Chapter

Neurotoxic Agents and Peripheral Neuropathy

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Abstract

Neurotoxicity may develop with exposure to various substances such as antibiotics, chemotherapeutics, heavy metals, and solvents. Some plants and fungi are also known to be neurotoxic. Neurotoxicity can develop acutely within hours, or it can develop as a result of exposure for years. Neurotoxicity can be presented with central or peripheral nervous system findings such as neurobehavioral symptoms, extrapyramidal signs, peripheral neuropathy. Peripheral nerve fibers are affected in different ways by neurotoxicant injury. The pattern of injury depends on the target structure involved. The focus of this chapter includes signs, symptoms, pathophysiology, and treatment options of neurotoxicity.

Keywords: neurodegeneration, neuropathy, neurotoxic, mechanisms of neurotoxicity, chemicals

1. Introduction

The direct or indirect effects of chemical or physical agents that disrupt the function or structure of the nervous system of humans or animals are called neurotoxicants [1]. Neurotoxicity can be presented with central or peripheral nervous system findings such as neurobehavioral symptoms, extrapyramidal signs, and peripheral neuropathy. Peripheral nerve fibers are affected distinctly by neurotoxicant injury. Mild or severe polyneuropathy involves the peripheral nerves, affecting the myelinated, thinly myelinated, and unmyelinated fibers. A wide variety of etiological factors can cause polyneuropathy. In addition to frequent causes such as diabetes mellitus, alcohol abuse, the peripheral nervous system is vulnerable to several rare conditions [2]. Toxic peripheral neuropathies are caused by various chemicals, a basic form of acquired polyneuropathy [3]. Neurotoxicity may develop when exposed to heavy metals, solvents chemotherapeutics, monomers, gases and pesticides. The focus of this chapter includes signs, symptoms, pathophysiology, and treatment options of several neurotoxic agents that cause peripheral neuropathy.

2. Heavy metals

Heavy metals are naturally occurring elements with a high weight and a density at least five times greater than water [4]. In other words, any toxic metal can be defined as heavy metal, regardless of its atomic weight or density [5]. The industrial activities of the modern world have caused a massive rise in human exposure to

heavy metals, and heavy metals have harmful effects on human health [6]. Heavy metals' contamination of water and air is an environmental threat, and hundreds of millions of people are being exposed worldwide. The concentration of heavy metals in water supplies, air, and food is evaluated in this respect [7, 8].

Heavy metals such as arsenic (As), lead (Pb), mercury (Hg), aluminum (Al), and cadmium (Cd) do not have any particular role in an organism and can be toxic even at low levels [9]. On the contrary, it has been reported that some of these heavy metals such as iron, magnesium, selenium, copper, zinc, cobalt, nickel, molybdenum, chromium, and manganese are essential nutrients that have functional roles for various diverse biochemical and physiological functions in the body [10]. However, in over adequate amounts, they may cause toxicities. Acute and chronic toxic effects of heavy metals have an impact on different organs of the human body. In addition to the nervous system disorders, gastrointestinal and kidney dysfunction, skin lesions, vascular damage, immune system dysfunction, birth malformations, and cancer are examples of the complications of heavy metals toxic effects [8, 11, 12].

2.1 Lead

Lead is a toxic heavy metal in different sources such as contaminated drinking water, battery manufacture, cosmetics, leaded gasoline, lead-based paint, cans, glazed ceramics, traditional herbal medicine products, water pipes, jewelry, tobacco smoke, and electronic cigarettes, and toys. Lead exposure can be considered a public health concern, especially in early childhood, because children have increased hand-to-mouth activity, so they are more at risk [13, 14]. While the half-life of Pb in the bloodstream is about 35 days, it is stored in bones for approximately 30 years [15, 16]. Oxidative stress, alterations in membrane biophysics, dysregulation of cell signaling, and the impairment of neurotransmission are considered the complex underlying mechanisms of lead-induced neurotoxicity [17].

One of the most critical endpoints of Pb toxication is neurological effects. Pb toxication frequently causes neuropathy in adults, while encephalopathy is mainly seen in children. Exposure to high Pb levels causes encephalopathy with signs such as hyperirritability, cerebellar findings, seizures, unconsciousness, and coma. It is reported that exposure to low Pb levels has been associated with impaired cognitive and intellectual function in children [18, 19]. In occupational exposure, it is reported that neurological signs and symptoms include weakness, forgetfulness, irritability, headache, impotence, decreased libido, vertiginous symptoms, and paresthesia in Pb exposure workers. Moreover, increased prevalence and severity of white matter lesions, changes in nerve conduction velocity, and alterations of somatosensory evoked potentials were documented [18, 19].

In lead toxicity, motor-predominant polyneuropathy, which causes the development of wrist-drop, may present. Additionally, because of secondary to autonomic nerve involvement, constipation may accompany [20]. After forbidden the usage of leaded gasoline, changes in lead mining practices, and the abandonment of lead-based paint, human exposure to the primary sources of Pb decreased. So the incidence of overt lead toxicity induced polyneuropathy decreased [21].

2.2 Arcenic (As)

Arsenic is an environmental toxin, and this heavy metal is widely distributed to the earth. Hundreds of millions of people consume inorganic contaminated tube well water [22, 23]. Burning the charcoal and metal foundry activities are known to cause atmospheric deposition of As. Excessive pesticides and fertilizers and mining use cause soil contamination with As [24, 25]. While As often exists in the world

crust in the trivalent atomic state (inorganic) with other heavy metals such as Pd, iron, copper, it is generally oxidized to pentavalent form in the soil and water. It is reduced to in trivalent atomic state in low oxygen situations, such as deep seawater [26]. Inorganic As is more potent and has been implicated in neurotoxic effects. The inorganic form should be distinguished from the non-neurotoxic organic As found in some fish and shellfish [21].

It is reported that traditional folk medicines can be the other sources of As [27, 28]. Some herbal medicines commercially available have been reported to contain heavy metals such as lead, mercury, and arsenic. Using these products may cause heavy metal toxicity and secondary peripheral neuropathy [26]. As causes various adverse effects on human health such as carcinogenic and non-carcinogenic [26].

The exact metabolic pathways of As are yet to be proved. However, oxidative methylation and glutathione conjugation are the primary pathways suggested [29]. The primary mechanism in As-induced neurological pathologies has been suggested oxidative stress with Vitro and in vivo studies [9]. While exposure to high levels of As induces primarily central nervous system findings, exposure to low levels causes primarily peripheral nervous system findings [18].

Single high dose exposure to As may lead to severe gastrointestinal and systemic symptoms such as nausea, diarrhea, vomiting, pain, dehydration, and weakness. It is usually the result of suicide- homicide or accidental poisoning. If the patient survives acute poisoning with As, neurological symptoms such as light-headedness, weakness, delirium, encephalopathy, and peripheral neuropathy develop [30].

Chronic neurological symptoms of As exposure are delirium, encephalopathy, and also peripheral neuropathy. In neuropsychological tests, while psychomotor speed and attentive processes were mildly impaired, verbal learning and memory were severely impaired [31, 32]. It is known that peripheral neuropathy may last for several years or even life-long, but on the other hand, in severe cases, diffuse sensorimotor polyradiculoneuropathy may be seen, similar to the Guillan–Barré syndrome. At the same time, chronic As exposure can cause painless sensory-predominant peripheral neuropathy [32].

The diagnosis of arsenic toxicity can be made by demonstrating high urinary and increased arsenic levels in the nails and hairs. Serum arsenic level estimation is not recommended because of the rapid clearance of arsenic. There is no gold standard specific treatment for chronic arsenic toxicity. For acute arsenic toxicity treatment, chelating agents such as BAL, D-penicillamine, and meso-2,3-dimercaptosuccinic acid are mainly used [33].

2.3 Mercury (Hg)

Mercury is heavy metal in the air, water, and soil in three chemical forms; metallic/elemental, inorganic, and organic Hg (methyl mercury and ethyl mercury). The elemental Hg is liquid at room temperature and can evaporate quickly. The vapor form of Hg is more dangerous and can is readily absorbed from the lungs (80%) and distributed throughout the body [8]. A wide variety of fields in that Hg have been used, such as gold mining, fluorescent light bulbs production, ingredients of antiaging creams, fungicides to protect plants against infections, and protection in multidose vials of vaccines [34, 35].

In the middle of the 1950s, around 200.000 people have affected by the consumption of organic Hg-contaminated fish in Minamata Bay, Japan. Because of chronic Hg toxicity, neurological signs and symptoms occurred, such as ataxia, weakness, numbness, disturbance in speech, chewing, and swallowing. Infants born with severe developmental disabilities from the poisoned pregnant women were reported. After that, the illness was called Minamata disease [36].

It is reported that organic mercury influences the dorsal root and trigeminal ganglia and causes paresthesia, usually just before causing widespread CNS dysfunction [20]. In nerve conduction studies, motor abnormalities were much more frequently reported than sensory abnormalities. Most frequently, findings were prolonged latencies and reduced amplitudes in both motor and sensory nerves. Nevertheless, interestingly, those abnormalities were shown more often in upper extremities, not lower extremities, a finding that differs from expectations [37]. Electromyography (EMG) was less frequently performed in the studies but reported results were always abnormal. The most frequently reported EMG findings (fibrillations, positive waves) were suggestive of active denervation and also reinnervation (prolonged motor unit potential duration, polyphasic motor unit potential durations) [38]. Electromyography (EMG) was less frequently performed in the studies but reported results were always abnormal. The most frequently reported EMG findings (fibrillations, positive waves) were suggestive of active denervation and also reinnervation (prolonged motor unit potential duration, polyphasic motor unit potential durations) [20].

2.4 Cadmium (Cd)

Cadmium is a highly toxic heavy metal. According to Agency for Toxic Substance and Disease Registry, Cd is the 7th most toxic heavy metal. The biological half-life of Cd is about 20–30 years in humans [39]. Cd exists naturally in unrefined rocks. Several sources of human exposure to Cd include mining works, contaminated groundwater use, commercial products (batteries, color pigments, several alloys, and Polyvinyl chloride, phosphate fertilizer) [40].

Exposure to Cd can be occurred by inhalation and also ingestion. It can accumulate into the lungs, olfactory bulb, and kidney [40]. Suggested mechanisms of Cd neurotoxicity include increased lipid peroxidation associated with oxidative stress and causing injury to the microvasculature of the brain. Experimental studies show that rats exposed to Cd, accumulation in choroid plexus, and Cadmium-related lipid peroxidation were demonstrated in brain areas such as the cerebellum and cerebral cortex [41, 42]. Cd neurotoxicity might be caused by defective neurogenesis, lead notably reduced neuronal differentiation and axonogenesis, leading to neuronal cell death [43].

Exposure to Cd causes very different neurological signs and symptoms of both the peripheral and central nervous systems. These are mental retardation, learning disabilities, behavioral pathologies [44]. Moreover, there is growing evidence about Cd-dependent neurotoxicity being one of the possible etiological factors of neurodegenerative diseases such as Alzheimer's, Parkinson's diseases, and sporadic amyotrophic lateral sclerosis [45, 46]. However, Little is known about the influence of cadmium on the peripheral nervous system. Experimental studies have shown that Cd can be a potent neurotoxicant for the peripheral nervous system. Viaene et al. investigated the influence of Cd on polyneuropathy in 13 retired, long-term Cd-exposed workers. They performed the neurological clinical examination, nerve conduction studies, and needle EMG were performed in the study. 54% of the retired Cd workers were diagnosed with polyneuropathy. The authors concluded that increased Cd body burden promotes PNP development at older age [47].

There is no consensus in the literature regarding the treatment of Cd toxicity. While clinical treatment protocols exist for the use of Ethylene Diamine Tetra Acetic Acid (EDTA), 2,3-Dimercapto-1-propane sulfonic acid (DMPS), and meso-2, 3-dimercaptosuccinic acid (DMSA), there are limited human studies. EDTA is the agent most widely accepted for clinical use. It should be noted that these chelation treatments applied during acute poisoning may aggravate damage to the

renal tubules. EDTA, which has a long history of safe use, is approved by the FDA to chelation heavy metals. It should not be given faster than one gram per hour nor in dosage greater than three grams per session. Cd is also significantly present in sweat during sauna, which appears to be a moderately successful modality for reducing the body burden of Cd without risk of tubular damage [48–50].

2.5 Tallium (T.I.)

Thallium is one of the heavy metals found in the earth's crust. Tl is colorless, odorless, and tasteless, and it has been used as a pesticide and rodenticide. Although the use of T.I. in this field has been abandoned in most western countries, there are still countries where it continues to be used. Thallium has been used in a wide variety of industries fields such as electronics, lamps, jewelry, pigmentation [51].

Thallium can contaminate by skin contact, inhalation of contaminated air, or food consumption from contaminated soil or water. Suggested mechanisms of T.I. neurotoxicity include lipid peroxidation and lysosomal enzyme beta-galactosidase in brain regions [52].

Toxication of T.I. causes neurological and non-neurological disorders. Anorexia, vomiting, gastrointestinal bleeding, abdominal pain, alopecia, cardiac arrhythmias are the best-known disorders. In a dose-dependent manner, neuropsychiatric signs have been reported as following; coma, delirium, seizure, hallucination, fatigue, emotional changes, ataxia, and loss of sensation, cranial neuropathy, and polyneuropathy [51, 53, 54]. Thallium-related polyneuropathy can become evident within 1–2 days. It is reported that a painful sensory-motor polyneuropathy mimicking Guillain-Barre's syndrome occurs. In delayed admission, patients are more prone to severe polyneuropathy and other neurological disorders [51, 55].

Treatment for thallium intoxication consists of termination from exposure, supportive care, and enhanced elimination. Prussian blue is approved as an oral agent to prevent absorption of thallium. It is reported that hemodialysis combined with the usage of Prussian blue helps treat patients even delayed admission [51, 55, 56].

3. Solvents

Solvents used in industry as degreasing agents, adjuvants, thinners, and cleaners are widespread. N-Hexane, carbon disulfide, ethylene oxide are widely used solvents [57]. Adhesives containing n-hexane are also widely used in the manufacture of leather goods [58]. Repeated occupational exposure of solvents can be both inhalation and skin contact. While the hexane concentration limit of organ damage through prolonged or repeated exposure is suggested as 5%, the organic solvents used in the adhesives may contain a higher percentage of n-hexane [59]. The toxic effects of organic solvents can be considered a public health problem even though regulations have been made that reduce usage limits [60]. The organic solvent syndrome is the mildest form of chronic exposure. Irritability, fatigue, and reversible difficulty to concentrate are the related symptoms [61]. The neurotoxicity of solvents may occur in both the peripheral nervous system and central nervous system [62].

3.1 N-hexane

The molecular mechanisms of peripheral neuropathy induced by hexane exposure have been investigated in several studies. ɣ-diketone 2,5-hexanedione, which is a neurotoxin, is the metabolite of n-hexane. ɣ-diketone 2,5-hexanedione is

the cause of sensory or sensory-motor peripheral neuropathy [63–66]. According to the suggested mechanism, the accused metabolite reacts with amino groups of proteins, including neuroproteins. Lysine-rich neuroproteins are especially vulnerable, including microtubule-associated proteins required for axonal transport. Disruption of axonal transport causes consecutive degenerative changes resulting in localized demyelination and remyelination, with initial changes in the most extensive and most prolonged axons in peripheral nerves and the spinal cord, with similar changes in shorter nerve fibers at a later stage. It results in distal symmetrical sensorimotor neuropathy supported by central-peripheral distal axonopathy [63].

Detailed neurological and neuropsychological examinations are recommended to confirming the clinical findings of central and peripheral nervous system dysfunctions in case of suspicion of toxication. Sensory abnormalities such as insensitivity to pinprick and touch, impaired two-point discrimination, changes in sensation to position, vibration, or temperature, diminished deep tendon reflexes are common neurological findings. Peripheral neuropathy is characterized by symmetrical progressive distal sensory and motor impairment [61, 62, 64]. Nerve conduction studies and electromyography should be performed to confirm peripheral neuropathy. It is reported that severe exposure and affected patients may develop muscle atrophy and foot drop [62]. Typical electrophysiological findings increase in distal latencies, slowing of nerve conduction velocities, conduction block with temporal dispersion, and the slowing down of transmission in electromyography in subjects with severe neuropathy [58, 62]. Neuroimaging Cranial magnetic resonance imaging (MRI) should be performed to detect the atrophic changes in the frontal lobes and cerebellum and white-matter lesions described after exposure to certain solvents [67, 68]. It is reported that acute, low-dose exposures might be related to specific changes in test performance, which improve after withdrawal from exposure. However, chronic exposure can also be associated with permanent cognitive changes [67].

3.2 Carbon disulfide

Carbon disulfide (CS2) is an organic solvent used for various industrial purposes, such as an insecticide, fresh fruit conservation, disinfectant against insects [69]. CS2 is a significant metabolite of the drug disulfiram used as a dissuasive for alcohol abuse. The occupational CS2 exposure can be by inhalation and skin contact. It is known that the highest degree of exposure is in the viscose rayon industry [70]. Exposure to carbon disulfide is likely to occur for the general population by inhaling contaminated ambient air, eating vegetables and fruits, or other food products containing carbon disulfide [69]. Since carbon disulfide has lipophilic nature, the distribution of C.S. 2 is easily in organs such as the brain and liver. C.S. 2 is metabolized to thiocarbamates in these organs, and it is considered that dithiocarbamates can take part in neurotoxic effects [71].

According to acute or sub-acute high-level exposures of CS2 can lead to unconsciousness, hallucinations, emotional lability, extrapyramidal signs, and polyneuropathy [69, 70]. It is reported that exposure of 200 to 500 ppm may cause death [69]. Peripheral neuropathy and extrapyramidal signs have been reported following chronic occupational low-level exposures. In low level (10 to 40 ppm) exposure, peripheral neuropathy may be asymptomatic and detected only electrophysiologically. As the concentration of CS 2 increases (20 to 60 ppm), a progressive sensorimotor distal asymmetrical polyneuropathy appears [72].

In neurological examination, findings include; paresthesia and dysesthesia tend to occur in a ‘stocking and glove’ distribution, loss of ankle and patellar reflexes, and diminished pain, touch, and vibration sensation in the distal lower limbs. In

some cases, recovery may be slow and incomplete, possibly because of residual axonal damage [73].

There is no typical clinical profile and routine laboratory tests, including cerebrospinal fluid (CSF) examination. Nevertheless, CSF should be performed for differential diagnosis. Nerve conduction studies and electromyography should be performed to confirm peripheral neuropathy. It is reported that long-term exposure and a cumulative dose of CS2 exposure are related to electrophysiological findings [74]. In the electrophysiological examination, reduced motor and sensory amplitudes, slightly slowed motor conduction velocities prolonged distal latencies are reported in exposed patients with neuropathy symptoms. In the same patient group, needle EMG revealed chronic, length-dependent denervation with decreased recruitment, large motor units, and fibrillation potentials [75].

3.3 Ethylene oxide (EO)

Ethylene oxide is a powerful sterilizer for medical materials and antiseptic for furs and some foods. It is a gas at room temperature. The occupational EO exposure can be by inhalation. Since EO is a water-soluble substance, it can quickly spread to all organs shortly after inhalation exposure [72]. EO is a potent alkylating agent and can interact with all cellular components, including DNA [76].

The principal neurotoxicant effect of EO is polyneuropathy. EO-related distal symmetrical axonal polyneuropathy has been reported in several cases reports in the 1980s, and Ohnishi et al. established an experimental model of EO neuropathy [77–80]. Kuzuhara et al. showed axonal degeneration with mild changes of the myelin sheath in sural nerve biopsies [79]. Neurotoxic effects may develop in both intermittent high doses and chronic prolonged low-dose exposure [72]. Gross et al. reported four cases who had occupational EO exposure. One of the cases had encephalopathy syndrome, and three of them had polyneuropathy [80]. In clinically symptomatic cases, distal extremity numbness and weakness, diminished sensation in the feet and hands can be initial symptoms. However, some of the cases can be asymptomatic. The electrophysiological examination reported reduced motor and sensory amplitudes and mildly slowed motor and sensory nerve conduction velocities [80, 81]. Gradual improvement of neurotoxicant effects was found associated with withdrawal from exposure [81].

4. Medications and peripheral nervous system toxicity

Antineoplastic drugs' most frequent and sometimes serious complication is chemotherapy-induced peripheral neuropathy (CIPN). The estimated prevalence of CIPN is 19–85% [82]. Compared to other peripheral neuropathies, such as painful diabetic polyneuropathy, patients with CIPN are likely to develop more severe symptoms, suffering from pain affecting both feet and hands, with faster progression. The high prevalence of CIPN among patients with cancer poses a serious problem for both patients and doctors administering the treatment. Due to the CIPN and related symptoms, sometimes it may be necessary to interrupt, stop, or reduce the dose of drugs, limiting the treatment's efficacy [83].

Platinum analogs (Cisplatin, oxaliplatin), taxanes (Paclitaxel), vinca alkaloids, and proteasome inhibitors (bortezomib) are the most commonly preferred antineoplastic medications. These are successfully used as first-line treatment for several solid and blood cancers, such as breast, lung, colorectal, gastric cancers, and multiple myeloma [84]. Although these antineoplastic medications have different chemical structures and mechanisms, chemotherapy-induced peripheral

neurotoxicity (CIPN) is one of their common side effects. The occurrence of CIPN varies according to the chemotherapeutic drugs, dose, duration of exposure, and method of assessment [85]. The highest rate of CIPN is reported in platinum analogs (70–100%), taxanes (11–87%), thalidomide, and its analogs (20–60%), and ixabepilone (60–65%) [86].

4.1 Platinum analogs; cisplatin, carboplatin, oxaliplatin

Platinum analogs interact with DNA, forming platinum-DNA compounds and cause apoptotic cell death. Most platinum analogs cause some degree of neurotoxicity. Dorsal root ganglion (Drg) is considered to be the primary target of neurotoxicity. It has been shown that platinum analogs cause apoptosis in dorsal root ganglia and morphological changes in the nucleus in-vitro [84]. Because of the lack of blood–brain barrier protection and be vascularized by fenestrated capillaries, the nuclei of Drg neurons are vulnerable to chemically-induced damages [87]. Platinum analogs induced peripheral neuropathy is a sensory neuronopathy caused by direct damage to Drg neurons, leading to an anterograde axonal degeneration. According to sensory neuronopathy, altered touch sensation, paresthesia in the distal extremities, tingling, altered touch sensation, proprioceptive loss, areflexia, and sensory ataxia occur. Patients frequently experience painful sensations, including spontaneous burning, electric shock-like pain, along with mechanical or thermal allodynia or hyperalgesia. Neuropathic pain symptoms have been reported, often even after treatment discontinuation [88, 89].

Since the 1980s, Cisplatin has been used to treat testicular, ovarian, and small cell lung cancers. Cisplatin administration induced severe toxicity, especially to the kidneys and nervous system [90]. Cisplatin causes primarily sensory neuropathy, characterized by distal parenthesis, progressing to proprioceptive loss, areflexia, and sensory ataxia [88]. Symptoms arise after cumulative doses above 300 mg/m2. Severe symptoms related to neuropathy have been reported to occur three to six months post-treatment cessation [91]. Electrophysiological studies have typically shown marked reduction in sensory action potential amplitudes with relative preservation of conduction velocity, indicative of axonal loss [84, 91]. Motor and autonomic symptoms and signs are infrequent but may occur in severe cases. Treatment with platinum analogs has been rarely associated with acute inflammatory demyelinating polyradiculoneuritis in patients with solid tumors [92].

Carboplatin is known to be less toxic, with neuropathy observed in 13–42% of patients. At the same time, carboplatin may induce mild neurotoxicity in quarter patients, with moderate to severe neurotoxicity in 5% of patients [93]. Peripheric neurotoxic side effects are common with high doses (800–1600 mg/m2) [94]. Electrophysiological studies reveal a reduction in compound sensory and motor amplitudes. Experimental studies have reported that at very high doses (10–15 mg/kg), carboplatin induces neurotoxicity and associated platinum deposition in the dorsal root ganglion, similar to Cisplatin [84].

Oxaliplatin has been effectively used as a first-line therapy against colorectal cancer. Its neurotoxicity may develop both acute and chronic. Acute and rapidly reversible peripheral neuropathy occurs in approximately 65–98% of patients within hours of drug infusion at a dose ranging 85–130 mg/m2 and may last up to one week. In 12 cycles of chemotherapy received, symptoms may persist up to 21 days or longer. Myelotoxicity and enteric and peripheral neuropathy may be induced by chemotherapy with oxaliplatin [95]. Cold-induced neuropathic symptoms are the most important difference in the clinical presentation between oxaliplatin and cisplatin-induced neuropathy [96]. Chronic peripheral neuropathy occurs in approximately 50–70% of patients, described as a pure sensory, axonal

neuropathy [95]. Patients frequently experience distal paresthesia, sensory ataxia, jaw pain, leg cramps. Electrophysiological studies of oxaliplatin-induced peripheral neuropathy reduce the sensory action potentials with preserved motor amplitudes and conduction velocities. However, spontaneous activity can be obvious, suggesting an immediate effect of the drug on the axonal excitability rather than structural damage [84, 97].

4.2 Taxanes; paclitaxel

Paclitaxel, docetaxel, cabazitaxel are the class of taxanes that act on microtubules, interfering with the normal cycling of microtubule depolymerization and polymerization. The incidence of CIPN according to taxanes may be very high (11 to 87%), and the highest rates are reported for Paclitaxel [98]. Neuropathy caused by taxanes usually emerges as a dominant sensory neuropathy with the stocking-and-glove distribution. The manifestations are paresthesias, dysesthesias, numbness, altered proprioception, and loss of dexterity predominantly in the toes and fingers. Motor and autonomic involvement are infrequent [99]. Neurological symptoms and findings are dose-dependent and tend to improve after stopping the treatment. However, some patients experience symptoms up to 1–3 years and sometimes lifelong after the therapy [100]. Microtubule disruption, mitochondrial dysfunction, axonal degeneration, altered calcium homeostasis, altered expression and function of ion channels, production of pro-inflammatory cytokines are the suggested underlying mechanisms of CIPN [101, 102].

Paclitaxel is a microtubule-binding antineoplastic drug commonly used to treat various solid tumors like lung, breast, and ovarian cancer. Paclitaxel is highly potent against proliferating neoplastic cells, but neurons not dividing cells are vulnerable to Paclitaxel. The treatment with paclitaxel affects the peripheral nervous system and primarily causes sensory axonal polyneuropathy [103]. Peripheral nerves biopsies have revealed a pathology of axonal degeneration, secondary demyelination, and, in cases of severe neuropathy, nerve fiber loss has also been observed [104].

4.3 Vinca alkaloids; vincristine

Vinca Alkaloids are developed from the Madagascar periwinkle plant, including vincristine, vinblastine, vinorelbine, and vindesine. These drugs are commonly prescribed to treat various tumors, such as Hodgkin and non–Hodgkin lymphoma, testicular cancer, and non–small cell lung cancer [102]. Vinca alkaloids have well-documented effects on microtubules – including binding to tubulin and inhibiting microtubule Dynamics [105].

Vincristine was approved in July 1963 by the United States Food and Drug Administration (FDA). It is one of the most common anticancer drugs used in pediatrics oncology. However, its clinical use is accompanied by severe side effects, such as peripheral neuropathy and neuropathic pain leading to treatment discontinuation. Both sensory and motor dysfunctions characterize peripheral neuropathy related to vincristine [106]. The duration and therapeutic doses received by patients directly affect the severity of symptoms. Besides sensory symptoms, patients also experienced muscle weakness and cramping. Changes in axonal transport and dorsal root ganglia resulting in Wallerian degeneration, altered ion channels activity and hyperexcitability of peripheral neurons, production of pro-inflammatory cytokines are the suggested underlying mechanisms of vincristine-induced peripheral neuropathy [101].

Vincristine use in Charcot–Marie–Tooth disease (CMT) patients has a black box warning added by the FDA. The CMT patients with the ERG2 gene mutation and

polymorphism in the CEP72 gene are associated with increased risk and severity of drug-induced neuropathy [107, 108].

There is no specific treatment for vinca alkaloid-induced peripheral neuropathy. Pyridoxine or pyridostigmine can be having a certain efficacy in vincristine-induced neuropathy. A topical capsaicin cream was demonstrated to give benefit in peripheral neuropathy. In neuropathic pain, carbamazepine, imipramine, or lignocaine can be used [101].

4.4 Proteasome inhibitors; bortezomib

Bortezomib is a reversible proteasome inhibitor antineoplastic drug that is successfully used against multiple myeloma and some types of solid tumors. It was first described as an inflammation inhibitor, but with its cytotoxic effects, it began to be used in cancer therapy. Bortezomib was approved in 2003 by FDA as a single agent against advanced myeloma but is now mostly used in combination therapies [109]. Although bortezomib is generally well tolerated, the most frequent limiting factor for its clinical use is a painful peripheral neuropathy side effect. Bortezomib-induced peripheral neuropathy is attributed to paresthesias, dysaesthesias, burning sensations, numbness, sensory loss, reduced proprioception, and vibratory sensation. Besides these symptoms and signs, demyelinating neuropathy may also be present. Deep tendon reflexes and autonomic innervation of the skin are reduced in patients treated with bortezomib [110]. Chronic, distal, and symmetrical sensory peripheral neuropathy is typical neuropathy induced by bortezomib.

Neuropathic pain symptoms have been reported to continue for weeks, months, or even years after treatment discontinuation.

Bortezomib-induced peripheral neuropathy is reported in approximately one-third of the patients [111]. Suggested mechanisms of bortezomib-induced peripheral neuropathy are increased sphingolipid metabolism in astrocytes, inflammation related to TNFa and IL-1, mitochondrial damage, reactive oxygen radical production, and alteration in Ca++ signaling [101].

5. Others

5.1 Acrylamide

Monomeric acrylamide is a potent neurotoxin used in different industrial and laboratory processes. Acrylamide is readily absorbed by inhalation, ingestion, or dermal contact. The acrylamide exposure affects the central nervous system (CNS) and peripheral nervous system (PNS). Chronic and high-level exposure to this water-soluble chemical mostly causes peripheral neuropathy. The peripheral neuropathy causes impairment in the arms and legs of exposed workers. Several studies reported that short-term occupational exposure to acrylamide resulted in weakness of lower extremities, loss of deep tendon reflexes and sensations in distal limbs, and numbness preceded by skin peeling from the hands [112–114]. Moreover, it has been shown that longer exposure involved more severe symptoms, including cerebellar dysfunction followed by peripheral neuropathy. Based on numerous investigations and risk assessments, acrylamide is generated in food preparation processes involving high temperatures [115, 116]. Different pathogenetic mechanisms were hypothesized; however, the exact mechanism of action is not completely elucidated. Like other toxic neuropathies, the prognosis of neuropathy is associated with the degree of central axonal degeneration. Three important hypotheses currently considering acrylamide neurotoxicity include inhibition of kinesin-based

fast axonal transport, alteration of neurotransmitter levels, and direct inhibition of neurotransmission [117].

5.2 Styrene

Styrene is a colorless solvent found in paints, plastics, and resins. It is one of the essential monomers usually used in plastic production. This compound can cause intoxication when inhaled in high concentrations for longer periods. There are few case reports regarding styrene-induced peripheral neuropathies. Early studies demonstrated abnormal neurological findings in humans exposed to styrene in low doses [118]. Styrene-induced peripheral neuropathy is characterized by neuropathic symptoms that start within a few days after significant exposure to styrene. Goba et al. reported that two workers presented with styrene-induced neuropathy. The workers had sensory-motor peripheral neuropathy of a demyelinating type [119].

5.3 Organophosphates

Organophosphates (OP) are chemical substances involved in the main components of herbicides, pesticides, and insecticides. Acute or chronic exposure to organophosphates causes several toxic effects in humans and animals. The exposure to organophosphates might be accidental or intentional. The organophosphate intoxication may occur after exposure to pesticides, either through occupational contact or suicide attempts. Acute toxic effects and delayed toxic neuropathy are related to central and peripheral nervous system involvement. The main effect of OP exposure is poisoning; however, peripheral neuropathy has been linked to chronic exposure. Several recent cases were reported associated with organophosphate-induced delayed neuropathy (OPIDN) after ingestion of organophosphate insecticides. The peripheral neuropathy associated with organophosphate intoxication may be seen with mild exposure. The mechanism of OPIDN is explained by loss of function of both motor and sensory axons located distally and ascending and descending tracts of the spinal cord [120, 121]. Organophosphate-induced delayed neuropathy is an uncommon clinical condition characterized by a distal paresis in the lower limbs and sensory symptoms. Electrophysiological findings show motor axonal neuropathy. The delayed onset of peripheral neuropathy and axonal motor involvement without a progressive course is needed for the diagnosis. Organophosphates can irreversibly bind to acetylcholine esterase (AChE) and prevent the breakdown of acetylcholine (ACh). The liberation of ACh overstimulates the muscarinic and nicotinic receptors. The main mechanism of OPIDN development is related to the inhibition of neuropathy target esterase (NTE) via phosphorylation. Neuropathy target esterase is an essential integrated membrane protein in neurons that takes part in axonal maintenance [122]. Its activity plays a crucial role in axonal maintenance since it facilitates the transport of macromolecules to the end of axons [120].

The symptoms are attributed to the effects on sensory and motor nerves with a typical axonal length-associated pattern. Lower extremities are predominantly affected. However, upper extremities are affected at higher OP exposure. The prognosis of peripheral neuropathy varies due to clinical involvement. It is primarily associated with the age of the individual (a younger age is associated with mild neuropathy), type of organophosphate, the persistence of myelopathic features, pyramidal involvement, degree of CNS involvement to peripheral nerve dysfunction [120, 123, 124]. There is no treatment approved for OPIDN, and the recovery is slow and partial. Thivakaran et al. reported a 15-year-old female who developed OPIDN with a smaller dose of chlorpyrifos [124]. Akçay et al. reported a similar

case diagnosed with organophosphate-induced delayed neuropathy (OPIDN) complicated with central nervous system findings. They observed partial improvement in muscle strength despite motor axonal polyneuropathy [125]. In addition, Moretto et al. reported electrophysiological findings in 11 patients with acute OP poisoning [126]. Three of these patients developed OPIDN, mainly sensory-motor polyneuropathy. The diagnostic approach should be made carefully in peripheral neuropathy patients, excluding other possible causes, especially those who did not display cholinergic toxicity before the onset of neuropathy. Early recognition of OP poisoning and a professional approach to intoxication can be life-saving.

6. Conclusion

Chemicals have toxic effects on the human body. Neurotoxicity demonstrates acute and chronic manifestations. A toxic chemical can produce an acute toxic response, besides prolonged exposure of a toxin may result in slowly developing chronic disease. In many cases, the putative neurotoxic damage present many years after initial exposure to the toxin. Therefore, the clinical signs elicited and symptoms expressed should be interpreted carefully. The neurotoxicity level and the circumstances of the exposure determine clinical presentation. The clinical signs and symptoms due to neurotoxicity may be expressed in central and peripheral nervous systems. Moreover, toxic agents disrupt cellular processes and result in epigenetic changes. While several heavy metals cause DNA damage which leads to carcinogenesis, the peripheral nervous system is also vulnerable to toxin-induced damage. A peripheral neuropathy may have its origin in the neurone, axon, myelin sheath or either Schwann cells. Patients may present with length-dependent sensorimotor peripheral neuropathy as well as mononeuropathy or radicular pathology. Organophosphates and acrylamide have been associated with severe damage to the motor nerve terminal. Many chemicals have the ability to cause axon damage including acrylamide, arsenic, carbon disulfide, n-hexane, lead, organic mercury, perhexilene, and thallium. Hexachlorophene and perhexilene have been involved in myelin disruption. Also, methyl mercury is well-known neurotoxin cause neuronopathy. Here, we discuss the peripheral nervous system manifestations of heavy metals, solvents, chemotherapeutics, monomers, gases and pesticides in detail.

Conflict of interest

The authors declare no conflict of interest.

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