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Review / Derleme

Neurotoxicological Effects of Environmental and Occupational Agents

Çevresel ve Mesleksel Ajanların Nörotoksik Etkileri

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Abstract

There are numerous chemicals throughout the world, some of which have a dose- or exposure-related toxic effect. The effects of iatrogenic causes in particular can be better defined. It is hard to prove that in laboratories toxic substances have toxic effects in everyday life, however (e.g. workplaces). Today, the pathophysiological effects of neurotoxic agents are still unknown. This review discusses the neurotoxic effects on the nervous system of scientifically established environmental and occupational agents.

Keywords: Neurotoxicity, environmental neurotoxins, occupational neurotoxins

Öz

Dünyada birçok kimyasal madde bulunmakta ve bu kimyasalların bir kısmının doz ya da maruz kalınan süre ilişkili toksik etkileri bulunmaktadır. Özellikle iyatrojenik nedenli olanların etkileri daha iyi tanımlanabilmektedir. Ancak, laboratuvarlarda toksik olduğu tespit edilen maddelerin günlük hayatta da (örneğin; işyerlerinde) toksik etkiye sahip olduğunu kanıtlamak zordur. Günümüzde nörotoksik ajanların patofizyolojik etkileri hala tam bilinmemektedir. Bu derlemede bilimsel olarak kanıtlanmış çevresel ve mesleksel ajanların sinir sistemi üzerine olan nörotoksik etkilerine değinilecektir.

Anahtar Kelimeler: Nörotoksisite, çevresel nörotoksinler, mesleksel nörotoksinler

Introduction

Throughout human history, toxins have attracted the attention of both researchers and many people interested in the subject. Apart from the biological toxins that take place in nature in different forms, with the development of industry, it is not possible to see the near or distant toxic effects of many chemicals, from radiation to environmental wastes and toxic agents, on all living things, and in some cases, it is not possible not to be exposed to these toxins (1).

Despite the increased awareness of the subject in recent years, it is difficult to fully reveal and describe the pathogenic effects of these environmental toxic agents. Especially in clinical practice, there are difficulties in the diagnosis and treatment of diseases that may develop due to exposure to toxins in different areas of working life. These difficulties can be listed as the fact that we do not know exactly how chemicals affect the systems, that we, as physicians, ignore the question of exposure to toxic agents when we encounter symptoms and signs of illness, and that our experience on the subject is limited. It would be valuable to know that many systems, from the cardiovascular system to the central and peripheral nervous systems, are affected at different intensities as a result of exposure to environmental or occupational toxins, and to use this information in our clinical practice (1,2). In this article, we aimed to review the neurotoxic effects of environmental and occupational agents in the light of the information in the literature and find out how we could raise awareness on the subject.

1. Basic Principles in Neurotoxicology

Today, the risk of neurological and neuropsychiatric diseases is gradually increasing as a result of exposure to heavy metals and many different environmental neurotoxic agents. Exposure

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to neurotoxins can affect any part of the central, peripheral, autonomic, or neuromuscular nervous system. In cases where no recent exposure to a neurotoxic agent has been reported, it is difficult to diagnose clinically (3).

In neurological diseases caused by known (classical) neurotoxins, the effect is usually symmetrical and non-focal. Symptoms almost always occur during or shortly after acute exposure. In thallium, arsenic, and organophosphate toxicities, which cause some toxic neuropathies, this period may extend up to 2-3 weeks. However, in neurological symptoms arising months to years after acute exposure, the doctor should eliminate the neurotoxic cause. Headache, cognitive and psychiatric disorders, visual disturbances, seizures, ataxia, tremor, rigidity, weakness, and sensory loss can be seen as symptoms. The clinic is often monophasic, and when the toxin exposure is terminated, it is expected that neurological symptoms will not progress and will decrease over time (4).

The situation is a little more complicated in cases where the history is not clear, or in chronic exposure. In clinical practice, non-specific symptoms can be confused with neurodegenerative, metabolic, nutritional, neoplastic, and psychiatric diseases (5,6). While the nanotechnology revolution has led to a wide variety of innovative products and applications, it has raised concerns about the potential exposure of the general population to the molecules and chronic neurotoxicological effects on the nervous system. Compared to larger particles, inhaled nanosized materials can cause deposition in the olfactory region during nasal breathing and transport to the olfactory bulb and brain. It has chronic neurotoxic effects with cumulative accumulation (3,7). Due to the detection of non-specific findings in laboratory, imaging, and electrophysiological examinations, difficulties in measuring the putative agent in body tissues (the level decreases as time passes), and the lack of an objective diagnostic criterion, neurotoxic diseases are on the list of differential diagnosis of almost all diseases in neurology clinics.

It may be difficult to determine when and how severe the toxin is exposed and to define the symptoms it causes in children or adults. For example; neurotoxic effects of methyl mercury, especially during intra-uterine development, have been demonstrated in both animal and clinical studies (8). Children who were exposed during prenatal development had more impairment in concentration, speech, and neuropsychological measurements than those who were not exposed (8,9). In adults, it was shown that methyl mercury exposure particularly affected the granular cells of the visual cortex and cerebellum (10).

The clinical picture that will emerge as a result of neurotoxic exposure is generally seen in all exposed individuals. If it is seen in a single person, it is difficult to explain that the clinical picture is caused by the toxin because the clinical symptoms are non-specific. Toxication can occur in a single person in cases where the chemical interacts with different substances (alcohol, cigarette, substance use, etc.) or when personal protection is not taken care of (use of mask, not washing after exposure, etc.) (11,12).

2. Neurotoxic Effect of Organic Chemicals

Acrylamide: Acrylamide (ACR) is a water-soluble vinyl monomer. It is used to produce polyacrylamide, which has wide applications in petrochemistry, papermaking, textile manufacturing, water treatment, and scientific research projects. The monomeric form of ACR is a water-soluble powder and is used in different chemical and industrial processes. While the polymer state is non-toxic, monoacrylamide has been found to exhibit neurotoxicity, carcinogenicity, and reproductive toxicity in various animal species (13). ACR has received wide attention around the world because it is produced during the cooking of processed starchy foods at temperatures >120 °C. It is found in baked, fried, and deep-fried foods that are commonly consumed (such as bread, french fries, chips, breakfast cereals, crackers, and biscuits). The average daily ACR intake for adults is approximately 0.5 lg/kg body weight (14). In a recent study conducted in our country with 263 participants, it was reported that the ACR level in Turkish coffee was below the toxicological reference values in terms of routine drinking frequency and volume dimensions (15).

The mechanism of ACR neurotoxicity is explained by impaired cholinergic transmission and redox imbalance in the central and peripheral nervous systems (16). In particular, ACR, which has a chemical relationship with glutathione, increases reactive oxygen radicals (hydroxide, hydroxy peroxide, nitrite), pro-inflammatory (TNF-alpha, interleukin-1b, nitric oxide synthetase) cytokines, lipid peroxidation, and oxidative stress. It has also been reported in current *in vivo* and *in vitro* studies that it causes a decrease in antioxidant capacity and may play a role in the etiology of neurodegeneration (15).

Clinically, peripheral neuropathy is the most common; however, symptoms may differ depending on the duration and severity of the exposure. It causes length-dependent axonal neuropathy that affects both motor and sensory fibers of varying severity (17). Sensory neuropathy findings often tend to improve, but cerebellar ataxia and spasticity are permanent. Large myelinated axons are involved early. Histopathology shows distal axonal neurofilament deposition, involvement of ascending sensory fibers in the posterior column, spinocerebellar pathways, and corticospinal pathways. Postganglionic sympathetic efferent nerve involvement is also responsible for sudomotor dysfunction (15,18). Confusion, hallucinations, decreased attention span, sleep disturbances, and encephalopathic changes are observed in acute high-dose exposure. Exposure to ACR has been shown to cause neurotoxicity, genotoxicity, developmental toxicity, and carcinogenicity in experimental models (19). In case of reports, it was reported that symptoms of parkinsonism, ataxia due to cerebellar dysfunction, hyperhidrosis, weight loss, muscle weakness, numbness in the extremities, and dermatitis might occur after 10 years of chronic exposure (11,20). The clinical manifestations can be summarized as acute/chronic encephalopathy, toxic neuropathy, and seizures (Table 1). Measurement of the hemoglobin-ACR compound in diagnosis can predict the development of peripheral neuropathy. There is no specific treatment. In recent studies in rats, it has been hypothesized that the notoginsenoside R1 molecule may show protective properties by stopping mitochondrial apoptosis caused by ACR (21).

Allyl chloride: It is used in the production of epoxy resins, some insecticides and polyacrylonitrile. Exposure causes toxic polyneuropathy (mixed sensorimotor distal neuropathy). The clinical status regresses and may improve upon the termination of exposure. Lipid peroxidation and antioxidation imbalance are blamed for the pathophysiology. There are studies suggesting that serum catalase and malondialdehyde levels can be used as biomarkers in early exposure. There is no specific treatment (12,22).

Table 1. Neurotoxic effect of organic chemicals

	Acute	Chronic
Acrylamide	Confusion, hallucination, sleep disturbance, encephalopathy	Peripheral neuropathy, parkinsonism, cerebellar dysfunction, hyperhidrosis, dermatitis
Carbon disulfide	Psychosis, somnolence	Behavioral, cognitive, memory impairment, decreased vision
Carbon monoxide	Multifocal neurologic findings, delirium	Chronic encephalopathy
Ethylene oxide	Reversible encephalopathy, severe headache, nausea	Peripheral sensorimotor axonopathy, polyneuropathy, mild cognitive impairment
Hexocarbon	Headache, hallucination, euphoria	Progressive sensorimotor polyneuropathy
Methylbromide	Delirium, encephalopathy, psychosis, ataxia, myoclonus	Polyneuropathy
Organochloroquine pesticides	Delirium, coma	Mild cognitive impairment, benign intracranial hypertension, tremor, ataxia
Organophosphates	Cholinergic crisis	Polyneuropathy
Tolven	Central nervous system depression, narcosis effect	Parkinsonism, pancerebellar disorder
Trichloroethylene	Headache, nausea	Facial muscle weakness, ptosis, vocal cord paralysis, chronic encephalopathy

Carbon disulfite: It is used in solvents or stain removers, some varnishes and insecticides, perfumes, and the ebonitization of rubber, in the production of rayon and cellophane films. It is transmitted by inhalation, gastrointestinal tract (GIS), and transdermal route. Acute exposure causes psychosis and drowsiness. Long-term subacute exposure; causes memory, behavioral and cognitive impairments, as well as nerve demyelination, cyto-structural damage, and progressive paralysis of the extremities. Extrapyramidal or pyramidal deficits have been reported in cases with decreased vision, and loss of pupillary and corneal reflexes. In a study conducted in 2018 in which 372 patients with chronic carbon disulfide exposure were examined; it was reported that 84.7% had sleep disorders, 84.4% dizziness, 79.8% headache, and 72.8% numbness in the extremities (23). However, the mechanism of its neurotoxicity is not known yet, and it is hypothesized that it may trigger reversible central neurochemical effects that impair the vestibulo-ocular reflex (24). Epidemiological studies of chronic exposure have shown conflicting results, particularly with regard to the reproductive and cardiovascular systems. The therapeutic and bioregulatory effects are also discussed today. Central deficits may be permanent. There is no specific treatment (Table 1) (25,26).

Carbon monoxide: It is the most common cause of death from toxicology. It is an undetectable gas because it is tasteless, colorless, and odorless. Intoxication is common in miners, oil and repair shop workers. Severe poisoning may occur as a result of poorly ventilated home heating systems, stoves, and suicide attempts outside the workplace. Tissue hypoxia occurs by decreasing the oxygen-carrying capacity of the blood (27). Acute intoxication symptoms are non-specific, such as headache, dizziness, nausea, and drowsiness, and the history is the most important stimulant for clinical suspicion. Upon clinical suspicion, COHb, CO levels, cardiac and neurological examination, brain imaging [brain tomography, magnetic resonance imaging (MRI), MR spectroscopy] methods, and neurophysiological tests should be performed in the diagnosis (28). Structural brain damage is observed due to anoxia. While the globus pallidus and cerebral white matter are most frequently affected in radiological imaging, the infratentorial area is rarely involved (Figure 1) (29). Chronic encephalopathy syndrome occurs with chronic exposure. In severe cases, the damage is permanent. It is recommended to add diffusion-weighted images and spectroscopy to conventional MRI sequences, as only diffusion restriction can be detected on imaging, albeit rarely. This is valuable both in the diagnosis of delayed CO leukoencephalopathy and in the determination of prognosis (30). In pathology studies, bilateral necrosis of the globus pallidus is a typical pathological finding, but not specific. In addition, necrosis in the hippocampus, diffuse atrophy in the cerebral cortex, and severe demyelination in the centrum semiovale are detected; axons are relatively preserved. However, these findings are also not specific; similar findings are also observed in hypoxic-ischemic events. The prognosis is poor. Partial or complete recovery is observed in 10%. Patients die due to multifocal neurologic findings, delirium, and akinetic mutism. The place of hyperbaric oxygen in treatment is controversial. In studies conducted in our country, it has been noted that the first treatment for CO poisoning is 100% oxygen for at least 6 hours and that hyperbaric oxygen therapy can be administered in order to reduce the half-life of COHb, taking into account prognostic factors, but national protocols are needed. In our clinical experience, we think that hyperbaric oxygen therapy provides partial benefit in some patients both clinically and radiologically (Figure 1, 2) (31,32).

Ethylene oxide: It is used as an alkylating agent in the sterilization of medical materials and chemical synthesis. The by-product ethylene chlorohydrin is very toxic. It has been used in salted spices and vegetable-based seasonings for a while, but it has been revealed that ethylene oxide reacts with organic spice components and causes toxic residues. Therefore, the use of this substance in spice irradiation is prohibited. Severe headache, nausea, and severe reversible encephalopathy are observed in acute exposure, while it causes peripheral sensorimotor axonopathy and mild cognitive changes in chronic exposure. Ethylene oxide remaining in the tubes during dialysis creates the risk of polyneuropathy in the patient (33).

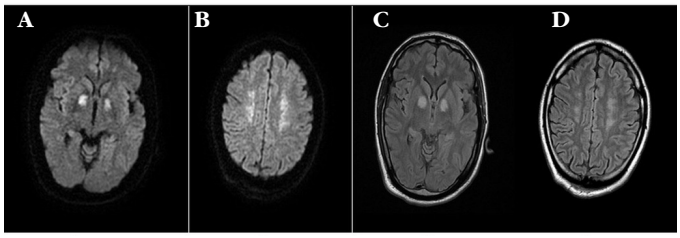

Figure 1. A 31-year-old male, carbon monoxide intoxication; signal increase in bilateral globus pallidus in diffusion-weighted images (A, B) and FLAIR (C, D) magnetic resonance imaging

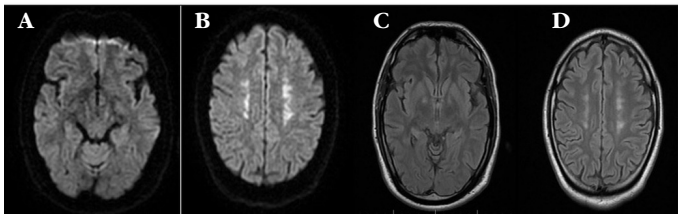

Figure 2. A 31-year-old male, carbon monoxide intoxication, clinical improvement after hyperbaric oxygen therapy, significant regression of the lesions in diffusion-weighted images (A, B) and FLAIR (C, D) magnetic resonance imaging performed at the 3rd week

It causes neuropathy limited to the cranial nerves in those exposed to trichlor ethylene and another ethylene derivative, perchloroethylene solvents, which are used in long-term anesthesia from other ethylene derivatives. It is included in the differential diagnosis of trigeminal neuropathy and optic neuropathies. Protective respiratory devices should be used in sterilization processes using this substance, especially for healthcare workers (11,12).

Hexocarbon solvents: The metabolite 2.5 hexanedione is responsible for neurological toxicity. These substances are used as solvents in varnish, painting inks, rubber, and some adhesives. It is also used in the production of acrylic coating and in the shoe industry. Exposure is by inhalation or skin contact. Acute inhalation causes euphoria, headache, and hallucinations, while chronic inhalation causes insidious sensorimotor polyneuropathy. Skin exposure also causes progressive distal sensorimotor axonal polyneuropathy. Axonal transport disorder plays a role in its pathophysiology, and myelin retraction or focal demyelination is detected in areas of giant axonal swelling (20). Different from other toxic neuropathies in its electrophysiology, demyelination findings are detected. Central involvement can be detected by showing sensory evoked potential abnormalities. Post-exposure symptoms may progress for 1 month. Polyneuropathy partially resolves up to 2-3 years. In severe forms, the damage is permanent (11,12,34).

Methyl bromide: Methyl bromide (MB) is a highly toxic pesticide that, in addition to being an ozone depletion agent, causes acute or chronic toxicity to fumigators and related workers (35). It is found in fire extinguishers, coolant sprays, insecticides, and disinfectants. It is odorless and colorless. Acute inhalation causes encephalopathy, delirium, headache, nausea, confusion, psychosis, changes in affect, myoclonus, ataxia, visual disturbances, and chronic exposure causes polyneuropathy without systemic symptoms. Optic atrophy and upper motor neuron changes are other long-term exposure complications that may be encountered. Diagnosis is made by measuring MB levels in serum or urine (36). A hemodialysis is a treatment option, and chelation therapy is controversial. The prognosis is generally good (11,12). Park et al. (36) reported that electroencephalographic changes were observed in asymptomatic patients and that careful monitoring of personnel at risk was recommended.

Methyl alcohol: It is found in many substances such as paint, polish, de-icing solutions, antifreeze, and gasoline mixtures in the industry. Formaldehyde and formic acid are metabolites responsible for toxication, toxic symptoms occur due to metabolic acidosis. Intoxication occurs mostly orally (fake alcohol, etc.), rarely by inhalation and skin. Symptoms are related to the central nervous system (CNS), visual system, and GIS. Headache, dizziness, visual disturbances (seeing a blizzard), confusion, acute renal failure, abdominal pain, and pancreatitis symptoms occur, and extrapyramidal and dementia findings may be observed in chronic or severe toxication. It can result in serious consequences such as blindness and death. The most known intoxication in the world was the event in which 323 people were poisoned and 41 died in 1951 due to fake whiskey containing 35-40% methanol. In our country, there are publications reporting that many people die because of intoxication caused by fake alcohol (37,38). The inhalation limit recommended by ACGIH (Association Advancing Occupational and Environmental Health, USA) is 200 ppm on average in 8 hours, the health-threatening level is 6000 ppm. The maximum permissible concentration in skin contact is 200 ppm (270 mg/m^3) (39,40,41).

Although there is no specific finding on imaging, it has been reported in the literature that neuron degeneration and hemorrhage in the parietal cortex can be detected in 85.7%, putaminal lesions in 7.7%, and spongy lesions in the optic chiasm in 7.1% (42). A case of methyl alcohol intoxication diagnosed in our clinic had bilateral putaminal involvement in MRI scans (Figure 3). Providing airway patency, perfusion and ventilation is the mainstay of treatment. In the acute phase, gastric lavage may be partially effective. The main treatment is the administration of one of the ethanol or fomepizole antidote treatments. Indications for starting treatment are a plasma methanol concentration of ≥20 mg/dl (6.2 mmol per liter), an osmolar gap of >10 mOsm/L per liter with confirmed toxic methanol ingestion, and the presence of at least two of the next three conditions with a strong suspicion of methanol poisoning: Arterial pH below 7.3, serum bicarbonate level below 20 mmol/l, osmole deficit above 10 mOsm/kg (43). Hemodialysis is another treatment option. In addition, it is

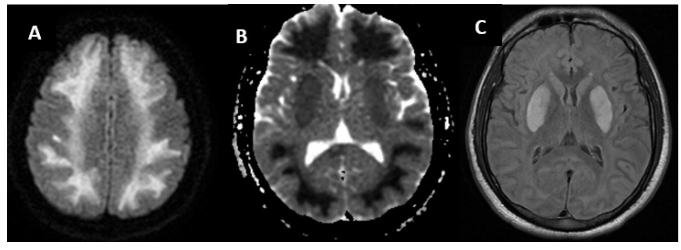

Figure 3. A 42-year-old female patient, methyl oxide intoxication, A. widespread deep white matter involvement in diffusion-weighted images magnetic resonance imaging (MRI), B. deep white matter involvement areas in ADC map MRI, C. bilateral putamen involvement in FLAIR MRI

recommended that all patients receive folic or folinic acid at a dose of 50-100 mg intravenously every 4 hours. In addition, it may be necessary to give very high amounts of bicarbonate ($NaHCO_3$) to reach normal pH values (44).

Orgonochloroquine pesticides: Delirium and coma are observed in acute high-dose toxication of this substance, known as dichl orodiphenyldichloroethylene. Mild cognitive disorders, benign intracranial hypertension, tremor, and ataxia can be observed in chronic exposure. There is no specific treatment and symptomatic treatment is recommended (11,12).

Organophosphates: Although often used as pesticides or herbicides, they are also used as petroleum additives, lubricants, antioxidants, fire retardants, and plastic modifiers. Examples of this group are triorthocresyl phosphate, leptophos, trichlorfon, mipafox, chlorfibros, dichlorvos, monocrotophos, malathion, and parathion. The mechanism of action of intoxication is inhibition of the neuropathy target esterase (NTS) enzyme found in all neurons. Toxicity may develop from the skin, the GIS, and by inhalation. The main intoxication picture, which can be fatal, is the cholinergic crisis. In this case, the symptoms are nausea, increased salivation, headache, weakness, bronchospasm, tremor, chest pain, pulmonary edema, bradycardia, cyanosis, convulsion, and in most patients coma. In treatment, intravenous pralidoxime (1 g) and subcutaneous atropine (1 mg) should be administered together. However, adequate respiratory support must be provided before treatment. Although serum acetylcholinesterase level remains abnormal for a long time, the clinical status begins to improve within 1 week (45,46).

The worldwide accepted biomarker for acute organophosphate poisoning is the measurement of serum paraoxonase level. Carbamate insecticides may also cause a similar condition, but the clinic is milder and the treatment response to atropine is better.

The second clinical condition associated with acute exposure is late polyneuropathy (after 2-3 weeks) which occurs before a cholinergic crisis occurs. This clinic is found in many patients, especially with the use of alcohol together with triorthotrexil. However, the existence of such a condition related to chronic low-dose exposure has not been scientifically proven. The sensory deficit is detected in neurological examination, the Achilles reflex is typically absent. Over time, upper motor neuron findings accompany the clinical picture but, the cranial nerves are typically spared. Although its neurotoxic mechanism of action is not fully understood, it acts with different mechanisms ranging from acute acetylcholine esterase inhibition to oxidative stress, axonal transport deficit, neuroinflammation, and autoimmunity. In neuropathy, the measurement of NTS in lymphocytes can be used as a clinical biomarker. The period that develops with acute cholinergic crisis and neuropathy is defined as an intermediate syndrome. Neuropathy has a good prognosis. Dipperflue syndrome is another clinical condition identified in farmers exposed to substance intoxication. After organophosphate suspected exposure, the complaints like headache, pharyngitis, myalgia, and non-specific sensory symptoms can occur (45,46). In a current review on the relationship between microbiota and organophosphate, publications showing that microbiota amount decreased after organophosphate poisoning were shared. The authors suggested further investigation of this issue with next-generation sequencing targeting 16S rRNA, as it might contribute to the mechanism of toxicity and improve existing clinical symptoms (47).

Solvent mixtures: It is a condition characterized by the deterioration of cognition in house painters who are exposed to organic solvents for the first time. In this syndrome, also called painter's encephalopathy, it is reported that cognitive and mental status isadversely affected due to long-term (more than ten years) low-level solvent exposure. However, since it is difficult to diagnose objectively, its recognition as an occupational disease and its widespread acceptance has led to controversy. It was defined as an occupational disease in the European Occupational Diseases List and the International Labor Organization Occupational Diseases List in 2009. A decline in memory and concentration are among the earliest symptoms. After cessation of exposure, the clinic usually does not progress, but cognitive impairment may persist even after exposure is discontinued (12). Studies have shown that in occupational exposure to hydrocarbon solvents, symptoms of Parkinson's disease may start early and the clinical findings may be more severe. There is less evidence that it precedes the onset of Alzheimer's disease and that it increases its severity (48).

Styrene: It is used in the production of plastics and some resins. It is transmitted by inhalation and skin. Decreased psychomotor performance has been reported in intoxication. Decreased color vision and contrast differentiation are among the clinical findings defined in intoxication (11,12).

Toluene: Toluene is used as a solvent in many areas of industry. It is often taken by inhalation and easily reaches the nervous system. The neurobehavioral and neurotoxic effects of toluene are well known in experimental models and animal studies; however, its genotoxicity is still discussed (49). Reactive oxygen species that cause oxidative stress and DNA damage play a role in toluene toxicity. It has been suggested that allergic stimulation may affect the toluene sensitivity threshold via modulation of neurotrophin-related genes. Therefore, it is reported that individuals with different immunogenetic backgrounds have different susceptibility to toxic chemical exposure. In animal experiments, it has been revealed that toluene-induced oxidative DNA damages cause genotoxicity in different brain regions, including the cortex, cerebellum, and hippocampus (49). Acute, high-dose toluene exposure causes depression and narcosis in the CNS. Multifocal irreversible CNS dysfunctions such as cognitive impairment, cerebellar intentional tremor, and ataxia are detected in chronic high-dose inhalation, which is frequently seen in adolescents. With continued use, dysarthria, nystagmus, visual, hearing, olfactory, and pancerebellar disorders develop. Parkinsonism findings (such as resting tremor, bradymia, and anteflexion posture) may also be seen in long-term exposure. On imaging, cortical and cerebellar atrophy, and multifocal non-specific lesions in cerebral white matter are observed. In pathological examinations, diffuse demyelination with relative preservation of neurons is detected (50).

Trichloroethylene: It is a thinner used in dry cleaning and tire production. Intake is mostly by inhalation. It is also abused because it triggers euphoria. While non-specific findings (headache, drowsiness, etc.) are observed in acute low-dose toxication, encephalopathy accompanied by facial muscle weakness, ptosis, and vocal cord paralysis can be observed in chronic low-dose exposure (11,12).

The neurotoxic clinical effects of the mentioned organic chemicals are summarized in Table 1.

3. Neurotoxic Effects of Metals

The neurotoxic properties of metals and metalloids depend on several factors, including dose and route of exposure, chemical forms of the elements, metabolism (nutritional status, biochemistry of accumulation and detoxification), and kinetics (distribution and elimination).

Aluminum: Aluminum has no known biological role in the body, but adverse physiological effects of this metal such as the formation of oxidative stress have been observed in mammals. It is used in various cosmetic, pharmaceutical, and dental care applications in the industry (51). The tolerable upper limit for drinking water is 900 µg/l. Although it was reported in a study conducted in Iran that there was more aluminum in breast milk than in drinking water, the bias in the result should be taken into account because the total environmental aluminum exposure of these mothers was not known, and it could be concluded that different studies with appropriate methodology were needed for such an interpretation (51,52). While it remains unclear whether oxidative stress is a major cause or simply a consequence of cellular dysfunction associated with neurodegenerative diseases, accumulating evidence suggests that impaired mitochondrial energy production and increased mitochondrial oxidative damage are associated with the pathogenesis of neurodegenerative disorders. Aluminum, which is involved in the production of reactive oxygen species, can disrupt mitochondrial pathways and lead to oxidative stress. Therefore, it plays a role in the etiology of neurodegenerative diseases (51). It has been reported in some publications that aluminum, especially in vaccines and drug ingredients, causes autism spectrum disorder and autoimmune diseases; however, when the methodological features in the studies are taken into consideration it is a thought accepted by scientists that it is not appropriate to directly associate aluminum-containing substances in these etiologically multifactorial diseases (53). A blood aluminum level of 60 µg/l (2.3 µmol/l) is considered the critical limit. However, although the serum level is above 60 µg/l, dysfunction may not be seen in every patient. It cannot be said with certainty that there is no dysfunction below this level. Dialysis encephalopathy is observed in intoxication. Speech disorder, cognitive decline, seizures, and myoclonus are prominent in this clinical presentation (53).

Arsenic: Toxicity occurs when taken orally (trivalent form) in murder and suicide attempts. By inhaling molten copper and lead ores, arsenic compounds can be recovered. Chronic exposure is also induced by drinking arsenic-laced water, inhaling equipment or minerals, and using unlawfully forbidden arsenic-laced medications. Acute-subacute intoxication may result in headache, hypotension, tachycardia, vascular collapse and death. In chronic exposure, GIS disorders, and Mess lines (not specific) which are signs of nail matrix disorder can be observed (12). Various mechanisms appear to play a key role in arsenic neurotoxicity, such as oxidative stress, apoptosis, thiamine deficiency and decreased acetylcholinesterase activity are described. The observed neurotoxicity predominantly affects the sensory nerves, with less effect on the motor nerves. Recent studies have shown axonal degeneration mainly in small myelinated and unmyelinated fibers (26,28). Polyneuropathy can be detected by using electrophysiological examination in asymptomatic patients in the early period. Proprioception and vibration sense is often impaired. For this reason, it can be compared to tabes dorsalis. It may be confused with acute inflammatory demyelinating polyneuropathies (Guillain-Barré syndrome) clinically, considering that it initially starts with sensory symptoms, numbness in the feet, painful paresthesias, and later involvement in the hands. There is weakness in the distal extremity muscles and a stocking-and-glove sensory loss. When the exposure is terminated, symptoms may improve, but sequelae may occur in severe exposure. Subacute onset neuropathy, abdominal pain, tachycardia, vomiting, diarrhea, vasomotor collapse, and hypotension are observed in high-dose arsenic exposure. Changes in consciousness can be observed after GIS findings. Organic psychosis is also among the conditions that can develop. In addition, cognitive and behavioral disorders may accompany (12,54). In diagnosis, blood arsenic level is 7 ng/100 ml or above with normal cerebrospinal fluid (CSF) findings. In chronic exposure, arsenic can be detected in the hair, and nails, especially in the pubic area, even months and years later. In addition, high levels of arsenic in the urine are detected. Urine arsenic level above 25 micrograms/24 hours is abnormal and remains high for several weeks. Apart from toxic (inorganic) arsenic, there is also (organic) arsenic in seafood, so for the diagnosis of toxication, seafood should not have been eaten recently before the examination. On electrodiagnostic examination, nerve conduction velocities are slowed and typically denervation is observed in the distal extremity muscles. It is included in the differential diagnosis of demyelinating polyradiculopathy (loss of F response, slowing of motor conduction velocity and partial conduction block findings are common). In chronic exposure, axonal degeneration is detected in myelinated fibers in sural nerve biopsy. In treatment, effective chelators such as arsenic removal, British antilewisite, penicillamine, and water-soluble dimercaprol derivatives are used (Table 2). Chelator use in the early period may prevent the development of neuropathy (11,12,54).

Lead: Inorganic and organic lead compounds are toxic to human health. With the elimination of lead-containing paints today, symptomatic case reports are rare in North American and European countries. Absorption is by inhalation rather than the intestinal route. Blood lead level above 1.93 mmol/l has a toxic effect. Despite the dramatic decrease in death rates due to lead toxicity since 1960, side effects on mental and auditory functions and the development of children are seen due to its cumulative effects at low doses. Lead absorbed from all tissues primarily accumulates in bone tissue. Exposure to batteries, odor, dust, and spray containing lead, working in automobile radiator repair, working in the production of gasoline containing lead, working in the manufacture of weapons, and inhalation of lead-containing gas in manufacturers burning batteries as a fuel source are the main sources of exposure. Systemic symptoms such as abdominal pain, diarrhea, constipation, pale skin, headache, weight loss, and jaundice may occur (11,12,54). It is stated that increased capillary permeability, damage to the capillary endothelium, scattered hemorrhage areas, and cerebral edema may occur due to the rapid increase in lead levels in the brain as a result of acute lead exposure in children, leading to confusion, personality changes, seizures, and coma (54). Mental retardation, learning difficulties, hyperactivity, and behavioral problems may occur due to low dose chronic exposure, especially in children. In chronic exposure in adults,

Table 2. Chelation therapies and side effects

Dosage and Indication	Side effects
British antilewisite (BAL)	
1. Acute lead encephalopathy Dose: 75 mg/m² IM every 4 hours for 5 days 4 mg/kg every 4 hours in children and adults **2. Acute inorganic arsenic poisoning** Dose: 3 mg/kg IM every 4 hours for 48 hours and then twice a day for 7-10 days **3. Acute mercury poisoning** Dose: 5 mg/kg IM initially, then 2.5 mg/kg every 12 to 24 hours (maximum use is 10 days) until clinical improvement	Lacrimation, vomiting, salivation, rhinorrhea, headache, painful injection, injection site sterile abscess, hemolysis in those with G6PD deficiency, chelation of essential metals (long-term), decomposition with acidic urine, avoid in patients with peanut allergy
Dimercaprol derivatives (DMSA, succimer)	
1. Mild to moderate lead poisoning (acute or chronic) Dose: Children 350 mg/m² 3 times a day for 5 days, followed by 350 mg/m² twice daily for 14 days, adults 10 mg/kg 3 times a day for 5 days, 10 mg/kg twice daily for 14 days **2. Arsenic poisoning** Dose: 10 mg/kg/dose every 8 hours for 5 days **3. Mercury poisoning** Dose: 10 mg/kg orally 3 times daily for 5 days, then twice daily for 14 days if gastrointestinal tract is intact	Gastrointestinal side effects such as diarrhea and vomiting, metallic taste, slight increase in liver enzymes, rarely chills, rash and reversible neutropenia
Prussian blue	
1. Thallium poisoning Dose: 3 g 3 times a day for adults, a total of 9 g; for children 1 g 3 times a day 3 g in total **2. Cesium poisoning** Dose: 3 g 3 times a day for adults, a total of 9 g; for children 1 g 3 times a day 3 g in total	Constipation, abdominal pain, blue stools
CaNa2EDTA	
Sodium EDTA can cause life-threatening hypocalcemia and should not be used **1. Lead encephalopathy** Dose: 1500 mg/m²/day, approximately 50-75 mg/kg/day by continuous IV infusion, administer 4 hours after first dose of dimercaprola **2. Moderate lead poisoning (blood lead level <70 mg/dl)** Dose: CaNa2EDTA, 1000 mg/m²/day; 50 mg/m² every 4 hours, approximately 25-50 mg/kg/day of dimercaprol (the first dose of dimercaprol should be given 4 hours before the first dose of CaNa2EDTA to prevent redistribution of lead to the brain)	Renal failure, life-threatening hypocalcemia with use, weakness, headache, fatigue, chills or fever, myalgias, anorexia, sneezing, nasal congestion, anemia, transient hypotension, prolongation of prothrombin times
D-penicillamine	
1. Lead, mercury and copper toxicity Dose: 1-1.5 g/day, given orally in 4 divided doses. Rarely used due to significant complications and presence of more appropriate treatments	Allergic reaction (especially in patients allergic to penicillin), aplastic anemia, agranulocytosis, renal failure

personality changes, dementia, rigidity, epileptic seizures, optic atrophy, and visual disturbances may occur. In chronic exposure, bilateral radial nerve neuropathies may develop. Laboratory examinations show hypochromic microcytic anemia and basophilic streaking in erythrocytes. Slowing of conduction rates in nerve conduction study, lead excretion above 7.2 micromol/l in 24-hour urine, and blood levels above 3.8 micromol/l are detected. CSF examination is normal and urine lead level is increased (0.2 mg/l). In treatment; the first step should be the removal of the source causing lead exposure, initiation of antiedema treatment for increased intracranial pressure (mannitol, steroid, and ICP monitoring), chelators such as calcium, Ca-ethylene diamine tetra-acid, disodium versenate and penicillamine (in adults) can be added (Table 2). Recovery begins within 2 weeks from the start of treatment. The mortality rate in acute encephalopathy is less than 5% (12,54,55).

Manganese: Manganese (Mn), which is involved in the production of cellular metabolic signals, is found in industrial and mineral products. It often enters the body by inhalation. However, beyond occupational exposures, excessive dietary or drinking water intake are other sources of overexposure. The World Health Organization reported the daily Mn consumption amount for an adult to be between 0.7 and 10.9 mg (56). Although oxidative stress secondary to increased mitochondrial function and energy deficiency is held responsible for Mn-induced neurotoxicity, it is known in recent publications that Mn toxicity is multifaceted

and genetic modulation of Mn transport (uptake and flow) in the body plays a role in this toxicity, but the relationship between Mn exposure and neurotoxicological effects is explained below. The underlying molecular mechanisms have not been fully elucidated (57). In neurotoxicology, it causes significant neuronal loss in the basal ganglia, especially the globus pallidum. Mn is primarily excreted by the liver. In those with liver disease, its concentration in the brain increases due to overexposure. Mn is found in astrocytes in the brain. Recent studies have reported that the basis of excitotoxic neuronal damage caused by Mn is formed as a result of disruption of the astrocytic cycle of glutamine and glutamate. In addition, several genes responsible for its neurotoxic effect have also emerged. Clinically, it may present with psychiatric findings such as emotional lability and irritability. Weakness, impotence, parkinsonism, increased tone, increased deep tendon reflexes, and myoclonic jerks can be observed in the whole body. The blood Mn level is above 0.075 ppm. There is often no tremor. Motor symptoms may rarely improve with L-dopa treatment (54,57).

Mercury: Like aluminum, mercury can be found in industrial products and drinking water. The upper limit in drinking water is 1 µg/l (52). Inorganic mercury is used in the paper and pump industry, and in the manufacture of electrical materials and paints. Organic mercury is found in fish and animals living in polluted environments and in fungicides. Selective neurotoxicity caused by mercury is mentioned in genetic screenings in genetically traceable model systems such as flies, worms, and zebrafish, and in recent studies on human-based neuronal stem cell model systems. However, the pathophysiology of intoxication is not yet known. Mercury is toxic to cerebellum granular cells and occipital lobe neurons. Axonal degeneration and demyelination are seen in peripheral nerves. Early findings may include tremors in the extremities, head, tongue, and eyelids with intermittent panic, paresthesias in the extremities, progressive distal muscle weakness, and cerebellar ataxia. Peripheral visual impairment, blindness, speech disorder, and hearing difficulties can be seen. Seizures, mania, dementia, and hallucinations can be seen in severe patients. Psychomotor retardation and epileptic seizures can be seen in children (54).

Another clinical picture related to this metal intoxication is Minamata disease, which occurs due to the consumption of seafood obtained from areas contaminated with methylmercury. In this disease described 50 years ago, neurological findings such as stocking-and-glove sensory defect, ataxia, vision, and hearing loss are observed (58).

In the diagnosis, the amount of mercury in the hair sample is checked. Amounts of less than 100 ppm are asymptomatic and generally safe. The amount above 500 ppm is always associated with symptoms. In electrophysiological examinations, disorders due to central dysfunction are observed. Sensory symptoms are associated with the sensory cortex or dorsal root ganglion, not peripheral, while visual symptoms are associated with cortical involvement. Amyotrophic lateral sclerosis-like clinical picture or predominantly motor neuropathy after intense elemental mercury exposure were defined. In treatment; chelation with penicillamine, selenium, and vitamin E can reduce neurotoxic effects (58).

Thallium: It is widely used as an insecticide, rodenticide, and hair removal agent. Intoxications are seen due to accidental or suicidal ingestion by children. It is responsible for severe neuropathy and CNS damage. It causes damage to mitochondrial pathways, especially by causing oxidative stress in primary hippocampal neurons (59). Progressive neuropathic syndromes occur in seven days. It can cause cranial neuropathies, including optic nerve involvement and ptosis. In more severe patients, ataxia, confusion, and coma can be seen. In case of chronic progressive sensory neuropathy, alopecia observed 2-4 weeks after exposure is valuable in the retrospective diagnosis of thallium intoxication. The presence of thallium in body tissues or urine is essential for diagnosis. Absorption of orally ingested thallium may be inhibited by gastric lavage. Oral potassium ferric ferrocyanide (Prussian blue), which prevents intestinal absorption, together with intravenous potassium chloride, enhanced diuresis, and hemodialysis are useful in treatment (11,12).

Tin: Inorganic tin is used in industrial soldering, paint making, food packaging, and tin plates. Its inorganic form does not cause toxicity in the CNS. However, preservative forms for wood, textiles, glass, paper, and leather using the organic form of tin [triethyl and trimethyltin (TMT)] are toxic. In animal experiments, it has been reported that TMT has a neurotoxic effect by negatively affecting lysosomal pH, especially in neurons in the hippocampus, and by disrupting macroautophagy and lysosomal autophagy at the molecular level (60). Clinically, TMT intoxication affects different areas of the CNS, including the brain stem, limbic system, and cerebral cortex. GIS findings, generalized body aches, visual disturbances, headache, behavioral changes such as emotional lability and anger attacks, depression, loss of libido and appetite, disorientation, and cognitive and sleep disorders can be seen. If it is due to triethylene, edema in the cerebral white matter and endothelial proliferation in small veins are seen. In addition, weight loss, vertigo, hypothermia, weakness, and papilledema may develop. Behavioral changes improve after exposure ends (11,12,60).

Antimony, bismuth, cadmium, chromium, cobalt, copper, nickel, selenium, and zinc are other neurotoxic heavy metals. Clinical features of acute and chronic intoxication due to these metals are summarized in Table 3. In addition to these difficulties in diagnosis, in patients in whom the neurotoxic agent can be detected, appropriate treatment should be administered to prevent neurodegeneration and to achieve survival without sequelae. The recommended chelation treatments for heavy metal poisoning are summarized in Table 2 (54).

Table 3. Symptoms of toxication of other heavy metals

	Acute	Chronic
Antimony	Ulcer, hemorrhagic gastritis, vomiting, diarrhea	Papulopustular spotting in sebaceous/sweat glands, pancytopenia
Bismuth	Abdominal pain, acute renal failure	Myoclonic encephalopathy (Creutzfeldt- Jacob disease like syndrome), blue-black discoloration of the gums (Bismuth lines)
Cadmium	Nausea, vomiting, diarrhea, acute renal failure	Parkinsonism, olfactory disorder, restrictive lung disease, pulmonary fibrosis, osteomalacia (Itai-Itai disease)
Chromium	Nausea, vomiting, diarrhea, disseminated intravascular coagulopathy, burn, contact dermatitis	Nasal septal perforation, pulmonary fibrosis, pneumoconiosis, occupational asthma bronchiale
Cobalt	Cardiomyopathy, polycythemia, thyroid hyperplasia	Cardiomyopathy, asthma bronchiale, 8th cranial nerve damage, visual problems
Copper	Nausea, vomiting, diarrhea (blue colour), conjunctival irritation, hypotension, hemolysis	Hepatolenticular degeneration, hepatotoxicity, Kayser-Fleischer ring
Nickel	Cerebral edema, acute lung injury	Intestinal pneumonitis, myocarditis, nickel dermatitis
Zinc	Transient anosmia, nausea, vomiting, diarrhea	Myeloneuronopathy (due to copper deficiency), sideroblastic anemia, myelodysplastic syndrome

Conclusion

In conclusion, it is very difficult to diagnose clinically intoxication of environmental or occupational neurotoxic agents due to the lack of objective/specific clinical and laboratory findings secondary to their exposure. The clinician should keep neurotoxicity in mind in all kinds of neurological symptoms and take a good history to prevent possible incorrect or delayed diagnosis and to prevent sequelae.

Ethics

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: U.E.T., S.K., Design: U.E.T., S.K., Data Collection or Processing: R.G.G.Ç., U.E.T., S.K., Analysis or Interpretation: R.G.G.Ç., U.E.T., S.K., Literature Search: R.G.G.Ç., U.E.T., S.K., Writing: R.G.G.Ç., U.E.T., S.K.

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