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Review

Toxic Encephalopathy

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This article schematically reviews the clinical features, diagnostic approaches to, and toxicological implications of toxic encephalopathy. The review will focus on the most significant occupational causes of toxic encephalopathy. Chronic toxic encephalopathy, cerebellar syndrome, parkinsonism, and vascular encephalopathy are commonly encountered clinical syndromes of toxic encephalopathy. Few neurotoxins cause patients to present with pathognomonic neurological syndromes. The symptoms and signs of toxic encephalopathy may be mimicked by many psychiatric, metabolic, inflammatory, neoplastic, and degenerative diseases of the nervous system. Thus, the importance of good history-taking that considers exposure and a comprehensive neurological examination cannot be overemphasized in the diagnosis of toxic encephalopathy. Neuropsychological testing and neuroimaging typically play ancillary roles. The recognition of toxic encephalopathy is important because the correct diagnosis of occupational disease can prevent others (e.g., workers at the same worksite) from further harm by reducing their exposure to the toxin, and also often provides some indication of prognosis. Physicians must therefore be aware of the typical signs and symptoms of toxic encephalopathy, and close collaborations between neurologists and occupational physicians are needed to determine whether neurological disorders are related to occupational neurotoxin exposure.

Key Words: Occupational diseases, Nervous system diseases, Toxic encephalopathy

Introduction

Chemicals capable of damaging the central nervous system (CNS) are ubiquitous in the environment, particularly in occupational settings. Industrial processes are major sources of some of the most well-known neurotoxins. According to the United States Environmental Protection Agency, more than 65,000 commercial chemicals are currently used in the US, and 2,000-3,000 new chemicals are added to this list each year [1]. We do not know how many neurotoxic chemicals are used in industry at present, but an unadventurous estimate might suggest more than 1,000 [2]. People may be exposed to these neurotoxins due to their occupations, or occasionally at home or through other inadvertent mechanisms.

The CNS is protected from toxic exposure to some extent, but it remains vulnerable to the effects of certain chemicals found in the environment. Nonpolar, lipid-soluble substances (e.g., organic solvents) gain the easiest access to the CNS, where neurons are particularly susceptible due to their high lipid contents and metabolic rates. Both gray matter and white matter can be easily damaged by lipophilic toxins [3].

The term "toxic encephalopathy" is used to indicate brain dysfunction caused by toxic exposure [4]. Toxic encephalopathy includes a spectrum of symptomatology ranging from subclinical deficits to overt clinical disorders. The clinical manifestations of toxic encephalopathy are related to the affected brain regions and cell types [4]. This article schematically reviews the clinical features, diagnostic approaches to, and toxicological implications of toxic encephalopathy. The review focuses on the most significant occupational causes of toxic encephalopa-

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thy, but does not address iatrogenic (pharmaceutical) causes or the neurotoxic effects of illicit recreational drugs or alcohol.

Basic Principles of Neurotoxicology

Several basic principles of neurotoxicology are particularly relevant to the understanding of toxic encephalopathy [5,6].

First, there is a dose-response relationship in the majority of toxic encephalopathies. That is, the higher the level of exposure, the more severe the symptoms. Similarly, the greater the duration of exposure, the higher the likelihood of irreversible symptoms. In general, neurological symptoms appear only after the cumulative exposure has reached a threshold. Individual susceptibility varies over a limited range, and idiosyncratic reactions seldom occur.

Second, toxic encephalopathy typically manifests as a nonfocal or symmetrical neurological syndrome. The presence of significant asymmetry, such as weakness or sensory loss of only one limb or on only one side of the body should suggest an alternate cause. This principle is very useful when evaluating a patient with a presumed neurotoxic injury. However, electrolyte, glucose, and cortisol levels, liver function and renal function tests should be used to distinguish toxic encephalopathy from metabolic encephalopathy, which also presents symmetrical signs.

Third, there is usually a strong temporal relationship between exposure and symptom onset. After acute exposure, the immediate symptoms are often a consequence of the physiological effects of the chemical. Maximum symptoms generally occur with maximum exposure, and little delay in onset is seen. These symptoms typically subside when the chemical is eliminated from the body. However, delayed or persistent neurological deficits sometimes occur after toxic exposure.

Fourth, the nervous system has a limited capability to regenerate compared to other organs, such as the liver or hematopoietic system. Thus, more sequelae persist after the removal of a neurotoxic agent, compared to toxic diseases of other organs.

Fifth, multiple neurological syndromes may occur in response to a single neurotoxin, depending on the level and duration of the exposure. For example, acute, high-level exposure to carbon disulfide produces psychosis, whereas chronic moderate exposure causes atherosclerosis-related health effects [7,8].

Sixth, clinical disorders of the CNS have varying presentations, often involving a host of nonspecific symptoms. Furthermore, few neurotoxins cause patients to present with a pathognomonic neurological syndrome. The symptoms and signs of neurotoxin exposure may be mimicked by various psychiatric, metabolic, inflammatory, neoplastic and degenerative diseases of the nervous system [9]. Therefore, it is crucial to take a good occupational history and perform a detailed neurological examination when diagnosing a toxic encephalopathy.

Seventh, asymptomatic toxic encephalopathy may be seen in occupational or environmental settings [10]. Neuropsychological studies have shown that workers in paint manufacturing or painting facilities often have subclinical neuropsychological deficits [4,11], and recent studies have revealed that asymptomatic toxic encephalopathies are a very common phenomenon [4]. Subclinical deficits usually recover after the exposure ceases, whereas clinical disorders usually do not recover.

Eighth, the timing of exposure relative to critical periods of CNS development may explain some of the variations in susceptibility. The many discrete neuronal populations and interacting systems of the nervous system develop at variable rates throughout the first three decades of life. Toxic exposures may exert profound effects when the organism is in a particularly vulnerable stage, resulting in problems that would not occur in response to exposures at other stages of life. The most prominent example of this phenomenon is the susceptibility of infants to lead encephalopathy [12].

Finally, neurotoxins may reduce the functional reserves of the brain, potentially making the cells more vulnerable to the effects of aging and leading to accelerated senescence. This may explain the observation that in some cases deterioration may continue for many years, even after exposure has ceased.

Clinical Syndromes of Toxic Encephalopathy

The major clinical syndromes of toxic encephalopathy include diffuse acute or chronic toxic encephalopathy, cerebellar syndrome, parkinsonism, and vascular encephalopathy [4,13]. Various neurotoxins, including heavy metals, organic solvents and other chemicals, have been found to be responsible for these relatively specific neurological syndromes [8,9].

Acute diffuse toxic encephalopathy

Acute diffuse toxic encephalopathy reflects a global cerebral dysfunction of rapid onset (typically days or weeks), and may be associated with alterations in the level of consciousness. The neurotoxins that produce acute encephalopathy interfere with basic cell functions in the brain [4]. Most of these agents gain entry because they are highly lipid soluble and can readily diffuse across membranes. The causative agents include organic solvents, which can alter cellular membrane function, and some gases (e.g., gas anesthetics, carbon monoxide, hydrogen sulfide, and cyanide), which can diffusely affect brain function. Heavy