Age of onset of complications in patients with pyruvate kinase deficiency: Analysis from the Peak Registry

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BACKGROUND

- Pyruvate kinase (PK) deficiency is a rare, hereditary form of anemia[1]
- Chronic hemolysis is the primary consequence of PK deficiency, which leads to a spectrum of complications[1–3]
- Patients may develop certain complications at an early age, due to the disease or side effects of supportive treatments, and they may have greater prevalence of complications at an earlier or later age than experienced by the general population[1–3]
- The Pyruvate Kinase Deficiency Global Longitudinal (Peak) Registry (NCT03481738) was initiated in 2018 as a retrospective and prospective observational study to provide insight into the disease burden and longitudinal effects of PK deficiency[4]
- The Peak Registry aims to enroll up to 500 adult and pediatric patients at ~60 sites in up to 20 countries[4]

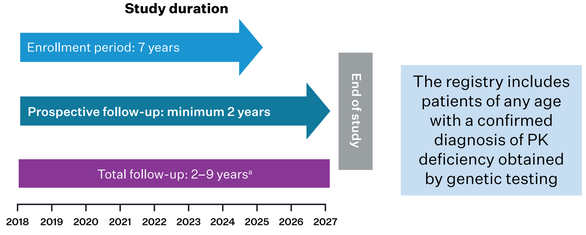
OBJECTIVE

- **To describe the age of onset and age distribution of select symptoms, comorbidities, and complications in patients with PK deficiency enrolled 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



The registry includes patients of any age with a confirmed diagnosis of PK deficiency obtained by genetic testing

[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 patients with available age data as of 01December2021
- Data on demographics, laboratory values, and medical history, inclusive of comorbidities and complications and their onset dates, were summarized descriptively
  - Baseline characteristics, medical history, and laboratory values were summarized by pediatric (<18 years of age) and adult patients (≥18 years of age)
  - Continuous variables were summarized using number of patients, mean, SD, median, and range, excluding patients for whom the response was "Unknown"
  - Categorical variables were summarized by the number and proportion of patients within each category, excluding patients for whom the response was "Unknown"
- Data on comorbidities and complications represented the lifetime history (from birth through most recent registry follow-up visit), except for iron overload
  - History of iron overload was evaluated up to registry enrollment only

RESULTS

Baseline characteristics

- A total of 218 patients (101 pediatric patients, <18 years; 117 adult patients, ≥18 years) with available age data were included (**Table 1**)
- The median (range) age at enrollment was 19 years (0–77)

Medical history

- 44.5% (94/211) of patients had been splenectomized prior to enrollment, at a median (range) age of 6 years (1–27) (**Table 1**)
- 44.6% (90/202) of patients had received chelation therapy prior to enrollment
- 25.6% (53/207) of patients had never received a transfusion
- Of patients with transfusion frequency data in the 12 months prior to enrollment, 18.0% (33/183) were regularly transfused (≥6 transfusions) and 82.0% (150/183) were non-regularly transfused (0–5 transfusions) during those 12 months

Table 1. Baseline characteristics and medical history

	All patients	Patients by age	
	N=218	<18 yrs n=101	≥18 yrs n=117
Baseline characteristics			
Age at enrollment, median (range), yrs	19 (0–77)	6 (0–17)	33 (18–77)
Female, n (%)	120 (55.0)	53 (52.5)	67 (57.3)
Medical history			
Age at PK deficiency diagnosis,[a] N'	206	97	109
Median (range), yrs	3 (–1 to 68)[b]	1 (–1 to 17)[b]	15 (0–68)
Never transfused, n/N' (%)	53/207 (25.6)	10/99 (10.1)	43/108 (39.8)
Ever transfused, n/N' (%)	154/207 (74.4)	89/99 (89.9)	65/108 (60.2)
Transfusion status over the 12 months prior to enrollment			
Regularly transfused (≥6 transfusions in the 12 months prior to enrollment), n/N' (%)	33/183 (18.0)	24/87 (27.6)	9/96 (9.4)
# of transfusions over the 12 months prior to enrollment, mean (SD)	9.8 (3.01)	9.6 (2.60)	10.2 (4.06)
Non-regularly transfused (0–5 transfusions in the 12 months prior to enrollment), n/N' (%)	150/183 (82.0)	63/87 (72.4)	87/96 (90.6)
# of transfusions over the 12 months prior to enrollment, mean (SD)	0.6 (1.25)	1.1 (1.62)	0.3 (0.69)
Unknown transfusion frequency, n	30	12	18
Ever had splenectomy, n/N' (%)	94/211 (44.5)	31/100 (31.0)	63/111 (56.8)
Age at splenectomy, N'	90	30	60
Median (range), yrs	6 (1–27)	5 (2–12)	6 (1–27)
Ever had chelation therapy, n/N' (%)	90/202 (44.6)	49/98 (50.0)	41/104 (39.4)

The number of patients with known results (denoted as N') was used as the denominator in the 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 represents patients diagnosed *in utero*; PK, pyruvate kinase; yr, year

Hematologic and iron markers

- At enrollment, median (range) hemoglobin in the overall cohort was 9.0 g/dL (5.8–18.3) (**Table 2**)
- The median (range) ferritin level in the cohort was 664 µg/L (17–6208); median ferritin levels tended to be higher in pediatric patients (<18 years: 782 µg/L [51–3547]; ≥18 years: 460 µg/L [17–6208])

Table 2. Hematologic and iron markers at enrollment

	All patients	Patients by age	
	N=218	<18 yrs n=101	≥18 yrs n=117
Hemoglobin, N'	117	54	63
Median (range), g/dL	9.0 (5.8–18.3)	8.5 (5.8–14.4)	9.5 (6.7–18.3)
Reticulocyte percent, N'	43	17	26
Median (range), %	6.2 (1.8–42.5)	5.3 (1.8–42.5)	7.6 (2.6–40.7)
Indirect bilirubin, N'	62	28	34
Median (range), mg/dL	2.90 (0.6–12.0)	3.13 (0.6–12.0)	2.47 (0.7–9.1)
Lactate dehydrogenase, N'	62	25	37
Median (range), U/L	245 (133–2949)	568 (135–2949)	217 (133–849)
Ferritin, N'	72	27	45
Median (range), µg/L	664 (17–6208)	782 (51–3547)	460 (17–6208)

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

Age of onset of complications

- The most common comorbidities in the cohort included iron overload (48.6%), mental health issues (14.2%), cholecystitis (13.9%), liver disease (10.2%), osteopenia (5.5%), osteoporosis (2.5%), deep vein thrombosis (5.3%), and pulmonary hypertension (4.6%) (**Table 3**)
- The median (range) age of onset was 27 years (9–74) for mental health issues; 25.0% had onset <18 years of age
- Liver disease often occurred early in patients with PK deficiency, with half of patients having onset age <2 years, and a median (range) onset age of 1 year (0–57)
- Median (range) age of onset was 35 years (9–76) for osteopenia and 33 years (9–64) for osteoporosis

History of iron overload[a,b]

- Iron overload often occurred at an early age (72.9% had onset at <18 years), with a median (range) age of onset of 5 years (0–68) (**Table 3**)
- Onset of iron overload also occurred in adulthood (14.1% aged 18–<40 years; 11.8% aged 40–<65 years)
- In patients who were regularly transfused in the 12 months prior to enrollment (≥6 transfusions), 75.8% had a history of iron overload, with a median (range) age of onset of 3 years (1–45), vs 42.2% of patients who were non-regularly transfused in the 12 months prior to enrollment (0–5 transfusions), with a median (range) age of onset of 6 years (1–68)
- Iron overload occurred in 15.1% of patients who had never been transfused, with a median (range) age of onset of 50.5 years (47–68)

Table 3. Lifetime prevalence and age of onset of select complications, comorbidities, and management in patients with PK deficiency

Comorbidity or complication	Lifetime prevalence, n/N' (%)	Total patients with known complication onset age, n	Complication onset age, n							Onset age, median (range), yrs
			0–<2 yrs (n=11)	2–<12 yrs (n=66)	12–<18 yrs (n=24)	18–<40 yrs (n=74)	40–<65 yrs (n=36)	≥65 yrs (n=7)		
Liver disease[a]	20/196 (10.2)	20	10	5	0	1	4	0		1.0 (0–57)
Hepatitis B	7/201 (3.5)	7	0	2	0	4	1	0		29.0 (4–51)
Hepatitis C	3/199 (1.5)	3	0	2	0	1	0	0		5.0 (2–21)
Sepsis	9/199 (4.5)	9	5	2	0	1	1	0		1.0 (0–47)
Pulmonary hypertension	9/196 (4.6)	6	3	0	1	1	0	1		8.0 (0–77)
Pulmonary embolism	4/94 (4.3)	4	0	0	0	3	1	0		31.0 (18–55)
Deep vein thrombosis	5/94 (5.3)	5	0	0	0	3	1	1		35.0 (29–66)
Portal vein thrombosis	3/94 (3.2)	3	0	0	0	3	0	0		24.0 (23–26)
Osteopenia	11/199 (5.5)	9	0	1	1	4	2	1		35.0 (9–76)
Osteoporosis	5/199 (2.5)	5	0	1	0	2	2	0		33.0 (9–64)
Cholecystitis	28/201 (13.9)	23	0	7	7	7	2	0		15.0 (3–58)
Cholangitis	1/199 (0.5)	1	0	1	0	0	0	0		7.0 (7–7)
Mental health (including depression and anxiety)[b]	26/183 (14.2)	20	0	2	3	10	3	2		27.0 (9–74)
History of iron overload[c,d]	102/210 (48.6)	85	7	49	6	12	10	1		5.0 (0–68)
Lifetime transfusion history										
Never transfused	8/53 (15.1)	6	0	0	0	0	5	1		50.5 (47–68)
Transfusion history in the 12 months prior to enrollment										
Regularly transfused[e]	25/33 (75.8)	25	1	19	3	1	1	0		3.0 (1–45)
Non-regularly transfused[f]	62/147 (42.2)[g]	51	5	27	2	8	8	1		6.0 (1–68)
Splenectomy	90/94 (95.7)	90	2	76	7	5	0	0		6.0 (1–27)

N' represents the number of patients with data available; [a]Liver disease combines terms "Cirrhosis," "Non-alcoholic fatty liver disease," and "Non-alcoholic steatohepatitis"; [b]n=3 non-specified mental health conditions; [c]For lifetime prevalence, history of iron overload defined at enrollment as ever having received: 1) chelation therapy; 2) phlebotomy for removal of iron; or within 3 months of enrollment had any of: 3) ferritin >1000 µg/L; 4) liver MRI (including FerriScan®) >3 mg Fe/g dry weight; 5) cardiac T2* MRI ≤20 ms; [d]For age distribution, iron overload defined as a history of "ever chelation" or "ever phlebotomy"; [e]≥6 transfusions in the 12 months prior to enrollment; [f]0–5 transfusions in the 12 months prior to enrollment; [g]3 patients did not have available data to determine history of iron overload; MRI, magnetic resonance imaging; PK, pyruvate kinase; yr, year

Ongoing jaundice

- Of 67 patients with jaundice and known onset age, median (range) age at onset was 0 years (0–54)
- Of these patients, 69.7% (46/66)[c] had ongoing jaundice at enrollment, 41.3% of whom were aged 18–<40 years (**Table 4**)
  - The overall median (range) age of patients with ongoing jaundice was 16.5 years (0–50)

[a]For lifetime prevalence, history of iron overload defined at enrollment as ever having received: 1) chelation therapy; 2) phlebotomy for removal of iron; or within 3 months of enrollment had any of: 3) ferritin >1000 µg/L; 4) liver magnetic resonance imaging (including FerriScan®) >3 mg Fe/g dry weight; 5) cardiac T2* MRI ≤20 m
[b]For age distribution, iron overload defined as a history of "ever chelation" or "ever phlebotomy"
[c]n=1 missing "is condition ongoing"

Table 4. Number of patients who experienced jaundice and the age of patients with ongoing jaundice

Complication or comorbidity	Lifetime prevalence (total patients who experienced event), n/N' (%)	Ongoing jaundice (N =46)						
		Analysis age, n/N'						Age at enrollment, median (range), yrs
		0–<2 yrs	2–<12 yrs	12–<18 yrs	18–<40 yrs	40–<65 yrs	≥65 yrs	
Jaundice[a]	81/193 (42.0)	3/46	12/46	9/46	19/46	3/46	0/46	16.5 (0–50)

Number of patients with known results (denoted as N') was used as the denominator in the calculation of percentages. Patients with data missing, or with response as "Not Reported" or "Not Done" were excluded from the denominator; [a]Includes 1 patient diagnosed with jaundice twice; yr, year

SUMMARY

- **Patients with PK deficiency have experienced a wide range of comorbidities and complications throughout their lives, many of which occurred at an early age**
- **Patients aged 18–<40 years not only commonly experienced jaundice and iron overload, but many patients also reported mental health issues**
- **Osteopenia, osteoporosis, liver disease, and cholecystitis were observed at young ages, earlier than would be expected in the general population[5–7]**
- **Commonly observed very early in life, jaundice is a symptom that continues unresolved for many patients with PK deficiency well into adulthood**

Clinicians, including pediatric specialists, should be aware of the complications from PK deficiency and the importance of early, regular monitoring, which could lead to improvements in prevention and outcomes for these patients

Acknowledgments: We would like to thank the patients and study investigators for taking part in this study (full list of investigators can be accessed via the QR code). Editorial assistance was provided by Alex Watson, MSc, Adelphi Communications, Macclesfield, UK, and supported by Agios Pharmaceuticals, Inc.

Disclosures: This study was funded by Agios Pharmaceuticals, Inc.

A Glenthøj: Agios, bluebird bio, Bristol Myers Squibb, Novartis, Novo Nordisk, Pharmacosmos – consultancy/advisory board; Saniona, Sanofi – research support; **RF Grace:** Agios, Novartis, Sobi – research funding; Agios, Sanofi – consulting; **EJ van Beers:** Agios – advisory board member; Agios, Novartis, Pfizer, RR Mechatronics – research funding; **J-L Vives Corrons:** nothing to disclose; **B Glader:** Agios – consultancy; **KHM Kuo:** Agios, Alexion, Apellis, bluebird bio, Celgene, Novartis, Pfizer – consultancy; Alexion, Novartis – honoraria; Bioverativ – membership on an entity's Board of Directors or advisory committees; Pfizer – research funding; **C Lander:** Agios PK Deficiency Patient Advocacy Advisory Council – patient representative; **D Pospíšilová:** nothing to disclose; **H Kanno:** nothing to disclose; **J Williams:** Agios – employee and shareholder; **Y Yan:** Agios – employee and shareholder; **B McGee:** Agios – employee and shareholder; **P Bianchi:** Agios – scientific advisor

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Presented at the 64th American Society of Hematology (ASH) Annual Meeting and Exposition, December 10–13, 2022, New Orleans, LA, USA, and Virtual