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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

metals can also cause acute encephalopathies; this is more commonly associated with organic metals (e.g., methyl mercury, tetraethyl lead and organic tin) than with inorganic metals (e.g., mercury, lead and tin) [4]. Virtually any organic solvent has the potential to produce acute diffuse toxic encephalopathy, the clinical manifestations of which depend on the neurotoxin and the intensity of exposure, and can range from mild euphoria with a normal examination, to stupor, seizure, coma, and even death. In general, the greater the exposure, the more severe the impairment of cerebral function and consciousness. The cerebral cortex is more sensitive to these toxins than is the brainstem: even when consciousness is lost, brainstem function typically remains intact. Diagnosis does not generally present a challenge for acute syndromes, because the exposure and clinical manifestations are likely to be closely linked in time. In patients with severe acute toxic encephalopathy, magnetic resonance imaging (MRI) of the brain may show focal areas, most commonly bilateral basal ganglia, or diffuse areas of edema [14-16]. The treatment of diffuse acute encephalopathy is primarily supportive, starting with removal of the exposure source. For most of the neurotoxins that act diffusely on the brain, recovery from acute exposure is complete [4].

Chronic toxic encephalopathy (CTE)

CTE usually represents a chronic persistent diffuse injury to the brain resulting from cumulative or repeated exposures (often over a period of months or years), to solvents or (occasionally) heavy metals. The clinical manifestations of CTE usually involve varying degrees of cognitive impairment [4].

CTE is an established, internationally recognized condition that results from excessive occupational exposure to solvents via inhalation or skin contact. In 1985, the World Health Organization (WHO) published diagnostic criteria for CTE caused by exposure to solvents [11,17]. The most recent International Classification of Diseases document (no. 10) defines CTE [18], and the Diagnostic and Statistical Manual for Mental Disorders, Fourth Edition [19] lists the condition as a form of substance-induced persistent dementia.

The severity of CTE is graded as I-III or 1, 2A, 2B, and 3 [11,17]. Type I CTE and types 1 and 2A CTE include subjective symptoms relating to memory, concentration, and mood. At this stage, clinicians may miss the diagnosis by considering these symptoms as a psychiatric issue due to altered mood [4]. Type II CTE and type 2B CTE are characterized by objective evidence of attention and memory deficits, decreased psychomotor function [11], and/or learning deficits [17] on neurobehavioral testing. The taking of detailed occupational and medical histories, as well as standardized neurobehavioral testing, are the cornerstones of the standard diagnostic process. Workers with a history of repeated episodes indicative of acute solvent intoxication (e.g., light-headedness, dizziness, headache and nausea) over a period of many years; a history of insidious onset of attention, memory, and mood problems; and objective evidence of impairment on standardized neurobehavioral tests (i.e., deficits in attention, memory, learning and/or psychomotor function) should be considered as meeting the diagnostic criteria for type II CTE or type 2B CTE. Type III CTE and type 3 CTE are often accompanied by neurological deficits and neuroradiological findings. This type of CTE often manifests clinical features, whereas types I and II show subclinical deficits. The MRI findings in patients with CTE are nonspecific, although there may be slight brain atrophy; MRI findings mainly support the differential diagnosis of CTE by ruling out other brain diseases. Thus, non-solvent etiologies should be considered if there are major findings on the brain MRI of a patient with suspected CTE [20]. Most cases of CTE are of type II or 2B [21]. The Finnish criteria for CTE usually includes the criterion of more than ten years of daily exposure at work [22]. Follow-up is also important in diagnosing patients with CTE. Subtle changes in mental functioning due to intoxication often go unrecognized unless the clinician specifically assesses these changes using sophisticated neuropsychological tests [8].

The high index of suspicion gives clues to diagnosis of CTE. The diagnosis of CTE requires a careful clinical assessment that 1) establishes that there is evidence for abnormality, mainly on neuropsychological testing; 2) determines that there is good evidence of a relationship to exposure to a potentially hazardous neurotoxin; and 3) excludes any other underlying causes. Specific therapies for CTE are limited. The patient should be separated from the neurotoxic exposure as soon as possible. Once the toxin has been removed, the reversibility of the brain damage will depend on the grade of CTE [4,23].

The important question of whether CTE can progress to the development of dementia has not yet been answered. Increasing evidence suggests that most forms of degenerative dementia have a multi-factorial cause involving genetic, biological, and chemical factors [13]. Further studies are needed to clarify the issue.

Cerebellar syndromes

Gait ataxia, dysarthria, intention tremor, gaze-evoked nystagmus, dysmetria and adiadochokinesia can all result from cerebellar dysfunction [13]. Neurotoxin-induced cerebellar syndrome, which is a clinical entity that can be differentiated from solvent-induced CTE or carbon-disulfide-induced vascular encephalopathy [13], is sometimes accompanied by other neu-

rological findings. If a patient presents with cerebellar dysfunction, a detailed history of his or her occupation and neurotoxin exposure should be obtained.

Methyl mercury intoxication (Minamata disease)

Methyl mercury intoxication, known as Minamata disease, causes damage to the granule cell layer in the cerebellum, bilateral diffuse cerebellar atrophy, and microscopically diffuse loss of the granule cell layer in the cerebellar cortex [24]. The major clinical features of the disease include progressive cerebellar ataxia and disturbance of the sensory functions of the cerebral cortex. Cerebellar ataxia manifests as gait ataxia, dysarthria, intention tremor, gaze nystagmus, dysmetria and dysdiadochokinesia. In addition, injuries to the somatosensory, visual, auditory or olfactory cortexes of the cerebrum can manifest as visual impairment, hearing impairment, olfactory problems, gustatory disturbance and cerebral cortex-related somatosensory disturbances [24]. Concentric constrictions of the visual fields are characteristic findings due to damage to the calcarine cortex [13]. In Minamata disease, atrophy of the visual calcarine cortex and the cerebellum has been demonstrated on computed tomography (CT) and MRI [25-27], and significantly decreased blood flow has been shown in the cerebellum on single-photon emission computed tomography (SPECT) [27]. Fetal Minamata disease is a typical congenital toxic encephalopathy. Serious disturbances in mental and motor development are observed in all cases of fetal Minamata disease. Affected individuals show significant bilateral impairments in chewing, swallowing, speech, gait, other coordination and involuntary movement such as dystonia. These symptoms have been associated with the brain damage that is typical of Minamata disease [28].

Methyl bromide intoxication

Methyl bromide is a highly toxic gas that is used widely as an insecticidal fumigant for dry foodstuffs. It can be toxic to both the CNS and the peripheral nervous system [29,30]. Most neurological manifestations of methyl bromide intoxication occur as a result of inhalation. Chronic exposure can cause peripheral polyneuropathy, optic neuropathy and cerebellar dysfunction, sometimes with neuropsychiatric disturbances [29,30]. Typically, occupational history is vital to the diagnosis of bromide intoxication.

Organic tin intoxication

Organic tins, such as the dimethyl and trimethyl compounds, are widely used as polyvinyl-chloride stabilizers, catalysts and biocides [31]. Selective cerebellar dysfunction is most prominent upon recovery from coma due to acute severe organic tin intoxication [31]. It is easy to diagnose acute organic tin intoxication in patients whose work history and circumstances of exposure are known, and whose signs and symptoms are typical and consistent with those reported in the literature.

A fluid attenuated inversion recovery (FLAIR) MRI taken 15 days after an acute organic tin intoxication showed extensive symmetrical high-signal lesions throughout the white matter of the brain, indicating diffuse brain edema [15]. In a follow-up study three years after an acute organic tin poisoning case, brain MRI showed cerebellar atrophy and ^{18}F-fluorodeoxyglucose positron emission tomography (PET)/CT revealed mildly decreased metabolic activity in the pons and in both cerebellar hemispheres [31].

Parkinsonism

Manganese intoxication (manganism)

Manganism is one of the most typical forms of parkinsonism. Chronic excessive exposure to manganese (Mn) can affect the globus pallidus, resulting in parkinsonian signs and symptoms, sometimes along with psychiatric features called locura manganica or Mn madness. Historically, miners developed psychosis due to exposure to Mn at levels of up to several hundred milligrams per cubic meter [32].

The clinical course of manganism can be divided into three stages: at the first stage, patients with manganism usually have prodromal neuropsychiatric symptoms such as asthenia, apathy, somnolence, irritability, emotional lability, or frank psychoses. At the second stage, bradykinetic-rigid parkinsonian syndrome with dystonia, which is reversible, presents as the main clinical feature [4]. Patients in the last stage are notable for aggravation of the signs and symptoms described as above. The clinical progression has been found to be irreversible and persistent after the cessation of exposure in some cases [33]. Early diagnosis of manganism is therefore important.

The mechanism underlying this response to Mn exposure is not yet clear, but it has been suggested that an initial insult to the globus pallidus during Mn neurotoxicity can result in increased activity in the subthalamic nucleus, which is normally under tonic inhibition by the globus pallidus in the basal ganglia circuitry [34]. Diagnosis of classical manganism requires a history of occupational Mn exposure, typical neurological findings such as bradykinesia, rigidity and postural instability, and the exclusion of other neurological diseases related to the basal ganglia, such as Parkinson's disease (PD), secondary parkinsonism due to traumatic, vascular, or iatrogenic damage, and atypical parkinsonism syndromes [35].

The differential diagnoses of this disorder can be summarized using clinical features and neuroimaging data (Table

Table 1. Comparison of the features of manganism and Parkinson's disease

Feature	Manganism	Parkinson's disease
Bradykinesia/rigidity	Typical	Typical
Symmetry	Symmetrical	Asymmetrical
Resting tremor	Less frequent, mainly intentional tremor	More frequent
Dystonia	More frequent	Less frequent
Gait disturbance	More frequent	Less frequent
Gait	Cock walk	Festinating gait
Propensity to fall backward	Typical	Not typical
Response to L-dopa	Poor response	Good response
Signal intensities in globus pallidus in T1-weighted MRI	Bilaterally increased*	Normal
DAT SPECT/fluorodopa PET	Normal	Markedly decreased

*A negative MRI signal can occur if manganese exposure ceased at least six months previously.
MRI: magnetic resonance imaging , DAT SPECT: dopamine transporter–single-photon-emission computed tomography, PET: positron emission tomography. (From reference 35)

1) [35-37].The pathological lesions caused by manganism are typically degenerative lesions of the globus pallidus, sometimes with less-frequent and less-severe injuries to the substantia nigra (SN). By contrast, in PD the SN is typically involved while the pallidostriatal complex is spared [38].

A Mn-induced, bilateral and symmetrical increase in signal intensity, confined mainly to the globus pallidus and midbrain, can be observed on T1-weighted MRI in Mn-exposed individuals, but no alterations are typically seen on T2-weighted MRI or CT scans [39]. Increased signals on T1-weighted MRI were observed in both asymptomatic Mn-exposed workers and in patients with experimental or occupational Mn poisoning [40-42]. However, these increased signal intensities generally resolved 6-12 months after the cessation of Mn exposure [42,43]. Thus, a high T1 signal on MRI may reflect the target organ dose of recent occupational Mn exposure, but may not necessarily reflect manganism in the spectrum of Mn symptomatology [44].

At lower exposure levels, less severe, subtle, and preclinical neurobehavioral effects have been widely reported in various occupational and environmental settings [45]. Concerns have been raised about whether chronic exposure to low levels of Mn can induce PD [43,46]. In fact, PD is not a single disease, but rather a heterogeneous group of clinically similar conditions. It is possible that some individuals diagnosed with PD have neurotoxin-related PD that is likely to have been overlooked because most cases are not attributable to neurotoxin exposure. However, future work will be required to clarify whether Mn exposure induces PD and/or affects the progress of this condition.

Others

Acute carbon monoxide poisoning can result in a delayed extrapyramidal syndrome that begins two to three weeks after recovery from the initial exposure. The parkinsonian features can be progressive and are associated with symmetrical degeneration of the globus pallidus [47]. Abnormalities may be seen in brain CT and MRI [48-50]. Carbon monoxide poisoning can also result in cognitive impairment and akinetic mutism associated with subcortical white matter lesions, especially in the bifrontal area [48-50]. Parkinsonian features have occasionally been associated with methanol [51], carbon disulfide [52], paraquat and rotenone [53,54], and cyanide poisoning [55].

Vascular encephalopathy

Carbon disulfide poisoning is a highly typical and frequently encountered vascular encephalopathy [8,56]. Patients with carbon disulfide poisoning exhibit various clinical characteristics, including multiple brain infarctions [57-59], peripheral neuropathy [60], coronary heart disease [61], retinopathy including microaneurysm of the fundus [62], hypertension [56], glomerulosclerosis of the kidney [63], and parkinsonian symptoms [52]. These findings indicate that the basic mechanisms underlying carbon disulfide poisoning involve atherosclerotic changes in blood vessels [56,64]. The clinical manifestations of vascular encephalopathy (e.g., hemiparesis and speech disturbance)

in cases of chronic carbon disulfide poisoning are similar to those observed in patients with atherosclerotic cerebrovascular disorders [56,59]. Many patients presenting with acute cerebrovascular stroke-like symptoms, sometimes with hypertension or diabetes, have been misdiagnosed as having suffered cerebrovascular attacks. Thus, the possibility of carbon disulfide poisoning must not be overlooked when physicians make differential diagnoses in patients with vascular encephalopathy.

Historical records of carbon disulfide poisoning in Japan suggest the presence of a dose-response relationship. Psychosis and peripheral neuropathy due to carbon disulfide poisoning among rayon industry workers were first reported in 1932 and 1934, respectively [65]. In the 1930s, when the Japanese first began producing rayon, carbon disulfide poisoning was the most common occupational disease in Japan [66], and psychosis resulting from very high exposure was a predominant health problem. Since 1949, rayon manufacturers have collaborated with university researchers in Japan to control carbon disulfide concentrations in the workplace and to monitor the incidence of carbon disulfide poisoning [66]. By the 1960s, atherosclerosis (which is associated with moderate exposure levels) became the main type of carbon disulfide poisoning in Japan [66]. Since 1980s, similar clinical features (e.g., atherosclerosis) have been observed in Korean workers with carbon disulfide poisoning, probably due to the transfer of the rayon industries from Japan in the 1960s [67].

Neurodegenerative diseases

Amyotrophic lateral sclerosis (ALS)

ALS is a neurodegenerative disease with an annual worldwide incidence of 2-4 cases per 100,000 individuals [68]. A few cases have been reported in Korea [69]. The association between ALS and exposure to solvents or lead is unclear, and even the best-designed incidence studies have produced conflicting results [70,71].

Other neurodegenerative diseases

It is reported that exposure to solvents, aluminum, mercury, or pesticides is implicated in the development of Alzheimer's disease, which is the most common neurodegenerative disease [2]. However, evidence for this causal relationship is limited and further studies are required. PD was dealt with in the manganism section above.

Diagnostic Approaches for Toxic Encephalopathy

A diagnosis of toxic encephalopathy can be made after documentation of the following: 1) a sufficiently intense or prolonged exposure to the neurotoxin; 2) a neurological syndrome appropriate for the putative neurotoxins; 3) evolution of symptoms and signs over a compatible temporal course; and 4) exclusion of other neurological disorders that may account for a similar syndrome [6].

The exposure history, physical examination, neurological examination, and additional laboratory and radiological studies are particularly important for diagnosing a toxic encephalopathy. An overt toxic encephalopathy is not difficult to recognize if a patient develops a well-described clinical syndrome after exposure to a well-known neurotoxin, or if other workers at the same site develop similar clinical pictures. The more difficult (and more common) situation is when a symptomatic individual presents with either an unclear history of exposure or an apparently trivial exposure to a known or suspected neurotoxin. In this situation, careful evaluation of the case is essential [5].

Acquisition of a detailed exposure history

The patient's exposure history is central to an accurate clinical diagnosis. Many problems can be overlooked or misdiagnosed because the person has not been questioned about his or her job and its related hazards. The occupational history should include information about the person's current occupation, job task, place of employment, and dates of attendance on that job [72]. Exposure data such as workplace airborne concentrations are crucial. A detailed evaluation of the nature, duration, and intensity of the exposure is essential for every evaluation. A description of the availability and use of personal protective equipment will provide further information about the extent of possible exposure. It is also important to ask questions about hobbies, and inadvertent exposure from any source should be considered [72]. For the diagnosis of toxic encephalopathy, it is likely to be helpful if information on similar problems observed in others at the worksite is available.

Neurological examination

After a careful history is obtained, clinical examination should be carried out to establish the type and degree of dysfunction. The physical examination should include a general examination followed by a detailed neurological examination. Non-neurological signs may be a clue to toxic exposure; examples of systemic clues include blue gums in lead intoxication, Mees' lines in arsenic poisoning, and acrodynia in mercury poisoning [3]. The neurological examination will generally comprise assessment of mental function (mental status examination), cranial nerve function, muscle strength and tone, reflexes (muscle stretch and cutaneous), sensation, station and gait [5]. A

complete and rigorous neurological examination is necessary to properly define the clinical neurological syndrome involved. Once defined, a differential diagnosis can be entertained, and occupational versus non-occupation or toxic versus non-toxic causes can be determined.

Clinical laboratories

When a patient is seen close to the time of exposure it may be possible to measure the offending chemical such as lead and mercury or its metabolite in blood or urine. Biomarkers can demonstrate that there has been exposure to the relevant toxin and that the exposure was of sufficiently severity to give rise to a clinical syndrome. It is obligatory in those cases in which there is an acute illness in relation to exposure. However, problems will undoubtedly occur in those cases where there is a delay between exposure and the development of clinical symptoms. Furthermore, for most neurotoxins biomarkers are not readily available [4,13].

There may be occasionally be paraclincal features in hematological and biochemical tests indicating red blood cell changes as in the case of lead poisoning, or liver function test abnormalities as in the case of some organic solvent poisoning. For most of neurotoxins, however, clinical laboratory tests are not helpful for diagnosis [4,13].

Neurobehavioral testing

Neurobehavioral (neuropsychological) testing, which is an accepted methodology for assessing the functional integrity of the CNS, has been used extensively to evaluate subclinical neurotoxic effects on cognition, memory, alertness, executive function, mood and psychomotor skills [73-75]. There is a wide spectrum of neuropsychological tests, and the selection must be tailored to each situation. Neurobehavioral testing is generally administered by an examiner, as in the Neurobehavioral Core Test Battery from the WHO [73]. Recently, however, many of the tests have been adapted for use on a personal computer. In toxic encephalopathy due to various neurotoxins (e.g., heavy metals or organic solvents), neuropsychological studies have been useful in evaluating subclinical findings [45,75,76]. Indeed, since the 1990s, subclinical neuropsychological deficits detected by neurobehavioral testing have replaced overt clinical findings as the basis of occupational exposure limits for various neurotoxicants [44,77]. Neurobehavioral tests are also used as diagnostic criteria for CTE.

Electroencephalography (EEG)

EEG, which records the electric activity of the brain, has been used to evaluate occupational neurotoxic exposures [78,79]. The changes that are most obvious on EEG, such as diffuse slowing, are often associated with toxic encephalopathy [4]. However, the observed abnormalities are not specific, meaning that EEG has only a limited value in detecting and characterizing toxic encephalopathy [9]. With the advent of recent technological advances in neuroimaging, EEG is now used less frequently as a neurodiagnostic method, and more often in evaluating epilepsy.

Evoked potentials (EVPs)

Sensory EVPs are widely used in clinical neurology as an index of the integrity of the sensory CNS pathways. Compared to EEG, EVPs can provide more quantitative information and can be used to assess a sensory pathway from the receptor to the cortex. Among the EVPs, the visual evoked potential (VEP), auditory evoked potential (AEP), and somatosensory evoked potential (SEP) are most often used in evaluating neurotoxic disease and other neurological disorders [79]. However, many variables can confound interpretation, and the results are not specific to neurotoxic disease [4] and thus should be interpreted with caution [80]. Marked AEP abnormalities have been associated with toluene exposure [81,82], but these studies were performed in toluene abusers, who are exposed to much higher levels than those usually found in occupational settings.

Neuroimaging studies

Since the invention of CT and MRI scanners, tremendous progress has been made in the medical imaging of the human body. Neuroimaging can be divided into two groups: morphological neuroimaging (anatomy-based imaging) such as CT and MRI, and functional neuroimaging (physiology-based imaging) such as magnetic resonance spectroscopy (MRS), functional MRI, diffusion tensor imaging (DTI), SPECT, and PET. At present, with the introduction of new technologies and the solving of technical problems related to the local production of radioisotopes, neuroimaging is shifting from morphological to functional [83,84].

CT

Modern CT scanners are capable of performing multiple slices with rapid data acquisition and overlapping sections using continuously moving X-ray emitters (spiral CT). These methods enable the rapid production of exquisite images with three-dimensional reconstruction capabilities. In the brain, the use of X-ray contrast agents and angiography has improved intracranial imaging, but CT remains almost exclusively an anatomical imaging tool [83-86]. In terms of neurotoxin-related damage, CT is valuable for ruling out other naturally occurring disorders

of the nervous system, and it can reveal nonspecific changes (e.g., cortical atrophy) in individuals chronically exposed to organic solvents in the workplace [87].

MRI

MRI provides images that enhance either the fatty component (so-called 'T1-weighted' images) or the water component (so-called 'T2-weighted' images) of tissues. It has emerged as the pre-eminent imaging modality for visualizing neurological diseases in the central nervous system, because it can distinguish gray and white matter, zones of demyelination, and brain edema [83,88]. The distinction between gray and white matter lesions is crucial because gray matter is more vulnerable to anoxic or ischemic insults due to its higher metabolic demands for oxygen and glucose [89]. White matter changes, such as leukoencephalopathy, are usually better seen on MRI, whereas calcifications and hemorrhages are readily detectable by CT. However, the severity and extension of brain lesions on morphological neuroimaging do not necessarily match the severity of clinical status [89]. T1-weighted MRI can detect paramagnetic metals, such as Mn, making it uniquely useful in Mn neurotoxicology. On T1-weighted MRI, Mn exposure causes bilateral symmetrical increases in signal intensity that are confined to the globus pallidus and midbrain [39-41,46].

MRS

Numerous whole-body MR scanners now operate at magnetic fields of 1.5 Tesla (T) or above, meaning that they can perform localized proton MRS without additional hardware [90]. The latest very-high-field strength (i.e., 3 T or more) MRI systems generate images that combine anatomical and physiological measurements. *In vivo* proton magnetic resonance spectroscopy ($[^1H]$-MRS) is an image-guided, noninvasive method for monitoring neurochemical metabolites in the brain [90]. Currently, $[^1H]$-MRS is most commonly employed to obtain metabolic information that may aid in the diagnosis of many neurological diseases, and also allows the evaluation of disease progression and treatment response [91]. Although MRS permits noninvasive *in vivo* measurement of brain metabolites, only a few MRS investigations have assessed the neurological effects of neurotoxins in environmental or occupational health. Aydin et al. [92] demonstrated decreased N-acetylaspartate (NAA) in the cerebellar white matter and centrum semiovale along with increased myoinositol (mI) in toluene abusers. Several recent reports have analyzed the impact of lead exposure on brain metabolism *in vivo* in adults and children [93-96], while two other studies employed MRS to investigate the potential neurotoxic effects of chronic Mn exposure on the brain [97,98]. In particular, Guilarte et al. [97] assessed the toxic effects of chronic Mn exposure on the levels of brain metabolites in non-human primates. This $[^1H]$-MRS study found that the NAA/creatine (NAA/Cr) ratios in the parietal cortex and frontal white matter were decreased after Mn exposure, indicating ongoing neuronal degeneration or dysfunction. NAA is known to serve as a neuronal marker [99], and a reduction in brain NAA levels can be interpreted as indicating neuronal dysfunction or loss [100]. However, Kim et al. [98] found no significant difference between welders and control subjects in this measure. Similarly, Chang et al. [101] recently showed that the NAA/Cr ratios in both the anterior cingulate cortex and parietal white matter did not differ significantly between welders and controls. However, they found that the mI levels in the anterior cingulate cortex, but not in the parietal white matter, were significantly lower in welders compared with control individuals. Furthermore, in the frontal lobe of the brain, the mI/Cr ratio was significantly correlated with verbal memory scores and blood Mn concentrations. This study therefore suggested that the depletion of mI in welders may reflect a possible glial cell effect (rather than a neuronal effect) associated with long-term exposure to Mn. More recently, Dydak et al. [102] used the MEGA-PRESS sequence to determine γ-aminobutyric acid (GABA) levels in the thalamus, and found that Mn-exposed subjects showed significant decreases in the NAA/Cr ratio of the frontal cortex, and significant increases in the GABA level of the thalamus. Further MRS-based studies will be required to fully assess the various brain metabolites in Mn-exposed workers.

Functional MRI

Functional MRI (fMRI) uses standard clinical MRI hardware to collect information regarding brain metabolism changes associated with neuronal activity. As neuronal activity and the resulting demand for oxygen increase, the supply of oxygenated hemoglobin correspondingly increases, along with the MR signal measured on T2* images. This generates blood-oxygenation-level-dependent (BOLD) contrasts [103].

The use of fMRI to study neurological diseases has become much more common over the last decade, but employing fMRI to assess neurotoxicity in humans is a rather novel approach. There have not yet been any reports on functional MRI findings in metal neurotoxicity. Chang et al. [104] were the first to use fMRI and sequential finger-tapping to investigate the behavioral significance of additionally recruited brain regions in welders who had experienced chronic Mn exposure. Their findings suggest that fMRI may help us uncover evidence of compromised brain functioning in patients with subclinical manganism. The observation that the cortical motor net-

work was excessively recruited in the chronically Mn-exposed group is in line with the emerging concept that adaptive neural mechanisms are used to compensate for latent dysfunctions in the basal ganglia. Chang et al. [105] also combined fMRI with two-back memory tests to assess the neural correlates of Mn-induced memory impairment in response to subclinical dysfunction in the working memory networks of welders exposed to Mn for extended periods of time. These fMRI findings indicated that welders might need to recruit more neural resources to their working memory networks in order to compensate for subtle working memory deficits and alterations in working memory processes.

DTI

DTI, which is a unique method for characterizing white matter micro-integrity [106], can reveal the orientation of white matter tracts *in vivo* and yields indices of microstructural integrity by quantifying the directionality of water diffusion [107,108]. A few previous studies have explored the toxic encephalopathy associated with exposure to environmental neurotoxins, such as mercury [109], Mn [110], methanol [111], and carbon monoxide [112] using diffusion-weighted image (DWI) analysis. However, few studies have reported DTI-detected alterations of microscopic integrity within the white matter of subjects experiencing environmental neurotoxic exposure [113]. Kim et al. [114] used DTI to investigate whether welders exposed to Mn exhibited differences in white matter integrity. White matter microstructural abnormalities (decreased fractional anisotropy [FA]), which correlated with deficits in motor and cognitive neurobehavioral performance, were observed in welders, as compared to controls.

SPECT

SPECT is a widely distributed functional imaging modality that is more easily accessible and less expensive than PET, but has a lower resolution [39]. SPECT allows the imaging of regional blood flow, metabolism and neurotransmitter receptors with relatively good spatial resolution. SPECT of patients with Minamata disease showed significantly decreased blood flow in the cerebellum [27]. In a case of acute lithium intoxication, the CT and MRI were normal, but a SPECT scan indicated significant focal perfusion defects, predominantly involving the left temporo-parietal area and the right posterior parieto-occipital area [115]. Huang et al. [116] reported that the striatal ^{99m}Tc-TRODAT-1 uptake in dopamine transporter (DAT) SPECT was nearly normal in Mn-induced parkinsonism, but was markedly reduced in PD. Various ligands that bind to DAT, such as [^{123}I]-β-CIT, [^{123}I]-fluoropropyl-CIT and ^{99m}Tc-TRODAT-1, have been used in SPECT studies to elucidate the function of the dopaminergic nigrostriatal pathway, and thus to differentiate manganism from PD [46,116,117].

PET

PET uses short-lived positron-emitting isotopes to mark biologically active compounds. PET isotopes have such short half-lives that they must be produced in on-site cyclotrons to be available in quantities viable for clinical use. PET relies on a visibly labeled ligand to provide image specificity [84,118,119]. Specific ligands have been developed to help elucidate the function of the dopaminergic nigrostriatal pathway. For example, the ligand [^{18}F]-dopa provides information about the conversion of L-dopa to dopamine [120]. In nonhuman primates and humans with manganism, the [^{18}F]-dopa PET scan (which provides an index of the integrity of the dopaminergic nigrostriatal pathway) is normal [39,121-123]; by contrast, reduced dopamine uptake occurs in the striatum and particularly the posterior putamen of PD patients [39,124]. Thus, [^{18}F]-dopa PET scans have been used to differentiate manganism from PD [46,116,117]. In addition, ^{18}F-fluorodeoxyglucose (^{18}F-FDG) PET may be used to show metabolic activity in the brain. In a follow-up study of an acute organic tin poisoning case three years after diagnosis, ^{18}F-FDG PET/CT revealed mildly decreased metabolic activity in the pons and in both cerebellar hemispheres [31]. Similarly, decreased metabolism in the thalamus, basal ganglia, temporal lobe and inferior parietal lobe have been observed in hydrogen sulfide poisoning using ^{18}F-FDG PET [125].

Clinical Implications

Many toxic encephalopathies may go unrecognized. In the absence of a detailed neurological examination and comprehensive work history, physicians may overlook the possibility of previous or current neurotoxin exposure. The recognition of toxic encephalopathy is important for clinicians for several reasons: 1) diagnosis can protect others (e.g., workers at the same worksite) from further harm by reducing exposure to the toxin; 2) diagnosis often provides some indication of prognosis; and 3) recognition of neurotoxic exposure can bring about improved hygiene measures that may protect other workers.

Physicians must be aware of the typical signs and symptoms of toxic encephalopathy, and they should also pay attention to less typical, rather vague symptoms and signs because the toxicological characteristics of toxic encephalopathy may be less typical, particularly in cases of long-term, low-dose exposure, perhaps combined with the effects of aging. Close col-

laborations between neurologists and occupational physicians are needed to determine whether neurological disorders are neurotoxin-related.

Summary

CTE, cerebellar syndrome, parkinsonism and vascular encephalopathy are commonly encountered clinical syndromes of toxic encephalopathy. Few neurotoxins cause patients to present with pathognomonic neurologic syndromes. The symptoms and signs of toxic encephalopathy may be mimicked by many psychiatric, metabolic, inflammatory, neoplastic and degenerative diseases of the nervous system, so the importance of good history-taking and a comprehensive neurological examination cannot be overemphasized in the diagnosis of toxic encephalopathy. Neuropsychological testing and neuroimaging typically play ancillary roles.

Conflict of Interest

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

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