Characterizing iron overload by age in patients diagnosed with pyruvate kinase deficiency: A descriptive analysis from the Peak Registry

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BACKGROUND

- Pyruvate kinase (PK) deficiency is a rare, congenital, glycolytic enzyme defect caused by mutations in the *PKLR* gene, leading to reduced red cell-specific form of PK (PKR) enzyme activity, defective glycolysis, and decreased red blood cell life span[1,2]
- Despite existing supportive therapies, many patients with PK deficiency experience significant complications, including iron overload[2]
- Iron overload may occur in over 60% of patients with PK deficiency, but remains clinically underappreciated despite the potential to cause long-term organ damage and impact growth in children[2,3]
- To better understand the characteristics and disease burden of patients, the observational PK Deficiency Natural History Study (NHS; NCT02053480) enrolled 254 adult and pediatric patients with PK deficiency at 31 sites across 6 countries between 2014 and 2017, and followed patients for 2 years[4,5]
- The Peak Registry (NCT03481738) was developed as a global retrospective and prospective observational study of patients diagnosed with PK deficiency to continue and expand on the NHS by enrolling approximately 500 adult and pediatric patients at ~60 sites in up to 20 countries[6]

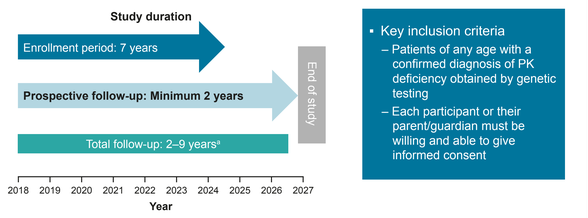
OBJECTIVE

- **To describe the characteristics and disease burden of patients with PK deficiency and a history of iron overload by age group (pediatric cohort, <18 years; adult cohort, ≥18 years) enrolled in the Peak Registry as of the data cut-off date of 24March2020**

METHODS

- The Peak Registry is a global retrospective and prospective observational study of adult and pediatric patients diagnosed with PK deficiency (**Figure 1**)

Figure 1. Study design and duration



[a]Participants in the Peak Registry who were originally included in the NHS and for whom data are integrated within the Peak Registry may have a cumulative follow-up exceeding 11 years; NHS, Natural History Study; PK, pyruvate kinase

- Patients were eligible for inclusion in this analysis if they had available demographic information as of the data cut-off date of 24March2020
- For this analysis, patients were considered to have a history of iron overload if:
  - They had ever received:
    - Chelation therapy
    - Phlebotomy for removal of iron
  - Or within 3 months of enrollment they had any of the following:
    - Ferritin >1000 ng/mL
    - Liver MRI (including FerriScan®) >3 mg Fe/g dry weight
    - Cardiac T2* MRI ≤20 ms
- Data on demographics, medical history, treatment, clinical assessment, and laboratory testing were collected at study enrollment via electronic case report forms
- All analyses reported here were summarized descriptively among patients with a history of iron overload

RESULTS

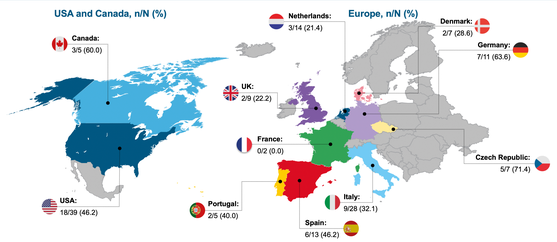
- As of the 24March2020 data cut-off, 41% (57/140) of patients had a history of iron overload based on available data
  - Data from these 57 patients were used for this analysis (**Table 1, Figure 2**)
- 51% (29/57) of patients with a history of iron overload were <18 years of age

Table 1. Baseline demographics of Peak Registry patients with a history of iron overload

Characteristic	Total N=57	Pediatric <18 yrs N=29	Adult ≥18 yrs N=28
Age at enrollment, N'	57	29	28
Mean (SD), yrs	22.2 (18.4)	7.7 (4.6)	37.3 (14.8)
Female, n/N' (%)	25/57 (43.9)	14/29 (48.3)	11/28 (39.3)
Race, n/N' (%)			
Asian	4/48 (8.3)	3/25 (12.0)	1/23 (4.3)
Black or African American	1/48 (2.1)	1/25 (4.0)	0 (0.0)
White	42/48 (87.5)	20/25 (80.0)	22/23 (95.7)
Other	1/48 (2.1)	1/25 (4.0)	0 (0.0)
Ethnicity, n/N' (%)			
Hispanic or Latino	10/50 (20.0)	8/26 (30.8)	2/24 (8.3)
Not Hispanic or Latino	40/50 (80.0)	18/26 (69.2)	22/24 (91.7)

N' represents number of patients with data available; SD, standard deviation; yr, year

Figure 2. Proportion of patients with a history of iron overload in each Peak Registry enrollment country



N represents the total number of patients from each country enrolled in the Peak Registry as of 24March2020; n represents the number of patients with a history of iron overload enrolled in each country

- Most adults had an M/M mutation, whereas almost half of pediatric patients had an M/NM mutation (**Table 2**)
- Around 22% of adult patients had never received a transfusion
- Two-thirds of pediatric patients and nearly 80% of adult patients were non-regularly transfused (0–5 transfusions) in the 12 months prior to enrollment
- Approximately half of pediatric patients and 85% of adults had been splenectomized, with a median age of 6 years at splenectomy

Table 2. Medical history of Peak Registry patients with a history of iron overload

Parameter	Total N=57	Pediatric <18 yrs N=29	Adult ≥18 yrs N=28
Age at PK deficiency diagnosis, N'	53	27	26
Median (range), yrs	1.0 (–1 to 55)[a]	1.0 (–1 to 11)[a]	3.0 (0–55)
Genotype, n/N' (%)			
M/M	16/36 (44.4)	3/15 (20.0)	13/21 (61.9)
M/NM	14/36 (38.9)	7/15 (46.7)	7/21 (33.3)
NM/NM	6/36 (16.7)	5/15 (33.3)	1/21 (4.8)
Never transfused, n/N' (%)	6/56 (10.7)	0/29 (0.0)	6/27 (22.2)
Regularly transfused (≥6 transfusions in the 12 months prior to enrollment), n/N' (%)	13/47 (27.7)	8/24 (33.3)	5/23 (21.7)
# of transfusions over the 12 months prior to enrollment, mean (SD)	10.1 (3.01)	10.6 (3.02)	9.2 (3.11)
Non-regularly transfused (0–5 transfusions in the 12 months prior to enrollment), n/N' (%)	34/47 (72.3)	16/24 (66.7)	18/23 (78.2)
# of transfusions over the 12 months prior to enrollment, mean (SD)	0.8 (1.34)	1.1 (1.45)	0.6 (1.20)
Unknown transfusion frequency, n	9	5	4
Ever had splenectomy, n/N' (%)	39/57 (68.4)	15/29 (51.7)	24/28 (85.7)
Age at splenectomy, N'	36	14	22
Median (range), yrs	6.0 (1–23)	6.0 (4–12)	6.5 (1–23)

N' represents the number of patients with data available; [a]Age at diagnosis values of –1 represent patients suspected of having been diagnosed *in utero*; M/M, missense/missense; M/NM, missense/non-missense; NM/NM, non-missense/non-missense; PK, pyruvate kinase; SD, standard deviation; yr, year

- In never-transfused adult patients, hemoglobin values at enrollment varied from 9.3 to 11.3 g/dL (**Table 3**)
- Median percent reticulocyte count ranged from 6.1 to 31.0% for both never-transfused and ever-transfused patients

Table 3. Baseline hematologic markers in Peak Registry patients with a history of iron overload

Variable	Total N=56		Pediatric <18 yrs N=29		Adult ≥18 yrs N=27	
	Never transfused n=6	Ever transfused n=50	Never transfused n=0	Ever transfused n=29	Never transfused n=6	Ever transfused n=21
Hemoglobin[a], N'	4	32	0	19	4	13
Median (range), g/dL	10.90 (9.3–11.3)	8.40 (6.7–12.5)		8.30 (6.8–10.8)	10.90 (9.3–11.3)	8.60 (6.7–12.5)
Percent reticulocyte count[a], N'	1	13	0	8	1	5
Median (range), %	6.08 (6.1–6.1)	31.00 (2.2–42.5)		11.34 (2.2–42.5)	6.08 (6.1–6.1)	33.95 (27.3–40.7)
Indirect bilirubin[a], N'	3	15	0	7	3	8
Median (range), mg/dL	2.53 (2.2–5.2)	3.83 (1.5–23.1)		3.80 (2.9–6.2)	2.53 (2.2–5.2)	4.38 (1.5–23.1)
Lactate dehydrogenase[a], N'	1	11	0	3	1	8
Median (range), IU/L	420.0 (420–420)	228.0 (135–2949)		206.0 (135–2949)	420.0 (420–420)	233.5 (153–478)

N' represents the number of patients with data available; [a]The highest value within 3 months of enrollment is presented in the event of multiple assessments; IU, international units; yr, year

- Median ferritin levels of ever-transfused adult and pediatric patients were >1100 ng/mL (**Table 4**)
- Almost all ever-transfused patients had received chelation therapy
- Of the 6 patients who had never been transfused, 3 (50%) had received chelation therapy and 3 (50%) had received therapeutic phlebotomy

Table 4. Baseline iron markers in Peak Registry patients with a history of iron overload by transfusion status

Variable	Total N=56		Pediatric <18 yrs N=29		Adult ≥18 yrs N=27	
	Never transfused n=6	Ever transfused n=50	Never transfused n=0	Ever transfused n=29	Never transfused n=6	Ever transfused n=21
Ferritin[a], N'	3	19	0	12	3	7
Median (range), ng/mL	395.9 (308–706)	1164.0 (180–2499)		1104.0 (180–2499)	395.9 (308–706)	1164.0 (506–2263)
Ever had chelation therapy, n/N' (%)	3/6 (50.0)	46/49 (93.9)	0	28/29 (97.0)	3/6 (50.0)	18/20 (90.0)

N' represents the number of patients with data available; [a]The highest ferritin value within 3 months of enrollment is presented in the event of multiple assessments; yr, year

- Patients had iron overload independent of splenectomy status (**Table 5**)
- The majority of patients received chelation therapy independent of splenectomy status and age

Table 5. Baseline iron markers in Peak Registry patients with a history of iron overload by splenectomy status

Variable	Total N=57		Pediatric <18 yrs N=29		Adult ≥18 yrs N=28	
	Splenectomized n=39	Non-splenectomized n=18	Splenectomized n=15	Non-splenectomized n=14	Splenectomized n=24	Non-splenectomized n=4
Ferritin[a], N'	14	8	7	5	7	3
Median (range), ng/mL	1013.2 (180–2499)	877.0 (308–2000)	681.0 (180–2499)	1283.0 (830–2000)	1164.0 (506–2263)	395.9 (308–706)
Ever had chelation therapy, n/N' (%)	35/38 (92.1)	15/18 (83.3)	15/15 (100.0)	13/14 (92.9)	20/23 (87.0)	2/4 (50.0)

N' represents the number of patients with data available; [a]The highest ferritin value within 3 months of enrollment is presented in the event of multiple assessments; yr, year

STRENGTHS AND LIMITATIONS

Strengths

- Peak Registry participants span a broad age range, allowing for robust analyses in both pediatric and adult patients
- The Peak Registry includes trial sites across a variety of geographic regions, which allows for the capture of disease management practices across a diverse patient population
- The breadth of clinical data points collected within the Peak Registry allows for a "history of iron overload" classification that is consistent with clinical practice and previous publications of iron overload in PK deficiency[1,2]

Limitations

- Spontaneous data collection leading to gaps in the available data, consistent with most registries, resulted in low N' numbers for some parameters (eg, ferritin levels), thus making interpretation of the data difficult
- The definition of iron overload used here is limited by the data available; for example, lifetime history data of chelation therapy are available, but other components of the definition, such as ferritin levels, liver MRI, or FerriScan® results, are based only on patients' data in the 3 months leading up to enrollment, suggesting this analysis may underestimate the lifetime prevalence of iron overload in the cohort
- Since many participating sites are considered Centers of Excellence, their associated patterns of testing, screening for complications, and disease management may not be representative of the entire PK deficiency healthcare treatment community

CONCLUSIONS

- **Iron overload is a common complication in PK deficiency, affecting 41% of patients in this cohort, which occurs regardless of age, genotype, splenectomy status, or transfusion status**
- **Iron overload occurs in both adult and pediatric patients who are not regularly transfused, and even in patients who have never been transfused, independent of hemoglobin level**
- **An evaluation and regular monitoring of iron overload in all patients with PK deficiency, independent of transfusion status, splenectomy history, or genotype, should be started early in life and should continue throughout adulthood**

The longitudinal (up to 9 years) design of the Peak Registry will allow for continued monitoring and follow-up of iron overload and related long-term complications in patients with PK deficiency

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References: 1. Tanaka KR et al. *Blood* 1962;19(3):267–95. **2.** Boscoe AN et al. *Eur J Haematol* 2021;106(4):484–92. **3.** Chonat S et al. *Pediatr Blood Cancer* 2021;68(9):e29148. **4.** Grace RF et al. *Blood* 2018;131(20):2183–92. **5.** van Beers EJ et al. *Haematologica* 2019;104(2):e51–3. **6.** Grace RF et al. *Blood* 2019;134:(Suppl. 1):2223.

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