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Does cold hypersensitivity increase with age in sickle cell disease?

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Sickle cell disease (SCD) is a genetic disease due to a single nucleotide mutation in the β-globin gene on chromosome 11, resulting in the substitution of valine for glutamate at the sixth amino acid [10]. The disease is characterized by hemoglobin polymerization, red cell sickling and hemolysis, and multiple complications. Recent advances in its treatment have significantly prolonged patients' life expectancy, yet little progress has been made in understanding and treating the hallmark of the disease—pain, a lifelong companion of people living with SCD [1,16]. In fact, pain and SCD are so intimately intertwined that African tribal words for the disease, spoken centuries before the first description of SCD by Dr. Herrick [7] in the Western literature, are onomatopoeic for pain.

Myths and misunderstanding exist for pain in SCD. Patients experience both acute pain crisis and chronic pain [18,20]. The latter can be more severe than cancer pain or labor pain during childbirth [20]. To this day, it remains controversial whether there is a component of

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neuropathic pain in SCD, although accumulating evidence would suggest so [12,13,20]. Additional evidence came from animal studies in which transgenic mice exhibited long-lasting evoked hypersensitivity to mechanical, heat, and noxious cold stimuli [8,11,19].

In this issue of *Pain*, Zappia et al. [21] have taken advantage of the available Berkeley sickle cell transgenic mouse model [15] to study hypersensitivity to mild cold (23 °C) in SCD. Berkeley mice lack mouse α and β hemoglobin genes, and express exclusively human α and sickle β hemoglobins. Among various SCD models, Berkeley mice represent a serious form of sickle cell anemia, and have a phenotype that closely mimics many features of severe SCD in humans, including severe hemolytic anemia, irreversibly sickled red cells, increased rigidity of erythrocytes, and extensive multiple organ damage [9,15]. First, Zappia et al. applied an innovative operant assay for temperature preference using 2 plates that can be independently programmed to different temperatures. Berkeley mice spent significantly less time on the plate set to 23 °C than that at 30 °C. In contrast, control mice spent an equal amount of time on each plate. Thus, Berkeley mice exhibit hypersensitivity to both mild (this study) and extremely cold stimuli [4]. Clinically, patients with SCD have enhanced pain sensitivity to cold environments [2,12,17].

Moreover, Zappia et al. [21] found that aged Berkeley mice (average age, 18.4 months) spent even less time on the 23 °C plate in comparison with the younger Berkeley mice (average age, 7.9 months). The difference was not caused by altered activity, because all mice crossed the 2 chambers about the same number of times. It should be noted that the observation was not the pain transition seen in patients with SCD, which occurs in their late teens or earlier 20s when patients not only appear to have an increase in painful episodes with age but also have an increase number of painful episodes [2,12,17]. In an earlier report, this research team reported that subjects with SCD had lowered thresholds for cold pain and detection [3], consistent with the current findings from the mice. Age was found to be associated with increased sensitivity to cold, heat, and mechanical stimuli in patients with SCD as well as healthy controls; however, subjects were 15 to 16 years old in the study, and, based on the mean and standard deviations (minimum and maximum ages were not reported), all were younger than 35 years. Another team studied children and adolescents 10 to 18 years of age using quantitative sensory testing (QST) measurements, and found that increased sensitivity to cold pain was site dependent compared to that in controls [14]. The forearm ($P = .03$) showed sensitivity, but the thenar eminence ($P = .084$) did not [14]. Our group reported sensitivity to cold, heat, and mechanical stimuli in 25 adults with SCD, 12 of whom were >40 years of age and 13 of whom were <40 years of age, and no age differences in sensitization were observed when the QST measurements were conducted at 2 painful sites and one nonpainful site [5,6]. All 3 studies included small samples, and only one study had older adults, which means that additional research is needed to clarify the inconsistent findings and to relate them to basic science findings regarding sensitivity of hairy and glabrous skin, which are well known to differ in sensitivity to non-noxious and noxious stimuli.

In many ways, the clinical QST studies were consistent with the current findings from the Berkeley sickle mice. On the other hand, there is some discordance among the clinical findings and the basic science study. First, only aged Berkley sickle mice, not aged control

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mice, showed cold sensitivity compared with younger mice (Fig. 3A). In addition, the enhanced pain sensitivity in aged-Berkeley mice appeared to be limited to mild-cold stimuli, as the sensitivity to light mechanical touch was not changed in aged Berkeley mice (supplemental Fig. S1).

What was the molecular basis for enhanced cold response in Berkeley sickle mice? Zappia et al. further performed some elegant and comprehensive functional and genetic studies. They found that C fibers from Berkeley mice displayed increased sensitivity to cold detection, which is in agreement with the behavioral observation [21]. Things, however, were considerably more complicated at the molecular or mRNA levels. There were no changes for the transcripts of the usual cold "suspects," including transient receptor potential melastatin (Trpm8) and transient receptor potential ankyrin 1 (Trpa1) channels, and 2-pore domain potassium channels, Kcnk2, Kcnk4, and Kcnk10. A polymerase chain reaction (PCR) array of 84 additional genes found a 2.7-fold increase of mRNA for the substance P receptor and 1.6-fold increase of mRNA for endothelin 1 in sickle vs. control animals.

Although we do not know exactly how Berkeley mice develop hypersensitivity to mild cold, it is clear that these mice have long-lasting cold hypersensitivity (>10.5 months). Cold, including cold weather, is known to exacerbate pain in patients with SCD [2,12,17], which may be due to the underlying neuropathic pain conditions. Fully characterizing pain in SCD will help to develop preventive and treatment strategies for patients with SCD. Lack of sufficient normative QST data for younger and older African American adults presents an immediate impediment to moving the field forward.

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References

1. Ballas SK, Lusardi M. Hospital readmission for adult acute sickle cell painful episodes: frequency, etiology, and prognostic significance. Am J Hematol. 2005; 79:17–25. [PubMed: 15849770]
2. Baum KF, Dunn DT, Maude GH, Serjeant GR. The painful crisis of homozygous sickle cell disease. A study of the risk factors. Arch Intern Med. 1987; 147:1231–4. [PubMed: 3606281]
3. Brandow AM, Stucky CL, Hillery CA, Hoffmann RG, Panepinto JA. Patients with 711 sickle cell disease have increased sensitivity to cold and heat. Am J Hematol. 2013; 88:37–43. [PubMed: 23115062]
4. Cain DM, Vang D, Simone DA, Hebbel RP, Gupta K. Mouse models for studying pain in sickle disease: effects of strain, age, and acuteness. Br J Haematol. 2012; 156:535–44. [PubMed: 22171826]
5. Ezenwa, MO.; Molokie, RE.; Suarez, ML.; Wang, ZJ.; Wilkie, DJ. Pain in sickle cell disease: BASIC and clinical science advances and future directions. Honolulu, HI: May. 2012 Quantitative sensory testing in sickle cell disease: relationship to self-report measures of neuropathic pain.
6. Ezenwa MO, Molokie RE, Wang ZJ, Yao Y, Suarez ML, Pullum C, Fillingim RB, Wilkie DJ. Safety and utility of quantitative sensory testing among adults with sickle cell disease: indicators of neuropathic pain?. [submitted for publication].

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7. Herrick JB. Peculiar elongated and sickle-shaped red blood corpuscles in a case of severe anemia. Arch Intern Med. 1910; 6:517–21.
8. Hillery CA, Kerstein PC, Vilceanu D, Barabas ME, Retherford D, Brandow AM, Wandersee NJ, Stucky CL. Transient receptor potential vanilloid 1 mediates pain in mice with severe sickle cell disease. Blood. 2011; 118:3376–83. [PubMed: 21708890]
9. Ieremia J, Blau CA. Limitations of a mouse model of sickle cell anemia. Blood Cells Mol Dis. 2002; 28:146–51. [PubMed: 12064910]
10. Ingram VM. A specific chemcial difference between the globins of normal human and sickle-cell anaemia haemoglobin. Nature. 1956; 178:792–4. [PubMed: 13369537]
11. Kohli DR, Li Y, Khasabov SG, Gupta P, Kehl LJ, Ericson ME, Nguyen J, Gupta V, Hebbel RP, Simone DA, Gupta K. Pain-related behaviors and neurochemical alterations in mice expressing sickle hemoglobin: modulation by cannabinoids. Blood. 2010; 116:456–65. [PubMed: 20304807]
12. Molokie RE, Wang ZJ, Wilkie DJ. Presence of neuropathic pain as an underlying mechanism for pain associated with cold weather in patients with sickle cell disease. Med Hypotheses. 2011; 77:491–3. [PubMed: 21763079]
13. Molokie RE, Wilkie DJ, Wittert H, Suarez ML, Yao Y, Zhao Z, He Y, Wang ZJ. Mechanism-driven phase I translational study of trifluoperazine in adults with sickle cell disease. Eur J Pharmacol. 2014; 723:419–24. [PubMed: 24211787]
14. O'Leary JD, Crawford MW, Odame I, Shorten GD, McGrath PA. Thermal pain and sensory processing in children with sickle cell disease. Clin J Pain. 2014; 30:244–50. [PubMed: 23629596]
15. Paszty C, Brion CM, Manci E, Witkowska HE, Stevens ME, Mohandas N, Rubin EM. Transgenic knockout mice with exclusively human sickle hemoglobin and sickle cell disease. Science. 1997; 278:876–8. [PubMed: 9346488]
16. Platt OS, Thorington BD, Brambilla DJ, Milner PF, Rosse WF, Vichinsky E, Kinney TR. Pain in sickle cell disease. Rates and risk factors. N Engl J Med. 1991; 325:11–6. [PubMed: 1710777]
17. Smith WR, Bauserman RL, Ballas SK, McCarthy WF, Steinberg MH, Swerdlow PS, Waclawiw MA, Barton BA. Climatic and geographic temporal patterns of pain in the Multicenter Study of Hydroxyurea. PAIN®. 2009; 146:91–8. [PubMed: 19683393]
18. Smith WR, Penberthy LT, Bovbjerg VE, McClish DK, Roberts JD, Dahman B, Aisiku IP, Levenson JL, Roseff SD. Daily assessment of pain in adults with sickle cell disease. Ann Intern Med. 2008; 148:94–101. [PubMed: 18195334]
19. Wang ZJ, Wilkie DJ, Molokie R. Neurobiological mechanisms of pain in sickle cell disease. Hematology Am Soc Hematol Educ Program. 2010; 2010:403–8. [PubMed: 21239826]
20. Wilkie DJ, Molokie R, Boyd-Seal D, Suarez ML, Kim YO, Zong S, Wittert H, Zhao Z, Saunthararajah Y, Wang ZJ. Patient-reported outcomes: descriptors of nociceptive and neuropathic pain and barriers to effective pain management in adult outpatients with sickle cell disease. J Natl Med Assoc. 2010; 102:18–27. [PubMed: 20158132]
21. Zappia KJ, Garrison SR, Hillery CA, Stucky CL. Cold hypersensitivity increases with age in mice with sickle cell disease. PAIN®. 2014; 155:2476–85. [PubMed: 24953902]