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Doppler-defined pulmonary hypertension and the risk of death in children with sickle cell disease followed for a mean of three years

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Summary

Pulmonary hypertension (PH) is associated with increased mortality in adults with sickle cell disease (SCD), but its prognostic significance in children is unknown. Eighty-eight children with SCD were followed after echocardiographic screening for PH. After a mean follow-up of 3 years, all 18 subjects with PH were alive. In our children, as in adults with SCD, PH was associated with increased haemolysis. In contrast, our subjects with PH did not have overt systemic disease observed in adults. PH may be a manifestation of progressive organ damage from chronic haemolysis and systemic vasculopathy that ultimately leads to early death in adulthood.

Keywords

sickle cell disease; pulmonary hypertension; tricuspid regurgitant jet velocity; children; survival

Pulmonary hypertension (PH) is an ominous complication in adults with sickle cell disease (SCD). Approximately one-third of adults screened with echocardiography have PH, defined as an elevated tricuspid regurgitant jet velocity (TRV) of ≥2·5 m/s (Gladwin *et al*, 2004). Moreover, an elevated TRV is strongly associated with an increased risk of mortality in adults (Gladwin *et al*, 2004; Ataga *et al*, 2006; De Castro *et al*, 2008). The prospective SCD-PH screening study (Machado & Gladwin, 2005) found that patients with PH had a 40-month mortality rate of 40% compared with <2% for those without PH. This increased risk

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Authorship: contributions

M.T.L. designed the study, collected, analysed and interpreted the data, and wrote the report; T.S. collected clinical and laboratory data; M.A.K. reviewed the echocardiogram and obtained TRV measurements; E.B.R. assisted in the design and initiation of the study; R.J.B. assisted in the initiation of the study and provided helpful discussion and advice; G.M.B. provided helpful discussion and advice, and co-wrote the report. All authors reviewed and approved the final version of the manuscript.

Conflict-of-interest disclosure

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of death occurs despite milder elevations of pulmonary artery pressure, lower pulmonary vascular resistance, and higher cardiac output than are observed in patients with idiopathic or other forms of secondary PH (Machado & Gladwin, 2005; De Castro *et al*, 2008). Whether PH is a direct cause of death in SCD or is a manifestation of multi-organ disease from systemic vasculopathy remains uncertain (Kato *et al*, 2007; Klings, 2008).

In children with SCD, reports indicate that PH also occurs with a similar prevalence of about 30% (Kato *et al*, 2007), but the prognostic significance and natural history of PH in children with SCD are unknown. To determine the survival of children with SCD with Doppler-defined PH, we conducted a longitudinal follow-up of 88 paediatric subjects after echocardiographic screening for PH. We also examined factors associated with PH to elucidate whether risk factors identified in adults are also observed in children.

Methods

Patient population

In 2004–2007, 94 consecutive subjects followed in our Paediatric Sickle Cell Center were screened for PH by echocardiography performed at steady-state, defined as: ≥2 weeks from an acute illness including pain crisis, acute chest syndrome, febrile illness, or hospital admission, and ≥3 weeks from a transfusion. Six without obtainable TRV were excluded. Thus, data from 88 subjects, aged 5–19 years (median 13), were collected: males = 45 (51%), females = 43 (49%); haemoglobin SS = 59 (67%), SC = 23 (26%), S/β^0Thalassaemia = 4 (5%), S/β^+Thalassaemia = 1 (1%), S/hereditary persistence of fetal haemoglobin = 1 (1%). Subjects included 65% of our total 5–19 years-old patient population with similar age (median 13 years-old), gender (53% males), and sickle phenotype (64% SS).

Echocardiography

All echocardiograms were performed at our institution's Paediatric Echocardiography Laboratory according to a standardized protocol following the guidelines of the American Society of Echocardiography. PH was defined as TRV of ≥2·5 m/s by Doppler echocardiography (Gladwin *et al*, 2004).

Data collection

Survival outcome was determined by tracking the status of subjects from their screening echocardiogram until their last visit at our Centre as of October 2008. Those without subsequent clinic visits were considered 'lost to follow-up'. Demographic information and clinical history were collected from medical records. Laboratory data were steady-state values obtained within 6 months of the echocardiogram. Clinical and laboratory variables are specified in Table I.

All data collected were anonymized prior to analysis. The study was approved by the Institutional Review Board of the Columbia University with consent form waiver.

Statistical analysis

Patients were categorized into two groups: (i) PH (TRV ≥ 2·5 m/s); (ii) No PH (TRV < 2·5 m/s). Continuous variables were summarized as means and standard deviations and compared between the two groups using two-sided Student's *t*-test. Categorical variables were summarized as proportions and compared between the two groups using Fisher's exact test. *P* values ≤ 0·05 were considered significant. Subgroup analysis excluding 18 chronically transfused patients was similarly performed. Variables from this subgroup with $P \leq 0{\cdot}1$ were included in a logistic regression model for multivariate analysis of predictors

of PH. Results of the regression analyses are presented as odds ratios with 95% confidence intervals and *P*-values.

Results

Of the 88 subjects, 18 (20%) had TRV ≥2·5 m/s (median 2·6, range 2·5–3·1). Patients with PH were 7–19 years-old (median 15 years), predominantly male (12 of 18 patients) and included 14 (78%) SS, two SC, two S/β^0Thalassaemia. After a mean follow-up of 39·4 ± 8·7 months (median 38·2), all 18 patients with PH were alive. Except for one subject with TRV of 3·1 m/s, all 17 others had a repeat echocardiogram after an average interval of 16·8 ± 8·0 months (median 16·7 months). Five of eight patients with an initial TRV of 2·5 m/s had TRV <2·5 m/s on repeat study, while all those with TRV of at least 2·6 m/s had persistent TRV ≥2·5 m/s. Mean difference in TRV between initial and repeat echocardiogram was 0·2 m/s. None had received specific treatment for PH; one had undergone successful bone marrow transplantation from a matched sibling donor. After a mean follow-up of 36·1 ± 13·7 months (median 38·7), 67 of 70 subjects with normal TRV were alive; three were lost to follow-up.

Table I presents data from the 88 subjects to identify factors associated with PH. Patients with PH had higher lactate dehydrogenase (LDH; $P = 0{\cdot}04$) and platelet count ($P = 0{\cdot}02$), history of chronic transfusion therapy ($P = 0{\cdot}05$) and, in males, history of priapism ($P = 0{\cdot}04$). No significant differences were observed in age, gender, sickle phenotype, oxygen saturation, history of pain crisis, acute chest syndrome, asthma, hydroxycarbamide therapy, cerebrovascular disease (CVD), sepsis, splenectomy, white-blood cell count, haemoglobin, reticulocyte count, bilirubin, aspartate aminotransferase (AST), alanine aminotransferase, alkaline phosphatase, creatinine or ferritin.

To further examine the relationship of PH and haemolysis, a subgroup analysis was performed excluding 18 chronically transfused patients, as transfusions can alter laboratory indicators of haemolysis (Lezcano *et al*, 2006). Of these 70 subjects, those with PH had higher LDH ($P = 0{\cdot}02$) and AST ($P = 0{\cdot}03$). Variables associated with TRV ≥2·5 m/s with $P \leq 0{\cdot}1$ on univariate analysis were considered for the logistic regression model. AST, total and indirect bilirubin, and oxygen saturation were excluded because each was highly correlated with LDH ($r = 0{\cdot}80, 0{\cdot}53, 0{\cdot}59, -0{\cdot}52$ respectively), leaving LDH, female gender, and platelet count in the model (Table II). Only LDH was independently associated with PH (odds ratio = 1·6, 95% confidence interval = 1·2–2·1, $P = 0{\cdot}004$).

Discussion

Our study showed that PH diagnosed by echocardiography was not associated with death in children with SCD followed for a mean of 3 years. This result contrasts with the greatly increased risk of death (relative risk ~10) that has been reported in adults with SCD and PH followed for a mean of 1·5–5 years (Gladwin *et al*, 2004; Ataga *et al*, 2006; De Castro *et al*, 2008). Our smaller sample size, milder severity of PH in our subjects, and lower over-all risk of mortality in the paediatric population may have contributed to the enhanced survival in our cohort. Statistically, the zero numerator in our sample size of 18 still allows a maximum risk of death of 17% at the 95% confidence interval (Hanley & Lippman-Hand, 1983). Longer follow-up of these subjects into adulthood may reveal an increased rate of death, as reported in adults (Ataga *et al*, 2006). Our observation provides evidence that PH in childhood SCD may not have the same *immediate* grave prognostic significance found with PH in adult SCD and supports the hypothetical model of the progression of PH during childhood into adulthood, with potential reversibility in children (Kato *et al*, 2007). Further

follow-up of our cohort would be necessary to ultimately define the prognostic significance of Doppler-defined PH in childhood.

Similar to adults, in our children with SCD, PH was associated with increased LDH, a laboratory marker of haemolysis, and priapism in males, a clinical feature linked to haemolysis (Kato *et al*, 2006a). PH was also associated with chronic transfusion therapy for stroke prevention. This is possibly related to the link between PH and CVD, another haemolysis-associated manifestation (Kato *et al*, 2006b). Indeed, our data showed a modest association between PH and CVD. Conceivably, both CVD and PH developed in our subjects prior to initiating chronic transfusions. The consistent association of haemolysis with PH in both children and adults suggests that haemolysis is biologically related to the development of PH.

By contrast, in our children with SCD, PH was not associated with laboratory indicators of renal or liver disease that have been observed in adults with SCD and PH (Gladwin *et al*, 2004; Ataga *et al*, 2006; De Castro *et al*, 2008; Gordeuk *et al*, 2008). While our study may be underpowered to detect significant correlations of PH with systemic disease, our findings are consistent with other paediatric studies, including a large prospective study (Minniti *et al*, 2009), that assessed these factors (Pashankar *et al*, 2008; Minniti *et al*, 2009). Concurrent systemic disease in adults could be age-related contributory factors to PH. Alternatively, the less obvious systemic disease in children with PH indicate that renal and liver diseases could be associated manifestations of progressive, cumulative organ damage resulting from haemolysis-induced endothelial dysfunction and end-organ vasculopathy that become apparent in adulthood, ultimately leading to increased mortality.

Our findings provide insights into the prognostic significance of Doppler-diagnosed PH in children with SCD. The less ominous outcome in children supports the value of early screening for PH and potential for preventive therapy in children to avert premature death in adults with SCD. Hydroxycarbamide and chronic transfusion, currently standard treatment for vaso-occlusive complications, are underutilized for haemolysis-associated manifestations (Taylor *et al*, 2008). Although hydroxycarbamide has not been shown to affect the prevalence of PH in SCD (Gladwin *et al*, 2004), pilot data in children suggest that hydroxycarbamide could improve elevated TRV (Pashankar *et al*, 2009). Chronic transfusion has also been shown to reduce haemolysis in SCD (Lezcano *et al*, 2006). A strategy to identify children at risk for haemolysis-associated vasculopathy using a simple biomarker, such as LDH or detection of elevated TRV, followed by preventive therapy with hydroxycarbamide, transfusions, or other means of decreasing haemolysis could potentially improve survival in SCD.

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Table I

Comparison of clinical and laboratory characteristics of 88 subjects with and without pulmonary hypertension.

Characteristic	PH (TRV ≥ 2·5 m/s) No.	PH (TRV ≥ 2·5 m/s) Mean ± SD or proportion (fraction)	No PH (TRV < 2·5 m/s) No.	No PH (TRV < 2·5 m/s) Mean ± SD or proportion (fraction)	*P*-value
Demographics					
Age (years)	18	13·8 ± 3·3	70	12·8 ± 3·8	0·27
Gender (female)	18	0·33 (6/18)	70	0·53 (37/70)	0·22
Sickle phenotype (SS)	18	0·78 (14/18)	70	0·64 (45/70)	0·42
Clinical history					
Oxygen saturation (%)*	18	97 ± 3	70	98 ± 2	0·09
Vaso-occlusive pain crisis†	18	0·44 (8/18)	70	0·46 (32/70)	1
Acute chest syndrome‡	18	0·39 (7/18)	70	0·46 (32/70)	0·8
Asthma	18	0·33 (6/18)	70	0·27 (19/70)	0·82
Hydroxycarbamide therapy§	18	0·17 (3/18)	70	0·14 (10/70)	0·72
Chronic transfusion therapy	18	0·39 (7/18)	70	0·16 (11/70)	0·05
CVD (stroke or abnormal TCD)	14	0·5 (7/14)	49	0·22 (11/49)	0·09
Sepsis	18	0·22 (4/18)	70	0·07 (5/70)	0·08
Splenectomy	18	0·17 (3/18)	70	0·19 (13/70)	1
Laboratory data					
Markers of haemolysis					
Haemoglobin (g/l)	18	89 ± 18	70	95 ± 17	0·26
Reticulocyte count (%)	18	10·1 ± 4·3	70	8·5 ± 5·4	0·19
Lactate dehydrogenase (u/l)	18	578 ± 323	68	408 ± 196	0·04
Total bilirubin (μmol/l)	18	63·3 ± 35·9	70	49·6 ± 35·9	0·12
Indirect bilirubin (μmol/l)	17	42·8 ± 41	70	35·9 ± 32·5	0·51
Aspartate transaminase (u/l)	18	46 ± 20	70	37 ± 23	0·14
Markers of inflammation					
White blood cell count ($\times 10^9$/l)	18	11·3 ± 2·6	70	10·6 ± 3·7	0·38
Platelet count ($\times 10^9$/l)	18	475 ± 115	70	398 ± 153	0·02
Liver					

Characteristic	PH (TRV ≥ 2·5 m/s) No.	Mean ± SD or proportion (fraction)	No PH (TRV < 2·5 m/s) No.	Mean ± SD or proportion (fraction)	*P*-value
Direct bilirubin (μmol/l)	17	22·2 ± 20·5	70	13·7 ± 18·8	0·14
Alanine transaminase (u/l)	18	19 ± 8	70	21 ± 28	0·69
Alkaline phosphatase (u/l)	18	162 ± 78	70	156 ± 66	0·77
Renal					
Creatinine (μmol/l)	18	44·2 ± 17·7	70	44·2 ± 17·7	0·76
Iron					
Ferritin (lg/l)	18	1155 ± 1786	70	824 ± 1616	0·48
Males only (*N* = 45)					
Priapism	12	0·42 (5/12)	33	(4/33)	0·04

PH, pulmonary hypertension; SD, standard deviation; CVD, cerebrovascular disease; TCD, Transcranial Doppler.

*By pulse oximetry.

†History of vaso-occlusive crisis (VOC) was defined as at least one hospital admission for VOC or at least three outpatient visits for VOC.

‡ACS was defined as history of radiographic evidence of a new pulmonary infiltrate associated with fever, respiratory symptoms, or hypoxia.

§Patients were considered to be on hydroxycarbamide therapy if they were on the medication for at least 6 months prior to the echocardiogram.

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Table II

Logistic regression analysis of predictors of pulmonary hypertension (TRV ≥ 2·5 m/s) *.

Independent variable	Odds Ratio (95% CI)	*P*-value
Lactate dehydrogenase (100 u/l)†	1·6 (1·2–2·1)	0·004
Female gender	0·2 (0·04–1·1)	0·06
Platelet count (100 × 10^9/l)†	1·2 (0·7–2·1)	0·6

CI, confidence interval.

*Analysis included 68 of 70 patients who were not on chronic transfusion (two patients had missing data). Independent variables considered for the model were those associated with TRV of ≥2·5 m/s with *P*-value of ≤0·1 on univariate analysis: LDH (*P* = 0·02), AST (*P* = 0·03), oxygen saturation (*P* = 0·06), total bilirubin (*P* = 0·06), indirect bilirubin (*P* = 0·06), platelet count (*P* = 0·08) and female gender (*P* = 0·1). AST, total bilirubin, indirect bilirubin and oxygen saturation were excluded as each was highly correlated with LDH.

†Variables lactate dehydrogenase and platelet count were rescaled to 100-unit.