Iron Overload Is Highly Prevalent in All Disease Severity States in Pyruvate Kinase Deficiency (PKD)

Eduard J. van Beers, MD, PhD[1], Wilma Barcellini, MD[2], Stefan W. Eber, MD[3], Janet L. Kwiatkowski, MD[4], Jennifer A. Rothman, MD[5], Ellis J. Neufeld, MD, PhD[6], Mukta Sharma, MD, MPH[7], D Holmes Morton, MD[8], Bertil Glader, MD, PhD[9], Nina Kollmar, MD[10], Hassan M. Yaish, MD[11], Jenny M. Despotovic, DO, MS[12], Christine M. Knoll, MD[13], Yves D. Pastore, MD[14], Kevin Kuo, BSc, MD[15], Peter E. Newburger, MD[16], Marcin W Wlodarski, MD[17], Alexis A. Thompson, MD[18], Yaddanapudi Ravindranath, MBBS[19], Winfred C. Wang, MD[20], Heng Wang, MD[21], Joachim Kunz, MD[22], Vicky R. Breakey, BSc, MD, MEd, FRCPC[23], Melissa J. Rose, DO[24], Melissa Rhodes, MD[25], Heather A. Bradeen, MD[26], Sujit Sheth, MD[27], Dongjing Guo, MS[6], Wendy B. London, PhD[6] and Rachael F. Grace, MD[6]

[1]Van Creveldkliniek, University Medical Center Utrecht, Utrecht, Netherlands; [2]Oncohematology Unit Physiopathology of Anemias Unit, Foundation IRCCS Cà Granda Ospedale Maggiore Policlinico, Milan, Italy; [3]Red cell laboratory, Children's Hospital, University Würzburg, Schwerpunktpraxis für Pädiatrische Hämatologie-Onkologie, Munich, Germany; [4]Children's Hospital of Pennsylvania and Perelman School of Medicine of the University of Pennsylvania, Philadelphia, PA; [5]Duke University Medical Center, Durham, NC; [6]Dana Farber Boston Children's Cancer and Blood Disorder Center, Boston, MA; [7]Children's Mercy Hospital, Kansas City, MO; [8]Central Pennsylvania Clinic, Belleville, PA; [9]Stanford University, Lucile Packard Children's Hospital, Palo Alto, CA; [10]Klinikum Kassel GmbH, Kassel, Germany; [11]Primary Children's Hospital, University of Utah, Salt Lake City, UT; [12]Texas Children's Hematology Center, Baylor College of Medicine, Houston, TX; [13]Phoenix Children's Hospital, Phoenix, AZ; [14]CHU SainteJustine, Montreal, QC, Canada; [15]University of Toronto, University Health Network, Ontario, Canada; [16]University of Massachusetts Medical School, Worcester, MA; [17]Division of Pediatric Hematology and Oncology, Department of Pediatrics, University of Freiburg, Freiburg, Germany; [18]Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL; [19]Wayne State University School of Medicine, Children's Hospital of Michigan, Detroit, MI; [20]St. Jude Children's Research Hospital, Memphis, TN; [21]DDC Clinic for Special Needs Children, Middlefield, OH; [22]Zentrum für Kunderund Jugendmedizin, Heidelberg, Germany; [23]McMaster University, Hamilton, ON, Canada; [24]Nationwide Children's Hospital and The Ohio State University College of Medicine, Columbus, OH; [25]University of Mississippi Medical Center, Jackson, MS; [26]The University of Vermont Children's Hospital, Burlington, VT; [27]New York Presbyterian Hospital, Weil Cornell Medical College, New York, NY

BACKGROUND

- Pyruvate Kinase Deficiency (PKD) is the most common glycolytic defect which causes congenital non-spherocytic hemolytic anemia.
- The prevalence of iron overload is not well described for PKD.
- A multicenter Natural History Study has been established to better characterize the spectrum of symptoms and complications of PKD.

OBJECTIVE

- To describe the demographic features and prevalence of iron overload in regularly transfused and non-regularly transfused patients with PKD.

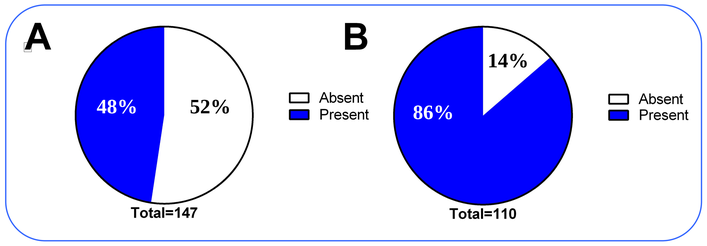
METHODS

- 203 patients enrolled on the Natural History Study at 29 IRB approved sites in North America and Europe from March 2014 to April 2016.
- Participants were confirmed to have two pathogenic *PKLR* mutations.
- Children < 1 year of age (n=9) were excluded from this analysis, because elevated ferritin levels in this age group are less reliably related to iron overload.
- Iron overload was defined as:
  - **Current iron overload**: plasma ferritin >1000 ng/mL or chelation therapy during the 12 months prior to enrollment.
  - **Historic iron overload**: prior MRI showed liver iron content (LIC) >3 mg/g dry weight or ever on chelation therapy.
- Tests of association were performed using Fisher's exact test (categorical) and Wilcoxon rank sum test (continuous). Linear associations between variables were measured by Pearson correlation coefficient.

RESULTS

- Of the 194 patients, 111 (57%) were adults ≥18 years and 83 (43%) were children. The median age at enrollment was 20.6 y (range: 1.3-69.9). Splenectomy had been performed in 65% (126/194).
- Ferritin levels had been completed for 72% (140/194) and MRI LIC for 32% (62/194).
- 48% (70/147) of patients had current iron overload and 86% (95/110) had historic iron overload (Figure 1).

Figure 1. Prevalence of iron overload in PKD



Prevalence of iron overload: **(A)** current iron overload was 48% (70/147), **(B)** historic iron overload was 86% (95/110) .

Table. Iron Status, as defined by ferritin >1000 ng/ml and/or chelation therapy in the 12 months prior to enrollment, and clinical characteristics

	Current Iron Overload		
CHARACTERISTICS	**Absent (n=77)**	**Present (n=70)**	**P**
Female sex	60%	51%	0.3[1]
Amish	35%	21%	0.09[1]
Age at enrollment (y)	20.4 (6.5, 36.6)	28.1 (14.0, 45.7)	0.046[2]
Hemoglobin (g/dl)	9.2 (8.4, 10.2)	8.6 (7.9, 9.1)	0.004[2]
Reticulocyte count (10^9/L)	0.2 (0.1, 0.8) n=30	0.5 (0.2, 0.7) n=21	0.4[2]
Bilirubin (mg/dl)	3.7 (2.4, 4.8) n=69	4.2 (2.8, 6.5) n=59	0.03[2]
Ferritin (ng/ml)	414 (255, 583) n=77	1225 (926, 2100) n=63	<0.0001[2]
LIC (mg/g)	4.0 (2.0, 5.2) n=26	6.0 (4.4, 9.0) n=25	0.0009[2]
Transferrin saturation (%)	40 (33, 56) n=45	71 (46, 87) n=34	0.0003[2]
Splenectomized	57%	81%	0.002[1]
Chelation in prior 12 months	0%	58%	<0.0001[1]
Transfusion Status*			
Never regularly transfused	38%	16%	<0.0001[1]
Historically regularly transfused, currently not regularly transfused	51%	41%	
Regularly Transfused	11%	43%	

[1]-p-value of Fisher's exact test
[2]-p-value of Wilcoxon rank sum test
Numbers are medians (IQR) or percentages
* Transfusion Status was defined by individuals sites

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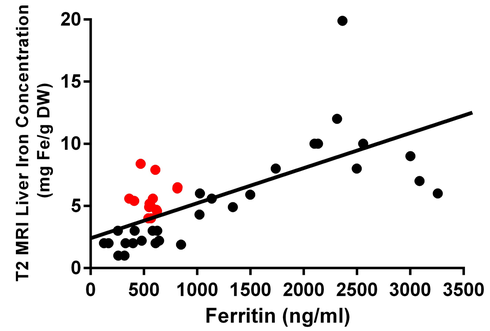
Figure 2. Correlation between ferritin and LIC



Correlation between ferritin and LIC (r=0.62, p<0.0001). Red circles indicate the individuals with a mean ferritin <1000 ng/mL but a LIC >3 mg/g DW.

RESULTS

- Baseline characteristics in patients with and without iron overload are shown in the Table.
- Even patients who were never regularly transfused and had a hemoglobin >8.7 g/dl, the prevalence of iron overload was 26% (8/31).
- The frequency of iron overload was significantly higher in patients who had a prior splenectomy (p<0.0001), even after controlling for transfusion history (p<0.0001). However, Amish patients had a higher rate of splenectomy than non-Amish (96% vs. 52%) but a lower rate of iron overload (34% vs. 51%).
- The frequency of iron overload was significantly higher in those with a lower baseline Hb (p=0.004) and higher bilirubin (p=0.03).
- Age was associated with iron overload (p=0.046); although, the age range of patients with iron overload was broad (1.3-69.9 years).
- Data on cardiac iron status was available for 66 patients. Only 2 had cardiac iron overload (defined as T2* <20 ms); they were age 5 (T2* 17.8 ms, LIC 5 mg/g) and 22 years (T2* 19.7 ms, LIC 14 mg/g) at the time of the MRI.

CONCLUSIONS

- Iron overload is a common, serious complication in PKD, regardless of age, disease severity, or transfusion status.
- The relationship between splenectomy and risk of iron overload needs further exploration.
- Although ferritin correlates with LIC for the PKD population overall, at the individual patient level, ferritin is not a good predictor of LIC and a ferritin <1000 ng/ml does not exclude hepatic iron overload.
- We recommend that all patients with PKD starting at age 1 year should be screened annually for iron overload using ferritin and, at least once, using MRI.

Author Contact Information: Rachael.Grace@childrens.harvard.edu E.J.vanBeers-3@umcutrecht.nl