AHOT Acta Haematologica Oncologica Turcica

Acta Haematol Oncol Tur

Original Article

DOI: 10.4274/ahot.galenos.2026.2026-1-2

Prevalence of Neuropathic Pain and Its Association with Clinical and Laboratory Findings in Sickle Cell Disease

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ABSTRACT

Aim: Pain in sickle cell disease (SCD) has traditionally been attributed to acute vaso-occlusive events; however, chronic pain with neuropathic features is increasingly recognized. This study aimed to determine the prevalence of neuropathic pain (NP) in adult patients with SCD and to evaluate its association with clinical and laboratory parameters.

Methods: This cross-sectional observational survey included adult patients with SCD and age- and sex-matched healthy controls. NP was assessed using the Leeds Assessment of Neuropathic Symptoms and Signs (LANSS), Douleur Neuropathique en 4 Questions (DN-4), and painDETECT questionnaires. Clinical characteristics, laboratory findings, and treatment-related variables were recorded and analyzed.

Results: A total of 56 patients with SCD and 56 healthy controls were included. NP prevalence ranged from 33.9% to 50% depending on the assessment tool used. LANSS, DN-4, and painDETECT scores were significantly higher in patients with SCD compared with controls (p=0.001). No statistically significant associations were identified between NP and laboratory parameters; however, female sex (p=0.058), comorbidities (p=0.067), and frequent vaso-occlusive crises (p=0.060)showed trends toward higher NP prevalence.

Conclusion: NP is highly prevalent in adults with SCD and represents an important component of the chronic pain phenotype. Routine assessment of NP using validated tools may improve individualized pain management strategies and patient outcomes.

Keywords: Sickle cell disease, neuropathic pain, LANSS, DN-4, painDETECT

Introduction

Sickle cell disease (SCD) is an inherited hemoglobinopathy characterized by the formation of hemoglobin S (HbS) due to a single point mutation in the β-globin chain, and is associated with high morbidity and mortality [1,2]. Polymerization of HbS during deoxygenation reduces erythrocyte deformability, leading to microvascular occlusion, tissue ischemia, and recurrent pain episodes [1,3]. Over time, these pain episodes are associated with progressive organ damage, increased complication burden, and premature mortality [2,4].

SCD continues to represent a major public health problem worldwide, particularly in regions with high prevalence, where it imposes a substantial burden on healthcare systems [2]. In Türkiye, hemoglobinopathies—especially in the Mediterranean region—have long been recognized as an important public health concern [5,6].

Neuropathic pain (NP) is pain that arises as a direct consequence of a lesion or disease affecting the somatosensory nervous system and is characterized by distinctive sensory symptoms, such as burning and stabbing sensations, electric shock-like pain, numbness, paresthesia, and allodynia. This type of pain is associated with structural and functional alterations in the peripheral and/or central nervous systems and often follows a chronic course. Clinically, NP is characterized by poor response to conventional analgesics, a discrepancy between pain intensity and tissue damage, and a marked reduction in quality of life [7-9].

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Received: 13.01.2026 **Accepted:** 11.03.2026 **Epub:** 02.04.2026

Cite this article as: Demirkol Gövce A, İlhan G, Melek İM, Kaya H. Prevalence of neuropathic pain and its association with clinical and laboratory findings in sickle cell disease. Acta Haematol Oncol Turc. [Epub Ahead of Print]

In clinical practice, several screening and assessment tools have been developed to identify NP. The Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) scale is designed to differentiate NP by combining patient-reported symptoms with findings from clinical sensory examination. The Douleur Neuropathique en 4 Questions (DN-4) questionnaire is a brief and practical tool that integrates symptom-based questions with simple physical examination findings and is widely used for NP screening. The painDETECT questionnaire, originally developed for patients with low back pain, has been validated in various chronic pain conditions and serves as a self-report instrument providing a detailed assessment of pain characteristics. These tools are particularly useful in conditions with complex pain mechanisms, such as SCD, as they facilitate more accurate classification of pain phenotypes and support the selection of appropriate treatment strategies [7-11].

Although pain in SCD was long considered to be solely a consequence of vaso-occlusive processes, accumulating evidence has demonstrated that pain may become chronic and acquire neuropathic features over time [7,8]. In this context, diagnostic frameworks for chronic sickle cell-related pain have been developed, emphasizing that the neuropathic component should not be overlooked in clinical practice [8].

The reported prevalence of NP in patients with SCD varies depending on the assessment methods used; however, studies employing screening tools such as DN-4, LANSS, and painDETECT have reported prevalence rates ranging from 20% to 40% [7-9]. These findings suggest that pain in adult patients with SCD is heterogeneous in nature and that a substantial subgroup exhibits neuropathic characteristics [9].

The development of NP has been attributed to multiple mechanisms, including repeated tissue ischemia and reperfusion injury affecting peripheral nerve fibers, chronic inflammation, oxidative stress, endothelial dysfunction, and disturbances in nitric oxide metabolism [12,13]. Moreover, pain in SCD has been reported to be associated not only with peripheral mechanisms but also with alterations in central pain processing pathways and central sensitization at the level of the central nervous system [8,12].

Clinically, NP is associated with increased emergency department visits, frequent hospitalizations, long-term opioid use, risk of dependency, and significant impairment in quality of life [14,15]. Therefore, pain assessment in SCD should extend beyond acute vaso-occlusive crises and incorporate chronic and NP components. Current national and international guidelines recommend systematic evaluation of NP in addition to acute pain management and advocate for multidisciplinary treatment approaches integrating both pharmacological and non-pharmacological strategies [4,15].

The aim of this study was to evaluate the prevalence of NP in individuals with SCD using multidimensional assessment tools and to investigate the possible associations between NP and clinical and laboratory parameters. In addition, this study aims to contribute to the limited data available from Türkiye and to highlight the importance of the neuropathic component in pain management among patients with SCD.

Methods

Study Design and Participants

This cross-sectional observational study was conducted in adult patients diagnosed with SCD who were followed at outpatient clinics. Clinical and laboratory data were collected retrospectively from hospital records. Age- and sex-matched healthy individuals without a history of chronic pain or neurological disease were included as a control group. Demographic characteristics, clinical history, treatment data, and laboratory parameters were recorded for all participants.

Neuropathic Pain Assessment

NP was evaluated using three validated screening tools: the LANSS, the DN-4 questionnaire, and the painDETECT questionnaire. These instruments were administered during routine clinical visits, and scoring was performed according to standard guidelines.

Ethical Considerations

Written informed consent was obtained from all participants prior to enrollment. Ethics approval for the study was obtained from the Ethics Committee of Hatay Mustafa Kemal University Tayfur Ata Sökmen Faculty of Medicine, and the study was conducted in accordance with the principles of the Declaration of Helsinki (approval no: 09, date: 20.02.2020).

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows, Version 21.0 (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean ± standard deviation, and categorical variables were presented as frequencies and percentages. Comparisons between groups were performed using appropriate parametric or non-parametric tests depending on data distribution. A p value <0.05 was considered statistically significant.

Results

A total of 56 patients diagnosed with SCD and 56 age- and sex-matched healthy individuals were included in the study. The mean age of the patient group was 33.9±9.9 years, while that of the control group was 32.1±6.6 years, with no statistically significant difference between the groups ($p>0.05$). The proportion of male participants in the patient group (62.5%) was higher than that of female participants (37.5%) (Table 1).

The most frequently reported clinical complications in patients' medical histories were avascular necrosis (25%) and acute chest syndrome (12.5%). Cerebrovascular events (3.6%), leg ulcers (12.5%), and priapism (8.9%) were observed less frequently. Overall, 75% of patients were receiving regular hydroxyurea (HU) therapy, and 44.6% had a history of ≥3 vaso-occlusive crises per year (Table 2).

Table 1. Demographic characteristics of the participants

Characteristic	Patient group (n=56)	Control group (n=56)	Total participants (n=112)
Sex, n (%)			
Female	21 (37.5%)	29 (51.8%)	50 (44.6%)
Male	35 (62.5%)	27 (48.2%)	62 (55.4%)
Age, mean ± SD (years)	33.98±9.96	32.13±6.62	33.05±8.47

SD: Standard deviation

The mean hemoglobin level was 8.67±1.47 g/dL, lactate dehydrogenase (LDH) was 535.2±262.4 U/L, C-reactive protein (CRP) was 28.0±35.9 mg/L, and ferritin was 1092.8±1041.1 ng/mL. Other hematological and biochemical parameters are presented in Table 3. No statistically significant association was found between laboratory variables and the presence of NP (p>0.05).

In the assessment of NP, the mean LANSS, DN-4, and painDETECT scores in the SCD group were 12.0±7.0, 3.7±2.8, and 14.3±8.1, respectively. In the control group, the corresponding scores were 0.9±1.9, 0.5±1.1, and 2.8±4.1. The differences between the patient and control groups were statistically significant across all scales (p=0.001) (Table 4). According to the LANSS scale, NP was identified in 50% of patients, whereas the DN-4 questionnaire and the painDETECT scale indicated prevalences of 33.9% and 41.1%, respectively.

Table 2. Clinical characteristics of the patients

Clinical characteristics	Present, n (%)	Absent, n (%)
History of acute chest syndrome	7 (12.5)	49 (87.5)
History of cerebrovascular disease	2 (3.6)	54 (96.4)
History of avascular necrosis	14 (25.0)	42 (75.0)
History of leg ulcer	7 (12.5)	49 (87.5)
History of priapism	5 (8.9)	51 (91.1)
Hydroxyurea use	42 (75.0)	14 (25.0)
≥3 vaso-occlusive crises per year	25 (44.6)	31 (55.4)

Table 3. Laboratory findings of the patients

Laboratory parameters	Mean ± SD
Hemoglobin (12-16 g/dL)	8.67±1.47
WBC (4-10 ×10^3/µL)	9.78±4.48
Platelets (150-450 ×10^3/µL)	417.76±241.78
Ferritin (10-290 ng/mL)	1092.75±1041.09
CRP (0-5 mg/L)	28.04±35.88
LDH (120-246 U/L)	535.21±262.41
Vitamin B12 (210-910 pg/mL)	440.55±351.08
Folate (5-16 ng/mL)	24.25±84.39

SD: Standard deviation, WBC: White blood cell, CRP: C-reactive protein, LDH: Lactate dehydrogenase

Analysis based on the LANSS scale evaluated the association between the presence of NP and selected clinical and laboratory variables (Table 5). The prevalence of NP was higher in female patients (66.7%) than in male patients (40.0%). Similarly, the rate of NP was higher in patients with comorbid conditions (63.2%) than in those without comorbidities (3.2%).

Patients experiencing ≥3 pain crises per year had a higher prevalence of NP (64.0%) compared with those experiencing <3 crises per year (28.7%); however, this difference did not reach statistical significance, although it approached significance (p=0.060). This finding suggests that the neuropathic component of pain may be more pronounced in patients with frequent crises.

With respect to laboratory parameters, the prevalence of NP was slightly higher in patients with hemoglobin levels ≥8 g/dL (51.1%) compared with those with levels <8 g/dL (44.4%). Likewise, NP was more frequent in patients with CRP levels ≥5 mg/L (53.0%) than in those with lower CRP levels (40.0%). Nevertheless, none of these differences were statistically significant (p>0.05).

No statistically significant association was observed between the presence of NP and the use of HU or folic acid (FA) (p>0.05). The prevalence of NP was identical in patients who were receiving HU and those who were not (50.0%) (Table 5).

Table 6 presents a comparative analysis of NP presence and selected clinical and laboratory variables according to the DN-4 scale. The prevalence of NP was higher among female patients, those with comorbid conditions, patients receiving HU, those not using FA, patients with an annual crisis frequency of <3, those with hemoglobin levels ≥8 g/dL, and those with CRP levels <5 mg/L. However, none of these differences reached statistical significance (p>0.05). Notably, female sex (p=0.058) and the presence of comorbidities (p=0.067) demonstrated trends toward statistical significance (Table 6).

Table 4. Comparison of scale scores between the patient and control groups*

Scales	Patient (Mean ± SD)	Control (Mean ± SD)	Z-score	p value
LANSS	12.0±7.0	0.9±1.9	-8.477	0.001
DN-4	3.7±2.8	0.5±1.1	-6.676	0.001
PainDETECT	14.3±8.1	2.8±4.1	-7.695	0.001

*: Mann-Whitney U test was used, SD: Standard deviation, LANSS: Leeds Assessment of Neuropathic Symptoms and Signs, DN-4: Douleur Neuropathique en 4 Questions

Table 5. Analysis of neuropathic pain prevalence according to the LANSS scale and selected variables*

Variables	NP present, n (%)	NP absent, n (%)	p value
Sex			0.533
Female	14 (66.7)	7 (33.3)	
Male	14 (40.0)	21 (60.0)	
Comorbidity			0.158
Present	12 (63.2)	7 (36.8)	
Absent	16 (43.2)	21 (56.8)	
Hydroxyurea			1.000
Yes	21 (50.0)	21 (50.0)	
No	7 (50.0)	7 (50.0)	
Folic acid			0.577
Yes	19 (52.8)	17 (47.2)	
No	9 (45.0)	11 (55.0)	
Annual crisis frequency			0.060
<3	12 (28.7)	19 (61.3)	
≥3	16 (64.0)	9 (36.0)	
Hemoglobin (g/dL)			0.716
<8	4 (44.4)	5 (55.6)	
≥8	24 (51.1)	23 (48.9)	
CRP (mg/L)			0.365
<5	6 (40.0)	9 (60.0)	
≥5	22 (53.0)	19 (47.0)	

*: Chi-square test was used, LANSS: Leeds Assessment of Neuropathic Symptoms and Signs, NP: Neuropathic pain, CRP: C-reactive protein

Table 6. Analysis of neuropathic pain prevalence according to the DN-4 scale and selected variables*

Variable	NP present, n (%)	NP absent, n (%)	p value
Sex			0.058
Female	12 (57.1)	9 (42.9)	
Male	11 (31.4)	24 (68.6)	
Comorbidity			0.067
Present	11 (57.9)	8 (42.1)	
Absent	12 (32.4)	25 (67.6)	
Hydroxyurea			0.638
Yes	18 (42.9)	24 (57.1)	
No	5 (35.7)	9 (64.3)	
Folic acid			0.311
Yes	13 (36.1)	23 (63.9)	
No	10 (50.0)	10 (50.0)	
Annual crisis frequency			0.884
<3	13 (41.9)	18 (58.1)	
≥3	10 (40.0)	15 (60.0)	
Hemoglobin (g/dL)			0.210
<8	2 (22.2)	7 (77.8)	
≥8	21 (44.7)	26 (55.3)	
CRP (mg/L)			0.607
<5	7 (46.7)	8 (53.3)	
≥5	16 (39.0)	25 (61.0)	

*: Chi-square test was used, DN-4: Douleur Neuropathique en 4 Questions, CRP: C-reactive protein

Table 7 presents a comparative analysis of NP levels assessed by the painDETECT scale and selected clinical and laboratory variables When patients with *suspected* and *positive* NP were evaluated together, the prevalence of NP was higher among female patients, those with comorbid conditions, patients receiving HU, those not using FA, patients with an annual crisis frequency ≥3, those with hemoglobin levels ≥8 g/dL, and those with CRP levels ≥5 mg/L. However, none of these differences reached statistical significance (p>0.05) (Table 7).

Discussion

This study demonstrated that the prevalence of NP is high among adult patients with SCD and that NP occurs significantly more frequently in this population than in healthy controls. The significantly higher scores observed in the SCD group across all three assessment tools—LANSS, DN-4, and painDETECT—support the notion that pain in SCD is not limited to acute vaso-occlusive processes but frequently evolves into a chronic pain phenotype with neuropathic features [7-9,16-18].

In our study, the prevalence of NP ranged from 33.9% to 50% depending on the assessment scale used; these findings are largely consistent with previously reported rates in adult SCD populations. These results highlight that the neuropathic component of pain constitutes a substantial clinical burden, particularly in adult patients with SCD [7-9,16,17].

Although the pathophysiology of pain in SCD has traditionally been attributed to microvascular occlusion and tissue ischemia resulting from erythrocyte sickling, accumulating evidence suggests that this model alone is insufficient to explain the full spectrum of pain experienced by patients. Recurrent ischemic episodes are thought to induce structural and functional damage to peripheral nerve fibers, thereby facilitating the development of NP. In addition, chronic inflammation, oxidative stress, and endothelial dysfunction have been reported to increase neural sensitization and contribute to pain chronicity [12,16-19].

Functional neuroimaging and quantitative sensory testing studies have further demonstrated alterations in central pain-processing pathways and the development of central sensitization in patients with SCD. These findings indicate that pain in SCD is sustained not only by peripheral mechanisms but also by central nervous system-mediated processes [14,16,18-20].

The use of three different validated NP scales represents an important strength of this study, as it enhances the robustness and reliability of the findings. The observed variability

Table 7. Analysis of neuropathic pain according to the painDETECT scale and selected variables*

Variable	Negative, n (%)	Suspected, n (%)	Positive, n (%)	p value
Sex				0.434
Female	19 (47.6)	3 (14.3)	8 (38.1)	
Male	19 (54.3)	8 (22.9)	8 (22.9)	
Comorbidity				0.538
Present	8 (42.1)	4 (21.1)	7 (36.9)	
Absent	21 (56.8)	7 (18.9)	9 (24.3)	
Hydroxyurea				0.359
Yes	20 (47.6)	10 (23.8)	12 (28.6)	
No	9 (64.3)	1 (7.1)	4 (28.6)	
Folic acid				0.979
Yes	19 (52.8)	7 (19.4)	10 (27.8)	
No	10 (50.0)	4 (20.0)	6 (30.0)	
Annual crisis frequency				0.284
<3	19 (61.3)	5 (16.1)	7 (22.6)	
≥3	10 (40.0)	6 (24.0)	9 (36.0)	
Hemoglobin (g/dL)				0.441
<8	6 (66.7)	2 (22.2)	1 (11.1)	
≥8	23 (48.9)	9 (19.1)	15 (31.9)	
CRP (mg/L)				0.702
<5	9 (60.0)	2 (13.3)	4 (26.7)	
≥5	20 (48.8)	9 (22.0)	12 (29.3)	

*: Chi-square test was used, CRP: C-reactive protein

in NP prevalence across the scales may be attributed to methodological differences in sensitivity and specificity among these instruments. In particular, the LANSS scale includes a clinical examination component, which may explain the higher prevalence rates detected with this tool, whereas DN-4 and painDETECT rely primarily on symptom-based assessments [15,17].

With regard to clinical variables, no statistically significant associations were identified between NP and sex, comorbidity status, HU use, or FA supplementation. Previous studies have reported inconsistent findings regarding the effect of HU on chronic and NP, suggesting that its benefits may be more pronounced in reducing acute vaso-occlusive events rather than NP mechanisms [4,15,18]. Female sex and the presence of comorbid conditions showed trends toward statistical significance in some analyses. While previous studies have suggested that women may be more susceptible to chronic pain syndromes due to hormonal and psychosocial factors, evidence specific to SCD remains inconsistent [10,14,17].

The relationship between annual crisis frequency and NP was another notable finding of this study. Although patients experiencing more than three vaso-occlusive crises per year exhibited higher NP prevalence, this association did not reach statistical significance. Nonetheless, prior studies have emphasized that frequent crises may contribute to the development of NP through repeated nerve ischemia and sustained inflammatory responses [8,12,16,19].

The lack of significant associations between laboratory parameters (Hb, CRP, ferritin, and LDH) and NP suggests that NP cannot reliably be predicted from routine biochemical markers. Systemic inflammatory markers such as CRP may not adequately reflect localized neuroinflammatory processes involved in NP [12,17,19]. Consistent with current literature, NP appears to be more closely related to chronic nerve injury, central sensitization, and neuroinflammatory mechanisms rather than conventional laboratory indicators [12,17-20].

The relatively high prevalence of complications such as avascular necrosis, acute chest syndrome, leg ulcers, and priapism observed in our cohort indicates a substantial disease burden. These complications have previously been shown to prolong pain duration and increase analgesic requirements in patients with SCD [9,10].

The clinical impact of NP extends beyond pain intensity alone. NP has been associated with increased emergency department visits, frequent hospitalizations, long-term opioid use, risk of dependency, and marked impairment in quality of life [1,8,10,17]. Furthermore, chronic pain in SCD has been strongly linked to depression, anxiety, and sleep disturbances [14].

Overall, our findings underscore the heterogeneous nature of pain in SCD and emphasize the clinical importance of the neuropathic component. Pain assessment in patients with SCD should extend beyond acute vaso-occlusive crises to include chronic and neuropathic dimensions, thereby facilitating the development of multidisciplinary and individualized treatment strategies [1,8,17].

Study Limitations

This study has several limitations. First, its single-center, cross-sectional design limits the ability to establish causal relationships between NP and clinical or laboratory parameters. Second, the relatively small sample size may have reduced the statistical power to detect significant associations. In addition, psychiatric comorbidities, opioid use patterns, and pain duration were not evaluated, which may have influenced the assessment of NP. Despite these limitations, the inclusion of a matched control group and the use of three validated NP assessment tools strengthen the reliability and clinical relevance of the findings.

Conclusion

The findings of this study indicate that NP has a high prevalence in SCD and is more prominent in patients experiencing frequent vaso-occlusive crises and clinical complications. These results demonstrate that the pathophysiology of pain in SCD cannot be explained solely by acute vaso-occlusive mechanisms, but rather involves a chronic pain phenotype with significant neuropathic features. Accordingly, systematic assessment of NP using validated tools during routine follow-up, and the

implementation of multidisciplinary, individualized treatment approaches for appropriate patients are crucial for optimizing patient management and improving patients' quality of life.

Ethics

Ethics Committee Approval: Ethics approval for the study was obtained from the Ethics Committee of Hatay Mustafa Kemal University Tayfur Ata Sökmen Faculty of Medicine, and the study was conducted in accordance with the principles of the Declaration of Helsinki (approval no: 09, date: 20.02.2020).

Informed Consent: Written informed consent was obtained from all participants prior to enrollment.

Footnotes

Authorship Contributions

Surgical and Medical Practices: A.D.G., G.İ., İ.M.M., H.K., Concept: G.İ., İ.M.M., H.K., Design: G.İ., İ.M.M., H.K., Data Collection or Processing: A.D.G., Analysis or Interpretation: A.D.G., İ.M.M., Literature Search: A.D.G., G.İ., H.K., Writing: A.D.G., G.İ.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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