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CASE REPORT

Pathophysiology of Peripheral Nerve Injuries : A Brief Review

Brajesh Singh[1], Prabal Deb[2], Bishakha Deb[3]

Abstract

Peripheral nerve injury can be disturbing for a patient. The complicated dynamic degenerative processes are influenced by several factors. This article reviews the elemental mechanisms involved in a variety of nerve injuries. It emphasizes some of the important aspects of the complicated processes that underlie the pathophysiology of nerve injury. This review will help clinicians managing patients with peripheral nerve injuries possess a clear understanding of the peripheral nervous system's response to trauma and various pathogenetic processes in the background. It is envisaged that a better understanding of the degenerative and regenerative processes involved will one day assist in the development of new therapies to treat central nervous injury.

Keywords: Nerve injury; Degeneration; Endoneurium; Schwann cells.

Introduction

Peripheral nerve injuries (PNI) are common in various types of trauma that result in dysfunction of sensory and motor nerves. They do not involve processes like mitosis and cellular proliferation like other cells[1]. Stretch-related injuries are the most common type, which can give rise to complete loss of continuity as is observed in brachial plexus avulsion[2]. Similarly another common cause of PNIs are knife blade lacerations that result in gross injuries[3]. Compression type of injuries, on the contrary, tend to affect both sensory and motor function[4]. In most cases of nerve injuries mechanical compression and ischemia are additional factors complicating subsequent management and prognostic outcome.

✉ Prabal Deb
+91 9868169645
debprabal@gmail.com

[1] Head, Division of Biochemistry, Department of Laboratory Sciences, Command Hospital, Kolkata, West Bengal, INDIA

[2] Professor & Head, Department of Laboratory Sciences, Command Hospital, Kolkata, West Bengal, INDIA

[3] MBBS Student, Topiwala National Medical College, Mumbai Central, Mumbai, INDIA

Despite the rapid advancements in medical sciences, repair of peripheral nerve injuries remains a challenge to surgeons with the proficiency restricted to only a handful of experts. Most cases of minor injuries have satisfactory outcome. Though rarely lacerated injuries may have spontaneous recovery, but in vast majority of patients the damage is more severe; are associated with open wounds; tend to report late to an expert and thus management becomes challenging and recovery guarded. It is well understood that time period for any denervation and nerve repair is very long and time consuming. The rate of nerve regeneration is approximately 1mm/ day.[5] There is paucity of data pertaining to incidence of PNI, especially in the Indian scenario, since most of the cases are not reported or documented. However Noble et al. have reported 2.8% PNIs among trauma patients.[6] This review aims to discuss the various pathophysiology of nerve injuries.

Anatomy

Understanding the anatomy is essential in comprehending the pathophysiologic concepts that underlie the clinical management of patients with PNIs[7]. Nerve fiber is the smallest anatomical subunit of a nerve. Assembly of nerve fibers form fascicles that are surrounded by an inner endoneurium. Each fascicle is surrounded by perineurium; which maintains the intra-fascicular pressure and strength of the nerve. Outer epineurium encloses collection of fascicles, which are again enclosed by areolar tissue. Cells other than neurons maintain and help in functions of the peripheral nerves[8]. Myelin contain Schwann cells that help in trophic support. Myelin normally restrict transfer of ions to the nodes of Ranvier from axon hence plays a vital role in conduction velocity. The myelinated fibers include large motor neurons (Type Aα), followed by afferent muscle spindles (Type Aβ). Nerve conduction velocities in theses neurons are approximately 30-120m/s. Type-C un-myelinated neurons are concerned in pain and temperature transmission. Postganglionic sympathetics perform a slow conduction approximately reported at 1-2 m/s.[9]

Diagnosis

Detailed history that includes accurate documentation of time of events constitutes the most important part in the diagnosis of a case with suspected nerve injury. Testing for PNIs vary within types of injuries. Vibration and sensation are tested using several methods[10]. Two-point discrimination is another method to examine group A axons slow fibers. Similarly pick-up tests are useful to test sensibility and tactile gnosis[11,12]. Motor function is analyzed in a similar way like upper and lower limbs in a neurological examination. Nerve conduction studies or electrical muscle stimulation or electromyography (EMG), are few of special tests used to confirm a nerve injury. Nerve conduction studies are done to measure conduction velocities where as EMG analyzes electrical potentials in muscle fibers[13]. Blood flow to the nerve is analyzed by doppler studies[14].

Nerve Injury Types

The classification of nerve injury was initiated by Seddon who classified it into three broad categories: neurapraxia, axonotmesis, and neurotmesis. In neurapraxia, transient functional loss is observed without affecting loss of nerve continuity. A complete disruption of the nerve axon and surrounding myelin along with preservation of perineurium and epineurium is observed in axonotmesis. Complete denervation is achieved by axon and myelin degeneration which occurs distal to the point of injury. Neurotmesis causes complete functional loss because of disconnection of a nerve and messenchymal guide[15]. Sunderland's classification systems further classify nerve injuries to five categories according to severity. A first-degree injury is comparable to Seddon's neurapraxia and a second-degree injury is equivalent to axonotmesis. Third-degree nerve injuries occur when there is disruption of the axon[16]. While Seddon classification is simpler to follow, Sunderland grading is more often used by surgeons to take a decision on intervention. Further, a mixed type of injury has been reported in addition to the existing classification[17].

Degeneration and Regeneration

A sequence of degenerative processes takes place before regeneration of nerve fibers can occur[18]. The process of regeneration depends largely on severity of injury and degenerative changes. First-degree injuries involve mild pathological changes hence lacking any degeneration or regeneration. In second-degree injury a little histological changes is marked at the injury site or proximal to it. Distal to the injury site often involves Wallerian (or anterograde) degeneration. In this degeneration, both axons and myelin fragment, which begins within hours of injury. As per the ultrastructural point of view, both neurotubules and neurofilaments are disarrayed, and due to varicose swellings the axonal contour becomes irregular. Hence there is lack of impulse conduction due to loss of axonal continuity within 2-4 days post injury[19].

Another group of cells like Schwann cells play an important role in Wallerian degeneration. Within 1 day of injury they initially become active and exhibit the nuclear and cytoplasmic enlargement along with increased mitotic rate. This rapid cell division result in dedifferentiated daughter cells those are capable of up-regulating gene expression for a number of molecules which help to support in the degeneration as well as repair process[20]. The degenerated axonal and myelin debris cleaned up by Schwann cells are projected to macrophages[21]. This leads to movement of macrophages into the region of trauma, through a hemopoietic route and walls of capillaries that become permeable in the region of injury[7]. The overall effort by Schwann cells and macrophages help in phagocytosis and thereafter the site of injury becomes clear within time period of 1 week to several months.

In addition endoneurial mast cells also play a crucial role in this process[22]. With a marked proliferation, these cells release histamine and serotonin like molecules which apparently enhance capillary permeability thereby enhance the passages of macrophages. Although a noticeable swelling of endoneurial tubes is initiated in response to the trauma, but later on the size decreased post first 2 weeks of injury[23]. Consequently after the regeneration is complete, the nerve fiber remnants are formed of Schwann cells surrounded by the endoneurial sheath are left. In third-degree injury the severed nerve fibre is retracted due to the elastic nature of is endoneurium[24]. The local trauma initiates a vital inflammatory response due to the hemorrhage and edema caused. Hence the injured segment swells owing to the proliferation activity of fibroblasts[7].

Distal and Proximal Segment

Distal to the injured segment, the regeneration of axons is impaired by intrafascicular injury. In this segment Wallerian degeneration features quite similar to that of second-degree injuries. This impairment leads to prolonged denervation of endoneurial tubes. These tubes normally shrink within 3 to 4 months post injury[25].

The outer surface of Schwann cell basement membrane is deposited with collagen along with the thickening of endoneurial sheath. The destruction of the endoneurial tube through progressive fibrosis is ensured if it the tube does not receive a regenerating axon[26]. Bands of Büngner, the collapsed endoneurial tubes represented by Schwann cell processes, are microscopically visible at this stage. These bands illustrate the neuro-supportive role of Schwann cells, for further growth of axons after the nerve injury[27].

In fourth- and fifth-degree injuries, Schwann cells and axons feature to be also no longer restrained. There is disruption of fasciculi as well as endoneurial tubes. The reactive epineurial and endoneurial fibroblasts accompanied by proliferated Schwann cells are present at the severed ends within 24 hours[9]. These cells proliferate vigorously for a prolonged period. The mast cells degranulation and infiltration in macrophages probably contribute to increased capillary permeability. These responses are dependent on degree of trauma to both the nerve and the surrounding tissues. All these viscous processes lead to swelling of the nerve ends. The swollen nerve ending is comprised of fibroblasts, macrophages, disorganized Schwann cells, capillaries, and collagen fibers. Regenerating axons forming whorls within scar tissues, try to reach proximal end or inside the surrounding tissue and few of them reaches the distal stump. Multiple factors like the severity of injury, amount of scar formation and the delay before the axons reach the injury site, affect these process[28]. For a prolonged period the endoneurial tubes shrink and fibrose if they are left unoccupied. This is followed by complete obliteration by collagen fibers.

Proximal Segment

Neuronal cell bodies change and proximal nerve fibers are modified at the proximal end of injury site. The shortening of axon and myelin happens due to degradative action by Schwann cells. Either the proximal degradation can be negligible covering the injury site till the next node of Ranvier or it can entirely extend up to the cellular body. Degeneration of the cellular body in severe injury leads to the Wallerian degeneration and phagocytosis of the entire proximal segment cases[29].

Without any connections to appropriate end of organs, the proximal segment axon is reduced in size which results in minimization of nerve conduction velocity[30]. The axonal growth development and regeneration happens in a parallel fashion. Recovery of the cellular body is incomplete without the reestablishment of functional peripheral connections[31]. This might obstruct the potential of final axons.

Within few hours of injury, there is chromatolysis which involves dissolution of the lysis of migrated nucleus of cell body in the cell periphery, nissl granules and rough endoplasmic reticulum. This causes disintegration of nuclear components and rapid proliferation of peri-neuronal glial cells. The extension of glial cell processes to the affected neuron possibly causes isolation of neurons for its recovery phase by interrupting synaptic connections[32].

The chance of cell death is more frequent as cell survival is not certain post severe nerve injury. Micro-environmental condition of injury site is presumed to play a role in neuronal cell death although the process is poorly understood[33]. The peripheral nerve environment is reported long back to be a key factor to take part in the regeneration failure[34]. Richardson et al. have reported the improved regeneration capacity of neurons in peripheral milieu rather than in a central environment[26]. The presence of trophic molecules including NGF, brain-derived neurotrophic factor, and others in this environment is documented to influence cell survival post injury[35,36]. Local events at injured peripheral nerve trunks are reported to have an significant influence on the likelihood of successful nerve regeneration[37].

Conclusion

The course of peripheral nerve degeneration and regeneration is not that simple. Neurons loose to regenerate if the connection is lost. Although extensive researches are attempted to find out substitute for surgical repair, outcome is never promising. An attempt to use a nerve conduit for peripheral nerve repair has been easier for surgeons but still not successful. The effects of a nerve injury can be devastating. Establishing any restorative method to simulate the nerve regenerative microenvironment in the brain and spinal cord, is still not explained by pathophysisology. Progressive continuation must be focused on physiologic mechanisms of neuro-degeneration and regeneration for significant progress in clinical treatments to be expected in the future. An improved understanding about injured peripheral nerve microenvironment may lead to different therapeutic approaches that can enhance regeneration and reduce pain.

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