Heterogeneity of Hemoglobin H Disease in Childhood

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BACKGROUND

Early diagnosis during newborn screening or infancy has enabled the observation of the natural history of hemoglobin H disease, a subtype of α-thalassemia.

METHODS

We analyzed longitudinal clinical data for patients with hemoglobin H disease arising from the deletion of three of four α-globin genes (HbH) and from hemoglobin H Constant Spring (HCS), caused by the deletion of two α-globin genes and the Constant Spring mutation.

RESULTS

We identified 86 patients with hemoglobin H disease (48 through newborn screening). Of these patients, 60 (70%) had HbH, 23 (27%) had HCS, and 3 (3%) had other, nondeletional forms of hemoglobin H disease. The parental ethnic background was Asian in 81% of patients, Hispanic in 5%, and African American in 3%, whereas mixed ancestry was observed in 10% of patients. Among the patients with deletional hemoglobin H disease, 15% had one or both parents with African-American ancestry. Growth was normal in patients with HbH during the first decade, but growth deficits began during infancy in those with HCS. Anemia was more severe in patients with HCS at all ages (P<0.001). Acute worsening of anemia with infections requiring urgent blood transfusion was observed in patients with HCS but not in those with HbH. The probability of receiving at least one transfusion by the age of 20 years was 3% for patients with HbH and 80% for those with HCS (P<0.001). Among patients with HCS, transfusions occurred in 13% of infants and 50% of children under the age of 6 years; splenectomy was associated with a significant improvement in hemoglobin levels (P = 0.01) and a reduction in the number of transfusions.

CONCLUSIONS

HCS should be recognized as a distinct thalassemia syndrome with a high risk of life-threatening anemia during febrile illnesses. HbH was not associated with an increased rate of severe anemia with infections and was managed without blood transfusions. Many patients with these disorders had mixed ethnic backgrounds, which highlights the need for extended newborn screening in populations that are traditionally considered to be at low risk for hemoglobin H disease.
HEMOGLOBIN H DISEASE IS PREVALENT in parts of Asia and around the Mediterranean, as well as in countries with migration from these regions. In this disease, patients have compound heterozygosity for α⁺-thalassemia, which is caused by the deletion of one α-globin gene and is widely distributed, with carrier rates approaching 70% in some areas of the world, and for α⁰-thalassemia, which is caused by the deletion of two α-globin genes in cis and was formerly restricted to populations from certain regions but is now being observed in other ethnic groups. Point mutations in the gene encoding α-globin that lead to α⁺-thalassemia are rare. Among these mutations is the variant that causes hemoglobin Constant Spring (named for the Jamaican community where it was first identified), which is caused by a mutation in the stop codon of the α₂-globin gene that is characterized by 31 extra amino acid residues at the C-terminus of the α chain; this hemoglobinopathy is found predominantly in persons of Southeast Asian ancestry.

Hemoglobin H disease usually arises from the combination of α⁺-thalassemia with deletional α⁺-thalassemia, also called deletional hemoglobin H disease (HbH). Nondeletional hemoglobin H disease, such as hemoglobin H Constant Spring (HCS), is less common but has a more severe clinical course than HbH.

Owing to an increase in the incidence of hemoglobin H disease in the United States, a review was recently undertaken to determine whether this condition should be added to existing newborn screening programs. It was determined that hemoglobin H disease is a well-studied condition, with carrier rates which is caused by the deletion of one α-globin gene and is widely distributed, with carrier rates which are lacking. It was also determined that the availability of such data is essential for formulating public health policy. Hemoglobin H disease can be detected during infancy through routine screening for anemia or at birth through newborn screening, as is performed in California. The diagnosis of hemoglobin H disease in the presymptomatic period has provided the opportunity to study its natural history during childhood.

METHODS

PATIENTS
We followed patients with hemoglobin H disease at Children’s Hospital and Research Center Oakland (CHRCO), using uniform guidelines for management (for details, see the Supplementary Appendix, available with the full text of this article at NEJM.org). Diagnosis was confirmed by thin-layer isoelectric focusing, and specific α-globin gene deletions or mutations were identified by multiplex-gap polymerase-chain-reaction assay. In California, newborn screening with the use of dried blood samples that are analyzed by means of high-performance liquid chromatography was introduced in 1998 after a 2-year pilot program. Samples containing more than 25% hemoglobin Bart’s (a tetramer of γ chains whose level reflects the deficiency of α chains in the fetus) were selected for confirmatory testing at the Hemoglobinopathy Reference Laboratory at CHRCO. Folic acid was prescribed for all patients. Medical records were inspected for clinic visits, growth data, hematologic indexes, and documentation of splenectomy or blood transfusion. Blood samples that were obtained during the 3-month period after transfusion were excluded from analysis.

The study was conducted with approval from the institutional review board, and the requirement for informed consent was waived. The authors contributed to the development of guidelines for clinical management and follow-up of patients.

STATISTICAL ANALYSIS
We compared growth data with World Health Organization standards to calculate age- and sex-specific z scores, including z scores for weight and height according to age and for weight according to height. We measured the liver iron concentration on SQUID (superconducting quantum interference device) biosusceptometry (Ferritometer Model 5700, Tristan Technologies) in micrograms per gram of wet liver and then multiplied by 6 to convert to milligrams per gram of dry liver. We plotted longitudinal trends in hemoglobin and growth and compared HbH with HCS using t-tests, linear regression, and log-rank analyses. We analyzed data for patients under 18 years of age, with the exception of ethnic group, genotype, and iron assessment, for which observations from all patients were combined. Data from some patients in this analysis have been reported previously.
born screening. The diagnosis was HbH in 60 patients (70%), HCS in 23 (27%), and other, non-deletional hemoglobin H disease in 3 (3%). The parental ethnic background was Asian in 70 patients (81%), Hispanic in 4 (5%), and African American in 3 (3%), whereas mixed ancestry was observed in 9 (10%). Among the 60 patients with HbH, the most frequent ethnic backgrounds were Chinese (13 patients, 22%), Filipino (13 patients, 22%), Laotian (8 patients, 13%), and other Asian groups (11 patients, 18%); 15% of patients were of African-American heritage, with both parents identified as African American for 3 patients and one parent for 6 patients (Table 1). The 23 patients in the HCS group were less heterogeneous, with 14 patients (61%) of Laotian ancestry, followed by Chinese ancestry for 5 patients (22%) and Cambodian ancestry for 4 patients (17%).

In the HbH group, the most frequent genotype was the Southeast Asian double-gene deletion with the 3.7-kb deletion in 41 patients (68%), followed by the Filipino type with the 3.7-kb deletion in 10 (17%), the Southeast Asian double-gene deletion with the 4.2-kb deletion in 7 (12%), and the Mediterranean type with the 3.7-kb deletion in 2 (3%). In the HCS group, the disorder was associated with the Southeast Asian double-gene deletion in every case except one, which was the Filipino type.

The median duration of follow-up was 2.6 years (range, 0.1 to 14.6) in the HbH group and 9.7 years (range, 0.3 to 18.2) in the HCS group. The median age at the last follow-up visit was 5.9 years (range, 0.1 to 72.2) in the HbH group and 16.6 years (range, 2.6 to 31.1) in the HCS group. During the period of observation, a single death was recorded from a malignant brain tumor in an adult with HCS.

GROWTH

Growth was significantly delayed in children with HCS, as compared with those with HbH (Fig. 1). The mean (±SD) weight-for-age z score in the HbH group was $-0.06\pm0.42$, as compared with $-0.91\pm0.29$ in the HCS group ($P<0.001$). The height-for-age z score was also significantly lower in the HCS group ($-1.29\pm0.43$), as compared with the HbH group ($-0.43\pm0.49$, $P<0.001$). The mean between-group difference in the height-for-age z score, which favored the HbH group, was less among children between the ages of 6 and 12 years (0.27, $P=0.13$) than among those less than 6 years of age (1.24, $P<0.001$). Weight was proportional to height in both groups (weight-for-height z score, 0.04 in the HbH group and 0.00 in the HCS group; $P=0.31$).

HEMOGLOBIN, RETICULOCYTES, AND BILIRUBIN

There were significant differences in hemoglobin levels between the HbH group and the HCS group (Fig. 2A). In the HbH group, the mean hemoglobin level was 8.5 g per deciliter (range, 6.9 to 10.7) among infants 1 to 3 months of age and 8.6 g per deciliter (range, 7.0 to 10.6) in those 4 to 6 months of age; in the HCS group, the corresponding levels were 7.0 g per deciliter (range, 5.8 to 9.5) and 8.2 g per deciliter (range, 7.0 to 9.9). The mean hemoglobin level increased to 9.4 g per deciliter (range, 7.9 to 11.4) among patients between the ages of 4 and 6 years in the HbH group ($P<0.001$) but was unchanged in the HCS group, at 7.2 g per deciliter.

### Table 1. Disease Occurrence in 86 Patients with Hemoglobin H Disease or Hemoglobin H Constant Spring Disease, According to Ethnic Group.*

<table>
<thead>
<tr>
<th>Ethnic Group</th>
<th>Hemoglobin H†</th>
<th>Hemoglobin H Constant Spring</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>60</td>
<td>23</td>
</tr>
<tr>
<td>Chinese</td>
<td>13</td>
<td>5</td>
</tr>
<tr>
<td>Filipino</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>Laotian</td>
<td>8</td>
<td>14</td>
</tr>
<tr>
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<td>4</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>African American</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Both parents</td>
<td></td>
<td></td>
</tr>
<tr>
<td>One parent‡</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Cambodian</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
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<td></td>
</tr>
<tr>
<td>Hmong</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Other Asian§</td>
<td>4</td>
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</tr>
<tr>
<td>Other¶</td>
<td>3</td>
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</tr>
</tbody>
</table>

* Ethnic group was self-reported.
† Three patients with other forms of nondeletional hemoglobin H disease (two with Chinese ancestry and one with Hispanic ancestry) are not included in this category.
‡ The ethnic backgrounds of the other parent were Vietnamese (one patient), Laotian (one patient), Chinese (one patient), and Hispanic (three patients).
§ This category includes three patients with mixed Asian ethnic background and one patient whose ethnic background was not classified.
¶ All patients in this category had one parent with Asian ethnic background.
deciliter (range, 3.8 to 8.7; P = 0.80). Consequently, the difference in mean hemoglobin levels between the two groups became greater with age, from 1.0 g per deciliter (95% confidence interval [CI], 0.6 to 1.3) in infants to 2.2 g per deciliter (95% CI, 1.7 to 2.8) in older children.

The average mean corpuscular hemoglobin was 16.6 pg (range, 14.3 to 24.7) in the HbH group and 18.6 pg (range, 14.8 to 24.8) in the HCS group (P < 0.001). The average mean corpuscular volume was also higher in the HCS group (65.2 fl; range, 48.7 to 80.7) than in the HbH group (54.0 fl; range, 46.0 to 76.0; P < 0.001). Among patients in the HCS group, the mean corpuscular hemoglobin was 3.4 pg lower and the mean corpuscular volume was 13.4 fl lower when hemoglobin E was co-inherited (P < 0.001 for both comparisons). This effect was not observed in patients with HBH and co-inheritance of hemoglobin E.

The absolute reticulocyte count and bilirubin level were consistently higher in patients with HCS (Fig. 2B and 2C). The mean absolute reticulocyte count was 88,200 per cubic millimeter in the HbH group, as compared with 292,200 per cubic millimeter in the HCS group (P < 0.001). The mean serum bilirubin levels were 0.56 mg per deciliter (9.6 μmol per liter) and 2.53 mg per deciliter (43.3 μmol per liter), respectively (P < 0.001).

**BLOOD TRANSFUSION**

Only one transfusion was given in the HbH group in patients under the age of 20 years. The patient was a 2-year-old boy with severe pneumonia who was receiving mechanical ventilation and who had a hemoglobin level of 7.4 g per deciliter (Fig. 3). This patient did not require another transfusion during 7 years of follow-up. In the HbH group, the probability of transfusion by 20 years of age was 2.8%. Two adults with HbH — a 26-year-old woman who had a hemoglobin level of 7.6 g per deciliter during a febrile illness and a 30-year-old woman who was undergoing surgery — received one transfusion each.

Patients with HCS had a very high risk of severe anemia leading to urgent blood transfusion. The hemoglobin level before the first blood transfusion ranged from 2.0 to 7.4 g per deciliter and was 6 g per deciliter or less in all but one patient. The probability of undergoing at least one transfusion was 13% by the age of 1 year, 39% by the age of 5 years, 75% by the age of 10 years, and 80% by the age of 20 years. The median age at the first transfusion was 5.9 years. The youngest patient with HCS to undergo transfusion was a 3-month-old infant who had a hemoglobin level of 6.0 g per deciliter. Two other infants with HCS underwent transfusion at 4 and 11 months, respectively.

**TRANSFUSION EVENTS**

All episodes of acute worsening of anemia leading to blood transfusion — 45 events in total — occurred in the HCS group. Transfusions were pre-
cipitated by infections in 37 events (82%), with the majority of events (60%) diagnosed as viral illness owing to an unknown source or organism. Among the 37 infection-associated events, pneumonia was diagnosed in 8 events (22%), streptococcal pharyngitis in 2 (5%), and other infections in 3 (8%). Of the 45 total events, 8 (18%) involved transfusion in the absence of febrile illness, and a hospital visit was scheduled either for routine follow-up (6 events) or asthma (2 events).

In 27 episodes for which laboratory tests were obtained, increases in serum bilirubin levels preceding transfusion were observed in most cases, with a mean level of 4.9 mg per deciliter (83.8 μmol per liter), ranging from 0.8 to 11.8 mg per deciliter (13.7 to 201.8 μmol per liter); such increased levels of bilirubin indicated a worsening of hemolysis. The absolute reticulocyte count, which was available for 33 transfusion events, was less than 200,000 per cubic millimeter in 11 events (33%), 200,000 to 300,000 per cubic millimeter in 16 events (48%), and more than 300,000 per cubic millimeter in 6 events (18%). Three episodes of acute parvovirus infection were documented in the HCS group, leading to blood transfusion in 2 patients. The lowest hemoglobin level in the entire
group was observed in a 13-year-old girl in whom the level fell from 8.2 g per deciliter to 2.0 g per deciliter during acute parvovirus infection.

**Splenectomy**

No patient with HbH underwent splenectomy. Five patients with HCS underwent splenectomy between the ages of 3.9 and 13.0 years because of the need for frequent blood transfusion. The average baseline hemoglobin level before splenectomy was 6.8 g per deciliter (range, 6.4 to 7.4), which increased to 9.7 g per deciliter (range, 7.0 to 11.3) after splenectomy (P<0.01). Individual increments in hemoglobin in these five patients after splenectomy were 0.4, 2.8, 3.7, 3.8, and 4.0 g per deciliter. After splenectomy (with all procedures performed by means of laparotomy), portal-vein thrombosis developed in one patient, but no complications were observed in the other patients. Splenectomy reduced or eliminated acute hemolytic episodes requiring urgent transfusion in four of the five patients.

**Iron Overload**

In the HbH group, the serum ferritin levels did not increase significantly between birth and 18 years (P=0.12); the median ferritin level was 40 ng per milliliter (range, 5 to 182), with 18% of values under 20 ng per milliliter and 14% more than 100 ng per milliliter. In patients over the age of 18 years, there was a strong positive correlation between ferritin level and age (P<0.001) (Fig. 4A). In the HCS group, ferritin levels were elevated in young children and continued to increase during follow-up (P=0.002). The median ferritin level was 72 ng per milliliter (range, 1 to 795) at 1 to 2 years of age and 330 ng per milliliter (range, 66 to 1420) at 12 to 17 years (Fig. 4B).

Hepatic iron measurements in three patients in the HbH group and nine patients in the HCS group between the ages of 10.0 and 70.7 years showed a mean liver iron concentration of 10.6 mg per gram of dry liver (range, 1.4 to 29.8 in 29 observations) (Fig. 4C). There was a significant correlation between the liver iron concentration and the serum ferritin level (r=0.54, P=0.002), and the ratio of ferritin (measured in nanograms per milliliter) to the liver iron concentration (measured in micrograms per gram of wet liver) was 0.48 (range, 0.07 to 1.19). No significant correlation was seen between the liver iron concentration and age (r=-0.068, P=0.73).

**Quality of Life**

Patients with HCS had an increased number of annual clinic visits, by a factor of 1.7, and an increased number of annual hospital admissions, by a factor of 3.9, as compared with patients with HbH (P<0.001). However, the physical abilities of children with HCS at baseline were not significantly compromised, as assessed by participation in physical education at school. Chronic fatigue was reported in 3 adults with HCS who had not undergone splenectomy. Among 11 patients with HCS who were older than 20 years of age at the last follow-up visit, the highest level of educational achievement was a college degree in 7, a high school diploma in 3, and less than a high school diploma in 1. Of 8 patients who had completed their education, 4 were employed full time and 3 were employed part time; 1 was a homemaker. Three women were married, and all had had successful pregnancies. Children with HbH had no chronic fatigue, limitation of physical activity, or evidence of learning problems. Limited data from the 5 adults with HbH who were included in follow-up analysis did not suggest a compromise in employment opportunities or family life associated with the disorder.
Our data on longitudinal follow-up of 86 patients with the use of uniform management guidelines suggest that HCS is a clinical entity that is distinct from HbH, distinguished by susceptibility to severe anemia during infectious illness. Patients with HCS have a significant growth delay, require intermittent blood transfusions, have iron overload in the first decade of life, and have a good response to splenectomy. A similar drop in hemoglobin during infection does not occur in patients with HbH, and blood transfusion appears to be unnecessary in the management of this disorder. Although no deaths that were related to thalassemia occurred in our study, the significant risk of life-threatening anemia in patients with HCS indicated the need for careful monitoring and prompt intervention during febrile illness.

Patients with HCS made up 27% of the entire group and 15% of those in whom the disorder was diagnosed through newborn screening. The latter proportion is higher than that reported in statewide data for newborn screening in California, in which 5% of all patients with hemoglobin H disease had HCS.\textsuperscript{8,11} The discrepancy is likely to be the consequence of regional variation in ethnic groups within California and is reflected in the remarkable preponderance of patients with HCS in our study who were Laotian, an ethnic group that accounts for 1.5% of the Asian population in the state.\textsuperscript{14} All the cases with serious clinical symptoms that we observed were in the HCS group, whereas children with HbH had a predictably benign course. Other mutations in the \(\alpha\)-globin gene are likely to be important for determining the phenotype of nondeletional hemoglobin H disease in populations in which the Constant Spring mutation is not prevalent.\textsuperscript{15}

The genotypic data are similar to those in earlier studies from Asia,\textsuperscript{3-5,16-18} showing that the Southeast Asian double-gene deletion with the 3.7-kb deletion was the most frequent genotype for HbH and that there is an almost exclusive

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**Figure 4. Serum Ferritin Levels in Patients with Deletional Hemoglobin H Disease (HbH) and Hemoglobin H Constant Spring Disease (HCS) and Correlation with Liver Iron Concentration.**

The trend for ferritin levels according to age on the basis of linear regression (dashed line) increases after the age of 18 years in patients with HbH (Panel A) and increases from birth to the age of 30 years in those with HCS (Panel B). A significant correlation between the serum ferritin level and liver iron concentration is shown in patients with HbH and HCS, with the dashed line indicating the linear regression of liver iron concentration as compared with ferritin (Panel C).
association between the hemoglobin Constant Spring mutation and the Southeast Asian double-gene deletion. Among patients with HbH, ethnic diversity was evident. Among 15% of patients with HbH, one or both parents were African American, an ethnic group in which α²-thalassemia is very uncommon. Since α²-thalassemia has wide prevalence among several different populations, the number of patients of mixed ethnic background who have HbH is predicted to increase in the United States. This finding has implications for newborn screening and genetic counseling for population groups in which HbH was rarely observed in the past.

Data on growth among patients with HbH during the first decade of life were reassuring, since there was no significant deviation in mean weight or height from the normal population. In contrast, growth deficits in patients with HCS were identified early and were persistent. In a study in Thailand, deficits in z scores were reported for both weight and height according to age in children and adolescents, with a greater height deficit among patients with the nondele-
tional hemoglobin H syndromes. This finding suggests that close attention to growth is required and that nutritional and hematologic associations with growth delay should be evaluated.

The reduction in hemoglobin levels among patients with HCS, as compared with those with HbH, is well recognized and is attributed to the damage to red-cell membranes from precipitation of oxidized chains of hemoglobin Constant Spring. Between-group differences in hemoglobin levels are evident in early infancy, and our data show that this disparity increases from birth to 5 years of age, owing to the increase in hemoglobin levels in patients with HbH. The difference in older children in our series may have been exaggerated by the inclusion of low hemoglobin values in patients with HCS during infectious episodes or from splenomegaly. If the baseline hemoglobin values at steady state are considered, then the difference between HbH and HCS is probably 1.0 g per deciliter rather than 2.2 g per deciliter, as we observed.

The natural history of HCS is distinguished by the acute worsening of anemia during infection, leading to an urgent need for blood transfusion. Half of patients with this disorder undergo transfusion by the age of 6 years, and most patients receive at least one transfusion by the age of 20 years. The need for transfusion in our study was triggered by a drop in the hemoglobin level to less than 6 g per deciliter. The nadir hemoglobin level during febrile episodes is difficult to predict. We recorded hemoglobin levels of 4 g per deciliter or less on several occasions, including one instance of a hemoglobin value of 2.0 g per deciliter (Fig. 2A). Infants with HCS are at risk for severe anemia and may require one or more transfusions by the age of 1 year. This unpredictable and early requirement for blood, albeit in a small proportion of patients, shows that life-threatening anemia may develop in infants before the diagnosis can be made through conventional means in the absence of newborn screening.

Like previous studies, our study showed that transfusion in the absence of fever was uncommon (accounting for 20% of the transfusion episodes). Most febrile illnesses were attributed to viral infection without a specific cause. Fever was accompanied by worsening hemolysis, but the reticulocyte compensation was inadequate in many cases, which may have contributed to the rapidity of the drop in hemoglobin. No patient in our series required long-term use of red-cell transfusion as provided in patients with β-thalassemia major. Indeed, patients with HCS who had symptomatic anemia or needed multiple transfusions benefited from splenectomy. The early assessment of hemoglobin during episodes of fever and preventive approaches, such as annual influenza vaccination, may reduce the occurrence of severe anemia. Substantial fatigue was observed in a subgroup of older patients with HCS, a finding that raises concern that the quality of life of patients may deteriorate with age. This finding is similar to a previous observation on health-related quality of life in patients with β-thalassemia, but our data suggest that adults who have not undergone splenectomy are at increased risk for fatigue. Although these results were limited by the small number of adults who participated in active follow-up, they indicate the need for long-term studies to define quality of life in patients with hemoglobin H syndromes.

In our study, the risk of severe anemia leading to blood transfusion was minimal among patients with HbH. In the 3 patients with HbH who underwent transfusion (1 child and 2 adults), the hemoglobin level before transfusion was more than 7 g per deciliter in each case. We have not observed a hemoglobin value of less than 6.7 g.
per deciliter in 237 patient-years of observation involving 60 patients with HbH. This finding from our single-center study differs considerably from those of previous studies, in which 14 to 42% of patients with HbH underwent transfusion. Our data provide strong support for the expectant management of anemia in patients with HbH during febrile illness. A short-term drop in hemoglobin to a dangerously low level does not appear to be part of the natural history of HbH. Thus, avoiding exposure to blood products is a desirable therapeutic goal. Secondary factors should be sought in patients with HbH in whom severe anemia develops.

Differences in the rate of blood transfusion may partly explain why iron overload arises early in patients with HCS but is delayed until the third decade in patients with HbH. The utilization of iron for physiologic needs during growth may also protect children with HbH from iron overload. In our patients, serum ferritin levels were predictive of liver iron concentrations, but the ratio between ferritin and liver iron concentration was low. Thus, since patients with HbH and HCS can have severe liver iron overload even with a moderate elevation in serum ferritin levels, they should undergo periodic monitoring of liver iron concentration to guide therapy.

Our data support the usefulness of universal newborn screening for hemoglobin H syndromes, since life-threatening anemia can develop in young infants with HCS. We suggest that HCS be recognized as a thalassemia syndrome that is distinct from HbH so that the appropriate treatment approach can be devised for each group.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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