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Special Issue

The implications of injury in the developing nervous system on upper extremity function

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ABSTRACT

Study design: Literature review.
Purpose: The corticospinal system (CS) and peripheral nervous system (PNS) are common sites of damage during the early stages of life. The prenatal or immediately prenatal period is the most common time for damage to occur. Here we briefly review the basic features of the development of the CS and the PNS and the clinical consequences of injury to or improper development of these systems on upper extremity (UE) function.
Results: The proper development of both the CS and PNS is necessary to achieve adequate function of the (UE). Injury or improper development of these systems can lead to upper extremity dysfunction and limit participation in activities of daily living.
Conclusions: Both the PNS and CS play major roles in the proper functioning of the UE. A better understanding of their roles and common developmental disorders is needed to move rehabilitation of motor impairments forward.

Organization of the PNS

The PNS is comprised of motor neurons whose cell bodies are located in the spinal cord and brainstem and project to peripheral ganglia. Peripheral ganglia are located outside the central nervous system (CNS) and are not enclosed within the blood brain barrier (BBB). The PNS consists of two parts; somatic and visceral. The somatic PNS contains the motor neurons that innervate skin, joints and muscles directly, and is largely under voluntary control.[1] The visceral PNS, or autonomic nervous system (ANS), consists of the neurons that innervate the autonomic ganglia; neurons in these ganglia innervate the internal organs, blood vessels and glands. The ANS is largely under involuntary control.[1]

Peripheral neurons also contribute to the development and maintenance of associated tissues.[2] The mutual interdependence of motor neurons and the muscles they innervate is an example. If a nerve fails to connect with a muscle during development the nerve degenerates; likewise if a muscle is denervated, the muscle degenerates.[3]

Developmental plasticity of the PNS

Guided migration

During embryonic development a group of neurons clustered on the "crest" of the neural tube, the neural crest cells, form most of the PNS as well as some other tissues.[4] Neural crest cells migrate extensively and give rise to diverse structures with different functions and phenotypes, including the dorsal root, sympathetic, parasympathetic, and enteric ganglia.[4] Neural crest cells that migrate at different levels of the cephalocaudal axis have different fates, indicating that their differentiation into adult phenotypes is influenced by the environment at that axial level.[4] These cell populations are, however, multipotent with respect to their prospective fates, and are capable of assuming different phenotypes if their environment changes.[4] For example, when transplanted into a new environment, neural crest cells differentiate according to their new location, supporting the idea that local environmental cues rather than intrinsic factors determine their fate.[4] A number of molecular cues have been identified that guide neural crest cells including cues that support migration and other cues that act as repellents to restrict growth.[5,6] In some cases, the same molecular cues control multiple aspects of neural crest development.[7] Cues in bone

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morphogenetic proteins, for example, are involved in *induction*, an event that establishes the migratory and multipotent characteristics of the neural crest, and at later stages in the *initiation of migration* of the neural crest cells.[8] The process by which one molecular signal controls different responses at different stages of development is unclear but indicates developmental changes in the intrinsic response of the neurons.[7]

The degree of plasticity in cell fate (e.g., cephalocaudal specification) is greater than has previously been appreciated.[7] In addition to chemical gradients and molecular signaling cues that influence axonal outgrowth and migration, microfluidic flow in the environment near the region of the growth cone (tip of the axon).[2] This microfluidic flow modifies the direction of growth cones and determines their destination. The accuracy of axonal path finding is crucial to the proper formation of functional neural circuitry.[2] Advances in *in vivo* time-lapse imagining revealed the highly dynamic nature of both cell movements and the contacts between neural crest cells and their neighbors. While much remains to be understood regarding the mechanisms that underlie guided migration, the nervous system is highly plastic during development and this plasticity can be leveraged into treatments for developmental disorders or injuries.[7]

Peripheral nerve injury

The majority of peripheral nerve injuries (PNI) are traumatic, occur in the upper extremity, and disproportionately affect infants and young healthy people. Severe nerve injuries include both sensory and motor deficits that can result in complete paralysis of the affected limb and thus have a devastating impact on a patients' quality of life.[9] Following an insult to neurons in the PNS, axonal degeneration follows a sequence of events within the zone of trauma and extends both caudal and rostral to this zone.[10] Within 24 h, the distal portion of the axon begins to die and axonal debris is phagocytosed by blood-born macrophages and proliferating Schwann cells.[11] Schwann cells and macrophages clear the environment surrounding the damaged axons. This provides a supportive environment for successful axonal regeneration.[10]

Denervation of the sensory or motor targets following a PNI reduces the representation of the region supplied by the injured nerves in the motor cortex and expands representation of adjacent regions.[12] This is due to alterations in activity of spared sensory and motor groups and is an example of activity-dependent plasticity in the brain in response to a peripheral lesion.[12]

Approximately 60% of patients regain useful function after a PNI.[13] The lack of functional recovery in the remaining 40% of the population is thought to occur because: 1) axons stop elongating and form neuromas; 2) axons that do elongate form sprouts that innervate more than one peripheral nerve branch; or 3) misguided regeneration into the wrong nerve, as when a motor axon grows into a sensory nerve or vice versa.[13] Epineural surgical repair remains the gold standard reconstruction technique using either direct end-to-end nerve repair or interposition autologous nerve grafts.[10] Epineural repair involves lining up both the internal nerve fascicles and the surface epineural blood vessels patterns[10] and suturing the proximal and distal epineural layer of the nerve sheath.[14]

Prognosis after PNI

Clinical examination and/or surgical exploration are used to assess severity of the injury during the first six weeks following PNI.[10] After this period nerve conduction studies (NCS, motor and sensory assessment) and electromyograms (EMG, motor assessment) are effective for diagnosis. During the three to six month period when fibrillations in the denervated muscle are not present, NCS and EMG can map nerve recovery over time and identify whether the lesion is neuropraxic or axonotometric.[10] A neuropraxic lesion results in a temporary loss of motor and sensory function due to blockage of nerve conduction and usually lasts an average of six to eight weeks before full recovery. An axonotometric lesion is more severe because it indicates a disruption of the axon, with Wallerian degeneration occurring below the site of injury. Unfortunately this diagnosis occurs after the most opportune time for surgical intervention. Therefore, additional tests to diagnose injury severity in the acute period are needed.[10]

Perinatal brachial plexus injury (PBPI)

The brachial plexus (BP) originates from the anterior rami of cervical (C5–C8) and thoracic (T1) segments of the spinal cord. Multiple divisions of BP components create a network which gives rise to nerves for the muscles and skin of the chest and upper limb.[15]

There are both traumatic and nontraumatic causes of PBPI in infants and children. Traumatic injuries are typically caused by a traction injury due to shoulder dystocia during vaginal delivery.[16] Nontraumatic PBPI can stem from localized tumors or a widespread infection.[16]

PBPI is the most common cause of brachial plexus injury (BPI) in children[15] and typically occurs as a result of extreme lateral traction of an infant's head away from the shoulder during the last phase of delivery resulting in variable traction or stretch neuronal lesion.[2] Approximately, 50% of the PBPI patients have identifiable impairment of hand function by about 15 months of age.[17] Sequelae of PBPI are related to the initial lesion of the BP, as well as the lesion to the osteoarticular system at the level of the proximal humerus and damage to the deep periarticular muscles of the shoulders.[18] Neuroapraxia, axonotmesis and root avulsions are associated with lesions to the sensory, motor and autonomic nerves of the BP. While the shoulder is the most frequently affected joint in PBPI, the forearm, wrist and hand frequently have disabling deformities.[3] Surgeons propose early surgical intervention to avoid permanent impairments.[19,20] When surgical treatment is not possible, pharmacological approaches with neuroprotective molecules could be useful.[21]

Treatment of impairments due to brachial pluxus injury is an emerging field in neurorehabilitation.[15] The time that it takes for nerve reinnervation is similar in children compared to adults and is not related to age.[22] The extent of recovery depends on many other variables, such as complexity of injury and timing of diagnosis and treatment.[23]

Development of the corticospinal system

The corticospinal system (CS) largely develops postnatally when human infants and infants of many animal species begin to express adaptive and visually-guided movements.[24] Early motor system development may rely on active learning and experience that directs the myriad of structural changes taking place as the motor pathways grow toward their targets.[24] The CS is the last motor system to develop, and it develops concurrently with the expanding motor skills of the infant. The expansion and increased precision of motor skills during this period is an example of activity-dependent plasticity in which use can determine function. The CS, therefore, is useful for assessing activity-dependent processes in development and recovery of function.[24]

Movement is organized with contributions from *upper motor neurons* in cortical areas, the cerebellum and basal ganglia, and *lower motor neurons* in the spinal cord that exit in peripheral nerves.[3] Axons from upper motor neurons descend in the spinal cord via two main groups of pathways: the lateral pathways that