

Hereditary spherocytosis: Consequences of delayed diagnosis

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Abstract

Objective: To determine whether patients with undiagnosed hereditary spherocytosis hospitalized for transfusions might have avoided hospitalization via earlier diagnosis.

Study design: Charts of all (N=30) patients with hereditary spherocytosis seen in pediatric hematology at West Virginia University-Charleston were reviewed. Family and transfusion history and presence of neonatal jaundice were recorded. Complete blood count and reticulocyte values during infancy were available for 20 of 30 patients, while baseline steady-state values were available for all 30.

Results: Transfusions were given to 22 patients; 12 of 14 with an aplastic crisis were undiagnosed. In 10 of 12, the severity of anemia led to hospitalization (3 to intensive care). All 10 had prior mean corpuscular hemoglobin concentration and/or red cell distribution width elevations and a history of neonatal jaundice; 7 of 10 had a positive family history.

Conclusions: Undiagnosed hereditary spherocytosis may lead to inpatient transfusions for severe anemia. Earlier detection of hereditary spherocytosis is easily achievable and may reduce hospitalizations via closer monitoring.

Keywords

Hereditary spherocytosis, aplastic crisis, anemia

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Background

Hereditary spherocytosis (HS) is the most common inherited cause of hemolytic anemia in Caucasians, with an estimated incidence of one in 2000 to one in 5000 in ethnically northern European populations.¹⁻³ The underlying problem is a defect in the red cell membrane, leading to a shortened red cell lifespan. Numerous mutations have been described which have been associated with a wide spectrum of clinical severity.²⁻⁴

The diagnosis is usually made in childhood, with anemia, jaundice and/or splenomegaly as major presenting clinical features. Inheritance is most commonly autosomal dominant with a family history known or identifiable in approximately 75% of patients. The remainder represents new mutations or relatively uncommon autosomal recessive forms of the disease.^{1,2}

The shortened red cell lifetime is reflected in a chronically elevated reticulocyte (retic) count. However, since a retic count is not part of a routine complete blood count (CBC), prior studies have sought to identify findings on the routine CBC that are strongly suggestive of HS. Previous reports have identified the mean corpuscular hemoglobin

concentration (MCHC) and red cell distribution width (RDW) as key parameters suggesting the diagnosis of HS.^{5,6} Incubated osmotic fragility (OF) testing has traditionally been viewed as confirmatory, although more sensitive techniques have been reported.⁷

It is well known that infections, especially parvovirus infections, can lead to erythroid precursor arrest and thus the development of profound anemia/aplastic crisis in patients with shortened red cell survival at baseline.⁸ A known diagnosis of HS might lead to earlier detection of aplastic crises, thus avoiding severe anemia and hospitalization for transfusion as illustrated by the following case.

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A 5-year-old female patient (patient 28) presented to our emergency room with abdominal pain, fever and headaches. She had a 6-day history of feeling ill with intermittent fevers. On examination, the patient was pale, tachycardic and lethargic. There was a III/VI systolic ejection murmur. CBC showed hemoglobin (Hgb) of 3.6 with 0% retics. The patient was admitted for transfusion, and pediatric hematology was consulted. Family history was positive for HS, including that of the father, who had undergone splenectomy at 8 years of age. Studies obtained on this child in her first 5 years of life included seven CBC tests, three retic counts, three ferritin levels, three serum iron tests and one each of iron binding capacity, B12, folate and hemoglobin electrophoresis. Review of prior CBC values showed consistently elevated RDW and MCHC; retic count was elevated in all three prior studies. In spite of this family history and abnormal laboratory findings, the patient had never been seen by pediatric hematology nor diagnosed with HS. An OF test 3 months after transfusion was consistent with HS.

Patients and methods

After approval by the Charleston Area Medical Center/West Virginia University institutional review board (IRB), all patient charts coded as spherocytosis were identified via a comprehensive review of institutional records. As this was a retrospective chart review of existing patients, the IRB indicated that no patient consent was needed. All patient data were de-identified and the records were maintained in a locked office. A total of 30 patients with a confirmed diagnosis of HS were seen between 1 January 1990 and 31 August 2013. All available institutional records as well as supplemental records from primary care physicians were evaluated.

Each patient chart was reviewed to determine age at diagnosis, family history, jaundice in the newborn period (with peak bilirubin levels), infant CBC (earliest values available at age \leq 13 months), baseline (steady-state) CBC and retic count, development of aplastic crisis, need for transfusion and location of initial transfusion (outpatient, hospital or intensive care unit). Since the number of CBC determinations was highly variable, baseline values were selected as representative of the patient in a state of good health. All patients with abnormal baseline MCHC and/or RDW values had these consistently regardless of the number of CBC tests available for review. Detailed family history and initial transfusion location were reviewed and confirmed with parents of the patients.

Patient number (PN) was assigned consecutively; missing data in Table 1 (baseline values) indicate inability to locate this information. PNs in Table 2 (patients admitted for transfusion) identify the same patients consecutively numbered in Table 1 to enable comparisons of baseline values for these patients.

Results

Of the 30 patients, 20 had CBC data available from the first 13 months of life (1 RDW missing); the others had no such retrievable data, likely due to the age of some records. All had baseline data available during childhood (1 RDW missing). All red cell parameters were reviewed: mean corpuscular volume and mean corpuscular hemoglobin were consistently normal. The MCHC and RDW values from the infant data are displayed in Figure 1(a) and (b), respectively. Since we had considerable variability in age at first obtainable CBC, no calculations were done for this group. However, 18 of 19 available RDW values were elevated as were 16 of 20 MCHC values. The only patient with a normal infant RDW had an elevated MCHC and a positive family history. The patient missing an RDW had an elevated MCHC. Both patients had substantially elevated RDW values later in life (baseline).

The baseline values in all 30 patients as well as history of neonatal jaundice (NJ), family history, initial transfusion age and baseline retic counts are shown in Table 1. Baseline values were all obtained prior to splenectomy and after 2 years of age (except patient 2 at 14 months). We used institutional abnormal values for MCHC (\geq 34.8 g/dL) and RDW ($>$ 14%) which were virtually identical to those used by Michaels et al.⁵ Our MCHC values showed a mean of 35.9 with a standard deviation of 0.93; 27 of 30 were elevated. The RDW values demonstrated a mean of 19.5 with a standard deviation of 4.0; 28 of 29 available values were elevated. All patients had elevated MCHC and/or RDW.

NJ (indirect bilirubin \geq 15) was documented in 26 of 30 patients, including all who were transfused at the time of initial presentation. The median age at diagnosis was 15 months; the mean of 40 months was skewed by the five patients diagnosed between 90 and 183 months and was 21 months when those patients were excluded. We did not evaluate the mean age of first abnormal CBC since there was no consistent age for which we were able to obtain CBC results and data were thus limited. Many patients had a stated history of anemia at ages earlier than we were able to retrieve any CBC results. Every patient had some abnormality (Hgb, MCHC, RDW or, if obtained, retic count) in every CBC but the number of such tests was highly variable for different patients. OF was positive in 27 of 27 patients; in three cases; this test was electively omitted due to positive family history with laboratory findings consistent with the diagnosis (MCHC, RDW, retic count).

Of the 30 patients, 22 had a history of transfusion, with 12 being transfused at initial presentation, prior to diagnosis or pediatric hematology referral; 10 of these 12 were transfused as inpatients. The other 10 included 2 premature infants who were multiply transfused in the neonatal intensive care unit prior to diagnosis, 7 being followed by pediatric hematology (all transfused as outpatients) and 1 who was chronically transfused for over 2 years prior to referral.

Table 1. History and baseline lab values.

PN	FH	NJ	TX Age	MCHC, g/dL	RDW%	Retic%
1	Y	Y	None	34.6	14.1	3.8
2	Y	Y	2 m	35	20.3	9.5
3	N	N	None	36	14.1	6
4	Y	Y	76 m	36	25	12
5	N	Y	3.5 m	34.9	16.1	8.9
6	Y	Y	84 m	38	–	10.6
7	Y	Y	21 d	36.5	23	10
8	Y	Y	16 d	35	21.5	7
9	Y	Y	17 d	35.4	19.4	9.6
10	Y	Y	8 d	36.2	17.8	6.5
11	Y	Y	91 m	35	20.4	7.7
12	Y	Y	None	36.8	17.1	4.2
13	N	Y	13 d	36.7	20.8	8.7
14	Y	Y	108 m	36	28	11.8
15	Y	Y	183 m	37.5	20.5	11.5
16	Y	Y	42 m	34.7	28.3	13.8
17	N	Y	Infant	35.2	18.4	8
18	N	Y	21 d	34.5	26	12
19	Y	Y	NICU	36.7	12.7	2.7
20	Y	Y	25 m	35.5	20.4	2.4
21	N	Y	160 m	37.5	18.5	9
22	Y	Y	114 m	36.4	15.2	5.4
23	N	Y	NICU	35.5	24.2	13.1
24	Y	N	None	35.8	14.5	2.4
25	Y	Y	None	35.6	20.6	18.6
26	Y	N	None	36.3	18.4	12.8
27	Y	Y	None	35.7	19	3
28	Y	Y	60 m	36	17	5
29	Y	Y	47 m	35.3	19	7
30	Y	Y	None	37.5	16.5	4

PN: patient number; FH: family history; Y: positive; N: negative; NJ: neonatal jaundice; TX Age: age at first transfusion in days (d) or months (m); MCHC: mean corpuscular hemoglobin concentration; RDW: red cell distribution width. MCHC mean = 35.9; standard deviation = 0.93; RDW mean = 19.5; standard deviation = 4.0.

Table 2. Inpatient transfusions: previously undiagnosed patients.

PN	FH	NJ	TX Age	DX Age	Min Lag	Hgb	Retic%	Location
2	Y	Y	2 m	6 m	4 m	6.2	14.5	INPT
5	N	Y	3.5 m	12 m	3.5 m	4.6	12	PICU
6	Y	Y	84 m	90 m	42 m	6.4	3.1	INPT
11	N	Y	91 m	92 m	86 m	5.5	2.3	INPT
14	Y	Y	102 m	108 m	78 m	2.8	ND	PICU
15	Y	Y	183 m	186 m	157 m	4.0	2.5	INPT
16	Y	Y	42 m	47 m	42 m	5.3	2.2	PICU
21	N	Y	160 m	164 m	34 m	6.2	9.2	INPT
28	Y	Y	60 m	63 m	46 m	3.6	0	INPT
29	Y	Y	47 m	50 m	37 m	5.2	2.7	INPT

PN: patient number (corresponds to Table 1); FH: family history; NJ: neonatal jaundice; TX Age: age at first transfusion in days (d) or months (m) (all from Table 1); DX Age: age at diagnosis in months; Min Lag: minimum lag time in months (from earliest known abnormal complete blood count to DX Age); Hgb: hemoglobin at time of admission; Retic%: retic count at time of admission; Location: location of transfusion; INPT: general inpatient ward, PICU: pediatric intensive care unit.

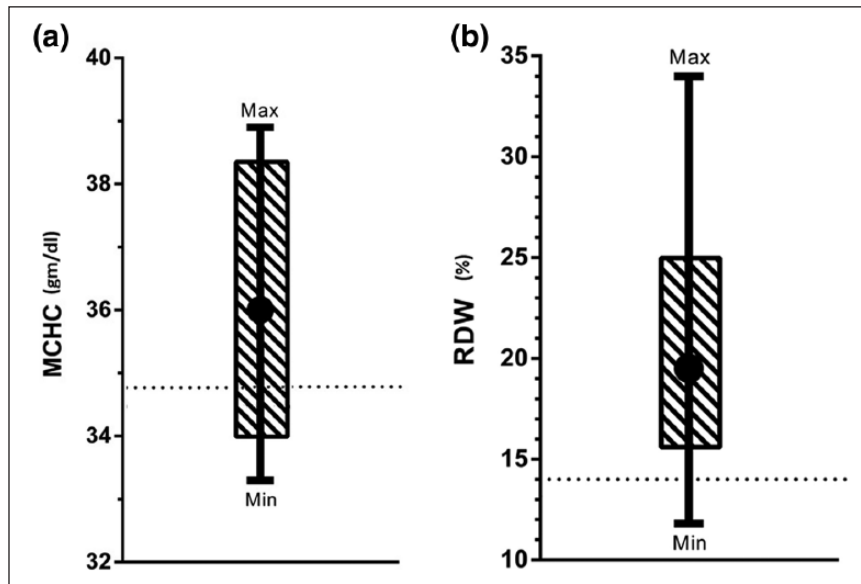


Figure 1. (a) Infant MCHC: mean of 36 is represented by black dot, shaded area indicates 90% of all data and dotted line shows cutoff for abnormal MCHC (34.8g/dL). (b) Infant RDW: mean of 19.5 is represented by black dot, shaded area represents 90% of data and dotted line shows cutoff for abnormal RDW (14%).

MCHC: mean corpuscular hemoglobin concentration; RDW: red cell distribution width.

The 10 patients admitted for transfusion without an established diagnosis of HS were all profoundly anemic (mean Hgb 5) as seen in Table 2, which includes admission Hgb and retic counts. Based on clinical concerns about cardiovascular stability, three patients were admitted to the pediatric intensive care unit (PICU) for monitoring during the initial transfusion while the other seven were admitted to the general inpatient (INPT) ward. Three of these 10 patients had a significant retic response but were transfused due to symptomatology and/or other clinical concerns.

A particular focus of our study was to determine diagnostic lag time, measured as the time from which initial laboratory and/or historical features strongly suggested HS to the time at which the diagnosis was actually established, especially evaluating those patients admitted for transfusion prior to diagnosis. Lag times are certainly underestimated due to our inability to obtain earlier childhood records or initial CBC results and are thus based on the earliest known CBC. Lag times shown in Table 2 suggest that HS could have been diagnosed well prior to the patients presenting with severe anemia. In addition, 23 of 30 patients (Table 1) had a positive family history, although this was often not obtained until after the patient was seen at our center or was not appreciated as being of significance.

Discussion

Others have shown that MCHC and RDW are highly predictive of HS.^{5,6} Michaels et al.⁵ evaluated 112 patients >12 months of age and found MCHC >35 and RDW >14 (almost identical to values we used) to have a sensitivity of

50% and a specificity of 100% for the identification of HS. Christiansen and Henry reviewed over 150,000 live births in the Intermountain Healthcare system and concluded that 90% of the infants with HS were not diagnosed as early as possible. They also found that an MCHC ≥ 36 had 82% sensitivity and 98% specificity for identification of HS.⁶ Elevated MCHC values are also seen in direct antiglobulin test positive hemolytic anemia. However, Christiansen and Henry found the MCHC values significantly higher in HS patients and noted that a negative antiglobulin test essentially eliminates the diagnosis of antibody-mediated hemolytic anemia.

Our study certainly confirms that elevated MCHC and/or RDW imply HS regardless of the age of the patient. Every patient with available data had an elevated MCHC and/or RDW both in infancy (Figure 1(a) and (b)) and at post-infancy baseline (Table 1). Combined with a history of NJ and a positive family history (often not obtained), these features very strongly suggested HS. Unlike the prior larger studies, we obtained detailed follow up and focused on severe anemia or aplastic crisis as the initial presentation of HS in undiagnosed patients. We sought to determine whether patients hospitalized for aplastic crises might have been diagnosed prior to that event, based on a routine CBC as well as patient and family history. We did not consider the retic count in this analysis since this is not routinely ordered by primary care physicians.

A recent policy statement from the American Academy of Pediatrics⁹ recommends routine screening for anemia via determination of Hgb value at 12 months of age (unless evaluated at an earlier age for clinical reasons). This statement

indicates that only 40% of anemia detected via such screening is due to iron deficiency. While the statement does not mention obtaining a CBC, we would suggest that a CBC (preferably with a retic count) as well as family and dietary history be obtained; we believe that findings suggestive of HS via history/MCHC/RDW/retic count should lead to a pediatric hematology referral.

Our study is limited by retrospective data collection and having only 30 patients. However, we tracked the detailed history of each patient and found that all who required admission for emergency transfusions were admitted prior to the diagnosis of HS (Table 2), with 3 of the 10 being admitted to the PICU based on clinical judgments. The mean hemoglobin value for these 10 patients was 5 g/dL. Seven of these 10 patients had a positive family history (only obtained in 2 prior to being seen at our center and not felt to be of significance in either case). All eight of the patients hospitalized between 42 and 183 months of age with severe anemia/aplastic crises had abnormal CBC findings documented between 34 and 157 months prior to their admission. This represents an underestimate of lag time since earliest CBC results could often not be obtained. These eight older patients included six with a positive family history which had either not been obtained (5) or was not appreciated as relating to a diagnosis of HS (1).

Conclusion

Infants and young children with a history of otherwise unexplained NJ and findings of elevated MCHC and/or RDW on a CBC should have their family history carefully examined (mild cases may be unknown to the family and/or have only a history of gallstones), should have a CBC and retic count check and should be referred to pediatric hematology for further evaluation of possible HS.

Earlier referral to pediatric hematology should enable the diagnosis of HS to be established at a younger age, thus reducing the lag time to diagnosis of HS. With an established diagnosis and heightened awareness, it should be possible to monitor patients more closely and detect impending aplastic crisis sooner. We can only hope that that prior diagnosis, education and greater awareness would lead to a lower threshold for checking a CBC/retic count in the mildly symptomatic patient; it is not possible to prove that earlier diagnosis would lead to changes in behavior on the part of parents or primary care physicians. This would not change the need for transfusions but hopefully would allow needed transfusions to be given on an outpatient basis in less

severely anemic patients, as was true for all seven patients being followed up by pediatric hematology, who required transfusions. Potential consequences of severe anemia, such as silent cerebral ischemia and infarction,¹⁰ as well as hospitalization costs could thus be avoided. Additionally, diagnosed patients would be spared the trouble and costs of repeated lab testing aimed at uncovering the cause of the anemia, as is illustrated by the patient (patient 28) described in the “Background” section.

Declaration of conflicting interests

All authors declare no potential conflicts of interest.

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