MINI-SYMPOSIUM: HAND TRAUMA

(ii) Nerve injuries

Lars B. Dahlin*

Summary

A peripheral nerve can be injured in different ways, varying from a simple nerve compression, a complete transection or laceration and also as traction lesions such as brachial plexus injuries (including avulsion of spinal nerve roots). A thorough history and examination of the patient is crucial to make a correct diagnosis of the lesion, so that the correct treatment can be initiated immediately. Basic knowledge of factors influencing results is essential for all surgeons dealing with these injuries. The macro- and microanatomy of the nerves, and neurobiological events in neurons and Schwann cells after injury are important when assessing the possibilities for repair and reconstruction of nerve injuries (early and late) and to understand the principles for rehabilitation are vital. Focus should also be on the individual patient’s ability to cope with the injury. Future research includes pharmacological treatment strategies as an adjunct to surgery.

Introduction

A nerve injury is one of the most difficult conditions that a surgeon treats and the outcome causes frustration for the patient and the surgeon. The injuries range from minor nerve compression injuries and simple transection injuries to severe nerve injuries, such as the lacerations and avulsion injuries, e.g., brachial plexus injuries. Most peripheral nerve injuries affect the upper extremity function and induce severe suffering for the individual patients, not only in their professional life but also impairing their leisure activities. The prevalence of the most common nerve compression lesion, carpal tunnel syndrome is around 3% and the treatment of this frequent lesion induces a burden on the health care system. When dealing with compression lesions, which may occur at various locations, one should consider the possibility of a concomitant neuropathy, e.g., diabetes. Sensory motor dysfunction in the extremity may also have other causes, such as tumours, inflammation and autoimmune conditions e.g. chronic inflammatory demyelinating polyneuropathy (CIDP). Some conditions have a familial component, e.g., hereditary neuropathy with liability to pressure palsies (HNPP) and chromosome 17. However, the focus in the present review of peripheral nerve lesions will be on transection and lacerations, and their treatment. For the specific strategies regarding brachial plexus lesions the reader is referred to other reviews.1

Transection injuries of peripheral nerves

Transection injuries of peripheral nerves, caused by e.g., glass or knife, are more rare than compression lesions and are often combined with injuries to adjacent structures...
(e.g., tendons). Even if these nerve injuries only constitute around 3% of hand injuries, the total cost of treatment to society of an employed person with a median nerve injury in the forearm may be around 50,000€ mainly due to the loss of productivity (sick leave). The most common transection injury, complete or partial, is a digital nerve injury (incidence 6.2/100,000 inhabitants/year), which mainly affect men (75%) in a productive age (median age 29 years). In the present article, neurobiological changes after injury, diagnostic aspects, principles for nerve repair, reconstruction and rehabilitation will briefly be reviewed.

Factors influencing results

Many factors can influence functional recovery after nerve injury. Age is important reflected by a much better capacity in children less than 10 years. This is probably due to their potential for central adaptation where the child can more easily learn the new language told by the hand from misdirected nerve fibres after regeneration. Age may explain more than 50% of the variance in functional sensibility after nerve injury but the capacity for verbal learning and the visuo-spatial logic capacity are also brain factors, explaining 17% and 13% of functional sensibility, respectively. Regeneration is influenced by the timing of nerve repair where several important aspects, such as upregulation of transcription and growth factors, Schwann cell proliferation, neuronal cell death, particularly of sensory neurons, repair and reconstruction technique and target degeneration have been emphasised. Neurobiological data favour early repair (within weeks) after injury. This is supported by the poor clinical results when repair is late (reconstruction after 6 months post-injury). A pure motor nerve, such as the posterior interosseous nerve, shows a favourable recovery after repair, while the outcome of the repair of a mixed nerve at a proximal location causes frustration, indicating that the type of nerve it is crucial. The level of nerve injury is important since proximal lesions have less favourable results. This depends on the long regeneration distance, greater cell death, down-regulation of cellular injury-induced processes in Schwann cells and target denervation. This is particularly important in brachial plexus lesions (e.g., complete root avulsion). A crush lesion shows better regeneration than a transection lesion demonstrating the importance of the type of injury.

Diagnosis of nerve injuries

Treatment of partial or complete nerve injuries is dependent on the timing of nerve repair. Therefore, any inadequate diagnostic or surgical procedure of the nerve injury will worsen the results of the repair. By making a correct diagnosis and initiating appropriate treatment, the physician or the surgeon, to whom the patient is primarily admitted, can influence the final result. Diagnosis of a nerve injury depends on an adequate basal examination of function in the extremity. Thus, detailed knowledge of anatomy is crucial, particularly for the hand and arm, since injuries mostly affect the upper extremity. The history of the trauma and the location and characteristics of the wound should be recorded. Motor and sensory functions are tested in all patients. Function of the muscles innervated by the specific nerve is tested against resistance. Sensory function is tested by touching the area of innervation. The use of surgical forceps (slightly pinching the skin) is compared with areas of known normal sensation. Loss of sudomotor function is seen early (< 1 h) after injury and may be a helpful sign in children. Electrophysiological investigation is not useful initially, but may be considered in selected cases around three weeks after the injury when signs of degeneration and muscular denervation are apparent. Ultrasound examination (foreign body), MRI and CT can also be used in certain cases (the latter two in brachial plexus injuries) but should not delay any exploration.

Neurobiology and nerve injury

For every physician and surgeon dealing with nerve injuries it is crucial to understand the structure of a peripheral nerve and neurobiological events that occur after nerve injury. The neuron consists of the cell body that is located in the ventral horn of the spinal cord (motor) or in the dorsal root ganglia (sensory) and of the axon that is projecting out to the target in the periphery. A neuron is a highly delicate structure containing an intracellular axonal transport system. The transport occurs along microtubules both in antegrade and in retrograde directions. Interference with axonal transport induces changes both in the periphery and in the nerve cell body. Signal transduction mechanisms, which are the events that occur between the binding of a signal to cell surface and the physiological outcome of such a message induced by a specific molecule occur normally, but are particularly important after transection of an axon.

After transection of a nerve the Ca$^{2+}$-dependent proteases are activated in the distal axon leading to axonal disintegration. Macrophages and Schwann cells invade and proliferate, respectively, and both contribute to the removal of myelin and the disintegrated distal axons. In the remaining part of the neuron there is probably a series of different, partly overlapping phases in time, of regenerative events after nerve transection (see review Dahlin). Early signals arrive within seconds to minutes after the injury and after hours to days intermediate signals, transferred via retrograde transport, convey information about the severity of axonal injury reinforcing early events and triggering further changes. The signals may both be positive, i.e. formed in the axoplasm or released from cells in the environment and taken up at the site of injury, or negative, i.e. loss of normally transported substances. The positive signals that originate from the surroundings of the transected axonal tip or released by the cells at site of injury may also reach the nucleus up to weeks after injury thereby characterising a third phase of the regenerative event.

Recently, the occurrence of activated or conformationally modified proteins, connected with specific signals to get access to the retrograde transport, and emanating from the site of lesion is highlighted. Nuclear localisation signals are attached to retrograde transported signals and are conveyed to the cell body where the import through the nuclear pores depends on importins. Importin β forms a complex with the nuclear localisation signal-bearing signal proteins that are
activated. The activated retrograde injury signals may include Erk1/2 (extracellular signal-regulated kinases 1 and 2), JNK (c-Jun N-terminal kinase), ATF3 (activating transcription factor 3), STAT3 (signal transducer and activator of transcription 3). These signals induce "down-stream" signal transduction responses (Fig. 1) in the cell body with the purpose of initiating the complex genetic growth programme (Fig. 2). Signal pathways and their regulations are complex and still incompletely understood. Leukaemia inhibitory factor (LIF), interleukin-6 (IL-6) and ciliary neurotrophic factor (CNTF) are other retrograde injury signals. Finally, the last phase in the process probably induces signals from the target that stop the outgrowth of the axon when the target is reinnervated.

The signal transduction process also involves signals that are attached to receptors on the cell membrane, including enzyme-linked protein tyrosine receptor kinase (TRK) receptors, G-protein-coupled receptors (bind to G-protein, α, β and γ subunits) and iron channels. The major three important cascades that are activated by the stimulation of the trk, which includes phosphorylation of the different steps and cross talk among the various lanes, are depicted in Fig. 1. c-Jun N-terminal kinase (JNK) activates the transcription factor c-Jun also by phosphorylation (p-c-Jun), which is followed by induction of ATF3 within hours in the cell body. ATF3 is associated with axonal outgrowth, while there is a Janus role of c-Jun, i.e. important both for induction of apoptosis, protection, and regeneration after nerve injury. Interestingly, there seems to be differential regulation of ATF3 in motor and sensory neurons with a prolonged expression of ATF3 in the latter when a nerve injury is not repaired.

Genes are expressed early in neurons after the nerve injury (already within 24 h). Up-regulation of the neuropeptide PACAP in sensory neurons varies depending on the size of the specific neuron. The precise functions of all genes expressed in neurons are not known, but the injury-induced genes are necessary to direct the regenerative events and axonal outgrowth. Interestingly, there is a difference in expression of various stress-related and growth-related proteins in neurons in neonates and adults. Apoptosis of neurons after injury is considered more extensive in neonates, an important point when discussing treatment strategies of brachial plexus lesions in adults and newborns. The task for future research is to define the most significant components of the regeneration programme in neurons, a target for pharmacological intervention, particularly important for the injury-induced cell death mostly occurring in sensory neurons. Programmed cell death (apoptosis) includes activation of caspases that are triggered by

---

Figure 1 Various steps of signal transduction in cells are shown schematically. In neurons and Schwann cells, ligands stimulate receptors after injury with a subsequent activation of intracellular "downstream" steps of mitogen activated protein kinases (MAPK) aiming at inducing alterations in gene expression and production machinery. Reproduced by permission from Dahlin.
pro-apoptotic molecules that are released from mitochondria or through cell surface death receptors. Cell death in newborn mice and rats may be prevented by deletion of pro-apoptotic Bax protein, inhibition of caspase-3 or the whole family of caspases. Apoptosis probably begins within 24 h after injury. Experimentally, it has been shown that treatment with N-acetyl-cystein can prevent sensory cell death after injury.  

Schwann cells play a fundamental role after injury and contain similar signal transduction steps as in the neuron. There is a close connection between the Schwann cells and the axon; the precise knowledge about the regulation of Schwann cell—axon interaction needs further clarification. There are time dependent alterations of the various steps in the Schwann cells, which are important for timing of nerve repair and reconstruction. The concept of early repair and reconstruction is based on the knowledge that there is a robust increase of many factors and their receptors in Schwann cells after injury (some within 15 min) and that the expression of many substances, such as the transcription factor ATF3, decreases over time. If denervation is prolonged, Schwann cells may not respond to stimulation of outgrowing axons due to unresponsiveness e.g., glial growth factors and down-regulation of c-erB tyrosine kinase receptors, and decrease in glial cell-line-derived neurotrophic factor (GDNF).

Outgrowth of axons after injury is a delicate process orchestrated by signal transduction mechanisms, which include integration of signals at the growth cone, actin polymerisation and microtubular assembly; all interfering with extracellular matrix and integrins (Fig. 2). Dynamic processes occur in the growth cone, where the extended filopodia palpate the environment to find the optimal growth direction. Elongation of axons is dependent on repulsive mechanisms triggered by negative guidance cues leading to collapse of the growth cone and the filopodia; another target for research aiming at introducing new therapy strategies in the future.

**Nerve repair**

Primary nerve repair is done immediately after or within the first 2 days following a transection injury, unless it is a minor sharp injury (minimal stab wound) distal to a PIP joint in some of the fingers (not index or thumb) in which case it may...
Nerve injuries

The technique of attaching a distal nerve end of an injured nerve to innervate critical motor or sensory nerves distally, such as transfer of the terminal branch of a spinal nerve root, which can be handled by nerve transfers. This technique recruits expendable in contrast to motor nerves of which very few redundant or unimportant nerve fascicles from a donor nerve or intrafascicular dissection should be avoided since survival of the Schwann cell depends initially on diffusion from the surroundings and later in the process on revascularisation from surroundings and attached nerve ends.

Nerve transfers

A proximal nerve injury can be transformed into a distal one by the use of nerve transfers. This technique recruits redundant or unimportant nerve fascicles from a donor nerve to innervate critical motor or sensory nerves distally, i.e. close to the targets. Initially this novel technique was used at the brachial plexus level but can now be used more distally in the upper extremity to transform a high nerve lesion to a distal one.

A specific problem in brachial plexus lesions is avulsion of spinal nerve roots, which can be handled by nerve transfers at the plexus level, such as transfer of the terminal branch of the accessory nerve to the suprascapular nerve or several intercostal nerves to the musculocutaneous nerve. Avulsed spinal nerve roots can also be treated with ventral root reimplantation. The reader is referred to other extensive literature regarding brachial plexus reconstructions.

End-to-side nerve repair

The technique of attaching a distal nerve end of an injured nerve end-to-side to an uninjured donor nerve, when there is no proximal nerve end available, is a technique that was reintroduced in 1990s. Even if it has been used successfully clinically, the main controversy has been the mechanism(s) behind outgrowth of axons into the attached distal nerve
end. In double-labelling studies true collateral sprouting has been observed, but this is probably not the main mechanism. Some degree of nerve injury to the donor nerve is probably necessary to achieve activation of the neuron to get axonal outgrowth. Even if recovery of muscles innervated by the attached distal nerve segment do occur, end-to-side nerve repair technique is more often used for sensory nerve reconstruction.
Alternatives to nerve grafts

Recently, a large number of experimental and clinical studies have been published with different alternatives to nerve grafts, including veins, with or without inserted muscles, various muscle preparations, tendons and tubes, but the common problem is the lack of Schwann cells in the alternatives. Schwann cells can be obtained from cell cultures but the procedure is time consuming. However, a dissociation technique, where Schwann cells can acutely, in a limited number, be harvested and added to a matrix, has recently been presented. For short nerve grafts, for example in a digital nerve defect, the longitudinal suture technique may be an alternative.

Nerve allografting has been debatable and may require a lifelong treatment with immunosuppressive drugs, such as FK506 (Takrolimus), with potential adverse effects. FK506 per se does probably not have any positive effects on axonal regeneration. Recent development in immunosuppressive strategies in transplantation by blocking T-cell costimulation, thereby inducing long-term maintenance of immunosuppression, may also work for nerve allografting. New nerve allograft products, including such prepared by an extraction procedure, which does not contain Schwann cells or other cells, are in the pipeline.

Tendon transfers

In cases where it’s not possible to repair or reconstruct a nerve injury, e.g. when the injury is more than 1–2 years old, tendon transfers may be an alternative. An example is the case of a radial nerve injury in conjunction with a fracture of the humerus with the patient presenting 2 years later with a healed fracture but complete loss of radial nerve function. A choice of well suited and simple tendon transfers for such a condition include PT to ECRB, PL to EPL and FCU to EDC.

In cases where it’s not possible to repair or reconstruct a nerve injury, e.g. when the injury is more than 1–2 years old, tendon transfers may be an alternative. An example is the case of a radial nerve injury in conjunction with a fracture of the humerus with the patient presenting 2 years later with a healed fracture but complete loss of radial nerve function. A choice of well suited and simple tendon transfers for such a condition include PT to ECRB, PL to EPL and FCU to EDC. There is a variety of transfers that can restore hand and arm function in patients after different nerve injuries. It is important that the patient’s individual requirements are taken into account when planning the tendon transfers. It may also be advisable when reconstructing a radial nerve at the upper arm level to simultaneously transfer PT to ECRB as an internal splint.

Rehabilitation after nerve injuries

Postoperatively, the nerve repair or the reconstruction should be protected with immobilisation (from 10 days up to 6 weeks). Regeneration of axons is followed by advancement of the Tinel’s sign (easy technique) and by subsequent return of muscle reinnervation; e.g. of radial nerve innervated muscles in the forearm. The surgeon should supervise the rehabilitation of the patient, including physiotherapy and occupational therapy, with the purpose of achieving full passive and active range of motion.

Sensory relearning and re-education

After nerve injury there are dramatic and extensive functional reorganisational changes in the brain, which are particularly important in view of misdirection of regenerating sensory axons. This requires remodelling and relearning processes in the brain to adapt to such misdirection; processes that are probably extremely dynamic in young children. However, the adult brain has difficult problems learning the new language told by the hand after nerve injury. Sensory relearning, which is based on sensory re-educational protocols, is therefore of crucial importance and a necessary clinical routine to regain sensation. The principle includes exercising the perception of touch and the ability to localise such touch and later touching and exploration of various items with different shapes and textures with and without vision (see review by Lundborg). The patient’s motivation is a factor that highly influences the effectiveness of such a relearning procedure. The mechanism(s) behind cortical remodelling is the focus for intense research. Based on such knowledge, strategies are now evolved to enhance sensory relearning where onset and timing have been emphasised. Early (i.e. before reinnervation of hand) and late postoperative phases (i.e. some reinnervation of the injured nerve area) include use of other sensory modalities, such as the auditory sense. In the late postoperative phase a multimodal approach is adapted where vision, smell, taste and hearing are used simultaneously. Bilateral training is emphasised in order to integrate information from contralateral and ipsilateral sides. Use of pharmacological tools has been tried. Recently, the use of topical application of local anaesthetic (EMLA cream) on the forearm to improve sensation in the hand after a nerve injury has been described.

Nerve repair—evaluation of outcome

To assess outcome after nerve repair a protocol is required to follow reinnervation. For median and ulnar nerve injuries a novel model instrument has been presented including examination of various components for sensory, motor and pain/discomfort domains, where the total score of individual patients can be compared to a reference curve based on patients followed for 5 years. Such information can provide the surgeon, the therapist and the patient with valuable information about the reinnervation. If there is a shift of the curve particular attentions may be needed. Regeneration in motor nerves (e.g. after brachial plexus reconstruction) can be followed by evaluation of the strength of individual muscles reinnervated by the specific nerves.

Pain problem

Rehabilitation of nerve injuries includes handling of any pain problems, which may even include a complex regional pain syndrome (type 2) as recently reviewed. This is particularly important after brachial plexus lesions where substantial pain problems may occur in preganglionic avulsion injuries. A close contact with devoted physicians with experience on pain problems is recommended. Minimising alldynia, a symptom appearing during the regeneration process, and cold intolerance after nerve injuries are other topics for future research.
Nerve repair and reconstruction in the future

The microsurgical technique has been much improved during the last decades but other strategies are required to improve results. Such strategies involve the use of the extensive information obtained about the delicate mechanisms in signal transduction and the possibility to use pharmacological tools as an adjunct to surgery. We need to direct the research where a differential approach may be more appropriate between injuries to different nerve trunks, the location of the injury, the method of repair and reconstruction, and also to focus on specific strategies (coping strategies) used by patients to overcome disability. Timing of repair as well as initiation of the recently developed rehabilitation programs, utilising the plasticity of the central nervous system, is important.

A problem is also the lack of well-performed multicenter studies (randomised and prospective) with a sufficient number of comparable patients with similar types of injuries and repair or reconstruction procedures. A comprehensive protocol is required to make assessment of functional recovery. However, the complex pattern of brachial plexus nerve injuries and the individual surgical solutions required make scientific comparisons difficult. Finally, an exciting future direction is the use of nano-structures to sort axons and direct growth in nerve grafts and artificial nerve grafts, perhaps making it possible to modulate the growth of axons on nano-imprinted patterns.

Acknowledgements

The research of the author is supported by grants from Swedish Research Council (Medicine), Zoega’s Fund for Medical Research, Region Skåne and Funds from the University Hospital Malmö, Sweden. I want to express my sincere gratitude to my secretary Tina Folker and to my colleague Trygve Strömberg for help with the manuscript.

References