



Commentary

How benign is sickle cell trait?

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The complications of sickle cell disease (SCD) arise from the presence in red cells of the mutated haemoglobin, HbS, which replaces the normal adult Hb, HbA. HbS has a single amino acid substitution whereby valine replaces glutamic acid in the 6th codon of the β chain. Most SCD patients inherit two copies of the sickle gene (homozygous HbSS individuals – sometimes termed sickle cell anaemia, SCA). About a third of SCD patients co-inherit HbS with a second abnormal Hb, HbC, in which lysine replaces glutamic acid in the same codon (heterozygous HbSC individuals). There are also a number of rarer genotypes of SCD such as HbS/ β thalassaemia.

The initial event in pathogenesis of SCD is the ability of the neighbouring molecules of HbS to aggregate into long, rigid polymers following deoxygenation. There are multiple sequelae including altered red cell rheology, fragility, increased cation permeability and stickiness. These events result in the two main complications of SCD, a chronic anaemia and acute episodes of ischaemia, which can elicit pain and also damage multiple tissues in organs including the brain, lungs, bones and kidney.

Sickle cell trait (SCT) individuals inherit one copy of HbA and one of HbS (HbAS). The selection pressure for HbS lies in the relative protection of these heterozygotes from the severest form of malaria, *Plasmodium falciparum*. There are hundreds of millions SCT individuals worldwide. About 9% blacks (3 million people), 0.2% Caucasians and 1.5% babies in USA have SCT. In the UK, there are about a quarter of a million individuals with SCT. Prevalence is even higher in areas endemic for malaria, with SCT reaching around 25% in some parts of Africa and up

to 60% in some areas of Saudi Arabia. Without screening, there is thus a high likelihood of recipients of blood transfusion being given SCT red cells in these countries.

SCT red cells contain about 40% HbS (in the absence of co-inheritance of other haemoglobinopathies such as α thalassaemias), with HbA representing the balance. The presence of HbA dilutes HbS and greatly reduces the probability of polymer formation. Haematological parameters of SCT individuals are largely normal – Hb levels, red cell size and shape and a lack of intravascular haemolysis. Whilst some mild abnormalities are present, including reduced red cell deformability, these are usually considered subclinical (Tripetto et al., 2009). The propensity for HbS polymerisation and red cell sickling is enhanced by hypoxia, acidosis and hypertonicity and can be induced in SCT red cells *in vitro* although it remains questionable whether polymerisation occurs to a significant extent *in vivo* (O'Connor et al., 2012).

On the whole, SCT is generally regarded as a benign condition (Steinberg, 2001). Notwithstanding, there are reports to the contrary. “Exercise collapse associated with SCT” (or ECAST) has been described in the military and elite civilian athletes (Jones et al., 1970; Harmon et al., 2012). High levels of exertion have been associated with rhabdomyolysis and death. Acute problems are usually avoided with good hydration, oxygenation and avoidance of temperature extremes and it has been questioned whether SCT is the true precipitating cause (O'Connor et al., 2012; Steinberg, 2001; Kark and Ward, 1994). The major clinical importance of SCT lies with genetic counseling and family planning (e.g. NHS screening programme & Sickle Cell Disease Association of America).

Several complications have been increasingly linked to SCT, however, including splenic infarction at high altitude, venous thromboembolism and renal damage. The latter probably represent the most serious, with an increased risk of renal medullary cell carcinoma, haematuria and nephropathy (Goldsmith et al., 2012). Inability to concentrate urine (hyposthenuria) correlates with amount of HbS polymer in SCT individuals (Gupta et al., 1991). Medullary hypoxia, acidosis and sluggish blood flow all promote HbS polymerisation and contribute to the particular vulnerability of this organ.

In *EBioMedicine*, Osei-Hwedieh et al. present data which show that older stored samples of human SCT red cells have increased fragility *in vitro* and also decreased *in vivo* survival in a mouse model (Osei-Hwedieh et al., 2016). These results are perhaps not surprising, but their work emphasises that our appreciation of the condition is incomplete and highlight the need for further studies including use of SCT red cells for transfusion, especially in areas of greater prevalence of the genotype.

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Policies on the use of SCT blood donors differ across the world. In some countries, people with SCT can act as blood donors, but only the plasma is used, as the red cells cause problems with blocking filters used for leucodepletion (Bodensteiner, 1994). Elsewhere, SCT red cells may be transfused into patients, but would usually be avoided in certain situations, such as when the recipient has SCD or is a neonate (Novak and Brown, 1982).

The present paper suggests that more caution should be used when considering or producing guidelines on blood donation from people with SCT. The majority of the countries where SCT is very prevalent, however, are in sub-Saharan Africa where safe blood transfusion is often not available, and donation from relatives is often the norm. In these circumstances, it may be difficult to argue that it is better to avoid transfusions from those with SCT, when the alternative may be no transfusion at all.

Disclosure

The authors declared no conflicts of interest.

References

- Bodensteiner, D., 1994. White cell reduction in blood from donors with sickle cell trait. *Transfusion* 34, 84.
- Goldsmith, J.C., et al., 2012. Framing the research agenda for sickle cell trait: building on the current understanding of clinical events and their potential implications. *Am. J. Hematol.* 87, 340–346.
- Gupta, A.K., et al., 1991. Effects of α thalassaemia and sickle polymerization tendency on the urine-concentrating defect of individuals with sickle cell trait. *J. Clin. Investig.* 88, 1963–1968.
- Harmon, K.G., et al., 2012. Sickle cell trait associated with a RR of death of 37 times in national collegiate athletic association football athletes: a database with 2 million athlete-years as the denominator. *Br. J. Sports Med.* 46, 325–330.
- Jones, S.R., Binder, R.A., Donowho Jr., E.M., 1970. Sudden death in sickle-cell trait. *N. Engl. J. Med.* 282, 323–325.
- Kark, J.A., Ward, F.T., 1994. Exercise and hemoglobin S. *Semin. Hematol.* 31, 181–225.
- Novak, R.W., Brown, R.E., 1982. Multiple renal and splenic infarctions in a neonate following transfusion with sickle cell trait blood. *Clin. Pediatr.* 21, 239–241.
- O'Connor, F.G., et al., 2012. ACSN and CHAMP summit on sickle cell trait: mitigating risks for warfighters and athletes. *Med. Sci. Sports Exerc.* 44, 2045–2056.
- Osei-Hwedieh, D.O., et al., 2016. Sickle cell trait increases red blood cell storage hemolysis and post-transfusion clearance in mice. *EBioMedicine* 11, 239–248.
- Steinberg, M.H., 2001. Sickle cell trait. In: Steinberg, M.H., Higgs, D.R., Nagel, R.L. (Eds.), *Disorders of Hemoglobin: Genetics, Pathophysiology, and Clinical Management*. Cambridge University Press, Cambridge, pp. 811–830.