Comorbidities and complications in pediatric patients with pyruvate kinase deficiency enrolled in the Peak Registry

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BACKGROUND

- Pyruvate kinase (PK) deficiency is a rare hemolytic anemia caused by mutations in the *PKLR* gene[1]
- PK deficiency and its supportive treatments are associated with a wide spectrum of comorbidities and complications[2,3]
- Data indicate there is a high disease burden in pediatric patients with this condition, although the full breadth of clinical presentations and complications has yet to be fully characterized[2,4]
- To better understand the longitudinal clinical implications of PK deficiency, including the natural history of the disease, treatments and outcomes, and the variability in clinical manifestations and disease burden, the Pyruvate Kinase Deficiency Global Longitudinal (Peak) Registry (NCT03481738) was initiated in 2018[5]
- The Peak Registry is a global, retrospective and prospective, observational study of patients with PK deficiency, with a targeted enrollment of up to 500 adult and pediatric patients at ~60 sites in up to 20 countries[5]

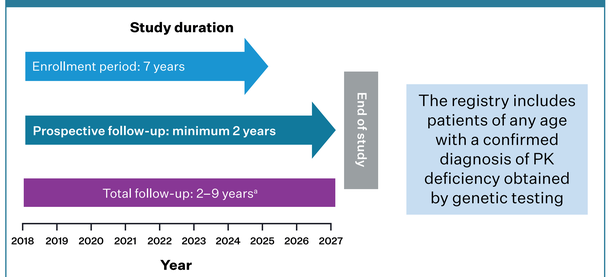
OBJECTIVE

- **To further describe the comorbidities and complications experienced by pediatric patients with PK deficiency in the Peak Registry**

METHODS

- The Peak Registry opened for enrollment in 2018 and will continue enrolling until early 2025
- All participants are followed prospectively for at least 2 years and for up to 9 years (**Figure 1**)

Figure 1. Peak Registry study design and duration



[a]Participants in the Peak Registry who were originally included in the PK Deficiency Natural History Study from 2014 to 2017 and for whom data are integrated within the Peak Registry may have a cumulative follow-up exceeding 11 years
PK, pyruvate kinase

- This analysis included pediatric patients (<18 years) with available age and classifiable *PKLR* genotype data as of 01December2021
- Patients were grouped into cohorts by age at enrollment (<6, 6–<12, 12–<18 years) and genotype (missense/missense [M/M]; missense/non-missense [M/NM]; non-missense/non-missense [NM/NM])
- Demographic data, laboratory values, and medical history inclusive of comorbidities and complications were described for all patients with available data
  - Continuous variables were summarized using mean, SD, median, and range
  - Categorical variables were summarized by number and proportion of patients within a category
- Categories of comorbidities and complications with high clinical significance to the neonatal and pediatric PK deficiency population were included in this analysis (Supplemental information [QR code] contains the full list of comorbidities and complications collected)[2,4]

RESULTS

Baseline characteristics

- As of 01December2021, 81 pediatric patients in the registry had available age and classifiable *PKLR* genotype data
- Baseline characteristics are shown in **Table 1**

Medical history

- The majority (91%) of patients had received ≥1 transfusion (ever transfused) prior to or at enrollment (**Table 1**), with younger patients (<6 years) numerically more likely to have been ever transfused
- Most patients had a history of iron overload, regardless of age or genotype

Table 1. Baseline characteristics and medical history

	All patients	Patients by age			Patients by genotype		
	N=81	<6 yrs n=34	6–<12 yrs n=30	12–<18 yrs n=17	M/M n=43	M/NM n=28	NM/NM n=10
Baseline characteristics							
Age at enrollment, mean (SD), yrs	7.0 (4.69)	2.4 (1.67)	8.3 (1.93)	13.7 (1.53)	7.0 (4.63)	5.9 (4.51)	9.6 (4.79)
Female, n (%)	43 (53.1)	19 (55.9)	12 (40.0)	12 (70.6)	25 (58.1)	12 (42.9)	6 (60.0)
Medical history							
Age at PK deficiency diagnosis,[a] N'	77	34	28	15	41	26	10
Median (range), yrs	1.0 (–1 to 14)[b]	0.0 (–1 to 4)[b]	1.0 (–1 to 11)[b]	6.0 (–1 to 14)[b]	0.0 (–1 to 14)[b]	0.0 (0–11)	2.0 (–1 to 11)[b]
Never transfused, n/N' (%)	7/79 (8.9)	2/34 (5.9)	3/28 (10.7)	2/17 (11.8)	3/42 (7.1)	4/27 (14.8)	0/10 (0.0)
Ever transfused, n/N' (%)	72/79 (91.1)	32/34 (94.1)	25/28 (89.3)	15/17 (88.2)	39/42 (92.9)	23/27 (85.2)	10/10 (100.0)

The number of patients with known results (denoted as N') was used as the denominator in calculation of percentage. Patients with data missing, or with response as "Not Reported" or "Not Done" were excluded from the denominator; [a]Age at PK deficiency diagnosis = year of PK deficiency diagnosis – year of birth; [b]Age of PK deficiency diagnosis of –1 may represent patients diagnosed *in utero*
M/M, missense/missense; M/NM, missense/non-missense; NM/NM, non-missense/non-missense; PK, pyruvate kinase; yr, year

Hematologic and iron markers at enrollment

- Median (range) hemoglobin in the M/M, M/NM, and NM/NM cohorts was 8.9 g/dL (6.2–12.3), 8.5 g/dL (5.8–11.5), and 7.5 g/dL (7.1–8.3), respectively (**Table 2**)
- Overall, the median (range) indirect bilirubin level was 3.13 mg/dL (0.6–12.0)
- The median (range) ferritin level in the cohort was 714 µg/L (51–2997); median ferritin levels tended to be highest in younger children, associated with transfusion frequency (<6 years: 829 µg/L [123–2000]; 6–<12 years: 698 µg/L [51–2997]; 12–<18 years: 451 µg/L [102–2499])

Table 2. Hematologic and iron markers at enrollment

	All patients	Patients by age			Patients by genotype		
	N=81	<6 yrs n=34	6–<12 yrs n=30	12–<18 yrs n=17	M/M n=43	M/NM n=28	NM/NM n=10
Hemoglobin, N'	47	15	22	10	25	14	8
Median (range), g/dL	8.4 (5.8–12.3)	8.6 (5.8–12.3)	8.5 (7.1–12.0)	8.0 (6.8–11.4)	9.0 (6.2–12.3)	8.5 (5.8–11.5)	7.6 (7.1–8.3)
Reticulocyte percent, N'	16	8	7	1	12	3	1
Median (range), %	7.0 (2.2–42.5)	3.8 (2.2–29.1)	9.1 (3.6–42.5)	34.8 (34.8–34.8)	7.0 (3.2–42.5)	3.9 (2.2–29.1)	9.3 (9.3–9.3)
Indirect bilirubin, N'	28	9	14	5	16	9	3
Median (range), mg/dL	3.13 (0.6–12.0)	3.16 (0.9–7.1)	3.00 (0.6–12.0)	3.90 (2.4–8.7)	2.90 (0.6–7.1)	3.90 (0.9–8.7)	3.90 (3.8–12.0)
Lactate dehydrogenase, N'	23	8	10	5	16	6	1
Median (range), U/L	568 (135–2949)	807 (526–2949)	489 (206–1551)	598 (135–1798)	579 (135–1798)	500 (206–1081)	2949 (2949–2949)
Ferritin, N'	23	7	10	6	12	7	4
Median (range), µg/L	714 (51–2997)	829 (123–2000)	698 (51–2997)	451 (102–2499)	698 (51–1073)	864 (102–2997)	1127 (264–2499)

The number of patients with known results (denoted as N') was used as the denominator in calculation of percentage. Patients with data missing, or with response as "Not Reported" or "Not Done" were excluded from the denominator; M/M, missense/missense; M/NM, missense/non-missense; NM/NM, non-missense/non-missense; yr, year

Prenatal/neonatal management, comorbidities, and complications[a]

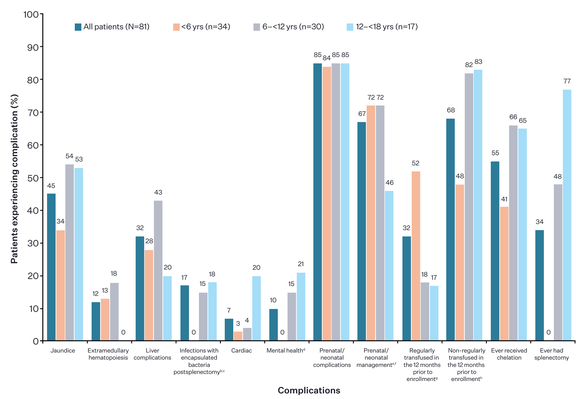
- The most common exam findings in neonates were neonatal jaundice (69%), hepatomegaly (21%), and splenomegaly (21%) (**Supplemental table 1** [QR code])
- Abnormal lab findings in neonates were common: anemia (62%), thrombocytopenia (20%), and hyperferritinemia (7%) (**Supplemental table 1** [QR code])
- Prenatal/neonatal complications occurred in most patients (85%), including preterm delivery (14%), pulmonary hypertension (7%), hepatopathy/hepatic failure/cholestasis (7%), cutaneous extramedullary hematopoiesis (4%), coronary artery disease (3%), *in utero* growth retardation (3%), and hydrops fetalis (1%) (**Figure 2, Supplemental table 1** [QR code])
- Prenatal/neonatal management was required in approximately two-thirds of patients, including phototherapy (52%) and exchange transfusion (24%) (**Figure 2, Supplemental table 2** [QR code])

Comorbidities and complications in pediatric patients[a]

- Liver complications, including fatty liver, cirrhosis, and hepatomegaly, occurred in 32% of patients and were common across age and genotype subgroups (**Figure 2, Figure 3**)
- In the 12 months prior to enrollment, 33% had received regular transfusions (≥6 transfusions in that period), with younger patients receiving regular transfusions more frequently (**Figure 2**)
- Lifetime history of splenectomy and chelation therapy was generally higher in older pediatric age groups and varied by genotype (**Figure 2, Figure 3**)
- Bone fracture and bone pain were the most common bone health problems (5% and 4%, respectively) (**Supplemental table 3** [QR code])
- Other notable complications were biliary events (21%), extramedullary hematopoiesis (12%), and cardiac complications (7%) including pulmonary hypertension (4%) (**Supplemental table 3, Supplemental table 4** [QR code])
- Approximately 10% of patients reported mental health issues including depression and anxiety (**Figure 2, Supplemental table 6** [QR code])

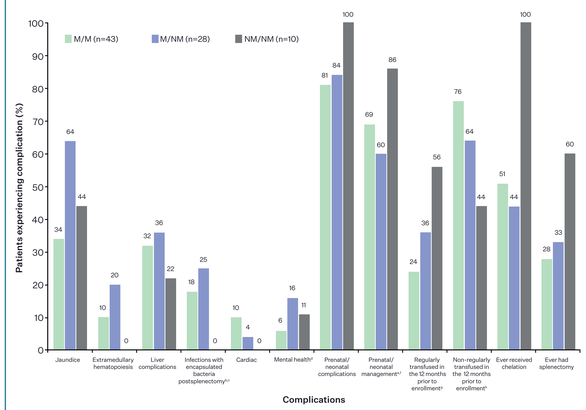
[a]Comorbidities and complications are derived from baseline and/or follow-up data

Figure 2. Lifetime history of comorbidities, complications, and management in each age group[a]



[a]Comorbidities and complications are derived from baseline and/or follow-up data; [b]Denominator is subjects with splenectomy and known infectious history; [c]n=1 non-specified infection; [d]n=1 non-specified mental health condition; [e]Liver transplant is 0/67; [f]n=3 non-specified prenatal/neonatal treatment; [g]≥6 transfusions in the 12 months prior to enrollment; [h]0–5 transfusions in the 12 months prior to enrollment; yr, year

Figure 3. Lifetime history of comorbidities, complications, and management in each genotype group[a]



[a]Comorbidities and complications are derived from baseline and/or follow-up data; [b]Denominator is subjects with splenectomy and known infectious history; [c]n=1 non-specified infection; [d]n=1 non-specified mental health condition; [e]Liver transplant is 0/67; [f]n=3 non-specified prenatal/neonatal treatment; [g]≥6 transfusions in the 12 months prior to enrollment; [h]0–5 transfusions in the 12 months prior to enrollment; M/M, missense/missense; M/NM, missense/non-missense; NM/NM, non-missense/non-missense

SUMMARY

- **Pediatric patients with PK deficiency experience a wide range of comorbidities and complications, even at an early age and regardless of genotype**
- **Neonates have varied presentations and complications (eg, hyperferritinemia, hepatic failure, thrombocytopenia, pulmonary hypertension) that may be difficult to recognize as PK deficiency, potentially leading to initial misdiagnosis and unnecessary treatments**

Awareness of the variable manifestations of PK deficiency may help clinicians appropriately diagnose, monitor, and manage pediatric patients

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