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Review Article

Peripheral Neuropathy & Animal Models of Peripheral Neuropathy: A Review

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ABSTRACT

Peripheral neuropathy is defined as damage to the peripheral nervous system resulting in a syndrome of sensory loss, muscle weakness and atrophy along with vasomotor symptoms, alone or in any combination.
There are more than 100 known types of peripheral neuropathy, each with its own characteristic symptoms, pattern of development, and prognosis. One study estimated that the prevalence of peripheral neuropathy in the family medicine setting is 8 percent in persons 55 years and older. The prevalence in the general population may be as high as 2.4 percent. A community-based study estimated the prevalence of peripheral neuropathy in patients with type 2 diabetes mellitus to be 26.4 percent. Peripheral neuropathy may be either inherited or acquired. Causes of acquired peripheral neuropathy include physical injury (trauma) to a nerve, tumors, toxins (Lolin Y, 1989), autoimmune responses, nutritional deficiencies, alcoholism (Ammendola A et al, 2001), and vascular and metabolic disorders. Symptoms are related to the type of affected nerve and may be seen over a period of days, weeks, or years. Muscle weakness is the most common symptom of motor nerve damage. Diagnosing peripheral neuropathy is often difficult because the symptoms are highly variable. A thorough neurological examination is usually required and involves taking an extensive patient, performing tests that may identify the cause of the neuropathic disorder, and conducting tests to determine the extent and type of nerve damage. The review focused on the drugs used to treat peripheral neuropathy. It included the Nutritive supplements, Topical Capsaicin Cream, Acupuncture, Magnets, Minerals & Drugs. The different animal models of the peripheral neuropathy also reviewed .

Key-words: neuropathy, peripheral neuropathy, animal models

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PERIPHERAL NEUROPATHY

Peripheral neuropathy is damage to nerves of the peripheral nervous system, which may be caused either by diseases of or trauma to the nerve or the side effects of systemic illness. Peripheral neuropathy is defined as damage to the peripheral nervous system resulting in a syndrome of sensory loss, muscle weakness and atrophy along with vasomotor symptoms, alone or in any combination (Rubin M, 2008).

PERIPHERAL NERVE ANATOMY

There are two parts of the nervous system: the brain and spinal cord (central nervous system) and the peripheral nerves (peripheral nervous system). The peripheral nerves run through the body like webbing, connecting all the parts of the body to the brain and spinal cord. Any disorder or problem involving damage to the peripheral nerves is called Peripheral neuropathy (Roeser HP et al., 1955).

A peripheral nerve trunk comprises of axons of multiple neurons bundled in connective tissue fascicles surrounded by perineurium (Rempel D et al., 1999). Within the nerve, microvasculature runs along the outer layer (epineurium) with a transverse capillary network perfusing the endoneureum. Each fascicle itself is comprised of endoneurium containing multiple neurons surrounded with myelin produced by Schwann cells (Kiyomi H et al., 2010). The soma and synaptic junction of the neuron cells is typically located at the basal ganglion roots of the spine with just the single axon traversing through the major length of the nerve trunk.

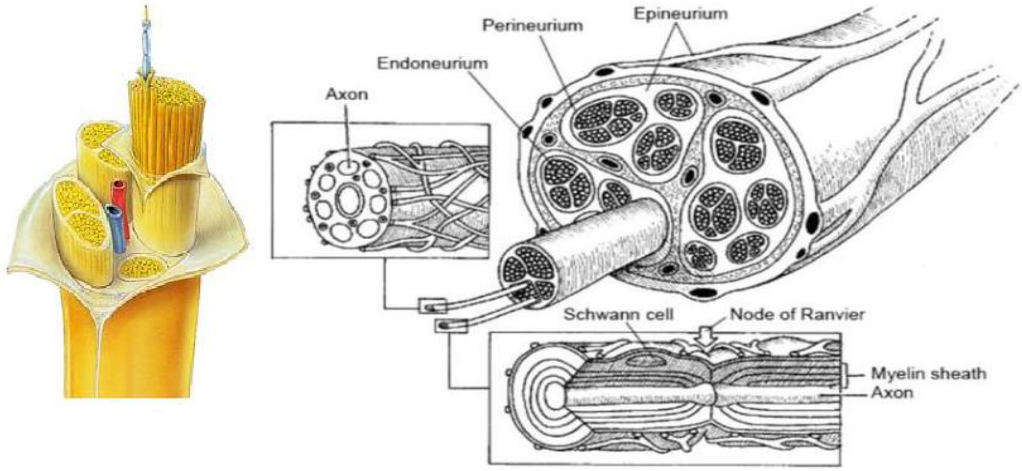

Figure 1 : Peripheral nerve anatomy

TYPES:

There are more than 100 known types of peripheral neuropathy, each with its own characteristic symptoms, pattern of development, and prognosis. The three major forms of nerve damage are included in: peripheral neuropathy, autonomic neuropathy, and mononeuropathy. The most common form is peripheral neuropathy, which mainly affects the feet and legs. The most common form of neuropathy is (symmetrical) peripheral polyneuropathy, which mainly affects the feet and legs on both sides of the body (Medifocus Guidebook, 2009).

Approximately 30% of peripheral neuropathy cases are linked to diabetes. Other common causes of neuropathy include autoimmune disorders, tumors, hereditary conditions, nutritional imbalances, infections or toxins. Another 30% of peripheral neuropathies are termed “idiopathic” when the cause is unknown.

There are several different ways to classify peripheral neuropathy. One of the most common classification systems takes into account the pattern and distribution of the pain and includes:

I. Mononeuropathy

Mononeuropathy is characterized by involvement of a single peripheral nerve. The most common cause of mononeuropathy is by physical compression of the nerve, known as compression neuropathy. Carpal tunnel syndrome and axillary nerve palsy are examples of this (Gabriel JM et al., 1997). The "pins-and-needles" sensation

of one's "foot falling asleep" (paresthesia) is caused by a compression mononeuropathy, albeit a temporary one which can be resolved merely by moving around and adjusting to a more appropriate position. Direct injury to a nerve, interruption of its blood supply (ischemia), or inflammation can also cause mononeuropathy.

II. Mononeuritis multiplex

Mononeuritis multiplex is simultaneous or sequential involvement of individual noncontiguous nerve trunks, either partially or completely, evolving over days to years and typically presenting with acute or subacute loss of sensory and motor function of individual nerves Mononeuritis multiplex may also cause pain, which is characterized as deep, aching pain that is worse at night, is frequently in the lower back, hip, or leg. It is caused by, or associated with, several medical conditions (Liu N et al., 2007): diabetes mellitus, vasculitides: polyarteritis nodosa, Wegener's granulomatosis, and Churg–Strauss syndrome; immune-mediated diseases like rheumatoid arthritis, lupus erythematosus (SLE), and sarcoidosis; infections: leprosy, lyme disease, HIV; amyloidosis; cryoglobulinemia; chemical agents, including trichloroethylene and dapsone.

III. Polyneuropathy

Polyneuropathy is a pattern of nerve damage which is quite different from mononeuropathy, and often more serious and affecting more areas of the body. The term "peripheral neuropathy" is sometimes used loosely to refer to polyneuropathy. In cases of polyneuropathy, many nerve cells in various parts of the body are affected, without regard to the nerve through which they pass; not all nerve cells are affected in any particular case. In distal axonopathy, one common pattern is that the cell bodies of neurons remain intact, but the axons are affected in proportion to their length. Diabetic neuropathy is the most common cause of this pattern. In demyelinating polyneuropathies, the myelin sheath around axons is damaged, which affects the ability of the axons to conduct electrical impulses (Gaist D et al., 2002). The third and least common pattern affects the cell bodies of neurones directly. This usually picks out either the motor neurones (known as motor neurone disease) or the sensory neurones (known as sensory neuronopathy or dorsal root ganglionopathy).

The effect of this is to cause symptoms in more than one part of the body, often on left and right sides symmetrically. As for any neuropathy, the chief symptoms include weakness or clumsiness of movement (motor); unusual or unpleasant sensations such as tingling or burning; reduction in the ability to feel texture, temperature, etc.; and impaired balance when standing or walking (sensory). In many polyneuropathies, these symptoms occur first and most severely in the feet. Autonomic symptoms may also occur, such as dizziness on standing up, erectile dysfunction and difficulty controlling urination.

EPIDEMIOLOGY:

One study estimated that the prevalence of peripheral neuropathy in the family medicine setting is 8 percent in persons 55 years and older. The prevalence in the general population may be as high as 2.4 percent. A community-based study estimated the prevalence of peripheral neuropathy in patients with type 2 diabetes mellitus to be 26.4 percent (Last JM, 1995).

Incidence of CIPN

The real incidence of CIPN has not been clearly established due to marked difference in the assessment methods and to the difficulty in demonstrating the presence of pre-existing neuropathy in patients undergoing second-line treatments after potentially neurotoxic first-line chemotherapy. Moreover, several neurotoxic antineoplastic drugs are used together in poly chemotherapy schedules for the treatment of selected kinds of solid or hematological cancers, with a subsequent possible increase in the incidence and severity of CIPN and/or the appearance of combined neurotoxicity.

CAUSES:

Peripheral neuropathy may be either inherited or acquired. Causes of acquired peripheral neuropathy include physical injury (trauma) to a nerve, tumors, toxins (Lolin Y, 1989), autoimmune responses, nutritional deficiencies, alcoholism (Ammendola A *et al*, 2001), and vascular and metabolic disorders. Acquired peripheral neuropathies are grouped into three broad categories: those caused by systemic disease, those caused by trauma from external agents, and those caused by infections or autoimmune disorders affecting nerve tissue (Perkins AT et al., 1997). One example of an acquired peripheral neuropathy is trigeminal neuralgia (also known as tic

douloureux), in which damage to the trigeminal nerve (the large nerve of the head and face) causes episodic attacks of excruciating, lightning-like pain on one side of the face. In some cases, the cause is an earlier viral infection, pressure on the nerve from a tumor or swollen blood vessel, or, infrequently, multiple sclerosis. In many cases, however, a specific cause cannot be identified. Doctors usually refer to neuropathies with no known cause as idiopathic neuropathies.

Physical injury (trauma) is the most common cause of injury to a nerve. Injury or sudden trauma, such as from automobile accidents, falls, and sports-related activities, can cause nerves to be partially or completely severed, crushed, compressed, or stretched, sometimes so forcefully that they are partially or completely detached from the spinal cord. Less dramatic traumas also can cause serious nerve damage. Broken or dislocated bones can exert damaging pressure on neighboring nerves, and slipped disks between vertebrae can compress nerve fibers where they emerge from the spinal cord.

Systemic diseases — disorders that affect the entire body often cause peripheral neuropathy. These disorders may include: Metabolic and endocrine disorders. Nerve tissues are highly vulnerable to damage from diseases that impair the body's ability to transform nutrients into energy, process waste products, or manufacture the substances that make up living tissue. Diabetes mellitus, characterized by chronically high blood glucose levels, is a leading cause of peripheral neuropathy in the United States. About 60 percent to 70 percent of people with diabetes have mild to severe forms of nervous system damage.

1. **Kidney disorders** can lead to abnormally high amounts of toxic substances in the blood that can severely damage nerve tissue. A majority of patients who require dialysis because of kidney failure develop polyneuropathy. Some liver diseases also lead to neuropathies as a result of chemical imbalances.

2. **Hormonal imbalances** can disturb normal metabolic processes and cause neuropathies. For example, an under production of thyroid hormones slows metabolism, leading to fluid retention and swollen tissues that can exert pressure on peripheral nerves. Over production of growth hormone can lead to acromegaly, a condition characterized by the abnormal enlargement of many parts of the skeleton, including the joints. Nerves running through these affected joints often become entrapped.

3. **Vitamin deficiencies and alcoholism** can cause widespread damage to nerve tissue. Vitamins E, B1, B6, B12, and niacin are essential to healthy nerve function. Thiamine deficiency, in particular, is common among people with alcoholism because they often also have poor dietary habits. Thiamine deficiency can cause a painful neuropathy of the extremities. Some researchers believe that excessive alcohol consumption may, in itself, contribute directly to nerve damage, a condition referred to as alcoholic neuropathy.

4. **Vascular damage and blood diseases** can decrease oxygen supply to the peripheral nerves and quickly lead to serious damage to or death of nerve tissues, much as a sudden lack of oxygen to the brain can cause a stroke. Diabetes frequently leads to blood vessel constriction. Various forms of vasculitis (blood vessel inflammation) frequently cause vessel walls to harden, thicken, and develop scar tissue, decreasing their diameter and impeding blood flow. This category of nerve damage, in which isolated nerves in different areas are damaged, is called mononeuropathy multiplex or multifocal mononeuropathy.

5. **Connective tissue disorders and chronic inflammation** can cause direct and indirect nerve damage. When the multiple layers of protective tissue surrounding nerves become inflamed, the inflammation can spread directly into nerve fibers. Chronic inflammation also leads to the progressive destruction of connective tissue, making nerve fibers more vulnerable to compression injuries and infections. Joints can become inflamed and swollen and entrap nerves, causing pain.

6. **Cancers and benign tumors** can infiltrate or exert damaging pressure on nerve fibers. Tumors also can arise directly from nerve tissue cells. Widespread polyneuropathy is often associated with the neurofibromatoses, genetic diseases in which multiple benign tumors grow on nerve tissue. Neuromas, benign masses of over grown

nerve tissue that can develop after any penetrating injury that severs nerve fibers, generate very intense pain signals and sometimes engulf neighboring nerves, leading to further damage and even greater pain (Ajani JA et al., 1990). Neuroma formation can be one element of a more widespread neuropathic pain condition called complex regional pain syndrome or reflex sympathetic dystrophy syndrome, which can be caused by traumatic injuries or surgical trauma. Paraneoplastic syndromes, a group of rare degenerative disorders that are triggered by a person's immune system response to a cancerous tumor, also can indirectly cause widespread nerve damage.

7. **Repetitive stress** frequently leads to entrapment neuropathies, a special category of compression injury. Cumulative damage can result from repetitive, forceful, awkward activities that require flexing of any group of joints for prolonged periods. The resulting irritation may cause ligaments, tendons, and muscles to become inflamed and swollen, constricting the narrow passageways through which some nerves pass. These injuries become more frequent during pregnancy, probably because weight gain and fluid retention also constrict nerve passage ways.

8. **Toxins** can also cause peripheral nerve damage. People who are exposed to heavy metals (arsenic, lead, mercury, and thallium) (Lolin Y, 1989), industrial drugs, or environmental toxins frequently develop neuropathy. Certain anticancer drugs, anticonvulsants, antiviral agents, and antibiotics have side effects that can include peripheral nerve damage, thus limiting their long-term use.

Infections and autoimmune disorders can cause peripheral neuropathy. Viruses and bacteria that can attack nerve tissues include herpes varicella-zoster (shingles), Epstein-Barr virus, cytomegalo virus, and herpes simplex-members of the large family of human herpes viruses. These viruses severely damage sensory nerves, causing attacks of sharp, lightning-like pain. Postherpetic neuralgia often occurs after an attack of shingles and can be particularly painful.

The human immunodeficiency virus (HIV), which causes AIDS, also causes extensive damage to the central and peripheral nervous systems. The virus can cause several different forms of neuropathy, each strongly associated with a specific stage of active immunodeficiency disease. A rapidly progressive, painful polyneuropathy affecting the feet and hands is often the first clinically apparent sign of HIV infection.

Lyme disease, diphtheria, and leprosy are bacterial diseases characterized by extensive peripheral nerve damage. Diphtheria and leprosy are now rare in the United States, but Lyme disease is on the rise. It can cause a wide range of neuropathic disorders, including a rapidly developing, painful polyneuropathy, often within a few weeks after initial infection by a tick bite.

Viral and bacterial infections can also cause indirect nerve damage by provoking conditions referred to as autoimmune disorders, in which specialized cells and antibodies of the immune system attack the body's own tissues. These attacks typically cause destruction of the nerve's myelin sheath or axon (the long fiber that extends out from the main nerve cell body).

Some neuropathies are caused by inflammation resulting from immune system activities rather than from direct damage by infectious organisms. Inflammatory neuropathies can develop quickly or slowly, and chronic forms can exhibit a pattern of alternating remission and relapse. Acute inflammatory demyelinating neuropathy, better known as Guillain-Barré syndrome, can damage motor, sensory, and autonomic nerve fibers. Most people recover from this syndrome although severe cases can be life threatening. Chronic inflammatory demyelinating polyneuropathy (CIDP), generally less dangerous, usually damages sensory and motor nerves, leaving autonomic nerves intact. Multifocal motor neuropathy is a form of inflammatory neuropathy that affects motor nerves exclusively; it may be chronic or acute.

Inherited forms of peripheral neuropathy are caused by inborn mistakes in the genetic code or by new genetic mutations. Some genetic errors lead to mild neuropathies with symptoms that begin in early adulthood and result in little, if any, significant impairment. More severe hereditary neuropathies often appear in infancy or childhood.

The most common inherited neuropathies are a group of disorders collectively referred to as Charcot-Marie-Tooth disease. These neuropathies result from flaws in genes responsible for manufacturing neurons or the

myelin sheath. Hallmarks of typical Charcot-Marie-Tooth disease include extreme weakening and wasting of muscles in the lower legs and feet, gait abnormalities, loss of tendon reflexes, and numbness in the lower limbs.

PERIPHERAL NEUROPATHY LAYOUT:

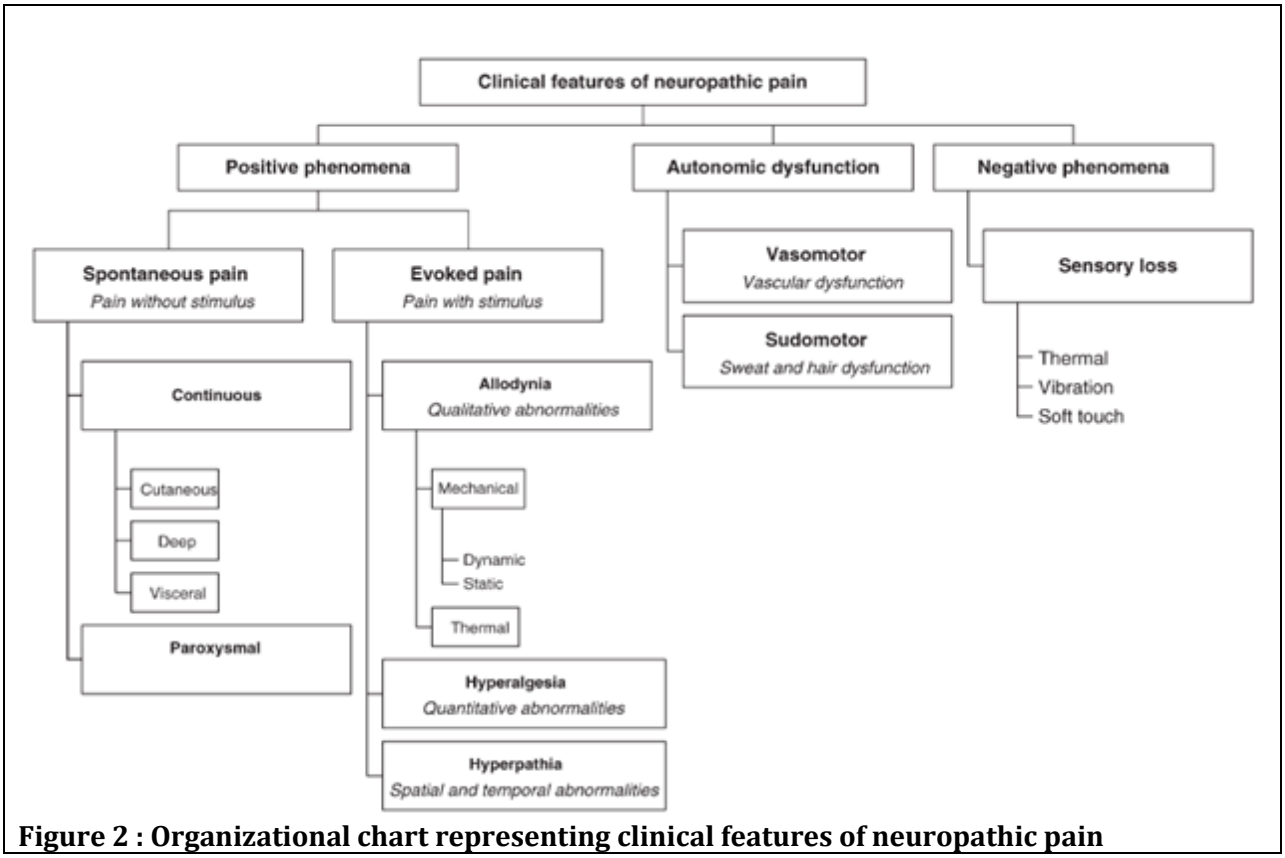

Figure 2 : Organizational chart representing clinical features of neuropathic pain

SYMPTOMS:

Symptoms are related to the type of affected nerve and may be seen over a period of days, weeks, or years. Muscle weakness is the most common symptom of motor nerve damage. Other symptoms may include painful cramps and fasciculation's (uncontrolled muscle twitching visible under the skin), muscle loss, bone degeneration, and changes in the skin, hair, and nails. These more general degenerative changes also can result from sensory or autonomic nerve fiber loss (Woolf CJ and Mannion RJ, 1999).

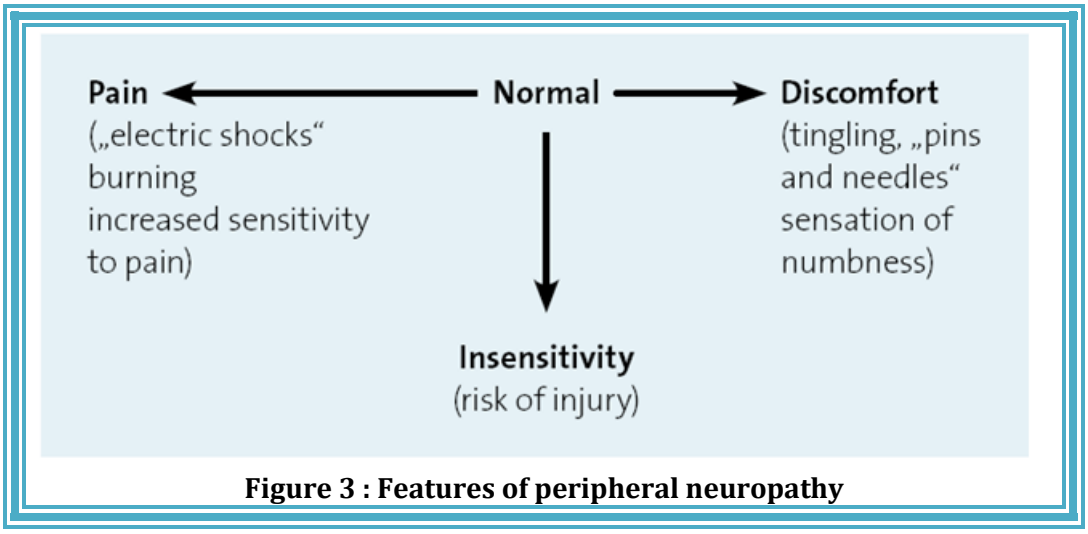

Figure 3 : Features of peripheral neuropathy

Sensory nerve damage:

Sensory nerve damage causes a more complex range of symptoms because sensory nerves have a wider, more highly specialized range of functions. Larger sensory fibers enclosed in myelin (a fatty protein that coats and insulates many nerves) register vibration, light touch, and position sense. Damage to large sensory fibers lessens the ability to feel vibrations and touch, resulting in a general sense of numbness, especially in the hands and feet. People may feel as if they are wearing gloves and stockings even when they are not. Many patients cannot recognize by touch alone the shapes of small objects or distinguish between different shapes. This damage to sensory fibers may contribute to the loss of reflexes (as can motor nerve damage). Loss of position sense often makes people unable to co-ordinate complex movements like walking or fastening buttons, or to maintain their balance when their eyes are shut. Neuropathic pain is difficult to control and can seriously affect emotional well-being and overall quality of life. Neuropathic pain is often worse at night, seriously disrupting sleep and adding to the emotional burden of sensory nerve damage.

Smaller sensory fibers without myelin sheaths transmit pain and temperature sensations. Damage to these fibers can interfere with the ability to feel pain or changes in temperature. People may fail to sense that they have been injured from a cut or that a wound is becoming infected. Others may not detect pains that warn of impending heart attack or other acute conditions. (Loss of pain sensation is a particularly serious problem for people with diabetes, contributing to the high rate of lower limb amputations among this population.) Pain receptors in the skin can also become over sensitized, so that people may feel severe pain (allodynia) from stimuli that are normally painless (for example, some may experience pain from bed sheets draped lightly over the body).

Symptoms of autonomic nerve damage:

Symptoms of autonomic nerve damage are diverse and depend upon which organs or glands are affected. Autonomic nerve dysfunction can become life threatening and may require emergency medical care in cases when breathing becomes impaired or when the heart begins beating irregularly. Common symptoms of autonomic nerve damage include an inability to sweat normally, which may lead to heat intolerance; a loss of bladder control, which may cause infection or incontinence (Woolf CJ, 1999); and an inability to control muscles that expand or contract blood vessels to maintain safe blood pressure levels. A loss of control over blood pressure can cause dizziness, lightheadedness, or even fainting when a person moves suddenly from a seated to a standing position (a condition known as postural or orthostatic hypotension).

Gastrointestinal symptoms:

Gastrointestinal symptoms frequently accompany autonomic neuropathy. Nerves controlling intestinal muscle contractions often malfunction leading to diarrhea, constipation, or incontinence. Many people also have problems eating or swallowing if certain autonomic nerves are affected.

DIAGNOSIS:

Diagnosing peripheral neuropathy is often difficult because the symptoms are highly variable. A thorough neurological examination is usually required and involves taking an extensive patient history (including the patient's symptoms, work environment, social habits, exposure to any toxins, history of alcoholism, risk of HIV or other infectious disease, and family history of neurological disease), performing tests that may identify the cause of the neuropathic disorder, and conducting tests to determine the extent and type of nerve damage.

A general physical examination and related tests may reveal the presence of a systemic disease causing nerve damage. Blood tests can detect diabetes, vitamin deficiencies, liver or kidney dysfunction, other metabolic disorders, and signs of abnormal immune system activity. An examination of cerebrospinal fluid that surrounds the brain and spinal cord can reveal abnormal antibodies associated with neuropathy. More specialized tests may reveal other blood or cardiovascular diseases, connective tissue disorders, or malignancies. Tests of muscle strength, as well as evidence of cramps or fasciculations, indicate motor fiber involvement. Evaluation of a patient's ability to register vibration, light touch, body position, temperature, and pain reveals sensory nerve damage and may indicate whether small or large sensory nerve fibers are affected.

Figure 4 : Diagnosis of peripheral neuropathy

Based on the results of the neurological exam, physical exam, patient history, and any previous screening or testing, additional testing may be ordered to help determine the nature and extent of the neuropathy.

Computed tomography, or CT scan, is a noninvasive, painless process used to produce rapid, clear two-dimensional images of organs, bones, and tissues. X-rays are passed through the body at various angles and are detected by a computerized scanner. The data is processed and displayed as cross-sectional images, or "slices," of the internal structure of the body or organ. Neurological CT scans can detect bone and vascular irregularities, certain brain tumors and cysts, herniated disks, encephalitis, spinal stenosis (narrowing of the spinal canal), and other disorders.

Magnetic resonance imaging (MRI) can examine muscle quality and size, detect any fatty replacement of muscle tissue, and determine whether a nerve fiber has sustained compression damage. The MRI equipment creates a strong magnetic field around the body. Radio waves are then passed through the body to trigger a resonance signal that can be detected at different angles within the body. A computer processes this resonance into either a three-dimensional picture or a two-dimensional "slice" of the scanned area.

Electromyography (EMG) involves inserting a fine needle into a muscle to compare the amount of electrical activity present when muscles are at rest and when they contract. EMG tests can help differentiate between muscle and nerve disorders.

Nerve conduction velocity (NCV) tests can precisely measure the degree of damage in larger nerve fibers, revealing whether symptoms are being caused by degeneration of the myelin sheath or the axon. During this test, a probe electrically stimulates a nerve fiber, which responds by generating its own electrical impulse. An electrode placed further along the nerve's pathway measures the speed of impulse transmission along the axon. Slow transmission rates and impulse blockage tend to indicate damage to the myelin sheath, while a reduction in the strength of impulses is a sign of axonal degeneration.

Nerve biopsy involves removing and examining a sample of nerve tissue, most often from the lower leg. Although this test can provide valuable information about the degree of nerve damage, it is an invasive procedure that is difficult to perform and may it cause neuropathic side effects. Many experts do not believe that a biopsy is always needed for diagnosis.

Skin biopsy is a test in which doctors remove a thin skin sample and examine nerve fiber endings. This test offers some unique advantages over NCV tests and nerve biopsy. Unlike NCV, it can reveal damage present in smaller fibers; in contrast to conventional nerve biopsy, skin biopsy is less invasive, has fewer side effects, and is easier to perform.

PATHOGENESIS OF PERIPHERAL NEUROPATHY:

Diabetic Peripheral Neuropathy

PN affects 30 percent of hospitalized and 20 percent of non-hospitalized individuals with diabetes (Ziegler D et al., 2004). The mechanisms underlying PN depend on etiology. According conventional theory the prolonged hyperglycemia results in the complications associated with diabetes, including neuropathy, PN can manifest even in individuals with abnormal glucose tolerance, a pre-diabetic condition (Hoffman-Snyder C et al., 2006). The pathophysiology of diabetic neuropathy includes increased oxidative stress yielding advanced glycosylated end products, polyol accumulation, decreased nitric oxide/impaired endothelial function (Cameron NE et al., 1997), impaired (Na^+/K^+)-ATPase activity (Stevens MJ et al., 1994), and homocysteinemia (Ambrosch A et al., 2001). Not only the nerve cells are more likely to be destroyed in a hyperglycemic environment, but repair mechanisms are also defective. Reduced levels of neurotrophic agents, including nerve growth factor and insulin like growth factor, have been noted in experimental diabetes.

Alcohol-related Neuropathy

Neuropathy associated with chronic liver disease/alcoholism appears to be associated with direct toxic effects of alcohol, malnutrition, thiamine deficiency, and genetics. The strongest correlation was there between incidence of axonal neuropathy (most commonly of the sural nerve) and total lifetime dose of ethanol, compared to other parameters examined (malnutrition and family history of alcoholism) (Ammendola A et al., 2001). Other B-vitamin deficiencies, including folate deficiency, have also been associated with the alcohol-related neuropathy (Lopez-Hernandez N et al., 2003).

Thyroid/Pituitary Neuropathies

Mucinous deposits in soft tissue resulting in nerve compression and carpal tunnel-like symptoms have been implicated in neuropathy associated with hyperthyroidism. Neuropathy associated with excess growth hormone or acromegaly has been associated with subperineurial-tissue proliferation and diminished myelinated and unmyelinated fibers (Perkins AT et al., 1997).

AIDS-associated Neuropathy

Peripheral neuropathy affects as many as one-third of individuals with acquired immunodeficiency syndrome (AIDS), most commonly manifested as distal, symmetrical polyneuropathy. A study of HIV-positive individuals found the incidence of neuropathy was significantly correlated with extent of immune deficiency (reflected in low CD4 counts) and malnutrition (decreased weight, hemoglobin, and serum albumin) (Tagliati M et al., 1999).

Drug-induced Neuropathy

Factors that render peripheral nerves susceptible to drug toxicity include a leaky blood peripheral nerve barrier (compared to the blood-brain barrier) and genetics (Weimer LH et al., 2003).

1. Antiretroviral Agents

Antiretroviral drugs used to treat individuals with HIV are implicated in PN. HIV-positive adults found exposure to didanosine (ddI) or stavudine (d4T) significantly increased the risk of developing PN zalcitabine (ddC) can also cause neuropathies (Weimer LH, 2003). It is believed the neuropathies occur in part because of drug-induced mitochondrial defects. In a rabbit model, zalcitabine resulted in demyelination via Schwann cell mitochondrial toxicity (Anderson TD et al., 1994). High lactic acid levels are associated with the use of antiretroviral drugs and may be used to differentiate drug induced versus AIDS-related neuropathy in people with HIV (Peltier AC et al., 2006).

2. Cancer Chemotherapeutic Agents

Numerous cancer chemotherapy drugs are associated with neurotoxicity and PN which include Cisplatin and its analogs, Vinka alkaloids (Vincristine, Vinablastine etc), Vinorelbine, 5-Fluoro uracil, 5-Azacytedine, Toxoids (Paclitaxel, Docitaxel), Cytarabine, Etoposide, Gemcitabine, Hexamethy melamine, Ifosphamide, Misonidazole, Bortezomib, Interferon.

High cumulative doses of cisplatin result in incidence of PN as high as 70-100 percent, with more conventional lower doses resulting in a PN rate of 12 percent. Impaired DNA repair mechanisms are believed to be the cause of PN in this population (Weimer LH, 2003).

Taxoids such as paclitaxel and docetaxel result in peripheral neuropathy, particularly at high doses. The mechanism is unknown but large arrays of disordered microtubules, a major effect on tumor cells, may be a cause of neurotoxicity (Weimer LH, 2003). Vinca alkaloids may exert neurotoxic effects by inhibiting microtubular assembly.

3. Lipid-lowering Drugs

PN is one of the less common side effects of the class of cholesterol-lowering drugs that inhibit 3-hydroxy-3-methyl-glutaryl coenzyme A (HMG CoA) reductase the so called statin drugs. People taking lipid-lowering drugs as a whole statins and fibrates another class of lipid-lowering drugs were significantly increases the neuropathy (Corrao G et al., 2004).

Potential mechanisms include interruption of cholesterol synthesis, resulting in disruption of cholesterol rich neuronal membranes, or inhibition of coenzyme Q10 synthesis (also inhibited by HMG CoA reductase), resulting in neuron mitochondrial damage (Vaughan TB et al., 2005).

GRADES (Treede RD et al., 2008)**:**

Table 1 : Classification of different grades of neuropathy

Grade 1 Mild	**Grade 2 Moderate**	**Grade 3 Severe**	**Grade 4 Disabling**	**Grade 5 Death**
Mild pain; does not interfere with function	Moderate pain; interferes with function but not activities of daily living	Severe pain; severely interferes with activities of daily living	Disabling	N/A
Asymptomatic; weakness on testing only	Symptomatic weakness; interferes with function but not activities of daily living	Weakness; interferes with activities of daily living	Disabling	Death
PN: Sensory Asymptomatic; loss of deep tendon reflexes or paresthesias	Sensory alteration or paresthesias; interferes with function but not activities of daily living	Sensory alteration or paresthesias; interferes with activities of daily living	Disabling	Death

DRUGS USED TO TREAT PERIPHERAL NEUROPATHY

Nutritive supplements

- **Acetyl-L-carnitine:** Acetyl-L-carnitine is an L-carnitine ester proposed to exert neuroprotective effects by various mechanisms including regulation of acetyl-coA, acetylation of tubulin and increasing NGF-induced histone acetylation (Verstappen CC et al., 2004). Acetyl-L carnitine has shown potential in neuro protection in multiple animal models of chemotherapy induced neuropathy including oxaliplatin, cisplatin, paclitaxel and vincristine. Recent studies have reported that acetyl-L-carnitine has a neuroprotective effect as well as being able to improve symptoms and electrophysiological parameters in patients with paclitaxel- or vincrstine-induced neuropathy.
- **Vitamin B12 (cobalamin) and folate:** Two biochemical reactions depend on vitamin B12. One involves methylmalonic acid as precursor in the conversion of methylmalonyl coenzyme-A (Co-A) to succinyl Co-A. The importance of this to the nervous system is unclear. The other is a folate dependent reaction in which the methyl group of methyl tetra hydro folate is transferred to homo cysteine to yield methionine and tetra hydro folate. The reaction depends on the enzyme methionine synthase, which uses cobalamin as a cofactor. Methionine is converted to S-adenosyl methionine (SAM), which is used for methylation reactions in the nervous system. Its deficit causes a peripheral neuropathy that can associate a myelopathy and encephalopathy if the deficit is sustained. Vitamin B12 has been traditionally used as a treatment for all types of neuropathies but there is still a lack of evidence for its recommendation.
- **Thiamine/Benfotiamine:** A vitamin B1 (thiamine) deficiency, which can be due to various underlying causes, is known to be a factor in peripheral neuropathy. For example, gastrectomy is associated with thiamine deficiency and resultant PN (Koike H et al., 2004). Benfotiamine is the most extensively studied form of thiamine for treatment of PN. Several clinical trials in healthy adults have demonstrated the superior absorption and bioavailability of this lipid soluble thiamine analogue compared to several water-soluble thiamine salts (Greb A et al., 1998). In addition, because of the lipophilic nature of benfotiamine, it may be more readily transported across cell membranes (Greb A et al., 1991), including neurons.
- **Pyridoxine:** Vitamin B6 deficiency may be associated with the development of peripheral neuropathy. In addition, in the form of pyridoxine HCl, high doses of B6 have been implicated as a cause of PN. Although the term pyridoxine often is used synonymously with vitamin B6, two other naturally occurring compounds pyridoxal and pyridoxamine possess biological activities similar to pyridoxine. All three compounds are converted to pyridoxal phosphate, the active co-enzyme important for amino acid metabolism. Pyridoxine deficit causes a well recognised sensory neuropathy that can progress to a motor neuropathy if the deficit persists. Curiously, the use of high doses of pyridoxine (1000mg/day or more) for several months causes a sensory neuropathy in a dose-dependent manner. There is a phase III trial underway that is studying the potential neuro protective effect in chemotherapy induced neuropathy of group B vitamins.
- **Biotin:** The B vitamin biotin has application for the treatment of uremic neuropathy. It is hypothesized that renal failure and subsequent metabolic imbalances result in impaired formation by the intestinal flora and absorption of biotin. In a small study, persons on dialysis suffering from PN were supplemented with a large dose of biotin 10 mg daily in three divided doses for 1-4 years. Marked improvements in paresthesia, restless legs, and difficulty walking were noted in all patients within three months (Yatzidis H et al., 1984).
- **Myo-inositol:** Myo-inositol is an important constituent of the phospholipids that make up nerve cell membranes. Because low nerve myo-inositol levels have been observed in the pathogenesis of peripheral neuropathy, the potential for supplementation has been explored. In an animal model of experimental diabetic neuropathy, nerve myo-inositol levels were diminished, with subsequent decreases in (Na^+/K^+)-ATPase activity and NCV (by 25-30%), axonal atrophy, and demyelination; dietary myo-inositol prevented these signs of nerve degeneration (Sima AA et al., 1997). In another animal model, experimental diabetes induced a decrease in motor NCV; this can be prevented by the Supplementation of 500 mg myo-inositol every day (Carrington AL et al., 1993).

Topical Capsaicin Cream for the Treatment of Peripheral Neuropathy

Numerous studies have evaluated the effect of capsaicin cream for the treatment of peripheral neuropathy. Capsaicin is an active principal of the herb Capsicum officinalis and is believed to stimulate afferent C-fibers (fibers in the mechano-heat class). The initial stimulation of C fibers results in burning and irritation that stimulates release of substance P (a pain-relieving neuropeptide) and other neuropeptides. Repeated exposures result in a diminution of the initial burning and irritation and a long-lasting analgesic effect (Weir DG et al., 1995).

Acupuncture for the Treatment of Peripheral Neuropathy

Several studies have examined the effect of acupuncture for the treatment of various types of PN diabetic, HIV associated, chemotherapy-induced, and mixed etiologies. Dose reduction or early termination of treatment with neurotoxic chemotherapy drugs is often necessitated due to significant PN (Wong R et al., 2006).

Magnets for the Treatment of Peripheral Neuropathy

It is hypothesized that electromagnetic fields may benefit PN by polarization of neurons that may be firing ectopically, resulting in neuropathy (Weintraub MI et al., 2004). Pulsed magnetic field therapy (strength of 20 gauss and frequency of 30 Hz) was used to treat persons suffering with PN of various etiologies diabetes, chronic inflammatory demyelinating polyneuropathy, mercury poisoning, pernicious anemia, paraneoplastic syndrome, tarsal tunnel syndrome, and idiopathic sensory neuropathy.

Cutting-Edge Conventional Treatments for Peripheral Neuropathy

Some cutting-edge conventional approaches to PN are on the horizon – treatments that potentially do more than just mask symptoms. Several small, "dual-action" peptides have been shown to have neurotrophic activity C-peptide and islet neogenesis associated protein peptide (both from pancreatic proteins), and derivatives of erythropoietin (Tam J et al., 2006).

Minerals for the Treatment of Diabetic Peripheral Neuropathy

- **Calcium and Magnesium infusion:** Plasma magnesium levels have been found to be significantly lower in diabetic subjects compared to controls. Despite the fact magnesium may be the most common mineral deficiency in diabetes, its clinical significance for peripheral neuropathy is unknown (Hasanein P et al., 2006). Calcium and magnesium infusions given before and after oxaliplatin infusion have demonstrated some benefit in reducing neurotoxicity and improving the reversibility of neuropathic symptoms in a single retrospective trial. The proposed etiology has been related to the oxaliplatin metabolite oxalate-mediated chelation of Ca^{2+} and Mg^{2+} ions. However, complete results from randomized controlled trials are awaited, necessary to ensure benefit without a reduction in therapeutic efficacy (Park1 SB et al., 2008).
- **Chromium:** A chromium deficiency can cause a peripheral neuropathy associated with impaired glucose tolerance (Jeejeebhoy KN et al., 1977). Infusion of as little as 250 µg chromium daily for three weeks reverses the abnormal nerve conduction (Verhage AH et al., 1996).

Drugs

1. **Amifostine:** Amifostine has been used as a radio protective agent but recently aminofostine has been postulated to be cytoprotective in chemotherapy. The proposed mechanisms of cytoprotection are decreasing the cisplatin DNA adducts as well as scavenging free radicals. It has been trialed with a number of chemotherapies, including cisplatin, paclitaxel, paclitaxel/platinum therapy and oxaliplatin (Verstappen CC, et al., 2004).
2. **Glutamine:** Glutamine is a non-essential gluconeogenic amino acid that is the main energy source for rapidly transporting nitrogen between tissues. Glutamine also up-regulates nerve growth factor mRNA, which may play a role in the protection of patients undergoing chemotherapy with neurotoxic agents. Some studies have demonstrated that there is a decrease in nerve growth factor levels during therapy, which correlates with severity of the neuropathy. There may be an additional benefit of glutamine as a centrally acting mediator of pain sensation by a complex mechanism involving glutamate down regulation (Gerardo Gutierrez-Gutierrez et al., 2010).

3. **Erythropoietin:** Erythropoietin, a hormone cytokine involved in blood cell development, may also possess potent neuroprotective and cytoprotective effects. Erythropoietin has been examined in experimental models of cisplatin-induced neurotoxicity, demonstrating neuroprotective efficacy in the absence of effects on tumour growth (Park1 SB et al., 2008).
4. **Thiol drugs:** Sulphur-containing thiol drugs have shown promise for protection of nerve from various neurotoxic chemotherapies, including vinca alkaloids, platinum compounds, and the taxanes. Glutathione, methionine, and cysteine are the sulphur-containing amino acids that physiologically counter oxidative stress, but these compounds have significant delivery problems and may protect the tumour from the chemotherapy effects as well limiting their use as neuroprotectants. A number of studies using parenteral reduced glutathione showed no loss of chemotherapy efficacy and demonstrated protective benefit (Arthur D et al., 2004).
5. **Venlafaxine:** Venlafaxine, an antidepressant used in the treatment of chronic pain, may target Na^+ channel function. Several case studies have been reported regarding venlafaxine mediated relief of the symptoms of chronic oxaliplatin and paclitaxel-induced neurotoxicity as well as marked reduction of acute oxaliplatin-induced neurosensory toxicity (Park1 SB et al., 2008). However, the results of further studies will be required to understand the role of antiepileptic and antidepressant medications in chemotherapy-induced neurotoxicity.
6. **Gabapentin:** Gabapentin, an anti-convulsant drug, has become the preferred first-line treatment for painful PN (Gail wilkes, 2007). It is currently being studied in large, national, prospective clinical trials. Some studies have shown benefit in treating painful peripheral neuropathy, while others have not.
7. **Xaliproden:** Xaliproden is a synthetic 5-HT1A receptor agonist that functions like NGF and minimizes damage to neurons in culture with oxaliplatin (Gail wilkes, 2007).

ANIMAL MODEL OF PERIPHERAL NEUROPATHY

Streptozotocin induced (diabetic) painful neuropathy

STZ (N-[methyl nitroso carbamoyl]-D-glucosamine) was dissolved in saline to a concentration of 50 mg/ml and administered 50 mg/kg i.v. into the tail vein of the rat followed by 0.5 ml of saline. Control rats received an equal volume of vehicle (saline). Starting on day 2 (24 h after STZ), levels of glucose were determined daily using a blood glucometer and found to be is 300 mg/dl in all STZ-treated rats. Ketone bodies in the urine were also determined, using Keto Diastix and found to be negative throughout the course of the study.

Nerve ligation induced peripheral neuropathy

Two models of traumatic nerve injury-induced pain were employed. Under pentobarbital (60mg/kg, i.p.) anaesthesia, the left sciatic nerve was exposed at high thigh level. Using a surgical microscope, the dorsum of the nerve was carefully freed from the surrounding connective tissue at a site just distal to the point at which the posterior biceps semi tendinous nerve branches the common sciatic nerve. A partial nerve injury was produced at this site either by placing four loosely tied ligatures (6-0 silk) around the sciatic nerve (chronic constriction injury) or by tight ligation around approximately a third to half the diameter of the sciatic nerve (partial nerve injury). Control rats were exposed to similar surgical conditions without nerve ligation.

Spared nerve injury

Under halothane (2%) anaesthesia the skin on the lateral surface of the thigh was incised and a section made directly through the biceps femoris muscle exposing the sciatic nerve and its three terminal branches: the sural, common peroneal and tibial nerves. The SNI procedure comprised an axotomy and ligation of the tibial and common peroneal nerves leaving the sural nerve intact. The common peroneal and the tibial nerves were tight-ligated with 5.0 silk and sectioned distal to the ligation, removing 2±4 mm of the distal nerve stump. Great care was taken to avoid any contact with or stretching of the intact sural nerve. Muscle and skin were closed in two layers. Crush controls (spared nerve crush group) were performed as above, except that the tibial and common peroneal nerves were crushed for 30 seconds by a pair of small arterial forceps with smooth protective pads over the blades. At the end of this procedure the nerves were completely attended and transparent. Sham controls involved exposure of the sciatic nerve and its branches without any lesion (Aley KO and Levine JD, 2002).

Chronic monoarthritis model

Monoarthritis was induced by intra-articular injection of 50 µl of complete Freund's adjuvant into the right ankle under brief isoflurane 5% anaesthesia. The complete Freund's adjuvant contained 6 mg of Mycobacterium butyricum suspended in 1 ml of an emulsion of liquid paraffin/0.9%NaCl/Tween 80 (6:4:1 v/v/v). The complete Freund's adjuvant solution was sterilized for 20 min at 120°C. Animals develop on the fifteenth day a monoarthritis of the right ankle with symptoms of oedemas and hyperalgesia (Isabelle Decosterd, 2000).

Inflammation-Induced Neuropathic Pain

The inflammatory cytokines are involved and plays a major role in generating the inflammatory neuropathic pain. The tumor necrosis factor, a molecule present in any inflammatory environment and also associated with the immune response to tumors, has been found to affect the firing of pain fibres. In one study, Linda Sorkin and her colleagues measured the discharge of normal C-fibres in situ with and without the application of TNF-I to the nerve in which the fibres travel. Normal C-fibres are almost completely silent in the absence of a painful stimulus, and begin to fire with the application of injurious levels of force to the skin. TNF-I induced spontaneous discharge in these fibres and greater sensitivity to peripheral stimulation. Spontaneous discharge in normally silent pain fibres translates into spontaneous pain, whereas a lowered activation threshold in pain fibres results in pain upon normally innocuous (allodynia) stimulation (David Balayssac et al., 2006).

Spinal ligation injury

The unilateral ligation of two spinal nerves (L5 and L6) was performed under pentobarbital anaesthesia (50 mg/kg i.p.). Briefly, the left para spinal muscles were separated from the spinous processes at the L4–S2 levels. The L6 transverse process was removed to identify visually the L4–L6 spinal nerves. The left L5 and L6 spinal nerves were isolated and tightly ligated with 6–0 silk thread. Following ligation, the wound was sutured and the rats were allowed to recover overnight, after which the testing began. In one control group (sham-operated rats), the surgery was performed in an identical manner, except that the spinal nerves were not ligated (Gary J and Bennett, 2010).

Peripheral neuropathy produced by a partial injury of the nerve supplying the tail

Under enflurane anaesthesia (0.5–2%), the left superior caudal trunk was exposed carefully from the surrounding tissues and transected at the level between the S3 and S4 spinal nerves, similar to the injury method. To prevent possible rejoining of the proximal and distal ends of the severed trunk, piece of the trunk, about 1 mm, was removed from the proximal end. This surgery eliminated the S1–S3 spinal nerve innervation of the tail via the superior caudal trunk. The inferior and superior trunks are composed and the level of the transection of the superior caudal trunk (Matias Ro ytta et al., 1999).

Peripheral nerve injury models

Peripheral neuropathic pain is a complex syndrome resulting from damage to the peripheral nervous system due to trauma, compression, neurotoxins, infection, immune and metabolic diseases, tumors, vitamin deficiencies, and other causes. A number of animal models have been reported to simulate human peripheral neuropathic conditions, most of which are based on procedures at or near sciatic nerves. Methods differ in the location and form of injury. The latter includes transection (Wall PD et al., 1979), loose or tight ligation (Kim SH et al., 1992), cryoneurolysis (DeLeo JA et al., 1994), crush (Devor M et al., 1979), perineural inflammation, and tumor invasion (Shimoyama M et al., 2002).

1. **Neuroma model:** Total sciatic nerve transection and ligation at multiple levels has been reported to study clinical conditions such as amputation (Wall PD et al., 1979). Following complete nerve transection at multiple locations along the sciatic nerve of rats and mice, a neuroma develops at the proximal nerve stump, consisting of regenerative nerves sprouting in all directions and observed self-attack and mutilation of the denervated limb by injured animals, and used the term 'autotomy' to describe the behavior that is probably caused by complete nerve differentiation of a limb. Although somewhat controversial, the presence of autotomy is generally considered a sign of spontaneous pain (Rodin BE et al., 1984). The extent of autotomy depends on the method (Wall PD et al., 1979) and location of neurectomy. Ethical considerations may also be an issue when

animals demonstrate excessive autotomy (Riopelle JM, 1992). In a neuroma model, allodynia and hyperalgesia, the characteristic symptoms of peripheral neuropathy, cannot be detected (Bennett GJ and Xie YK, 1988).

2. **Chronic constriction injury model (CCI or Bennett model):** Painful peripheral mononeuropathy conducted using the rat model in 1988. The model loosely ties the sciatic nerve (left or right side) with four chromic gut ligatures at the mid thigh level (Bennett GJ and Xie YK, 1988). CCI rats show behavioral signs of spontaneous pain such as mild to moderate autotomy, guarding, excessive licking and limping of ipsilateral hind paw, and avoidance of placing weight on the injury side. Hyperalgesia due to noxious thermal and mechanical stimuli is detectable, as are cold allodynia and tactile allodynia. All pain signs last for the entire duration of the study (over 2 months) (Attal N et al., 1990).
3. **Partial sciatic nerve ligation model (PSL or Seltzer model):** In an attempt to simulate causalgia as a result of partial nerve injury in humans and also reported a rat model of neuropathic (Seltzer Z et al., 1990). The experimental procedure involves the ligation of the ipsilateral sciatic nerve at the high-thigh level, so that 1/3–1/2 thickness of the sciatic nerve is trapped in the ligature. PSL rats exhibit signs of allodynia to von Frey hair stimulation and hyperalgesia to both thermal and mechno-noxious stimuli within hours of ligation; the symptoms last for over 7 months. Ligated rats also display signs of spontaneous pain in the forms of paw guarding and licking on the injury side. The evoked pain can develop into bilateral patterns (Seltzer Z et al., 1990).
4. **L5/L6 spinal nerve ligation model (SNL):** Another experimental mononeuropathy model simulating human causalgia was repoted (Lee BH et al., 1992). In the SNL, L5 and L6 spinal nerves are unilaterally and tightly ligated at a location distal to the dorsal root ganglia. Allodynia and hyperalgesia develop quickly after ligation, and last for at least 4 months. Although there are behavioral signs of spontaneous pain (guarding, licking, and lifting of ipsilateral hind paw), autotomy is absent in the SNL. Compared to CCI and PSL (Sommer C et al., 1998), the ligation site and extent (i.e. complete ligation) are more consistent in SNL. SNL also has the advantage of having separate injured and intact spinal segments. On the other hand, SNL requires the most extensive surgical procedures of the three models (Wang Z et al., 2001). CCI, PSL and SNL can all be produced in mice and are the three most widely used peripheral neuropathy models.
5. **L5 spinal nerve ligation:** When the L5/L6 ligation model was first reported, ligation of L4 or L5 spinal nerve was also reported (Kim SH et al., 1992). Ligation of L4 spinal nerve is not a useful pain model as it causes severe motor deficit and interferes with behavioural tests since it has an abundance of motor fibres. The L5 ligation model has not been fully characterized; however, L5-ligated rats also exhibited long lasting hyperalgesia and mechanical allodynia. Since single L5 nerve ligation is much easier to perform than the L5/L6 ligation, this model may provide a useful option, especially in studies involving mice (e.g. gene knockout or transgenic mice) (Fairbanks CA et al., 2000).

Cancer pain models

Pain is a common symptom in cancer patients, affecting 30–50% of patients undergoing active treatment for a solid tumor and 70–90% of those with advanced diseases. Whereas improving diagnosis and treatment methods are increasing the survival rate and life expectancy of cancer patients, cancer pain is increasingly becoming a bigger problem affecting the quality of life. Current treatment is largely based on empirical clinical experience with incomplete success. Cancer related pain may be caused by tumor infiltration or compression of nerve, plexus, or roots, immune reactive and pronociceptive substances released from tumors (Vecht CJ et al., 2000), or by treatment (chemotherapy, radiation, or surgery). Several studies have attempted to model chemotherapy-induced peripheral neuropathy. Three rodent models of bone cancer pain are available.

Chemotherapy induced peripheral neuropathy

Peripheral neuropathy and bone marrow suppression are two very frequent and severe side-effects of chemotherapy and are often the limiting factors for achieving effective doses (Lesage P et al., 1999). Neurotoxicity is particular problematic for vinca alkaloids, platinum compounds, and Taxols, although other chemotherapeutic agents are also capable of inducing neuropathy. Chemotherapy-induced neuropathy may continue after the

cessation of therapy (called 'coasting'). When administered to animals, these chemicals also produce neuropathy which may be used to study causes, prevention and treatment of their neurotoxicity (Vecht CJ et al., 2000).

1. **Vinka alkaloids (vincristine):** A single intravenous dose of vincristine (50, 100, or 200 $mgkg^{-1}$) causes a painful peripheral neuropathy in rats verified by mechanical hyperalgesia and mechanical allodynia. Doses of 100 or 200$mgkg^{-1}$ cause a rapid-onset neuropathy (three-to-five days) that lasts for more than two weeks after vincristine administration (Kiyomi Hori et al., 2010). A model of nociceptive neuropathy, induced by multiple doses of vincristine has been characterized by behavioral, electrophysiological and anatomical criterion. Behavioral tests of nociceptive function demonstrate mechanical hyperalgesia and allodynia, cold thermal hyperalgesia and warm thermal hypoalgesia. Changes in nociceptive measures are apparent within one week of the first dose of vincristine and remain significantly different for several weeks after the last dose. Axonal degeneration is observed in subcutaneous nerves and to a much lesser extent in the sciatic nerve. The degenerative changes are observed mainly in myelinated fibres and are restricted to the axon. The myelin fibres and are restricted to the axon. The myelin sheaths appear normal.
2. **Paclitaxel:** Recent rodent models of paclitaxel-induced sensory neuropathy have focused on perturbations in nociceptive function that are induced by low cumulative doses of paclitaxel (<15 mg/kg). At low cumulative doses, paclitaxel produces a painful neuropathy in mice and rats, which is characterized by decreased mechanical and thermal pain thresholds, and mechanical and cold thermal allodynia. Low doses do not result in systemic toxicity or motor impairment. The neuropathy develops rapidly (within hours) and is transient but can be maintained by administering repeated low doses of paclitaxel. A dose regimen of 1mg/kg per day with 10 doses given over 12 days produces a painful neuropathy characterized by mechanical hyperalgesia and allodynia and thermal hyperalgesia. The maximal decrease in mechanical thresholds is apparent by day five and is maintained for about six days after the last dose (Seung Keun Back et al., 2002).
3. **Oxaliplatin:** The first pain behavioral assessment in rats using oxaliplatin was reported cold and heat hypersensitivity with allodynia and hyperalgesia associated with mechanical allodynia, remaining after a 3-week follow-up. Moreover, so as to be clinically relevant and to mimic the effects observed in humans, especially hypersensitivity to cold, they also studied the effects of a single oxaliplatin injection showing a significant cold allodynia and hyperalgesia associated with a mechanical allodynia. An immune histo chemical study in the superficial layers of the spinal dorsal horn revealed a marked increase in substance P immune reactivity. Another acute model displaying a dose-dependent heat and cold allodynia with a mechanical hyperalgesia was assessed. They also assessed different inhibitors of several second messengers (protein kinase A, protein kinase C, NO, Ca^{2+}, Caspase), which failed to attenuate the acute mechanical hyperalgesia, whereas antioxidants (acetyl-L-carnitine, lipoic acid, vitamin C) and inhibitors of the mitochondrial electron transport chain (rotenone, 3-nitropropionic acid, antimycin, sodium cyanide, oligomycin) produced significant attenuation (Judith P et al., 2004).
4. **Cisplatin:** Recent rodent models of cisplatin-induced neuropathy use a range of low cumulative doses (7.5–20 mg/kg) administered with different dosing regimens. Cisplatin induced PN describes the changes in electrophysiological properties of sensory nerves, anatomical changes reflecting neuron or axon damage, and alterations in sensory function including decreased pain thresholds. Higher cumulative doses of cisplatin impair proprioceptive function. A rat model of low-dose cisplatin induced neuropathy examining all three measures of neuropathy sensory behavior, anatomy and electrophysiology has recently been described. A range of cisplatin doses (1, 2, or 3mg kg^{-1}) administered three times, twice, or once per week, respectively, for five weeks is used to induce neuropathy. These doses of cisplatin (cumulative doses of 15–20 mg kg^{-1}) induce mechanical hyperalgesia and allodynia, cold hyperalgesia and allodynia, and thermal hypoalgesia. Changes in sensory thresholds are evident one week after initiation of cisplatin treatment and are maintained for most measures until the end of the study (one-to-two weeks after the last dose of cisplatin). Axon degeneration, observed principally in the subcutaneous paw and to a lesser extent in the sciatic nerve and the lumbar spinal cord, is observed most frequently in large myelinated axons. Myelin sheaths remain normal. Degenerative changes are seen more frequently at the 2 mg and 3 mg dose. At a dose of 1 mg/kg, axon degeneration is rare and of low severity. Unmyelinated axons appear unaffected. The

2 mg/kg dose, given once per week for five weeks, is considered to provide the best balance between good general health and development of nociceptive neuropathy.

Peripheral neuropathy induced by diseases

In human, shingles and diabetes are two very common diseases with neuropathic pain sequellae. Diabetes mellitus is the leading cause of neuropathy patients, in the Western world (Simmons Z *et al.,* 2002). In one series of studies, neuropathy is present in 66% of diabetic patients (Dyck PJ et al., 1993), although this prevalence is lower in another patient population. Shingles is characterized by a very painful rash. Some patients suffer from postherpetic neuralgia following acute shingles, which can persist for many years and even for life.

In vitro models

Cultures of primary neurons or neuronal cell lines have been developed as in vitro models of chemotherapeutic drug induced neurotoxicity. These models are used to study the efficacy of potential neuroprotectant and to study mechanisms underlying drug-induced neurotoxicity Primary cultures of sensory or sympathetic neurons or neuronal cell lines have been used to test the efficacy of a wide variety of neuroprotective agents including anti-oxidants, anaesthetics and neurotrophic factors.

The neuronal cell lines most frequently used include the human neuroblastoma cell line SH-SY5Y and PC12 cells which are rat pheochromocytoma cells that can be differentiated to a neuronal phenol type by exposure to nerve growth factor. Neuronal cell death or inhibition of neurite outgrowth can be induced in cultures of primary neurons or neuronal cell lines by treatment with a toxic dose of a chemotherapeutic drug (Seung Keun Back et al., 2002). The efficacy of neuroprotective agents can then be assessed based upon their ability to prevent cell death or inhibition of neurite outgrowth in these cultures.

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