

11-1-2013

# Neuropathy, neuropathic pain, and sickle cell disease.

Samir K. Ballas

*Cardeza Foundation, Department of Medicine, Jefferson Medical College, Thomas Jefferson University,*  
samir.ballas@jefferson.edu

Deepika S Darbari

*Division of Hematology, Center for Cancer and Blood Disorders, Children's National Medical Center, Washington, District of Columbia*

## Let us know how access to this document benefits you

Follow this and additional works at: [https://jdc.jefferson.edu/cardeza\\_foundation](https://jdc.jefferson.edu/cardeza_foundation) Part of the [Hematology Commons](#)

### Recommended Citation

Ballas, Samir K. and Darbari, Deepika S, "Neuropathy, neuropathic pain, and sickle cell disease." (2013). *Cardeza Foundation for Hematologic Research*. Paper 31.  
[https://jdc.jefferson.edu/cardeza\\_foundation/31](https://jdc.jefferson.edu/cardeza_foundation/31)

This Article is brought to you for free and open access by the Jefferson Digital Commons. The Jefferson Digital Commons is a service of Thomas Jefferson University's [Center for Teaching and Learning \(CTL\)](#). The Commons is a showcase for Jefferson books and journals, peer-reviewed scholarly publications, unique historical collections from the University archives, and teaching tools. The Jefferson Digital Commons allows researchers and interested readers anywhere in the world to learn about and keep up to date with Jefferson scholarship. This article has been accepted for inclusion in Cardeza Foundation for Hematologic Research by an authorized administrator of the Jefferson Digital Commons. For more information, please contact: [JeffersonDigitalCommons@jefferson.edu](mailto:JeffersonDigitalCommons@jefferson.edu).

## **Commentary**

### **Neuropathy, Neuropathic Pain and Sickle Cell Disease**

Samir K. Ballas<sup>1</sup> MD, Deepika S Darbari<sup>2</sup> MD

<sup>1</sup>Cardeza Foundation, Department of Medicine, Jefferson Medical College, Thomas Jefferson University, Philadelphia, PA, <sup>2</sup>Division of Hematology, Center for Cancer and Blood Disorders, Children's National Medical Center, Washington, DC

Corresponding Author:

Samir K. Ballas MD FACP

Cardeza Foundation for Hematologic Research

1020 Locust Street

Philadelphia, PA 19107

Phone: 856-745-6380

Fax: 856-795-0809

E-Mail: [samir.ballas@jefferson.edu](mailto:samir.ballas@jefferson.edu)

**Text word count:** 2391

**Number of tables:** 2; **Number of figures:** 0

**Number of pages including title page and references:** 10;

**Number of References:** 15

**Running title:** Neuropathy, Neuropathic Pain and Sickle Cell disease

**Key words:** Neuropathy, Neuropathic pain, Sickle pain, Sickle Cell Anemia, Sickle Cell Disease

**Conflict of Interest:** The authors declare no competing financial interests

In this issue of the journal Alvarez and colleagues [1] describe pain and other non-neurological adverse events in children with sickle cell anemia (SS) and previous stroke who received hydroxyurea and phlebotomy or standard therapy with chronic transfusion and chelation. These children were recruited from the previously reported SWITCH study [2]. The primary endpoint of the study was to compare standard therapy (transfusions and chelation) with the alternative therapy (hydroxyurea and phlebotomy) in preventing secondary stroke and the reduction of transfusional iron overload in children with SS and previous stroke. The authors compared the rates of vaso-occlusive pain and other non-neurological adverse events such as acute chest syndrome, infection, infestation, etc. in each treatment arm. They showed that blood transfusion was more effective than hydroxyurea in reducing the painful episodes. In another article, also in this issue of the journal, Oliveros et al. [3] report pain experience in adolescents and adults (age 12-71 years) with thalassemia. Although thalassemia is not typically associated with pain, the authors report that of the 252 participants, 56% reported pain at least once over the course of the study, with 32% reported severe pain. Additionally, the pain burden increased with increasing age in patients with thalassemia. Moreover, the report by Oliveros et al.[3] is an extension of a previous recent study demonstrating significant correlation ( $p < 0.001$ ) of increased pain with increased age irrespective of diagnosis, gender, transfusion status, bone density or iron overload [4]. The effect of age on the frequency and severity of pain in SS, however, is not well studied and seems to be more complex. In one of the Multicenter Study of Hydroxyurea in Sickle Cell Anemia (MSH) follow-up studies the utilization of analgesics at home (which is a surrogate measure of pain) reached a peak at the age of 30-35 years and decreased after the age of 35 years especially in males. Moreover, in all the studies mentioned above, neuropathy and neuropathic pain were not mentioned, described or diagnosed thus raising the question whether they do not complicate SS and thalassemia or whether their diagnosis is missed. The known types of pain in patients with sickle cell disease (SCD) in general and SS in particular include the recurrent vaso-occlusive crises (VOC), the persistent pain between crises, chronic pain, pain due to therapy and pain due to co-morbid conditions. Anecdotally, therapy with opioids may be occasionally associated with hyperalgesia associated with some neuropathic features. Peripheral neuropathy has been described in SS but neuropathic pain has not been well

documented to date. This commentary will critically analyze this issue, review the definitions and describe the diagnostic criteria of neuropathy and neuropathic pain and their relation to SCD.

During the American civil war Dr. Mitchell from Philadelphia described pain following peripheral nerve trauma and published detailed accounts of what he called causalgia among soldiers who suffered severe trauma often resulting in amputations which, in turn, were associated with phantom pain in the missing limb. His findings are regarded as the first scientific approach to the study of the clinical features and pathophysiology of neuropathic pain. Until recently neuropathic pain has been considered secondary to trauma only. In 1994 the International Association for the Study of Pain (IASP) defined neuropathic pain as “pain initiated or caused by a primary lesion, dysfunction, or transitory perturbation of the peripheral or central nervous system”. In 2011 neuropathic pain was redefined as “pain caused by a lesion or disease of the somatosensory system [5] Most important in this new definition is that the word dysfunction was removed and a specific disease or lesion in the nervous system has to be specified. There has been some disagreement about this restrictive definition that excludes fibromyalgia and complex regional pain syndrome (CRPS) from the neuropathic pain group and stigmatizes them as dysfunctional pain syndromes[5]. Whether more changes of the definition may evolve remains to be seen.

Neuropathy and neuropathic pain are not synonymous and diabetic neuropathy, for example, is not always associated with pain. The prevalence of neuropathy among diabetics is 40-60% whereas neuropathic pain occurs in 10-16% of diabetics [6]. The presence or absence of neuropathy in diabetics is determined by a globally validated scale that includes the assessment of sensory modalities, muscle strength tests and reflexes on both sides of the body referred to as the

“diabetic neuropathy 4 (DN4)” scale. A score  $> 4$  in this scale indicates the presence of neuropathy. Another globally validated scale, the Leeds assessment of neuropathic symptoms and signs (LANSS) scale, is used to determine if diabetic neuropathy is painful or not; a score  $\geq 12$  on LANSS scale indicates the presence of painful neuropathy [7]. Unless these or other scales are validated for SCD, it is difficult to establish a firm diagnosis of neuropathic pain due to SCD. Suffice to say that patients with SCD who complain of burning, tingling, numbness, pins and needles and itching only may have neuropathy whereas those who have these symptoms and allodynia, hyperalgesia, and sensitivity to cold and heat may have neuropathic pain. Review of the literature showed reference to sickle neuropathy often but rarely to neuropathic pain [8].

Given that neuropathic pain describes disorders that involve aberrant somatosensory processing in the nervous system, a pathophysiologic classification divides these disorders into central and peripheral neuropathic pain. Both of these types of pain are rarely reported in association with SCD. This paucity of reports may represent an authentic low incidence or inability of care providers to differentiate neuropathic pain from the pain associated with the acute VOC typical of SCD. The current paradigm in pain literature is that persistent acute pain often results in chronic pain due to central sensitization and persistent chronic pain, in turn, may cause neuropathic pain possibly due to glial activation. Sickle cell pain is presumed to follow this sequence *pari passu* but there are no studies to support this hypothesis. Additionally differences in pathophysiology does not support managing sickle cell pain the way other pain syndromes are treated. Moreover, although there seems to be general consensus about the definition of acute and chronic pain, the definition of neuropathic falters and continues to change with time.

Novel approaches to determine neuropathic descriptors of sickle cell pain have been developed by Wilkie et al. [9]. They found significant overlap between nociceptive and neuropathic descriptors of pain in patients with SCD. Although their findings are preliminary, nevertheless, their methods may eventually lead to the establishment of tools to diagnose neuropathy and neuropathic pain in patients with SCD. Although neuropathic pain in patients with SCD is not well understood, its presence in the transgenic sickle mouse seems to be more convincing. Mice expressing sickle hemoglobin (Hb S) exhibited pain characteristics similar to those observed in patients with SCD [10]. Transgenic mice expressing various levels of Hb S demonstrated increase sensitivity to cold, heat, and mechanical stimuli and to deep tissue/musculoskeletal pain compared with their age-matched, controls. Hypoxia/reoxygenation further increased pain behaviors in these Hb S-expressing mice. Inflammatory mediators were markedly increased in the spinal cord of Hb S-expressing mice compared with control mice expressing normal human hemoglobin. Thus, these changes support the existence of inflammatory and neuropathic pain in sickle mice. Studies of pain sensitivities in humans with SCD, however, yielded varying results. Brandow et al [11] found that children with SCD exhibit hypersensitivity to thermal stimuli suggesting that peripheral or central sensitization may exist and could contribute to SCD pain; O’Leary et al.[12], however, found no evidence that children with SCD had altered heat pain thresholds compared with controls. Additionally detection of pain thresholds were not associated with history of pain, gender or laboratory markers of hemolysis suggesting the need for more human studies.

Central neuropathic pain, according to IASP, is caused by a lesion or dysfunction in the central nervous system . Given that SCD involves the CNS, we

would expect that central neuropathic pain might occur in this disease. However, except for acute headaches that may accompany cerebral hemorrhage or infection, central post-stroke pain is not reported in SCD. Neurological complications in SCD involving the CNS include cerebral infarction, intracranial hemorrhage, cognitive dysfunction, hearing loss, and a few cases of spinal cord infarction. The most striking neurological complication of SS is stroke due to cerebral infarction. The observed frequency varies from 6% to as high as 34%. If untreated, cerebral infarction may recur in two-thirds of affected patients. Central post-stroke pain has an estimated incidence of 8% of all strokes due to cerebrovascular accidents [13]. Reports of central post-stroke pain in SCD are absent from the literature. In fact, children who develop strokes due to sickle cell anemia and who are treated with chronic transfusion or exchange transfusion experience significant decrease (or even total absence) of painful episodes compared to their peers without stroke and without chronic transfusion. The reasons why post-stroke pain is not described in SCD are unknown. One possibility pertains to the location of the infarct, which usually involves the deep white matter or the cortex (Table I) and rarely involves the brain stem, the thalamus, or the spinal cord. Other possibilities include the difficulty in differentiating post-stroke pain from VOC and the prevention of further tissue damage and inflammation by the prompt initiation of therapy with blood transfusion or exchange transfusion. Moreover, in stroke and spinal cord injury, the onset of pain is often delayed unlike central pain due to other causes such as multiple sclerosis [13]. Thus in patients with SCD delayed central pain after a stroke may be easily ascribed to SCD rather to the stroke. Other types of central pain such as painful epileptic seizure, multiple sclerosis, Parkinson's disease, and syringomyelia have not been described in association with sickle cell syndromes.

Peripheral neuropathy and peripheral neuropathic pain result from damage to the peripheral nerves, plexus, dorsal root ganglion, or root. Hematologists are familiar with chemotherapy-induced peripheral neuropathy (CIPN) among patients with hematologic malignancies. Its incidence varies from 10% - 100% among the different chemotherapeutic agents depending on the type of drug, dosage and pattern of administration . The pathogenesis of CIPN is unknown. The coexistence of several mechanisms involving inflammation, direct cytotoxicity and deficiency in growth factors such as nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF) may be responsible for this syndrome . Hydroxyurea, a chemotherapeutic agent used in SCD has not been associated with peripheral neuropathy in patients with SCD.

The rarity of peripheral nerve infarction in SCD may be due to unusual anatomical and pathophysiological characteristics of the microvascular network that supplies peripheral nerves. Peripheral nerves receive their blood supply from the arteriae nervorum, which are of relatively larger diameter and form a rich and complex interconnecting network of nutrient vessels and may protect peripheral nerves from infarction because of its ability to maintain adequate blood circulation even if the patency of a primary nutrient vessel is compromised. Peripheral neuropathy in patients with SCD is not common. Table II lists the peripheral neuropathies that have been reported at least once in association with SCD. Electrophysiologic studies suggest that silent peripheral nerve involvement may precede overt clinical signs and symptoms. It may be possible for electrophysiological examinations to predict the diagnosis of peripheral neuropathy in patients with SCD prior to the onset of neurological signs and symptoms. The mental and mandibular neuropathies are the most commonly reported in patients with SCD. Mental nerve neuropathy has been reported in 10 patients with SS



between 1972 and 2012 Mandibular nerve neuropathy has been described in two patients one of whom had coexistent G6PD deficiency . Lesions of the mental nerve are associated with numbness of the chin, often referred to as the numb chin syndrome, and are believed to result from bone compression due to mandibular bone infarction. Mental nerve neuropathy was more common in females and was bilateral in one patient. All reported episodes of mental nerve neuropathy occurred during VOC and resolved with the resolution of the VOC.

A cross-sectional Brazilian study [14] determined orofacial manifestations in 150 patients with SS and compared them to 150 control subjects. Patients with SS had significantly higher prevalence of previous mental nerve neuropathy ( $p = 0.000$ ) and delayed tooth eruption ( $p = 0.006$ ) than controls. Moreover, previous mental nerve neuropathy was more frequent among females and previous mandibular pain was more frequent among individuals older than 21 years.

A Nigerian study evaluated 613 patients with SS attending outpatient clinics and 616 control subjects to determine the prevalence of neurological complications in SS using a uniform structured questionnaire [15]. Neurological abnormalities occurred in significantly higher percentage of patients (76%) compared to controls (32.1%). Among adolescents 38 out of 226 patients (16.8%) had localized sensory neuropathy and among adults 12 out of 291 patients (4.1%) had localized sensory neuropathy. The specific description and location of these neuropathies, however, were not mentioned. Headache was significantly higher in children and adolescents compared to controls, but not in adult [15].

A Turkish study determined peripheral nerve involvement electrophysiologically in 51 patients with SCD who were asymptomatic without

clinically evident neurological signs and symptom and compared them to 51 control subjects. Conventional electrophysiological studies of peripheral nerves were performed on all subjects [8]. Peripheral nervous system involvement was detected in 10 (19.6%) patients. Five (9.8%) patients had sensorimotor axonal neuropathy, two (3.9%) had sensory axonal neuropathy, one (2%) had ulnar sensory neuropathy and two (3.9%) had median sensory neuropathy. These findings suggest that silent peripheral nerve involvement may precede overt clinical signs and symptoms. Unfortunately, the authors did not follow these patients to determine if overt peripheral neuropathy develops in some or in all of them later on. Nevertheless, this study suggests that electrophysiological examinations may predict the diagnosis of peripheral neuropathy in patients with SCD prior to the onset of neurological signs and symptoms.

In summary neuropathy and neuropathic pain are not the same and not all patients with neuropathy have pain. Neuropathic pain is not well documented as a complication of sickle cell disease. Neuropathy, especially peripheral neuropathy, has been reported in patients with sickle cell disease, albeit uncommonly. Mental nerve neuropathy (AKA numb chin syndrome) is the most commonly reported neuropathy in SCD usually associated with VOC. More studies are needed to determine the prevalence of neuropathy and neuropathic pain in patients with SCD and to find if these are complications of the disease itself or due to co-morbidities.

## References

1. Alvarez, O., et al., *Pain and other non-neurological adverse events in children with sickle cell anemia and previous stroke who received hydroxyurea and phlebotomy or chronic transfusions and chelation: Results from the SWiTCH clinical trial*. American journal of hematology, 2013.
2. Ware, R.E. and R.W. Helms, *Stroke With Transfusions Changing to Hydroxyurea (SWiTCH)*. Blood, 2012. **119**(17): p. 3925-32.
3. Oliveros, O., et al., *Pain over time and its effects on life in thalassemia*. American journal of hematology, 2013.
4. Haines, D., et al., *Pain in thalassaemia: the effects of age on pain frequency and severity*. Br J Haematol, 2013. **160**(5): p. 680-7.
5. Jensen, T.S., et al., *A new definition of neuropathic pain*. Pain, 2011. **152**(10): p. 2204-5.
6. Erbas, T., et al., *Prevalence of peripheral neuropathy and painful peripheral neuropathy in Turkish diabetic patients*. J Clin Neurophysiol, 2011. **28**(1): p. 51-5.
7. de Moraes Vieira, E.B., et al., *Prevalence, characteristics, and factors associated with chronic pain with and without neuropathic characteristics in Sao Luis, Brazil*. J Pain Symptom Manage, 2012. **44**(2): p. 239-51.
8. Okuyucu, E.E., et al., *Peripheral nervous system involvement in patients with sickle cell disease*. Eur J Neurol, 2009. **16**(7): p. 814-8.
9. Wilkie, D.J., et al., *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**(1): p. 18-27.
10. Kohli, D.R., et al., *Pain-related behaviors and neurochemical alterations in mice expressing sickle hemoglobin: modulation by cannabinoids*. Blood, 2010. **116**(3): p. 456-65.
11. Brandow, A.M., et al., *Patients with sickle cell disease have increased sensitivity to cold and heat*. American journal of hematology, 2013. **88**(1): p. 37-43.
12. O'Leary, J.D., et al., *Thermal Pain and Sensory Processing in Children With Sickle Cell Disease*. Clin J Pain, 2013.
13. Boivie, j., *Central pain*, in *Wall and Melzack's Textbook of Pain*, S.B. McMahon and M. Koltzenburg, Editors. 2006, Elsevier Churchill Livingstone: London. p. 1057-1074.
14. Mendes, P.H., et al., *Orofacial manifestations in patients with sickle cell anemia*. Quintessence Int, 2011. **42**(8): p. 701-9.
15. Kehinde, M.O., E.O. Temiye, and M.A. Danesi, *Neurological complications of sickle cell anemia in Nigerian Africans--a case-control study*. J Natl Med Assoc, 2008. **100**(4): p. 394-9.