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Occupational Neurology*

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The nervous system is vulnerable to the effects of certain chemicals and physical conditions found in the work environment. The activities of an occupational neurologist focus on the evaluation of patients with neurological disorders caused by occupational or environmental conditions. When one is making a differential diagnosis in patients with neurlogical disorders, the possibility of toxic exposure or encounters with physical factors in the workplace must not be overlooked.

Central to an accurate clinical diagnosis is the patient's history. A diagnosis of an occupational or environmental neurological problem requires a careful assessment of the clinical abnormalities and confirmation of these disabilities by objective tests such as nerve conduction velocity, evoked potentials, electroencephalogram, neuropsychological batteries, or nerve biopsy. On the basis of information about hazards in the workplace, safety standards and environmental and biological monitoring can be implemented in the workplace to reduce the risks of undue injury.

Clinical manifestations of headache, memory disturbance, and peripheral neuropathy are commonly encountered presentations of the effects of occupational hazards. Physicians in everyday clinical practice must be aware of the signs and symptoms associated with exposure to possible neurotoxins and work methods. Occupational and environmental circumstances must be explored when evaluating patients with neurologic disorders.

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OCCUPATIONAL HISTORY

Central to an accurate clinical diagnosis is the patient's history. Many problems can be overlooked or misdiagnosed because the person is not questioned about the job and its related hazards. The *occupational history* should include information about the person's current occupation, job tasks, place of employment, and dates of attendance on that job. Exposure data are crucial. A checklist of potentially neurotoxic substances used in the work process should be made. A description of personal protective equipment and how it is used, if at all, will provide further information about the extent of possible exposure. Questions about previous occupations and hobbies are important, since exposures encountered in the past may be responsible for the presenting health problems. Inadvertent exposure may occur from contaminated clothing worn home by a spouse.

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A diagnosis of an occupational or environmental neurological problem requires a careful assessment of the clinical abnormalities and confirmation of these disabilities by objective tests such as nerve conduction velocity, evoked potentials, electroencephalogram, neuropsychological batteries, or nerve biopsy. Identification of substances within the environment by measuring air concentration and identification of the chemical or its metabolites in the blood, urine, hair, or fingernails establishes the culpable agent.

It is easy to make a diagnosis of chemical-induced intoxication or entrapment neuropathy in a patient whose work history and circumstances of exposure are known and whose signs and symptoms are consistent with those reported in similar cases in the literature. However, when a patient is seen by a physician and a neurologic diagnosis made in the absence of a detailed work history, the possible relationship to previous or current exposures may be overlooked. For example, neurological features suggestive of Parkinson's disease have been associated with previous exposure to carbon disulfide [1], carbon monoxide [2], manganese [3], and, more recently, accidental exposure to N-methyl-4-phenyltetrahydropyridine (MPTP). Although the clinical picture may be similar to common conditions, recognition of potential hazards as the true explanation for the development of abnormal functioning is the first step and is dependent upon knowledge of the toxicology of the conditions in and around work areas. The mechanisms for many neurotoxins are still obscure. On the basis of information about hazards in the workplace, safety standards and environmental and biological monitoring can be implemented in the workplace to reduce the risks of undue injury.

CLINICAL MANIFESTATIONS AND SYMPTOMATIC APPROACH

Headache

Despite the vagueness of the symptoms, the differential diagnosis of headache must include the effects of exposure to noxious substances. In various references concerning hazards in the workplace, headache is listed as a complaint following exposure to metal fumes and solvent vapors [4]. The source of intoxicant, its molecular form, route of entry, and dose of exposure all determine the acuteness and severity of the symptoms. In some instances the mechanism for pain is brain swelling (tin, lead) and, in others, transient hypoxia or vasodilatation (zinc, tellurium, manganese, and nickel) may account for the pain that is experienced.

Disturbance of Memory and Behavior

Subtle changes in mental functioning due to intoxication often go unrecognized unless looked for, using sophisticated neuropsychological test batteries [5,6]. Toxicity associated with exposure to lead has been discussed in the literature since ancient times. In the past, lead poisoning was frequently associated with signs of toxic encephalopathy and peripheral neuropathy [7]. More stringent controls in the workplace coupled with government regulations and stricter environmental standards have led to a decline in cases of industrial lead poisoning. Overt manifestations of lead-related neurotoxicity, including ataxia, confusion, convulsions, weakness, and paresthesias of the extremities are less often seen. Rather, subtle changes in neurologic dysfunction, such as disturbances of affect, psychomotor function, and nerve conduction have been reported among workers whose blood concentrations of lead were relatively low [8].

Intoxication with manganese is manifested earliest by neuropsychological disturbances, including euphoria, apathy, hallucinations, flight of ideas, compulsivity, agitation, and verbosity [9,10]. Inorganic mercury poisoning has been known to produce irritability, poor concentration, memory deficiencies, anxiety, and depression [11].

Attention is being focused on the possible effects of long-term exposure to various industrial solvents whose common property is their lipid solubility. Because of their avidity for fat, the nervous system is a major target organ. Effects of solvent exposure on the central nervous system (CNS) may be manifested as a mental disorder, an impairment in psychologic functioning, or as nerve damage. The acute, narcotic effects of solvent exposure have been known for a long time, since many solvents were at one time used as anesthetic agents. Symptoms resulting from acute exposure to solvents include feelings of intoxication, difficulty in concentrating, and dizziness [12]. Headache, nausea, and vomiting are also known to occur following exposure. Chronic neurotoxic effects of solvent exposure are characterized by fatigue, irritability, affect lability, depression, and short-term memory disturbances [13], as well as impairments in psychomotor speed, attention, and complex verbal reasoning. This has been referred to in the literature as a psycho-organic syndrome, implying damage to a neural element or from a biochemical disorder in the brain [12].

Exposure to high concentrations of toluene and trichloroethylene (TCE) can cause narcosis and anesthesia. Chronic exposure to TCE has been reported to cause losses in coordination, impairment of tactile senses, intolerance to alcohol, tremor, and anxiety [14]. Chronic exposure to toluene has been reported to cause fatigue, confusion, weakness, nervousness, and paresthesia of the skin [15]. Grabski [16] first reported a man who had encephalopathy secondary to toluene inhalation. Knox and Nelson [17] documented the residual damage in this same individual 14 years later. A similar long-term finding was made in a case of TCE 18 years after acute exposure [18].

Several investigations have shown that workers exposed to solvents for long periods of time exhibit disturbances of CNS functions. Since an excess of subjective symptoms, including headache, fatigue, impaired memory, loss of appetite, and diffuse chest pain, were reported by Swedish house painters, Hane and co-workers [19] conducted an epidemiologic study comparing house painters exposed to solvents with unexposed industrial workers. The group of painters were found to have significantly lower mean scores on psychological tests measuring intellectual capacity and psychomotor coordination than the referent subjects. The painters also had significantly lower performances than expected on memory and reaction time tests. Knave and his co-workers [20] found differences between workers exposed for several years to jet fuel and unexposed referent subjects in tests demanding close attention and high sensory motor speed. Hanninen and associates [21] found impairments in psychologic performances as well as personality changes among car painters. These included impairments in visual and verbal memory, reduction of emotional reactivity, and poorer performance on verbal intelligence tests. Seppalainen and Harkonen [22] found an increase in theta activity on EEG among workers exposed to styrene.

Disturbance of Peripheral Nerve Function

Certain substances have a toxic effect on the peripheral nervous system. Metal neurotoxins which produce neuropathy include lead, arsenic, and thallium. Methyl-butyl-ketone (MBK) and n-hexane are two solvents notorious for causing peripheral

nerve effects. TCE has a predilection for the trigeminal nerve and has been associated with motor and sensory losses of the face [14]. Physical factors such as repetitive manual motions may damage the peripheral nerves from actual external compression or true entrapment. Complaints of numbness and tingling or weakness are early signs of peripheral neuropathy, often prompting individuals to seek a neurologist's evaluation. The myelin sheath and/or axon are the targets of neurotoxins. The nature of pathologic change determines the clinical manifestations of the condition.

"Segmental demyelination" is the term used to describe primary destruction of the myelin sheath with relative sparing of the axon. The process results in slowed nerve conduction velocities. Characteristically, there is no evidence of muscle denervation, although atrophy has occurred as a result of disuse. Recovery is rapid once remyelination begins and is usually complete in mild to moderate neuropathies.

Axonal degeneration results from a metabolic imbalance of the entire neuron. Degeneration of the distal portion of the nerve fiber is evident; degeneration of the myelin sheath may occur secondarily. Unlike segmental demyelination, nerve conduction rates are usually normal and distal muscles show stages of denervation. Recovery is slow and incomplete.

Neuropathy Due to Metal Toxins

The toxicity of lead on peripheral nerves has been a topic of concern for many years. Current understanding of lead neuropathy is based upon the physiologic-pathologic correlations of Fullerton [23], who demonstrated slowing in motor nerve conduction velocities in the sciatic nerves of guinea pigs fed lead acetate. This disturbance was observed in myelinated fibers, with large fibers more affected than small fibers. Both segmental demyelination and axonal degeneration were noted.

The development of clinical features is insidious, occurring after several months of exposure with increased absorption and accumulation of lead. Numbness and tingling of the fingers and toes are the initial symptoms, followed by motor weakness. Blood lead levels and zinc protoporphyrin levels, the hematopoietic indicators of lead exposure, are elevated. Of particular interest is the fact that tissue stores of lead build up in the liver, muscles, and bones with continued exposure. As a result, autointoxication can occur even after exposure has ceased, depending upon the exchangeable fraction of lead in these tissue stores and its gradual leaching out into the blood system. Detection at an early stage of neuropathy allows for a significant degree of recovery from lead neuropathy if exposure is ended and excess lead is removed from the body tissues by chelation. Weakness, sensory changes, and paresthesia persist if the combined myelin-axonal degeneration has already occurred.

Clinical manifestations of arsenic neuropathy initially present as losses of sensation in the feet and hands. Dysesthesias are common. Position and vibration sensation are usually impaired, and there is reduced perception to painful stimuli. Motor impairment is gradual in its onset, involving the small muscles of the feet and hands. Arsenic reacts with an essential thiol, inactivating one component of the pyruvate and alpha-glutarate oxidase systems of enzymes. The site of toxicity is intracellular, causing axonal changes [24,25], and fragmentation of myelin occurs after axonal degeneration takes place [26]. Sensory fibers are affected before motor fibers, and distal fibers are attacked before proximal portions [27]. Because arsenic strongly binds to tissue, long-term chelation with penicillamine or 2,3-dimercapto-1-propanol is necessary to eliminate ongoing toxic destruction of nerve fibers. Once axonal damage and second-

ary myelin degeneration have occurred, there is little chance of regeneration and clinical recovery [25].

The neuropathy associated with thallium exposure is progressive, beginning with paresthesias of the extremities. Pain increases in severity as weakness and atrophy of muscles appear. The skin of the trunk is also painful to touch, and muscles and nerves are tender to pressure [28]. Animal experiments have demonstrated swollen neuronal mitochondria, whereas the adjacent Schwann cells are not swollen [29]. Treatment for thallium intoxication is geared toward facilitating its removal from tissues, especially the mitochondrial membranes [29]. Inconsistent results have been found using the various chelators, such as 2,3-dimercapto-1-propanol, penicillamine, edetate, and dithiocarbamate [6]. Potassium chloride therapy is considered useful as an adjunct because it exchanges potassium ions for thallium ions [30].

Neuropathy Due to Solvent Toxins

The neuropathy associated with MBK and n-hexane exposure is similar. Common to both is the metabolite, 2,5-hexanedione. Initial symptoms are characterized by tingling paresthesias in the feet and fingers, with loss of sensations to pinprick, temperature discrimination, and touch. In severe cases, sensation losses have been observed as high as the thigh and arm muscles, as well as the pelvic and hip girdles [31]. Vibration losses have been noted over the feet and legs. Intrinsic muscles of the hands and feet are affected. An outbreak of peripheral neuropathy from MBK exposure was observed in a plant producing color-printed, plastic-coated, and laminated fabrics [32]. Cianchetti and co-workers [33] observed toxic polyneuropathy in a group of Italian shoe industry workers whose significant exposure was n-hexane. Since n-hexane is a constituent of rubber cements, many glue sniffers have been observed to develop these symptoms.

Neuropathy Due to Mechanical Injury

Peripheral nerves can be mechanically damaged by lacerations or through compression, stretch, repeated trauma, and vibration [34]. Patients with acute trauma are easily identified by the emergency of the event. It is the gradual development of symptoms and signs of peripheral nerve dysfunction due to entrapment that can be overlooked in a worker until function is impaired enough to affect productivity and safety. This entrapment can occur as a result of repeated mechanical injury by forces applied directly from the outside, as when holding a tool in a certain position. Subacute and chronic syndromes of nerve dysfunction may also occur when a body part is compressed or maintained in a certain position for long periods of time. Intermittent and repeated blows to the areas where nerves lie close to the surface can produce changes in the nerve fiber structure and function. Certain work situations and tasks are more likely to result in nerve injury than others. Since the muscles of the upper extremities are most frequently used during many tasks, several anatomic sites here have greater potential for compression or entrapment. The ulnar nerve may become entrapped in the hand or at the elbow; the median nerve at the wrist or in the forearm; the radial nerve in the upper arm.

The median nerve can be compressed as it courses through the fascicles of the pronator teres muscle in the forearm. In a job requiring repetitive movement of this muscle, the muscle repeatedly contracts, the sublimis muscle edge tautens, and trauma to the nerve can result. Job tasks requiring pronation with forceful finger flexion and extension of the hands, as well as pinching motions of the fingers, have been associated

with the pronator syndrome. Symptoms include numbness and dysesthesias of the proximal forearm, the radial side of the palm, and the palmar side of the first three digits and half of the fourth.

When the median nerve is compressed at the wrist as it travels with the flexor tendons through the carpal tunnel, features of carpal tunnel syndrome develop. It is known to develop in workers whose jobs involve repeated flexion and extension of the wrist, particularly when flexion or extension is accompanied by pinching or gripping tasks [35]. This motion squeezes the nerve between the overlying tendons and the underlying flexor retinaculum. Carpal tunnel syndrome is characterized by bouts of pain and paresthesias of the wrist and the first three digits of the hand. Symptoms seem to increase in severity at night. Severe sensory symptoms may precede the development of muscle wasting or weakness, although weakness of the abductor pollicis brevis is an important sign. The individual often has difficulty unscrewing a bottle top or turning a key. Percussion of the median nerve at the wrists may create a sharp pain or tingling sensation (Tinel's sign). Wrist flexion combined with thumb-finger opposition may also create pain or tingling sensations (Phalen's sign).

It is important to recognize the possibility of nerve compression or entrapment in the work setting, since damage to the nerve is incomplete in the early stages, and an adjustment in the use of tools or equipment may prevent further damage and allow recovery. Changes in work-station design or in the design of hand-operated tools may prevent injury in other workers. Furthermore, simple surgical release of entrapped nerves, when necessary, will enable a worker to return to his or her previous job without further compromise of nerve function.

CONCLUSION

There are several categories of neurologic dysfunction that have been associated with exposure to neurotoxic substances. It is easy to make a diagnosis of a solvent- or metal-induced intoxication or entrapment neuropathy in a patient whose work history and circumstances of exposure are known, and whose signs and symptoms are consistent with those reported in the literature. However, when a patient is seen by a physician and a neurologic diagnosis is to be made in the absence of a detailed work history, the possible relationship to previous or current exposures may be overlooked. The mechanisms for many neurotoxins are still obscure. Morphologic, histochemical, and neurochemical studies of individual human cases and experimental animals, coupled with epidemiologic studies of occupational groups, may eventually reveal the characteristics of each toxin and how it interacts with biologic systems. On the basis of such information, safety standards and environmental and biologic monitoring can be implemented in the workplace to reduce the risk of undue absorption of known potential intoxicants or exposures to potentially harmful physical factors. Physicians in everyday clinical practice must be aware of the signs and symptoms associated with exposure to possible neurotoxins and work methods. Occupational and environmental circumstances must be explored when evaluating patients with neurologic disorders.

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