PKD Natural History Study

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The Pyruvate Kinase (PK) Deficiency Natural History Study is an international, longitudinal patient registry which aims to increase our understanding of PK Deficiency, the most glycolytic defect causing congenital non-spherocytic hemolytic anemia. This study is open at 27 European and North American centers and has enrolled 200 individuals with PK deficiency to date. This session will report on the demographic features, clinical symptoms, laboratory and radiologic findings, and management of the first 144 individuals participating in this study. The median age at enrollment is 20 years (range: newborn to 71 years) with equal males and females. This cohort is mainly Caucasian with the Amish representing one third of enrolled individuals. Perinatal complications are frequently reported including preterm birth, perinatal transfusions, and hydrops. Newborn jaundice was common requiring phototherapy and/or exchange transfusion. Nearly 70% of individuals have undergone splenectomy at a median age of 3 years (range: 7 months to 28 years). Although splenectomy was beneficial in the majority of individuals, it failed to decrease the transfusion burden in 11% of enrolled participants. Cholecystectomy had been performed in 37% of individuals at a median age of 14 years (range: 3 to 60 years). The majority of cholecystectomies occurred after splenectomy.

Four classification groups of clinical severity were determined by the degree of anemia, splenectomy status, and transfusion status. Reticulocyte counts were incrementally higher with increasing clinical severity. Increased clinical severity is also associated with a younger age at diagnosis and a higher rate of iron overload. Iron overload assessed by ferritin or T2* MRI liver iron concentration was common in all age groups regardless of transfusion history. However, up to a third of patients had not had iron status monitoring. In these individuals with PK deficiency, higher ferritin levels correlated with higher liver iron concentrations. Ferritin was significantly higher in individuals who had a prior splenectomy, even after controlling for their transfusion history.

PK Deficiency is transmitted as an autosomal recessive trait caused by both homozygous and compound heterozygote mutations in the *PKLR* gene. Genotype information is available on all enrolled participants. Molecular characterization confirmed the wide heterogeneity of PKD with 65 different mutations in this cohort identified to date, including: 42 missense, 20 disruptive mutations (7 splicing, 6 frameshift, 3 stop codons, and 4 large deletions), 2 inframe insertion/deletions, and 1 promoter variant. Twenty newly described mutations were identified in this study cohort. Sixty-six individuals were homozygous for the p.R479H mutation. Within this molecular homogeneous group, there was wide phenotypic variability in terms of history of transfusions, baseline anemia, and history of gallstones.

The PK Natural History Study cohort is the largest assembly of individuals with PK Deficiency to date. Complications correlate with disease severity but also occur in milder phenotypes. Prospective data from the Natural History Study will provide guidance for monitoring and treatment in this rare anemia.