

## **Risk of severe dengue is higher in patients with sickle cell disease: a scoping review**

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Travelers with sickle cell disease (SCD) face considerable medical risks when traveling to developing tropical countries, including malaria, bacterial infections, hypovolemia, and sickle cell-associated vaso-occlusive crises.<sup>1</sup> With increasing number of international travelers<sup>2</sup>, increasing number of travelers with SCD will travel to destinations where dengue is frequent.<sup>3</sup> Immunopathological features of SCD patients may increase the risk of severe dengue. Activated monocytes in SCD might activate endothelial cells (EC) through different cytokines that contribute to SCD associated microvascular occlusions, altering EC apoptosis, immune responses and hemopoiesis.<sup>4</sup>

We therefore did a scoping review to address the question whether sickle cell is associated with severe dengue. The PubMed search included the terms “dengue” or “severe dengue” or “dengue haemorrhagic fever” AND “sickle cell”. We had 20 hits. Of these 20 articles, only 7 articles were deemed to be relevant with actual cases reported, and the full text was accessed. Table 1 summarizes the findings.

All case reports document a fatal outcome of a dengue infection in patients with sickle cell disease. However, from case reports the incidence or relative risk cannot be inferred, as case reports tend to be biased towards reporting more severe outcomes. However, the Cuban experience highlighted that there may indeed be an association of SCD with severe outcomes due to dengue infections: of the three deaths reported during a dengue outbreak in Havana 2001 to 2002, 2 were in patients with SCD.<sup>5</sup> A retrospective analysis of 40 patients in Jamaica with confirmed dengue and SCD in the years 2010-2012 showed a significantly higher case fatality ratio among SCD patients: 12.5% among patients with either haemoglobin SC disease or homozygous SS disease when compared to that of the general population 0.41% ( $p < 0.0001$ ). The unadjusted odds of dying among those with haemoglobin SC disease compared with the group with homozygous SS disease was OR = 4.4 (95% CI 0.6 to 31.7). The predictors of mortality independent of sickle cell disease genotype were a lower haemoglobin concentration at presentation with an OR of 0.57 (95% CI, 0.35 to 0.94). This is in contrast to dengue haemorrhagic fever in patients without SCD where an increasing haematocrit heralds severe dengue. Adjusting for haemoglobin concentration at presentation increased the risk of death for the SC genotype relative to SS genotype with an OR = 13.4 (95% CI 1.1 to 160.3).<sup>6</sup>

From the limited data available to date, it appears that the risk of fatal dengue may be higher among patients with a relatively mild genotype (haemoglobin SC), although no firm conclusions can be drawn on the incidence and extent of risk. The highest frequency of sickle cell disease is found in tropical regions, particularly sub-Saharan Africa, tribal regions of India and the Middle East. Migration of substantial populations from these high prevalence areas to low prevalence countries such as Europe has dramatically increased in recent

decades. For individuals with SCD traveling to dengue endemic countries, frank counseling about the risks, vigilant preventative measures, and contingency planning for illness while abroad are necessary aspects of the pre-travel visit. SCD patients will need closer monitoring to detect the onset of capillary leakage and other complications of dengue. Haematocrit is more difficult to interpret in such patients, and a normal to low haematocrit does not exclude severe dengue.

## References

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