

Traumatic Spinal Cord Injuries

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NEUROPATHOLOGY

In this Forensic Science Newsletter we will discuss **traumatic spinal cord injuries**.

GENERAL INFORMATION

The earliest known reference to traumatic lesions of the spinal cord are found in the Edwin Smith Surgical Papyrus. In this Egyptian treatise, six cases of injury of the cervical spine were described. This was followed by reports of evidence of arrow wounds of the spine in prehistoric man in Europe and in the graves of the American Indians. Such injuries were uncommon in medieval times. They became more common after the introduction of gunpowder and after the industrial revolution, for they resulted largely from gunshot wounds, accidents in heavy industries, and subsequently automobile injuries. During the last half of the eighteenth century and the nineteenth century, cases were reported by Matsy (1766), Sir Charles Bell (1816), Abercrombie (1828), Sir Astley Cooper (1829), Mayo (1836), and Ollivier (1837). A number of spinal injuries were described during the American Civil War. Concussion of the spine occurred in railway accidents both in Europe and the United States. A clinical syndrome resulting from such injuries was discussed by Erickson (1875), a British surgeon, which became known as the "Railway Spine." The first thoroughly documented study of the effects of sudden total cord transection was by Theodor Kocher in 1896, which was based on his observations of 15 patients. There were many instances of injuries to the spine in World War I and II, which were the results of penetrating bullets, shrapnel, and shell fragments.

During World War I, Riddoch, and later Head and Riddoch, gave what are now considered the classic descriptions of spinal transection in humans; Lhermitte and Guillain and Barré are credited with refining those observations. Little could be done during this period with fully 80% dying in the first few weeks, primarily from infections; survival was possible only if the spinal cord lesion was partial.

World War II marked the turning point in the understanding and management of spinal injuries. The introduction of sulfa drugs and penicillin saved the lives of many who would have died from infections. The arrival of these antibiotics and the subsequent ability to control skin, bladder, and pulmonary infections permitted the survival of many soldiers with spinal cord injuries. Those who survived however created the therapeutic

problems of the paraplegic and quadraplegic. For these problems, special centers, and the care and rehabilitation of the paraplegic and quadraplegic patients were brought to a high level. Studies conducted in these centers greatly enhanced our knowledge of the functional capacity of the chronically isolated spinal cord. Kuhn, Munro, Martin and Davis, Guttman, Pollock, and Pollock and associated made especially important contributions to this subject.

MECHANISMS OF SPINAL CORD INJURY

The usual circumstances of spinal cord injury, typically occurs in the following sequence in civilian practice: motor vehicle and motorcycle accidents, falls, gunshot or stab wounds, diving accidents, crushing industrial injuries, and birth injury, In 1985, Kraus reviewed the incidence, prevalence, causes and outcome in his discussion of the epidemiological aspects of acute spinal cord injury, which was published in the *Central Nervous System Trauma Status Report*. Bethesda, MD: National Institute of Neurological and Communicative Disorders and Stroke. He noted that more than 70 million people required medical attention or restriction of activity because of spinal injuries in all cases. This resulted in 144 million bed-days of disability and 433 million days of restricted activity. Approximately 10%-20% of all hospital admissions for nervous system trauma are due to injuries of the spinal cord. Worldwide, spinal cord injuries occur at annual rates of between 13 and 50 cases per million people. In the United States, the annual incidence of spinal cord injury has been given as 5 cases per 100,000 population; males predominate (4:1). Each year approximately 3,500 persons die due to their spinal injury, and another 5,000 are left with complete or nearly complete loss of spinal cord functions.

In the United States, the highest incidence of traumatic paraplegia is found in individuals involved in head-on collisions or those ejected from their vehicle. Drivers or passengers of sports utility vehicles, trucks, or larger vehicles are especially vulnerable to spinal injuries, suffering nearly twice the expected rate of this complication than occupants of automobiles, bicycles, or other motorized vehicles.

Diving accidents often result in spinal cord injury, affecting primarily young males between the ages of 15 and 25. These injuries usually involve damage between the fourth and sixth cervical spinal cord levels, sustained when the diver's head strikes the bottom of the pool, causing compression or burst fractures of the spinal column. Football is associated with spinal injuries at a rate of approximately 2-14 cases per 100,000 population. Rugby and trampoline accidents are also represented in the sport associated spinal injuries, as are water skiing and snow skiing, ski jumping, motorcycle racing, off road vehicles such as ATVs (all terrain vehicles) and UTVs (utility vehicles) and intense contact sports or sports where falls are common.

Although trauma may involve the spinal cord alone, the vertebral column is almost invariably injured at the same time. Not uncommonly, along with the spinal cord injury are associated injuries to the brain.

Traumatic lesions of the spinal cord, spinal nerve roots, and spinal meninges, usually are the result of fracture-dislocations, pure fractures, and pure dislocations (Figs 1 & 2). The spinal cord that is situated beneath any of these injuries is traumatized by direct compression as a result of dislocation of spinal bones, or buckling of the ligaments inside the spinal canal. The relative frequency of the three types of injury are roughly 3:1:1. Except for missile, shrapnel, and stab wounds, a direct blow to the spine is a relatively uncommon cause of spinal cord injury. In nonmilitary injuries to the spinal cord, most fractures and dislocations of the spinal column are the result of force applied at a distance from the site of the disruption of the spinal column. All three types of spinal injury are usually produced by a vertical compression of the spinal column, to which either anteroflexion or retroflexion (hyperextension) is added (Fig. 3).

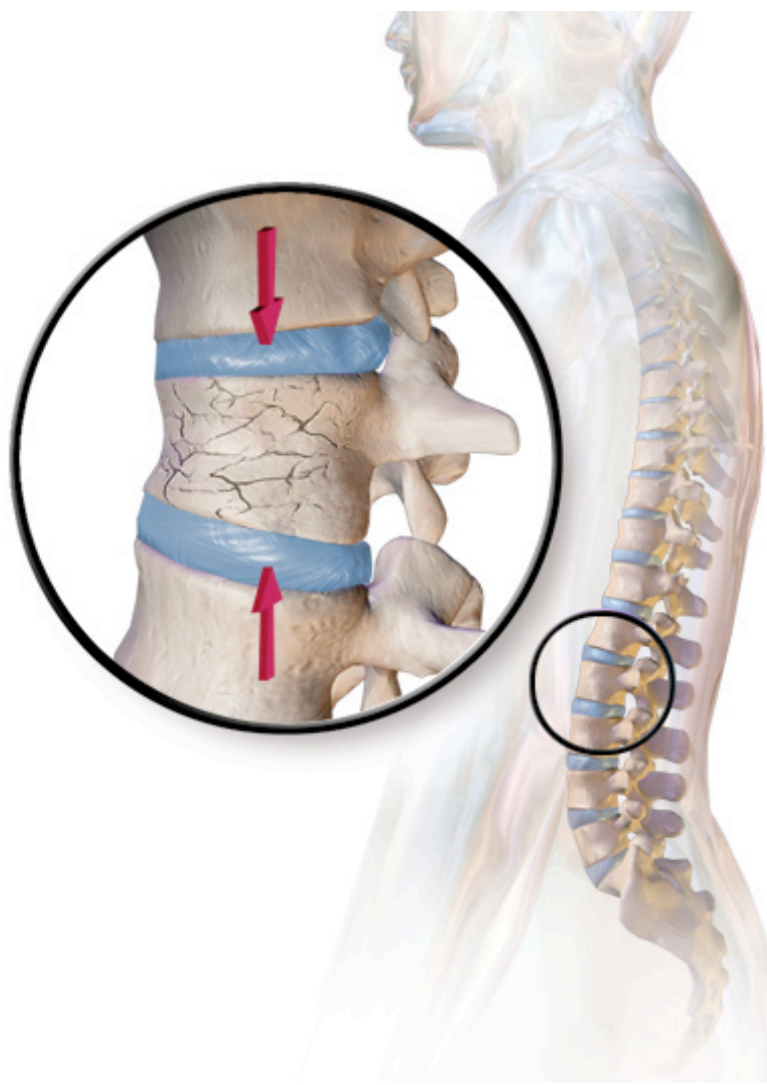


Fig. 1. This is an illustration of a compression fracture. (en.wikipedia.org)



Fig. 2. This is an MRI of a fracture and dislocation of C4 vertebra with spinal cord compression. (en.wikipedia.org)

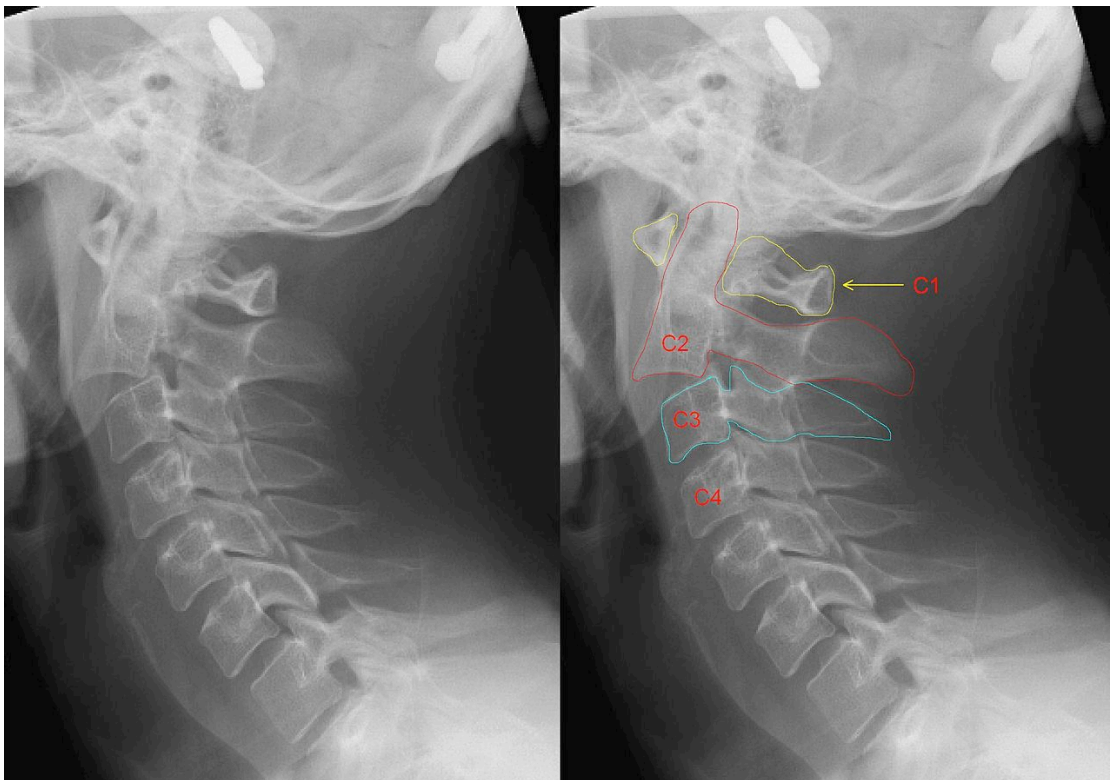


Fig. 3. The above is a CT scan of the neck showing evidence of severe hyperextension manifested by C2 (outlined in red) having moved forward with respect to C3 (outlined in blue). (en.wikipedia.org)

ANATOMIC CONSIDERATIONS

Injuries to the spinal cord depend partly on whether the trauma to the vertebral column is direct or indirect and partly on the level at which the vertebral column received the trauma. The deformities of bone, which result are determined by variations in the structure of the vertebral column at its various levels. For example, mobility is the primary function of the cervical spine. To facilitate this function the bones of the cervical vertebrae, most especially C1 (atlas) and C2 (axis), are smaller and lighter in structure. In contradistinction, the lumbar vertebrae purpose is to help support the weight of the body, and permit movement, although not to the degree of the cervical vertebrae. Because it is a heavier structure, the lumbar vertebrae and underlying spinal cord are less susceptible to indirect trauma than the cervical spine. However, the response to direct trauma is approximately constant at the different spinal levels.

The common sites of spinal cord injury are at the levels of the upper cervical, the middle and lower cervical, the lower thoracic, and the upper lumbar vertebrae. In an early study done by Wortis and Sharp (1941), they observed that in about three-fourths of all cases of fracture of the cervical vertebrae, the underlying spinal cord and or nerve roots were injured. Slightly more than half of the fractures of the thoracic spine and only about one-fourth of the fractures of the lumbar vertebrae were accompanied by spinal cord or nerve root damage. What also must be remembered is spinal cord and nerve root damage following spinal trauma may be greatly delayed. The spinal cord or nerve roots may be slowly compressed by exuberant callus formation in the canal or in the foramina, by the hypertrophic bony changes of secondary spondylitis deformans or by herniation of an intervertebral disc into the canal. Infection of the spinal meninges may follow a penetrating wound. Intraspinous hemorrhage or thrombosis may occur days or even weeks after the initial injury.

CERVICAL VERTEBRAE AND SPINAL CORD INJURIES

Upper Cervical Injuries

When analyzing spinal cord injuries of the **upper cervical spinal cord** you need to be aware of the anatomy of this region. C1 (atlas), the first cervical vertebra, supports the head (Fig. 4). It is unique in that it does not have a centrum, which has been replaced by the dens, a bony protuberance of C2 (axis) (Fig. 5). C1 is held in place by several ligaments. The dens is held in place by the transverse ligament. The transverse ligament divides the vertebral canal of C1 into two compartments. The anterior compartment is occupied by the dens and the posterior compartment by the spinal cord and its coverings. C2, the axis, is the second cervical vertebra, acts as an axial for rotation of C1, the atlas, and the head, around the dens (odontoid process), which projects upward from the superior surface of body.

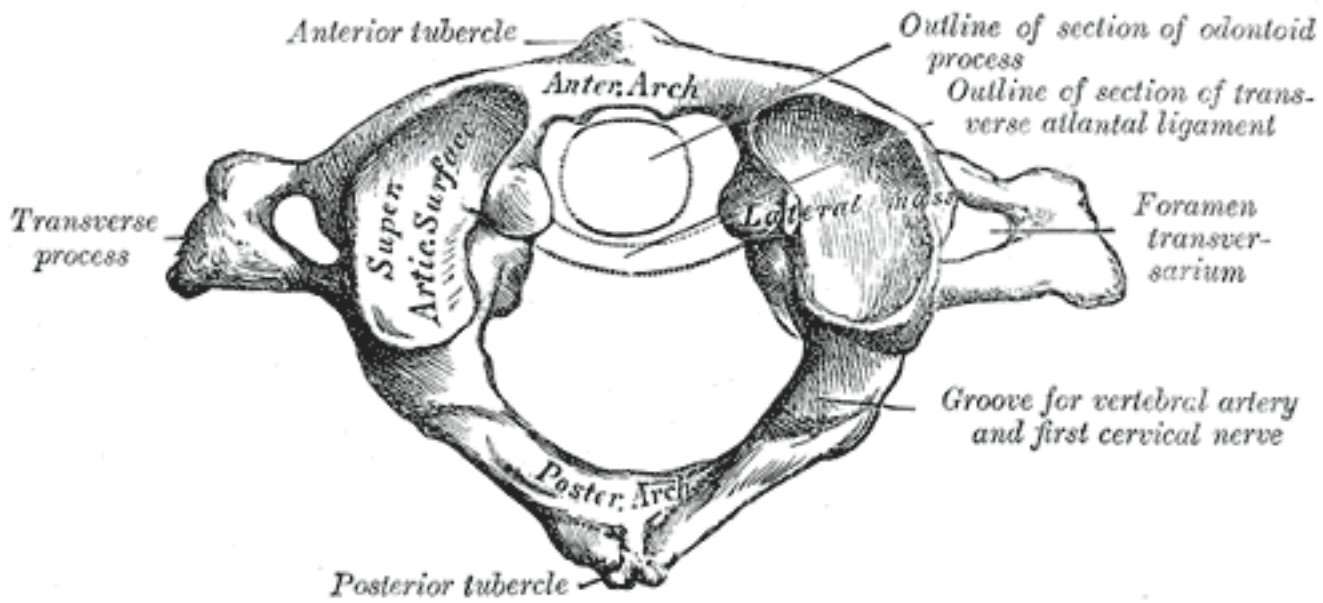


Fig. 4. This is an illustration of the structure of the atlas, the first cervical vertebra (C1). (en.wikipedia.org)

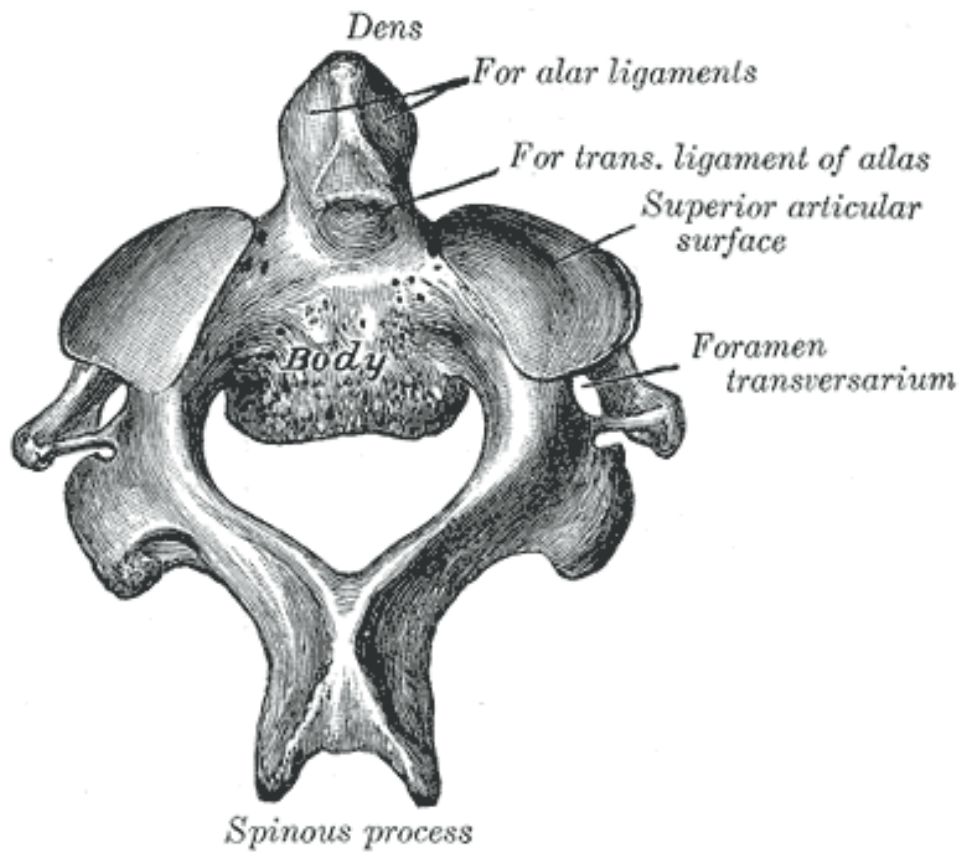


Fig. 5. This is an illustration of the anatomy of the axis, C2. (en.wikipedia.org)

Injuries to the upper cervical vertebrae and the underlying spinal cord may occur through several mechanisms, such as, compression (vertical loading), compression/flexion, compression/extension, tension, tension/extension, tension/flexion, torsion, horizontal shear, and lateral bending. Disruption of the transverse ligament can occur in anterior-posterior shear or rotational injuries of the cervical vertebrae, causing atlantoaxial (C1-C2) subluxation. Compression loading due to a blow to the top of the head or a fall in which the victim lands on the top of their head, may cause a compression fracture of the anterior and posterior arches of the atlas (C1) with lateral displacement of the lateral masses onto the axis. Another type of fracture that is associated with sudden hyperextension is the so-called hangman's fracture, which consist of a fracture of the pedicles of C2, causing an anterior dislocation of C2 and or C3, with or without odontoid process fracture (Fig. 3). This type of injury is seen in judicial hangings and automobile accidents in which the neck is suddenly hyperextended and rotated.

Sudden hyperextension, such as that due to a violent load to the face and or jaw as can occur when a pedestrian is struck face on by a vehicle, resulting in the person being propelled into the windshield or when an unrestrained vehicular passenger strikes the dashboard, often results in injury to the upper cervical vertebrae. Typically, the injury is to C1-C4, most especially the C1/C2 complex. The most common injury in these cases is a dislocation of the atlantooccipital joint. The mechanism of the fracture of C1 (atlas) is believed to be due the axial impact via the head, when the occiput is held rigidly in line with the spine by the contracted neck muscles. Not uncommonly, this fracture or dislocation is often associated with a fracture of the odontoid of the axis (C2). Such hyperextension injuries tend to force the vertebral body forwards and, if there is significant displacement, the arch of the atlas (C1) is intruded into the spinal canal with the consequent risk of cord damage. In addition, hyperextension can cause the ligamentum flavum to corrugate and intrude into the anterior part of the spinal canal to impinge on the spinal cord.

An unusual fracture that can occur with sudden hyperextension is the ring fracture of the base of the skull. This occurs when a pedestrian is struck from behind by a vehicle. This type of fracture represents an avulsion fracture of the base of the skull. Typically, such fractures are associated with lacerations of the pontomedullary junction and or the cervicomedullary junction.

Middle and Lower Cervical Injuries

Injuries to the cervical vertebrae and underlying spinal cord between C4 and C8 constitute the middle and lower cervical injuries (Fig. 6). Injuries to this segment of the cervical vertebrae and underlying spinal cord are the most common type of immediately nonfatal spinal injury. Spinal cord lesions may occur with or without spinal fractures, however, spinal ligamentous injury is usually present, causing dislocation or subluxation. When the middle cervical spine is fractured, dislocated, or subluxated, spinal cord injury is usually more severe than similar injuries sustained to the upper

cervical region, and usually there is a higher incidence of complete rather than incomplete lesions associated.

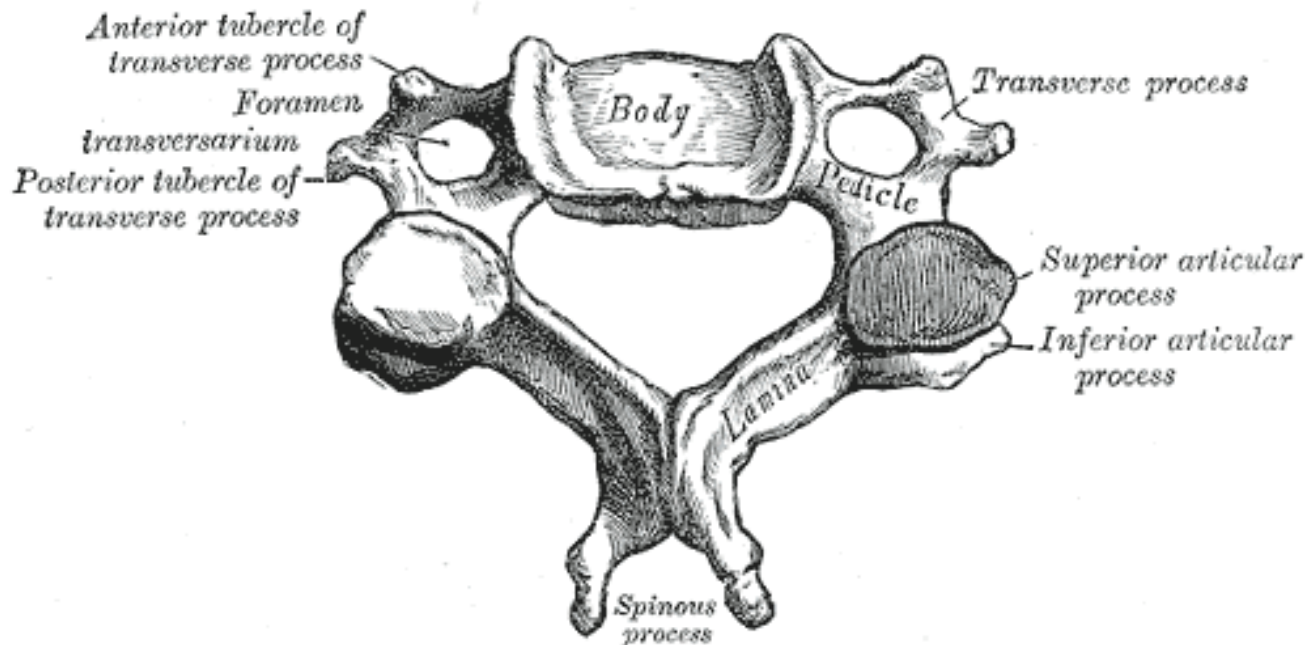


Fig. 6. This is an illustration of the anatomy of the C3-C7 cervical vertebrae. (en.wikipedia.org)

The mechanisms of these injuries typically are one or more of the following: hyperflexion, hyperextension, hyperrotation, or compression of the vertebral column.

In the case of cervical flexion injury, the head has usually been bent sharply forward when the force is applied. The cervical vertebrae are forced together at the level of maximum stress, driving the anteroinferior edge of the upper vertebral body into the one below, sometimes splitting it in two. The posterior part of the fractured body is displaced backward and compresses the cord. Concomitantly, there is tearing of the interspinous and posterior longitudinal ligaments. Less severe degrees of anteroflexion injury produce only dislocation of adjacent cervical vertebrae at one of several levels. Increase vulnerability to the effects of anteroflexion, and to some extent to retroflexion injuries, is increased by the presence of cervical spondylosis or ankylosing spondylitis or by a congenital narrowness of the spinal canal. Such hyperflexion injuries can occur with blows to the back of the neck, shallow water diving, motorcyclists flipping forward from their cycles, in rollover vehicular accidents when the victim is unrestrained, wrestling matches or fights in which a hammerlock is used, in posterior vehicular impacts and in vehicular-pedestrian accidents in which the vehicle strikes the pedestrian head on causing a sudden hyperflexion of the neck.

In cervical hyperextension injuries, the mechanism is one of vertical compression with the head in an extended position (Fig. 3). Stress is mainly on the posterior elements

(the laminae and pedicles) of the midcervical vertebrae (C4-C6), or sometimes at higher levels as discussed above on page 4. The resulting fracture or fractures may be unilateral or bilateral. Such disruption of the spinal architecture allows for displacement of one vertebral body upon the adjacent one with compression of the cord between the laminae of the lower vertebra and the body of the one above. Spinal cord damage can occur in hyperextension without apparent fracturing or misalignment of the vertebrae. In these instances, the spinal cord damage is considered to be caused by a sudden inward bulge of the ligamentum flavum or by transient vertebral dislocation that is permitted because of ligamentous disruption.

Rotational forces are quite common in motor vehicular accidents. Such forces may produce subluxation with facet interlocking, as well as other forms of dislocation with impingement of the spinal canal.

Clinical Presentation of Cervical Injuries

Typically, in significant lesions occurring at the level of C4-C5 or above, the victim will experience loss of motor function at the time of the injury, manifested as quadraplegia (paralysis of both upper and lower extremities), and paraplegia (paralysis of both lower extremities) with lesions of the thoracic cord. These clinical presentations are accompanied by immediate atonic paralysis of the bladder and bowel, gastric atony, loss of sensation below a level corresponding to the spinal cord lesion, muscular flaccidity, and almost complete suppression of spinal segment reflex activity below the lesion. As a result of their sudden separation from higher levels of control, the neural elements below the lesion essentially fail to perform their normal function.

Immediately following the spinal cord injury, there is a complete loss of function below the level of injury. This may occur in incomplete injuries to the spinal cord, causing the injury to appear more severe than it is. This phenomenon, is referred to as **spinal shock**, which can last for a few hours to a few weeks. Below the level of injury, spinal shock manifest as flaccid paralysis of all skeletal muscle; loss of all spinal reflexes; loss of pain, proprioception, and other sensations; bowel and bladder dysfunctions with paralytic ileus; and loss of thermoregulation. A return of spinal reflexes indicates the end of spinal shock with initial reflex return occurring usually in 1-3 days.

Thoracic, Lumbar and Sacral injuries

The thoracic vertebral column from T1 to T10 has much more resistance to injury than does the cervical vertebrae and underlying spinal cord due to the added stability of the thoracic rib cage and costovertebral ligaments (Fig. 7). To produce a fracture, dislocation or a rotational injury in this portion of the thoracic vertebral column would require enormous force, consequently such lesions are seldom seen. However, the lower thoracic and lumbar vertebral column, T11 to L5, are far more susceptible to injury due to increased flexibility in this region and the lack of lateral stability of the ribs. Fractures and dislocation injuries are quite common and can occur with or without spinal cord injury. Also, rotational and flexion forces play a greater role in vertebral and

spinal cord injuries than hyperextension forces. Compression injuries in this region of the vertebral column are uncommon.

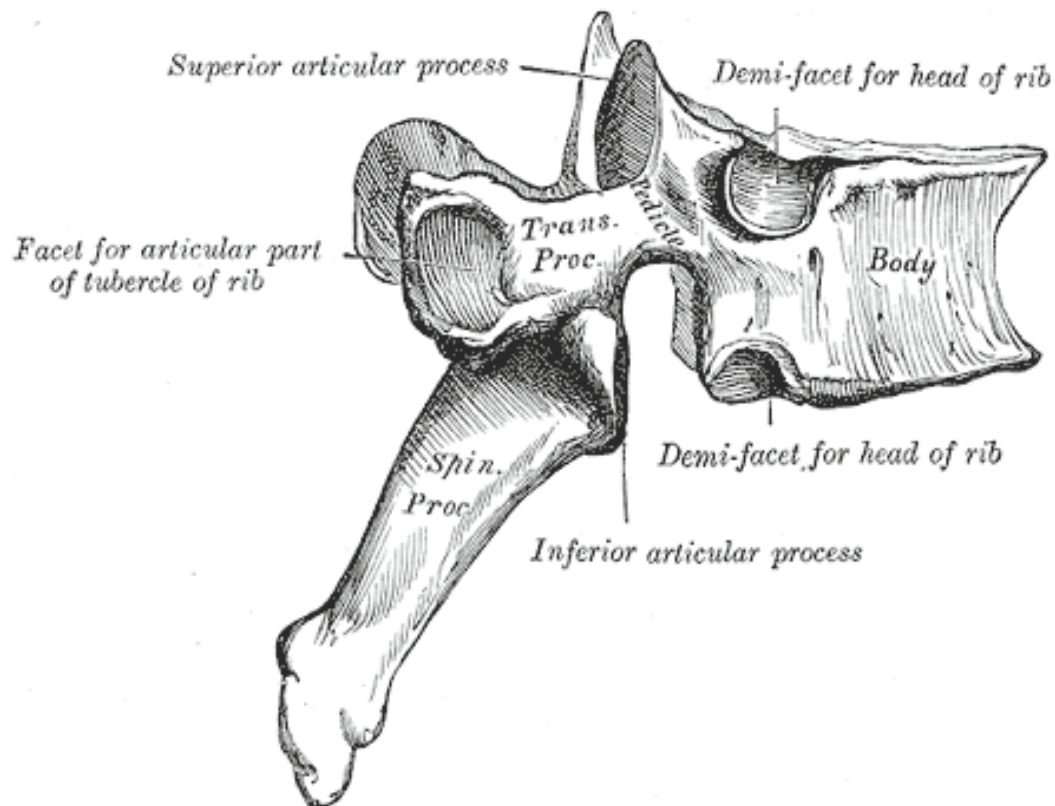


Fig. 7. This is a typical thoracic vertebrae looking at it from the lateral side. (en.wikipedia.org)

In the lower lumbar vertebrae and sacral region compression fractures are most common with or without injury to the spinal cord (Fig. 8). These type of injuries are common in victims who sustain sitting-position injuries and in military pilots whose aircraft crashes in a pancake fashion (belle in). Fractures in this location are quite common in those patients who have osteoporosis, disorders of calcium-phosphorus metabolism and metastatic or primary carcinoma.

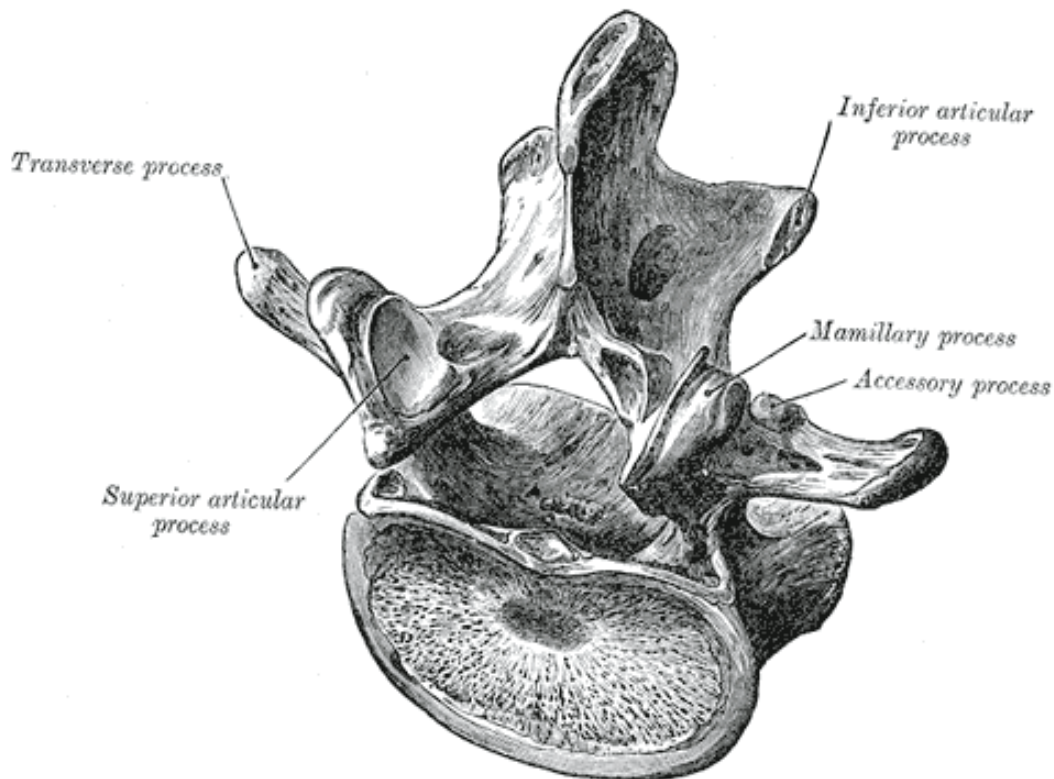


Fig. 8. This is a typical lumbar vertebrae. (en.wikipedia.org)

Clinical Presentation of Thoracic, Lumbar and Sacral Injuries

In patients with cervical or upper thoracic cord injuries, **neurogenic shock** may develop. **Spinal shock** is the loss of sensation accompanied by motor paralysis with initial loss but gradual recovery of reflexes following a spinal cord injury. Reflexes in the spinal cord below the level of injury are depressed (hyporeflexia) or absent (areflexia), while those above the level of injury remain unaffected. The 'shock' in spinal shock does not refer to circulatory collapse, and should not be confused with **neurogenic shock**, which is potentially life-threatening.

Neurogenic shock is represented by spinal cord injuries at or above T6, in which there is a loss of **autonomic** innervation from the brain manifested by a loss of brainstem and higher center control of the sympathetic nervous system. The parasympathetic nervous system is preserved, the normal synergy between the sympathetic and parasympathetic nervous systems is lost in the cervical and high thoracic spinal cord lesions. The loss of sympathetic outflow results in hypotension due to peripheral vasodilation. In essence, neurogenic shock is the sudden loss of vasomotor tone throughout the body, resulting in massive dilation of the veins. Such venous dilation causes a decrease in venous return to the heart due to venous pooling of blood. In addition, slowing of the heart rate (bradycardia) develop due to **uninhibited parasympathetic stimulation**. This typically resolves in about 3-6 weeks. Sacral parasympathetic loss may be encountered in lesions below T6 or T7.

Without the **autonomic nervous system**, the human heart beats at a rate of approximately 100 beats per minute, which is the spontaneous rate produced by the pacemaker cells in the sinoatrial node situated in the wall of the right atrium. During rest the normal heart rate is much lower reflecting the inhibiting action of the parasympathetic tone. The parasympathetic fibers, controlling the heart, exit the brain at the brainstem level, specifically at the level of the vagus nerve (cranial nerve X). In contrast, the sympathetic control of the heart originates from the upper thoracic spinal segments (T1-T5). Trauma to the cervical spinal cord will therefore typically only influence the spinal sympathetic neurons involved in heart regulation. **Remember, sympathetic and parasympathetic innervations usually function in opposition to each other.** Parasympathetic action depresses the heart rate, while activation of the sympathetic nervous system causes an increase in heart rate and stroke volume to increase the cardiac output when needed.

Unopposed parasympathetic control is believed to cause episodes of marked bradycardia and asystolia. Injuries to the spinal sympathetic pathways that control the heart and maintain the vascular tone below the level of the spinal cord injury are more likely to develop neurogenic shock and cardiac arrhythmias (**autonomic dysreflexia**) that can contribute to early mortality following spinal cord injury.

Autonomic dysreflexia, as discussed above is a permanent complication of spinal cord injuries at or above T6 vertebra, which results from the loss of coordinated autonomic responses to physiologic stimuli. Autonomic dysreflexia occurs in the fourth phase of spinal shock (1-12 months following the spinal cord injury) and is characterized by unchecked sympathetic stimulation below the spinal cord lesion due to loss of brain regulation (inhibition). The underlying pathophysiology is believed to be due to the sprouting of afferent fibers in the thoracolumbar dorsal horns and necrosis of the descending white matter connections to sympathetic preganglionic neurons, which result in autonomic dysreflexia.

It manifests as an uninhibited or exaggerated sympathetic response to noxious stimuli, which can lead to extreme hypertension through vasoconstriction. The parasympathetic system will respond by vasodilation and bradycardia above the level of the lesion, but is not sufficient to correct the elevated blood pressure. Traumatic spinal cord injuries below T6 do not produce these dramatic effects because the splanchnic innervation allows for compensatory dilatation of the splanchnic vascular bed.

This is a potentially life-threatening complication that may occur any time after the spinal shock has resolved. It is characterized by a sudden episode of hypertension, headache, bradycardia, upper-body flushing and lower body vasoconstriction, piloerection (goose bumps), sweating, and loss of bladder and bowel control. The hypertension can vary between being asymptomatic to a hypertensive crisis, which may lead to a cardiac arrest due to bradycardia and or intracranial hemorrhage.

The usual stimulus initiating autonomic dysreflexia is activation of visceral or cutaneous pain receptors below the level of injury. A not uncommon cause is a full bladder, constipation, pressure sores, fractures, or occult visceral disturbances.

Stimulation of afferent pain receptors causes the sympathetic efferents in the cord to discharge, resulting in reflex vasoconstriction. Continuous discharge by these sympathetic efferents below the level of the spinal cord injury causes a significant increase in blood pressure. The resulting hypertension initiates the baroreceptors response. Such a response decreases the heart rate as well as dilation of vessels above the level of injury. This response is responsible for the upper body flushing. Descending signals from the brain cannot get past the spinal cord injury, thus inhibition of the sympathetic neurons below the level of injury does not occur.

PATHOPHYSIOLOGY OF SPINAL CORD INJURY

The pathophysiology of spinal cord injury has two components, a **primary component** and a **secondary component**. The **primary component** involves the initial mechanical injury during which fracture and or dislocation of the vertebral column due to flexion, extension, dislocation or distraction forces related to rotation, results in forces being applied to the spinal cord, which cause disruption of axons, blood vessels, and cell membranes. This is followed by the delayed onset of the **secondary component**, which involves vascular dysfunction, edema, ischemia, excitotoxicity, electrolyte shifts, free radical production, inflammation, and delayed apoptotic cell death. As discussed above, immediately following the spinal cord injury are neurological deficits, which are followed by the secondary component hours to days after the injury, which causes, to varying degrees, a protracted period of tissue destruction.

Perhaps another way to look at the pathophysiology of spinal cord injury is that it consist of multiple contiguous phases over distinct time periods, which can be categorized as **immediate, acute, intermediate, and chronic stages of spinal cord injury**.

Immediate Phase: This phase begins at the time of the injury lasting approximately 2 hours. In the above description it would represent the **primary component**. As stated above it is that phase in which there is traumatic disruption of axons, blood vessels, cell membranes followed immediately by the death of neurons and glia. Occurring simultaneously is the development of **spinal shock, neurogenic shock followed by autonomic dysreflexia**.

It is during this period, swelling of the cord due to edema in the traumatized area occurs, often associated with hemorrhage into the central gray matter. This hemorrhage may extend several spinal segments above and below the injured portion of the spinal cord. Disruption of cell membranes and ischemia leads to neuronal and glia cell death. It is believed the main pathological process is impaired perfusion at the cellular level leading to ischemia. Ischemia develops immediately after the spinal cord injury and can continue for at least 24 hours.

Ischemia in of itself causes a decrease in energy due to the lack of delivery of glucose and oxygen to the tissues, which results in a decrease in ATP stores due to mitochondrial dysfunction. In neurons most of the ATP supply is produced by mitochondria. It is believed the post-traumatic ischemia is due to focal narrowing of sulcal arterioles and intramedullary capillaries, along with their fragmentation, aneurysmal dilatation or occlusion. The disruption of the microvasculature also leads to petechial hemorrhages in the white matter of the spinal cord.

Along with the above morphologic changes, pathophysiological processes are immediately generated. As an example, an inflammatory response is initiated almost immediately manifested by the activation of macrophages and microglia, which is followed by the release of proinflammatory cytokines such as TNF α , IL-1(IL- β), IL-6, and IL-10. Inflammatory cytokines are low molecular weight proteins that regulate the body's immune response. In addition, bradykinin, prostaglandins, leukotrienes, platelet activating factor and serotonin accumulate at the lesion site within a few hours.

Excitatory amino acids, glutamate and aspartate, increase within a few minutes of the trauma to the spinal cord, which leads to the development of excitotoxicity. Excitotoxicity is a term coined by Dr. John Olney in 1969, which describe a reaction that occurs when neurons are exposed to excess glutamate and aspartate extracellularly. Dr. Olney noted that when neurons are exposed to excess glutamate, there is a delayed reaction, which ultimately results in the death of the neuron. It was subsequently shown that excessive glutamate allows for the uncontrolled intracellular entry of calcium into the neuron through glutamate receptor controlled calcium channels. This uncontrolled entry of calcium into the neuron activates cell death (apoptosis) signaling pathways that lead to cell death. Apoptosis will be discussed on page 17. The **immediate phase** is followed by the **acute phase**.

Acute Phase: This phase last form 2-48 hours. In this phase there is a continuation of the above processes, which include hemorrhage, edema, demyelination, the formation of cavities within the traumatized cord, along with axonal and neuronal necrosis and a series of pathological changes which end with infarction.

The edema may be vasogenic or cytotoxic. Vasogenic edema is the leakage of plasma fluid into the extracellular space due to the breakdown of the BBB. Cytotoxic edema results from intracellular swelling after cell death. Both forms of edema can cause pressure-induced ischemia caused by diminished blood flow to the injured region. Edema is seen from 3 hours to 3 days after the traumatic injury.

There is an inflammatory response which involves vascular changes, cellular responses, and chemical mediators. There is an influx of neutrophils within the first day, which peaks at day 2, and most are gone by day 3. It is believed the neutrophilic response is neurotoxic in nature, as these cells normally act to eradicate infection through the release of free radicals and neutrophil extracellular traps that are released to trap pathogens through a process called NETosis. There is also evidence of increased levels of glutamate, excitotoxicity, oxidative damage, ischemia, Ca⁺⁺ dependent NO production, free radical damage, ionic dysregulation, and lipid peroxidation in cell membranes.

Ionic dysregulation following spinal cord trauma leads to abnormalities in the concentration of electrolytes as well as gradient changes, which play a significant role in the death of neurons and glia. The most important ion in the causation of cell death is the dysregulation of Ca^{++} . The intracellular increase in Ca^{++} leads to the activation of phospholipases, proteases, phosphorylases, calpains, mitochondrial dysfunction and free radical production, which in turn leads to cell death.

As in the **immediate phase**, excitotoxicity due to the toxic levels of glutamate and aspartate, leads to the intracellular influx of Na^+ and Ca^{++} which in turn leads to the continuing death of both neurons and glia. The actual causation of the death of these cells is believed to be due to toxic levels of glutamate, which leads to a failure of energy dependent transporters, especially Na^+ K^+ adenosine triphosphotase membrane transporter, which normally functions to regulate extracellular concentrations of ions, glutamate, and other molecules.

Free radicals (reactive oxygen species [ROS]) are chemical species containing oxygen. Examples are peroxides, superoxide, hydroxy radical, and singlet oxygen. Although **ROS** are a normal byproduct of metabolism, during times of stress, such as would occur in a traumatic spinal cord injury, ROS levels increase dramatically, which can in turn damage cell structures. Thus, to maintain cell viability, it is important that ROS are not generated above their normal metabolic rate, for the increased production of free radicals makes a substantive contribution to the secondary damage seen in spinal cord injury. Free radicals lead to lipid peroxidation and cell membrane damage, which in turn leads to axonal disruption and the death of both neurons and glia. It also causes the dysfunction of organelles, as well as contributing to the dysregulation of calcium through the oxidation of membrane lipids. The detection of these free radicals reaches its zenith at approximately 12 hours and remains elevated for approximately 1 week, returning to its basal level at 4-5 weeks. The most important of the free radicals in the causation of ROS-mediated injury is the peroxynitrite radical generated by the reaction of nitric oxide and superoxide radical.

Other nitric oxide-derived compounds that play a role in cell injury and death by inducing **nitrosative stress** are **reactive nitrogen species (RNS)**, which are nitric oxide-derived compounds, including nitroxyl anion, nitrosonium cation, higher oxides of nitrogen, S-nitrosothiols, and dinitrosyl iron complexes. **RNS** are a family of antimicrobial molecules derived from nitric oxide and superoxide produced via the enzymatic activity of inducible nitric oxide synthase 2 (NOS2) and NADPH oxidase respectively. NOS2 is expressed primarily in microglia in the brain after the induction by cytokines and microbial products, most especially interferon-gamma ($\text{IFN-}\gamma$) and lipopolysaccharide (LPS). RNS have been recognized as playing a crucial role in the physiologic regulation of many, if not all, living cells, such as smooth muscle cells, cardiomyocytes, platelets, and nervous and juxtaglomerular cells. They possess pleiotropic properties on cellular targets after both posttranslational modifications and interactions with reactive oxygen species. Elevated levels of RNS have been implicated in cell injury and death most especially when they act together with ROS by inducing

nitrosative stress. Nitrosative stress results in damage to membrane fatty acids and functional proteins mediated by N_2O_3 (dinitrogen trioxide).

Cellular response to injury involves primarily the activation of **microglial cells**. Microglial cells are the principal immune cell of the brain. They respond to injury by proliferating, developing elongated nuclei, forming aggregates around small foci of tissue necrosis or congregating around cell bodies of dying neurons. Microglia are responsible for the overall maintenance of the brain and spinal cord. They are constantly scavenging the brain and spinal cord for plaques, damaged or unnecessary neurons and synapses, and infectious agents. Microglia are extremely sensitive to even small pathological changes in the brain and spinal cord. The origin of the microglia within the brain and spinal cord is believed to be from monocytes within the blood that move into the brain and cord during early embryonic development, then differentiate into microglia that share many surface markers or antigens with their blood borne and systemic visceral counterparts, monocytes and macrophages (i.e., CR3 and CD68).

The activated microglial cell exist in one of two states: **non-phagocytic** and **phagocytic**.

The **non-phagocytic** microglial cells undergo morphological changes including thickening and retraction of their branches, uptake of MHC class I/II proteins, expression of immunomolecules, secretion of cytotoxic factors, secretion of recruitment molecules, and secretion of proinflammatory signaling molecules, which results in a proinflammatory signal cascade.

The **phagocytic state** is the activated phagocytic microglia, which are the maximally immune responsive form of microglia. It is this form of microglia that has the antigen presenting, cytotoxic and inflammatory mediating signaling. They also can phagocytose foreign materials and display the resulting immunomolecules for T-cell activation. These cells travel to the site of injury, engulf the foreign or injured cellular material and in the process secrete proinflammatory factors (cytokines and chemokines) to promote more cells to proliferate and come to the site of injury.

Thus, the microglia, when activated secrete a number of anti- and proinflammatory cytokines, chemokines, prostaglandins, trophic factors, free radicals, lipid peroxidation products, NO, and three-forms of of excitotoxins: glutamate, aspartate, and quinolinic acid (QULN). QULN is a downstream product of the kynurenine pathway, which metabolizes the amino acid tryptophan. It has a potent neurotoxic effect. Within the brain, QUIN is only produced by activated microglia and macrophages.

Studies have shown proinflammatory cytokines can cause a release of excitotoxins from microglia as well as astrocytes at the same time the released excitotoxins can cause the further release of immune proinflammatory cytokines from the same cells. Exposure to the individual proinflammatory cytokines in-of-themselves is not neurodestructive. However, certain combinations of these proinflammatory cytokines can be very neurodestructive, such as the combination of IL-1 and TNF- α . What the evidence

suggest, it is the combination of proinflammatory cytokines and excitotoxins that leads to neurodestruction, rather than the inflammation alone.

What appears to occur since both proinflammatory cytokines and excitotoxins release occurs simultaneously, is a synergistic neurodestructive cascade is set in motion. This synergism between the immune cytokines and excitotoxic levels of glutamate, aspartate, and QULN also have similar effects on the blood brain barrier (BBB), brain vasculature, development of edema, and metabolic changes seen in traumatic injuries to the brain and spinal cord.

Immediately following the spinal cord injury there is an increase in the **BBB** permeability, which is due to the direct mechanical disruption caused by the primary injury as well as the effects on the endothelial cells of the BBB by the inflammatory mediators (TNF α and IL-1 β) and other compounds (reactive oxygen species, nitric oxide, histamine, matrix metalloproteinases, and elastase) and excitotoxic levels of glutamate, aspartate, and QULN generated after the spinal cord injury. The peak BBB permeability occurs at 24 hours, returning to normal levels within 2 weeks.

Cell Death following spinal cord injury is due to two processes; **necrosis** or **apoptosis**.

Necrosis is the primary reason why neurons die within the spinal cord following a traumatic injury. As discussed above, The main mechanism underlying the pathological processes in spinal cord injury is the lack of energy due to impaired perfusion at the cellular level and ischemia. Ischemia begins immediately after the traumatic spinal cord injury and if not treated, deteriorates in the first 3 hours and continues for at least 24 hours. Ischemia causes lack of energy through a decrease in the quantity of glucose and oxygen delivered to the tissues, which results in a decrease in ATP stores. Cells that die as the result of an acute injury usually swell and burst due to loss of cell membrane integrity, the process of which is called **necrosis**.

Apoptosis is a process by which cells, which are no longer needed or become a threat to the organism, undergo a **programmed cell death**. This process involves a specific proteolytic cascade that causes the cell to shrink and condense, to disassemble its cytoskeleton, and to alter its cell surface so that a neighboring phagocytic cell, such as a macrophage, can attach to the cell membrane and digest the cell. In contradistinction to necrosis, apoptosis is an orderly cell death that results in disassembly and phagocytosis of the cell before any leakage of its contents occurs, and the neighboring cells usually remain healthy.

Apoptosis can be initiated through one of two cell death signaling pathways, the **intrinsic pathway** and the **extrinsic pathway**. In the **intrinsic pathway** the cell kills itself because it senses cell stress, while in the **extrinsic pathway** the cell kills itself because of signals from other cells. Both pathways induce cell death by activating enzymes referred to as **procaspases**, which are inactive, to **caspases**, which are proteases, or enzymes that degrade proteins. The activated caspases then kill the cell by degrading

proteins indiscriminately. Calcium plays a role in apoptosis by having the cell initiate intracellular apoptotic signaling in response to stress, which causes cell death. The intracellular increased calcium concentration due to immunoexcitotoxicity causes damage to the cell membrane, which triggers the release of intracellular apoptotic signals by the damaged cell.

What is important to understand, in traumatic spinal cord injuries, apoptosis does not play a significant role in spinal cord neuronal cell death. Neuronal cell death in the spinal cord is primarily due to **necrosis**. This is not to say neuronal apoptosis does not occur in the spinal cord. An example of apoptotic neuronal cell death within the spinal cord is the death of **oligodendroglia**. Although, oligodendroglia can die as a result of necrosis, due to the fact like all neurons they are very sensitive to ischemic injury, hence like neurons they undergo necrosis, they also readily undergo apoptosis following a spinal cord injury. The apoptotic cell death of the oligodendroglia is due to the activation of their Fas receptors by activated microglia, which express the Fas ligand. Cell death of the oligodendroglia comes about through the interaction of the Fas receptors and Fas ligands, which activate the caspase cascade leading to degradation of proteins through the process of apoptosis, which leads to cell death. The loss of the oligodendroglia leads to demyelination of the axons. The effect of demyelination, as well as other forms of axonal injury, such as traumatic disruption, lipid peroxidation, and ischemic swelling, are associated with the potential death of the oligodendroglia. It is the death of the oligodendroglia which contributes to the process of wallerian degeneration (page 18).

Subacute Phase: This phase lasts from approximately 2 days to 2 weeks following the spinal cord injury. During this phase the phagocytic response is maximal, removing cell debris, especially the growth-inhibitory components of myelin debris from the traumatized area of the spinal cord.

An important component of the subacute phase is the development of an **astrocytic scar**. The astrocytic scar is produced by the astrocytes at the periphery of the necrotic region of the traumatized spinal cord. These peripheral astrocytes become activated by proliferating and growing multiple, large cytoplasmic processes that ultimately form an astrocytic scar, also referred to as a glial scar. The downside of this astrocytic scar is it interferes with axonal regeneration. However, not all aspects of the astrocytic scar are negative. For example, these scars help to reestablish ionic homeostasis as well as the integrity of the BBB.

Intermediate Phase: This phase extends from the 2 week mark to the 6 month mark and is represented by the further development of the astrocytic scar and regenerative axonal sprouting, along with elimination of necrotic debris, the resolution of edema, the revascularization of tissue, and the restoration of the BBB.

Chronic Phase: This phase begins at the 6 month mark following the traumatic spinal cord injury and is characterized by further development of the astrocytic scar and the development of cysts and or syrinxes within the necrotic area of the traumatized cord, as well as wallerian degeneration and schwannosis.

Wallerian degeneration is the anterograde disintegration of axons and their myelin sheaths that have been transected during the traumatic spinal cord injury. It is characterized by distorted and fragmented myelin sheaths with absent or malformed axons. Wallerian degeneration is a long process and may take more than a year to complete. The astrocytic scar eventually replaces the destroyed myelinated axon. Along with the astrocytic scar, the traumatized area of the spinal cord may also show a mesenchymal scar composed of fibrous connective tissue and collagen.

Within the chronic phase you will often see the development of single, multiple, or multiloculated cyst and syrinxes. These cavities are typically filled with extracellular fluid, often containing residual macrophages, small quantities of connective tissue, and blood vessels. These cavities represent the healing phase of the necrotic process.

Schwannosis is an aberrant intra- and extramedullary proliferation of Schwann cells with associated axons. They are similar in appearance to the traumatic neuromas that occur in injured peripheral nerves. The Schwann cells are introduced into the spinal cord after penetrating injuries. Like the astrocytic scar and mesenchymal scar, schwannosis can present a physical barrier to the healing of the traumatized cord. The aberrant axons that are a part of schwannosis can cause pain, spasticity, and other abnormal responses in the patient with a traumatized spinal cord that has entered this clinical phase.

Summary

Traumatic lesions of the spinal cord usually result from injuries which cause vertebral fractures. The spinal cord may, however, be injured by vertebral dislocation without fracture or by penetrating wounds of the canal. The common sites of injury are at the levels of the upper cervical, the mid cervical, the lower cervical, the lower thoracic, and the upper lumbar vertebrae. In approximately three-fourths of the cases of fracture of the cervical vertebrae, the spinal cord is injured. Slightly more than half of the fractures of the thoracic spine and only about one-fourth of the fractures of the lumbar spine were associated with spinal cord injury.

There are two components to spinal cord injury, a primary component and secondary component. The primary component is the immediate local effect of the mechanical violence. The secondary component, the changes of which occur at the site of the injury as well as above and below it. The secondary component is manifested by vascular dysfunction, edema, ischemia, necrosis, excitotoxicity, electrolyte shifts, free radical production, inflammation, and delayed apoptotic cell death.

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