Peripheral Nerve Injury and Repair

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5th Year Medicine

Clinical Points

- Degradation and regeneration of peripheral nerves is distinct from that of nerves in the central nervous system
- Prognosis of peripheral nerve injury is dependant upon age, the nerve injured, the level of the injury, the degree of injury and the timing of repair
- A sophisticated degradation process occurs following injury, before regeneration of a nerve can take place
- Management of peripheral nerve injuries has remained largely unchanged over the last century
- Management of peripheral nerve injuries requires a multi-disciplinary team

ABSTRACT

Peripheral nerve injury can be devastating for a patient. A host of factors influence the highly dynamic degenerative processes that ensue. This article introduces some fundamentals of the mechanisms involved and current treatments available. It serves to highlight some of the more important aspects of the highly sophisticated processes that underlie the pathophysiology of injury and recovery. As will be seen, the regenerative capacity of peripheral nerves is remarkable. Hopefully, a better understanding of the regenerative processes involved will one day assist in the development of new therapies to treat central nervous injury.

Anatomy of the peripheral nerves - General Features

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[1].

The peripheral nerves comprise the cranial and spinal nerves linking the brain and the spinal cord to the peripheral tissues. There are 31 pairs of spinal nerves which contain a mixture of sensory and motor fibres. They are formed by fusion of anterior and posterior nerve roots. The posterior rami of the spinal nerves generally supply the erector spinae muscles and skin of the trunk, whilst the anterior rami innervate the limbs together with the muscles and skin of the anterior part of the trunk. The anterior rami supplying the upper and lower limbs are redistributed within brachial and lumbosacral plexuses respectively.

There are 12 pairs of cranial nerves which are concerned with receiving information and controlling activities of the head and neck and, to a lesser extent, the thoracic and abdominal viscera. Unlike spinal nerves, only some are mixed in function and so carry both motor and sensory fibres. Others are purely motor or sensory e.g. the olfactory nerve is purely sensory.

Microscopic structure

Peripheral nerve fibres have been classified in relation to their conduction velocity, which, in general is proportional to size and function. Group A consist of fibres up to 20μm in diameter (subdivided into α, β, γ and δ), Group B up to 3μm in diameter, and Group C up to 2μm in diameter. The widest fibres appear to conduct most rapidly. However, it is not possible to make a precise estimation of function from mere size. The largest myelinated fibres may be motor or proprioceptive, and the smallest, whether myelinated or not, are autonomic or sensory[2]. However it is not possible to designate individual fibres on the basis of structural features alone[3].

Within a given peripheral nerve, fibres are organised in separate bundles known as fascicles. Less than half of the nerves are enclosed within myelin sheaths. The remaining unmyelinated fibres travel in deep gutters along the surface of Schwann cells. Each Schwann cell is surrounded by a network of reticular collagenous fibres, 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.

Generally regional arteries supply nerves by a series of longitudinal branches which anastomose freely within epineurium, so that nerves can be displaced widely from their beds without risk to their blood supply.

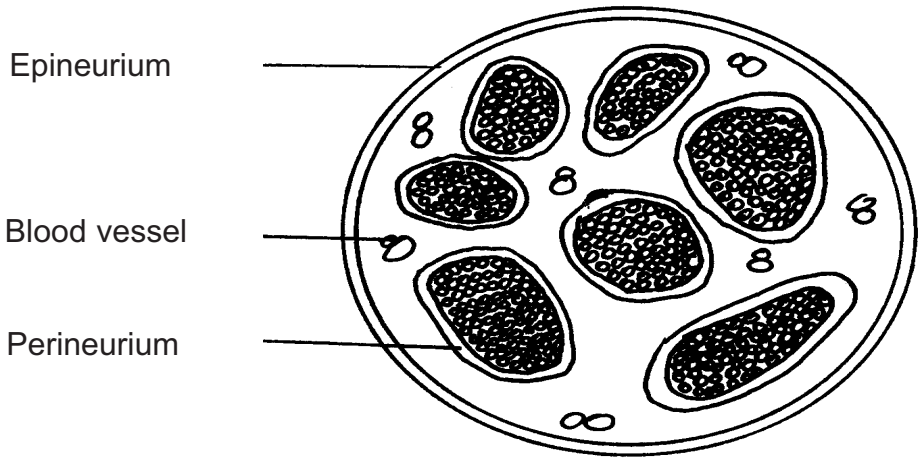

Figure 1. Schematic representation of a cross-section of a typical individual nerve fibre.

Classification of Nerve Injury

To help clinicians grade the degree of injury to a peripheral nerve, various systems have been developed which correlate microscopic changes after injury with symptoms of the patient. These systems can give a fairly accurate prognosis of a particular injury type. The two systems used most widely are those developed by Seddon [4] and by Sunderland [5].

Seddon's classification, which is used more frequently in a clinical setting than Sunderland's, consists of three terms to describe injury to a peripheral nerve. Ranging from least to most severe these are: neuropraxia, axonotmesis and neurotmesis. Neuropraxia is a mild form of injury. Here, there is little or no structural damage with no loss of nerve continuity. Symptoms are transient and most likely due to an ion-induced conduction block, thought to result from a mixture of mechanical compression and ischaemia. There is no severance or tearing of the neural elements and there is little or no histological change seen. The effects appear to be reversible, unless ischaemia persists for approximately 8 hours. Examples of this type of injury include entrapment neuropathies, such as carpal tunnel syndrome, and Saturday night palsy, a radial nerve paralysis caused by pressure on the arm after the person has fallen asleep, usually during an alcoholic binge. There is excellent recovery from neuropraxia, normally within weeks or months. Axonotmesis is the term used when there is complete interruption of the nerve axon and its myelin sheath, but the mesenchymal structures including perineurium and epineurium are either completely or partially intact. This type of injury may be seen in isolation, as with a birth-related brachial plexus injury, or in association with fractures such as a radial nerve injury secondary to a humeral fracture. Lacerations, including those caused by broken glass, are also a common type of injury that may cause axonotmesis. Whereas these can be complete transections, usually some element of nerve continuity remains[6]. Most research involves lacerating animal nerves as this type of injury may be easily reproduced. Therefore, a large proportion of our knowledge on peripheral nerve injuries is represented by this injury type. Prognosis for axonotmesis depends on the extent of injury, with increasing severity related to poorer outcome. Neurotmesis occurs when a nerve, along with its surrounding stroma, becomes completely disconnected. There is no spontaneous recovery and even after surgery prognosis is poor. This type of injury is only seen in major trauma.

Sunderland's classification differs from Seddon's in that five different classes are used. First degree injuries are equivalent to neuropraxia. 2nd, 3rd and 4th degree injuries are equivalent to axonotmesis, the difference being the degree of mesenchymal damage to the nerve. In 2nd degree injuries recovery is good whilst in 4th degree injuries recovery is poor. Fifth degree injuries are equivalent to neurotmesis.

Reponse of Neural tissue to Injury- Degradation and Degeneration

Degradation in the distal segment

In the mildest form of injury (neuropraxia) there is no histological change in the nerve fibre and full recovery is expected. This is also the case for 2nd degree injuries, the mildest form of axonotmesis. In the more severe cases of injury, an active Ca^{2+} mediated process- known as Wallerian degeneration, takes place distal to the lesion[7].

Within hours of injury, myelin and axons break up to form ellipsoids. By 48 to 96 hours after injury, axonal continuity is lost and conduction of impulses no longer occurs. Degradation of the myelin and axons occurs due to a Ca^{2+} activated release of proteases by Schwann cells. The Schwann cells are of vital importance in Wallerian degeneration, as they rapidly divide into daughter cells that up-regulate gene expression for

molecules to assist in both the degeneration and regeneration processes. The Schwann cells also work in conjunction with macrophages, supplying them with cell debris to engulf and remove. There is a co-dependence between these cells as the macrophages are mitogenic to Schwann cells and participate with Schwann cells in the provision of trophic (feeding) and tropic (guidance) factors for regenerating axons. Obviously, there are a number of mediators that play a role in Wallerian degeneration. These mediators include serotonin and histamine released by mast cells which enhance macrophage migration and are also therefore pivotal in the process. It is possible other mediators may be involved but have yet to be discovered.

The end result of the dynamic Wallerian degeneration is a shrunken nerve skeleton with intact connective tissue and perineural sheaths and multiplying Schwann cells. In more severe injuries the process is complicated by vigorous inflammation and oedema. Fibroblasts proliferate and a dense fibrous scar causes a fusiform swelling of the injured segment. In 4th and 5th degree injuries, many axons form whorls within the scar tissue, or are turned back along the proximal segment or into the surrounding tissue. These factors all reduce the likelihood of regenerating axons reaching the proximal stump.

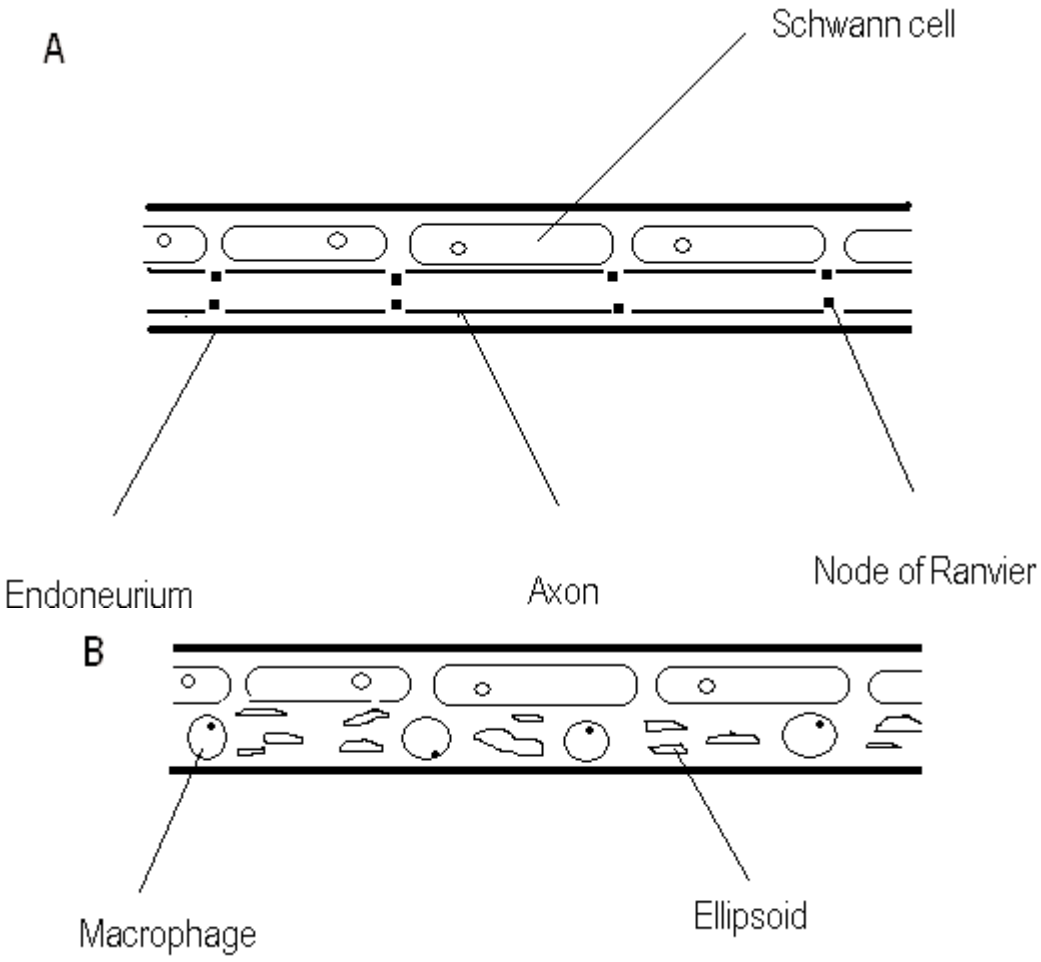

Figure 2. A normal uninjured nerve fibre. (A) Early events of Wallerian degeneration taking place in an injured nerve. (B) The axon has been degraded into ellipsoids and is being engulfed by macrophages.

Regeneration in the Proximal Segment

As with distal segment nerve degeneration, changes in the proximal segment also depend on the severity of injury. Proximal degradation is usually minimal. However, with more severe injury the cellular body may be damaged, in which case the entire proximal segment undergoes Wallerian degeneration. The cell body and axons are interdependent in recovery. A predictable phenomenon is that within 6 hours of injury, the nucleus migrates to the periphery of the cell where Nissl granules and rough endoplasmic reticulum break up and disperse. This phenomenon is called chromatolysis. It is thought to act as a signal for glial cells to extend processes to the affected neuron and interrupting synaptic connections, providing isolation of the affected neuron and thus permitting recovery. The situation is complicated in the proximal segment due to apoptosis. The incidence of apoptosis related cell death in dorsal root ganglia neurons ranges from 20-50%[8].

Regeneration of peripheral nerves

As discussed earlier, recovery is complete in 1st degree (neuropraxia) and 2nd degree injuries. With more severe damage, as per the degeneration phase, the process of regeneration is dependant upon the severity of injury and site of the lesion. In a mixed nerve there is no difference between growth and maturation of the sensory and motor fibres[9]. In less severe injuries, the regenerative and reparative processes begin almost immediately .With more severe injuries, however, regeneration begins only once Wallerian degeneration is complete. The sequence of regeneration is anatomically dependant, beginning at the cell body's proximal segment, proceeding to the distal segment, the injury site itself , and finishing at the end organ. Degradation provides the right environment for regeneration. Various genes are up-regulated primarily to produce vast amounts of lipid and protein for axonal regrowth[11]. The proximal stump branches, or growth cones, contain anchoring filopodia that extend towards the distal stump. Schwann cells in the distal stump extend to engage with the filopodia via cell surface adhesion molecules. It is not surprising that if the gap between these two stumps is wide, regeneration does not occur without surgical repair. Failure of the two stumps to meet produces a neuroma consisting of whorls of regenerating axons trapped in scar tissue at the site of the initial injury. Following amputation of a limb, an amputation neuroma can be a source of severe pain. The first signs of axonal re-growth take place between 24 hours and 1 week post injury. The peripheral nerve's ability to regenerate lasts approx. 12 months after injury [6]- an important factor in the timing of surgery.

Management of Peripheral Nerve injuries

As with any type of trauma A B C (Airway, Breathing, Circulation) should be assessed and maintained if appropriate. Trauma life support should be instigated if necessary. The grade of a nerve injury may be ascertained by interpreting clinical and neurophysiological findings according to Seddon's classification[4].

The level of the injury can usually be deduced by thorough examination and knowledge of the anatomical distribution of the nerves. Two-point discrimination is particularly useful for assessing sensation in the hand as it is an objective measurement and normality (approx. 4mm on the finger pulps) excludes significant nerve injury[10]. With neuropraxia supportive measures are all that is required. This is usually also the case for milder cases of axonotmesis. With more severe forms of axonotmesis, surgery may be required. A proper assessment of the degree of damage may necessitate exploration under anaesthesia. Assessing compound muscle action potential with electro-diagnosis is also helpful to classify the injury (although initially axonotmesis and neurotmesis pictures appear identical

Table 1. Adaptation of Seddon's Classification of Nerve Injury4

	Neuropraxia	Axonotmesis	Neurotmesis
Motor loss	Complete	Complete	Complete
Sensory loss	Partial sparing	Complete	Complete
Autonomic function	Spared	Absent	Absent
Nerve conduction distal to injury	Present	Absent	Absent
Fibrillation on EMG*	Absent	Present	Present
Recovery	Rapid, Complete	1mm per day, good	1mm per day, always incomplete

* electromyography

and only differ as time elapses)[11]. Neurotmesis can easily be detected upon exploratory surgery as the nerve can be seen to be completely transected. In neurotmesis, surgery is indicated as there is no hope of spontaneous recovery.

The timing of surgical nerve reconstruction is important for optimal recovery. In every case of acute injury, the surgeon must decide whether a primary repair or an early secondary repair is the treatment of choice. Timing can be divided into immediate, early (1 month), delayed (3-6 months), and late (1-2 years or more). Immediate repair is preferred when the nerve has been lacerated and there has been a clean cut. The nerve ends should also be uninjured. If there is a high degree of injury surrounding the nerve, surgery may have to be delayed until inflammatory processes operating in the vicinity have dampened.

Early reconstruction is preferred for injuries caused by blunt trauma or avulsion, which are thought to have caused complete nerve destruction. Nerve grafts are usually indicated as the nerve ends have usually contracted and/or scars need to be resected. Autologous nerve grafts provide regenerating axons with a natural guidance channel, populated with functioning Schwann cells surrounded by their basal lamina[12]. Harvesting of nerve grafts results in co-morbidity that includes scarring, loss of sensation, and possible formation of a painful neuroma. The graft used is usually from the sural nerve.

Delayed reconstruction is preferred when the degree of injury has not yet been ascertained. For example, if the extent of axonotmesis is unclear, then it is recommended to hold off on surgery, as natural recovery is better than surgical repair. However, the quality of motor recovery decreases steadily after a 6 month delay of repair[13]. Late reconstruction is generally only carried out for pain control, such as neuroma resection. The current surgical standard is epineural repair with nylon suture. To span gaps that primary repair cannot bridge without excessive

tension, nerve cable interfascicular autographs are employed[14]. It has been found that an injury to a peripheral nerve trunk associated with end-to-side nerve repair, activates neurons and non-neuronal cells (via nuclear translocation of activating transcription factor 3) and may contribute to sprouting of axons into the nerve attached end-to-side[15]. It is unclear how much this technique is being used clinically however.

Surgical success appears to vary widely. Sensory recovery appears to be similar for most nerves[16]. However, motor function varies according to individual nerves. In one study, the motor recovery in ulnar nerves was 71% lower than that in median nerves[17].
It appears that age (younger patients fare better), site, the nerve injured, and delay, significantly influence prognosis after micro-surgical repair. After surgery the affected area should be immobilised for approx. 6 weeks. After this, movement is encouraged and physiotherapy is most useful. Strength exercises may be performed along with the use of electro-stimulating devices. These are thought to improve synchronisation of motor unit firing and increase efficiency of motor units. After several weeks there is muscle fibre hypertrophy which results in a further increase in strength. Patients should be followed up regularly in the post-operative period to gauge extent of recovery. This should involve physical examination and electromyography (EMG).

The Future?

Current research is focussing on the development of a molecular therapy for nerve injury. Whether a novel therapy could be used exclusively on its own or used to augment surgery remains to be seen. Progress has been slow, as the testing of potential therapies is restricted to laboratory studies only. Neurotrophic factors which could theoretically expedite degeneration, and hence regeneration, have been the subject of intense study. It is thought that using natural factors in pharmacological doses could enhance recovery. One study found that the prognosis following nerve repair would be enhanced by the controlled release of a combination of neurotrophins, glial-cell-line derived neurotrophic factor family ligands (GLFs) and the neuropoietic cytokines (the three main families of neurotrophic factors) at higher concentrations than used in previous conduit designs[18]. Other studies appear to focus on the downstream effects of these neurotrophic factors; looking at for example the suggestion that up-regulation of HNK-1 glycan can promote functional recovery[19].
Despite a huge amount of studies, treatment for peripheral nerve injury remains largely unchanged.

CONCLUSION

It can be seen that peripheral nerve injury and repair is a highly sophisticated and active process. The effects of a nerve injury can be devastating. It is hoped that in the future, more successful treatments will become available. In the meantime, clinicians, physiotherapists, occupational therapists and the greater multidisciplinary team involved, will undoubtedly continue to provide expertise and outstanding care.

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