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Peripheral Nerve Injury: A Review Article

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ABSTRACT

Traumatic peripheral nerve injuries are among most important cause of physical disability among young adults. Most partial injuries and some complete injuries recover without operative intervention, with early return of function appearing to be the most significant prognostic factor in these cases. Return of function over time depends to a great extent on the underlying neuropathologic condition of the nerve. Although some nerve injuries recover spontaneously, in some cases surgery is the only therapeutic option for the improvement of neurological deficits or control of neuropathic pain. We aimed to review the classification and management of peripheral nerve injury, with emphasize on clinical aspect.

Keywords: Peripheral nerve; Injury; Repair

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INTRODUCTION

Peripheral nerve injuries were first studied systematically during the American Civil War by neurologist S. Weir Mitchell. Many of the advances in knowledge about peripheral nerve injuries have occurred during wartime, from physicians on both sides of the front. Acute peripheral nerve injuries are one of the complications of trauma affecting the extremities, and is present in 3 10% of patients, depending on the mechanism of trauma [1,2]. Nerve injuries result in approximately $150 billion spent in annual health-care dollars in the United States [3]. Etiologies of traumatic peripheral nerve injury include penetrating injury, crush, traction, ischemia, and less common mechanisms such as thermal, electric shock, radiation, percussion, and vibration [4]. These traumatic injuries are a significant cause of physical disability that affects mainly young adults of working age. Although some nerve injuries recover spontaneously, in some cases surgery is the only therapeutic option for the improvement of neurological deficits or control of neuropathic pain [5].

We aim to review the classification and management of peripheral nerve injury, with emphasize on clinical aspect.

Peripheral Nerve Anatomy

It is essential for clinicians to have an understanding of basic anatomy in order to classify and subsequently treat a nerve injury. The cells of the nervous system vary more than those in any part of the body [6]. Three types of cells comprise the peripheral nervous system: neuronal cells, glial cells, and stromal cells. Peripheral nerves convey signals between the spinal cord and the rest of the body. Nerves are comprised of various combinations of motor, sensory, and autonomic neurons. Efferent neurons (motor and autonomic) receive signals through their dendrites from neurons of the central nervous system, primarily using the neurotransmitter acetylcholine among others. Afferent (sensory) neurons receive their signals through their dendrites from specialized cell types, such as Paccinian corpuscles for fine sensation and others. These signals are sent to the CNS to provide sensory

information to the brain and possibly interneurons in the spinal cord when a reflex response is necessary [7].

Peripheral nerve fibers have been classified in relation to their conduction velocity, which, in general is proportional to size and function which is shown in Table 1 [8-10]. However it is not possible to designate individual fibers on the basis of structural features alone [11].

Within a given peripheral nerve, fibers are organized in separate bundles known as fascicles. Less than half of the nerves are enclosed within myelin sheaths. The remaining unmyelinated fibers travel in deep gutters along the surface of Schwann cells. Each Schwann cell is surrounded by a network of reticular collagenous fibers, the endoneurium. Each fascicle is covered by an epithelium, the perineurium. All of the fascicles are surrounded by epineurium (a loose vascular tissue) which encloses an individual nerve. Microvessels progressively branch through the nerve according to the structural layers providing blood to the axons. Due to their more peripheral location, epineural vessels are more susceptible to trauma than the deeper vessels of the nerve [12].

Electrophysiology of Peripheral Nerve

Both nerve conduction studies and needle electromyography contribute significant information in the evaluation and management of traumatic peripheral nerve injury [4,13]. In neurapraxia, the compound muscle action potential (CMAP) and nerve action potential (NAP) elicited on stimulation distal to the lesion are maintained indefinitely. Stimulation proximal to the lesion reveals partial or complete conduction block, with varying degrees of loss of CMAP amplitude, change in CMAP configuration and slowing of conduction velocity, depending on the attributes of a particular lesion. These abnormalities should improve or disappear when remyelination is complete, provided there is no persistent pressure on the nerve. In a complete neurapractic lesion, needle EMG will show no motor unit action potentials (MUAPs) under voluntary control, but fibrillations are not present. The predominant abnormality on needle EMG in partial neurapraxia is abnormal recruitment. The electrodiagnostic picture in axonotmesis and neurotmesis depends on the time that has passed between the injury and the evaluation. The CMAP and NAP distal to the injury decrease in amplitude in rough proportion to the degree of axon loss. This loss of amplitude is complete by day 9 for CMAPs and day 11 for NAPs [14,15]. Although conventional teaching usually holds that an electrodiagnostic study should not be done until about 3 weeks after the injury, a great deal of important information can be obtained by studies done in the first week. Some textbooks state that an EMG performed within days of nerve injury, even a severe injury, will be normal [16].

Overally, optimal timing for an electrodiagnostic study depends upon the clinical question being asked: (1) immediate to 7 days for localization; telling complete from incomplete, (2) 1–2 weeks for telling complete vs. incomplete; sorting axonotmesis or neurotmesis from neurapraxia, (3) 3–4 weeks for the most diagnostic information from a single study, and (4) 3–4 months for detecting reinnervation.

Classification and Grading

There are two commonly used classification schemes for peripheral nerve injury: the Seddon and the Sunderland, which is demonstrated in Table 2 [17,18].

In neuropraxia (Sunderland grade 1), the mildest

Table 1. Nerve Fiber Types and Properties

Fiber Class	Myelin	Diameter (Mm)	Conduction Velocity (m/s)	Spinal Cord Tract	Location	Function
Aα	+	6-22	30-120	Ipsilateral dorsal column	Efferent to muscles	Motor
Aβ	+	6-22	30-120	Contralateral spinothalamic tract	Afferent from skin and joints	Tactile, proprioception
Aγ	+	3-8	15-35	Ipsilateral dorsal column	Efferent to muscle spindles	Muscle tone
Aδ	+	1-4	5-30	Contralateral spinothalamic tract	Afferent sensory nerves	Pain, cold, temperature, touch
B	+	1-3	3-15	Preganglionic	Preganglionic sympathetic	Various anatomic functions
sC	-	0.3-1.3	0.7-1.3	-	Postganglionic sympathetic	Various anatomic functions
dC	-	0.4-1.2	0.1-2.0	Contralateral spinothalamic tract	Afferent sensory nerves	Various anatomic functions, pain, warm, temperature, touch

Table 2. The Seddon and Sunderland classifications of nerve injury

Seddon	Process	Sunderland
Classification of nerve injury		
Neurapraxia	Segmental demyelination	First degree
Axonotmesis	Axon severed but endoneurium intact (optimal circumstances for regeneration)	Second degree
Axonotmesis	Axon discontinuity, endoneurial tube discontinuity, perineurium and fascicular arrangement preserved	Third degree
Axonotmesis	Loss of continuity of axons, endoneurial tubes, perineurium and fasciculi; epineurium intact (neuroma in continuity)	Forth degree
Neurotmesis	Loss of continuity of entire nerve trunk	Fifth degree

form of injury, there is a reversible conduction block, manifested clinically as loss of function, which persists for hours to days. There is either minimal or no discernible histopathologic alteration in nerve structure. In some (more severe) neuropraxic injuries, axons have localized thinning and mild segmental demyelination. The initial clinical examination often shows incomplete and sparing of autonomic function. In patients exhibiting complete loss, an initial single clinical assessment cannot distinguish neuropraxia from more severe injuries. Grade 1 injuries are characterized by excellent spontaneous recovery over days to weeks and rarely over some months [19,20].

In an axonotmetic (Sunderland grade 2) lesion, axon continuity is disrupted but with relative sparing of the connective tissue structure of the nerve, the fascicular integrity is maintained, as is the fine endoneurial network, with minimal endoneurial edema and fibrosis. After division of the nerve fiber, wallerian degeneration occurs in the distal axon. Degeneration of the axon also occurs for a variable distance proximal to the site of nerve injury. The elongating tips of regenerating axons are guided toward the end-organ by the intact endoneurial basement membrane. The rate of regeneration averages approximately 1 mm a day or an inch per month, parameters that are useful in serial clinical evaluation of the patient while awaiting possible return of function. Grade 2 injuries often recover effectively without the need for operative intervention. When the damage is confined to the membranous structures within the fascicle, a Sunderland grade 3 lesion is present. Additional involvement of extrafascicular connective tissue denotes a grade 4 injury with variable degree of intrafascicular fibrosis resulting in, frustration of regenerating axons and leading to their aberrant regrowth, despite gross continuity of the nerve itself. The resulting neuroma in continuity contains a meshwork of connective tissue entwined with fine-caliber, poorly myelinated axons [21-23].

In a grade 5 injury, there is anatomic severance (neurotmesis) of the entire nerve. Grade 5 injuries almost always require repair, and the only important consideration is the timing of repair. For sharply divided nerves (e.g., laceration by glass or knife), acute repair within hours to a day or two is ideal. More bluntly lacerated nerves are repaired 3 to 4 weeks after injury. This delay allows the longitudinal extent of injury to be fully delineated and declared so that debridement of the nerve to healthy proximal and distal stumps can be performed before repair [24,25].

Neuropathology and Mechanism of Peripheral Nerve Injury

The endoneurium surrounds individual myelinated axons and groups of unmyelinated ones. Fascicles are collections of axons which are surrounded by perineurium. The epifascicular (internal) epineurium lies between fascicles. The peripheral nerve trunk is a collection of fascicles, and the epineurial (external) epineurium surrounds the nerve trunk proper. The endoneurium is longitudinally oriented while the perineurium and epineurium are circumferential [17]. Plexuses of microvessels run longitudinally in the epineurium, and send transverse branches through the perineurium to form a vascular network consisting primarily of capillaries in the endoneurium. Nerve trauma increases the permeability of the epineurial vessels, which are more susceptible to compression trauma than the endoneurial vessels. Higher pressure levels or more prolonged compression will also injure the endoneurial vessels, leading to intrafascicular edema, which may lead to secondary injury to the nerve [26].

Multiple mechanisms, including traction, stretch, contusion, laceration (transaction), missiles (gunshot wounds), compression and ischemia (crush), thermal and electrical injuries, injection injuries and iatrogenic causes may result in peripheral nerve injury.

There are various proposed mechanisms that are thought to lead to compression injuries. From an anatomical standpoint, the narrowing of openings leads to increased pressure at that site, compressing blood vessels and leading to nerve ischemia, as occurs with vasculitis and artherosclorotic diseases Nonetheless, there is little doubt that the majority of peripheral nerve compression fall under the general class of neurapraxia, or Grade I

nerve injuries, and commonly occur in locations where nerves pass through narrow anatomical openings. The most common sites in the upper extremity are the carpal tunnel and the cubital tunnel [27,28].

Crush injuries typically occur from an acute traumatic compression of the nerve from a blunt object, such as a bat, surgical clamp or other crushing object that does not result in a complete transection of the nerve. In contrast, transection injuries, also known as neurotmesis or grade V nerve injuries, have a complete discontinuation of the nerve, commonly due to a laceration from a knife, gunshot and glass shard [29]. Moreover, most of these injuries probably often represent mixed injuries of the sort suggested by Dellon and MacKinnon [30].

In sharp penetrating trauma (e.g., glass, knife, and razor blade injuries) with nerve injury, primary exploration and suture repair of the divided nerve, aided by micro-techniques and magnification, in the operating room is best. At times, the nerve is found to be merely contused or bruised during exploration, as in the majority of patients with nerve damage from gunshot wounds or high-velocity missiles. The contused and divided nerve ends are sutured, using large non-absorbable suture, to fascial tissue under some distraction (to minimize retraction) adjacent to each other. The definitive nerve repair is performed at a secondary exploration after several weeks have elapsed to allow the extent of longitudinal injury to declare itself [31].

Injury to peripheral nerves secondary to injection is a serious complication of intramuscular drug administration. Any nerve is at risk, but the proximal radial nerve and the sciatic nerve in the buttock are by far the most common ones injected. Damage may occur from the needle itself, but mostly it is secondary to the toxic effects of the drug or agent being instilled in the intra-neural compartment. In the typical scenario, needle placement results in an immediate electric-like shock sensation down the extremity. Concomitantly, on injection of the agent, severe radiating pain and paresthesias result. The patient usually experiences a severe pain described with adjectives such as burning, searing, electrical or a numbing sensation along the course of the injected nerve occurs. In approximately 10% of cases, a delayed onset of neuropathy occurs the symptoms are often less dramatic, described variously as a burning pain, a deep discomfort, or bothersome paresthesias down the limb and in the distribution of the affected nerve. When incomplete, motor loss is usually greater than sensory neuritic pain, of variable intensity and often accompanies the neurological deficit [32].

Treatment Considerations

Approach to the patient with a peripheral nerve problem is fundamentally clinical. The neurological examination remains the cornerstone in evaluating a peripheral nerve condition and has not been easily supplanted by imaging advances. Majority of peripheral nerve problems either improve or remain unchanged, whereas only a small minority of condition deteriorates [33,34].

The emergent management of a patient who is suspected of having sustained peripheral nerve injury differs greatly from that of the patient who is seen electively or even urgently in the clinical setting. In any trauma patient, attention to life-threatening airway, respiratory, circulatory, and CNS injuries always take first priority before limb injuries are addressed. In multitrauma victims, nerve injuries and brachial plexus injuries are relatively frequent, affecting 5% and 1% of trauma patients, respectively. These injuries can be diagnosed at the initial trauma encounter in more than 60% of cases. In patients with an altered level of consciousness, an asymmetrical neurological examination, with loss of function confined to one limb when accompanied by loss of DTRs, can be suggestive of nerve injury. The precise distribution of nerve injury, even in the comatose patient, can also be ascertained by assessing the lack of autonomic function (sweating and loss of wrinkling after immersion of hand or foot in water), as suggested by Kline and Hudson's. Any patient with a soft tissue, tendon, bone, joint, or vascular injury in the limb should be examined for nerve damage. The rule of thumb to exclude a nerve injury is to verify that the most distal aspect of the nerve is functioning [35,36].

Return of function over time depends to a great extent on the underlying neuropathologic condition of the nerve; those with a large neurotrnetic component do not generally recover, whereas those with a neuropraxic or axonotmetic pathology, or both, may recover. The primary indication for operative exploration of the nerve injury in continuity is lack of clinical or electrophysiologic recovery. In practice, more proximal nerve injuries and distal injuries not exhibiting spontaneous recovery are candidates for exploration [37,38].

The optimal timing for exploration of a nerve injury that is in continuity is greatly influenced by the mechanism of injury. Injuries that are relatively more focal such as those produced by gunshot wounds, iatrogenic causes, stab wounds, lacerations, and fracture associated contusions are best explored 2 to 3 months after wounding. Lengthier lesions resulting from severe contusion or stretch are ideally explored 4 to 5 months after onset [1,39]. Also, cell

therapy and transplantation may benefit patients with chronic nerve injuries [40].

Clinical outcome differs from no return to a very good return of function in grade 3 injuries. In contrast, the grade 4 injury represents the most severe pathology for a neuroma in continuity. Clinical recovery seldom occurs, unless operative resection and repair are undertaken [41].

Management of the patient with a peripheral nerve injection injury essentially follows the guidelines established for any patient with a nerve lesion in continuity. Most partial injuries and some complete injuries recover without operative intervention, with early return of function appearing to be the most significant prognostic factor in these cases. Patients not exhibiting spontaneous recovery over approximately 4 months, as well as the occasional patient with medically intractable neuritic pain syndrome, are candidates for surgical exploration of the injury site, with external and internal neurolysis and nerve repair, depending on intraoperative findings.

REFERENCES

1. Hudson AR, Hunter D. Timing of peripheral nerve repair: important local and neuropathological factors. Clin Neurosurg 1977;24:391-405.
2. Lundborg G. Richard P. Bunge memorial lecture. Nerve injury and repair - a challenge to the plastic brain. J Peripher Nerv Syst. 2003 Dec;8(4):209-26.
3. Taylor CA, Braza D, Rice JB, Dillingham T. The incidence of peripheral nerve injury in extremity trauma. Am J Phys Med Rehabil. 2008 May;87(5):381-5.
4. Robinson LR. Traumatic injury to peripheral nerves. Muscle Nerve 2000;23:863–73.
5. Campbell WW. Evaluation and management of peripheral nerve injury. Clin Neurophysiol 2008;119:1951-1965.
6. Kandel, Schwartz, Jessell. Principles of Neuroscience. 4th edition. Mcgraw-Hill;2000 p34.
7. Jobe MT, Martinez SF. Canale & Beaty: Campbell's Operative Orthopaedics. 12th ed. Elsevier; Philadelphia: 2013. Peripheral Nerve Injuries. pp. 3063–3065. Ch 62D.
8. Berde CB, Strichartz GR. Local Anesthetics. In: Eriksson I, Fleisher LA, Wiener-Kronish JP, Young WL, editors. Miller's Anesthesia. 7th ed. An Imprint of Elsevier; Churchill Livingstone: 2009. p. 917.
9. Miner JR, Paris PM, Yealy DM. Marx, et al., editors. Pain Management. Mark: Rosen's Emergency Medicine. 7th ed. 2010.
10. Sinnatamby S. Last's Anatomy Regional and Applied. 10th ed. Churchill Livingstone; 2000. p10.
11. Fitzgerald M.J.T, Folan-Curran J, Clinical Neuroanatomy and related Neuroscience. 4th ed. W.B. Saunders; 2002 p68.
12. Rydevik B, Lundborg G. Permeability of intraneural microvessels and perineurium following acute, graded experimental nerve compression. Scand J PLast REconstr Surg. 1977;11:179–87.
13. Aminoff MJ. Electrophysiologic testing for the diagnosis of peripheral nerve injuries. Anesthesiology 2004;100:1298–303.
14. Partanen JV, Danner R. Fibrillation potentials after muscle injury in humans. Muscle Nerve 1982;5:S70–3.
15. Massey JM, Sanders DB. Single-fiber EMG demonstrates reinnervation dynamics after nerve injury. Neurology 1991;41:1150 1.
16. Belzberg AJ. Acute nerve injuries. In: Rengachary SS, Ellenbogen RG, editors. Principles of neurosurgery. 2nd ed. Edinburg: Elsevier Mosby; 2005. p. 387–95.
17. Sunderland S. The anatomy and physiology of nerve injury. Muscle Nerve 1990;13:771–84.
18. Seddon H. Three types of nerve injury. Brain 1943;66:237–88.
19. Dumitru D, Zwarts MJ, Amato AA. Peripheral nervous system's reaction to injury. In: Dumitru D, Amato AA, Zwarts M, editors. Electrodiagnostic medicine. 2nd ed. Philadelphia: Hanley and Belfus; 2001. p. 115–56.
20. Wilbourn AJ. Peripheral neuropathies associated with vascular diseases and the vasculitides. In: Brown WF, Bolton CF, Aminoff MJ, editors. Neuromuscular function and disease. Philadelphia: Saunders; 2002. p. 1229–62.
21. S. Sunderland, Nerve Injuries and Their Repair: A Critical Appraisal, Churchill Livingstone, New York, NY, USA, 1991.
22. S. Sunderland, "The function of nerve fibers whose structure has been disorganized," Anatomical Record, vol. 109, no. 3, pp. 503–513, 1951.
23. Mackinnon SE, Dellon AL. Surgery of the peripheral nerve. Thieme; New York: 1988.
24. Schmid DB, Salyapongse N. Nerve injury and repair. Curr Orthop Pract 2008;19:475-480.
25. G. D. Bittner, T. Schallert, and J. D. Peduzzi, "Degeneration, trophic interactions, and repair of severed axons: a reconsideration of some common assumptions," Neuroscientist, vol. 6, no. 2, pp. 88–109, 2000.
26. Hall S. Mechanisms of repair after traumatic injury. In: Dyck PJ, Thomas PK, editors. Peripheral neuropathy. Elsevier, Saunder; Philadelphia: 2005. pp. 1403–33.
27. Tapadia M, Mozaffar T, Gupta R. Compressive neuropathies of the upper extremity: update on pathophysiology, classification, and electrodiagnostic findings. JHS. 2010;35A:668–677.
28. Pham K, Gupta R. Understanding the mechanisms of entrapment neuropathies. Review article. Neurosurg Focus. Feb.2009;26(2):E7.
29. Zochodne DW, Levy D. Nitirc Oxide in damage, disease and repair of the peripheral nervous system. Cell Mol Biol (Nosi-le-grand) 2005;51:255–67.

30. Dellon AL, Mackinnon SE, Seiler WA. Susceptibility of the diabetic nerve to chronic compression. Ann Plast Surg.1988;20:117–119.

31. Stanec S, Tonkovic I, Stanec Z, Tonkovic D, Dzepina I. Treatment of upper limb nerve war injuries associated with vascular trauma. Injury 1997;28:463–8.

32. Menorca RMG, Theron S. Fussell TS, Elfar JC. Peripheral Nerve Trauma: Mechanisms of Injury and Recovery. Hand Clin. 2013 Aug; 29(3): 317–330.

33. Pfister BJ, Gordon T, Loverde JR, Kochar AS, Mackinnon SE, Cullen DK. Biomedical engineering strategies for peripheral nerve repair: surgical applications, state of the art, and future challenges. Crit Rev Biomed Eng. 2011;39(2):81-124.

34. Lundborg G. A 25-year perspective of peripheral nerve surgery: evolving neuroscientific concepts and clinical significance. J Hand Surg Am. 2000 May;25(3):391-414.

35. Dahlin LB. Nerve injury and repair: from molecule to man. In: Slutsky DJ, Hentz VR, editors. Peripheral nerve surgery: practical applications in the upper extremity. Churchill Livingston, Elsevier; Philadelphia: 2006. pp. 1–22.

36. Battison B, Papalia I, Tos P, Geuna S. Peripheral nerve repair and regeneration research: a historical note. Int. Rev. Neurobiol. 2009;87:1–7.

37. Aguayo AJ, Peyronnard JM, Bray GM. A quantitative ultrastructural study of regeneration from isolated proximal stumps of transected unmyelinated nerves. J. Neuropathol. Exp. Neurol.1973;32:256–270.

38. Shokrzadeh A, Seddighi A, Seddighi AS. Therapeutic Results of Transcutaneous Electrical Nerve Stimulation in Post Laminectomy Syndrome. Global Journal of Health Science. 2(2):137-41, 2010.

39. Thomsen NOB, Dahlin LB. Injury to the radial nerve caused by fracture of the humeral shaft: timing and neurobiological aspects related to treatment and diagnosis. Scand J Plast Reconstr Surg Hand Surg 2007;41:153-157.

40. Oraee-Yazdani S, Hafizi M, Atashi A, Ashrafi F, Seddighi AS, Hashemi SM, et al. Co-transplantation of autologous bone marrow mesenchymal stem cells and Schwann cells through cerebral spinal fluid for the treatment of patients with chronic spinal cord injury: safety and possible outcome. Spinal Cord. 2016 Feb;54(2):102-9.

41. Diao E, Vannuyen T. Techniques for primary nerve repair. Hand Clin 2000;16:53–66, viii.