# Upper limb peripheral neuropathy in sickle cell anemia: MR neurography appearances

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## Abstract

Sickle cell anemia is an inherited disorder with many systemic complications. Peripheral neuropathy related to this disorder has been sparsely reported. We report an interesting case of upper limb peripheral neuropathy from sickle cell disease with emphasis on MR neurography appearances and electrophysiology correlation.

**Key words:** Sickle cell anemia; peripheral neuropathy; MRI, MR neurography; MRN

## Introduction

Sickle cell anemia is the most common inheritable hemoglobinopathy in the United States with an expected prevalence of 1 in 625 patients at birth.[1,2] Unlike the well-recognized and common central nervous system complications, peripheral nerve involvement in sickle cell disease is rare.[3] Literature review of peripheral neuropathy related to sickle cell disease is limited to case reports, most commonly involving the mental nerve.[4-6] Other reported involvements include the mandibular nerve,[7] trigeminal nerve,[8] optic nerve,[9,10] median nerve,[11] and lower extremity (sural, tibial, and peroneal) nerves.[12,13] The diagnosis in these case reports was mainly established on clinical basis supplemented by electrophysiological studies.

We present a case report of a patient with sickle cell disease who clinically developed bilateral ulnar neuropathies and highlight the diagnostic evaluation with novel use of MR neurography (MRN), which also showed other unsuspected neuropathies. Electrophysiology findings and diffusion tensor imaging (DTI) appearances are also illustrated.

## Case Report

A middle-aged woman with a long-standing history of sickle cell disease (Hb-SS) presented at the institutional outpatient clinic for evaluation of pain, weakness, and ulnar-sided atrophy in both of her upper extremities. She was in her normal state of health till 6 months prior to the presentation, where she developed sudden pain in the left hand without antecedent trauma. The symptoms did not resolve with oral analgesics and blood transfusion therapy. The pain was described as a "pressure sensation" with

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"pins and needles" in the third, fourth, and fifth digits of her left hand. There was subsequent onset of similar pain in the contralateral right hand about 48 hours later. Progressive weakness of both hands started in another 48 h with difficulty in bilateral finger movements. She was given a trial of hydrocodone and meloxicam and also started on oral vitamin D and nortriptyline 50 mg without pain relief or symptomatic improvement. The pain and weakness in both hands remained stable since then. There was no recent history of trauma, change in the level of activities, or unusual factors. Her other significant past history included depression and previous bilateral total hip replacements as a complication, sickle cell disease-related osteonecrosis. No prior sickling episodes requiring neuropathy work-up were documented.

Physical examination revealed bilateral mild clawing posture of the fourth and fifth digits with active weakness in extension and decreased sensation in bilateral ulnar nerve distribution. Passive extension was preserved. There was intrinsic atrophy of both hands. Hypersensitivity of the ulnar nerve at the elbow was noted bilaterally, more so on the left. Systemic review revealed no additional relevant clinical finding.

Her autoimmune disease work-up was negative. Active sickle crisis was clinically excluded at the time of presentation. She underwent a nerve conduction study, which showed evidence of bilateral ulnar neuropathies [Figure 1]. Bilateral ulnar motor responses recording at the first dorsal interossei had normal latencies, severely decreased amplitudes, and normal conduction velocities. The right ulnar antidromic sensory response had mildly prolonged latency and severely decreased amplitude. The left ulnar antidromic sensory response was absent.

MRN of both elbows and upper arms were subsequently performed on a 3-Tesla system for suspected bilateral ulnar nerve entrapment at the cubital tunnels (Achieva, Philips, Best, Netherlands) using an extremity flex coil. The MRN technique included 2D axial T1-weighted (TR/TE, 700/9, slice 4 mm) and fluid-sensitive T2-weighted turbo-spin echo spectral adiabatic inversion recovery (4,000/65/4) sequences with high matrix resolution (256 × 256 to 448 × 448).

**Motor Summary Table**

| Stim Site | NR | Onset (ms) | O-P Amp (mV) | Neg Area (mVms) | Neg Dur (ms) | Site1 | Site2 | Delta-0 (ms) | Dist (cm) | Vel (m/s) |
|---|---|---|---|---|---|---|---|---|---|---|
| **Right Ulnar (FDI) Motor (FDI)** | | | | | | | | | | |
| Wrist | | 2.5 | 0.9 | 3.28 | 5.78 | Wrist | FDI | 2.5 | 7.0 | |
| B Elbow | | 5.9 | 1.0 | 3.47 | 7.66 | B Elbow | Wrist | 3.4 | 22.0 | 65 |
| A Elbow | | 7.8 | 0.8 | 2.61 | 6.88 | A Elbow | B Elbow | 1.9 | 12.0 | 63 |
| **Left Ulnar (FDI) Motor (FDI)** | | | | | | | | | | |
| Wrist | | 3.3 | 0.5 | 1.34 | 4.84 | Wrist | FDI | 3.3 | 7.0 | |
| B Elbow | | 6.6 | 0.3 | 0.98 | 6.72 | B Elbow | Wrist | 3.3 | 22.0 | 67 |
| A Elbow | | 8.3 | 0.4 | 1.33 | 5.78 | A Elbow | B Elbow | 1.7 | 12.0 | 71 |

**Anti Sensory Summary Table**

| Stim Site | NR | Peak (ms) | O-P Amp (μV) | Site1 | Site2 | Delta-0 (ms) | Dist (cm) | Vel (m/s) |
|---|---|---|---|---|---|---|---|---|
| **Right Ulnar Anti Sensory (5th Digit)** | | | | | | | | |
| Wrist | | 4.1 | 2.0 | Wrist | 5th Digit | 3.4 | 11.0 | 32 |
| Wrist | | 4.3 | 2.9 | | | | | |
| **Left Ulnar Anti Sensory (5th Digit)** | | | | | | | | |
| Wrist | NR | | | Wrist | 5th Digit | | 11.0 | |

**Waveforms:**

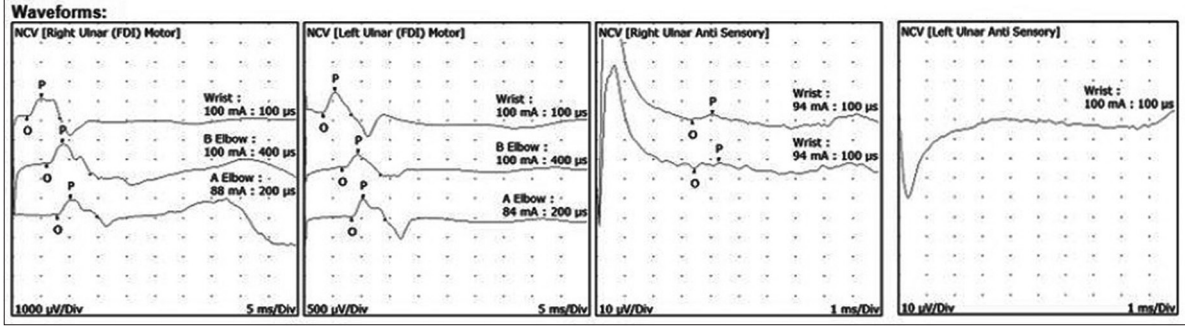


**Figure 1:** Electrophysiology testing shows the summary and waveforms of the motor and antisensory testing at the right and left ulnar nerve at the levels of the wrist, and below and above the elbow. Bilateral ulnar motor responses recording at the first dorsal interossei had normal latencies, severely decreased amplitudes, and normal conduction velocities. The right ulnar antidromic sensory response had mildly prolonged latency and severely decreased amplitude. The left ulnar antidromic sensory response was absent

Nerve-selective coronal 3D diffusion-weighted reversed fast imaging with steady-state free precession (3D DW-PSIF, TR/TE, 12/2.5, voxel-0.9 mm, water selective fat suppression) and axial diffusion tensor imaging (b-0,600, 15 directions of interrogation, slice 4 mm) were also acquired.

Bilateral ulnar nerves showed abnormal diffuse thickening and marked T2 hyperintensity, more pronounced on the left side consistent with bilateral ulnar neuropathy [Figure 2]. There was also minimal flattening of both ulnar nerves at the cubital tunnels with some loss of signal intensity, suggesting a mild degree of superimposed compression [Figures 2 and 3]. Bilateral median and radial nerves also appear mildly enlarged and moderately hyperintense, suggestive of additional neuropathic changes. Axial T1W imaging of the included field-of-view at the level of the elbow revealed fatty atrophy of bilateral pronator teres, biceps, brachialis, and brachioradialis muscles consistent with chronic denervation change [Figure 4].

DTI showed decreased fiber tracks in both ulnar nerves, more prominent on the left side. The fiber tracts for both median and radial nerves were relatively preserved [Figure 5]. The fractional anisotropy (FA) and apparent diffusion coefficient (ADC) of the ulnar nerves measured 0.50, 1.80 and 0.51, 1.40 × $10^3$ $mm^2/s$ on the left and right sides, respectively. DTI findings were consistent with bilateral ulnar neuropathies. The FA and ADC values for the median nerves (0.64/1.24 left, 0.68/1.22 right) and radial nerves (0.53/1.60 left, 0.64/1.31 right) were within normal limits.

Subsequent biopsy of the left first dorsal interosseous muscle and flexor carpi ulnaris muscle confirmed chronic denervation atrophy of both muscles with depopulation of intramuscular nerve twigs. Biopsy of the left dorsal sensory ulnar nerve showed advanced chronic axonal neuropathy. There was no evidence of inflammatory or vasculitic myopathic process on pathology. The patient was managed conservatively.

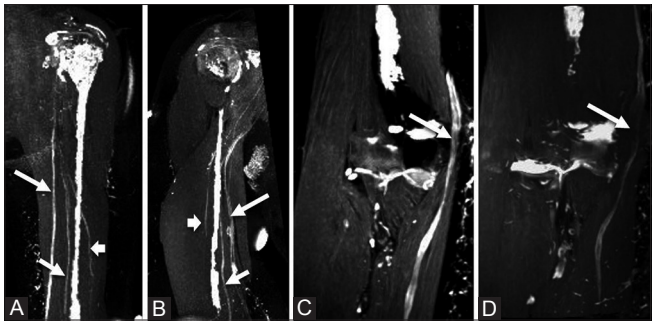


**Figure 2(A-D):** Coronal (A) and (B) reformatted DW-PSIF maximum intensity projection images through the left and right arm, respectively, show the abnormally enlarged and markedly hyperintense ulnar nerves (long arrows). The slightly prominent and moderately hyperintense median nerves (medium arrows) and radial nerves (short arrows) are also seen. Extensive intramedullary bone infarcts in both humeral shafts are leading to hyperintense marrow signal. Focused imaging of left and right elbow (C, D) demonstrate both abnormal ulnar nerves, left > right with diffuse lesions. Notice mild flattening of the nerves in the tunnels with slight decreased signal of the nerves related to mild superimposed entrapments of the swollen nerves coursing through the confined space of the cubital tunnels

## Discussion

Peripheral nervous system involvement in sickle cell disease can be a significant source of neuropathic pain and disability, which is gaining recognition as a rare complication. While the exact pathogenesis has not been established, the generally accepted hypothesis was proposed by Shields *et al*. in a report of a patient with an acute proximal median mononeuropathy. The authors suggested that it is likely a spectrum of electrophysiological and pathological alterations secondary to an ischemic insult during a sickling crisis, ranging from transient metabolic conduction block to segmental demyelination or Wallerian degeneration.[3,11] Shields *et al*. further proposed that the relative rarity of peripheral nerve involvement may be due to the extensive vascular supply around peripheral nerves, which naturally confers resistance to an ischemic insult. Hence, only a combination of predisposing factors, such as dehydration, acidosis, or sickling in conjunction with anatomically vulnerable nerves, such as at the watershed or vascular overlap zones, may be affected due to an ischemic insult.

In our patient, the bilateral ulnar neuropathies were unequivocally shown on MRN and positively correlated

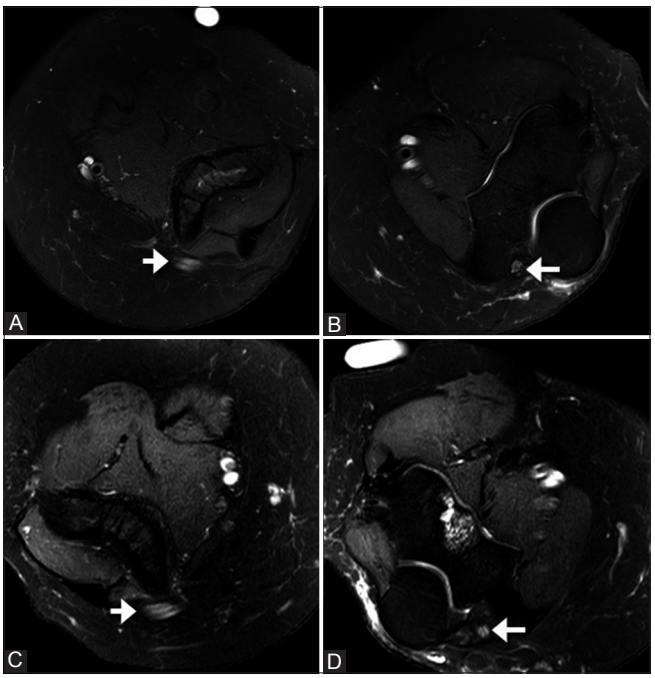


**Figure 3 (A-D):** Sequential T2-weighted SPAIR images proximal to (A) and within the cubital tunnel (B) show the hyperintense and flattened ulnar nerve on the left side (arrow). Similar findings are seen on the right side (C and D, arrow)

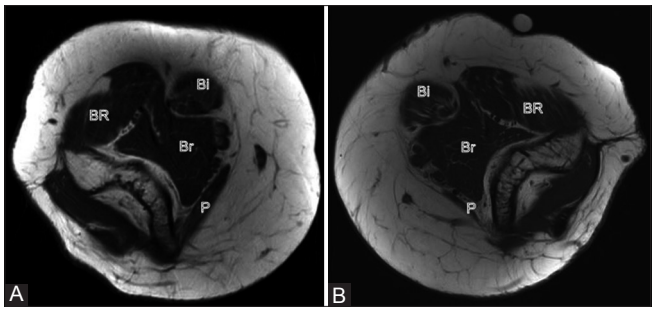


**Figure 4(A and B):** Axial T1-weighted images of the left (A) and right (B) elbows show fatty atrophy of the pronator teres (P), brachialis (Br), brachioradialis (BR), and biceps (Bi) muscles, in keeping with chronic denervation change

with the nerve conduction study and biopsy findings, resulting in a high diagnostic confidence. While a rare entity, clinical observation studies have suggested that the common nerves in humans susceptible to ischemia in systemic conditions are the extremity nerves, including the tibial, peroneal, and sural nerves and the ulnar, median, and radial nerves.[14-16] In our case, the anatomically vulnerable swollen ulnar nerves located within the confined spaces of the cubital tunnels showed a greater extent of clinical involvement, reflective of a combination of both ischemic and compressive effects. In addition, MRN also demonstrated neuropathic changes of bilateral median and radial nerves, which the patient did not have clinical symptoms, suggesting subclinical involvement. This corroborates with the study by Okykucu *et al*. in 2008, which evaluated 51 sickle cell patients and controls for peripheral neuropathy on conventional electrophysiological tests and concluded that subclinical peripheral neuropathy is not uncommon in sickle cell disease.[3]

The authors believe that this is the first case report in the literature describing bilateral ulnar, median, and radial neuropathies in sickle cell disease and the first to describe the use of 3T-MRN to aid the diagnosis of neuropathy and superimposed entrapment. Prior case reports mostly relied on clinical diagnosis and electrophysiological tests for diagnosis, with some patients undergoing conventional magnetic resonance imaging mainly to exclude possible mass lesions or other causes.[4-13] High field, 3-T imaging allows better fat-saturation with acquisition of thin-section images of high signal-to-noise ratio (SNR) and improved spatial resolution.[17] MRN also offers distinct advantages over nerve conduction studies by noninvasive coverage of all regional nerves in the symptomatic extremity, allowing comprehensive and systematic assessment of the entire peripheral nerve system in the symptomatic limb in a single sitting, allowing for a quicker and more confident diagnosis and shortened time to therapy. MRN could also depict bone marrow infarcts of the humerus. In addition, MRN allows temporal correlation by detecting regional denervation changes [Figure 4]. In the acute setting, muscle denervation

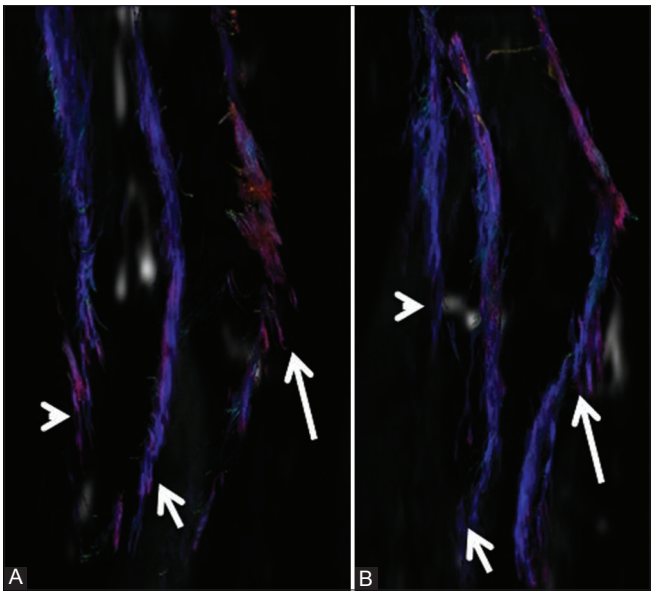


**Figure 5 (A and B):** DTI shows reduced fiber tracks in bilateral ulnar nerves (long arrows) consistent with chronic neuropathy, more pronounced on the left side (A) than on the right (B). The fiber tracks of both median (short arrows) and radial nerves (arrowheads) are relatively preserved

is seen as abnormal hyperintensity on fluid-sensitive T2-weighted sequence with preserved muscle bulk. In the chronic setting, fatty infiltration and atrophy on T1-weighted sequence are typical. A combination of changes is seen in the subacute setting. T2-signal abnormalities can be maximized by using long TE of approximately 90–130 ms, which will also reduce magic angle artifacts.[17] With 3D imaging, TE of 70–80 ms on fat suppressed imaging is enough to conspicuously depict the intraneural edema.

Diffusion imaging also allows selective depiction of extremity nerves.[18] Inclusion of a nerve-selective 3D isotropic sequence such as 3D DW-PSIF further enhances relative nerve conspicuity by effective suppression of vascular flow signal through diffusion-sensitive gradients. To maximize the inherently low SNR from diffusion-weighting, multiple signal averages (2 to 3) are used and the *b*-value is kept in the range of 50–60 s/mm$^2$. Patients should be reminded to keep still to minimize the known pitfall of motion sensitivity, which may result in motion artifacts.[17] This enables excellent nerve visualization in multiplanar reconstructions and their signal alterations [Figure 2].

Our case also highlights the use of diffusion tensor imaging (DTI) as an emerging tool in assessing peripheral nerve pathology.[19] Based on the principle of anisotropy, DTI provides information on fiber trajectory and also quantitative assessment of nerve microstructure and function. Calculations of the ADC and derivations of the mean diffusivity and FA can be obtained. Neuropathic changes lead to decreased FA and increased ADC values.

Increasing FA values within the peripheral nerves has been shown to correlate with motor and sensory functional recovery in animal models and may have a role for monitoring clinical recovery.

## Conclusion

MRN of the peripheral nerves is a powerful diagnostic tool and provides comprehensive assessment of sickle cell disease patients with suspected clinical or subclinical peripheral neuropathy. Used in tandem with electrodiagnostic studies, MRN increases the diagnostic confidence and provides direct objective evidence of neuromuscular pathology as well as the presence or absence of superimposed entrapment and excludes a regional mass lesion.

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Nil.

### Conflicts of interest

There are no conflicts of interest.

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