Brain iron in Sickle Cell Disease?

Fenella Kirkham, MD research, and Karin Shmueli, PhD, University College London

Iron status may play a crucial role in organ damage in Sickle cell disease (SCD) but the mechanisms involved are not clear, particularly whether there is any connection between iron accumulation in the brain and the risk of silent cerebral infarction (SCI). To investigate further, Miao et al (1) have exploited the emerging technique of MRI quantitative susceptibility mapping (QSM), which provides a measure of tissue magnetic susceptibility that is strongly correlated with its iron content. They report QSM evidence for iron accumulation in the putamen, substantia nigra and red nucleus in adolescent and young adult patients with sickle cell disease (SCD) compared with controls. As originally documented pathologically in normal people and confirmed in R2* and QSM MRI studies, they found, combining patients with SCD and controls (1), an increase in susceptibility with age in the substantia nigra (figure 1), red nucleus and dentate nucleus.

The effect of anemia on brain iron has received little attention and it is of interest that there was a significant negative correlation between hemoglobin levels and susceptibility when both SCD and healthy subjects were considered (1). It is possible that this is driven by increased levels of (high susceptibility) deoxyhemoglobin in hypoxic regions in anemic patients. Anemic hypoxia might even have a role in determining iron accumulation over the lifespan, perhaps as part of a homeostatic mechanism driving improvement in tissue oxygenation. Even for patients on chronic transfusion regimes, brain susceptibility was not associated with somatic iron status, providing reassurance that iron overload in the body does not appear to result in brain iron accumulation, although larger studies are warranted. There was no difference in susceptibility in controls with HbAA and HbAS genotypes so these groups were combined, but comparisons could not be made between those with

HbSS, HbS$\beta_0$thalassemia and HbSC genotypes in the relatively small number of patients.

As the authors point out, excessive brain iron could accelerate neurodegeneration in SCD as has been shown in other conditions, e.g. Parkinson's disease, amyotrophic lateral sclerosis (ALS), multiple sclerosis and Alzheimer's disease (2). There are relatively few studies of neurological symptoms and signs in adults with SCD associated with MRI findings. However, the extrapyramidal movement disorders typical of Parkinson's and the progressive paralysis of ALS have not been documented in SCD in manuscripts cited in Pubmed and appear to be rare in London (one case across the 5 centers seeing large numbers of adults; personal communication Jo Howard, Paul Telfer, Anne Yardumian, Elizabeth Rhodes, Josu de la Fuente) and in the USA (no cases reported in one large center; personal communication Lori Jordan). In addition, although demyelination similar to that seen in multiple sclerosis is a candidate to explain the white matter abnormalities seen on diffusion tensor imaging (3) as well as T2-weighted imaging, the current paradigm is that these are SCI (4) and the focus has been on the association with stroke risk.

The authors suggest a link between iron accumulation and SCI in SCD patients: they found significantly higher susceptibility in the Globus Pallidus and Substantia Nigra of SCD patients with SCI. However, it is not clear what the mechanism linking basal ganglia iron accumulation to white matter damage (SCI) might be. The accumulation of SCI starts very early (figure 1) (4), before the trajectory of the iron accumulation in SCD appears to diverge from that seen in controls (Russell Murdoch, personal communication). In one cited study in children with SCD (5), and in another looking

at adults with β-thalassemia (6), who also accumulate SCI, brain iron on QSM was actually significantly lower in the Globus Pallidus of SCD patients than controls. This suggests that the basal ganglia and white matter pathologies may not be causally linked but may both be related to another factor, such as hypoxic exposure. The data of Miao and others (7) in SCD suggest iron accumulation in the choroid plexus, the epithelial cells of which appear to control iron delivery into the cerebrospinal fluid (8). This does, however, make it difficult to reference the susceptibility values to cerebrospinal fluid, so Miao et al chose to reference their deep grey matter values to the splenium of the corpus callosum. This white matter structure returns an abnormal diffusion tensor imaging signal in SCD patients in association with low oxygen saturation (3). It is important to note that QSM reflects tissue components of both positive and negative susceptibility, e.g. calcifications and myelin, in addition to iron and deoxyhemoglobin. These complexities illustrate how difficult it may be to tease apart the mechanisms at play here.

The key question is whether iron accumulation triggers cognitive decline in SCD. There is some QSM evidence for an association of increased brain iron in the hippocampus, and temporal and frontal lobes with the accumulation of amyloid-β plaques and cognitive *decline* in Alzheimer's disease (9). However, there are as yet no QSM, pathological or positron emission tomography (9) studies showing evidence that pathology involving amyloid-β deposition underlies cognitive difficulties in SCD. In fact, pediatric studies have demonstrated that susceptibility in the caudate nucleus is positively correlated with cognitive function, including working memory and spatial IQ (10), suggesting that higher brain iron levels are associated with *better* cognition in children in the general population, although there are no published data

in SCD. To better understand the importance of iron accumulation in development and cognitive decline, it will be important to investigate susceptibility, in addition to the basal ganglia nuclei and cerebellum investigated here, in the deep white matter, hippocampus, frontal, temporal, parietal and occipital lobes, ideally in parallel with other neuroimaging techniques looking at cerebral hemodynamics and tissue structure. Studies over small age ranges may be required as in some of these areas, the effect of age is definitely non-linear and may not even be monotonic.

If brain iron accumulation does turn out to be causally associated with cognitive decline in older patients with SCD, we will need to fully understand the mechanisms to be able to prevent this. The role of chelating agents could be considered although these have not yet proved beneficial in diseases such as Parkinson's disease. We look forward to further imaging studies to clarify the role and mechanisms linking anemia, hypoxia and brain iron accumulation in SCD.

Disclosures

The authors have no relevant disclosures

Legend

Figure 1: Susceptibility plotted against age in the Substantia Nigra of SCD patients and controls from the supplement to the manuscript by Miao et al (1) with best fit line (broken), Left y-axis. Cumulative prevalence of silent cerebral infarction with age in children and young adults with SCD from Kassim et al (4) with best fit line (unbroken), Right y-axis. Courtesy of Xin Miao, John Wood and Mark Rodeghier.

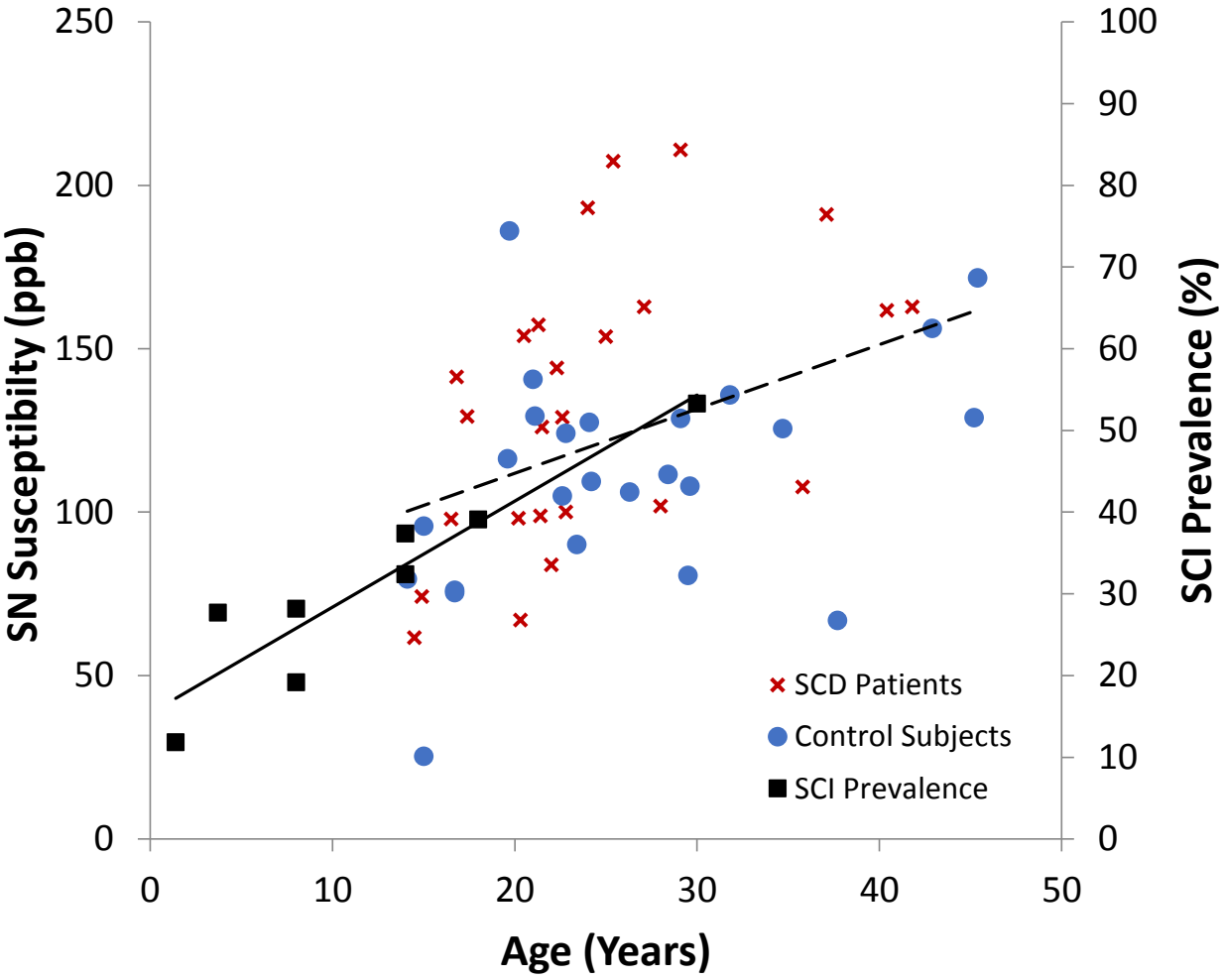
References

1. Miao X, Choi S, Tamrazi B, Chai Y, Vu C, Coates TD, Wood JC. Increased brain iron deposition in patients with sickle cell disease: an MRI quantitative susceptibility mapping study. Blood. 2018;
2. Eskreis-Winkler S, Zhang Y, Zhang J, Liu Z, Dimov A, Gupta A, et al. The clinical utility of QSM: disease diagnosis, medical management, and surgical planning. NMR Biomed. 2017; 30(4):e3668.
3. Kawadler JM, Kirkham FJ, Clayden JD, Hollocks MJ, Seymour EL, Edey R, et al. White Matter Damage Relates to Oxygen Saturation in Children with Sickle Cell Anemia Without Silent Cerebral Infarcts. Stroke. 2015;46(7).
4. Kassim AA, Pruthi S, Day M, Rodeghier M, Gindville MC, Brodsky MA, et al. Silent cerebral infarcts and cerebral aneurysms are prevalent in adults with sickle cell anemia. Blood 2016;127(16):2038–40.
5. Shmueli K, Kawadler JM, Carmichael DW, Clark CA Kirkham FJ. Susceptibility mapping in sickle cell anaemia patients with and without chronic blood transfusions. Proc Intl Soc Mag Reson Med. 2015;286.
6. Qiu D, Chan GC-F, Chu J, Chan Q, Ha S-Y, Moseley ME, et al. MR quantitative susceptibility imaging for the evaluation of iron loading in the brains of patients with β-thalassemia major. AJNR Am J Neuroradiol. 2014 Jun; 35(6):1085–90.
7. Qiu D, Brown RC, Sun B, Palasis S, Burns TG JR. Abnormal iron levels in the brain of pediatric sickle cell disease patients: a study using quantitative susceptibility mapping (QSM). Proc Intl Soc Mag Reson Med. 2014;897.
8. Mesquita SD, Ferreira AC, Sousa JC, Santos NC, Correia-Neves M, Sousa N,

et al. Modulation of iron metabolism in aging and in Alzheimer's disease: relevance of the choroid plexus. Front Cell Neurosci 2012;6:25.

9. Ayton S, Fazlollahi A, Bourgeat P, Raniga P, Ng A, Lim YY, et al. Cerebral quantitative susceptibility mapping predicts amyloid-β-related cognitive decline. Brain. 2017;140(8):2112–9.

10. Carpenter KLH, Li W, Wei H, Wu B, Xiao X, Liu C, et al. Magnetic susceptibility of brain iron is associated with childhood spatial IQ. Neuroimage. 2016; 132:167–74.


250
200
150
100
50
0
SN Susceptibilty (ppb)
100
90
80
70
60
50
40
30
20
10
0
SCI Prevalence (%)
0
10
20
30
40
50
Age (Years)
SCD Patients
Control Subjects
SCI Prevalence