The characteristics of pediatric patients with pyruvate kinase deficiency and iron overload

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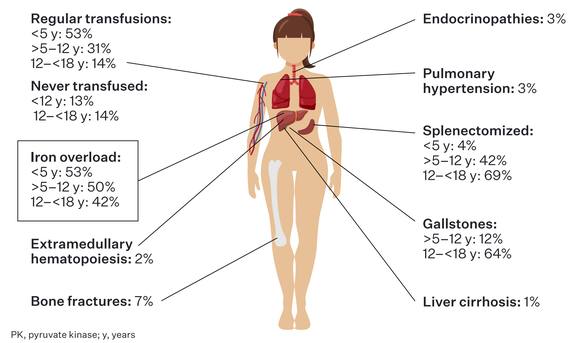
BACKGROUND

- Pyruvate kinase (PK) deficiency is a rare, lifelong condition that results in chronic hemolytic anemia and serious complications such as iron overload (**Figure 1**)[1–4]
- Iron overload occurs in transfused and non-transfused patients with PK deficiency[5]
- The accumulation of iron promotes oxidative damage in various organs, which can induce endocrine and end-organ dysfunction[6]
- Chelation therapy is the mainstay of clinical management of iron overload in patients with PK deficiency; however, chelation therapy may be associated with clinical complications and also worsen health-related quality of life[4,6,7]

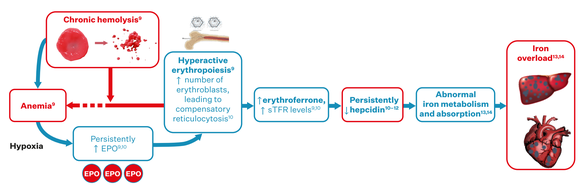
Figure 1. PK deficiency in children and adolescents[8]



PK, pyruvate kinase; y, years

- Chronic hemolysis combined with hyperactive erythropoiesis contributes to iron overload in PK deficiency, regardless of transfusion status (**Figure 2**)

Figure 2. Pathophysiology of iron overload in PK deficiency



EPO, erythropoietin; PK, pyruvate kinase; sTFR, soluble transferrin receptor

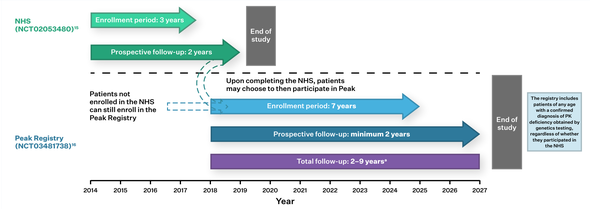
OBJECTIVE

- **To describe the characteristics of children and adolescents with PK deficiency and iron overload according to transfusion status, using real-world data**

METHODS

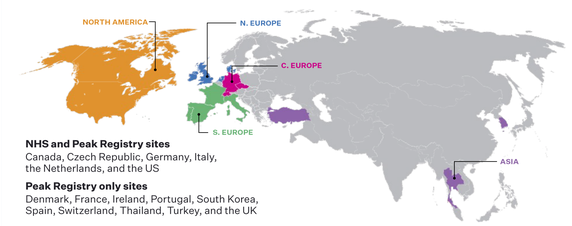
- The PK Deficiency Natural History Study (NHS), which enrolled patients in 2014–2017 (complete), and the subsequent Peak Registry, which began in 2018 (ongoing, recruiting) to build on the NHS (increased geographic reach, broader data collection, longer patient follow-up), were designed as retrospective and prospective, longitudinal, observational studies (**Figure 3** and **Figure 4**)
- Following assessment, comparable data from the two studies were integrated to form a merged database, providing an enlarged sample size and prolonged follow-up
- Data from the two studies were assessed and results combined/integrated where statistically feasible, with adjustments (eg, conversion of units) where necessary
- Data were extracted from the merged database with a data cutoff for the Peak Registry of 13May2022
- The study was conducted in accordance with the ethical principles of the Declaration of Helsinki; when appropriate, informed consent and assent were obtained from all enrolled patients and/or their guardians

Figure 3. Study design and duration



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

Figure 4. NHS and Peak Registry study sites



C., Central; N., Northern; NHS, PK Deficiency Natural History Study; S., Southern; UK, United Kingdom; US, United States

Patient inclusion/exclusion and cohorts

- Patients aged 1–<18 years at enrollment in the Peak Registry or NHS with a confirmed diagnosis of PK deficiency and a history of iron overload were included in this analysis
- Patients were grouped into cohorts by transfusion status in the 12 months prior to enrollment (regularly transfused [RT; ≥6 transfusions] or not regularly transfused [NRT; <6 transfusions]) and by age at enrollment (1–<6, 6–<12, or 12–<18 years)

Statistical analysis

- Available data were summarized for each cohort using descriptive statistics

Iron overload

- Ferritin data were available for:
  - NHS patients in the 12 months prior to enrollment and during the follow-up period
  - Peak Registry patients in the 3 months prior to enrollment and during the follow-up period
- Liver iron concentration (LIC) and cardiac magnetic resonance imaging (MRI) data:
  - The last three measurements were available for NHS patients and during the follow-up period
  - Available for Peak Registry patients in the last 3 months and during the follow-up period
- History of iron overload was defined as:
  - Having ever received chelation/phlebotomy OR
  - The presence of any of the following criteria:
    - Ferritin >1000 ng/mL
    - LIC by MRI >3 mg Fe/g dry weight
    - Cardiac T2* MRI ≤20 ms

RESULTS

- Of 135 total pediatric patients, approximately two-thirds of children with PK deficiency (92/135, 68%) had iron overload (**Table 1** and **Supplemental table 1** [QR code])

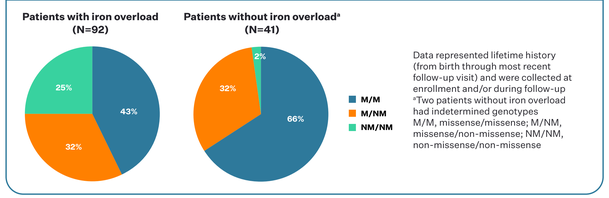
Table 1. Iron overload characteristics at baseline

Characteristics at baseline	Overall N=92[a]	NRT n=42	RT n=49
Ferritin, median (Q1, Q3), ng/mL	880 (492, 1356)	714 (219, 1436)	917 (639, 1318)
Baseline LIC by T2* MRI, median (Q1, Q3), mg Fe/g dw	5.90 (3.04, 10.6)	4.40 (3.90, 5.90)	7.10 (2.20, 10.6)
Baseline LIC by FerriScan®, median (Q1, Q3), mg Fe/g dw	5.95 (4.70, 15.55)	5.35 (3.60, 10.85)	7.00 (4.95, 19.65)
Baseline cardiac T2* MRI, median (Q1, Q3), mg Fe/g dw	32.9 (26.0, 36.2)	32.5 (20.0, 36.2)	33.3 (27.3, 40.0)
Received chelation therapy, n/N' (%)	82/85 (96.5)	34/35 (97.1)	47/49 (95.9)

N' represents the number of patients with data available. [a]Transfusion status of one patient was unknown. dw, dry weight; LIC, liver iron concentration; MRI, magnetic resonance imaging; NRT, not regularly transfused; Q, quartile; RT, regularly transfused

- Iron overload occurs regardless of age, transfusion status, or genotype (**Figure 5** and **Supplemental table 2** [QR code])
- Of those with iron overload:
  - Median (range) age at diagnosis was 1 year (prenatal–14)
  - 53% were RT and 46% were NRT
  - Iron overload occurred across genotypes

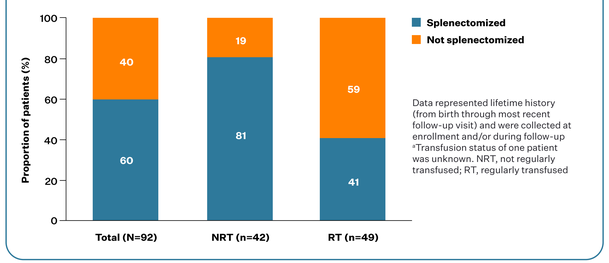
Figure 5. Genotypes among pediatric patients



Data represented lifetime history (from birth through most recent follow-up visit) and were collected at enrollment and/or during follow-up
[a]Two patients without iron overload had indetermined genotypes M/M, missense/missense; M/NM, missense/non-missense; NM/NM, non-missense/non-missense

- Overall, 55 (60%) patients with history of iron overload had undergone splenectomy
- Splenectomy was more common in the NRT than the RT cohort (81% vs 41%, respectively; **Figure 6**)
  - All patients in the 12–<18 years cohort had undergone splenectomy (**Supplemental table 2** [QR code])
- The NRT cohort had a higher median (quartile [Q]1, Q3) hemoglobin (8.4 g/dL [7.6, 9.2]) vs the RT cohort (7.9 g/dL [7.1, 9.2]) (**Supplemental table 3** [QR code])
- Reticulocyte percentage was numerically higher in NRT patients than RT patients (median [Q1, Q3] 20.1% [8.5, 31.4] and 10.1% [3.8, 18.6], respectively) (**Supplemental table 3** [QR code])
- Patients without splenectomy had higher median (Q1, Q3) indirect bilirubin (3.6 mg/dL [2.7, 5.9]), lactate dehydrogenase (881 IUL [672, 1423]), and ferritin levels (1038 mg/dL [595, 1359]) than those who had undergone splenectomy (3.0 mg/dL [1.9, 4.0], 244 IUL [182, 479], and 743 ng/mL [337, 1112], respectively) (**Supplemental table 4** [QR code])

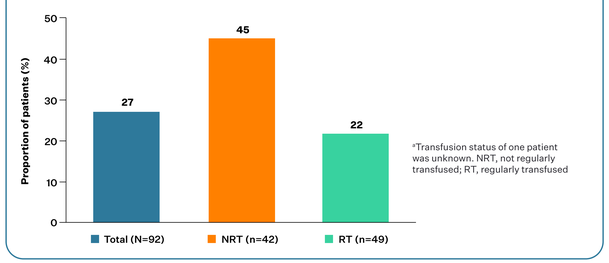
Figure 6. Lifetime history of splenectomy, by transfusion status[a]



Data represented lifetime history (from birth through most recent follow-up visit) and were collected at enrollment and/or during follow-up
[a]Transfusion status of one patient was unknown. NRT, not regularly transfused; RT, regularly transfused

- Chelation was ongoing in 78% of RT and 54% of NRT patients
- A higher proportion of patients in the NRT cohort than the RT cohort experienced complications from chelation therapy (**Figure 7**)
  - Complications included hearing loss, retinal changes, renal issues, gastrointestinal issues, and neutropenia (collected from the NHS only)

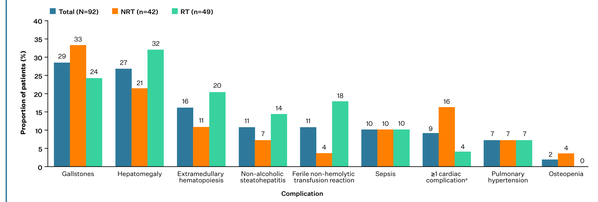
Figure 7. Complications from chelation therapy[a]



*Transfusion status of one patient was unknown. NRT, not regularly transfused; RT, regularly transfused

- Overall, pediatric patients experienced disease complications (**Figure 8**) such as gallstones (29%), hepatpmegaly (27%), extramedullary hematopoiesis (16%), sepsis (10%), and pulmonary hypertension (7%)
- More RT patients than NRT patients experienced extramedullary hematopoiesis, hepatomegaly, and non-alcoholic steatohepatitis
- More NRT patients than RT patients experienced osteopenia and ≥1 cardiac complication (which were arrythmia, cardiac failure congestive, or left ventricular hypertrophy)

Figure 8. Complications in children with iron overload



Subjects with "Not Reported," "Not Done," or missing responses were also excluded from the denominator; transfusion status of one patient was unknown. [a]Arrythmia, cardiac failure congestive, or left ventricular hypertrophy. NRT, not regularly transfused; RT, regularly transfused

LIMITATIONS

- Among pediatric patients who did not meet the criteria for history of iron overload, 29% did not have ferritin or MRI data during follow-up, suggesting that the prevalence of iron overload may be under-reported and that many patients are not being routinely monitored
- Some variables were captured differently in the NHS and Peak Registry, which may result in selection bias or under-reporting of some data
- As data have been reported descriptively, no analytic techniques to control for potential confounding variables have been implemented

CONCLUSIONS

- **Iron overload occurred in over two-thirds of pediatric patients with PK deficiency from the NHS and Peak Registry**
- **Iron overload was reported across age range, transfusion status, splenectomy status, and genotypes**
- **Medical complications associated with iron overload were highly prevalent in pediatric patients, regardless of transfusion status**

Given the high prevalence, early age of onset, and associated medical complications of iron overload, these data support recent guideline recommendations[17] to initiate regular screening in children with PK deficiency regardless of baseline disease characteristics

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References and supplemental materials are available via the QR code

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