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Diffusion Tensor Imaging: The Future of Diagnostics in Amputation Neuromas

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Abstract

Each year in the United States, approximately 185,000 people undergo limb amputations. Their recovery can be complex as many will suffer from either phantom pain, infection, ulceration, stump pain, and/or painful neuromas. Painful neuromas complicate rehabilitation and have devastating effects on quality of life. Neuromas are difficult to diagnose with current methods, which include clinical exam, ultrasound and Magnetic Resonance (MR) neurography. Individually, these techniques are often inadequate and cannot reliably distinguish neuromas from complex regional pain syndrome, phantom pain, abscess formation, osteomyelitis or local tumor recurrence. Without a clear diagnosis, amputation neuroma patients are turned away, neglected and /or treated with overly conservative measures. Enhanced detection of neuromas following amputations or traumatic peripheral nerve injuries would allow for earlier surgical intervention and minimized physical disability. Diffusion Tensor Imaging (DTI) is a non-invasive MRI based approach that probes tissue at the microstructural level and has recently demonstrated exciting potential for neuroma diagnosis. Unlike current detection methods, DTI measures water diffusion anisotropy and provides quantitative parameters to describe abnormal nerve growth. Nerve degeneration and/or regeneration in animal models can be monitored with DTI and tractography based on its sensitivity to nerve microstructure. Our lab has further employed DTI for detection of suspected neuromas in animals that failed to recover after sciatic nerve injury and neurorrhaphy. With future advancements in human DTI peripheral nerve protocols, earlier neuroma detection and surgical intervention will be possible.

Keywords: Neuroma; MRI; DTI; Diffusion tensor imaging; Fractional anisotropy; Amputation

Abbreviations: DTI: Diffusion Tensor Imaging; VUIIS: Vanderbilt University Institute of Imaging Science; SPAIR: Spectral Attenuated Inversion Recovery; FA: Fractional Anisotropy; RD: Radial Diffusivity; AD: Axial Diffusivity; MD: Mean Diffusivity; ADC: Apparent Diffusion Coefficient

Introduction

Neuromas result from a disruption in the normative nerve regeneration process after amputation or following a traumatic nerve laceration, surgery, and/or crush injury [1,2]. These abnormal nerve proliferations are characterized by disorganized axonal growth outside the severed epineural sheath and they typically develop at the distal end of the transected nerve. Each year in the United States approximately 185,000 people undergo limb amputations [3]. It is believed that due to an increased prevalence of vascular disease, diabetes, and trauma the prevalence of limb loss is expected to double by 2050 [4]. Unfortunately, associated postamputation pain can be physically debilitating, making ambulation with prosthesis unbearable [5]. Painful neuromas are often refractory to medicinal therapies, and surgical intervention is the definitive treatment [5,6]. The bulbous neuroma can be resected followed by interventions such as proximal nerve reattachment to a nearby normal nerve or neurorrhaphy, targeted muscle reinnervation, nerve grafting, or epineural closure [6,7]. Nonetheless, roughly 61% of amputation patients report some residual pain. Forty nine percent of amputees' stump-related pain is presumed to be caused by neuromas [8]; however, neuromas may be overlooked or misdiagnosed as phantom pain, infections, ulceration, cicatrization, or stump pain [9,10]. Enhanced detection of neuromas following amputations or traumatic peripheral injuries would improve surgical management and help minimize physical disability.

Radiographic imaging of neuromas can be difficult and there is no 'gold standard' imaging protocol [11]. High resolution

Ultrasound (US) and Magnetic Resonance Imaging (MRI) have been implemented to detect nerve damage; [12,13] however, the disruption of normal anatomy and inflammation around an amputation site can interfere with the precision necessary to adequately describe a neuroma. Furthermore, MRI of small caliber nerve trunks in below-the-knee amputations are difficult to visualize [12]. Better diagnostic techniques are needed to help differentiate painful neuroma from complex regional pain syndrome, phantom pain, or local tumor recurrence after a cancer related amputation.

Our experience

Though current diagnostics methods are inadequate for amputation neuromas, novel imaging protocols have demonstrated promising results. In our experience, a 26-year-old female with a history of polyarteritis nodosa presented with left lower extremity pain approximately 19 months after a below-the-knee amputation. Given her amputation history and physical exam findings, there was a high clinical suspicion for neuroma or nerve entrapment. As part of her neuroma workup a lower extremity non-joint MRI was performed with and without contrast using standard hospital MRI technology. The sequences obtained included axial T1, axial T1 with Fat Suppression (FS), axial T2 with FS, coronal Short Tau Inversion Recovery sequence (STIR), coronal T1, sagittal proton density with FS, axial T1 with FS post contrast and coronal T1 with FS post contrast sequences of the left lower extremity (Figure 1). The radiologist's impression described a positive fluid collection and surrounding inflammation with signal abnormalities within the adjacent residual tibia. The differential diagnoses included mechanical, inflammatory, and infectious causes. Osteomyelitis was strongly considered given the presumed adjacent abscess formation. The radiologist report concluded there was no evidence of a neuroma. Prior to performing a surgical exploration and possible resection of the suspected neuroma, the Vanderbilt University Institute of Imaging Science (VUIIS) performed an additional scan under an Institutional Review Board approved MRI research study. The VUIIS houses experts of Philips scanners who can perform specialized scans with higher resolution than the scans utilized in the clinical/hospital setting.

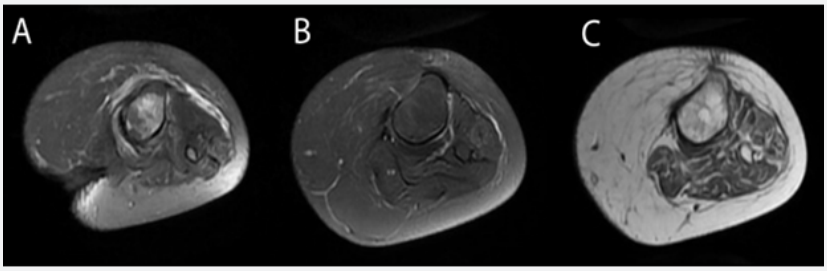

Figure 1: Left Lower Extremity on MRI Cross-Section A) AX T2 with FS; B) AX T2 with FS; C) AX T1.

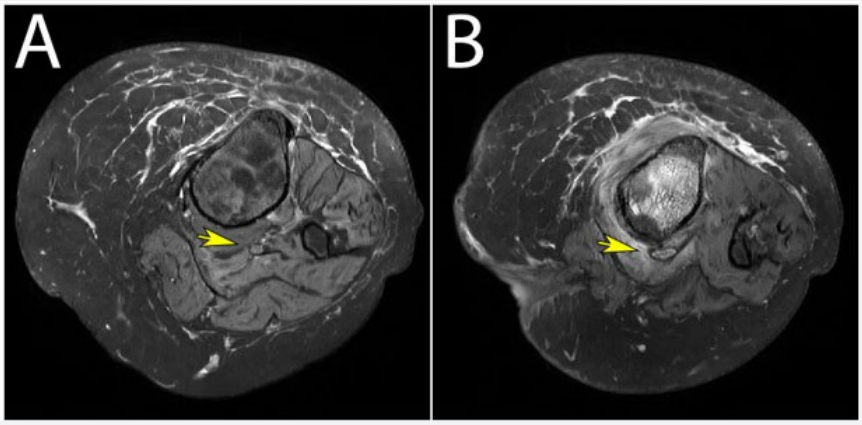

Figure 2: A. Proximal View of Left Lower Extremity on MRI Cross-Section with Tibial Nerve Neuroma (Yellow Arrow), B. Distal View of Left Lower Extremity and Tibial Nerve Neuroma (Yellow Arrow).

The scan conducted at VUIIS included a proton-density-weighted MRI with Spectral Attenuated Inversion Recovery (SPAIR) and gradient-reversal fat suppression techniques to achieve the more detailed and clearer images seen in Figure 2. Utilizing the Philips SPAIR fat suppression, we achieved an enhanced visualization of irregular thickening of the tibial nerve at the distal end of the stump (Figure 2, yellow arrows). After surgical exploration and resection, the surgical pathology report confirmed our suspicion and agreed with our specialized MRI findings. A traumatic neuroma (Figure 3 & 4) was found adjacent to the nerve with surrounding foreign body giant cell reaction (no osteomyelitis was identified).

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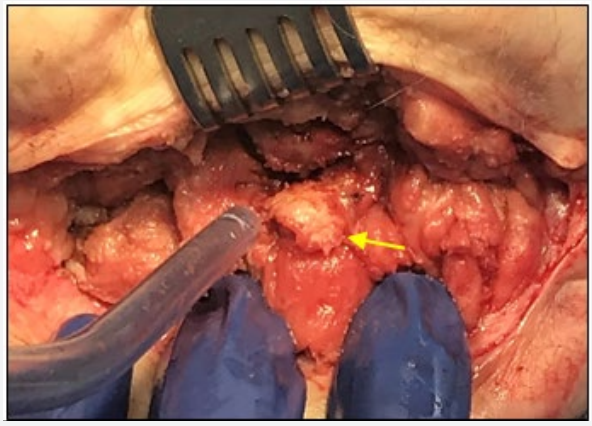

Figure 3: Tibial Neuroma (Yellow Arrow).

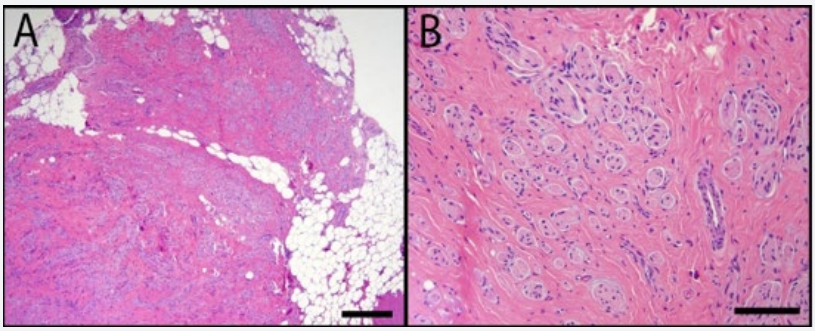

Figure 4: H&E Stained Sections Showed Haphazardly Arranged, Variably Sized Nerve Fascicles within a Background of Dense Fibrosis, Consistent with a Traumatic Neuroma. A. Scale Bar = 400μm, B. Scale Bar = 100μm.

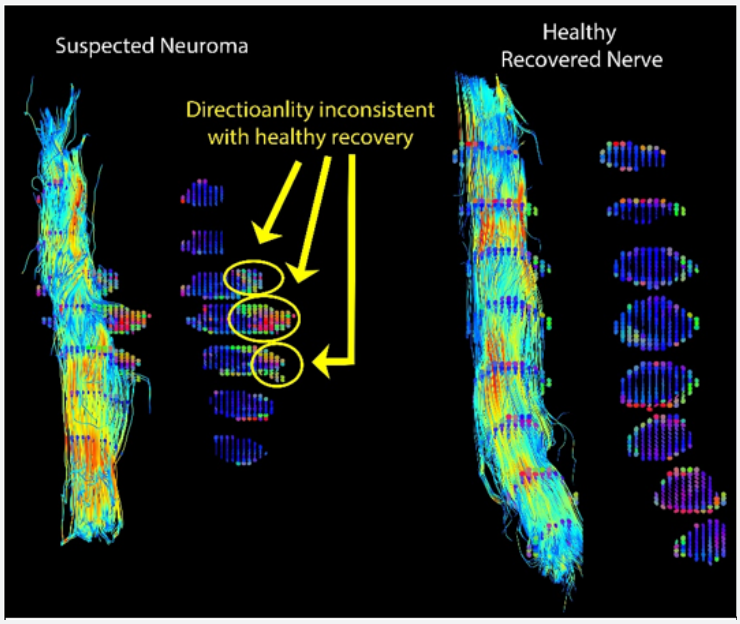

Figure 5: MRI DTI Tractography and Slice-Wise View of Directionality Vectors of Example 12 Week Transected and Repaired Rat Sciatic Nerves. Suspected Neuroma (Left) and Healthy Recovered Nerve (Right).

Discussion

Improved detection of peripheral neuromas and irregular nerve regeneration could drastically change patient outcomes and improve overall quality of life. Even with technical advancements, current imaging modalities cannot always differentiate neuroma proliferations from peripheral nerve

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neoplasms, an important distinction in the case of local recurrent cancer [11,14]. This may be due to abnormal scarring, edema, and abscess formation. MRI techniques still require a high level of expertise to enhance the area of interest and eliminate bright signals from fatty atrophy and/ or anatomical abnormalities [12]. When imaging neuromas, some experts suggest using the low signal intensity on T1-weighted images and intermediate to high signal intensity on T2-weighted MR images [15]. Neuroma images typically demonstrate scarring and an absence of a target sign; they can, however, give off a low signal intensity ring on T1 and T2 weighted images [1,15,16]. Existing limitations of standard MRI scans for neuroma patients include problematic issues with metal screening safety and accessibility depending on the state of the patient's disability, as the subject is required to lay on a table for up to an hour at a time for scanning. Lastly, the abnormal structure of fat, muscle, and bone create a unique challenge to apply MRI scans that were developed for use on healthy subjects.

Diffusion Tensor Imaging (DTI) is a non-invasive MRI based approach that characterizes tissue at the microstructural level. DTI was developed in the 1980s [17,18] and has since then revolutionized MRI detection of human central nervous system pathology including strokes [19], brain tumors [20], multiple sclerosis [21-23] schizophrenia, aging [24], and other cancers [21-26]. DTI measures water diffusion along multiple directions, measuring the effect of tissue barriers that results in diffusion anisotropy. In healthy nerves, the ordered arrangement of axons results in an Apparent Diffusion Coefficient (ADC) that is lower perpendicular to axons than parallel to them. Unlike high resolution ultrasounds and MR neurography, diffusion along multiple directions can be measured with DTI by quantifying indices that describe its diffusion anisotropy. Some of the most important indices are: fractional anisotropy (FA = 0-1, lower values indicate low anisotropy), radial diffusivity (RD, diffusivity perpendicular to the axons), axial diffusivity (AD, diffusivity along the axons), and mean diffusivity (MD, mean value across all directions). The scope of DTI technology has gradually expanded to include the peripheral nervous system; however, image precision remains a challenge due to the small caliber nerves, requiring high spatial resolution balancing signal to noise ratio and time limitations while addressing field inhomogeneity, fat suppression, distortion and motion, [27] was among the first to demonstrate DTI's use in human peripheral nerves when he accurately scanned and produced DT images of the sciatic nerve in 3 healthy human subjects [28].

In subsequent years, Hiltunen et al. [29] successfully produced DT images, 3D tractography, ADC and FA measurements of the radial, median, ulnar, tibial and peroneal nerves. Hiltunen and coworkers concluded that FA values vary with thickness of the nerve. Meek et al. [30] was among the first to use DTI in a human subject with an isolated lesion of the median nerve. The lesion was repaired 1 month prior to imaging, and therefore Meek et al. [30] exhibited the utility of DTI in differentiation of intact and regenerative nerve fibers in the median nerve. Others further support DTI use in peripheral nerves and are seeking to create standard parameters for detection of axon and myelin sheath integrity of distal nerves of the wrist [31]. DTI functionality in peripheral nerve pathology continues to grow and now encompasses traumatic peripheral nerve injuries [30], carpal and cubital tunnel syndromes [31,32] as well as neoplasms. To date DTI of peripheral neuromas has not been thoroughly studied. Our lab has used DTI parameters to detect suspected neuromas in animals that failed to recover after sciatic nerve injury and repair.

Using diffusion MRI techniques and measurements, neuromas that are characterized by dense and incoherent axonal sprouting may be distinguishable from fully regenerated nerves with coherent axonal structure. In addition, virtual fiber tracts (employing DTI measurements to extract the primary direction of diffusion) could provide information regarding the reduced fiber coherence present in neuromas. Nerve degeneration and/ or regeneration in animal models can be monitored with DTI and tractography based on its sensitivity to nerve microstructure. DTI (axonal packing derived diffusivities) and fiber tracking (differences in fiber coherence) techniques have the potential to become an early biomarker in the study and differentiation of neuromas from other regenerating and degenerating nerves after trauma and surgical repair.

Experiments studying the application of MRI DTI to assess the regeneration of sciatic nerves in a rat model have been conducted in our lab. Post-experimental analysis of complete transection and repair in animals 12 weeks after surgical procedure revealed a possible neuroma. Figure 5 displays the DTI tractography and slice-wise directionality vectors for our suspected neuroma as well as that of a healthy recovered sample. In the slice-wise images of the suspected neuroma, the DTI measurements indicate areas of the nerve where no primary eigenvector can be distinguished. This indicates that the damaged and recovering axons present in this region are dysfunctional and extend in multiple directions, which does not allow for tractography images to be generated in this region. Conversely, in the healthy recovering nerve, the slice-wise DTI measurements consistently indicate axonal extension along the primary eigenvector, producing a tractography image where the entire nerve is fully represented. The preliminary outcomes in animal models are promising and have prompted our research team to employ DTI technology for humans suffering from suspected amputation neuromas.

Conclusion

Amputation patients face adversity adjusting to their new physical limitations, prosthesis rehabilitation, mental exhaustion, and lingering pain. A painful neuroma should be surgically resected shortly after its discovery, but unfortunately current diagnostic methods are inadequate for proper detection and often prolong the repair process. With further advancements

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in research and the development of human DTI neuroma protocols, new technology could revolutionize the management of patients suffering from painful neuromas.

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