Serum ferritin and total units transfused for assessing iron overload in adults with sickle cell disease

Blood transfusion therapy usage in sickle cell disease (SCD) is increasing (Drasar et al, 2011) and with this comes the potential for morbidity and mortality associated with the consequent iron overload. Whilst patients treated with regular blood transfusions have their iron indices monitored regularly and are under regular clinical review, patients receiving sporadic blood transfusions can accrue a substantial iron load relatively unnoticed. Serum ferritin (SF) is a widely available and cost-effective screening test for iron overload but can be unreliable in SCD due to the inflammatory nature of the condition, even in the steady state (Adamkiewicz et al, 2009). R2 magnetic resonance imaging (R2MRI) is a recognized non-invasive method of estimating liver iron concentration (LIC) (St Pierre et al, 2005) but has limited availability. A simple method of assessing iron load in patients having regular and intermittent transfusions is therefore needed to enable appropriate targeting of resources.

We present a retrospective review of the patients entered in our sickle cell database at King’s College Hospital [KCH], London, covering data from a 20-year period, from 1st January 1990 to 31st January 2011. Six hundred and sixty adult SCD patients ranging from 16 to 80 years of age (mean 35 years, standard deviation [SD] ± 11.08) had steady-state SF levels and an accurate transfusion history. Fifty-seven percent of patients were female and patient genotypes consisted of HbSS 62%, HbSC 31.7%, HbSβ® 1.8% and HbSβ® 4.5%. LIC was assessed non-invasively by R2MRI (Ferriscan®) in 52 patients and cardiac T2® was performed concurrently in 18 cases. R2MRI is a well-validated method of assessing liver iron load and therefore these patients formed the final study group. Clinical characteristics obtained were age, frequency of transfusion (regular versus sporadic), total top-up units transfused (TUT) and transfusion rate (TUT/top-up years). Exchange transfused units were not included in the analysis. Patient consent was formally obtained for the R2MRI scans under ethics number 08/H1101/123. Data were not normally distributed and therefore Spearman’s rank test was used to compare the data (P < 0.05 was used to define statistical significance).

Of the 660 patients, 317 (48%) had received at least 1 unit of blood, 238 (75%) of which were HbSS. The study group of 52 patients (35 female) consisted of 48 HbSS, two HbSβ® and two HbSC with age ranging from 19 to 63 years (mean 38 years).

We initially assessed which parameters most effectively predicted iron loading in the liver, as there is currently no consensus on this (Adamkiewicz et al, 2009; Inati et al, 2010). We found (in contrast to Inati et al, 2010) that TUT correlated more strongly with LIC rather than transfusion rate (R = 0.71 P < 0.0001 for TUT versus R = 0.62 P < 0.0001 for TUT/top-up years). A positive correlation was found between SF and TUT/top-up years, however this was weaker than other published data (R = 0.48 P < 0.0001). SF correlated significantly with LIC (R = 0.91 P < 0.0001) but in a non-linear manner. We subdivided our patients according to SF < or ≥ 1000 µg/l (as per National Institutes of Health guidelines (Adams et al, 2004)) and TUT < or ≥ 20 units TUT (see Fig 1).

Twenty-seven of the 52 patients had SF ≥ 1000 µg/l, with a mean of 3995 µg/l (range 1004–16 000 µg/l) and all 27 patients had LIC ≥ 2 mg/g dry-weight [g DW] (range 2.1–43 mg/g DW, mean 22.6 mg/g DW). The normal range of LIC as estimated by R2MRI (Ferriscan®) was 0.7–1.8 mg/g DW. Of these 27 patients, 24 (89%) had received ≥ 20 TUT units (mean 166 units, range 36–342 units) while three patients with SF ≥ 1000 µg/l had received < 20 TUT, their LICs were just above 2 mg/g DW at 2.1, 2.1 and 2.3 mg/g DW, respectively. Twenty-five of the 52 patients in the study group had SF < 1000 µg/l with a mean of 258 µg/l (range 20–972 µg/l). Of these 25 patients, nine (36%) had received ≥ 20 units TUT and four of these nine patients had LIC ≥ 2, mean 5.2 mg/g DW (range 2.1–11.4). All 16 patients with SF < 1000 µg/l and who had received < 20 units TUT had LIC < 2 mg/g DW, mean 0.9 (range 0.6–1.2).

Transfusions were planned in 13 of the 27 patients with SF ≥ 1000 µg/l, the mean SF was 4712 µg/l (range 1454–16 000 µg/l) and mean TUT was 200 units (range 22–342 units) (see Table I). All 13 had increased LIC (mean 22 mg/g DW, range 4.7 to >43 mg/g DW). All were receiving chelation therapy but compliance was variable. Transfusions were sporadic in 14 (52%) of the 27 patients with SF ≥ 1000 µg/l; their mean SF was 3329 µg/l (range 1167–11 578 µg/l) and mean TUT was 102 units (range 12–335 units). Again, all had LIC ≥ 2 mg/g DW (mean 23, range 2.1 to >43). Of the 14 on sporadic transfusion and SF ≥ 1000 µg/l, 11 (61%) had LIC ≥ 7 mg/g DW (mean 29 mg/g DW range 8.5 to >43 mg/g DW), none of whom were receiving chelation at that time. All 18 cardiac T2®MRIs
performed had no evidence of cardiac iron loading (mean 34 ms, range 27–43 ms).

We present data on a mixed cohort of patients with SCD and variable chelation histories, which we feel represents the population of patients most clinicians involved in the care of patients with SCD will encounter. We conclude that sporadically transfused patients can become heavily iron overloaded, on par with those on transfusion programmes. Guidelines suggest that SF ≥ 1000 μg/l and LIC ≥ 7 mg/g DW are indications for commencing chelation therapy. Access to non-invasive liver iron quantification is limited; our data suggests that a combination of SF ≥ 1000 μg/l and TUT ≥ 20 units may be useful as a screening test. No patient who had received <20 units of blood had an LIC of ≥ 2 mg/g DW. Of the patients with SF ≥ 1000 μg/l, only those patients who had received ≥20 units of simple transfusion had LIC ≥ 7 mg/g DW. We suggest a combination of ≥20 top-up units transfusion with SF ≥ 1000 μg/l as a guide for initiating investigations for iron overload or commencing chelation therapy in SCD patients.

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Authorship contribution
ED collected, collated and analysed data, and co-wrote the manuscript; NV contributed to data analysis and reviewed manuscript; NI collected data and reviewed manuscript; MA (Marlene Allman) collected data; SLT conceived the audit project, advised on data analysis and co-wrote the manuscript.
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References


