JEND Journal of Electrodiagnosis and Neuromuscular Diseases

REVIEW ARTICLE

pISSN: 2733-6581 · eISSN: 2733-659X
J Electrodiagn Neuromuscul Dis 2023;25(3):92-99
https://doi.org/10.18214/jend.2023.00115

Peripheral Neuropathy in Older Adults

Jiafei Niu[1], Chitra Ganta[1], Luke Dogyun Kim[1,2]

[1]Center for Geriatric Medicine, Cleveland Clinic, Cleveland, OH, USA
[2]Cleveland Clinic Lerner College of Medicine, Case Western Reserve University, Cleveland, OH, USA

Peripheral neuropathies are commonly encountered in older adults, exhibit a wide spectrum of symptoms, and have diverse etiologies. In older adults, peripheral neuropathy is associated with increased falls, as well as functional and cognitive decline. The current medical management of peripheral neuropathy mostly involves symptomatic management. It is important to identify the underlying etiology of peripheral neuropathy and to address the risk of falls in older adult patients. Once the risk of falls is identified, fall prevention strategies need to be implemented.

Keywords: Peripheral nervous system diseases; Older adults; Falls

Received: October 17, 2023
Revised: December 5, 2023
Accepted: December 5, 2023

Corresponding author:
Luke Dogyun Kim
Center for Geriatric Medicine,
Cleveland Clinic, 9500 Euclid Ave X10,
Cleveland, OH 44195, USA
Tel: +1-216-444-6092
Fax: +1-216-445-8762
E-mail: kiml2@ccf.org

Introduction

Peripheral neuropathy (PN) is a commonly encountered neurologic condition with a wide spectrum of symptoms. The prevalence of PN increases with age owing to the physiological degeneration of the peripheral nervous system and the higher prevalence of diseases such as diabetes and cancer, which are known to be risk factors for PN in older adults [1]. It is estimated that PN affects 26% to 39.2% of those 65 years of age and older, in contrast to 2% to 8% of the general population [2,3]. PN has been shown to be associated with increased falls, functional and cognitive decline, and higher mortality [1,4]. This narrative review article aims to provide a summary of PN in older adults from the most recent literature. We will discuss the etiologies of PN commonly seen in older adults, present a systematic diagnostic approach, describe the treatment options for diverse types of PN, and discuss the clinical impact of PN in older adults.

Etiologies

Based on the number of nerves involved, PNs can be categorized into mononeuropathy, multifocal neuropathy and polyneuropathy [5]. Since most peripheral nerves carry both sensory and motor fibers, most PNs have both sensory and motor components. Broadly speaking, the mechanism of nerve injury in PNs can be demyelinating and/or axonal [6]. Demyelinating diseases, in which the integrity of the actual neuron is preserved, have a better prognosis than axonal injuries [7]. More than one etiology and type of PN can exist in the same patient.

1) Mononeuropathy

Mononeuropathies occur when a single nerve is injured by compression, trauma, or inflammation. Trauma and inflammation tend to cause an acute onset of symptoms, whereas compression often leads to a subacute-chronic presentation [5].

(1) Carpal tunnel syndrome

Carpal tunnel syndrome (CTS) occurs when the median nerve becomes entrapped when passing through the carpal tunnel bound by the transverse carpal ligament and the carpal bones [7]. The median nerve carries the sensory fibers that supply the first three fingers and the lateral side of the fourth finger. There-

fore, the classic manifestation of CTS is pain and/or paresthesia in the median nerve territory. These sensations can propagate proximally into the forearm and elbow. In more severe cases, the motor function of the median nerve is also impaired, leading to weakness in the abduction and opposition of the thumb and thenar atrophy. CTS is associated with repetitive hand and wrist movements and chronic pressure to the palm and wrist. Other risk factors include diabetes, obesity, hypothyroidism, and amyloidosis. CTS is a common disorder, with an estimated prevalence of 1% to 5% in the general population, and higher rates in older patients and those with obesity. It also has a predilection for the female sex, with a female-to-male ratio of 2–4:1 [5].

(2) Bell's palsy

Bell's palsy refers to acute idiopathic cranial VII nerve or facial nerve palsy and is the most common acute mononeuropathy. Its incidence ranges from 11.5 to 53.3 per 100,000 persons according to published epidemiological studies [8]. One Italy-based study found that the occurrence of Bell's palsy increased with age, and another Korea-based study noted a peak incidence in the seventh decade of life [9,10]. Patients present with acute onset unilateral facial weakness or complete inability of movement, reaching maximum severity around 48 hours. When the sensory component of the facial nerve is involved, patients can also experience postauricular pain and altered taste. Most patients achieve a complete recovery of facial nerve function, but approximately 25% of patients may develop persistent paresis, contractures, or synkinesis (i.e., involuntary facial movements). The initial presence of complete facial paralysis, advanced age, and delayed signs of recovery (> 3 weeks after symptom onset) are associated with a poorer prognosis [5,8].

The etiology of Bell's palsy remains uncertain. Multiple mechanisms of facial nerve injury have been proposed, including mechanical compression from anatomical variations of the temporal bone through which the facial nerve traverses after exiting the brain stem, viral infections (especially of the herpesvirus family), and ischemia. The diagnosis of Bell's palsy requires the exclusion of other causes of facial nerve palsy, such as trauma, malignancy, Ramsay Hunt syndrome, Lyme disease, and vascular insufficiency [8].

(3) Postherpetic neuralgia

Shingles is a common disease, with an estimated incidence of 1 million cases per year in the United States [11]. It is caused by reactivation of the varicella zoster virus (VZV) that had remained dormant in the sensory ganglia after the initial infection. During an episode of shingles attack, VZV virions replicate within the residing neuron and travel down the axon to reach the skin innervated by the same neuron, causing the characteristic dermatomal blistering rash. Postherpetic neuralgia is a chronic neuropathic pain thought to be caused by inflammatory nerve damage as the body combats the reactivated VZV and can last months to years after the rash heals. It affects 5% to 20% of patients who have had shingles and its frequency increases with age, seen in 30% or more of patients over the age of 80. Prodromal pain and severe pain concurrent with the rash are additional risk factors for developing postherpetic neuralgia. Patients can experience constant or intermittent unprovoked pain, allodynia, or hyperalgesia over the same dermatome(s) as the shingles rash [11].

2) Multifocal neuropathy

(1) Mononeuritis multiplex

Mononeuritis multiplex typically presents with asymmetric sensorimotor neuropathy, where at least two nerves in different body parts are involved. The symptoms are diverse and can include sensory or motor deficits, as well as pain. The onset is often acute, and the progression is frequently rapid [5]. Mononeuritis multiplex is not a primary neurologic pathology, but rather the neurologic manifestation of another underlying systemic disease, most often vasculitis that has led to nerve ischemia [12]. Other diseases associated with mononeuritis multiplex include rheumatologic disorders (such as systemic lupus erythematosus and Sjögren syndrome), viral infections (such as coronavirus disease 2019 [COVID-19], hepatitis C, and human immunodeficiency virus [HIV]), diabetes, and sarcoidosis [5]. While the epidemiology of mononeuritis multiplex is unknown, it is expected to be seen in more older adults when an underlying disease such as giant cell arteritis (GCA) affects this population. PN has been seen in 19% of patients with GCA and 23% of patients with microscopic polyangiitis in a large multinational observational study [13].

3) Polyneuropathy

(1) Acute: Guillain-Barre syndrome

Guillain-Barre syndrome (GBS) is the most common cause of acute flaccid paralysis, precipitated by an infection within 4 weeks prior to symptom onset in most cases [11,14]. It is thought that certain antigens on the pathogen structurally resemble some innate molecules in the peripheral nervous system, thereby triggering immune-mediated peripheral nerve demyelination and/or direct axonal injury. Infections associated with GBS include *Campylobacter jejuni*, cytomegalovirus, Epstein-Barr virus, influenza A, and arboviruses such as Zika virus [14,15]. The annual global incidence of GBS is quite low, at 1–2 per 100,000

person-years, and the frequency increases with age. GBS is clinically heterogeneous. The classic presenting symptom of GBS is ascending symmetric weakness that starts in the distal lower limbs. The weakness is rapidly progressive, peaking in approximately 2 weeks. Approximately 20% to 30% of patients can develop respiratory failure from the weakness and require intensive care. Hyporeflexia results from lower motor neuron damage. Sensory disturbance and pain frequently occur as well, sometimes preceding weakness, which could mislead the diagnosis. Autonomic fibers can also be involved and contribute to hemodynamic instability and cardiac arrhythmia. Recovery can take months, but most patients are able to walk independently 6 months after onset even without treatment. In most cases, GBS is a monophasic disease without relapse after recovery [1].

(2) Chronic: diabetic neuropathy

Diabetic neuropathy is the most common cause of PN in the developed world, accounting for 32% to 55% of all PNs across different populations [7]. The likelihood of developing neuropathy increases with the duration of diabetes and poor glycemic control, and 50% of patients with diabetes are expected to develop neuropathy along their disease course [16]. Most complications of diabetes, including diabetic neuropathy, are thought to be the results of vasculopathies stemming from chronic inflammation and the generation of advanced glycation end products. It has also been shown that diabetes impairs axonal regeneration after injury, which contributes to the lack of spontaneous recovery in most cases of diabetic neuropathy. There are multiple types of diabetic neuropathy that can also occur simultaneously.

Distal symmetric sensorimotor polyneuropathy accounts for more than half of diabetic neuropathy cases. Patients experience a gradual onset of sensory symptoms such as pain, numbness, and tingling in the distal limbs, creating a characteristic "stocking-glove" pattern [7].

Autonomic dysfunction is also commonly seen in patients with diabetes. Most epidemiological studies on diabetic autonomic neuropathy have focused on the cardiovascular subtype, which is characterized by impaired regulation of heart rate, decreased baroreflex sensitivity, and subsequent dysregulation of blood pressure leading to orthostatic hypotension. The reported prevalence of cardiovascular autonomic dysfunction varies widely, between 1% and 90%, among patients with diabetes. Diabetic autonomic neuropathy can also affect the vagus nerve and the enteric nervous system, potentially causing both abnormal stimulation (diarrhea and stool incontinence) and inhibition (gastroparesis and constipation) of the gastrointestinal tract. Urinary retention or urgency occurs when the genitourinary system is affected, and sleep apnea takes place when the respiratory system is involved [17].

Radiculoplexus neuropathy is another type of diabetic neuropathy. Diabetic amyotrophy, also known as diabetic lumbosacral radiculoplexus neuropathy, is thought to be an inflammatory process manifesting as microvasculitis that results in peripheral nerve ischemia. Patients present with acute onset unilateral pain, usually severe, and weakness in the proximal lower extremities associated with weight loss. Patients typically recover, at least partially, in months [16]. Mononeuropathy, such as oculomotor nerve palsy and CTS, can also take place in patients with diabetic neuropathy [5,16].

(3) Chronic: paraneoplastic neurologic disorders

Paraneoplastic neurologic disorders (PNDs) are part of paraneoplastic syndrome, which is a group of non-metastatic complications of an underlying malignancy [5]. PNDs are rare, seen in < 1% of cancer patients. All malignancies, except for primary central nervous system cancer, can produce neuronal antigens and trigger an autoimmune response against both the central and peripheral nervous systems. The cancers more commonly associated with PNDs are small cell lung cancer, breast cancer and gynecologic cancers. PNDs can affect all parts of the nervous system. Paraneoplastic PNs typically present with subacute onset of pain, numbness, and impaired proprioception in an asymmetric distribution. The much less common motor symptoms occur when either peripheral motor neurons or the neuromuscular junction (NMJ) is affected. Paraneoplastic peripheral motor neuropathy is driven by an acute inflammatory demyelination process, almost indistinguishable from GBS; whereas NMJ involvement often presents with gradual onset proximal muscle weakness, such as Lambert-Eaton myasthenic syndrome, a well-known NMJ disorder associated with small cell lung cancer caused by autoantibodies against the presynaptic voltage-gated calcium channels [18].

(4) Chronic: paraproteinemic neuropathy

Paraproteins refer to the monoclonal immunoglobulins produced from plasma cell disorders, including monoclonal gammopathy of undetermined significance, Waldenstrom macroglobulinemia (WM), and multiple myeloma [19]. Overall, the incidence of plasma cell dyscrasia, and therefore the risk of associated polyneuropathies, increases with age. The immunoglobulin M (IgM) M-protein has a much stronger association with peripheral polyneuropathy than IgA and IgG immunoglobulins. The pathophysiology of paraproteinemia-associated PN is not clearly elucidated. Since IgM M-proteins have demonstrated re-

https://doi.org/10.18214/jend.2023.00115

activity against several molecules (e.g., myelin-associated glycoprotein and ganglioside) with abundant presence in the nervous system, it is postulated that upon binding to their ligands, the immunogenicity of the monoclonal immunoglobulins leads to inflammatory damage to peripheral nerves. While demyelination is the most common injury pattern, axonal injuries can also be seen, especially in WM [19].

The clinical presentation depends on the mechanism of nerve injury. In demyelinating cases, larger, myelinated sensory nerves are affected, causing gradual onset of distal, symmetric paresthesia and sensory loss. Ataxia can occur from sensory disturbance. Motor neurons, also myelinated, can be involved as well, albeit less frequently [5,19]. Axonal injury has more heterogeneous presentations, with sensory, motor, and autonomic symptoms.

Monoclonal gammopathy has a much higher prevalence (approximately 10%) in patients with idiopathic PN compared to the general population. It is therefore wise to evaluate underlying plasma cell disorders in patients with PN without another apparent cause, especially in older adults [12]. Clinicians should also keep in mind that the concurrent presence of monoclonal gammopathy and PN does not necessarily imply a causal relationship between the two diseases, and that treatment for plasma cell disorders could sometimes be the actual cause of PN [12,19].

All plasma cell disorders have the potential to cause primary amyloidosis, when excessively produced light chains aggregate to form insoluble fibrils that deposit in various organs such as the heart, kidneys, liver, and peripheral nervous system. The incidence of primary amyloidosis increases with age, and the median age at diagnosis is 64 years. Furthermore, 17% to 35% of patients with primary amyloidosis develop PNs [20]. In contrast with M-protein-associated PN, nerve damage in primary amyloidosis is not immune-mediated, but rather from mechanical compression, ischemia, and neuron apoptosis as direct results of amyloid deposition [12,19]. Since small fibers are affected, typical symptoms include distal paresthesia and pain, and autonomic dysfunction. CTS is commonly seen as well. Primary amyloidosis should be suspected when patients also present with renal dysfunction and heart failure alongside PN [12,20]. Transthyretin amyloid (ATTR), especially the wide type, is another form of systemic amyloidosis that affects older adults. Because peripheral nervous system involvement is rare, ATTR will not be discussed in this paper.

(5) Chronic: medication-induced neuropathy

Multiple classes of drugs can cause PN by damaging neuron organelles and disrupting membrane ion channels. Medication-induced PN should have a clear temporal relationship with the initiation of the culprit medication. Chemotherapy agents are the most common offenders in older adults [21]. PN often becomes a dose-limiting side effect in about 30% of patients receiving chemotherapy [21]. Platinum-based agents, taxanes, and vinca alkaloids (especially vincristine) are well known to cause PN in a dose-dependent fashion [21]. Distal sensory neuropathy including pain, paresthesia, and decreased sensation is the predominant presentation with a gradual onset of weeks to months. Motor deficits are rare and only seen in cases of severe PN. While most PNs resolve gradually upon cessation of the causative medication, some can be persistent, such as cisplatin-induced chronic sensory neuropathy, where the medication accumulates in dorsal root ganglia and causes irreversible damage to neuronal DNA [21].

Immunotherapy has been rising in popularity in cancer treatment due to fewer side effects and better tolerability than cytotoxic chemotherapy. Immunotherapy inhibits checkpoints in the immune system and amplifies T cell activation to destroy cancer cells. This immune-boosting effect also increases the risk of autoimmune damage to organs, including the peripheral nervous system. Autoimmune PN occurs in $< 10\%$ of patients receiving immunotherapy, but the incidence becomes much higher when multiple agents are used simultaneously. Any location within the peripheral nervous system can be affected, leading to diverse sensorimotor presentations including cranial neuropathies and GBS, usually with an acute to subacute onset [22].

PNs can also develop from non-antineoplastic agents such as anti-retroviral and antimicrobial medications at lower frequencies. In patients who take anti-retroviral medications, PN occurs at varying rates depending on the specific agent, most commonly with the use of zalcitabine, stavudine, and didanosine. These drugs are thought to impair mitochondrial DNA replication, thus depleting neurons of adenosine triphosphate supply and leading to axonal degeneration of sensory fibers and distal sensory neuropathy. Isoniazid, an anti-tuberculosis drug, also interferes with vitamin B6 metabolism. Vitamin B6 supplementation is co-administered with isoniazid to prevent PN development. Another anti-tuberculosis drug, ethambutol, causes optic neuritis by affecting mitochondrial functions in retinal ganglion cells. Thankfully, the associated vision loss is reversible in most cases. Rarely, metronidazole can also cause PN with prolonged use [23].

As the incidence of Parkinson disease (PD) increases with age, it should be mentioned that levodopa, the mainstay treatment for PD, can disrupt vitamin B12 metabolism, leading to the development of PN, especially at a daily dose > 400 mg. The neu-

ropathy is typically sensory and mild in severity [23].

(6) Chronic: toxin and nutritional deficiency-induced neuropathy

Alcohol misuse is common among older adults. The 2005 to 2006 National Survey on Drug Use and Health found that 19% of men and 13% of women of age 50 and older consumed two or more drinks per day, and 14% of men and 3% of women of age 65 and older engaged in binge drinking. The number of older adults exhibiting problematic alcohol use is expected to increase with an aging population [24]. Alcohol-related PN can be seen in almost half of people with chronic alcohol dependence. They develop painful distal sensory neuropathy, mostly in the lower extremities with an insidious onset. The pathophysiology is multifaceted, including the direct neurotoxicity of alcohol, oxidative stress, and nutrition deficiency associated with long-term alcohol overuse [24].

Lead intoxication is now rare in developed nations. However, older adults have more exposure to environmental lead simply because they have lived longer. They are also more likely to have been in contact with lead-containing paint and gasoline before these materials were outlawed in the 1970s. Older adults are also at risk for more lead exposure from recreational activities like ceramic glazing and moonshine consumption [25]. Acute lead toxicity causes an acute motor-predominant neuropathy with weakness in finger and wrist extensors, whereas chronic lead neuropathy is mostly sensory. Concomitant cognitive impairment, gastrointestinal symptoms, and microcytic anemia with basophilic stippling frequently occur [25].

Vitamin B12 deficiency is common, affecting 5% to 20% of older adults, most often due to malabsorption such as in the case of atrophic gastritis or gastric bypass surgery. Other causes include low vitamin B12 intake and side effects of medications frequently used among older adults, such as metformin and proton-pump inhibitors [12,26]. Vitamin B12 deficiency leads to demyelination of large fibers, thereby impairing both sensory and motor functions. Demyelination can also occur in the central nervous system, affecting the corticospinal tract and dorsal column within the spinal cord and leading to subacute onset of sensory ataxia due to loss of proprioception [26].

Thiamine, or vitamin B1, plays crucial roles in neuron health maintenance and nerve regeneration when injury occurs. It serves as both an antioxidant and an essential coenzyme in energy production [27]. Since the body has extremely limited thiamine storage capacity, daily intake is essential. Older adults have significantly lower plasma levels of thiamine than younger people, regardless of comorbidities or medication use. This is due to inadequate intake and/or impaired absorption due to gastrointestinal lining atrophy. Chronic alcohol overuse is another noteworthy cause of thiamine deficiency [27]. PN due to thiamine deficiency is also known as dry beriberi. Motor symptoms including distal, facial, and laryngeal weakness are more common in the absence of alcoholism, whereas distal sensory neuropathy is the predominant feature when alcohol use disorder coexists with thiamine deficiency.

Diagnosis

After careful history-taking on medical comorbidities, onset, progressive symptoms, and motor or sensory symptoms, the clinician should first rule out central nervous system diseases, myopathy, or NMJ diseases to give a diagnosis of PN. Additionally, patients with well-established medical diagnoses that commonly presents with PN along with mild symptoms (such as diabetes or recent chemotherapy) would not need extensive tests and work-ups. Additionally, when we plan diagnostic work-ups, we should consider patients' goals of care, functional status, cognitive status, other medical comorbidities, and a review of current medications. One study showed that electrodiagnostic tests and magnetic resonance imaging, which account for most of the expenditures in the evaluation, rarely lead to changes in management [28].

Once we decide to pursue further diagnostic work-ups, we need to pursue electromyography and nerve conduction studies along with blood tests, such as serum glycohemoglobin, serum vitamin B12 level, serum methylmalonic acid level, thyroid function tests, serum protein electrophoresis, urine protein electrophoresis, and serum nuclear antibodies.

It is important to identify and address the risk of falls in the setting of PN in older adults. The Timed Up and Go (TUG) test is an easy tool to use in the office setting, and it has a strong prediction ability for future falls [29]. Once the risk of falls is identified, then we need to recommend fall prevention strategies [30].

Impacts of Peripheral Neuropathy on Older Adults

A rich body of literature demonstrates the negative impacts of PN on the health of older adults in multiple aspects. It has been long recognized that PN is an independent risk factor for falls due to impaired reflex, proprioception and decreased unipedal standing time. Patients with chronic neuropathic pain also report decreased quality of life (QoL) regardless of the specific etiology of the pain. In addition to causing direct suffering, pain also impairs sleep and exacerbates stress and mood disorders, which in

https://doi.org/10.18214/jend.2023.00115

turn can intensify the perception of pain. This is particularly concerning in older adults who tend to underreport their painful symptoms and are consequently under-treated or not treated. Neuropathic pain is usually more challenging to manage than nociceptive pain, further contributing to patient frustration and lower QoL. Recent evidence also suggests an association between lower extremity PN and development of dementia among those in the age group of 70 to 79 years in an incremental manner, such that a higher incidence of dementia is seen in patients who have more peripheral nerve impairment. This association could be explained by the shared risk factors, such as diabetes and age, between dementia and PN [31].

Treatments

Treatment of PN is aimed at managing the causative etiology when possible and treating the symptoms. The most common symptom for which patients seek medical help is neuropathic pain. Multiple disciplines are used to treat neuropathic pain, which can broadly be divided into pharmacological and non-pharmacological modalities. The cost of neuropathic pain to the United States health care system is projected to cross 10 billion dollars [32], but the economic burden of untreated pain resulting in loss of workdays or disability accounts for much higher losses, which makes adequate treatment of neuropathic pain especially important. We will discuss the general guidelines for treating neuropathic pain and touch on specific pathologies.

The pharmacological agents traditionally used for treatment of neuropathic pain are anticonvulsants such as gabapentin and pregabalin, antidepressants like tricyclic antidepressants (TCAs) and serotonin and norepinephrine reuptake inhibitors (SNRIs), topical anesthetics, capsaicin, and opiates. Unfortunately, none of the above medications are a complete panacea; their efficacy at best, is modest [33].

Based on the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) analysis, the current first-line medications for the treatment of neuropathic pain after assessing risks and benefits are gabapentinoids and SNRIs, such as, duloxetine and venlafaxine. The second-line agents are lidocaine patches and tramadol. Opiates are third-line agents and used only for pain refractory to the first- and second-line agents if patients report improvement in symptoms. Opiates are not as effective for neuropathic pain as they are for acute nociceptor pain stimuli, and they carry a substantial side effect overdose risk profile. The fourth-line agents are anti-epileptics like lamotrigine and cannabinoids [34].

Medications such as TCAs and muscle relaxers have sedating and anticholinergic properties. Gabapentinoids can cause dizziness and drowsiness and increase the risk of falls especially when used concomitantly with other centrally acting agents, including antidepressants and opioids [35]. Polypharmacy is common among older adults, causing a higher risk of adverse drug-drug interaction, which can be further prolonged and amplified by decreased renal function. Furthermore, underlying cognitive impairment and substance use can lead to inappropriate use or overuse of medications [36].

Conclusion

PN is common in older adults, in whom it is particularly strongly associated with falls. The current medical management of PN is mostly symptomatic management, and its efficacy is limited. It is important to identify and address the risk of falls in older adult patients with PN. Once the risk of falls is identified, fall prevention strategies need to be implemented.

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

ORCID

Jiafei Niu, https://orcid.org/0009-0006-0773-7509
Chitra Ganta, https://orcid.org/0000-0001-8536-8338
Luke Dogyun Kim, https://orcid.org/0000-0003-2396-4868

References

1. Mold JW, Vesely SK, Keyl BA, Schenk JB, Roberts M: The prevalence, predictors, and consequences of peripheral sensory neuropathy in older patients. J Am Board Fam Pract 2004;17:309–318.
2. Anish L, Nagappa M, Mahadevan A, Taly AB: Neuropathy in elderly: lessons learnt from nerve biopsy. Age Ageing 2015;44:312–317.
3. Hicks CW, Wang D, Windham BG, Matsushita K, Selvin E: Prevalence of peripheral neuropathy defined by monofilament insensitivity in middle-aged and older adults in two US cohorts. Sci Rep 2021;11:19159.
4. Lawler FH, Mold JW, Liao X, Bard DE: Peripheral neuropathy in older people is associated with reduced life expectancy. J Am Board Fam Med 2023;36:431–438.
5. Hanewinckel R, Ikram MA, Van Doorn PA: Peripheral neu-

ropathies. Handb Clin Neurol 2016;138:263–282.
6. Barohn RJ, Amato AA: Pattern-recognition approach to neuropathy and neuronopathy. Neurol Clin 2013;31:343–361.
7. Chung T, Prasad K, Lloyd TE: Peripheral neuropathy: clinical and electrophysiological considerations. Neuroimaging Clin N Am 2014;24:49–65.
8. Zhang W, Xu L, Luo T, Wu F, Zhao B, Li X: The etiology of Bell's palsy: a review. J Neurol 2020;267:1896–1905.
9. Monini S, Lazzarino AI, Iacolucci C, Buffoni A, Barbara M: Epidemiology of Bell's palsy in an Italian Health District: incidence and case-control study. Acta Otorhinolaryngol Ital 2010;30:198.
10. Kim MH, Park SY: Population-based study and a scoping review for the epidemiology and seasonality in and effect of weather on Bell's palsy. Sci Rep 2021;11:16941.
11. Mallick-Searle T, Snodgrass B, Brant JM: Postherpetic neuralgia: epidemiology, pathophysiology, and pain management pharmacology. J Multidiscip Healthc 2016;9:447–454.
12. Suzuki M: Peripheral neuropathy in the elderly. Handb Clin Neurol 2013;115:803–813.
13. Bischof A, Jaeger VK, Hadden RD, Luqmani RA, Pröbstel AK, Merkel PA, et al: Peripheral neuropathy in antineutrophil cytoplasmic antibody-associated vasculitides: insights from the DCVAS study. Neurol Neuroimmunol Neuroinflamm 2019;6:e615.
14. Willison HJ, Jacobs BC, van Doorn PA: Guillain-Barré syndrome. Lancet 2016;388:717–727.
15. Leonhard SE, Mandarakas MR, Gondim FA, Bateman K, Ferreira ML, Cornblath DR, et al: Diagnosis and management of Guillain-Barré syndrome in ten steps. Nat Rev Neurol 2019;15:671–683.
16. Hicks CW, Selvin E: Epidemiology of peripheral neuropathy and lower extremity disease in diabetes. Curr Diab Rep 2019;19:86.
17. Fujihara K, Kodama S, Horikawa C, Yoshizawa S, Sugawara A, Hirasawa R, et al: The relationship between diabetic neuropathy and sleep apnea syndrome: a meta-analysis. Sleep Disord 2013;2013:150371.
18. Rees JH: Paraneoplastic syndromes: when to suspect, how to confirm, and how to manage. J Neurol Neurosurg Psychiatry 2004;75 Suppl 2:ii43–ii50.
19. Chaudhry HM, Mauermann ML, Rajkumar SV: Monoclonal gammopathy-associated peripheral neuropathy: diagnosis and management. Mayo Clin Proc 2017;92:838–850.
20. Shin SC, Robinson-Papp J: Amyloid neuropathies. Mt Sinai J Med 2012;79:733–748.
21. Staff NP, Grisold A, Grisold W, Windebank AJ: Chemotherapy-induced peripheral neuropathy: a current review. Ann Neurol 2017;81:772–781.
22. Marini A, Bernardini A, Gigli GL, Valente M, Muñiz-Castrillo S, Honnorat J, et al: Neurologic adverse events of immune checkpoint inhibitors: a systematic review. Neurology 2021;96:754–766.
23. Jones MR, Urits I, Wolf J, Corrigan D, Colburn L, Peterson E, et al: Drug-induced peripheral neuropathy: a narrative review. Curr Clin Pharmacol 2020;15:38–48.
24. Chopra K, Tiwari V: Alcoholic neuropathy: possible mechanisms and future treatment possibilities. Br J Clin Pharmacol 2012;73:348–362.
25. Vig EK, Hu H: Lead toxicity in older adults. J Am Geriatr Soc 2000;48:1501–1506.
26. Leishear K, Boudreau RM, Studenski SA, Ferrucci L, Rosano C, de Rekeneire N, et al: Relationship between vitamin B12 and sensory and motor peripheral nerve function in older adults. J Am Geriatr Soc 2012;60:1057–1063.
27. Wilkinson TJ, Hanger HC, George PM, Sainsbury R: Is thiamine deficiency in elderly people related to age or co-morbidity? Age Ageing 2000;29:111–116.
28. Callaghan BC, Kerber KA, Lisabeth LL, Morgenstern LB, Longoria R, Rodgers A, et al: Role of neurologists and diagnostic tests on the management of distal symmetric polyneuropathy. JAMA Neurol 2014;71:1143–1149.
29. Barry E, Galvin R, Keogh C, Horgan F, Fahey T: Is the timed up and go test a useful predictor of risk of falls in community dwelling older adults: a systematic review and meta-analysis. BMC Geriatr 2014;14:14.
30. Stevens JA, Phelan EA: Development of STEADI: a fall prevention resource for health care providers. Health Promot Pract 2013;14:706–714.
31. Brenowitz WD, Robbins NM, Strotmeyer ES, Yaffe K: Associations of lower extremity peripheral nerve impairment and risk of dementia in Black and White older adults. Neurology 2022;98:e1837–e1845.
32. Ruiz-Negrón N, Menon J, King JB, Ma J, Bellows BK: Cost-effectiveness of treatment options for neuropathic pain: a systematic review. Pharmacoeconomics 2019;37:669–688.
33. Alles SR, Smith PA: Etiology and pharmacology of neuropathic pain. Pharmacol Rev 2018;70:315–347.
34. Finnerup NB, Attal N, Haroutounian S, McNicol E, Baron R, Dworkin RH, et al: Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis. Lancet Neurol 2015;14:162–173.

 https://doi.org/10.18214/jend.2023.00115

35. The 2023 American Geriatrics Society Beers Criteria Update Expert Panel: American Geriatrics Society 2023 updated AGS Beers Criteria for potentially inappropriate medication use in older adults. J Am Geriatr Soc 2023;71:2052–2081.

36. Haanpää ML, Gourlay GK, Kent JL, Miaskowski C, Raja SN, Schmader KE, et al: Treatment considerations for patients with neuropathic pain and other medical comorbidities. Mayo Clin Proc 2010;85(3 Suppl):S15–S25.