Prevalence and management of iron overload in pyruvate kinase deficiency: report from the Pyruvate Kinase Deficiency Natural History Study

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Prevalence and management of iron overload in pyruvate kinase deficiency: report from the Pyruvate Kinase Deficiency Natural History Study

Pyruvate kinase (PK) deficiency is the most common red cell glycolytic enzyme defect causing hereditary non-spherocytic hemolytic anemia. Current treatments are mainly supportive and include red cell transfusions and splenectomy. Regular red cell transfusions are known to result in iron overload; however, the prevalence and spectrum of transfusion-independent iron overload in the overall PK-deficient population has not been well defined. This analysis describes the prevalence and clinical characteristics of iron overload in patients enrolled in the PK Deficiency Natural History Study (NHS) with a focus on those patients who are not regularly transfused.

The PK deficiency NHS protocol (clinicaltrials.gov identifier: 02053480) was approved by each site’s Institutional Review Board (IRB) and/or Ethics Committee, and study procedures were in accordance with the Declaration of Helsinki. In Lancaster, Pennsylvania, USA, in which all enrolled patients are Amish, additional laboratory and radiological data were collected under a site-specific IRB-approved protocol. All patients gave informed consent. The NHS enrolled 278 patients with PK deficiency from June 2014 through April 2017 at 31 centers in 6 countries. A detailed description of the cohort is published elsewhere. Twenty-four patients were excluded due to the inability to confirm two pathogenic PKLR mutations. Patients under one year old at enrollment were also excluded (n=12) from this analysis, because ferritin is less reliably related to iron overload in this youngest age group, leaving 242 participants reported herein. Patients were defined as regularly transfused if they had received ≥ 6 transfusions in the 12 months prior to enrollment. At enrollment, 82% (198/242) of patients were not receiving regular transfusions; 38% (53/138) of these patients had iron overload as defined by ferritin. The patients with iron overload were older, more anemic, and more often splenectomized, and had a higher median total bilirubin (Table 1).

<table>
<thead>
<tr>
<th>Table 1. Characteristics of non-regularly transfused patients with pyruvate kinase (PK) and iron overload.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ferritin &gt;1000 ng/mL or chelation</strong></td>
</tr>
<tr>
<td><strong>Absent (85/138, 62%)</strong></td>
</tr>
<tr>
<td>Female sex</td>
</tr>
<tr>
<td>Amish</td>
</tr>
<tr>
<td>Age at enrollment (y)</td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
</tr>
<tr>
<td>Absolute reticulocyte count (10^6/L)</td>
</tr>
<tr>
<td>Total bilirubin (mg/dL)</td>
</tr>
<tr>
<td>Ferritin (ng/mL)</td>
</tr>
<tr>
<td>Liver iron concentration (mg/g DW)</td>
</tr>
<tr>
<td>Transferrin saturation (%)</td>
</tr>
<tr>
<td>Splenectomized</td>
</tr>
<tr>
<td>Chelation in prior 12 months</td>
</tr>
<tr>
<td>Never transfused</td>
</tr>
<tr>
<td>&lt;10 lifetime transfusions</td>
</tr>
<tr>
<td>≥10 lifetime transfusions</td>
</tr>
</tbody>
</table>

Numbers are medians (range) or absolute numbers/group total (corresponding percentage). n is shown only for those groups that do not contain the total. *Iron overload by ferritin was defined as the number of patients with ferritin>1000 ng/mL or who were treated with chelation therapy in the 12 months prior to enrollment. If a patient had >1 ferritin measurement in the 12 months prior to enrollment, the maximum ferritin value was used. Iron overload based on liver iron concentration (LIC) was defined as an LIC >3 mg Fe/g dry weight liver (DW) on T2* MRI in the 12 months prior to enrollment or who were treated with chelation therapy in the 12 months prior to enrollment. **P-values of Fisher’s Exact test or Wilcoxon Rank Sum test. ND: Not Done; testing is not appropriate or necessary within the same factor.
Baseline and retrospective clinically available data were used. Serum ferritin levels and quantitative (T2*) liver and heart magnetic resonance imaging (MRI) were used to assess iron overload. Patients were considered to have iron overload if: i) their highest ferritin was over 1000 ng/mL; or ii) they received chelation therapy in the 12 months prior to enrollment; or iii) their highest liver iron concentration (LIC) was >3 mg/g dry weight liver (DW) on T2* MRI; or iv) they had cardiac iron overload as defined by a cardiac T2* ≤20ms at any time in their history. The definition of iron overload as an LIC >3 mg/g DW was based on guidelines for β-thalassemia.3,4 Baseline characteristics and results are listed in Table 1. Of the 242 patients, 175 (72%) had ferritin levels measured within the prior 12 months. The median ferritin was 583 ng/mL (range, 17-5630 ng/mL). The overall prevalence of iron overload as defined by ferritin or chelation was 45% (82/181). Patients without ferritin monitoring had fewer transfusions (1% vs. 25% regularly transfused; P=0.0001) and a higher hemoglobin (Hb) level (median Hb 9.6 vs. 8.8 g/dL; P=0.01) (Online Supplementary Table S1).

An MRI for liver iron assessment was conducted in 65 (27%) patients in the 12 months prior to enrollment; 47 (72%) were from the Amish cohort and were obtained per protocol. Of the patients who were not receiving regular transfusions who had MRI or chelation data available, 82% (67/82) had iron overload as defined by MRI or chelation (Table 1). Of those patients who had never been transfused and had MRI or chelation data available, 6 of 7 patients met criteria for iron overload (6/7 splenectomy).

Magnetic resonance imaging for cardiac iron assessment was available for 75 (31%) patients. Five patients (7%) had cardiac iron overload; only one of these patients had LIC measured (5 mg Fe/g DW). These patients’ ages ranged from 3-34 years with a median number of lifetime transfusions of 39 (range, 10-90).

There were 68 patients aged 1-<10 years old. Of those who were not regularly transfused at enrollment but had received occasional transfusions, 82% (9/11) had iron overload as defined by MRI. The median number of lifetime transfusions in this group was 2.5 (range, 1-9). Of those under 10 years of age who had never been transfused (n=9), MRI was available for only one patient, which confirmed iron overload.

Forty-five patients had paired ferritin and LIC measurements available (Figure 1). Using a ferritin cut off of 1000 ng/mL, the sensitivity to predict LIC >3 mg/g DW was 53% and the specificity was 100%. At a ferritin cut off of 500 ng/mL but an LIC >3 mg/g DW of only 53%. A ferritin >1000 ng/mL is a conservative threshold for reporting the prevalence of iron overload defined by LIC was 82% in non-regularly transfused patients. Although ferritin levels correlated with LIC, ferritin levels of >1000 ng/mL had a sensitivity for LIC >3 mg/g DW of only 53%. A ferritin >1000 ng/mL is a conservative threshold for reporting the prevalence of iron overload given the specificity of 100% but likely underestimates its true prevalence in PK deficiency. Given that the ferritin >500 ng/mL had sensitivity of 90%, this is a better cut off if ferritin is used as a screening test for selecting patients for an MRI.

In this study, in non-regularly transfused patients, iron overload had also already occurred at a very young age. In non-regularly transfused patients, an MRI should be considered annually after one year of transfusions.

In this PK deficiency Natural History Study, the prevalence of iron overload defined by LIC was 82% in non-regularly transfused patients. Although ferritin levels correlated with LIC, ferritin levels of >1000 ng/mL had a sensitivity for LIC >3 mg/g DW of only 53%. A ferritin >1000 ng/mL is a conservative threshold for reporting the prevalence of iron overload given the specificity of 100% but likely underestimates its true prevalence in PK deficiency. Given that the ferritin >500 ng/mL had sensitivity of 90%, this is a better cut off if ferritin is used as a screening test for selecting patients for an MRI.

In this study, in non-regularly transfused patients, iron overload had also already occurred at a very young age. In non-regularly transfused patients, an MRI should be considered at the earliest age when the procedure can be performed without sedation, particularly in patients with ferritin levels >500 ng/mL. In regularly transfused patients, MRI should be considered annually after one year of transfusions.
cardiac iron overload after only 10 lifetime transfusions. Moreover, the youngest patient with cardiac iron overload in this cohort was three years old. This indicates that the number of prior transfusions might not predict which patients are most in need of screening for cardiac iron overload.

In the non-Amish cohort, splenectomy was associated with iron loading. However, this association is not clearly causal. Since splenectomy typically occurs in the more severely affected patients with PK deficiency, other factors associated with splenectomy, such as a lower Hb or increased transfusion burden, may be contributing to this relationship. Further study is needed to understand whether splenectomy is independently associated with iron loading in PK deficiency.

Although the study is biased by its retrospective nature and challenges related to rare disease registries, including variability between diagnostic and treatment standards, the results clearly show that in PK deficiency, there is a high prevalence of iron overload both in regularly transfused and not regularly transfused patients. Ferritin levels below 1000 ng/mL, Hb levels above 9 g/dL, young age, and/or an absence of regular transfusions do not exclude the possibility of iron overload in patients with PK deficiency. Therefore, iron screening is important in all patients with PK deficiency and should be monitored starting in childhood. Regular monitoring for iron overload and treatment, when needed, is imperative to the management of this patient population.


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