Exploring the association of reticulocyte count in different forms of HPFH during the infancy period

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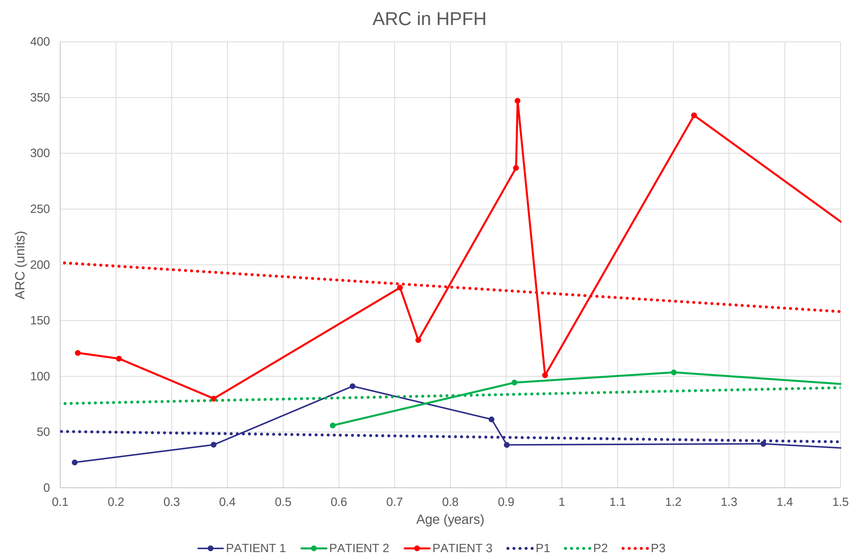
Background

- Reliable and consistent predictors of disease phenotype in pediatric patients with sickle cell anemia (SCA) are lacking.
- Elevated fetal hemoglobin (HbF) in the context of SCA has long been though to decrease the symptoms and severity of anemia in this condition.
- Hereditary persistence of fetal hemoglobin (HPFH) can be protective in patients with SCA due to prevention of HbS polymerization.
- Data suggests absolute reticulocyte count (ARC) in the first year of life can predict disease severity in children with SCA, but similar descriptions of ARC in children with elevated HbF or HbS/HPFH are lacking.
- Elevated ARC in children with SCA has been associated with the following:
  - Early hospital admission for painful crisis
  - Increased hospitalization during first three years of life
  - Acute chest syndrome
  - Splenic sequestration
  - Stroke
  - Death.
- Descriptions of ARC levels in patients with different HPFH mutations are lacking, including:
  - Deletional with pan-cellular distribution of HbF
  - Non-deletional, mendelian with pan-cellular distribution of HbF
  - Non-deletional, non-mendelian with hetero-cellular distribution of HbF
- Here, we describe associations between ARC, other hematological parameters, and clinical outcomes in a series of 3 patients with deletional and non-deletional HPFH.

Results

Patient	Mutation type	Gene Mutation Classification	Complications
P1	Deletional	HBB: HbS mutation (c.20A>T, p.E7V) with large heterozygous deletion spanning pseudobeta, delta, and beta globin genes resulting in classification as large deletional HPFH which is matching with Ghanian or Indian subtype of HPFH	None
P2	Non-deletional, mendelian	HBG1: Associated with CAR/Bantu haplotype (c.−320C>T) HBG2: Associated with CAR/Bantu haplotype, non-deletional HPFH (c.−255C>G)	None
P3	Non-deletional, non-mendelian	HBG1: A-gamma (G>A) polymorphism (c.−29G>A) HBG2: Xmn1 polymorphism (c.−211C>T)	Pain crisis including 2x dactylitis, 1x pain

Patient	%HbS	%HbF	Hemoglobin (g/dL)	MCV (fL/cell)	Absolute Reticulocyte Count (RBC/microL)
P1	61.5%	35.8%	12.1-13.4	73-93	22-91
P2	14.2%	85.5%	11.2-12.7	76-79	56-104
P3	17-67%	30-83%	10.2-11.3	77-88	80-347



Methods

- Retrospective chart review of 17 patients from our pediatric SCA clinic.
  - Diagnosed with HbS/HFPH with genetic confirmation
  - Medical records reviewed for hematologic parameters and clinical outcomes
  - Values represent patients steady state
  - All patients had FS on newborn screen
- We chose three representative patients to describe.
- No patients were on hydroxyurea during study period.
- Age ranges 2 months to 15 months

Discussion

- Elevated HbF alone cannot predict disease phenotype in patients with SCA.
- The non-deletional HPFH XMN1 mutation may be associated with elevated HbF and elevated ARC in infancy.
- Patients with XMN1 mutations are at risk for end organ damage and behave more like other patients with SCA.
  - They likely will benefit from hydroxyurea and other disease-modifying therapies despite having baseline elevated HbF levels
- Further investigation is also needed to determine how molecularly the XMN1 mutation leads to elevated HbF, elevated ARC, and other markers of hemolysis during infancy.

References

- Estepp JH, Smeltzer MP, Kang G, et al. A clinically meaningful fetal hemoglobin threshold for children with sickle cell anemia during hydroxyurea therapy. Am J Hematol. 2017;92(12):1333-1339. doi:10.1002/ajh.24906
- Meier, Emily Riehm, et al. “Reticulocytosis and Anemia Are Associated with an Increased Risk of Death and Stroke in the Newborn Cohort of the Cooperative Study of Sickle Cell Disease.” *American Journal of Hematology*, vol. 89, no. 9, Sept. 2014, pp. 904–906.
- Meier, Emily Riehm, et al. “Increased Reticulocytosis during Infancy Is Associated with Increased Hospitalizations in Sickle Cell Anemia Patients during the First Three Years of Life.” *Plos One*, vol. 8, no. 8, Aug. 2013, p. e70794.