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VISUALIZING AXON REGENERATION AFTER PERIPHERAL NERVE INJURY WITH MAGNETIC RESONANCE TRACTOGRAPHY

Diffusion tensor imaging (DTI) with tractography is an MRI technique that can visualize nerve pathways by taking advantage of anisotropy of water diffusion in tracts with longitudinally oriented fibers. To date, no study in humans has shown that DTI and tractography can follow regeneration of axons during recovery from traumatic peripheral nerve injury. We show that tractography is able to identify regenerating axons advancing through a graft repair of an injured nerve, and demonstrate correlation with evidence of recovery on serial clinical, electrodiagnostic, and muscle MRI assessments.

Case report. A 25-year-old man lacerated his popliteal fossa with a concrete saw, resulting in a common peroneal neuropathy, with paralysis of ankle dorsiflexion and toe extension and 4/5 eversion weakness. Electrodiagnostic studies performed 4 months after injury showed no innervation of tibialis anterior (TA) and extensor hallucis longus (EHL), supplied by the deep peroneal nerve. Muscles supplied by the superficial peroneal nerve, such as peroneus longus, were only partially denervated.

Methods. DTI and tractography of the peroneal nerve were performed on a 3T scanner (MR750, GE Healthcare, Milwaukee, WI) 2 months after injury. DTI was performed using FOCUS, a reduced field-of-view diffusion method that applies a 2D spatially selective RF excitation in single-shot echoplanar imaging sequence (FOCUS, 28 directions, repetition time 3,200 ms, echo time 55 ms, field of view 18×9 cm, acquisition matrix 256×144 , slice thickness 3.0 mm, voxel size 1.31 mm^3 , b value 600 s/mm^2).^{1,2} The scan was acquired over 3 averages to improve signal to noise ratio. Fractional anisotropy (FA) maps were calculated at each slice from a region of interest tracing the outline of the common peroneal nerve proximal to the injury, the site of transection/grafting, and the distal deep peroneal nerve (figure, C). Tractography was performed using FiberTrak software (GE Healthcare) by placing seed points along the nerve visualized on a corresponding axial T1-weighted image, and calculated

using FA minimum threshold of 0.18 and maximum turning angle threshold of 45° .

Results. On preoperative scans, the peroneal nerve was T2 hyperintense and enlarged. No nerve fibers were identified immediately distal to the site of nerve injury (figure, D). On MRI of the leg, TA and extensor digitorum longus (EDL) demonstrated diffuse T2 hyperintensity reflecting muscle denervation (figure, D).³

Surgical exploration of the nerve was performed 4 months after injury. The deep branch of the peroneal nerve was severely injured, did not transmit electrical impulses, and had a 7.5-cm segment of intraneural fibrosis. The superficial peroneal nerve was both in anatomical and electrophysiologic continuity (figure, A). The scarred segment was resected and the gap between proximal and distal stumps interposed with three 8.5-cm sural nerve grafts (figure, B).

One month after surgery, DTI showed a few axons extending past the repair site into the grafts and persistent muscle edema (figure, E). Thirteen months after surgery, the patient demonstrated significant recovery of foot dorsiflexion (TA 4+/5 strength) and toe extension (EHL 3/5 and EDL 4/5), EMG evidence of reinnervation of these muscles, and normal limb function. Repeat tractography identified regenerating nerve fibers extending through the grafts (figure, F). Muscle denervation changes seen on MRI had resolved.

FA values recorded on preoperative and postoperative scans were consistent with axonal regeneration. FA values increased with recovery in the grafts (preoperative 0, 1 month postoperative 0.20 ± 0.08 , 13 months postoperative 0.41 ± 0.04) and deep peroneal nerve distal to the grafts (preoperative 0.23 ± 0.06 , 1 month postoperative 0.19 ± 0.04 , 13 months postoperative 0.29 ± 0.09). Values from the proximal common peroneal nerve remained relatively stable (preoperative 0.45 ± 0.13 , 1 month postoperative 0.37 ± 0.07 , 13 months postoperative 0.36 ± 0.11).

Discussion. The feasibility of tractography to demonstrate peripheral nerve regeneration has been demonstrated in animal models,⁴ but unlike tractography of white matter tracts in the brain, tractography of peripheral nerves in human subjects has been limited by technical factors such as optimal scan plane selection, satisfactory image resolution, and prolonged scan

Operative exploration of the left peroneal nerve identified a damaged, scarred deep peroneal nerve branch (black arrow, A) and relatively preserved superficial peroneal nerve branch (asterisk, A and B). The deep peroneal nerve branch was resected and the resulting defect bridged with 3 sural nerve grafts (black arrowheads, B). A thresholded fractional anisotropy (FA) map (C) is shown fused to the corresponding axial T1-weighted image. The proximal common peroneal nerve is identified as a region of increased FA signal (arrow), and is encircled by a region of interest used to calculate average FA values. Preoperative magnetic resonance (MR) tractography demonstrates the proximal stump of the deep peroneal nerve branch with no axons identified distal to the point of transection (white arrow, D), and T2-weighted, fat-suppressed imaging of the proximal left leg identifies denervation edema in deep-peroneal innervated muscles (tibialis anterior and extensor digitorum longus, white arrowhead). Repeat MR tractography performed 1 month after surgical repair identifies sparse, disorganized axons distal to the proximal graft neurorrhaphy (white arrow), and persistent muscle edema (E). Tractography performed 13 months after nerve graft repair demonstrates an organized bundle of fibers traversing the nerve grafts and resolution of muscle edema (F).

time. Encouraging evidence emerged from a study of a single patient without clinical or EMG correlates of recovery.⁵

Successful management of traumatic nerve injury requires distinction between neurotmetic injuries, which require surgical intervention, and axonotmetic

injuries, which may recover spontaneously through axonal regeneration. Presently, monitoring of recovery from peripheral nerve injury is based on EMG assessments, but EMG cannot detect axonal regeneration before nerve fibers have reached and reinnervated their target muscle. Magnetic resonance neurography may

show evolution of signal changes with degeneration and regeneration following nerve injury.^{6,7} Magnetic resonance tractography, by visualizing growing nerve fibers, may allow distinction between axonotmetic and neurotmetic injuries earlier, thereby expediting necessary surgeries while reducing the need for exploratory nerve surgery.

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LIMBIC ENCEPHALITIS WITH mGluR5 ANTIBODIES AND IMMUNOTHERAPY-RESPONSIVE PROSOPAGNOSIA

In 1982, Dr. Ian Carr described personality changes and memory loss in his 15-year-old daughter, who had limbic encephalitis and Hodgkin lymphoma (HL).¹ He assumed “a circulating neurotransmitter-like molecule produced by the neoplasm” causing the brain disease, and noted that it “may be reversible and can be remembered as the Ophelia syndrome.” Almost 30 years later, Lancaster et al.² identified antibodies against the metabotropic glutamate receptor 5 (mGluR5) as Carr’s neurotransmitter-like molecule in 2 patients with limbic encephalitis and HL. Encephalitis was reversible in both patients receiving tumor treatment. The clinical spectrum is largely unknown and the role of immunotherapy is unclear.

Case report. A 30-year-old woman complained of night sweats, low-grade fever, fatigue for weeks, and 15-kg weight loss over 8 months. She had acute onset of progressive personality and mood changes, headaches, memory problems, disorientation, and affective incontinence. Lumbar puncture revealed

increased cell counts (25/μL) and intrathecal immunoglobulin G (IgG) synthesis; protein was normal. Extensive tests for infectious encephalitis or metabolic encephalopathy remained negative; repeated head MRIs were unremarkable. Diagnosis of limbic encephalitis of unknown etiology was established. The condition improved in the following weeks; however, deficits in attention and marked impairment of visuoconstructive abilities persisted. The patient complained about prosopagnosia and sleep-associated episodes of enuresis and involuntary movements.

Video-EEG evaluation 3 months later showed frequent episodes of complex abrupt movements out of waking state, tossing and turning in bed, and reduced responsiveness and vocalizations (video on the *Neurology*[®] Web site at Neurology.org). The episodes were not associated with seizure patterns on EEG, reminiscent of psychogenic nonepileptic seizures. However, the patient reported improvement under levitracetam and worsening after discontinuation.

Serum and CSF showed IgG antibodies against mGluR5 in indirect immunofluorescence using mGluR5-transfected HEK293 cells and rat brain sections (figure). The specific antibody index (ratio

Supplemental data
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