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ORIGINAL PAPER

# Functional Recovery Occurs Even After Partial Remyelination of Axon-Meshed Median and Ulnar Nerves in Mice

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## Abstract

Upper limb nerve injuries are common, and their treatment poses a challenge for physicians and surgeons. Experimental models help in minimum exploration of the functional characteristics of peripheral nerve injuries of forelimbs. This study was conducted to characterize the functional recovery (1, 3, 7, 10, 14, and 21 days) after median and ulnar nerve crush in mice and analyze the histological and biochemical markers of nerve regeneration (after 21 days). Sensory–functional impairments appeared after 1 day. The peripheral nerve morphology, the nerve structure, and the density of myelin proteins [myelin protein zero (P0) and peripheral myelin protein 22 (PMP22)] were analyzed after 21 days. Cold allodynia and fine motor coordination recovery occurred on the 10th day, and grip strength recovery was observed on the 14th day after injury. After 21 days, there was partial myelin sheath recovery. PMP22 recovery was complete, whereas P0 recovery was not. Results suggest that there is complete functional recovery even with partial remyelination of median and ulnar nerves in mice.

**Keywords** Median nerve · Ulnar nerve · Axonotmesis · Strength · Myelin

## Introduction

Nerve injuries are more common in upper limbs, and their treatment presents a challenge for physicians and surgeons; in particular, functional recovery is often limited [1]. The duration of regeneration and functional recovery varies between different nerves and types of injury, as well as in different animal models. To improve the treatment of these lesions, it is important to understand the neurobiology of the nerve injury. Functional deficits caused by nerve injuries can be recovered or compensated for by the following three endogenous neural mechanisms: reinnervation of denervated targets by regeneration of injured axons, reinnervation by collateral sprouting of undamaged axons in the vicinity, and remodeling of circuits within the central nervous systeming of undamaged axons in the vicinity and the remodelling of circuits within the central nervous system [2, 3].

The median and ulnar nerves provide a model in which motor and sensory axons segregate in different nerve branches distal to the wrist. This model has been seldom used due to the limited possibilities of assessing fine finger motor or sensory functions in small animals [4]. The most relevant outcome of successful peripheral nerve regeneration is functional recovery. Thus, recovery of function does not

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necessarily correlate with histological and electrophysiological evidence of regeneration [3]. After a nerve crush, the formation and compaction of new myelin sheath begins [5]. This compaction is an essential feature for correct myelin function. The myelin sheath primarily consists of lipids and a specific set of proteins such as myelin protein [5, 6], such as myelin protein zero (P0) and peripheral myelin protein 22 (PMP22) secreted by Schwann cells [5, 7]. P0 and PMP22 are required for the maintenance of membrane adhesion and myelin compaction [5, 6, 8]. Classically, the sciatic nerve has been the primarily studied model. In this study, we evaluated the functional recovery after injury to the ulnar and median nerves in mice, an unexplored model recently described by our laboratory. Therefore, we used a battery of tests to assess functional recovery that included assessment of the recovery of both motor and sensory functions. We then evaluated the histological and myelin protein recovery.

## Materials and Methods

### Animals

A total of 30 male Swiss mice (weighing 30–40 g and aged 3 months) were randomly assigned to the following two groups: sham-operated animals (n = 15) and nerve injury (median and ulnar, n = 15).

These animals were obtained from the animal facility of the Federal University of Santa Catarina (UFSC, Florianópolis, SC, Brazil) and housed in collective cages in a controlled environment (22 °C ± 1 °C; 12-h light/dark cycle, ON 7:00) with free access to food and tap water. All procedures related to animal care and experiments were conducted according to the Committee for the Ethical Use of Animals of the UFSC.

### Axonotmesis

First, the animals were anesthetized with 10 mg/kg xylazine and 80 mg/kg ketamine supplemented with 2% isoflurane in 100% oxygen. After shaving and preparing the skin with 10% povidone iodine, the median and ulnar nerves of the right forelimb were approached from the axillary region to the elbow and carefully exposed. The nerves were crushed for 30 s using a nonserrated hemostat clamp to produces axonotmesis [9]. Mice in the sham group were subjected to the same surgical procedure, with median and ulnar nerve exposure but without crush. Then, we performed a battery of behavioral tests to assess functional and sensory recovery at baseline (before surgery) and at 1st, 3rd, 7th, 10th, 14th, and 21st days after surgery. The animals were then sacrificed for histological and biochemical analyses of nerve recovery.

### Behavior

#### Grip Strength

This test was conducted by holding the mouse by its tail and placing it close enough to the grip meter to grasp it (BS-GRIP Grip Meter, 2 Biological Instruments, Varese, Italy) as described by Tos et al. [10].

The mouse was allowed to grasp the grid of the grip meter and lifted away from the grip meter until it lost its grip. The grip meter records the maximum weight the mouse is able to pull. Each mouse was tested three times, and the average weight for each mouse was recorded.

#### Paw Prints Analysis (PPA)

The animals were tested in a confined glass walkway with a length of 42 cm, width of 8.2 cm, and height of 15 cm. A video camera was placed at an angle of 90° below the apparatus, and a darkened cage was connected at the end of the corridor to attract the animals. Toe spread during walking, defined as the distance between the first and the fourth digits and between the second and the third digits, was measured using the Image Pro Plus (version 6.0) analysis software [4, 11, 12].

#### Motor Coordination

Paw placement during skilled locomotion was measured using the Ladder Rung Walking Test (LRWT) apparatus [13, 14]. The animals must go through the acrylic apparatus of 1-m length with alternate distances of horizontal bars (each arranged at 1-cm distance) on each crossing to avoid learning effects. The animals were trained to cross once in a day for a period of 1 week before the injury. During the training period, the horizontal bars were maintained with equal alternate distances. For the assessment, each session consisted of three trials per animal, during which the animal's performance was video recorded from a lateral perspective for further movement analysis. As described by Metz and Whishaw, [13, 14] we assessed the total errors in forelimb injury and scores obtained in the placement of paws and digits on the horizontal bar. Scores in the LRWT were defined as follows: score 1 was total limb fall (total miss); score 2, when the forepaw slightly fell after the limb slipped off the horizontal bar (deep slip); score 3, when the animal was placed on the rung but fell and was replaced in another rung (replacement); score 4, when the limb aimed for one bar but was placed on another (correction); score 5, when the limb was placed on the bar

with either digits/toes or wrist/heel (partial placement); and score 6 was considered when the animal placed its limb and supported its full weight (correct placement) (Video 1).

### Cold Allodynia

Mice were placed on a metal mesh covered with a plastic dome and habituated until their exploratory behavior diminished. Cold allodynia was measured by the acetone test as described by Choi et al. [15] where a 40-µl droplet of acetone was applied to the ventral right forepaw. During 60 s, we counted the time that mice dispensed in scratching, licking and shake the paw tested considering this behavior the response to cold allodynia [15–17].

## Histology

After 21 days of injury, the animals were anesthetized and perfused with 0.9% saline solution and 4% paraformaldehyde (Regen, Brazil) in 0.1 M phosphate-buffered saline (PBS, pH 7.4). For nerve analysis, one short segment (~3 mm) of the ulnar and median nerves was excised from within 3 mm of the crush injury site (distal portion). The specimens were fixed by immersion in a solution of 0.5% glutaraldehyde (Merck, Germany) and 4% paraformaldehyde (Reagen, Brazil) in 0.1 M PBS (pH 7.4) [18]. Then, the specimens were post-fixed in 1% osmium tetroxide ($OsO_4$, Sigma, USA) in PBS, dehydrated in alcohol and propylene oxide (Electron Microscopy Sciences, USA), embedded in resin (Durcupan, ACM-Fluka, Switzerland), and polymerized at 60 °C. Transverse semi-thin sections (1 µm) were obtained using an ultramicrotome (MT 6000-XL, RMC, Tucson, AZ) and stained with 1% toluidine blue (Merck, Germany). Images were captured using a digital camera coupled to a Quimis Microscope (Q07B, Brazil). We used the ImageJ software, version 1.48, to assess the myelin sheath, total number of myelinated fibers, and axon diameter to compare the sham and lesioned groups.

## Western Blotting

The expression of P0 and PMP22 was assessed in the samples of median and ulnar nerves by western blotting analysis. After the last behavioral assessment day, mice (n = 5 animals in each group) were anesthetized with isoflurane (1–2%, 100% $O_2$) and killed by decapitation. Then, the median and ulnar nerves were removed and homogenized in an ice-cold cell lysis buffer (Cell Signaling, Fisher Scientific, USA) plus phenylmethylsulfonyl fluoride (PMSF) and 1% Triton X-100. The homogenate was centrifuged at 15,000×*g* for 40 min at 4 °C, and the supernatant was retrieved to determine the protein content in each sample using the Bradford method (Bio-Rad, Hercules, CA, USA). Equivalent amounts of protein for each sample (40 µg) were mixed in a buffer containing 200 mM Tris, 2.75 mM β-mercaptoethanol, 10% glycerol, 2% sodium dodecyl sulfate (SDS), and 0.04% bromophenol blue and boiled for 5 min. Proteins were resolved by 10% SDS-polyacrylamide gel electrophoresis and transferred onto nitrocellulose membranes. The membranes were blocked by incubation for 2 h with 5% nonfat dry milk solution, washed with Tris-buffered saline (TBS-T), and then incubated overnight with anti-P0 (dilution: 1:1000, ab31851, Abcam, Cambridge, MA, USA) or anti-PMP22 (dilution 1:1000, ab61220, Abcam, Cambridge, MA, USA) antibodies. After washing with TBS-T, the membranes were incubated for 2 h with adjusted peroxidase-coupled secondary antibodies (1:5000). The immunocomplexes were visualized using the enhanced chemiluminescence detection system (Amersham Biosciences, UK). Membranes were then incubated for 5 min in a stripping buffer (Restore™ PLUS, Thermo Fisher Scientific, Waltham, MA, USA) at room temperature and incubated with mouse anti-β-actin (dilution: 1:50,000, monoclonal anti-β-actin–peroxidase antibody, A3854, Sigma-Aldrich, Co., St. Louis, MO, USA), which served as a loading control. The optical densities of specific bands were measured using an imaging analysis system (Scion Image for Windows, MD, USA) and expressed in arbitrary units.

## Statistical Analysis

Repeated measures ANOVA, followed by post hoc Newman–Keuls, was used for behavioral assessments. Results of histology and western blot analysis were compared using Student's *t* test for independent samples. Data are presented as mean ± standard error of mean (SEM). $P < 0.05$ was accepted as the level of significance.

# Results

There was no difference in baseline performance (pre-injury) in the behavioral battery tests between the two groups. First, the lesioned animals exhibited a drastic reduction in grip strength after 1, 3, 7, and 10 days of lesion, with recovery on the 14th day ($F_{1,20} = 67.2$, $P < 0.05$, Fig. 1a). The nerve injury induced finger spreading (1st to 4th fingers) during free walking, which lasted for a week (1, 3, and 7 days) and recovered on the 10th day ($F_{1,20} = 55.9$, $P < 0.05$, Fig. 1b). The nerve lesion also increased errors ($F_{1,20} = 20.2$, $P < 0.05$, Fig. 1c) and decreased the functional score ($F_{1,20} = 34.8$, $P < 0.05$, Fig. 1d) on ladder (LRWT) for 1 week (1, 3, and 7 days), returning to baseline on the 10th day. Cold allodynia appeared only on the

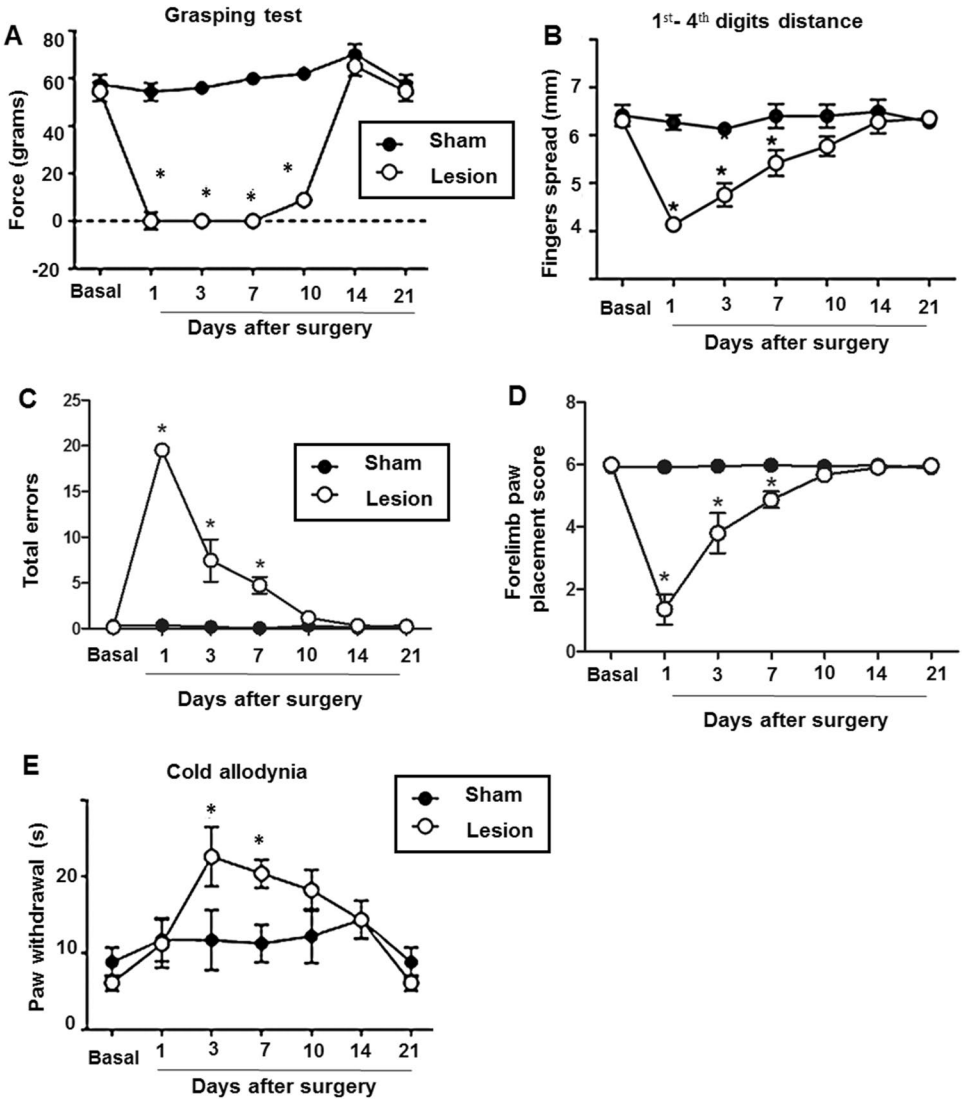


**Fig. 1** Median and ulnar axonotmesis impaired grasping strength (**a**), fingers during walking (**b**), and ladder performance (**c**, **d**) on the day after injury. Cold allodynia appeared on the 3rd day (**e**). Complete recovery lasted for 10 days. Data are expressed as mean ± SEM (n = 15 animals/group). *P < 0.05 versus sham group (repeated measures ANOVA, Newman–Keuls post hoc test)

3rd day after injury, returning to baseline level on the 10th day after injury ($F_{1,20} = 83.5$, P < 0.05, Fig. 1e).

Figure 2 depicts the histological profile of the median and ulnar nerves after 21 days of sham surgery (Fig. 2a) or axonotmesis (Fig. 2b). After 21 days, there was a decrease in the thickness of the myelin sheath (t14 = 3.3, P < 0.05, Fig. 2c) and the total number of myelinated fibers (t14 = 3.2, P < 0.05, Fig. 2d) and an increase in the axon diameter (t14 = 6.6, P < 0.05, Fig. 2e) of the crushed median and ulnar nerves. Similarly, the density of P0 of the crushed nerve was lower (t14 = 3.8, P < 0.05, Fig. 2h). Only the density of PMP22 returned to sham values after 21 days (t14 = 1.7, P > 0.05, Fig. 2g).

## Discussion

Axonotmesis, or 2nd degree Sunderland injury, indicates axonal damage with distal Wallerian degeneration but preservation of the endoneurial sheath [19]. A good functional recovery through the distal lesion is expected. In the present study, we demonstrated uncoupled sensory–motor and morphological recovery of crushed medial and ulnar nerves in mice. The forelimb nerve injury mimics well the traumatic nerve injuries noticed in young people [20, 21]. To our knowledge, our study is the first to describe the two most important peripheral myelin proteins, P0

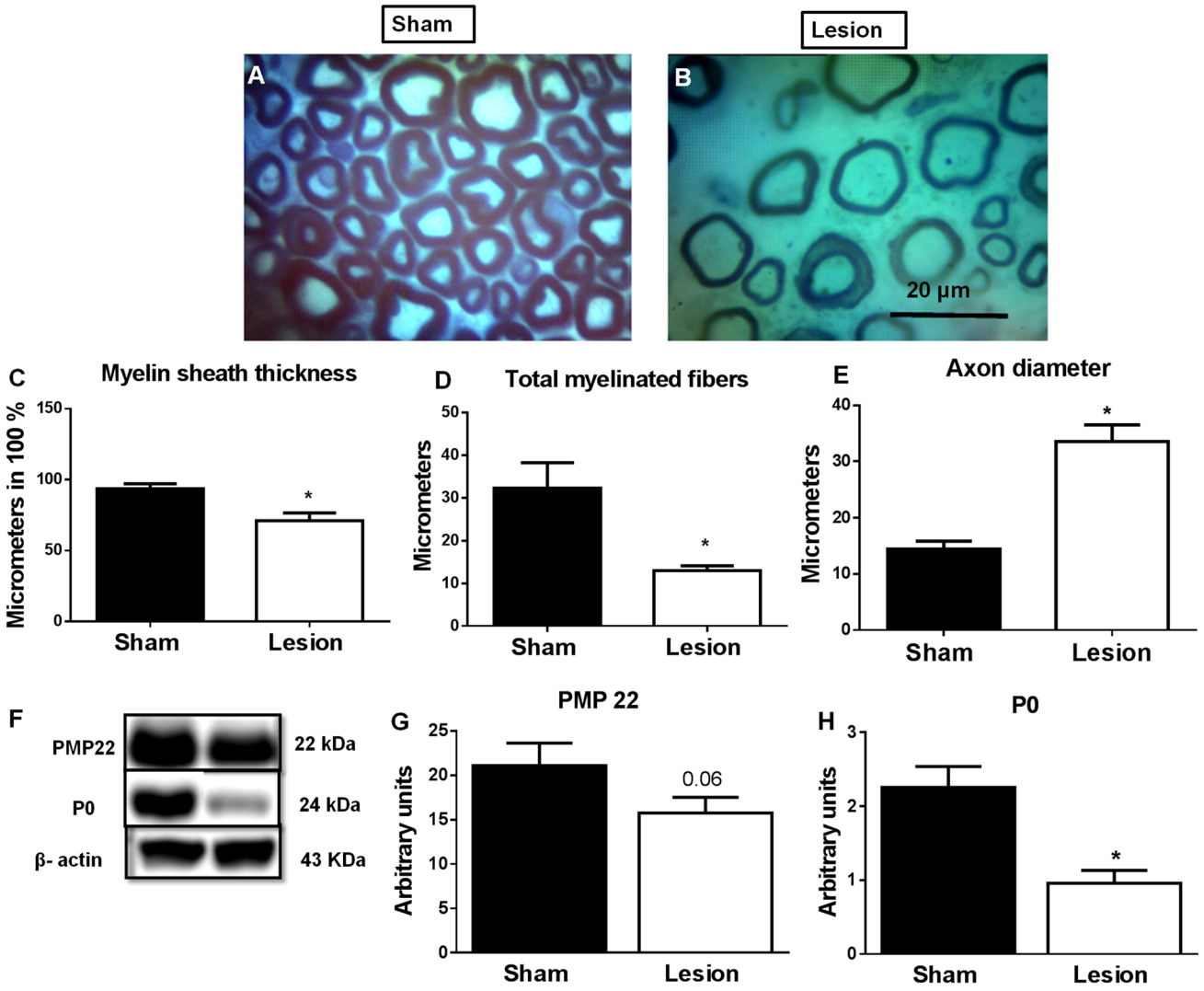


**Fig. 2** Demyelination persisted after 21 days of injury (**a**–**e**), except for PMP22 density (**g**). The increase in axon diameter is an experimental bias (**e**). The scale bar indicates 20 µm. Data are expressed as mean ± SEM (n = 6 animals/group). *P < 0.05 versus sham group (Student's *t* test). P0, myelin protein zero; PMP22, peripheral myelin protein 22

and PMP22, secreted by Schwann cells in crushed median and ulnar nerves [4, 9, 22]. The animals in this study displayed a sensory–motor recovery that was similar to that described in lesions of the sciatic nerve. After 10 days of nerve injury, the functional damage of axonotmesis disappeared, even though demyelination was still present on the 21st day. This result is similar to the sciatic nerve crush recovery reported in mouse [23]. Increased nerve diameter is a common bias of the model [24].

As axons regenerate, the axon–Schwann cell interactions are renewed triggers remyelination and functional recovery [25]. P0 is the major structural protein of peripheral nerve myelin. Functionally, P0 is a transmembrane protein and a member of the immunoglobulin gene superfamily, comprising approximately 50–70% of total myelin protein [26]. PMP22 is a polytopic membrane glycoprotein that comprises approximately 2–5% of myelin protein. Both these proteins are functionally attributed in myelin adhesion [27]. However, in the present study, the density of P0 remained lower after 21 days from axonotmesis in the recovered animals. P0 is an adhesion molecule required for developmental myelin compaction and persists in mature compact myelin [5, 7]. It is also involved in the spiraling process that leads to myelin formation and thus determines the appropriate myelin thickness. PMP22 accompanies functional and sensory recovery in lesioned mice. PMP22 influences myelination and cellular survival and proliferation [6]. It is also critical for actin-mediated cellular functions and for establishing lipid rafts [28]. The density of P0 was decreased in this study, confirming the degenerative process affecting the myelin-forming

compartment of Schwann cells of the peripheral nerves [29]. Although regeneration and remyelination could possibly occur in the peripheral nervous system, the remyelinated axons often have thinner myelin sheaths and a decreased internodal length, which results in slower conduction [30].

Our results suggest this scenario based on the PMP22 data, which was partially recovered. One hypothesis for this delay in the regeneration of the P0 protein may be due to myelin-associated glycoprotein (MAG). MAG plays a critical role in the formation and maintenance of myelin sheaths; it is localized on the inner membrane of the myelin sheath and interacts with axonal membrane proteins to attach the myelin sheath to the axon. Importantly, MAG has been well identified to inhibit or promote the outgrowth of axonal regeneration [31, 32].

In conclusion, results of this study suggest that there was no histological recovery in myelin diameter and axonal size, as well as in the P0 protein. However, functional and sensory recovery after median and ulnar axonotmesis occurred before complete remyelination in mice.

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## Compliance with Ethical Standards

**Conflict of interest** The authors have no personal or financial conflict of interest.

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