Review Articles

Current Concepts

Toxic Leukoencephalopathy

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Leukoencephalopathy is a structural alteration of cerebral white matter in which myelin suffers the most damage. Toxic leukoencephalopathy may be caused by exposure to a wide variety of agents, including cranial irradiation, therapeutic agents, drugs of abuse, and environmental toxins.[1] Toxic leukoencephalopathy particularly involves white-matter tracts devoted to higher cerebral function, causing clinical features that range from inattention, forgetfulness, and changes in personality to dementia, coma, and death. This review focuses on white-matter damage caused by toxins as distinguished from that caused by disorders such as multiple sclerosis, cerebrovascular disease, and metabolic disturbances.[2]

Although the prevalence of toxic leukoencephalopathy is unknown, the syndrome is increasingly being recognized among patients in whom neurobehavioral disturbances develop after exposure to toxins. The use of magnetic resonance imaging (MRI) has led to a greater appreciation of the damage that leukotoxic agents can inflict on white matter. The increasing success of antineoplastic drugs has produced a larger cohort of long-term survivors of cancer who have iatrogenic white-matter damage. Clarification of the neurologic effects of toluene, ethanol, cocaine, hallucinogenic drugs, and heroin has increased awareness that leukoencephalopathy can be a complication of substance abuse. Finally, the use of toluene and other organic solvents in the workplace has raised the possibility of toxic leukoencephalopathy as an occupational health hazard.

CLINICAL PRESENTATION

White matter makes up approximately half the cerebrum[3] and is composed of multiple interhemispheric and intrahemispheric tracts connecting cortical and subcortical structures of gray matter.[4] Although the role of white matter in movement, sensation, and vision is well known, cognition and emotion also depend on the integrity of white matter, because the majority of cerebral fibers are found in association with tracts and commissural tracts.[4,5] Leukotoxic agents disrupt or abolish neural transmission in widespread neurobehavioral pathways, and thus, the most distinctive clinical manifestations of leukoencephalopathy are changes in mental status.[1,4,5]

Toxic leukoencephalopathy should be part of the differential diagnosis in the case of any patient who presents with acute or chronic neurobehavioral deficits (Table 1) and who has a potential or known exposure to agents that are toxic to the cerebral white matter (Table 2). The clinical spectrum of toxic leukoencephalopathy generally parallels the severity of white-matter damage as well as its distribution, which is usually diffuse (Table 1). Mild cases are typified by a chronic confusional state with inattention, memory loss, and emotional dysfunction that may suggest a psychiatric disorder. Additional testing is usually necessary to distinguish a mild case of toxic leukoencephalopathy from psychiatric disease. More severe cases produce major neurologic sequelae such as dementia, abulia, stupor, and coma. In contrast to disorders of cortical gray matter such as Alzheimer's disease, toxic leukoencephalopathy does not primarily affect language, praxis, or perception.[1,4,5] The fact that language is usually preserved is especially important, because it may mask the presence of other neurobehavioral deficits.[4] Neurologic signs such as hemiparesis, sensory deficits, and visual loss are less prominent than changes in mental status unless focal necrosis of white matter also occurs.[1]

DIAGNOSIS

Toxic leukoencephalopathy can occur in any age group and any patient care setting, including outpatient clinics, inpatient wards, and critical care units. The diagnosis requires that the clinician have a high index of suspicion and that there be documented exposure to a toxin, neurobehavioral deficits, and neuroradiologic abnormalities in the patient. In cases of suspected toxic leukoencephalopathy, specific details of exposure to potentially leukotoxic agents should be sought, including exposure to cranial irradiation and current and past use of medications, alcohol, illicit drugs, over-the-counter preparations including herbs, and environmental and occupational toxins (Table 2). Exposure to organic solvents is common among those who are involved in the manufacture of paint, lacquer, varnish, rubber, and dyes and among those who work

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TABLE 1. SPECTRUM OF TOXIC LEUKOENCEPHALOPATHY.

VARIABLE	MILD DISEASE	MODERATE DISEASE	SEVERE DISEASE
Neurobehavioral manifestations	Confusion Inattention Forgetfulness Change in personality	Somnolence Apathy Memory impairment Dementia	Abulia Akinetic mutism Stupor Coma Death
Findings on neuropsychological evaluation	Sustained attention and memory-retrieval deficits Language normal Depression and anxiety often present	Marked deficits in attention, memory, visuospatial skills, and executive function Language relatively normal	Severe global impairment*
Findings on computed tomographic scanning	Usually normal	Possible mild hypodensity of white matter	Diffuse hypodensity of white matter Necrotic areas
Findings on MRI	Hyperintensity of periventricular white matter	Diffuse hyperintensity of white matter	Severe hyperintensity of white matter Necrotic areas
Neuropathological findings	Patchy intramyelinic edema with preservation of myelin	Widespread edema Demyelination with preservation of axons	Destruction of oligodendrocytes Axonal loss Necrosis

*In some cases, the patient is too impaired to be tested.

TABLE 2. CAUSES OF LEUKOENCEPHALOPATHY.*

CAUSE	AGENT OR CONDITION
Toxin	Antineoplastic agents (cranial irradiation, methotrexate, carmustine, cisplatin, cytarabine, fluorouracil, levamisole, fludarabine, thiotepa, interleukin-2, interferon alfa), immunosuppressive drugs (cyclosporine, tacrolimus), antimicrobial agents (amphotericin B, hexachlorophene), drugs of abuse (toluene, ethanol, cocaine, 3,4-methylenedioxymethamphetamine, intravenous heroin, inhaled "heroin" pyrolysate, psilocybin), environmental toxins (carbon monoxide, arsenic, carbon tetrachloride)
Genetic	Leukodystrophies (e.g., metachromatic leukodystrophy, Krabbe's disease, adrenoleukodystrophy, Pelizaeus–Merzbacher disease), aminoacidurias (e.g., phenylketonuria, maple syrup urine disease)
Demyelinating disease	Multiple sclerosis, acute disseminated encephalomyelitis, acute hemorrhagic encephalomyelitis, Schilder's disease, Marburg disease, Baló's disease (concentric sclerosis)
Infection	Acquired immunodeficiency syndrome dementia complex, progressive multifocal leukoencephalopathy, subacute sclerosing panencephalitis, progressive rubella panencephalitis, varicella–zoster encephalitis, cytomegalovirus encephalitis, Lyme encephalopathy
Metabolic disorder	Cobalamin deficiency, folate deficiency, hypoxia, hypertensive encephalopathy, eclampsia, high-altitude cerebral edema
Vascular disorder	Binswanger's disease, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy, cerebral amyloid angiopathy
Trauma	Diffuse axonal injury secondary to traumatic brain injury
Hydrocephalus	Early hydrocephalus, normal-pressure hydrocephalus

*This table emphasizes disorders in which the white matter is the primary target of damage on the basis of both neuroradiologic and neuropathological studies. However, clinically significant white-matter changes can be seen on MRI in some genetic diseases (e.g., neurofibromatosis, Hurler's syndrome, and myotonic dystrophy) and inflammatory diseases (e.g., systemic lupus erythematosus, Behçet's syndrome, Sjögren's syndrome, Wegener's granulomatosis, polyarteritis nodosa, scleroderma, isolated angiitis of the central nervous system, and sarcoidosis) in which the most prominent neuropathological abnormalities are in the gray matter. Tumors with the potential to infiltrate the white matter (gliomatosis cerebri, diffuse gliomas, and primary central nervous system lymphoma) may also cause dramatic changes in white matter that are evident on MRI.

in the dry-cleaning, paint-stripping, and degreasing industries. A careful psychiatric history should be obtained, since it might elicit information on a suicide attempt involving a leukotoxic agent such as carbon monoxide. Features supporting the occurrence of clinically significant intoxication include a well-documented exposure, the onset of symptoms after exposure, and a plausible dose–response relation.[6]

Physical examination typically reveals neurologic findings referable to the cerebrum, although cerebellar, peripheral-nerve, hepatic, cardiac, or hematologic injury may also be present. Documentation of chang-

es in mental status is essential for the diagnosis of toxic leukoencephalopathy. A pattern of deficits in attention, memory, visuospatial skills, executive function, and emotional status in the absence of aphasia suggests the occurrence of white-matter damage.[4] Useful tests include the Digit Span and Serial Sevens tests to detect inattention, the Three-Word Delayed Recall test to identify deficits of recent memory, clock drawing to assess visuospatial dysfunction, and alternating motor sequences to assess executive function.[7] Standardized tests of mental status such as the Mini–Mental State Examination[8] rely heavily on language and are thus relatively insensitive for the diagnosis of white-matter disorders.[4] Personality and emotional disturbances, reflected by apathy, depression, and anxiety, are common.[1,4]

When the initial results of the examination of mental status are equivocal, the patient should be referred for neuropsychological testing, since the results of this procedure can improve both the sensitivity and the specificity of the evaluation. Formal testing can detect subtle dysfunction in a patient's attention span, memory-retrieval ability, and executive function.[4] If none of these deficits are found, the patient can be reassured that no detectable brain damage has occurred.

Neuroimaging of the brain is indicated only if deficits are detected on mental-status examination or neuropsychological testing. Computed tomography is less expensive than MRI, but it often reveals only the most severe degree of toxic leukoencephalopathy, such as marked demyelination or necrosis (Table 1). T_2-weighted MRI is the procedure of choice because of its superior ability to display white matter.[9] Some patients with toxic leukoencephalopathy, particularly that due to ethanol exposure, may have normal results on conventional MRI, but the use of newer techniques of MRI, such as fluid-attenuated inversion recovery, diffusion, and magnetization transfer, may improve the detection of white-matter abnormalities in such patients.[10] These advances may prove particularly useful in distinguishing early or subtle toxic leukoencephalopathy from the psychiatric disorders with which it is confused.

Toxic leukoencephalopathy should not be diagnosed in the absence of corroborating neuroradiologic evidence. A normal finding on conventional MRI in a patient with definite neuropsychological deficits is more consistent with the presence of systemic disorders such as hypothyroidism, hepatic encephalopathy, or uremia. Neuroimaging may also be useful in identifying a mass lesion with subtle symptoms and signs such as a stroke, neoplasm, or abscess.

Leukoencephalopathy may be caused by toxins, but there is also a broad differential diagnosis of genetic, demyelinating, infectious, metabolic, vascular, traumatic, and hydrocephalic disorders[2] (Table 2). Although a detailed discussion of these leukoencephalopathies is beyond the scope of this review, clinical features (e.g., the patient's age, the presence or absence of a family history, and systemic disease manifestations) and MRI findings (e.g., the distribution of the lesions and the appearance of the ventricles) most often suggest the correct diagnosis. If these other causes can be ruled out, toxic leukoencephalopathy is likely. In our experience, which grows out of a hospital-based practice with patients with predominantly iatrogenic toxic leukoencephalopathy and a consulting service for those with occupational exposure, the specific toxins can be identified in most cases. In other settings, such as outpatient clinics that treat large numbers of patients with substance-abuse problems or critical care units that treat comatose patients who have had acute exposure to toxins, it may be difficult to establish a single or specific cause.

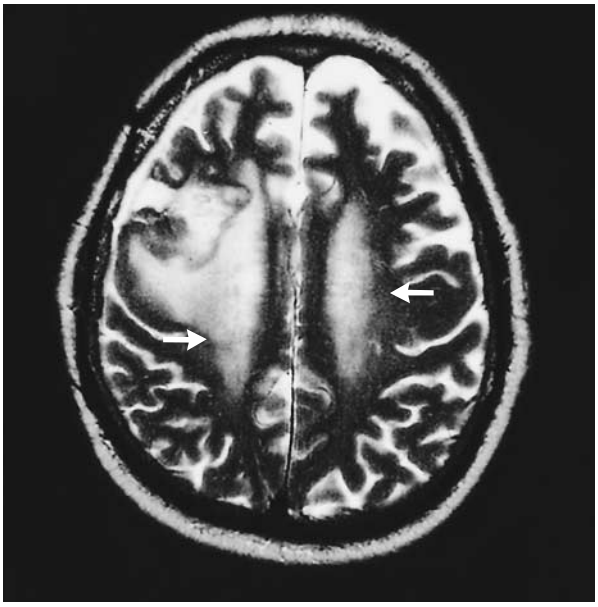
Laboratory testing has limited usefulness in chronic cases because the exposure often occurred years earlier or because no test exists to identify the suspected toxin. Toxicologic screening detects alcohol and cocaine if the exposure is recent. Testing for toluene toxicity is not widely available, but in some centers, a history of acute intoxication can be ascertained by the analysis of a specially collected and transported blood sample and a history of chronic exposure can be ascertained by the analysis of a 24-hour urine collection. The extent of exposure to carbon monoxide is quantitated by spectrophotometric testing for carboxyhemoglobin. Screening of urine for heavy metals detects cases of chronic arsenic poisoning, as well as toxicity from lead and mercury, both of which can produce white-matter edema or can secondarily damage the white matter.

WHITE-MATTER TOXINS

Neuroradiologic and neuropathological studies have been the primary means of identifying toxins that target cerebral white matter.[1] These reports provide evidence of the causes of toxic leukoencephalopathy but do not provide information on the prevalence of the disorder among persons who are exposed. However, given the continued introduction of new therapeutic agents, especially for cancer, and the continuing use by the public of recreational drugs, the number of leukotoxins is likely to grow.

Therapeutic Agents

Cranial irradiation and anticancer chemotherapy are well-established causes of toxic leukoencephalopathy (Fig. 1A). The degree of neurotoxicity resulting from cranial irradiation correlates with the total dose received, time–dose–fractionation schemes, and the volume of tissue irradiated,[11] but according to at least one estimate, some degree of neurobehavioral dysfunction develops in up to 28 percent of patients who receive cranial irradiation.[1,12] Radiation produces three stages of leukoencephalopathy: an acute reaction involving patchy, reversible edema of the white matter,



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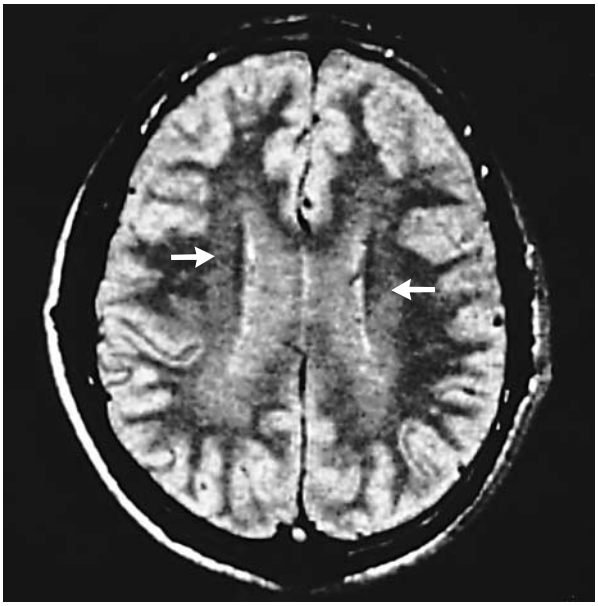

B

Figure 1. MRI Features of Toxic Leukoencephalopathy.

A T_2-weighted MRI scan in a man with a right frontal glioblastoma multiforme after radiation and chemotherapy with carmustine shows symmetric hyperintensity of the cerebral white matter (arrows in Panel A). Somnolence developed in parallel with the white-matter changes. A T_2-weighted MRI scan in a man with dementia and long-term toluene abuse shows symmetric hyperintensity of cerebral white matter with ventricular enlargement (arrows in Panel B).

a more sustained delayed reaction involving widespread edema and demyelination, and a severe delayed reaction involving the loss of myelin and axons as a result of vascular necrosis and thrombosis.[11] Toxic leukoencephalopathy is most likely to result from radiation delivered to the whole brain rather than local-field radiotherapy[13] and is increasingly recognized in those who survive cancer treatment for more than one year.[13]

Methotrexate and carmustine are the most commonly implicated anticancer drugs. Cisplatin, cytarabine, fluorouracil, levamisole, fludarabine, thiotepa, interleukin-2, and interferon alfa are also responsible in some cases.[1] The incidence of neurotoxicity depends on the route of delivery, the dose, and the drug used.[1] For example, leukoencephalopathy may occur in less than 10 percent of those who are treated intravenously with methotrexate,[14] but in up to 40 percent of those who are treated by the intrathecal route.[15] The effects of chemotherapeutic agents are similar to those of cranial irradiation, and combined therapy may be particularly injurious.[1] A reduction in normal white-matter volume correlates strongly with neurocognitive deficits in children with brain tumors who have received cranial radiation and chemotherapy.[16]

Toxic leukoencephalopathy has also been associated with various other agents. The immunosuppressive drugs cyclosporine and tacrolimus, used in organ transplantation, may produce white-matter changes on MRI that resolve once treatment is discontinued.[1] Rare causes include amphotericin B and hexachlorophene.[1] A report of two patients with a syndrome resembling acute disseminated encephalomyelitis after parenteral therapy with herbal extracts[17] suggests the potential for leukotoxicity from preparations of this kind.

Drugs of Abuse

Toxic leukoencephalopathy is a recognized risk of the excessive use of many different substances of abuse. Although the increasing prevalence of abuse is acknowledged, the incidence of toxic leukoencephalopathy among the users of these drugs is unknown. However, if white-matter damage occurs in even a small percentage of these persons, the problem may be clinically significant because of the large number of people who are exposed.

Study of those who abuse toluene has clearly established that this organic solvent can produce severe neurologic disability related to selective white-matter damage.[18-21] Exposure to toxic levels of toluene results from the intentional inhalation of volatile fumes from spray paints and glues.[18] The prevalence of toluene abuse is unknown, but 10 to 15 percent of young people in the United States are estimated to have used inhalants.[22] Prolonged inhalation of this highly lipophilic white-matter toxin results in dementia, ataxia, brain-stem dysfunction, and corticospinal

deficits.[18] Widespread hyperintensity of white matter is evident on MRI scans of affected patients (Fig. 1B), and the extent of the changes in white matter correlates with the severity of dementia.[21] Findings at autopsy include diffuse pallor of the cerebral and cerebellar white matter, with clusters of trilaminar inclusions within the cytoplasm of mononuclear cells and increased numbers of very-long-chain fatty acids, as are found in patients with adrenoleukodystrophy.[19,20] These findings suggest that the mechanisms of myelin degradation are similar in toluene leukoencephalopathy and adrenoleukodystrophy and confirm that myelin is the target of toluene.[19,20]

Evidence of the leukotoxicity of ethanol has also appeared. Alcoholism affects nearly 10 percent of the U.S. population,[23] and 50 to 70 percent of former chronic alcoholics who are sober and whose condition is medically stable have neuropsychological impairment.[24] Although some of this cognitive loss can be attributed to Korsakoff's amnesia resulting from damage to the dorsal medial thalamic nuclei and mammillary bodies induced by a thiamine deficiency,[25] white-matter damage also contributes to alcoholic dementia.[1] As compared with persons who are not alcoholic, persons with chronic alcoholism have a disproportionate loss of cerebral white matter,[26] and dogs exposed to alcohol have similar changes in white matter.[27] Persons with alcoholism may have an excessive number of hyperintense areas of white matter on MRI,[28] and disruption of the microstructure of white matter has been found on diffusion MRI studies of persons with alcoholism.[29] With abstinence, cerebral atrophy[30,31] and cognitive impairment[32] are partially reversible, and a decrease in atrophy correlates with a selective increase in white-matter volume.[33] The frontal white matter is preferentially affected in persons with chronic alcoholism,[34,35] which is consistent with studies documenting deficits in working memory,[34] attention,[35] and executive function[36] in these patients. The fetal alcohol syndrome includes among its potential features delayed myelination of the brain and agenesis of the corpus callosum.[37] Marchiafava–Bignami disease is a rare dementia of persons with chronic alcoholism that is characterized by atrophy and necrosis of white-matter tracts including the corpus callosum.[38] Persons with alcoholism may also have atrophy of the corpus callosum in the absence of necrosis and Marchiafava–Bignami disease.[39]

Several other illicit drugs have also been associated with leukoencephalopathy. In 1999, cocaine, 3,4-methylenedioxymethamphetamine (MDMA, or "ecstasy"), and heroin were used by an estimated 9.8 percent, 8.0 percent, and 2.0 percent, respectively, of high-school seniors in the United States.[40-42] Asymptomatic cocaine-dependent subjects have significantly more white-matter lesions on MRI than control subjects, suggesting that those who abuse cocaine are at increased risk for vasospasm-induced ischemia and infarction of white matter.[43] MDMA has been reported as a cause of toxic leukoencephalopathy,[44] putatively related to serotonergic axonal injury and secondary myelin damage from oxidative stress.[44-46] Intravenous heroin causes hypoxic–ischemic leukoencephalopathy,[47] and the inhalation of "heroin" pyrolysate, which is generated by heating the drug on aluminum foil, produces evidence of toxic leukoencephalopathy on MRI that correlates with neuropathological evidence of spongiform changes in white matter and the degeneration of multivacuolar oligodendrocytes.[1] The hallucinogen psilocybin has been tentatively linked with multifocal cerebral demyelination.[48]

Environmental Toxins

Carbon monoxide poisoning may occur as a result of accidental exposure or a suicide attempt. After an initial period of recovery,[1] cerebral demyelination can develop days to weeks after carbon monoxide intoxication. Although the delay in the appearance of leukoencephalopathy after carbon monoxide poisoning is unexplained, prolonged depression of oxygenation and circulation may be responsible.[1] Toxic leukoencephalopathy has also been described in persons who were exposed to arsenic and carbon tetrachloride.[1]

Occupational Exposure to Solvents

The possibility of brain damage from long-term exposure to low levels of toluene and other organic solvents is a health concern for many workers.[49] Some 50 million tons of organic solvents are produced annually in the United States, potentially exposing about 10 million workers,[50] mainly to mixtures of solvents including toluene, methanol, benzene, xylene, styrene, trichloroethylene, perchloroethylene, methylene chloride, and carbon disulfide. In the 1970s, the "chronic painters' syndrome," or "psycho-organic syndrome," was described in workers with occupational exposure to solvents who had symptoms of neurobehavioral impairment.[51] This syndrome has variously been viewed with support[52] or skepticism.[53] Debate continues because studies are hampered by the lack of documentation of the degree and duration of exposure, lack of adjustment for exposure to multiple solvents and coexistent alcohol and drug abuse and psychological abnormalities, ill-defined dose–response relations, the use of nonstandardized neuropsychological tests, and litigation issues.[49]

At permissible industrial levels, solvents are not an established cause of toxic leukoencephalopathy,[53,54] but a pattern of deficits in attention, memory, psychomotor speed, and visuospatial ability in persons with occupational exposure[52] suggests that these agents have subtle effects on cerebral white matter.[4] In workers who have been exposed to solvents, mild changes in white matter have been identified on MRI[55]; such changes were less severe than those with prolonged toluene abuse.[21] Toluene and other solvents may af-

fect white matter in a dose-dependent manner, so that toxic leukoencephalopathy only appears above a certain threshold of exposure. Prospective, controlled studies of workers at risk are needed that involve careful monitoring of exposures and the use of standardized neuropsychological measures and advanced neuroimaging techniques.

PREVENTION AND TREATMENT

Prevention of iatrogenic and illicit exposure to leukotoxins is critical, because treatment options are limited. Less toxic therapeutic regimens for cancer, improved drug-counseling programs for adolescents and young adults, and more effective education to reduce exposure to environmental toxins are all needed. In occupational settings, further efforts are needed to determine and maintain safe levels of exposure to organic solvents.

There is no uniform therapeutic approach to toxic leukoencephalopathy. Available therapies include corticosteroids, anticoagulation, and ventriculoperitoneal shunting for leukotoxicity from cranial irradiation, leucovorin for methotrexate-induced toxicity, and chelation for arsenic poisoning.[1] The development of specific therapies requires the identification of the site or sites damaged by individual leukotoxins, such as myelin, axons, oligodendrocytes, astrocytes, and the white-matter vasculature (Fig. 2). Future nonspecific therapies might include inducing intact oligodendrocytes to remyelinate demyelinated axons[59] or transplanting embryonic stem cells, which would subsequently differentiate into functional, myelinating oligodendrocytes.[60]

CONCLUSIONS

Toxic leukoencephalopathy is a disorder related primarily to the use of leukotoxic therapeutic agents, illicit-drug use, and occupational exposure to toxins. Whereas the percentage of exposed persons in whom leukoencephalopathy develops is unknown in the case of many of these agents, patients typically present with neurobehavioral dysfunction reflecting diffuse involvement of the cerebral white matter, which is best seen on T_2-weighted MRI scans. The differential diagnosis includes a broad range of nontoxic leukoencephalopathies. Physicians can help prevent or minimize

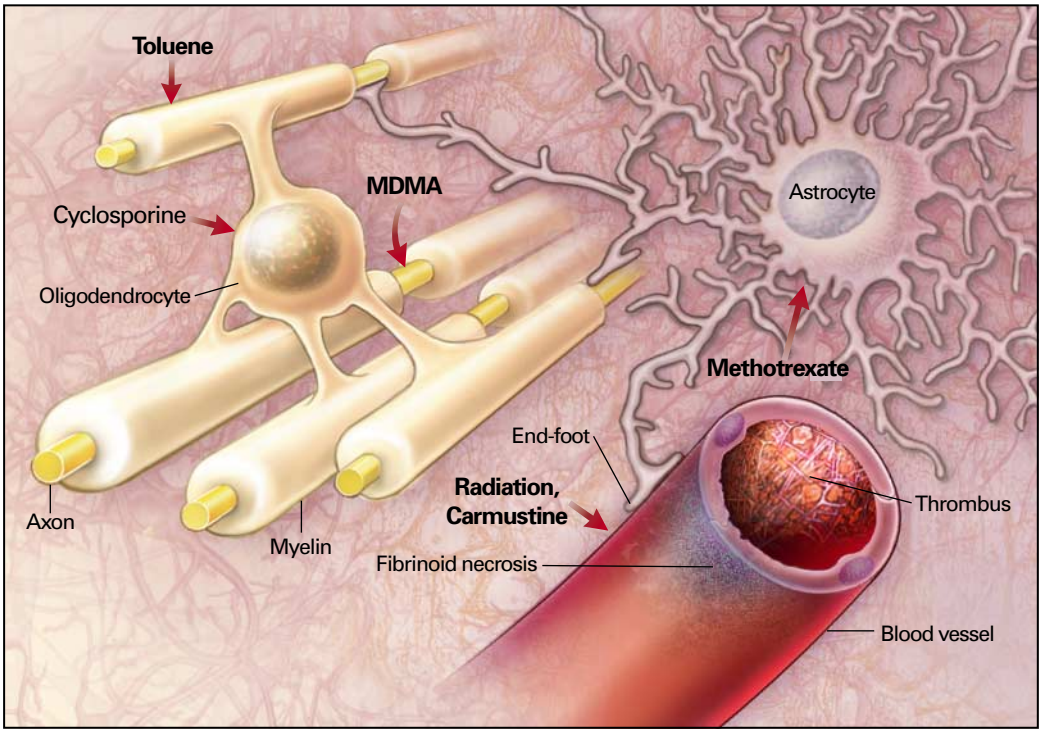

Figure 2. Targets of Toxins in Cerebral White Matter.

The cellular and tissue components of cerebral white matter include myelin, which is necessary for the conduction of neural impulses; oligodendrocytes, which are responsible for the formation of myelin; axons ensheathed by myelin; astrocytes, which regulate the metabolic environment and are the principal scar formers; and blood vessels. Examples of toxins that target each cellular or tissue component are shown, highlighting the diversity of pathophysiological mechanisms responsible for toxic leukoencephalopathy.[11,19,20,44-46,56-58] MDMA denotes 3,4-methylenedioxymethamphetamine.

toxicity, but therapeutic advances for established disease will require the identification of specific pathophysiological mechanisms. The occurrence of toxic leukoencephalopathy highlights the vulnerability of white matter to injury from toxins and underscores the important role of white matter in neurobehavioral function.

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