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SUPPORTING INFORMATION

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Characterization of the severe phenotype of pyruvate kinase deficiency

To the Editor:

Pyruvate kinase (PK) deficiency is the most common cause of hereditary non-spherocytic hemolytic anemia and is characterized by considerable genotypic heterogeneity, with over 350 documented pathogenic mutations in the *PKLR* gene.[1,2] Clinical manifestations range from a mild, asymptomatic well-compensated anemia to a severe transfusion-dependent hemolytic anemia from birth.[3,4] Other complications of PK deficiency include iron overload, pulmonary hypertension, endocrinopathies, liver failure, biliary disease, and extramedullary hematopoiesis, among others.[3,4] Splenectomy, a common supportive treatment, may partially ameliorate the anemia and reduce transfusion requirements.[5] Hemoglobin concentrations correlate poorly with symptoms in PK deficiency[6]; therefore, transfusion requirements are typically used to classify disease severity, with those who are regularly transfused (often labeled "transfusion-dependent") despite splenectomy assumed to be the most severely-affected subgroup. Our understanding of the clinical characteristics of this most severe subgroup is quite limited. Therefore, in this study, we aimed to describe the differences in clinical characteristics and disease complications between regularly transfused splenectomized patients with PK deficiency, and those who were also splenectomized but did not require regular transfusions. As is observed in other hereditary hemolytic anemias, we hypothesized that patients with pyruvate kinase deficiency requiring regular transfusions would have higher rates of disease complications.

Using data collected from the Pyruvate Kinase Deficiency Natural History Study (PKD NHS),[3] a prospective, international 30-site observational study, we aimed to compare demographics, complications, and laboratory results between two groups of patients with PK deficiency, defined by their clinical severity. All participants in the PKD NHS had molecularly confirmed PK deficiency and only splenectomized patients were included in this analysis. Regular transfusions were defined as ≥6 discrete red cell transfusion episodes per year. Transfusion frequency was observed over a 3-year period (divided into three 1-year periods) post-splenectomy. Patients were categorized into two groups based on transfusion frequency and splenectomy status. The most severe PK deficiency phenotype group was defined as one that received regular transfusions post-splenectomy. The comparison PK deficiency group

TABLE 1 Demographics, clinical characteristics, and laboratory characteristics of the most severe phenotype PK deficiency group versus the comparison PK deficiency group (n = 154 splenectomized patients with PK deficiency)

	Most severe PK deficiency phenotype: Splenectomized patients receiving regular transfusions, N = 30		Comparison PK deficiency group: Splenectomized patients not receiving regular transfusions, N = 124		
	N[a]	Median (range) or n (%)	N[a]	Median (range) or n (%)	*P* value[e]
Age at diagnosis (y)	29	0.7 (0-47.6)	117	0.2 (0-42.3)	.2
Age at enrollment (y)	30	26.2 (1.4-58.5)	124	22.7 (0.3-60.4)	.95
Gender	30		122		.013
Female		23 (77%)		63 (51%)	
Male		7 (23%)		61 (49%)	
Amish	30	1 (3%)	124	51 (41%)	<.001
Splenectomy	30	30 (100%)	124	124 (100%)	-
Age at splenectomy (y)	30	5 (1.6-25.8)	124	3.6 (0.4-37.8)	.011
Median hemoglobin post-splenectomy (g/dL)[b]	29	8.6 (6.3-11.0)	122	8.8 (6.5-12.3)	.3
Mean total bilirubin at enrollment (mg/dL)[b]	24	3.5 (1.3-11.0)	104	3.9 (1.0-17.6)	.95
Median lactate dehydrogenase at enrollment (U/L)	17	283.5 (142-1043)	57	215 (144-1007)	.2
Median absolute reticulocyte count ($x10^6$ cells/μL)[b]	17	1.2 (0-681)	56	0.8 (0.1-1274.6)	.09
Pulmonary hypertension	30	3 (10%)	122	5 (4%)	.2
Extramedullary hematopoiesis	29	3 (10%)	121	21 (17%)	.6
Liver cirrhosis	30	2 (7%)	122	5 (4%)	.6
Endocrinopathy					
Growth hormone deficiency	30	1 (3%)	124	4 (3%)	.999
Hypoparathyroidism	30	2 (7%)	124	2 (2%)	.2
Hypogonadal hypogonadism	30	1 (3%)	124	1 (1%)	.4
Thyroid disease	30	5 (17%)	122	7 (6%)	.06
Diabetes	30	2 (7%)	124	2 (2%)	.2
Bone fracture (any)	30	7 (23%)	124	27 (22%)	.8
History of iron chelation	30	27 (90%)	124	52 (42%)	<.001
Iron overload (defined by maximum ferritin >1000 ng/mL (2247 pmol/L) and/or iron chelation)	30	28 (93%)	108	55 (51%)	<.001
Total number of lifetime transfusions	29	77 (10-544)	121	15 (0-492)	<.001
Normalized PK enzyme activity[c] (%) at enrollment	15	−50 (−123.3-117.6)	31	−48.5 (−201.6-56.6)	.5
Genotype groups[d]	29		72		.7
M/M		14 (48%)		37 (51%)	
M/NM		8 (28%)		21 (29%)	
NM/NM		7 (24%)		14 (19%)	

Abbreviations: M, missense; NM, non-missense.

[a]Sample sizes are those with known data for the given characteristic.

[b]Pre-transfusion values.

[c]The normalized PK activity was calculated as: $[(PK_{obs} - PK_{LL}) \times 100]/(PK_{UL} - PK_{LL})$ where PK_{obs} is the observed PK enzyme value, and PK_{LL} and PK_{UL} are the lower and upper limits of the reference range, respectively.

[d]Analysis excluded Amish patients.

[e]Using Wilcoxon rank-sum test for continuous parameters, Fisher's exact test for binary parameters, and Cochran-Armitage Trend Test for the genotype groups comparison.

did not receive regular transfusions post-splenectomy. Phenotype stability over the 3-year period was also assessed. Continuous parameters were compared between the two groups using the Wilcoxon rank-sum test and binary parameters were compared using the Fisher's exact text. Different genotype classifications between the two groups were compared using the Cochran-Armitage test.

Of the 255 patients enrolled in the PKD NHS, 154 splenectomized patients were included in this analysis (30 patients in the most severe PK deficiency phenotype group and 124 patients in the comparison PK deficiency group). Patients in the most severe PK deficiency phenotype group were followed in 21 of the 30 participating centers. Results of the analysis comparing the two groups are described in Table 1. Given our definition of disease-severity, the most severely affected patients were more likely to have iron overload (93% vs 51%, $P < .001$), have received chelation therapy (90% vs 42%, $P < .001$), and have had more lifetime transfusions (median: 77 vs 15, $P < .001$) than the comparison PK deficiency group. The most severe patients were more likely to be female (77% vs 51%, $P = .013$) and older at the time of splenectomy (median age: 5 vs 3.6, $P = .011$). Rates of other PK deficiency complications including pulmonary hypertension, extramedullary hematopoiesis, liver cirrhosis, endocrinopathy, and bone fracture appeared similar between the two groups. Laboratory values, including hemoglobin, total bilirubin, normalized PK enzyme activity, and median absolute reticulocyte count appeared similar between the two groups. In a second analysis comparing the two groups, but with exclusion of the Amish population (N = 52), findings were unchanged except that the age of splenectomy was no longer significantly different (median: 5.1 vs 4.9 years, $P = .96$) between the most severe vs comparator PK deficiency group. The underlying genetic mutation patterns (missense mutations vs non-missense, such as frameshift variants or deletions) also appeared similar between the groups. Phenotype over time was fairly stable for patients who met the criteria for the comparator group at the time of enrollment, but variable for patients who met the criteria for most severe at enrollment, year 1, or year 2 (Table S1). Many of the latter patients alternated severity level from year-to-year; just six (27%) of the 22 patients who were most severe at any time point met the definition of most severe at all three time points.

In summary, splenectomized patients with PK deficiency who are not regularly transfused appear to have similar rates of PK deficiency-associated complications (except for iron overload), and similar relevant laboratory values and genotypes when compared to those who are regularly transfused. If severe hemolysis results in higher rates of PK deficiency complications and hemolysis severity drives transfusion frequency, the findings of this study are counterintuitive, in that iron overload (and associated chelation therapy, an expected complication of transfusions) was the only PK deficiency complication more common in the most severe phenotype group. The similarity observed between the most severe phenotype patients and comparison PK deficiency patients could result from a protective effect of transfusion, as has been described in thalassemia intermedia.[7] It could also suggest transfusion-dependence does not truly reflect disease severity, but is reflective of varying provider practices and/or patient symptoms. The latter hypothesis is supported by the fact that many patients classified as severe at baseline no longer met criteria for this classification one and 2 years later, demonstrating that transfusion requirements in patients with PK deficiency fluctuate significantly over time. Transfusion-dependence, therefore, does not necessarily imply a worse clinical outcome in PK deficiency. Furthermore, there are no transfusion guidelines for PK deficiency to help determine a universal transfusion threshold. Early in life, transfusion requirements often decrease with age likely due to fewer infection-associated hemolytic episodes, timing of splenectomy, and age-differences in tolerance of anemia. The opposite is sometimes seen later in life, with transfusion requirements increasing during middle-age, possibly due to physiologic age-related decline in cardiopulmonary fitness. Physiologic determinants of severity of disease in PK deficiency likely significantly relate to intrinsic red cell factors, such as PK protein levels[8] or non-PKLR red cell gene variants, of which transfusion requirements may be a poor surrogate.

Our analysis is limited by the lack of a standard threshold in patients with PK deficiency for the number of transfusions per year that meet criteria for regularly transfused. Use of a stricter definition (≥7 transfusions per year) would have significantly diminished the small sample size making comparisons between the two groups difficult, and likely diminished the relevance of the analysis as it would be defining a rather niche group in an already rare disease. Furthermore, the indication and goals for initiating (and discontinuing) regular transfusions, for example to treat a complication or improve subjective symptoms, were not collected.

In conclusion, the most severely affected patients with PK deficiency defined as a requirement for regular RBC transfusions following splenectomy have a similarly high rate of disease complications and laboratory abnormalities as splenectomized patients not requiring regular transfusions, with the exception of higher rates of iron overload. Transfusion requirements seem to fluctuate considerably over time and are not a valid marker of disease severity in PK deficiency. A prospective study of a universal transfusion protocol may be useful in understanding the role of transfusions in the management of patients with PK deficiency.

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H. Al-Samkari wrote the first draft of the manuscript and contributed to data analysis, creation of tables and figures, critical revision of the manuscript, and final approval; H. Al.-Sayegh contributed to data analysis, critical revision of the manuscript, and final approval; W.L. contributed to data analysis, critical revision of the manuscript, and final approval; R.G. contributed to study design, data collection, data analysis, creation of tables and figures, critical revision of the manuscript, and final approval; and the following authors contributed to data collection, critical revision of the manuscript, and final approval: E.v.B., D.M., W.B., S.E., B.G., H.Y., S.C., K.K., N.K., J.D., D.P., C.K., J.K., Y.P., A.T., M.W., Y.R., J.R., H.W., S.H., V.B., M.V., J.K., S.S., M.S., M.R., H.B., M.M., K.A.

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SUPPORTING INFORMATION

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Efficacy and safety of half-dose desmopressin for bleeding prophylaxis in bleeding disorder patients undergoing predominantly low to moderate risk invasive procedures

To the Editor:

Desmopressin (DDAVP), an analogue of vasopressin, has a been used for management of coagulation disorders for about four decades. The standard intravenous dose of DDAVP is 0.3 μg/kg of body weight, which is interestingly based on a study in five healthy controls.[1] This dose was found to produce a maximal response with no further increase in factor VIII activity (F VIII:C) levels at higher doses. The maximum dose in United States is often capped at 25 to 30 μg in obese patients.[2] Though infrequent, desmopressin has been associated with undesirable side effects including hyponatremia, thrombosis, headache and flushing.[3] Given the reported side effects as well as potentially higher risk of thrombosis in patients with normal or high von Willebrand factor (VWF) levels, the lower dose can theoretically have fewer side effects.

Recently, a lower dose of DDAVP, that is, 0.15 μg/kg of body weight has been reported in children with similar efficacy as the full dose.[4] However, there have been no studies reported in adults to the best of our knowledge. We carried out a retrospective review of adult patients with von Willebrand disease (VWD) with subsequent age-related normalization of their VWF levels.[5] And, in those with a platelet function disorder (PFD) or bleeding of unknown cause (BUC) with an increased bleeding score who received half dose DDAVP (0.15 μg/kg of body weight). Patients were eligible for half dose DDAVP if they had a history of VWD with subsequently normal or elevated VWF levels or a PFD (Bernard Soulier and Glanzman's thrombasthenia excluded), or BUC which was defined as an increased bleeding score with normal laboratory findings, despite extensive hemostasis testing. The medical record was reviewed for demographic information, age, weight, sex, family history, International Society of Thrombosis and Hemostasis Bleeding Assessment Tool bleeding score (ISTH BAT), VWF levels, reason for desmopressin, reason for dose reduction, bleeding control and sodium levels.

The study was approved by our Institutional Review Board and all patient data was de-identified. The efficacy of DDAVP was judged by bleeding control which was categorized as excellent, good, poor or no control. Excellent control was defined as hemostasis not clinically different from normal, good control as mildly abnormal hemostasis, for example slight oozing; poor control as moderate controllable bleeding, while no control was defined as severe hemorrhage that is difficult to control. The safety was assessed in terms of thrombosis, hypotension and hyponatremia; classified as mild, moderate and severe. Mild hyponatremia was defined as sodium levels of 130 to 134 mmol/L, moderate hyponatremia as Na of 125 to 129 mmol/L and severe hyponatremia as Na less than 125 mmol/L.

We identified 17 patients at our treatment center who received half dose DDAVP for a total of 33 procedures (baseline characteristics in Table S1). Among them, 82% were female with mean age of 50 years (range 18-71 years) and mean ISTH BAT score of 8.2 ± 3.7 (median score 7, range 4-17). So, 41.2% had either history of mild VWD or history of low VWF levels, 29.4% patients had PFD, 23.5% had BUC and only one patient (5.9%) had low VWF. The dose was capped in two out of 17 patients at 12 μg for weight more than 80 kg. These patients underwent a variety of procedures including upper/lower endoscopies with biopsy or device placement (12.1%), therapeutic and diagnostic laparoscopies (9.1%); genitourinary (21.2%), orthopedic (24.2%), dental (15.2%), ENT (9.1%) and miscellaneous procedures (9.1%). Twelve percent of these procedures were considered high risk, which included tonsillectomy, hip replacement, shoulder repair and bilateral mastectomy. Five patients had post-DDAVP levels assayed; mean levels of factor VIII coagulant activity (FVIII:C) were 164.6 ± 39.6, VWF: ristocetin cofactor assay (VWF:RCo) 107.8 ± 28.8 and VWF Antigen (VWF:Ag) 108.7 ± 16.7. Twelve patients received pre-operative and post-operative prophylaxis with either tranexamic acid or aminocaproic acid if the procedure was mucosal based. Bleeding control was excellent in 87.9% and good in 12.1% of procedures (Table 1). Among non-bleeding complications, hyponatremia occurred in 15.2% of procedures-there were two cases of mild and three of moderate hyponatremia. None of them were symptomatic. One patient had an episode of pre-syncope which was attributed to DDAVP use. There were no thrombotic complications (Table 1).