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Daytime steady-state haemoglobin desaturation is a risk factor for overt stroke in children with sickle cell anaemia

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Summary

Haemoglobin (Hb) desaturation could increase the risk of stroke in sickle cell anaemia (SS) by perturbing endothelial function and limiting oxygen delivery to the brain. We performed a nested case–control study of the Dallas Newborn Cohort to determine whether daytime steady-state Hb desaturation was associated with overt stroke in children with SS. Cases had SS and overt ischaemic strokes. Controls had comparable genotypes but no overt stroke. Cases had lower prestroke steady-state pulse oximetry values (SpO₂) than controls, and cases' SpO₂ fell even lower as the time to impending stroke decreased. The odds ratio for stroke was 1.32 for each 1% decrease in SpO₂. In conclusion, steady-state Hb desaturation is a risk factor for overt ischaemic stroke in children with SS. Decline in SpO₂ over time further increases this risk. Hb desaturation is easily measured, potentially modifiable, and could be used to identify children with SS at increased risk of stroke.

Keywords

sickle cell disease; stroke; risk factors; haemoglobin desaturation; pulse oximetry

Stroke is a serious but increasingly preventable complication of sickle cell anaemia (SS) (Adams *et al*, 1998; Ohene-Frempong *et al*, 1998). Several clinical and laboratory measures have been identified as risk factors for stroke, but much of the variability in the risk of stroke among children with SS remains unexplained (Ohene-Frempong *et al*, 1998; Quinn & Miller, 2004). Transcranial Doppler ultrasonography (TCD) is a screening tool to identify children at high risk of stroke. TCD screening in conjunction with chronic transfusion programs have begun to decrease the incidence of stroke (Fullerton *et al*, 2004), but TCD is imperfect. Despite abnormal TCD velocities, many children are not destined to have a stroke (Adams *et al*, 1998, 2003). Likewise, a small number of children with normal TCD velocities will, nevertheless, have a stroke (Adams *et al*, 1998, 2003). Additional risk factors and screening tools for stroke are still needed.

Steady-state haemoglobin (Hb) desaturation is a common finding in SS that is often thought to be benign (Rackoff *et al*, 1993; Homi *et al*, 1997; Quinn & Ahmad, 2005). Chronic Hb desaturation could contribute to the risk of stroke by perturbing endothelial function (Setty *et al*, 2003) and limiting oxygen delivery to the brain. There is only one previous report of Hb

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desaturation as a risk factor for stroke in SS (Kirkham *et al*, 2001), which found an association between nocturnal oxygen desaturation and strokes, transient ischaemic attacks and seizures (Kirkham *et al*, 2001). Nocturnal oxygen saturation is cumbersome to measure, and the association between daytime Hb saturation and overt stroke has not been reported. We hypothesized that daytime steady-state Hb desaturation was associated with and preceded overt stroke in children with SS.

Methods

We performed a nested case-control study of the Dallas Newborn Cohort (DNC), which is a newborn inception cohort of children with sickle cell disease (Quinn *et al*, 2004). Cases were defined as DNC subjects with SS or sickle- β^0 -thalassaemia ($S\beta^0$) who had clinically overt strokes and were born after 1 January, 1990. We chose this date before we performed any statistical analysis because complete data were likely to be available in our hospital's electronic medical record for subjects born after this date. All strokes occurred before a universal TCD-screening protocol was implemented. Controls were defined as cohort subjects with SS or $S\beta^0$ who did not have clinically overt stroke and were not receiving chronic red blood cell transfusions. DNC subjects who may have had clinically 'silent' strokes were included in the control population. Controls were characterized in a previous publication (Quinn & Ahmad, 2005).

For both cases and controls, we calculated mean steady-state oxygen saturation by pulse oximetry (SpO_2) and mean steady-state haematological data (Hb concentration and reticulocyte count). All steady-state values were calculated as rolling averages of approximately three of the most recent measurements obtained during routine 'well' or 'steady-state' clinic visits. SpO_2 was measured in room air using the Nellcor N-395 pulse oximeter (Nellcor Puritan Bennett Inc., Pleasanton, CA, USA). All steady-state values of cases were calculated from measurements that preceded their strokes. For cases, we additionally identified one SpO_2 measurement and one blood count that was recorded closest to but preceding each case's stroke (the proximate prestroke SpO_2); and we calculated the predicted steady-state SpO_2 of each case using a multiple linear regression model that included age, sex, and mean steady-state values of Hb and reticulocyte count (Quinn & Ahmad, 2005).

We compared both the steady-state SpO_2 and the proximate prestroke SpO_2 of cases with the steady-state SpO_2 of controls. The Wilcoxon rank sums test was used because SpO_2 data were not normally distributed. The predicted steady-state SpO_2 of cases was also compared with the steady-state SpO_2 of controls, but a statistical significance testing was not performed because predicted steady-state SpO_2 is a calculated, hypothetical value. To additionally control for baseline differences between cases and controls, we used multiple logistic regression to model the odds of stroke given SpO_2 while simultaneously controlling for several covariates (age, sex, and steady-state Hb and reticulocyte count). Bonferroni correction was used for three primary hypothesis tests and $P < 0.0167$ was considered to be statistically significant.

Results

We identified 22 cases with clinically overt ischaemic strokes (100% SS; 68% male). The mean age at time of stroke was 8.5 years. One subject's stroke was limited to the optic nerve; another had concurrent antiphospholipid antibodies. There were no haemorrhagic strokes. Twenty-one of 22 and 13 of 22 strokes occurred in individuals who had steady-state Hb concentrations less than the 75th percentile ($Hb < 90$ g/l) and the median ($Hb < 80$ g/l) for the sample respectively. The 390 controls (98% SS; 55% male; mean age 9.5 years) were characterized previously (Quinn & Ahmad, 2005).

The steady-state SpO₂ of cases was significantly lower than controls (94.2% vs. 96.3%; $P = 0.0014$). Moreover, the proximate prestroke SpO₂ of cases was even lower than their steady-state values (93.7% vs. 94.2%) and significantly lower than controls (93.7% vs. 96.3%; $P = 0.0006$). The proximate prestroke SpO₂ values were obtained at a median of 154 d (mean 254 d) preceding the stroke. The predicted steady-state SpO₂ for cases was 95.2%, meaning that the observed steady-state SpO₂ of cases (94.2%) was lower than would be expected for SS patients without stroke of the same age, sex, and steady-state values of Hb and reticulocyte count. The SpO₂ data with variances are illustrated in Fig 1.

The whole model test for the final logistic regression model was statistically significant ($P = 0.0002$; $R^2 = 0.1$). The odds ratio for stroke was 1.32 [95% confidence interval (CI) 1.15–1.51] for each unit (1%) decrease in SpO₂ while simultaneously controlling for age ($P < 0.0001$). As expected, age was also associated with stroke, with an odds ratio for stroke of 1.15 (95% CI 1.04–1.28) for each unit decrease (1 year) in age while controlling for SpO₂ ($P = 0.0091$). The area under the receiver operating characteristic curve was 0.75 for prediction of stroke using only SpO₂ and age. Sex and mean steady-state values of Hb and reticulocyte count were not independent predictors of stroke in the multivariable model.

We explored whether cases had other conditions, besides SS, that could also be associated with Hb desaturation. Seven of 22 cases had evaluations for inherited and acquired hypercoagulable states, and one subject was found to have transient antiphospholipid antibodies. The remaining cases did not have any other conditions that could be associated with Hb desaturation. Thirteen cases had echocardiograms, of whom one had a patent foramen ovale and four had tricuspid regurgitant jet velocities >2.5 m/s (three were 2.6 m/s and one was 3.2 m/s). None had clinical or echocardiographic evidence of right or left heart failure. Prestroke fetal Hb concentration was available in 15 cases, in whom the mean was 10.9% (median 9.3 and range 0–22.8). No patients were being treated with hydroxycarbamide at the time of their stroke. Finally, prior acute chest syndrome was not found to be associated with SpO₂ (Quinn & Ahmad, 2005).

Discussion

Our finding, that children with SS who develop a stroke have lower prestroke daytime SpO₂ values than children with SS who do not develop a stroke, has not been reported before. Steady-state Hb desaturation in SS is largely due to the presence of dyshaemoglobins and a shifted oxyhaemoglobin dissociation curve (Needleman *et al*, 1999) rather than co-morbid conditions. Although our observed 2–3% absolute difference in SpO₂ between cases and controls may seem numerically small, SpO₂ tends to overestimate arterial oxygen saturation by co-oximetry in SS (Needleman *et al*, 1999). Further, a modest decrease in SpO₂ might be physiologically deleterious to a region of the brain, for example, that is downstream of a critical stenosis in which oxygen extraction is already maximal. We also found that SpO₂ fell even lower closer to the time of the impending stroke, and the odds of stroke increase as the SpO₂ decreases. Therefore, a decreasing SpO₂ over time in a young child with SS might portend a clinically overt stroke.

This observation is novel, but our study has a number of limitations. Mainly, we cannot ascribe a causal relationship between Hb desaturation and stroke because this is a case-control study. Second, the multivariate model does not explain much of the variability in the odds of stroke. Therefore, other factors account for most of the risk of stroke, and Hb desaturation is but one explanatory variable. Third, we retrospectively assembled data that were obtained and documented for the purposes of routine clinical practice, so there is the possibility of different types of bias. Fourth, clinically ‘silent’ strokes could not be excluded from the control population because there was no uniform screening to detect them. If Hb desaturation was also a risk factor for silent stroke, then our study design would have underestimated the strength of

the relationship between desaturation and stroke. Finally, although we found no clear associations between co-morbid conditions and Hb desaturation, there was no systematic screening for such causes. However, desaturation is a known complication of SS itself (Rackoff *et al*, 1993; Homi *et al*, 1997; Needleman *et al*, 1999; Setty *et al*, 2003; Quinn & Ahmad, 2005).

Similar to previous work (Ohene-Frempong *et al*, 1998), we found that individuals with stroke tended to have lower steady-state Hb concentrations. However, we found no association between stroke and steady-state Hb concentration in a multivariate model that included SpO₂. That is, Hb was not associated with stroke when controlling for other factors. Because Hb correlates with SpO₂ (Homi *et al*, 1997; Setty *et al*, 2003; Quinn & Ahmad, 2005), we suggest that Hb concentration may be a proxy for SpO₂, which could be the proximate risk factor for stroke. Prior studies of risk factors for stroke that did not include SpO₂ as a predictor may have identified a confounding relationship between Hb and stroke because Hb correlates with SpO₂.

The strengths of this analysis include the use of a nested case-control design within a well-characterized cohort. We also attempted to limit bias by assembling cases and controls independently, and both authors abstracted data independently and resolved discrepancies before analysis of the data. Further, we statistically controlled for multiple comparisons and used multivariable methods to adjust for covariates. Finally, our findings are in accordance with a prior study of nocturnal Hb desaturation (Kirkham *et al*, 2001), and the temporal progression of desaturation that we observed preceding overt stroke argues in favour of a potential causal association.

In conclusion, daytime steady-state Hb desaturation is a risk factor for ischaemic stroke in children with SS. This desaturation is a feature of SS, not co-morbid conditions. Moreover, a decline in steady-state SpO₂ over time seems to further increase the risk of stroke. Hb desaturation, which is easily measured by pulse oximetry, is a potentially modifiable risk factor that could be used to better identify the sub-group of children with SS who have an increased risk of overt ischaemic stroke. For example, daytime SpO₂ measurements might be useful in conjunction with TCD to improve the accuracy of identification of high-risk children, especially those with normal or conditional velocities. Validation and testing of this new risk factor is needed.

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Fig 1.

Haemoglobin desaturation precedes clinically overt in children with sickle cell anaemia (SS). The predicted steady-state, measured steady-state, and proximate prestroke SpO_2 values of children with SS who develop overt stroke are lower than the steady-state SpO_2 of SS controls without overt stroke (mean $\pm$ standard error of the mean).