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PERIPHERAL NEUROPATHY-THE LEADING CAUSE FOR GENERAL WEAKNESS

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Peripheral neuropathy (PN), Postherpetic neuralgia (PHN), Autoimmune disorder-induced PN Toxic neuropathy, Chemotherapy induced peripheral neuropathy (CIPN), Charcot - Marie-Tooth disease-related PN.

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ABSTRACT: Peripheral neuropathy refers to many conditions that involve damage to the peripheral nervous system. In this article, we would like to discuss various aetiological factors and their manifestations, pathophysiology, diagnosis and treatment strategies of peripheral neuropathy. Generally, peripheral neuropathy is caused by many underlying disease conditions such as Diabetes mellitus, Shingles (postherpetic neuralgia), Vitamin B-12 deficiency, Alcoholism, Autoimmune disorders (Rheumatoid arthritis, Systemic lupus erythromatosus), Lyme disease, Syphilis, HIV, Exposure to toxins (lead), chemotherapies and Hereditary disorders such as Charcot-marie-tooth. The clinical presentations of peripheral neuropathy generally involve pain, burning or tingling sensations in the distribution of the affected nerves mostly in the hands and feet. The diagnosis of PN includes a physical examination, blood tests, a keen study of medical history, family history and lifestyle of the subject. Patients with peripheral neuropathy typically do not respond to traditional analgesics (paracetmol, NSAIDs) or weak opioids because these do not focus on treating various types of symptoms of PN. However, some Antidepressants, Serotonin or epinephrine reuptake inhibitors (SNRIs), Topical therapies and combinational therapies and non-pharmacological treatment were found to alleviate peripheral neuropathy symptoms.

INTRODUCTION: Peripheral nerves make up an intricate network that connects the vast communication centers like the brain and spinal cord to muscles, skin, and internal organs. Hence any damage to these nerves result in peripheral neuropathy (PN). Peripheral nerves send many types of sensory information to the central nervous system, such as a message that the feet are cold, *etc*. They also carry signals from the CNS to the rest of the body [1, 7, 8].

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Epidemiology: In epidemiological studies from various regions of India, The overall prevalence of the PN varied from 5 to 2400 per 10,000 people in various community studies [6]. Diabetic neuropathy, which is otherwise called Distal symmetrical polyneuropathy (DSPN) is a common disorder caused due to diabetes mellitus.

It was found that worldwide, 382 million people are currently affected by Diabetic Neuropathy 19 of which the incidence in south Indian people was recorded as 19.1%. Peripheral neuropathy, if it occurs in shingles condition, then it is referred to as postherpetic neuralgia. The risk of postherpetic neuralgia also goes up with age. More than 80% of cases of postherpetic neuralgia occur in people over 50 years old. In contrast, the incidence among people under 60 years of age was less than one in

50 and in people aged 60-69 years, about 7% of shingles progress to PN [67]. It has been estimated that 7-10% population are currently affected by alcoholic neuropathy in US60. Vitamin B-12 deficiency-related PN incidence is 10%, of which 25% are people over 80 years of age. The statistical survey reported that out of total 30 Rheumatoid arthritis patients, 10 (33%) had peripheral neuropathy [32, 34]. Prevalence of HIV-related PN ranges from 50% - 60% 41, 43 and cancer-related PN is in the range of 27.5% for all grades and 4.7% for high grade [3]. Hereditary charcot - marie tooth disorder associated PN was found to be affecting 150,000 people in US, and worldwide about 1 in 3000 individuals were affected [88]. The prevalence of Chemotherapy-induced peripheral neuropathy is age dependant with reported rates varying from 19% to > 85% and is highest in the case of platinum-based drugs (70-100%), taxanes (11-87%), thalidomide (20-60%). Recent studies put the prevalence of CIPN at approximately 68.1% when measured in the first month of chemotherapy [3, 9, 13].

Aetiology:

Cancer /Chemotherapy Induced Pn: Cancer is a disease caused by an abnormal, uncontrolled division of cells in the body [2]. Chemotherapy is a type of cancer treatment that uses one or more anti-cancer drugs as a part of the standardized treatment regimen. Chemotherapy may be given with a curative intent or aim to prolong the life or alleviate symptoms. The drugs used in chemotherapy can cause peripheral neuropathy 10, a set of symptoms caused by damage to nerves that control the sensations and movements of our arms, legs, hands, and feet.

Thus chemotherapy-induced peripheral neuropathy is a common side effect of selected chemotherapeutic agents 2 like the platinum drugs, taxanes, vinca alkaloids, thalidomide and bortezomib. Among taxanes, Paclitaxel was highly neurotoxic and had major chances to cause neuropathy followed by Docetaxel. The risk of developing severe taxane-induced CIPN is related to treatment interval between first and further chemotherapy [9, 13]. The morbidity associated with CPIN can lead to pronounced alterations in quality of life and independent performance of activities in daily living [13].

Some patients experience paradoxical worsening or intensification of symptoms after the cessation of the treatment known as the phenomenon of 'coasting', where either mild neuropathy worsens or new CIPN develops. A number of predisposing factors of CIPN have been identified, including patient age, previous medical history, lifestyle or direct cancer association [1, 18]. Chemotherapy-induced PN symptoms include numbness, discomfort, sensitivity to touch and burning sensation [13]. If internal organs are affected, symptoms include dizziness, constipation, and bladder difficulties. If muscles are affected, then muscle cramping, muscle weakness, muscle spasms are the symptoms [9, 13]. To diagnose PN that occurs during chemotherapy, some doctors recommend neurophysiologic tests such as electromyography to detect neuromuscular abnormalities, nerve conduction studies, quantitative sensory tests to further examine peripheral nerve function [2, 7, 8]. The electromyography measures electrical activity in response to nerve stimulation of the muscle [9, 10, 12].

The treatment strategies for CIPN involve both pharmacological and non-pharmacological pathways. The non-pharmacological treatment is to avoid injury by paying attention to home safety by using handrails on stairs to prevent falls and using potholders in the kitchen to avoid burns. The pharmacological treatment strategies suggested by oncologists may be to discontinue or reduce the dose of chemotherapy drugs that agitates PN. The recommended drugs are over-the-counter medicines, lidocaine patches, menthol creams, or a medication called Duloxetin [10]. However, some researchers suggest treatments such as vitamin E, calcium, magnesium, Anti-seizure drug, Antidepressants, and Glutathione -a vitamin that is rich in antioxidants [10, 15].

Diabetes Mellitus: Diabetes is a group of metabolic disorders in which there is a condition of increased blood glucose levels. The peripheral neuropathy that occurs due to DM is called diabetic neuropathy or distal symmetrical polyneuropathy (DSPN). DSPN affects both DM-I and DM-II [19]. DSPN is characterized by Numbness or tingling of the feet and lower legs, followed by pain or burning sensation (loss of sensation). Sometimes these symptoms can occur in the hands or arms also [26, 27, 28].

Pain affects the quality of life of patients, impacting the ability to perform daily activities, and may also cause mood swings [24]. The pathophysiology of diabetic neuropathy is that the increased blood glucose levels cause changes in blood vessels that supply blood to the peripheral nerves and finally damages the nerves [22]. Drinking alcohol, cigarette smoking, oxidative stress, nitrosative stress, microvascular changes, and central sensitization increases the risk of DSPN [19, 28]. Various diagnostic procedures are available for DN, one being physical examination based on symptoms like pain, numbness, and tickling [21, 28] other is vibration test which is done using a tuning fork of 128 Hz. A sensory examination can be performed on hands and feet bilaterally, and it is considered abnormal if the ankle and vibration reflexes are absent rather than reduced. Nerve biopsy can be done to exclude other causes of neuropathy.

Skin biopsy opts when all other above measures are negative in the diagnosis of small fiber neuropathy. Some peers suggest confocal corneal microscopy as an alternative for nerve biopsy, considering its non-invasive nature. Motor nerve conduction, F response, and sensory nerve conduction studies are also equally important methods of documentation used in follow-up therapy or as diagnostic strategies for diabetic neuropathy [22, 23, 26, 28]. The therapy of diabetic neuropathy includes anticonvulsants like Pregabalin, Gabapentin which act by binding to pre-synaptic voltage-gated calcium channels to decrease pain [22, 28]. Antidepressants like Duloxetine (serotonin inhibitor), Venlafaxine are suggested drugs that alleviate symptoms, and opioids like Tramadol, morphine are used to reduce the pain. Other agents like capsaicin topical cream, lidocaine patch, Alpha lipoic acid, Isosorbidedinitrate spray are also used to relieve the pain [26, 28].

Autoimmune Disorder (Rheumatoid Arthritis) Induced Pn: Autoimmune disorders are the conditions in which the body's immune system fails. An autoimmune disorder like Rheumatoid arthritis, a systemic inflammatory disease that mainly affects the joints, presents the PN as the clinical symptom. The causes of PN in rheumatoid arthritis include nerve entrapment, drug toxicity, and rarely amyloidosis. The neuropathic pain in rheumatoid arthritis shows the symptoms of numbness, vasculitis (inflammation of blood vessels), tingling, and burning sensation in the extremities [29, 31, 33]. The pathophysiology of PN in rheumatoid arthritis involves genetic factors, environmental factors (toxins, chemicals, bacteria), *etc*. These factors attack the immune system causing damage to the tissue around joints of elbows, shoulders, neck, knees, and ankles, causing nerve damage ultimately leading to PN [32, 37]. Patients with rheumatoid arthritis should regularly undergo electrophysiology testing to rule out the existence of peripheral neuropathy. Electro-physiological studies are the gold standard diagnostic tools performed by using the EMG instrument (oxford instrument co; UK) to diagnose neuropathy in patients with rheumatoid arthritis [29, 33]. Median, ulnar, peroneal and posterior tibial nerve conduction studies are performed unilaterally on the symptomatic side to diagnose the disease [29, 36, 39].

Rheumatoid arthritis induced. Peripheral neuropathy treatment involves NSAID's(Aspirin, Ibuprofen, and Aleve) to reduce joint inflammation and pain, DMARD's like Hydroxychloroquine, Methotrexate, Leflunomide are used to suppress the immune system and slow the onset of disease (RA), so that further progress of PN can be prevented. In some cases, surgery may also be recommended, or patients are advised to take safety measures to compensate for the loss of sensation [32, 35].

Hiv Induced Pn: HIV /AIDS is one of the leading causes of peripheral neuropathy [47]. The neurological complications of HIV mostly showed synergism in the presence of diabetes mellitus, possibly affecting 50% of all the individuals infected with HIV [43]. The pathophysiology of HIV-related DSPN is the neurotoxicity resulting from virus, along with the adverse effects of drugs used for treatment of HIV causing damage to the nerves and resulting in decreased nerve reflexes. The neuroinflammation associated with symptoms like burning, stiffness, prickling, tingling sensation is a common feature of HIV-associated peripheral neuropathy [45, 46, 48]. Diagnosis of HIV-induced PN is done by physical examination based on symptoms or by Electromyography [EMG], a test in which a needle is connected to a computer to study whether the patient's muscle is healthy or

affected by a disease of the muscle or nerve. Nerve conduction studies, including motor nerve conduction, F response and sensory nerve conduction studies, are also considered important documentation methods and follow-up of nerve functions in HIV/AIDS induced neuropathy. Skin punch biopsy reveals the damaged nerves, especially the damaged axon, a part of the nerve cell that transmits impulses [43, 45, 46]. Generally, antiretroviral therapy is used to treat HIV/AIDS, But for the treatment of HIV-induced neuropathy, other medications such as anticonvulsants like gabapentin, pregabalin and antidepressants like amitriptyline, duloxetine, which are selective serotonin reuptake inhibitors (SSRIs) have been prescribed to reduce the pain. Some topical agents, non-specific analgesics are also suggested. It is better to withdraw drugs like Stavudine, Dapsone (used for pneumocystis pneumonia), metronidazole (used to treat amoebic dysentery) and increase the risk of developing peripheral neuropathy [45, 50, 51].

Shingles (Post Herpetic Neuralgia): Herpes zoster, commonly called Shingles is an infection caused by same virus that causes Chicken poxm [67, 70]. Peripheral neuropathy occurs as a symptom of Shingles The first sign is long-lasting pain that might feel like burning or tingling on the side of the face, chest, and back. This can be improved to itching sensation, extreme sensitivity to touch followed by electric shock-like symptoms [67, 73, 75].

The pathophysiology involves entry of Herpes zoster and/or reactivation of chickenpox virus; this virus then travels down the nerve fibers and ultimately results in PN that is associated with painful skin rash. The risk of PHN generally increases with age, primarily affecting people older than 50 years. The diagnosis of shingles induced peripheral neuropathy can be done by the medical practitioner thorough examination of the skin, including physical examination possibly touching it in places to determine the borders of the affected areas [70, 74, 76].

The treatment of shingles includes antiviral agents like guanosine analogues (Acyclovir, Valacyclovir (Valtrex) three times per day. These medications target the virus by relying on viral kinases for phosphorylation that (kinases) are used to promote incorporation into viral DNA, thus disrupting replication. Therefore the disease can be reduced to a certain extent and further occurrence of shingles induced PN can also be prevented [70, 74, 76].

Peripheral Neuropathy In Lyme Disease Patients: Lyme disease is an inflammatory disease caused by the bacteria Borrelia burgdorferi transmitted to humans by biting an infected black-legged or deer tick. Lyme disease was once a more common disease in the northeast section of US is now spreading to southern and western parts of the country. The number of cases is constantly decreasing, but the risk of untreated lyme disease progressing to neurological disorders involving symptoms of pain in limbs, skin rashes, painful inflammation of joints, flu-like symptoms, irregular heartbeat, the stiff neck has been raised through years [52, 56]. The diagnosis can be done by neurological exam, electromyography, blood tests to identify the infective agent that causes Lyme disease or by nerve conduction velocity tests to indicate the percentage of damage to the nervesm [52, 56]. The therapy associated with Lyme disease is antibiotics to reduce or inhibit the organism and to alleviate the pain, along with steroids to reduce inflammation of the nerve. Sometimes Intravenous therapy and surgery may also be recommended based on the severity of the disease [52]. Avoiding exposure to the I. Scapularis or I. pacificus ticks by the use of protective clothing, tick repellants, checking the entire body for ticks daily, and prompt removal of attached ticks before transmission of these microorganisms can prevent the Lyme disease so that further occurrence of PN can be prevented [52].

Hereditary Disorder Related Pn [Charcot-Marie-Tooth]: Hereditary neuropathies are passed on genetically from parent to child, so they are sometimes called inherited neuropathies [91]. Generally, hereditary neuropathy depends on the group of nerves affected, for instance, Charcot - Marie tooth (CMT) disease was one of the most common types of hereditary neuropathies affecting motor and sensory nerves [91, 92]. More than 30 genes have been linked to CMT neuropathies out of which at least 4 genes are involved in the transmission of CMT from parent to child [90, 95]. Approximately 1 out of 3300 people is affected by CMT and the cases are constantly rising in years [87, 88]. There are subtypes for CMT; they are type IA

(CMTIA), CMT-4A, CMT-4BI, CMT-4B II, CMT-4C and CMT-4D. The symptoms of CMT include difficulty in lifting foot, unsteady balance, and poor hand coordination [90, 91]. The hereditary disorder is mostly diagnosed by genetic testing accompanied by some other procedures like nerve biopsy, neurological evaluations, nerve conduction tests [73, 74, 76]. The drug therapy for hereditary neuropathy are Acetaminophen, NSAIDs, Carbamazepine, Gabapentine (decreases neuropathic pain), Prednisone and immunoglobulins (reduces inflammation). The medications like vincristine, isoniazid and nitrofurantoin should be avoided to prevent any further nerve damage [89, 91, 92].

Toxic Neuropathy: On exposure to some of the metals such as lead, mercury, arsenic, thallium etc., peripheral nerves are susceptible to damage [77]. Lead is a ubiquitous, versatile, toxic heavy metal that has been used by mankind for many years. Research conducted in recent years has increased public health concerns about the toxicity of lead, even at low doses. Neuropathy is one most common complications of lead poisoning or leads intoxication in humans leading to axonal degeneration, but in some other cases, it primarily causes demyelinating neuropathy. The battery industry is one main setting related to lead intoxication [78, 84] others include pesticide arsenic, copper, acid arsenate, Paris green of leather industry and wood preservative. Neuropathy can also occur by inhalation of smoke from burning wood that has been preserved with arsenic from occupational dust or soil [78]. Long term exposure to thallium as intentional poison, insecticide or as rodenticide was sometimes mentioned as reason for progress of peripheral neuropathy [85]. Peripheral neuropathy from mercury exposure is also common, involving distal latency sensory slowing for short-term exposures, followed by motor slowing for more long-term exposures.

Inorganic and elemental mercury exposures are more likely to cause peripheral nervous system damage [77]. Central nervous system effects are more common with organic mercury exposure than inorganic mercury. On prolonged exposure to inorganic mercury, there will be a slow progression of generalized paralysis of limbs [77, 78]. Symptoms associated with toxic neuropathy are tingling and numbness in the feet which progresses to weakness and difficulty in walking. The diagnostic tests to evaluate toxins involve physical examination, neurological exam, electromyography, urine analysis, and blood tests. Management of toxic neuropathy can be done by using over-the-counter pain medication to reduce mild pain and for severe pain, use of tricyclic antidepressants, anticonvulsants (pregabalin, gabapentin), opiates, or topical capsaicin cream is recommended. Peripheral neuropathy can be prevented by avoiding exposure to toxins and avoiding drugs like acrylamide, alcohol, arsenic, brevetoxin, carbon disulphide, ethylene glycol, hexacarbions, lead, nitrous oxide, organophosphates, and saxitoxin [78, 81, 82].

Vitamin B-12 Deficiency Associated Pn: PN may occurs as a result of malnutrition [vit-B12 deficiency] for which there are many causes including poor nutrition caused by an unbalanced diet or alcoholism [100]. Additionally, a clear link has been established between a lack of vitamin B12 and PN. Decreased vitamin B 12 causes an increase in the risk of PN. The symptoms of vitamin B 12 deficiency cause anaemia [serious], nerve damage and nerve degeneration (PN) associated with pain, numbness, tinglingin hands or feet [99]. The pathophysiology is that lack of vitamin B 12 damages the myelin sheath (that surrounds and protects the nerves) so, results in nerve damage and leading to PN [103]. Lack of vitamin B 12 is associated with haematological, neurological, psychiatric manifestations. Generally, the symptoms include anaemia that may arise as a serious complication, pain, numbness, tingling sensation in the hands or feet [100, 104].

Alcoholic Neuropathy: Alcoholic neuropathy may experience either one or many symptoms ranging from mild to severe like limb cramps, loss of movement, muscle atrophy, muscle spasms or contractions, muscle weakness, numbness (loss of sensation), pins and needles, tingling or prickling, bowel and urinary system constipation, incontinence, urinary retention and diarrhoea. In some people other areas of the body are also involved leading to infertility and sexual dysfunction in men or difficulty in swallowing [58, 63]. Diagnosis for alcoholic neuropathy involves Nerve biopsy. A local anaesthetic was used to numb the area. The surgeon makes a small incision

and removes a portion of the nerve, usually from the ankle or the calf. The sample is then examined for abnormalities under a microscope. Nerve conduction velocities are normal or mildly slowed in patients with alcoholic neuropathy [58, 62, 63]. The best treatment a person with alcoholic neuropathy can do is to stop or significantly reduce alcohol intake. An inpatient detox may be suggested when a person's alcohol use disorder is very severe. Taking safety measures to compensate for loss of sensation, Quitting recreational drug habits, eliminating exposure to alcohol and other related liquids can stop progression of disease [61]. Alcoholic neuropathy can make daily life difficult, so it is essential to begin by managing the symptoms [58, 59, 63]. Community-based support is also available from voluntary organizations such as "Alcoholics anonymous "self-management" and "recovery training" to drive out the person from alcohol abuse. The pharmacological treatment involves vitamin supplements like vit-E, B6, B12, over-the-counter pain relief (for minor discomfort associated with alcoholic neuropathy), pain relief therapy such as capsaicin cream, tramadol and anticonvulsants (gabapentin) are recommended. Even physical therapy (gentle exercises and activities) can help with muscle and balance problems [58].

CONCLUSION: Thorough review of articles concludes that Peripheral neuropathy is one of the leading causes of general weakness that disturbs one's quality of life. Therefore, new research strategies must be carried out to provide standardized therapeutic outcomes that would ultimately give security to the nerves and prevent all kinds of damage that may occur to the "sensorium" of the body (nervous system).

Diabetes, being the first and most leading cause for PN, may also lead to insomnia and increases the chance of developing further neurological complications. So, utmost attention needs to be taken by thoroughly examining the feet for blisters, cuts or calluses. The next superior cause was analyzed to be Cancer, more likely breast cancer, a leading killer disease that uses chemotherapy as frontline treatment which aids in developing PN. The disease can be subsided by reducing the dosage of chemotherapeutic agents (cyclophosphamide *etc*). Apart from the above cases even the lifestyle of the present scenario; food habits, lack of sufficient physical activity and the comforts to which the people got accustomed altogether play a pivotal role in reverting into various pathological conditions of Peripheral neuropathy. Natural therapeutic strategies like massaging the pain area with warm oils or vaporous, acquiring traditional acupuncture techniques, and having hot bath could possibly relieve PN symptoms. Besides the therapy, establishing dietary habits that aid in overcoming vitamin deficiencies, especially choosing vit B12 rich foods (meat, eggs, low fortified dairy foods, and fortified cereals), a diet rich in fresh fruits and vegetables, legumes, whole grains, omega-3 rich foods (salmon, walnuts, chia seeds, flax seeds, cod liver oil), *etc.* and by avoiding sedentary lifestyle through a regular practice of meditation, exercises, getting rid of alcohol intake and smoking could help to maintain nerve health and reduces the risk of PN as well as other neurological disorders.

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Ethics Approval: This article does not contain any studies with human participants or animals performed by any authors.

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