Hanyang Medical Reviews

Hanyang Med Rev 2017;37:34-39
https://doi.org/10.7599/hmr.2017.37.1.34
pISSN 1738-429X eISSN 2234-4446

Review

Overview of symptoms, pathogenesis, diagnosis, treatment, and prognosis of various acquired polyneuropathies

Hyun-Jung Yu,[1] Seong-Ho Koh[2]

[1]Department of Neurology, Bundang Jesaeng Hospital, Gyeonggi, South Korea
[2]Department of Neurology, Hanyang University Guri Hospital, Gyeonggi, South Korea

Polyneuropathy includes a lot of diseases damaging peripheral nerves. It shows roughly the same areas on both sides of the body, featuring weakness, numbness, and burning pain. Polyneuropathy is known to usually begin in the hands and feet and progress to the arms and legs. Sometimes it can involve other parts of the body such as the autonomic nervous system. Lots of causes can induce acute or chronic polyneuropathy, so finding the original cause is most important for the treatment of polyneuropathy. There are too many different types of polyneuropathies to be discussed in this review, so we will discuss some of various acquired polyneuropathies such as diabetic neuropathy, vasculitic neuropathy, alcoholic neuropathy, Vitamin B12 deficiency neuropathy, and drug-induced neuropathy, with special focus on symptoms, pathogenesis, diagnosis, treatment, and prognosis.

Key words: Polyneuropathies; Symptoms; Diagnosis; Pathophysiology; Treatment

Corresponding Author: Seong-Ho Koh
Department of Neurology, Hanyang University Guri Hospital, Hanyang University College of Medicine, 153 Gyeongchun-ro, Guri 11923, Korea
Tel: +82-31-560-2267
Fax: +82-31-560-2267
E-mail: ksh213@hanyang.ac.kr

Received 15 Jan 2017
Revised 13 Feb 2017
Accepted 27 Mar 2017

INTRODUCTION

Polyneuropathy means a lot of diseases affecting peripheral nerves showing roughly the same areas on both sides of the body, featuring weakness, numbness, and burning pain [1]. Pathogenesis causing polyneuropathy usually begins in the hands and feet and progresses to the arms and legs [1]. Sometimes it can involve other parts of the body such as the autonomic nervous system. Uncountable causes can induce acute or chronic polyneuropathy, so finding the original cause is most important for the treatment of polyneuropathy.

Polyneuropathies are classified in different ways depending on cause, presentation, or classes of polyneuropathy (for example, the axon, the myelin sheath, or the cell body). Among these classifications, the classification based on classes of polyneuropathy can explain the pathogenesis and symptoms at the same time. Polyneuropathy in the axon is called distal axonopathy which is the result of interrupted function of the peripheral nerves and the most common response of neurons to metabolic or toxic disturbances, such as diabetes, kidney failure, connective tissue disease, deficiency syndrome, alcoholism, chemotherapy, and so on. People with distal axonopathy frequently present with sensorimotor disturbances. Disease in the myelin sheath is myelinopathy characterized with a loss of myelin or of the Schwann cells. This demyelination disturbs the conduction of action potentials through the axon of the nerve cells. Among various diseases causing myelinopathy, the most common one is acute inflammatory demyelinating polyneuropathy (AIDP). Damage of neurons in the peripheral nervous system results in neuronopathy. Neuronopathies can

be caused by motor neuron diseases, sensory neuronopathies, toxins, and chemotherapy agents [2].

There are too many different types of polyneuropathy to be discussed in this review, so we will discuss some of various acquired polyneuropathies such as diabetic neuropathy, vasculitic neuropathy, alcoholic neuropathy, vitamin B12 deficiency neuropathy, and drug-induced neuropathy, focused especially on symptoms, pathogenesis, diagnosis, treatment, and prognosis.

DIABETIC NEUROPATHY

Diabetic neuropathy (DN) is caused by damage of nerves due to diabetes mellitus (DM). The most common forms of DN include painful polyneuropathy, mononeuropathy multiplex, mononeuropathy, third nerve palsy, diabetic amyotrophy, autonomic neuropathy, and so on. DN occurs in the peripheral nerves: for example, sensory nerves, motor nerves, and the autonomic nervous system. Because it could damage all organs and systems, several distinct signs and symptoms can be caused depending on the injured nervous system. Signs and symptoms by DN often develop gradually with the passing years. The common symptoms are as follows: numbness and/or tingling of extremities; burning or electric pain; dysesthesia; trouble with balance; dizziness; vision changes; and so on.

When it comes to the pathogenesis of DN, diverse factors are suggested to be involved. First, DM is well known to induce microangiopathy. The first and most prominent change occurred in the small vessels by DM is narrowing in them. With disease progression, blood vessel abnormalities are seen aggravated with capillary basement membrane thickening and endothelial hyperplasia. All these abnormalities can cause diminished oxygen tension and hypoxia, which are the main factors provoking neuronal ischemia, known as a well-established characteristic of DB?. Thus, small blood vessel dysfunction is thought to occur early in diabetes and parallel the progression of neural dysfunction. Second, it is well established that elevation of glucose in cells cause a non-enzymatic covalent, which bonds with proteins and then makes glycosylated proteins, and some of them are emphasized in the pathogenesis of DN and other complications of DM. Third, the polyol pathway, also known as the sorbitol/aldose reductase pathway, seems to play important roles in diabetic complications, such as microvascular damage to the nerves [3].

Careful physical examinations are regarded to be the most important in the diagnosis of DN. The most meaningful physical examination findings suggesting neuropathy in the large fibers are known to be an abnormal decrease in vibration perception and/or pressure sensation [4]. Normal results on vibration testing or monofilament can make us exclude large fiber peripheral neuropathy due to DM. Electrophysiological studies including nerve conduction tests can be helpful for the diagnosis as well. They might show reduced functions in the peripheral nerves. However, the problem is that the results from nerve conduction tests might not be correlated with the severity of DN.

For the treatment of DN, tight glucose control should be preceded [5]. Next, numerous treatments can be applied to reduce pain and other symptoms by DN., antiepileptic drugs (AEDs), tricyclic antidepressants (TCAs), serotonin-norepinephrine reuptake inhibitors (SNRIs), and capsaicin cream can be prescribed for the control of pain in the patients with DN [6,7]. First of all, TCAs including amitriptyline, imipramine, nortriptyline, and desipramine are effective at decreasing painful symptoms but can cause various side effects which are dosage-dependent, so it should be prescribed carefully when done given at higher doses. Among diverse TCAs, amitriptyline is the most commonly used, but nortriptyline and desipramine are known to have fewer side effects. Second, in the case of SNRIs, duloxetine is being used for DN and venlafaxine is widely used as well. Inhibition of serotonin and norepinephrine by these SNRIs can reduce pain in the patients with DN as well as treat depression if it exists. Third, AEDs, such as gabapentin and pregabalin, are now recommended as the first-line drug for the treatment of pain in the patients with neuropathy [8]. Carbamazepine is also known to be effective but not necessarily safe for DN. Besides the above three treatment options, classic analgesics can also be prescribed for the patients with DN to reduce their pain. Physical therapy can be helpful for the patients with DN and may reduce dependency on pain relieving drug therapies. Transcutaneous electrical nerve stimulation (TENS) and interferential current (IFC) use a painless electric current and are known to reduce neuropathic pain, relieve stiffness, reduce edema, improve mobility, and heal foot ulcers. Except for these therapies, posture training, gait training, exercise programs [9], heat, hot wax, therapeutic ultrasound, etc. can be used for the patients with DN.

Although the above treatments can alleviate pain as well as some associated symptoms, DN is gradually aggravated. Loss of

sensation due to DN increases risk of injury to the feet and then can lead to infections that can progress to ulceration which might require amputation.

VASCULITIC NEUROPATHY

Vasculitis, primary or secondary, is one of the most important causes that induce peripheral neuropathy and sometimes vasculitic neuropathy (VN) may be the only manifestation of the underlying vasculitis [10]. VN can be a part of systemic vasculitis as well. Primary vasculitis predominantly affecting small arteries in the epineurium of nerve trunks can ensue ischemia of peripheral nerve and then VN. These types of primary vasculitis include polyarteritis nodosa (PAN), a variant form of eosinophilic granulomatosis with polyangiitis, rheumatoid arthritis (RA), granulomatosis with polyangiitis, systemic lupus, etc.

VN with clinical symptoms occurs in more than 75% of the patients with PAN. Clinical symptoms can be due to a mononeuritis multiplex, which is acute or subacute, with successive and/or simultaneous involvement of various nerve trunks over a relatively long period [11,12]. Also, distal symmetrical sensory and sensorimotor neuropathy occurs. In most cases of VN, the onset is unexpected and sudden and the deficit is severe. However, partial deficit due to partial damage of a nerve can be observed in many cases. Slow progression can be found in some elderly patients. Cutaneous vasculitis which is the most common non-neurological manifestation of PAN provokes livedo reticularis, cutaneous necrosis, nodules, and so on. Non-specific edema, frequently affecting one extremity, usually precedes the onset of VN. Arthritis, asthma, and renal involvement occur in about 10% of the patients with PAN. The ischemic neuropathy caused by necrotizing arteritis (NA) in PAN could be found as an isolated manifestation and in the context of a multisystemic disorder. The Churg and Strauss variant of PAN has disseminated NA with fever, eosinophilic infiltration, fulminant multisystem disease, extravascular granulomas, and so on. The lesions in the vessels and nerves confirmed in nerve biopsies from patients with the Churg and Strauss variant of PAN can be responsive to treatment and are like those found in PAN. NA and neuropathy are often observed in the patients with RA. NA in RA means a poor outcome. VN in patients with RA is commonly associated with a sensory and motor neuropathy or a purely sensory neuropathy. In Wegener's granulomatosis, characterized by granulomatous vasculitis of the upper and lower respiratory tract with or without glomerulonephritis, VN can be observed as one of the manifestations [13].

The diagnosis of NA causing VN needs histological confirmation, so sometimes biopsies should be performed in specific skin lesions. Perhaps, nerve and/or muscle biopsies need to be performed to find the characteristic lesions of muscular or epineurial arteries [14]. For the diagnosis of NA, small arteries with leukocytoclasia, polymorphonuclear cells, fibrinoid necrosis, and frequently sparing of adjacent venules should be confirmed.

For the treatment of VN and NA, prednisolone is recommended at a starting dose of 1mg/Kg/day. Combined treatment with cyclophosphamide or azathioprine may reduce prednisolone or other corticosteroids. In general, steroid therapy lasts for approximately 6-8 weeks and then tapering needs to be done slowly over 6-10 months, or more. Because of the axonal lesion by VN, sensorimotor deficit will take a long time (usually months) to improve. Motor recovery could be faster with physiotherapy, but residual pains are common [10].

ALCOHOLIC POLYNEUROPATHY

Alcoholic polyneuropathy (AP) is a neurological disorder caused by axonal degeneration of neurons in the sensory and/or motor systems. AP initially occurs from the distal ends of the longest axons in the body [15]. AP causes pain and/or motor weakness beginning from the feet and hands. And then, these symptoms progress centrally. AP is known to be caused by chronic alcoholism, but vitamin deficiencies can be associated with development of AP. Therefore, treatment should include nutritional supplementation, pain management, and abstaining from alcohol.

Axonal degeneration in AP often begins before any symptoms start and its symptoms usually are gradually aggravated over a long period. Weight loss can be a prodromal sign of AP in a chronic alcoholic suggesting that nutritional deficiencies can lead to AP. AP typically shows sensory and/or motor loss, as well as paresthesias. Symptoms due to AP develop symmetrically. The legs are most frequently affected first and the arms next. This phenomenon is called a stocking-and-glove pattern of sensory disturbances. Symptom severity of AP is quite different among patients. Some cases are seemingly asymptomatic but the most severe cases might have severe physical disability. When it comes to sensory

symptoms, abnormal sensations, numbness and/or painful sensations, and heat intolerance in the legs and arms are major complaints. Motor symptoms are known to gradually follow sensory symptoms and the most common ones include muscle cramps and weakness, erectile dysfunction in men, problems urinating, constipation, diarrhea, and so forth. Some people can experience frequent falls and gait unsteadiness due to ataxia caused by cerebellar degeneration, sensory ataxia, or distal muscle weakness. In severe cases, AP may also cause dysphagia, dysarthria, muscle spasms, and muscle atrophy.

Heavy alcohol consumption combined with nutritional deficiencies is considered as a main cause of AP. Frequently alcoholics suffer from loss of appetite, vomiting, and alcoholic gastritis, which all reduce absorption of nutrients [16]. The combination of the direct toxic effect of alcohol itself and a nutritional deficiency may result in AP. Describing in detail, ethanol and its metabolites (including acetaldehyde) are known to be toxic to the nervous system. If acetaldehyde from ethanol cannot be metabolized quickly, peripheral nerves might be damaged by the accumulated acetaldehyde [17]. Next, low thiamine levels due to a nutritional deficiency are usually present in those with AP and have been thought to be a cause of the nerve destruction. Thiamine plays important roles in glucose metabolism: decarboxylation of pyruvic acid, d-ketoglutaric acid, and transketolase. Thiamine deficiency may therefore disrupt keeping necessary ATP (adenosine triphosphate) levels in neurons by impaired glycolosis. Damage to the nervous system in AP begins with segmental thinning and loss of myelin on the peripheral ends of the longest nerves.

AP is very similar to other axonal degenerative polyneuropathies [18]. If alcoholics with sensorimotor polyneuropathy are confirmed with nutritional deficiencies, AP can be diagnosed. To confirm the diagnosis, other causes of similar clinical syndromes should be excluded. They include diabetic neuropathy, AIDP, beriberi, Charcot-Marie-Tooth disease, diabetic lumbosacral plexopathy, myotrophic lateral sclerosis, mononeuritis multiplex, and post-polio syndrome. Therefore, several tests need to be done to exclude all these diseases from AP. Alcoholism is frequently associated with nutritional deficiencies, so thiamine, folic acid, and vitamin B-12, which play essential roles in both the peripheral and central nervous system, should be evaluated as the first step in the diagnosis of AP.

There is no definitive treatment of AP. However, diverse treatments can be applied to the patients with AP to control their symptoms and promote independence. First of all, refraining from consuming alcohol is essential. Nutritional support is very important, as well. So, the patients with AP and nutritional deficiency can be supplied with an intravenous home parenteral nutrition formula. Vitamin supplementation (especially thiamine) must be included for the treatment of AP. Moreover, physical therapy is helpful for weakened muscles, gait, and balance. And, it is critical to make the patients understand that successful recovery often is not seen for several months because it can help them stick to the long-term treatment. In addition to the above treatments, pain control is very important for AP. The patients with AP usually complain of painful dysesthesias. This symptom can be reduced by using gabapentin, amitriptyline, or carbamazepine in combination with aspirin, ibuprofen, or acetaminophen. These agents have sedative and anticholinergic effects by blocking the active reuptake of norepinephrine and serotonin.

When it comes to the prognosis of AP, it is important to abstain from drinking alcohol completely. At early stages, the damage can be reversible when patients quit drinking and take appropriate amounts of numerous vitamins including thiamine. As the disease progresses, however, the damage may become permanent. Even after quitting alcohol and taking nutritionally balanced meals, patients with chronic and severe polyneuropathy might experience residual symptoms forever.

VITAMIN B12 DEFICIENCY NEUROPATHY

Peripheral neuropathy can be caused by malnutrition as described above and a lack of vitamin B12, an essential dietary nutrient, is clearly associated with peripheral neuropathy [19]. Vitamin B12 deficiency (B12D) can cause a lot of serious conditions such as vitamin B12 deficiency neuropathy (B12DN) and is known to be relatively common in elderly people. Several causes are associated with vitamin B12 deficiency and they include a strict vegetarian diet [20], the dysfunction of stomach acids, malabsorption syndromes, pernicious anemia, unexplained anemia, pancreatic diseases, gastritis, gastric or small intestine surgeries, ileal resection, Crohn's disease, HIV infection, multiple sclerosis, use of proton pump inhibitors, histamine 2 receptor antagonists, and so on.

B12D can cause nerve damage, spinal cord degeneration as well as serious anemia [21]. In terms of B12DN, B12D induces the damage of the myelin sheath surrounding and protecting nerves. The damage of the myelin sheath makes nerves not

function properly and leads to B12DN. If the underlying disease provoking B12D is not cured, the damage of the nerves induced by B12D might be permanently debilitating. Diverse symptoms can happen in B12DN: for example, numbness, tingling, and pain in feet and/or hands; sensory loss; lack of coordination; weakness; and so forth.

Numerous diagnostic tests should be done to diagnose B12D and B12DN. First of all, careful neurological exam is essential to check if the patients have B12DN and other neurological manifestations [21]. To clarify nerve damage due to B12D, nerve conduction velocity test and electromyography must follow. A blood test is necessary to evaluate anemia and the deficiency of vitamin B12.

For the treatment of B12DN, increase of vitamin B12 intake should be the first step. Vitamin B12 rich foods are dairy products, eggs and poultry, fish, red meat, and vitamin B12 supplements can be applied to the patients orally or parenterally. Early diagnosis and treatment are crucial for the prevention of permanent B12DN.

DRUG-INDUCED NEUROPATHY

Drug-induced neuropathy (DIN) is one of the important peripheral neuropathies. DIN means peripheral neuropathy caused by medications used in treatment, prevention, and diagnosis. Describing in detail, medications that can cause DIN include cardiovascular agents such as statins and amiodarone; chemotherapeutic agents such as vinca alkaloids, taxanes, platinum compounds, oxaliplatin, bortezomib, epothilones, and arsenic trioxides; antibiotics such as antimycobacterial agents, metronidazole, and nitrofurantoin; immunosuppressants such as etanercept, infliximab, adalimumab, interferons, and leflunomide; nucleoside reverse transcriptase inhibitors; levodopa; and triazole [22].

DIN may start weeks to months after initiating a certain drug and can reach a peak at or after the end of treatment. Patients with DIN usually suffer from pain and paresthesia. In other words, DIN usually shows a sensory polyneuropathy with pain and paraesthesia characterized by a glove stocking neuropathy. Motor symptoms are generally less manifest than sensory ones. However, the symptoms can completely resolve in most cases after stopping medications, although they can be only partially reversible or permanent in some cases [23].

DIN is often caused by demyelination of the peripheral nerves with or without axonal degeneration. To prevent DIN, numerous medicines can be administered and those include glutathione, intravenous calcium and magnesium, acetyl-L-carnitine, glutamine, venlafaxine, duloxetine, valproate, and interleukin-6 [22]. Prognosis varies depending on the severity of nerve damage done by the medication.

Conclusions

As described in this review, there are many different kinds of polyneuropathies although their symptoms and signs might look similar. Therefore, the exact differential diagnosis of polyneuropathy is very important in understanding their causes and pathogenesis and planning the best treatment options.

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