Evidence for end-to-side sensory nerve regeneration in a human

Case report

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A XOTOMY induces neurite outgrowth from the portion of the nerve on the proximal side of the axotomy and Wallerian degeneration in the distal stump. Because there is no longer a connection between the distal stump and neuronal cell bodies in the anterior spinal cord or dorsal root ganglion, it is assumed that no neurites should exist in the distal stump. The authors present the case of a patient who unexpectedly had a neuroma on the proximal end of the distal segment of a previously severed nerve. The lateral antebrachial cutaneous nerve had been surgically severed. Innervated by the radial nerve, a neuroma subsequently formed in the distal segment. Our hypothesis is that the proximal end of the distal portion of a severed nerve may be innervated by collateral sprouts of axons that branch at points of more distal plexus formation. This invokes a similar pathophysiology to the controversial notion of end-to-side nerve sprouting. Neuromas that develop on the “wrong side” of a nerve become an additional potential source of pain in patients with injured nerves.

KEY WORDS • neuroma • axonal sprouting • pain • nerve trauma • axonal regeneration • peripheral nerve

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how the connections were made. To determine how sensory axons in the distal LACN traveled to the central nervous system, a series of anesthetic blocks were performed. An anesthetic block of the proximal portion of the LACN did not affect the Tinel’s sign over the distal portion of the LACN. We next performed a radial nerve block; with this the Tinel’s sign disappeared entirely. We considered two possible sources of the connection: junctions between the superficial radial nerve (SRN) and the LACN at the peripheral terminals and, alternatively, junctions between the two nerves at more proximal points of postulated plexus formation. To test these possibilities, we administered a field block at the region of projected paraesthesias and pain at the base of the thumb and wrist. This block had no effect on the Tinel’s sign. This finding, in conjunction with the fact that the radial nerve block abolished the patient’s pain, supported the latter explanation.

The patient underwent a neurectomy of the SRN. At the time of the surgery, additional manipulation of the distal LACN was performed, which led again to referred pain and paraesthesias in the region of the base of the thumb. After the SRN was cut this phenomenon was no longer present.

The patient’s pain was eliminated for several weeks by the neurectomy of the SRN; however, the same pain later returned. Medical therapy including use of opiate medications was unsatisfactory. The patient ultimately underwent implantation of a peripheral nerve stimulator on the proximal portion of the SRN. The patient has done well with this final intervention as of his 18-month follow-up evaluation.

**Discussion**

Division of a peripheral nerve separates the axons in the distal portion of the nerve from the neuronal cell bodies in the dorsal root ganglion and the ventral spinal cord. In the distal portion of the nerve, wallerian degeneration occurs with a loss of axons but preservation of the endoneurial tubes. Within a few days, axonal sprouting develops from the severed axonal ends and distal internodes in the proximal segment. Successful reinnervation depends on the ability of sprouts to find distal endoneurial tubes. If the sprouts fail to find these distal Schwann cell guides, a neuroma forms manifested by a dense tangled mass of sprouts. The axons distal to the axotomy degenerate and, therefore, do not form a neuroma. The finding in this study of a neuroma on the proximal end of the distal portion of the severed nerve is thus unexpected. To account for this finding, a hypothetical model is shown in Fig. 2. It is well established that plexus formation occurs between the LACN and the SRN. In the situation in which a proximal neurectomy has been performed on the LACN, axons that originate in the SRN and travel through a plexus into the distal LACN remain connected to their cell bodies (Fig. 2) and, thus, survive the neurectomy. These axons in the distal LACN are juxtaposed to those Schwann cells devoid of axon contacts secondary to wallerian degeneration. This arrangement corresponds to an “end-to-side nerve graft.” Viterbo, et al., demonstrated in the rat that if a distal nerve segment of a divided nerve is coapted end to side to an intact nerve, axons from the intact nerve sprout into the distal nerve. This phenomenon, subsequently confirmed in other studies, may prove important for the repair of various nerve injuries.

Evidence from the present case suggests that axons originating from the SRN (the side portion of the graft) sprout from the axons juxtaposed to the degenerative LACN (the end portion of the graft) and grow centrifugally to provide innervation of the “distal” neuroma (the proximal end of the distal portion of the cut LACN). Whether the same sprouts that travel centrifugally also travel centripetally or whether sprouts travel one way to the exclusion of the other cannot be discerned from the data obtained in this study.

How widespread this phenomenon is and what nerves may be affected are open to speculation. LeRiche described a patient in whom the ulnar nerve had previously been completely divided. Similar to the present case, that patient underwent surgical exploration of the distal ulnar nerve (that portion of the nerve distal to the point of division) while receiving a local anesthetic. Mechanical manipulation and electrical stimulation of the nerve (but not the surrounding tissue) led to referred sensations in the hand. In that case, the median nerve, which commonly has connections with the ulnar nerve, was undoubtedly the source of sensory axons to the proximal end of the distal ulnar nerve.

Plexus formation between nerves is common. Therefore, distal neuromas in the context of nerve injury may be a common phenomenon. Moreover, surgery aimed at the elimination of nerve injury pain that only includes resection of the proximal neuroma becomes conceptually flawed and may well account in part for the frequent failure of this approach.

Other explanations of the findings in this case were considered. It might be suspected that branches from the proximal portion of the LACN that were not apparent to the surgeon provided connections to the distal segment of the LACN. Several observations suggest this was not the case: 1) an anesthetic block of the proximal LACN did not eliminate the Tinel’s sign over the distal neuroma; 2) an anesthetic block of the SRN and subsequent neurectomy of the SRN did eliminate the Tinel’s sign over the distal neuroma; and 3) at surgery, the distal neuroma was dissected from all surrounding soft tissues and this did not
End-to-side nerve regeneration

![Diagram of nerve regeneration](image)

**Fig. 2.** Drawing of the proposed model to account for findings in this case. Plexus formation occurs between the SRN and the LACN. The LACN was surgically divided and a neuroma formed on its proximal end. The axons in the distal LACN were initially separated from their cell bodies and, thus, underwent wallerian degeneration. In the model we propose that axons in the SRN that form a plexus with the LACN sprout centripetally to innervate the proximal end of the distal LACN, leading to a “distal neuroma.” DRG = dorsal root ganglion.

eliminate the referred sensations associated with manipulation of the distal LACN. We also considered the possibility that nerve connections between the LACN and SRN may occur at the terminals of sensory axons in the skin. This possibility was thought unlikely because the Tinel’s sign over the proximal end of the distal LACN was still present after a field block was performed in the innervation territory of the SRN.

In conclusion, the distal portion of a divided nerve can be spontaneously reinnervated by functional axons. Induction of sprouting by axons that join the nerve segment distal to the injury through an attachment to another nerve can account for this phenomenon. This case report also supports the contention that side-to-end nerve sprouting occurs in humans and may be used to foster functional restoration after nerve injury. Additionally, neuromas that develop on the “wrong side” of a nerve are a further potential source of pain in patients with injured nerves.

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**References**


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