



Low serum haptoglobin and blood films suggest intravascular hemolysis contributes to severe anemia in hereditary hemorrhagic telangiectasia

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Low serum haptoglobin and blood films suggest intravascular haemolysis contributes to severe anaemia in hereditary haemorrhagic telangiectasia

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CORRESPONDENCE TO

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To the Editor,

Hereditary haemorrhagic telangiectasia (HHT) results in iron deficiency anaemia due to chronic blood losses from telangiectasia and arteriovenous malformations in the nose and gastrointestinal tract. Patients with HHT can require very frequent intravenous iron infusions or blood transfusions, in addition to interventional and medical haemorrhage-limitation strategies such as Bevacizumab or Thalidomide. Generally, iron requirements reflect the rate of blood loss, with patients demonstrating appropriate suppression of hepcidin when iron deficient, and correcting anaemia if haemorrhage reduces and iron intake is supplemented. However, clinic audits showed that for a population with presumed iron deficiency, surprisingly high proportions had non-microcytic anaemias and/or were failing to correct haemoglobin in the setting of apparently sufficient iron as judged by serum ferritin. We hypothesised that reduced intravascular erythrocyte survival (haemolysis) might be augmenting anaemia, and introduced serum haptoglobin as a first line screen for HHT patients where iron requirements were considered potentially excessive for evident haemorrhage. Seven of the 27 selected patients had a haptoglobin below the normal range suggesting intravascular haemolysis could be contributing to erythrocyte losses. In support, blood films demonstrated features of haemolysis (such as polychromasia and spherocytes/elliptocytes) as commonly as those of iron deficiency; patients with lower haptoglobin were more severely anaemic; erythrocytes from patients with sub-normal haptoglobin did not demonstrate microcytosis or hypochromia as would be expected for purely iron deficiency anaemia; and several patients had HHT-independent haemolytic risks factors in addition to the turbulent blood flow through HHT arteriovenous malformations. Finally, in one transfusion-dependent patient with unexplained subnormal haptoglobins, the haemoglobin spontaneously rose by 34g/L after 7 days prednisolone treatment for asthma. We concluded that while the main HHT therapeutic emphasis must remain haemorrhage limitation and treatment of proven iron deficiency, intravascular haemolysis should be considered a potential contributor to anaemia in a proportion of HHT patients with severe anaemia. Erythrocyte protection strategies may then prove helpful adjuncts to anti-haemorrhagic and iron replacement therapies.

Severe anaemia as a result of iron deficiency is a common consequence of hereditary haemorrhagic telangiectasia (HHT). Almost all patients experience recurrent nosebleeds that frequently occur daily.[1] A smaller proportion have chronic gastrointestinal bleeding.[2] Controlling HHT blood losses reduces iron/transfusional requirements, as evidenced following nasal closure for patients with very severe epistaxis.[3] Unfortunately the majority of HHT patients have ongoing recurrent haemorrhage, and for many this results in substantial blood losses despite multiple interventional procedures and/or medical treatments such as Tranexamic acid, Thalidomide, Tamoxifen, and Bevacizumab. Bleeding and anaemia are established priorities for the HHT patient/professional consortium of the European Reference Network on Rare Multisystemic Vascular Diseases (VASCERN) - management of nosebleeds, and assessment of iron deficiency, are two of the five VASCERN HHT Outcome Measures.[4]

HHT patients are particularly heavy users of iron treatments and blood transfusions, despite normal iron handling as evaluated by appropriate suppression of hepcidin when iron deficient.[5] Furthermore, as in the general population,[6] serum iron and transferrin saturation index (TfSI) can increase acutely for several hours as secondary consequences of iron treatments for iron deficiency.[7] But two groups of HHT patients were puzzling and led us to seek evidence for additional causes of anaemia: The first were patients transferred from oral to intravenous iron, then to increasing frequencies of intravenous iron, while failing to correct the anaemia. The second reported bleeding had reduced but high transfusion requirements continued.

Formal haemorrhage adjusted iron requirements (HAIR) were developed and evaluated,[5] identifying a subgroup of HHT patients who had iron requirements out-of-proportion to known nasal, gastrointestinal, menstrual and other discernible blood losses. High proportions of clearly anaemic HHT patients (haemoglobin <110g/L) did not have the expected microcytosis or hypochromia for iron deficiency[8]: for example 106/221 (48%) had mean corpuscular volume (MCV) measurements at or above the lower limit of normal (Figure 1A). Furthermore, of all 87 HHT patients who were using iron treatments when reviewed between June 2015 and

June 2017, as a group, compared to oral iron users, intravenous iron users seemed to be failing to correct haemoglobin in the setting of apparently sufficient iron as judged by serum ferritin (Figure 1B).

Iron requirements out-of-proportion to blood losses, and two particular HHT patients (heterozygous for Hb-S and Hb D-Punjab respectively), led CLS to hypothesise that reduced intravascular erythrocyte survival may be contributing to the “failure to correct anaemia” state.

If intravascular haemolysis occurs, haptoglobin binding of haemoglobin $\alpha\beta$ dimers limits oxidative tissue damage from the release of free haemoglobin. This irreversible binding depletes haptoglobin from the circulation, and plasma levels take up to a week to recover.[9] Thus low serum haptoglobin represents not only a marker of haemolysis, but also an index of potentially limited physiological compensation mechanisms. Serum haptoglobin was therefore added to standard care pathways for 27 HHT patients with potentially out-of-proportion iron requirements, identified from the 90 HHT patients reviewed June 2017-March 2018. One case is illustrated in Figure 2A. Demographic details of all 27 patients are presented in Supplementary Table 1. The patients were aged 19-81ys and all were experiencing significant haemorrhage: Fifteen had nosebleeds at least daily, and these could be arterial rate bleeds, lasting more than an hour. Epistaxis severity scores[1] ranged from 0 to 8.59 out of 10.

As detailed below however, there was also evidence to suggest shortened intravascular red cell survival in 12 of the selected 27 cases, all of whom had anaemia that had been solely ascribed to haemorrhage-induced iron deficiency. All were receiving supplementary iron, with five receiving intravenous iron at least monthly. None had a known haemoglobinopathy or red cell disorder.

- Haptoglobin was below the normal range in 7/27 cases (Figure 2B). Low values could not be explained by impaired liver synthetic function as judged by serum albumin, and some haptoglobin values may have been elevated as an acute phase response due to subtle confounding inflammation.

- Of the eleven manually-evaluated blood films performed at the time of haptoglobin measurements, polychromasia was observed in 8/11 (72.7%), and spherocytes or elliptocytes in 5/11 (45.5%). These findings were seen as commonly as consequences of iron deficiency (Figure 2C).
- The process appeared more indolent than immune-mediated haemolysis: None of the 11 tested lactate dehydrogenase values exceeded 280 U/L, and bilirubin was ≤ 12 mmol/L in 21/24 cases. To date all direct antibody and haemoglobin electrophoresis tests have been negative (including in four patients with haptoglobin < 0.5 g/L). However, adding to the index case haemoglobinopathy traits, a haemolytic risk factor was subsequently identified in two of the haptoglobin cohort- glucose-6-phosphate dehydrogenase (G6PD) deficiency in one,[9] and severe hypophosphatemia[10] in a second. In a third with recurrently subnormal serum haptoglobin, there was an intriguing spontaneous haemoglobin increment of 34 g/L (without any change in nosebleeds) after an incidental 7 day course of prednisolone 30 mg od for asthma (Figure 2A). The magnitude and response duration exceeded that from 4 different erythrocyte transfusions in the preceding year.

Since recently-transfused red blood cells have shorter circulatory lifespans,[9] analyses concentrated on the 18 patients who had not been transfused in the previous month. Crude regression analyses demonstrated that HHT patients with lower haptoglobin had fewer erythrocytes ($p < 0.001$), lower haematocrit ($p = 0.006$) and lower haemoglobin ($p = 0.023$) indicative of more severe anaemia (Table 1). Findings were confirmed after adjustment for markers of inflammation using C-reactive protein (CRP, Table 1). CRP-adjusted regression also indicated trends for lower haptoglobin to be associated with a higher percentage of reticulocytes ($p = 0.047$), higher absolute reticulocyte counts ($p = 0.16$), and greater use of intravenous iron ($p = 0.10$, Table 1). A striking feature was that patients with sub-normal haptoglobin did not demonstrate usual iron deficient erythrocyte indices, but tended to have normal MCV (Figure 2D) and MCH, even when anaemic or iron deficient.

PubMed searches for “haemolysis” and “HHT” identified no publications on HHT, but it should not be a surprise that erythrocytes may have shorter life-spans in HHT patients with disturbed blood flow through arteriovenous malformations. Turbulent flow is a risk factor for haemolysis in the general population.[9] Even the smallest HHT telangiectasia usually contain direct arteriovenous communications,[11] larger pulmonary and hepatic AVMs each affect approximately 50% of cases,[4] and HHT patients have higher than normal cardiac outputs to compensate for AVMs.[12] Intravascular haemolysis occurs when the burden of erythrocyte membrane injury exceeds erythrocytic repair capacity.[9] One aspect to consider, is whether transient rises in serum iron and T/SI injure red cells as seen for endothelial cells.[6,13] It is noteworthy that erythrocyte survival was normal when measured in non HHT patients with Hb S[14] trait at sea level. Similarly, where haemolysis was identified in Hb D Punjab trait, it was attributed to coexisting haemoglobinopathies[15] We speculate that added stresses of the HHT vasculature, possibly combined with mild thrombotic angiopathy due to endothelial cell damage, may serve as stressors to normal erythrocytes, or erythrocytes with otherwise sub-clinical abnormalities, resulting in their indolent, but clinically significant early destruction. Hence reduced *in vitro* HHT erythrocyte deformability is predicted.

In conclusion, shortened intravascular erythrocyte survival should be considered as a potential contributor to anaemia in HHT if iron requirements are out-of-proportion to haemorrhagic losses. Erythrocyte protection strategies may then prove helpful adjunctive treatments, and represent an important focus for future studies.

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TABLE 1:**Haptoglobin relationships in 18 HHT patients who had NOT received a blood transfusion in the previous month**

	Range (median)	Crude regression		CRP-adjusted regression	
		coefficient	p-value	coefficient	p-value
Haptoglobin (g/L)	0-3.47 (1.1)	-	-	-	-
C-reactive protein (mg/L)	0.3-14.3 (2.5)	0.11	0.023	-	-
Red blood cells (x 10 ⁹ /L)	3.27-5.83 (4.61)	0.74	0.005	0.84	<0.001
Haematocrit	0.29-0.44 (0.40)	7.91	0.069	10.5	0.006
MCV (fl)	71.7-95.8 (87.8)	-0.065	0.018	-0.06	0.014
Lymphocyte count (x 10 ⁹ /L)	1-3 (1.6)	0.59	0.13	0.84	0.015
Haemoglobin (g/L)	88-147 (131.5)	0.011	0.32	0.025	0.023
White blood cells (x 10 ⁹ /L)	3.5-8.6 (7.2)	0.31	0.012	0.27	0.027
APTT (s) †	20.4-29.9 (24.5)	-0.13	0.048	-0.12	0.041
Epistaxis severity score	0-8.59 (6.23)	-0.073	0.24	-0.113	0.045
Reticulocytes (%)‡	0-5.3 (1.55)	-0.089	0.57	-0.30	0.047
MCH	22.3-30.7 (28.5)	-0.16	0.015	-0.13	0.054
Basophil count (x 10 ⁹ /L)	0-0.1 (0)	-8.67	0.08	-8.30	0.07
Albumin	27-46 (39)	0.013	0.76	0.078	0.075
Intravenous iron	Once - weekly (8-12 weekly)	-0.15	0.20	-0.17	0.10
Fibrinogen	1.86-5.40 (3.14)	0.55	0.11	0.44	0.11
Prothrombin time (s)	10.2-12.7 (11.2)	-0.43	0.22	-0.49	0.12
Reticulocyte count	0-174.4 (71.1)	-0.0002	0.97	-0.007	0.16

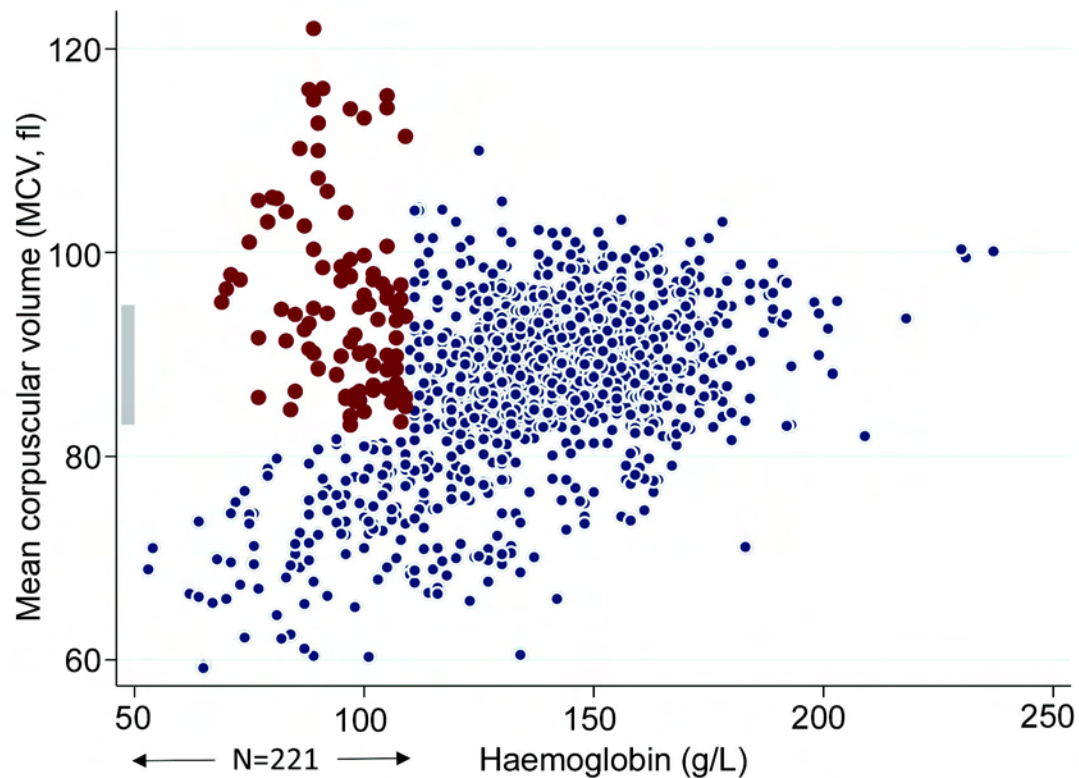
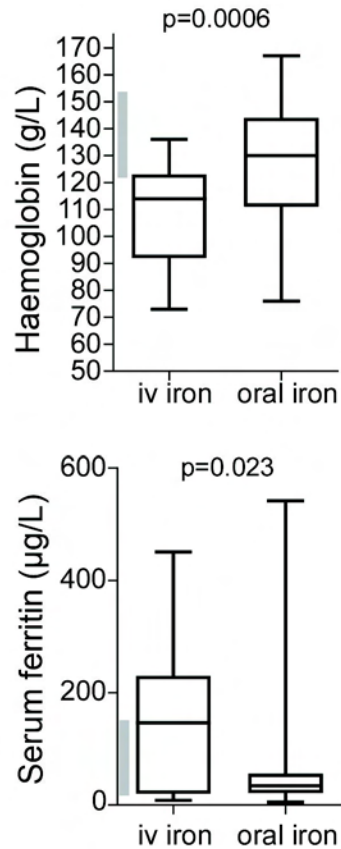
N= 18 except for † N=17, and ‡ N=10. Regression analyses were performed with ln(haptoglobin) as this was more normally distributed than haptoglobin (data not shown). Further relationships where adjusted p-values exceed 0.16 are provided in Supplementary Table 2- this includes sex, bilirubin, and red cell distribution width (p-values 0.38-0.93). Abbreviations: CRP, C-reactive protein; MCV, mean corpuscular volume; MCH, mean corpuscular haemoglobin; APTT, activated partial thromboplastin time

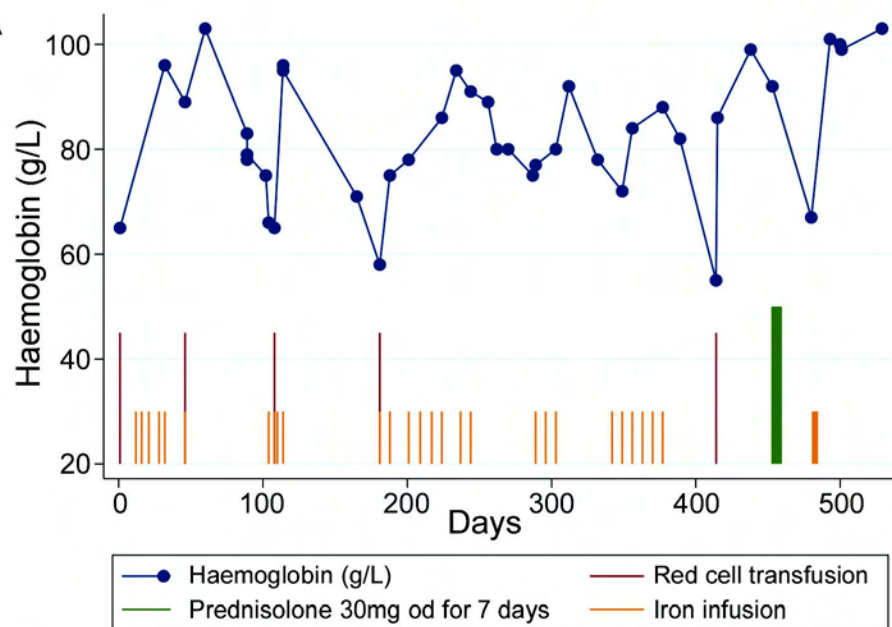
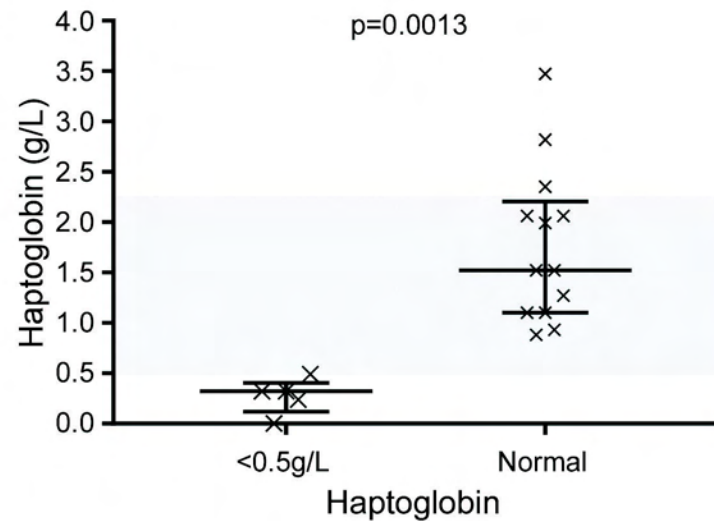
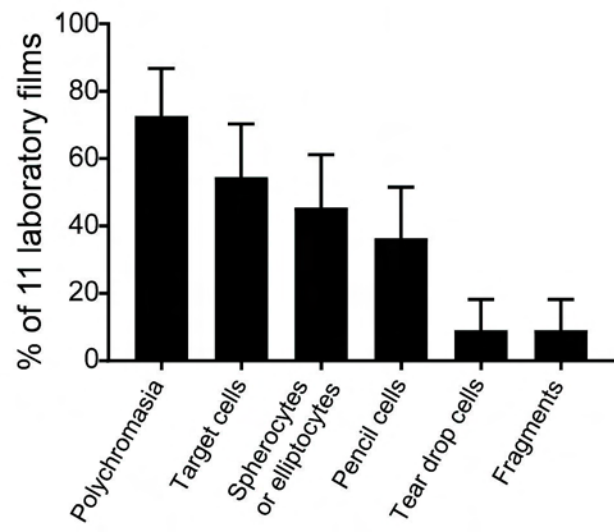
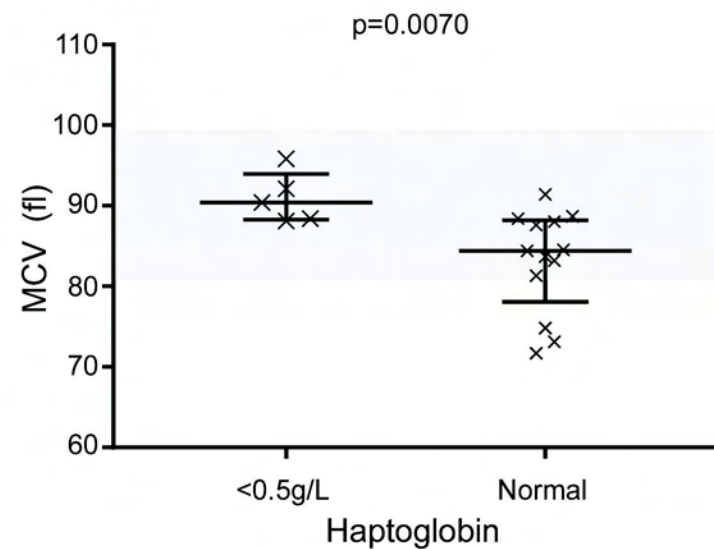
Figure 1: Non iron-deficient red cell and iron indices in HHT patients

A). Mean corpuscular volume (MCV) in 1409 datasets of 486 HHT patients, by haemoglobin. Red values indicate normal to high values in the 221 datasets where haemoglobin <110g/L). Note the number of datasets ranged from 1- 37 (median 3) per patient. **B)** Anaemia and iron indices in 86 consecutively reviewed HHT patients using iron- data indicate a single dataset per patient. All iron users were categorised by whether or not they used intravenous (iv) iron, or purely oral iron tablets. Upper graph: haemoglobin, lower graph: ferritin. Boxplot boxes indicate median (line) and interquartile range, error bars represent two standard deviations. Normal ranges indicated by grey bars.

Figure 2: Haemolytic markers in HHT patients

A) Serial measurements over 17 months of a typical severely anaemic HHT patient in the cohort of 27. Haemoglobin (blue symbols) in relation to iron infusions (yellow lines), red cell transfusions (red lines), and one week course of prednisolone 30mg od (for asthma, green). Three serum haptoglobin measurements were below the normal range (Supplementary Figure 1). **B)** Serum haptoglobin in 27 selected HHT patients, categorised by values above and below the lower limit of normal. Error bars demonstrate median and interquartile range. Shaded area represents normal range. **C)** Manual blood films reported in 11 of the 27 selected HHT patients: symbols demonstrate mean and 95% confidence intervals. **D)** Mean corpuscular volume (MCV) in HHT patients without recent transfusions, categorised by haptoglobin values above and below the lower limit of normal. Symbols demonstrate median and interquartile range. Note in B-D, data represent a single dataset per patient, and D presents data from the subset of those in Figure 2B who had not received a blood transfusion in the previous month. Data not shown for one patient who had previously been treated for a bone marrow pathology (though inclusion did not materially alter the analyses).

A**B**

A**B****C****D**

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SUPPLEMENTARY DATA

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Supplementary Table 1:
Demographic indices of the 27 HHT patients with serum haptoglobin measurements

	N (%)	minimum	maximum	p25	p75	Median
Sex (% female)	22 (81.5)					
Oral iron (mg/day) ‡	15 (55.5)	14	195	14	130	50
Intravenous iron (freq) †	13 (48.1)	once	weekly	twice	4-6 weekly	8-12 weekly
Red cell transfusion (freq) †	6 (22.2)	once	weekly	twice	4-6 weekly	8-12 weekly

	N	minimum	maximum	p25	p75	Median
Age (ys)	27	19	81	50	64	58
Haptoglobin (g/L)	27	0	3.47	0.49	1.99	1.16
Epistaxis severity score (0-10)	27	0	8.59	3.41	7.97	6.54
SaO ₂ (%)	27	93.75	99.5	96	97.5	96.5
Haemoglobin (g/L)	26	64	147	88	132	118
Haematocrit (%)	26	0.22	0.443	0.29	0.41	0.373
MCH (pg)	26	71.7	95.8	83.2	91.4	87.8
MCHC (g/L)	26	22.3	30.7	24.7	29.2	28
MCV (fl)	26	279	340	304	323	311.5
Red blood cells (x 10 ⁹ /L)	26	2.43	5.83	3.28	4.75	4.455
RDW (fl)	26	12.6	22.7	14.7	19.3	17.65
White blood cells (x10 ⁹ /L)	26	3.5	8.6	5.9	7.5	6.65
Platelet count (x10 ⁹ /L)	26	80	627	262	368	290.5
Mean platelet volume (fl)	26	9.1	12.8	9.8	11	10.65
Neutrophil count (x10 ⁹ /L)	26	1.8	6.8	3.5	5	4.3
Lymphocyte count (x10 ⁹ /L)	26	0.4	3	1	1.7	1.5
Monocyte count (x10 ⁹ /L)	26	0.3	1.4	0.5	0.6	0.5
Eosinophil (x10 ⁹ /L)	26	0	0.7	0.1	0.2	0.2
Basophil count (x10 ⁹ /L)	26	0	0.1	0	0	0
Reticulocyte count (x10 ⁹ /L)	17	0	301.2	38.7	152.7	78.3
Reticulocytes (%)	17	0	11.9	1.1	3.7	1.7
Prothrombin time (s)	20	10.2	12.7	10.65	11.45	11.15
APTT (s)	20	20.3	30.4	22	28.6	24.4
TfSI (%)	21	2	35	6	15	10
Serum iron (µmol/l)	21	2	24	4	11	8
Serum ferritin (µg/l)	21	4	154	17	81	25
Alanine transaminase (iu/L)	21	6	42	15	27	17
Alkaline phosphatase (iu/L)	22	37	259	58	110	84
Albumin (g/L)	22	27	46	35	42	37.5
Bilirubin (µmol/L)	21	4	68	5	11	6
Fibrinogen (g/L)	20	1.86	5.4	2.77	3.545	3.14
C-reactive protein (mg/L)	21	0.3	14.3	0.7	4.4	2.5

All measurements made on the same day as serum haptoglobin, between June 2017-March 2018. ‡ elemental iron content.† For numeric calculations of infusion/ transfusion frequency, never=0, once=1, twice=2, 3-4 times in life=3, 2-3 monthly=4, 4-6 weekly=5, alternate weekly=6, weekly=7. MCH: mean corpuscular haemoglobin, MCHC: mean corpuscular haemoglobin concentration, MCV: mean corpuscular volume, APTT: activated partial thromboplastin time, RDW: red cell distribution width, SaO₂:% haemoglobin binding sites occupied by oxygen, TfSI: transferrin saturation index.

Supplementary Table 2:
Extended relationships of same-day patient variables with ln(haptoglobin)

					Crude regression		CRP-adjusted regression	
	N	Median	Range	Q1, Q3	coefficient	p-value	coefficient	p-value
Haptoglobin (g/L)	18	1.1	0-3.47	0.49,2.06	-	-	-	-
C-reactive protein (mg/L)	18	2.5	0.3-14.3	0.6,4.4	0.11	0.023	-	-
Red blood cells (x 10 ⁹ /L)	18	4.61	3.27-5.83	4.42,4.9	0.74	0.005	0.84	<0.001
Haematocrit (%)	18	0.4035	0.29-0.44	0.37,0.43	7.91	0.069	10.5	0.006
MCV (fl)	18	87.8	71.7-95.8	83.2,90.4	-0.065	0.018	-0.06	0.014
Lymphocyte count (x 10 ⁹ /L)	18	1.6	1-3	1.3,2	0.59	0.13	0.84	0.015
Haemoglobin (g/L)	18	131.5	88-147	117,136	0.011	0.32	0.025	0.023
White blood cells (x 10 ⁹ /L)	18	7.15	3.5-8.6	6,7.7	0.31	0.012	0.27	0.027
APTT (s)	17	24.5	20.4-29.9	23.1,28.5	-0.13	0.048	-0.12	0.041
Epistaxis severity score (0-10)	18	6.23	0-8.59	2,7.1	-0.073	0.24	-0.113	0.045
Reticulocytes (%)	10	1.55	0-5.3	1.1,3.1	-0.089	0.57	-0.30	0.047
MCH (pg)	18	28.45	22.3-30.7	25.9,29.2	-0.16	0.015	-0.13	0.054
Basophil count (x 10 ⁹ /L)	18	0	0-0.1	0,0	-8.67	0.08	-8.3	0.07
Albumin (g/L)	18	39	27-46	36,43	0.013	0.76	0.078	0.075
Intravenous iron†	9/18	twice	Once-weekly	Twice, 2-3 monthly	-0.15	0.20	-0.17	0.10
Fibrinogen (g/L)	17	3.14	1.86-5.4	2.98,3.44	0.55	0.11	0.44	0.11
PT (s)	17	11.2	10.2-12.7	10.9,11.5	-0.43	0.22	-0.49	0.12
Reticulocyte count (x10 ⁹ /L)	10	71.1	0-174.4	52.3,139.2	-0.0002	0.97	-0.007	0.16
Neutrophil count (x 10 ⁹ /L)	18	4.3	1.8-6.8	3.7,5	0.27	0.07	0.20	0.19
Monocyte count (x 10 ⁹ /L)	18	0.55	0.3-1	0.5,0.6	-0.79	0.19	1.27	0.26
Oral iron (mg/day) ‡	10/18	67.5	14-195	15,130	-0.0017	0.64	-0.23	0.30
Eosinophil (x 10 ⁹ /L)	18	0.1	0-0.4	0.1,0.2	2.84	0.13	1.85	0.32
Alkaline phosphatase (iu/L)	18	75.5	37-212	58,100	-0.0014	0.76	-0.0038	0.37
								/

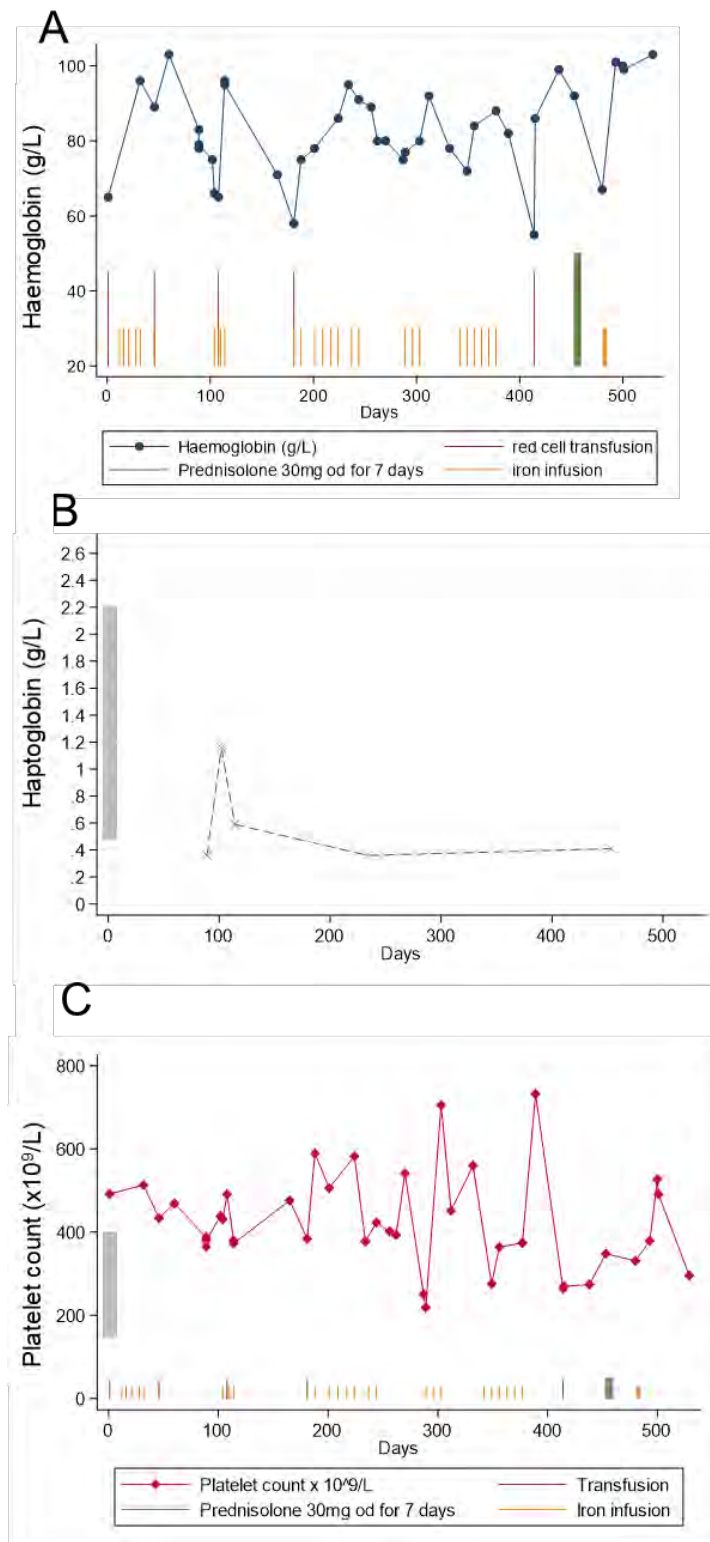
Thielemans L, Layton DM, Shovlin CL. Low serum haptoglobin and blood films suggest intravascular haemolysis contributes to severe anaemia in hereditary haemorrhagic telangiectasia. *Haematologica* 2018

.../					Crude regression		CRP-adjusted regression	
	N	Median	Range	Q1, Q3	coefficient	p-value	coefficient	p-value
Sex (% female)	14/18	77.7			-0.345	0.51	-0.42	0.38
SaO ₂ (%)	18	96.5	93.75-99.5	96, 97.5	-0.021	0.88	0.12	0.39
Serum ferritin (µg/l)	18	26	6-154	21,101	-0.0030	0.47	-0.003	0.41
Alanine transaminase (iu/L)	18	18	6-42	15,27	0.00023	0.99	0.015	0.45
Age (ys)	18	55.5	19-81	50,61	-0.0039	0.773	-0.009	0.47
Red cell transfusion †	2/18	twice	Once-twice	Once, twice	0.08	0.33	0.057	0.48
Bilirubin (µmol/L)	18	7	4-68	5,12	-0.0056	0.62	-0.005	0.62
Platelet count (x 10 ⁹ /L)	18	290	161-627	232,352	0.0015	0.41	0.0008	0.65
TfSI (%)	18	12.5	3-35	7,15	-0.027	0.30	-0.011	0.69
MCHC (g/L)	18	318	287-340	311,334	5.39	0.22	0.002	0.89
RDW (%)	18	15.9	12.6-22.7	14.5,18.9	0.056	0.43	0.006	0.93
Serum iron (µmol/l)	18	8.5	3-24	5,12	-0.025	0.54	0.003	0.93
Mean platelet volume (fl)	18	10.8	9.1-12.8	9.8,11.1	0.013	0.95	0.012	0.95

Regression analyses in the 18 patients who had not received a blood transfusion in the previous month, using natural log-transformed haptoglobin (ln(haptoglobin)) as the dependent (outcome) variable, as this was more normally distributed than haptoglobin (data not shown). Patient variables are ranked in order of strength of association in CRP-adjusted regression. ‡ elemental iron content.† For numeric calculations of intravenous iron and red blood cell transfusion frequency, a scale of 0-7 was used where never=0, once=1, twice=2, 3-4 times in life=3, 2-3monthly=4, 4-6 weekly=5, alternate weekly=6, and weekly=7. *MCH: mean corpuscular haemoglobin, MCHC: mean corpuscular haemoglobin concentration, MCV: mean corpuscular volume, PT: prothrombin time, APTT: activated partial thromboplastin time, RDW: red cell distribution width. SaO₂, % of haemoglobin binding sites occupied by oxygen. TfSI transferrin saturation index.

Data on the patients who had received a recent blood transfusion in the past month are not shown. This recently transfused group had more frequent intravenous iron infusions (odds ratio [OR] 2.20 (95% confidence intervals 1.05, 4.6, p=0.036). This group also tended to have higher epistaxis severity scores (OR 3.84 [0.64, 23.2]); higher haptoglobin (OR 1.67[0.56-5.01]; lower serum iron (OR 0.16 [0.016, 1.66]); lower TfSI (OR 0.68 [0.29, 1.15]); and lower bilirubin (OR 0.41 [0.067, 2.54]), though these and other trends did not reach statistical significance.

Supplementary Figure 1. Serial haptoglobin measurements



A) Haemoglobin (blue circles) and treatment data as presented in Figure 2A). **B)** Serum haptoglobin measurements (grey crosses). Between day 89 and day 104, there were two negative haemoglobin electrophoresis tests, a negative haemoglobin gene screen, and a negative extended direct antibody test. **C)** There was a past history of idiopathic thrombocytopenia purpura but platelet counts (red diamonds) were normal to high throughout this period and did not track haemoglobin. Normal ranges are indicated by grey bars. Timings of iron infusions (yellow lines), red cell transfusions (red lines), and 1 week course of prednisolone (green line) are indicated.