**- Max. hepatic iron concentration (MRI-based) (normal: < 36 µmol/g)- Corresponding Ferritin and Fibrinogen (if measured)**
P_1: Male (12 years)	β-Thalassemia major (infant)	Transfusion (infant), splenectomy (4 years) iron chelation (9 years) with Deferasirox & Deferiprone, currently Deferiprone (11 years)	2.655 (148/11.190)	2,35 (2,2/2,5)	27,1 (11,0/149,0)	6.329 (6.076/6.581)	05/2019: 56 - Ferritin: 711 µg/l
P_2: Male (18 years)	β-Thalassemia major (infant)	Transfusion (infant), splenectomy (unclear), iron chelation with Deferasirox & Deferiprone (13 years), currently Deferiprone (16 years)	4.618 (340/12.643)	2,1 (1,1/2,6)	95,6 (16,8/368,0)	6.810 (5.207/8.207)	02/2016: >350 - Ferritin: > 8.000 µg/l - Fibrinogen: 2,5 g/dl 06/2017: >350 - Ferritin: >5.047 µg/l - Fibrinogen: 2,2 g/dl

Patients (age)	**Diagnosis (age when diagnosed)**	**Treatment details (age when therapy began)**	**Average ferritin (min./max.) (normal: < 150 µg/l)**	**Average fibrinogen (min./max.) (normal: 2,1-4,0 g/dl)**	**Average GPT (min/max.) (normal: 7-44 U/l)**	**Average Cholinesterase (min./max.) (normal: 5.320-12.920 U/l)**	**- Max. hepatic iron concentration (MRI-based) (normal: < 36 µmol/g)- Corresponding Ferritin and Fibrinogen (if measured)**
P_3: Female (19 years)	β-Thalassemia major, familial mediterranean fever (unclear)	Transfusion (infant), splenectomy (unclear), iron chelation currently Deferasirox & Deferiprone (16years), colchicine	7.230 (3.555/24.890)	2,7 (0,5/5,4)	65,7 (12,3/283,0)	6.317 (5.003/8.576)	10/2017: 340 - Ferritin: 11.428 µg/l
P_4: Female (5 years)	β-Thalassemia major (2 years)	Transfusion (2 years), iron chelation with Deferasirox (4 years)	2.937 (1.328/5.183)	2,4	77,5 (15/645)	5.645	
P_5: Male (25 years)	β-Thalassemia major (6 months)	Transfusion (7 months), iron chelation with Deferoxamine (4 years), Deferasirox (22 years), currently Deferiprone & Deferasirox (23 years)	2.214 (341/>8.000)	2,4 (1,7/3,7)	21,5 (6,7/83,7)	5.111 (4.235/6.255)	07/2019: 397 - Ferritin: 5.157 µg/l
P_6: Female (13 years)	β-Thalassemia major (infant)	Transfusion (7 months), iron chelation (1 year, active ingredient unknown), currently Deferasirox (9 years), allogeneic stem cell transplantation (13 years)	2.570 (565/7.355)	2,2 (1,1/3,5)	24,6 (5/81,4)	5.861 (2.001/7.617)	07/2017: 180 - Ferritin: 3.045 µg/l - Fibrinogen: 1,1 g/dl
P_7: Male (24 years)	β-Thalassemia major (unclear)	Transfusion (unclear), iron chelation with Deferoxamine (unclear), currently Deferasirox (18 years), splenectomy (20 years)	1.049 (308/3.095)	1,7 (1,5/2,0)	27,1 (13,2/92,2)	7.722 (7.163/8.216)	02/2017: 150 - Ferritin: 996 µg/l - Fibrinogen: 1,5 g/dl

Patients (age)	**Diagnosis (age when diagnosed)**	**Treatment details (age when therapy began)**	**Average ferritin (min./max.) (normal: < 150 µg/l)**	**Average fibrinogen (min./max.) (normal: 2,1-4,0 g/dl)**	**Average GPT (min/max.) (normal: 7-44 U/l)**	**Average Cholinesterase (min./max.) (normal: 5.320-12.920 U/l)**	**- Max. hepatic iron concentration (MRI-based) (normal: < 36 µmol/g)- Corresponding Ferritin and Fibrinogen (if measured)**
P_8: Male (11 years)	β-Thalassemia major (infant), secondary porphyria cutanea tarda (9 years), Protein S deficiency	Transfusion (infant), iron chelation with Deferoxamine (20 months) and later Deferasirox (6 years), allogeneic stem cell transplantation (6 years) followed by bloodletting (between age 6 and 9), cloroquine (8 years)	3.991 (86/19.498)	2,1 (1,2/3,1)	145,9 (19,6/635)	5.844 (3.015/8.167)	04/2014: 320 - Ferritin: 3.565 µg/l - Fibrinogen: 2,0 g/dl
P_9: Male (7 years)	β-Thalassemia intermedia (unclear), dilated cardiomyopathy	Transfusion (unclear), high transfusion scheme (4 years), iron chelation with Deferasirox (4years)	2.064 (278/3.027)	2,1 (1,4/4,6)	34,9 (7,1/101)	6.286 (4.404/7.092)	03/2020: 82 - Ferritin: 2.453 µg/l - Fibrinogen: 1,5 g/dl
P_10: Female (7 years)	β-Thalassemia major (7 months)	Transfusion (infant), iron chelation with Deferasirox (2 years)	1.045 (436/>2.420)	2,5 (2,3/2,9)	20,7 (7/111,9)	6.215 (5.686/7.120)	08/2020: <36 - Ferritin: 496/ µg/l - Fibrinogen: 1,8 g/dl
P_11: Male (14 years)	β-Thalassemia major (prenatal)	Transfusion (3 months), iron chelation (2 years, currently Deferasirox),	923	2,0	15		03/2014: 200 - Ferritin: 923 µg/l - Fibrinogen: 2,0 g/dl
P_12: Female (5 years)	β-Thalassemia major (infant)	Transfusion (5 months), iron chelation with Deferasirox (4 years)	4.920 (3.711/7.034)	2,3	45 (14,8/172,5)	6.491	
P_13: Female (6 years)	β-Thalassemia major (5 months)	Transfusion (5 months), iron chelation with Deferasirox (5 years), died after GvHD in 11/2020	7.000 (5.968/8.400)	1,8	95,6 (6,8/805,5)	5.967	
P_14: Female (8 years)	Diamond-Blackfan-Anemia (4 months)	Transfusion (5 months), iron chelation with Deferasirox (20 months)	942 (258/1.515)	2,1 (1,9/2,7)	20,4 (10/68)		08/2018: 118 - Ferritin: 1.311 µg/l

Patients (age)	**Diagnosis (age when diagnosed)**	**Treatment details (age when therapy began)**	**Average ferritin (min./max.) (normal: < 150 µg/l)**	**Average fibrinogen (min./max.) (normal: 2,1-4,0 g/dl)**	**Average GPT (min/max.) (normal: 7-44 U/l)**	**Average Cholinesterase (min./max.) (normal: 5.320-12.920 U/l)**	**- Max. hepatic iron concentration (MRI-based) (normal: < 36 µmol/g)- Corresponding Ferritin and Fibrinogen (if measured)**
P_15: Male (12 years)	Diamond-Blackfan-Anemia (11 months)	Transfusion, allogeneic stem cell transplantation (4 years)	121 (14/429)	2,3 (1,2/3,6)	12,5 (9/16)		
P_16: Female (13 years)	Congenital dyseryt-ropoietic-anemia Type II (8 years)	Transfusion (4 months), high transfusion scheme (9 years), iron chelation with Deferasirox (10 years)	1.087 (315/2.425)	2,1 (1,4/2,7)	33,5 (8,8/369,8)	5.679 (5.042/6.326)	12/2016: 340 - Ferritin: 654 µg/l - Fibrinogen: 2,0 g/dl
P_17: Female (8 years)	Congenital dyseryt ropoietic anemia Type II (3 years)	Transfusion (3 years), iron chelation with Deferasirox (5 years)	1.175 (101/2.375)	2,1 (2,0/2,2)	57,9 (15/125)	5.124 (2.915/8.597)	09/2019: 351 - Ferritin: 2.203 µg/l - Fibrinogen: 2,2 g/dl

Table 1: Main patient characteristics of the tested group undergoing a high transfusion scheme because of transfusion dependent hematological diseases including diagnoses, treatments, maximal ferritin serum levels, fibrinogen levels and if performed maximal hepatic iron content measured by MRI

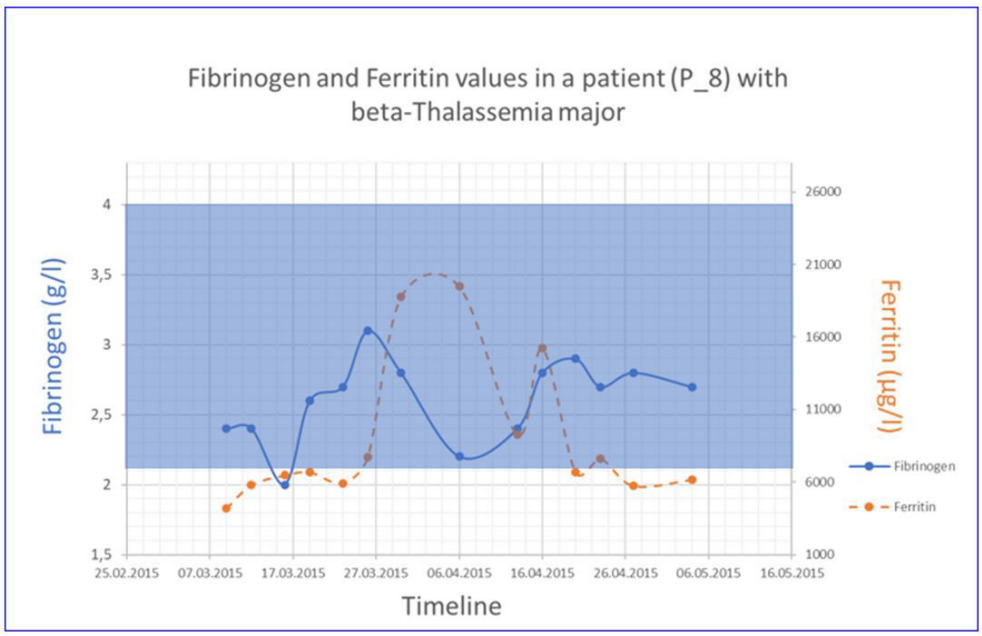

Figure 1: Time course of fibrinogen and ferritin levels of a patient with beta-thalassemia major within a period of high iron overload indicated by ferritin elevation. The physiological distribution of fibrinogen from 2,1 – 4,0 g/dl is shaded grey in the background of the graphs

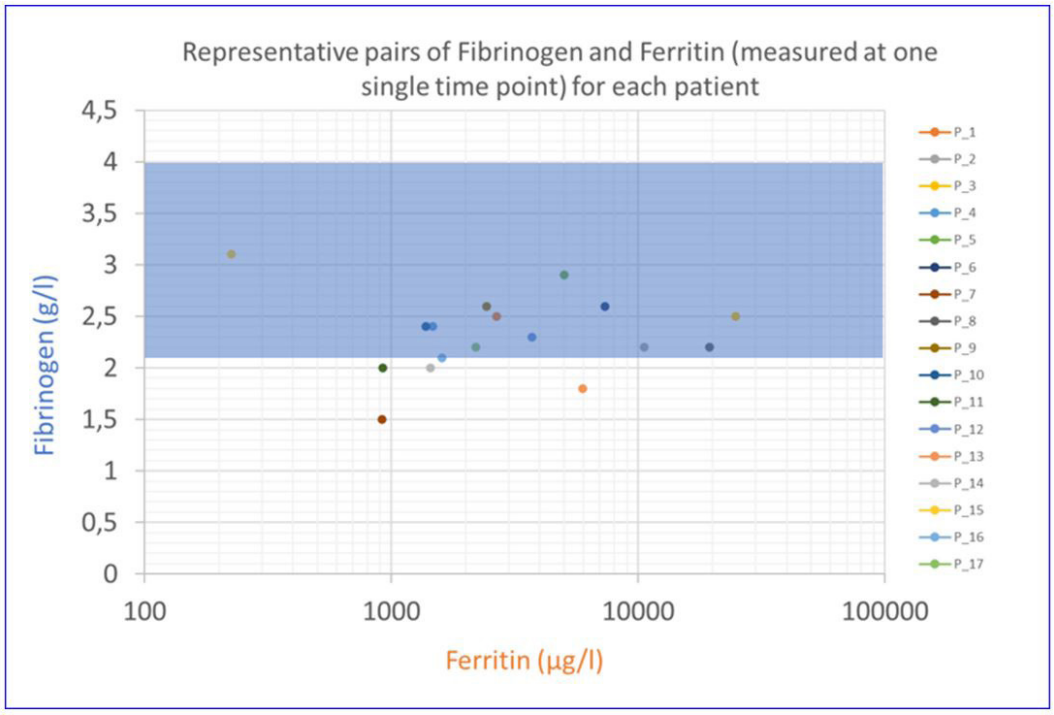

Figure 2: Representative pairs of Fibrinogen and Ferritin at a single time point for each study patient. The fibrinogen values consistently meet the lower part of the physiological distribution of fibrinogen from 2,1 – 4,0 g/dl which is shaded grey in the background

We retrospectively collected date from a heterogeneous group of 17 patients diagnosed with transfusion-dependent anemia and treated at the Children's University Hospital of Wuerzburg, Germany (details are given in table 1): 12 patients with beta thalassemia major, 1 patient with beta thalassemia intermedia, 2 patients with Diamond-Blackfan anemia and 2 patients with congenital dyserythropoietic anemia (CDA Type 2). Consent for chart review was routinely performed and approved by the local ethic committee. We found low or even reduced fibrinogen levels in all patients. To exclude that low fibrinogen may be associated with underlying hematologic disease, we analyzed fibrinogen in beta-thalassemia minor (n=5) and Fanconi Anemia patients (n=2), who did not require transfusions routinely. These patients never showed elevated serum ferritin values or other signs of iron overload. The fibrinogen levels of all of these patients matched the physiological distribution of human fibrinogen (2,1 g/dl – 4,0 g/dl). Following another approach in the group of patients with transfusion-dependent anemias, we demonstrated that fibrinogen levels are especially low in periods of elevated ferritin, as exemplified shown for one patient in figure 1. Pairs of ferritin and fibrinogen from the same blood draw are illustrated in figure 2. MRI-based measurements of hepatic iron content were performed in most of the tested patients revealing high iron values for the patients with reduced fibrinogen. Since MRI is only executed once a year, data and correlations are limited.

Conclusion

Chelation therapy has shown to be effective in reducing iron overload and can reduce morbidity and mortality significantly [9]. Even if chelation therapy may reduce iron overload, we know that patients with high transfusion regimes still have a long-term risk of iron overload. Therefore, a further improvement of clinical and labor chemical monitoring would be helpful to optimize regulation of chelation therapy. In the past measurement of ferritin has been the gold standard for observing patients with secondary haemochromatosis and navigating chelation therapy for years. Recent studies clarify that the exclusive measurement of ferritin should no longer be the only assessment and recommend taking a closer look at the patients´ clinical condition or the collection of additional laboratory parameters [10] as ferritin levels do not always correlate with the real iron overload and the MRI based quantification. Sensitive and elaborated imaging-based diagnostics of corporal iron accumulation is helpful but not consistently available everywhere and cannot be used on a daily basis to regulate chelation therapy. Furthermore, it is known that children with beta-thalassemia have a higher risk of thrombosis, which may be explained by a hypercoagulation due to a coagulation disbalance

[11]. One possible pathomechanism is the imbalance in the synthesis between plasminogen activators and inhibitors, affected by the Vitamin K-dependent liver synthesis which might be limited in patients with hepatic iron overload (Intagliata et al., [12]. Apparently, coagulation factors seem mostly unaffected by splenectomy [13]. This indicates that we may underestimate the role of coagulation in patients with hematological diseases and suggests that hematologic patients may benefit from routine monitoring of coagulation parameters. In our cohort we demonstrated, that fibrinogen, as a parameter of liver function seems to correlate with iron overload (ferritin and MRI-based) as exemplified shown in figure 1. For closer statistical analysis we consider our sample size as too small. Therefor a higher number of study members and prospective study design would be helpful to clarify the role of fibrinogen in this context. With these data from our retrospective analysis, we hope to contribute to a better surveillance of patients with secondary haemochromatosis. As immigration has led to a rise in cases of patients with beta-thalassemia in our country, we would like to motivate our colleagues to develop a platform for standardized treatment protocols for this patient group with the possibility of addressing questions for improved treatment approaches.

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