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Toxic Encephalopathy

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There is growing awareness that chronic intoxications by industrial, agricultural, iatrogenic, and environmental pollution may have teratogenic or oncogenic influence or may cause neurologic or psychiatric syndromes.

Toxic encephalopathy (TE) is the result of the interaction of a chemical compound with the brain. Disturbance of normal brain function is caused by:

1. depletion of oxidative energy;
2. nutritional deprivation affecting nerves and neurons;
3. exposure to foreign material which may be
   a. exogenous in origin,
   b. generated within the central nervous system, or
   c. generated within the body;
4. derangement of neurotransmission;
5. altered ion balance;
6. antigenic activity.

The list of examples of toxic encephalopathy is long and reflects the real difficulty in recognizing that slow deterioration of neurologic functions indicates poisoning by a toxin. In many cases, religious, superstitious, or racial "explanations" have been believed for a long time, before the true cause of the disorder was detected (1, 2).

Well known examples of toxic encephalopathy include:

1941—*Lathyrus sativus* peas, spastic paraparesis; the toxic agent was identified to be β-*N*-methylamino-L-alanine (BMAA);

1953—Guamalian type of Parkinsonism, caused by the seeds of *Cycas circinalis*; the toxic agent was identified as β-*N*-oxalylmethylamino-L-alanine (BOMAA);

1948—hexachloraphene encephalopathy;

1950—monosodium glutamate in baby food;

1953—Minamata disease, mercury encephalopathy;

1960—housepainters dementia, organic solvents;

1983—methylphenyltetrahydropyridine (MPTP), "synthetic heroin," causing striatal dopamine deficiency and Parkinsonism.

Clinically toxic encephalopathy presents with one of more of the following neurologic or psychiatric symptoms:

1. decreased concentration and consciousness;
2. excitability and convulsions;
3. motor and sensory disturbances;
4. extrapyramidal movement disorders;
5. disturbance of specific senses;
6. disturbance of coordination; and
7. behavioral and psychological changes (Bonhoeffer types).

Most of the intoxications of the central nervous system (CNS) are acute and require immediate treatment. The patients are usually referred to intensive care units. Imaging of the brain is only of secondary interest. The role of imaging be-

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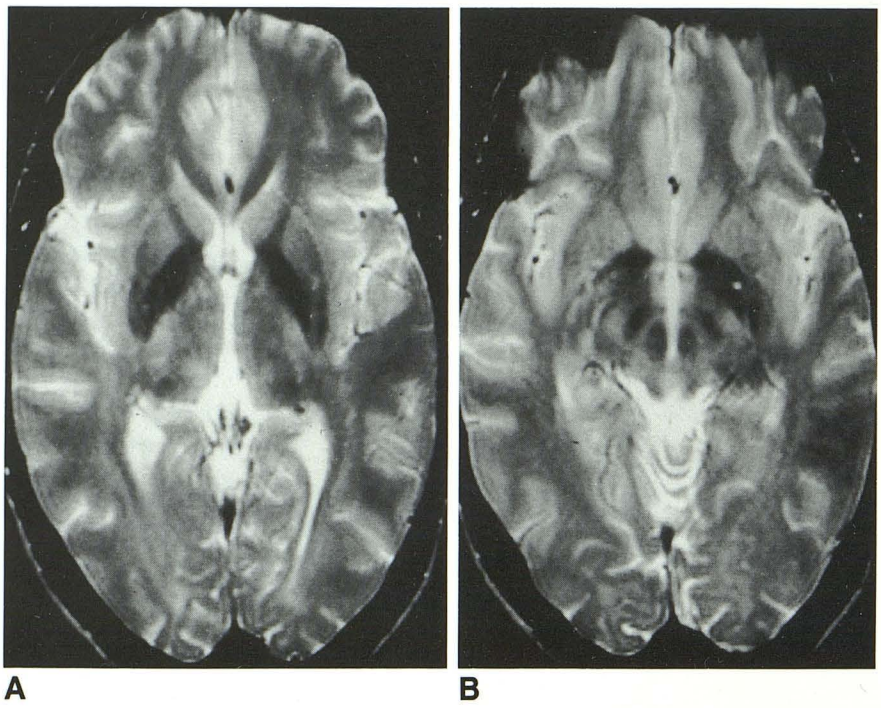


Fig. 1. Topistic area. T2-weighted images at the level of the foramen of Monro (*A*) and of the midbrain (*B*) show the morphology of parts of the extrapyramidal system, as indicated by the deposition of iron in the pallidum, the substantia nigra, and the red nucleus.

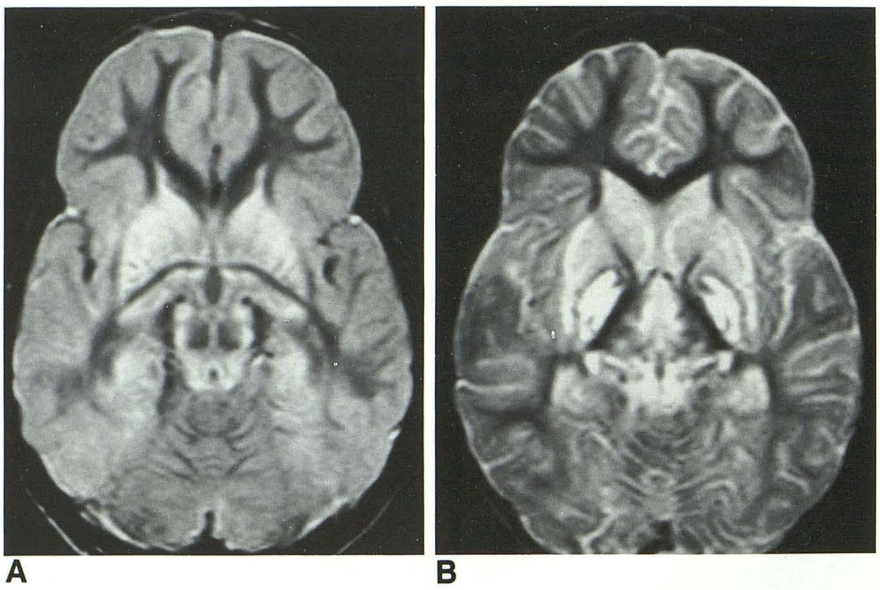


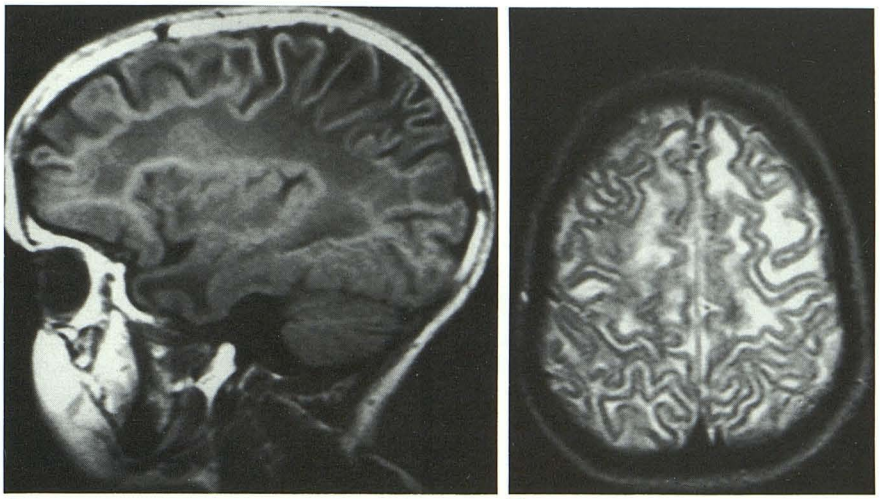
Fig. 2. A 3-year-old boy nearly drowned in a swimming pool at home. CT scan (data not shown) demonstrated the so-called "white cerebellum" and bilateral hypodensity of the pallidum. Proton density axial MR (*A*) and T2-weighted axial MR (*B*) through the basal ganglia show nearly symmetrical involvement of the caudate nuclei, the putamina, the globi pallidi, the thalami, the geniculate bodies, the gray matter in the wall of the third ventricle, and the periaqueductal gray matter. Extensive cortical laminar necrosis is observed.

comes more important in cases of subacute or chronic toxicity with residual neurologic damage. In such cases, magnetic resonance (MR) can sometimes demonstrate striking pathologic changes associated with the encephalopathy, and can be of importance for further diagnosis.

However, even in cases with histologically proven organic cerebral damage, computed tomography (CT) or MR is not always positive. For example, tardive dyskinesia is a severe movement disorder due to the chronic use of neuroleptic drugs. The pathology is well known. Histology shows a decrease in the number of ganglion cells in the substantia nigra. MR imaging shows no abnormalities. Similarly, in the acute malignant neuroleptic syndrome MR also shows no abnormalities.

Knowledge of the biomechanisms by which toxins cause encephalopathy helps us to understand the selectivity of the lesions seen in the imaging studies of toxic encephalopathy.

The characteristic MR images are the result of differences in regional vulnerability of brain tissue to environmental perturbations and to biochemi-



A B

Fig. 3. Vacuolating myelinopathy. This type of myelin disorder is seen with a number of conditions: hexachlorophene encephalopathy, triethyl tin encephalopathy, Canavan disease, and other organic acidopathies and aminoacidopathies.

A, Parasagittal T1 MR shows the characteristic swelling of the white matter in the subcortical U fibers and the stretching of the cortex. The involved area has low signal intensity and reaches into the arcuate fibers.

B, T2-weighted transverse MR through the supraventricular parietal region shows extensive white matter involvement including the U fibers. The gyri stand out against the background of swollen white matter.

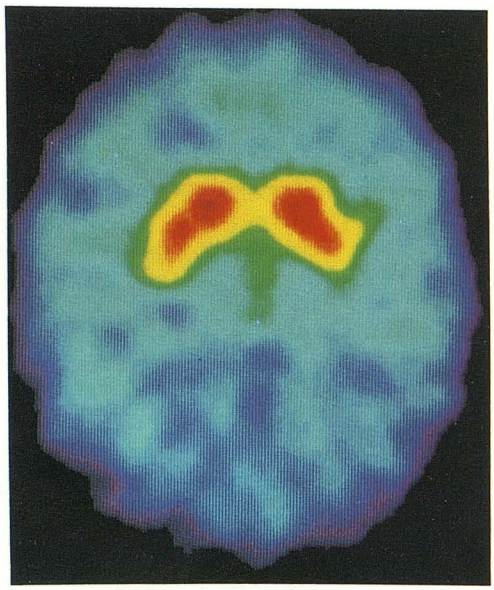


Fig. 4. Topistic area. PET demonstrates the distribution of ^{18}fluorodopa and illustrates the concept of a topistic area related to the distribution of a particular neurotransmitter.

cal changes. These differing vulnerabilities reflect a number of factors, of which the most important are

1. regional cerebral blood flow/oxygen demand;
2. distribution of neurotransmitters;
3. specific chemical affinity and vulnerability; and
4. developmental maturation of the patient at the time of intoxication.

Selective Vulnerability

As a general rule, specific groups of toxins tend to affect specific brain structures more than others. That is, certain regions and systems within the brain have greater affinity for and greater sensitivity to specific types of toxins. These regions of identical affinity and vulnerability were recognized by German neuropathologists who designated them the "Topistische Bezirke" or topistic topographical areas.

The topistic areas often involve more than one structure; indeed, they often encompass a whole functional chain of neurons and tracts. The principle of *functionally related systems* is well established. Topistic areas can readily be identified during normal physiologic development of the brain (Fig. 1) and in systemic degenerative disorders (3). Thus, in 1920, Flechsig already recognized that functionally related systems myelinate at the same time (4). Similarly, functionally related and interdependent nuclei appear to degenerate at the same time in multiple system atrophies such as Parkinson disease and progressive supranuclear palsy.

Other mechanisms of selective vulnerability are related to the *similarity in particular characteristics* that make the different geographic areas equally vulnerable to a particular noxious agent. Thus, apparently diverse areas may prove to have similar oxygen requirements, chemical compositions, and/or neurotransmitters.

Gray matter structures have a higher cellular activity and a higher oxygen requirement than white matter structures and, therefore, are more vulnerable to oxygen deprivation (Fig. 2). The damage that results from oxygen deprivation is actually mediated by toxic products, such as excitatory amino acids or free radicals that lead to irreversible neuronal damage and death. The

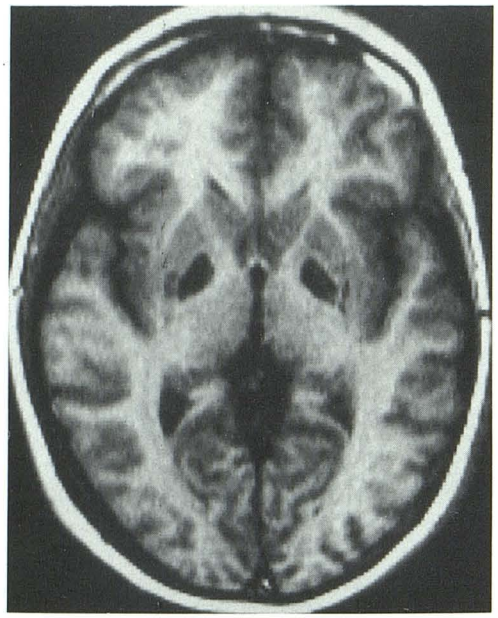


Fig. 5. Ecstasy encephalopathy. Selective involvement of the globus pallidus and the most dorsal part of the putamen in an 18-year-old girl, after drinking a love potion containing Ecstasy (3,4 methylenedioxymetamphetamine). Consequent behavioral changes required psychiatric hospitalization. Ecstasy influences particular neurotransmitter receptors.

selective vulnerability of gray matter structures to energy depletion is also reflected in the preferential affliction of gray matter structures in carbon monoxide (CO) intoxication (especially the pallidum), and Leigh disease (the gray matter around the third ventricle, the periaqueductal gray matter, the tectum and tegmentum of the brain stem, and the dentate nuclei). Wernicke encephalopathy, a toxic encephalopathy caused by thiamine deficiency in alcoholics, shows the same pattern of selective involvement as Leigh disease, plus involvement of the mammillary bodies, presumably because thiamine deficiency also influences energy metabolism.

An example of selective vulnerability resulting from specific chemical composition is found in myelin. Myelin has an especially high lipid content and shows especially slow turnover. As a result, all the myelinated tracts are particularly vulnerable to the accumulation of lipophilic substances and to lipid peroxidation. One instance of such intoxication has become famous in medical literature: hexachlorophene encephalopathy, a vacuolating myelinopathy, was found in infants that were washed with antiseptic hexachlorophene solutions for dermal problems. The skin of preterm neonates proved to be more permeable to these agents than the more mature skin, resulting in increased absorption and unfortunate toxicity. In adults, vacuolating myelinopathy has been described after the use of hexachlorophene solutions in vaginal tampons and as an antiseptic agent on burned areas. Intoxication with triethyl tin has identical effects (Fig. 3).

Topistic areas related to the distribution of a particular neurotransmitter are best visualized by positron emission tomography (PET). PET, for example, shows the distribution of ^{18}fluorodopa in the basal ganglia (Fig. 4). Methylphenyltetrahydropyridine (MPTP) interferes selectively with the dopamine neurotransmitters and leads to severe Parkinsonism. Tardive dyskinesia and malignant neuroleptic syndrome are other examples of toxic encephalopathy in a topistic area related to specific neurotransmitters. In this kind of involvement of a neurotransmitter system, imaging modalities usually do not show abnormalities. However, Figure 5 illustrates an example in which MR successfully depicts the topistic areas.

Selective vulnerability is also related to *the level of activity during development.* This concept was particularly stressed by Dobbing (5) and has broadened our insight into the origin of congenital malformations of the central nervous system (6). The greatest impact of noxious agents is on those structures that grow and develop at the highest rate at the time of insult. Thus, migrational disorders result when toxic insults are suffered in the third to fifth month of gestation, the period in which neuronal migration occurs (Fig. 6). Similarly, disorders of myelination are observed when toxic insults occur during the last trimester of pregnancy and the first year of life, because myelination of the CNS occurs at a high rate in these periods. Since normal myelination depends upon complex interactions between axons, myelin-forming oligodendrocytes and the provision of substrates by the environment, the delicate interactive process is easily disturbed by adverse factors such as nutritional deficiencies and intoxications (7).

Classification

To facilitate our analysis of TE we have classified the toxic encephalopathies by origin of the *toxins* within or outside the blood-brain barrier (endogenous vs exogenous) (Table 1). Exogenous TE is then further subdivided by whether the toxic substance originates inside or outside the body (exogenous-internal vs exogenous-external). This classification is imperfect because it

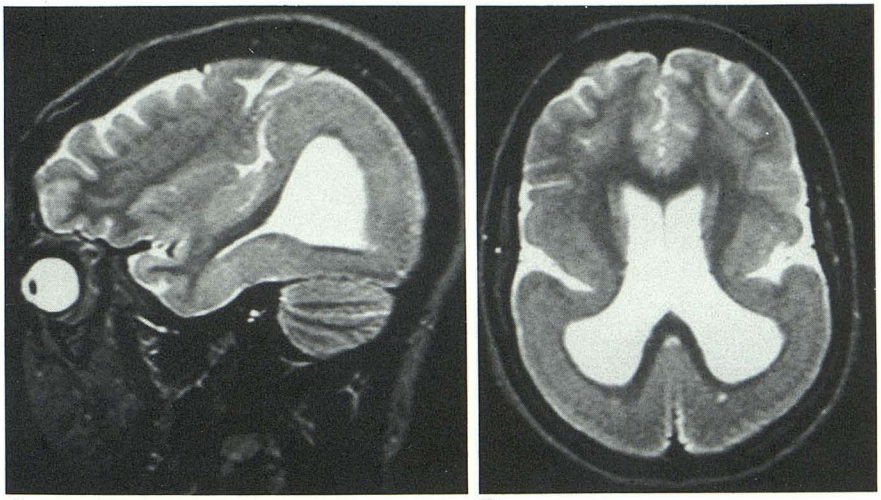


Fig. 6. Migration disorder; 14-year-old girl with psychomotor retardation and epilepsy. T2-weighted parasagittal and transverse images show a combination of an occipital lissencephaly and frontotemporal pachygyria, with linear heterotopia of the gray matter in the frontal lobes. Irregularities around the occipital horns suggest an encephaloclastic or toxic cause for the arrest of development.

depends in part, on observer bias. Thus, Gram-negative endotoxin can be classified either as exogenous-external, because the *Escherichia coli* infection stems from outside the body, or as exogenous-internal because the endotoxin causing the related encephalopathy is produced by the *E. coli* within the body. We prefer exogenous-internal, because the toxin itself is produced within—and in interaction with—the body.

The largest group of toxins are exogenous-external. Toxins within this group are usually categorized heterogeneously by chemical composition, source, and effect. Dietary and chemical deficiencies may lead to abnormal biochemical processing that produces effects comparable to intoxications. They may show patterns of damage by virtue of selective vulnerability. These deficiency states are included among the exogenous-external toxic encephalopathies.

Exogenous-External TE

The group of exogenous-external TEs includes all intoxications from iatrogenic, agricultural, industrial, environmental, and social (drugs, alcohol, nicotine) sources that affect the CNS.

To this group belong *Lathyrus sativus* peas, the Guamanian type of Parkinsonism, organic mercury poisoning, organic lead poisoning, and toluene exposure or sniffing; so do other well known encephalopathies associated with ethanol abuse, such as the Marchiafava-Bignami syndrome. Wernicke encephalopathy, and the Korsakoff syndrome, Iatrogenic exogenous-external TE includes all the TEs caused by the ingestion of prescribed drugs, such as anticancer agents, anticonvulsants, tranquilizers, and anesthetic gasses, or caused by medical treatments such as postdialysis progressive aluminum encephalopathy. The fetal intoxication syndromes can also be considered in this category.

Organic Mercury Poisoning

Ingestion of fish caught in the poisoned bay of Minamata led to a neurologic disorder that was eventually identified as being caused by organic mercury (8). Mercury intoxication has also been reported after accidental ingestion of wheat that had been treated with organic mercury compounds to prevent cropping. Neuropathology shows degeneration of the granular layer of the cerebellum and patchy loss of cells in the cerebral cortex, in particular the calcarine cortex.

MR images show the deposition of mercury in cerebellar structures and under the occipital cortex (Fig. 7).

Wernicke Encephalopathy

Wernicke encephalopathy (9–11) results from a deficiency of vitamin B1 (thiamine), and, as such, is not confined to chronic alcoholics. Because vitamin B1 is a cofactor of transketolase, thiamine deficiency causes decreased activity of this enzyme. The precise relationship of reduced enzyme activity to damage in the characteristic "topistic area" represented by Wernicke encephalopathy (Fig. 8) is conjectural. Korsakoff disease is now generally seen as a chronic stage of Wernicke encephalopathy, with consistent atrophy of the mammillary bodies and variable involvement of the dorsomedial nucleus of the thalamus.

TABLE 1:

TOXIC ENCEPHALOPATHY

- **EXOGENOUS**
  - **INTERNAL**
    - endotoxins
    - paraneoplastic toxins
    - uremia
    - ion balance disorders
  - **EXTERNAL**
    - **TOXIC SUBSTANCES**
      - classification
        - chemical composition
        - source: industrial, agricultural, iatrogen
        - effects: oncogens, teratogens, (para) sympathicomimetica, (para) sympathicolytica
    - **DEFICIENCIES**
      - vitamins
      - nutritients
- **ENDOGENOUS**
  - inborn errors of metabolism

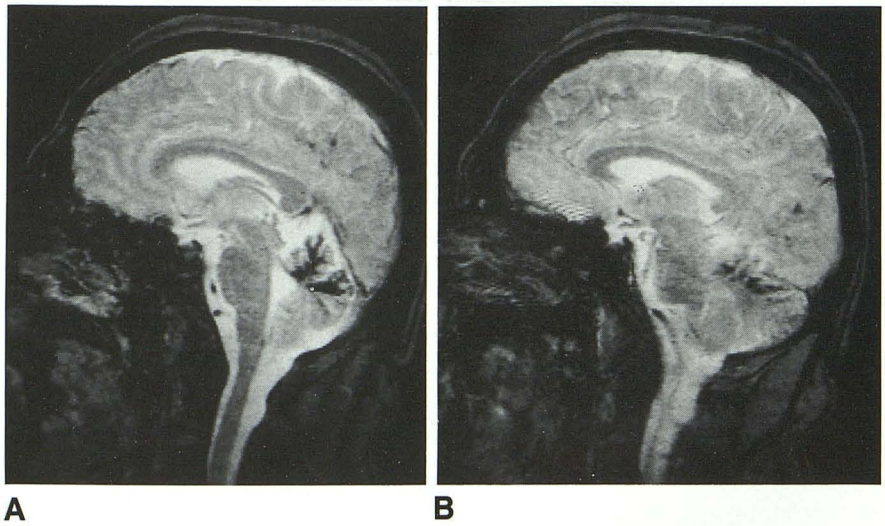


Fig. 7. Mercury encephalopathy; 50-year-old man with a 2-year course of progressive cerebellar and focal cerebral signs following use of a mercury-containing compound to prevent tulip bulbs from cropping. The midsagittal (*A*) and parasagittal (*B*) gradient recalled echo images show the magnetic susceptibility effect of the mercury deposits in the cerebellum and beneath the occipital cortex, extending the histopathologic findings in this region.

Cytostatic Agents

Cytostatics, such as methotrexate and 5 fluorouracil can lead to severe changes in the white matter (Fig. 9) when they are used to treat extracranial tumors, or intracranial tumors (often in combination with radiotherapy).

Heroin Pyrolysite

During the 1980s, a group of chronic heroin addicts in Amsterdam was discovered to manifest progressive neurologic symptoms after years of sniffing heroin. On neuropathologic examination, a vacuolating myelinopathy was discovered in these cases (12, 13). MR studies revealed extensive involvement of the white matter of the cerebral hemispheres and the cerebellum and clearly depicted the involved tracts from the parietal cortex to the brain stem (Fig. 10). The toxic substance in the heroin has not been discovered. One assumes that it must be a lipophilic substance.

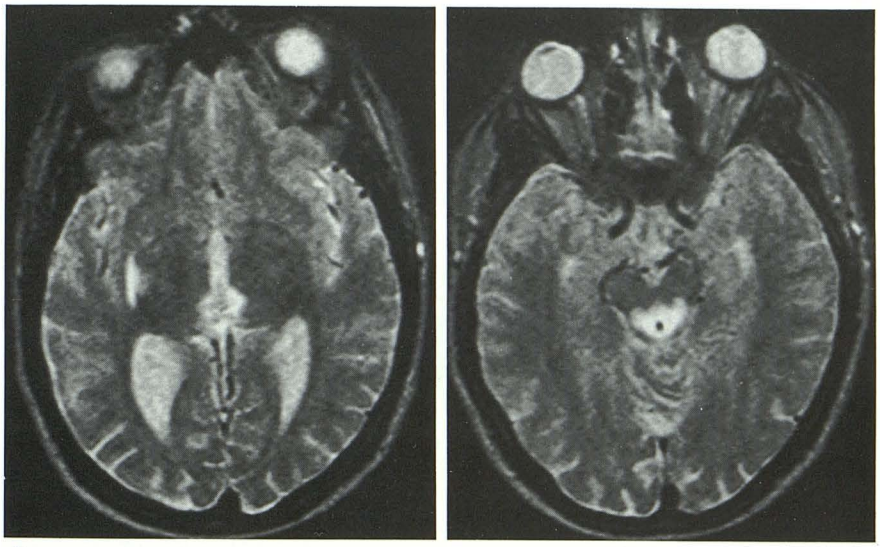


Fig. 8. Wernicke encephalopathy. T2 MR at the level of the third ventricle (*A*) and the midbrain (*B*) show abnormally increased signal in the putamen on the right side (*A*), the gray matter surrounding the third ventricle (*A*), and the periaqueductal gray matter (*B*). Wernicke encephalopathy has a characteristic distribution, comparable to Leigh disease and other disorders that influence the energy supply of the tissues.

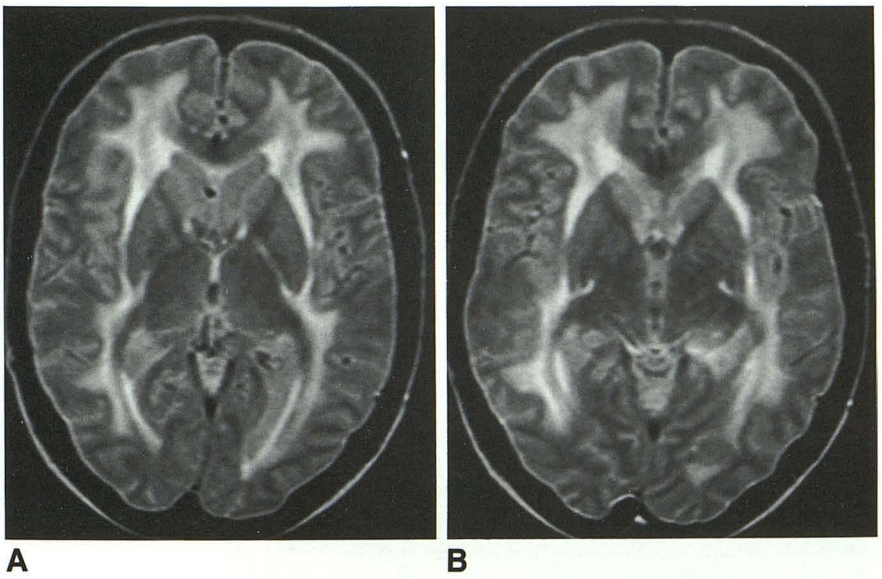


Fig. 9. Thirty-one-year-old woman treated with intrathecal methotrexate for leptomeningeal carcinomatosis, 2 years after mastectomy for breast carcinoma. T2 MR shows symmetrical involvement of the internal and external capsules and of the frontal and occipital white matter, sparing the U fibers.

Organic Solvents

Chronic inhalation of organic solvents or other preparations containing toluene is known to cause multifocal neurologic and mental disorders, cerebral, cerebellar and brain stem atrophy, and diffuse focal white matter abnormalities detectable by MR (Fig. 11) (14–17). Toluene is one example of a typical lipophilic substance that persists in the myelin for a long time, leading to severe functional disturbances.

Exogenous-Internal TE

The disorders caused by exogenous-internal toxins have in common a focal or generalized process in the body outside the blood-brain barrier that produces a toxin that crosses the barrier, enters the brain, and causes encephalopathy. Paraneoplastic syndromes and parainfectious degenerations belong in this category. Malignant disease anywhere in the body may have a remote effect on the peripheral nerves, the spinal cord, and on the brain, causing peripheral neuropathy, subacute necrotizing myelopathy, and encephalomyeloradiculitis. The encephalomyeloradiculitides group manifests in two different forms; brain stem "encephalitis," and so called limbic "encephalitis" in which the changes are restricted to the limbic system. These differing manifestations presumably reflect the differing selective vulnerability of brain structures to toxic agents. Parainfectious encephalopathy has been reported with

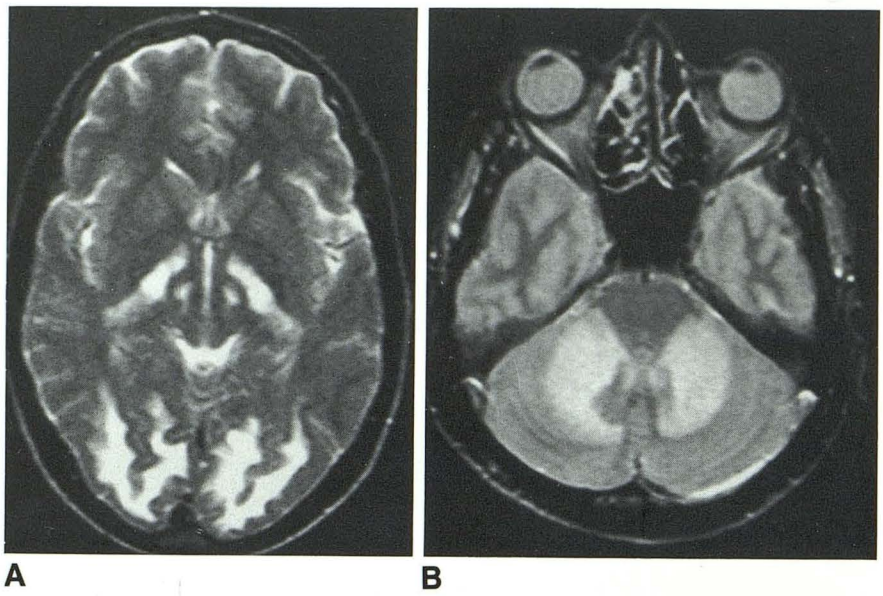


Fig. 10. Vacuolating myelinopathy from unknown toxin; 26-year-old man who sniffed heroin pyrolysite, polluted with a still unknown toxin. He and many others developed severe neurologic motor and coordination problems, secondary to pathologically confirmed vacuolating myelinopathy. All the patients' lesions were restricted to the white matter, in a characteristic distribution. *A*, T2 MR shows high signal intensity of the posterior limb of the internal capsule and of the centromedian nucleus of the thalamus. White matter lesions are present in the arcuate fibers of the occipital lobes. *B*, Proton density MR shows involvement of the cerebellar white matter.

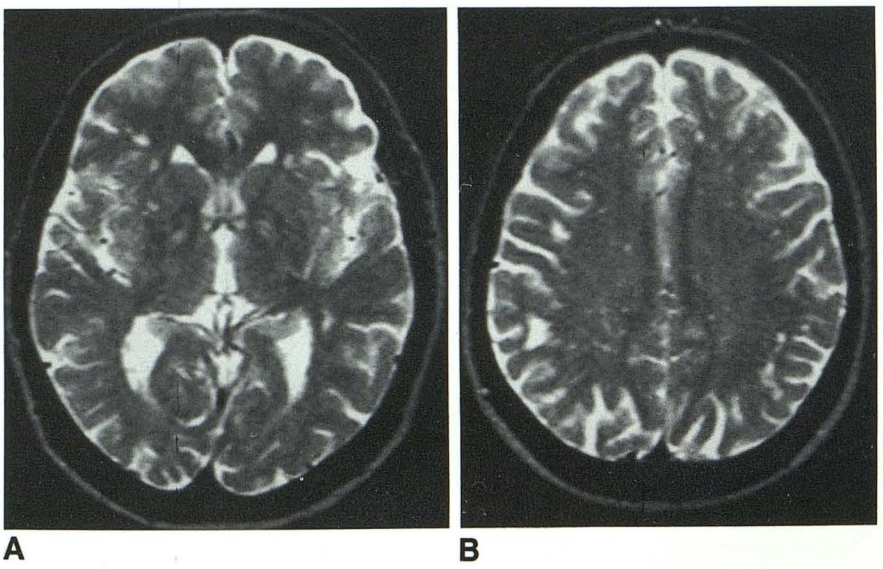


Fig. 11. Industrial toxin; 58-year-old man with progressive memory loss who worked in the paint industry for more than 40 years. The T2 MR show diffuse focal changes in the white matter and in the cortex. There is loss of cortical tissue, with widening of the subarachnoid spaces and the Sylvian fissure.

E. coli, mycoplasma, and diphtheria infections. Changes in the ion balance are held responsible for central pontine and extrapontine myelinolysis. Porphyria, an inborn error of metabolism, may lead to a peripheral neuropathy and encephalopathy with foci of myelin loss, myelin pallor, and ischemic changes in the gray matter that are probably secondary to vasospasm.

Hepatocerebral syndromes may be the result of an inborn error of metabolism such as Wilson disease. In Wilson disease, the encephalopathy is caused by ceruloplasmin deficiency leading to excessive deposition of copper in tissues, especially the globus pallidus. Hepatorenal syndromes may also result from cirrhosis or portocaval shunts with acquired hepatic failure, probably mediated by hyperammonemia. This form will be discussed more extensively later, because it produces special changes in signal intensity on MR.

Central Pontine Myelinolysis

Central pontine myelinolysis (CPM) is a demyelinating disorder involving mainly the central part of the pons. CPM develops against the background of other conditions. It occurs mostly in alcoholics but has been reported in association with diabetic ketoacidosis, psychogenic excessive water drinking, inappropriate antidiuretic hormone secretion, malnutrition, and chronic debilitating diseases. The underlying cause is derangement of serum sodium concentration, particularly

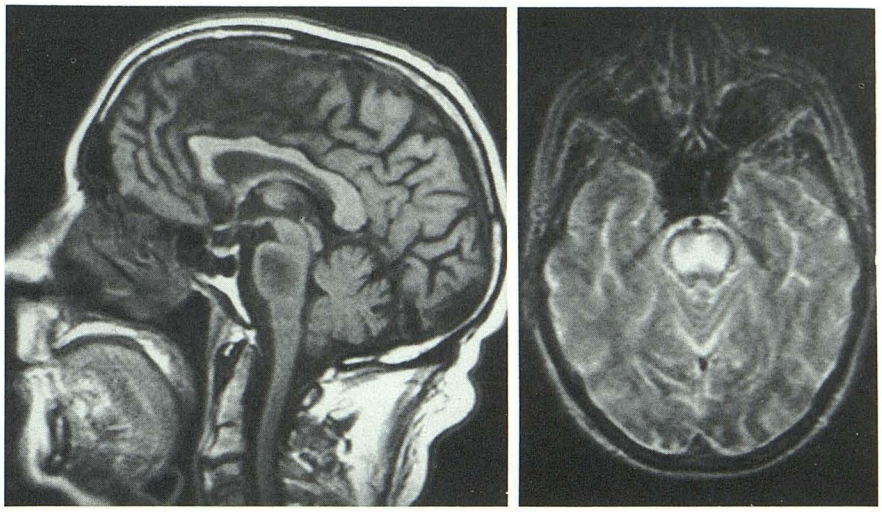


Fig. 12. Central pontine myelinosis; 56-year-old-man, admitted 3 weeks before the MR for general malaise, vomiting, and desiccation. A hyponatremia of 111.5 mmol/L was corrected in 2 days to 134 mmol/L. Shortly thereafter, he developed severe neurologic symptoms. Midsagittal T1 MR (*A*) and transverse T2 MR (*B*) demonstrate the characteristic features of central pontine myelinolysis, typically sparing the outer rim of the pons. In this case, the clinical condition gradually improved and the MR abnormalities gradually regressed incompletely.

a too rapid correction of hyponatremia. The relation of CPM to alcoholism arises because alcohol blocks the expression of antidiuretic hormone. Alcohol withdrawal leads to a rapid return of antidiuretic hormone function, causing hyponatremia. Aggressive treatment with intravenous infusions of hypertonic solutions may then precipitate the CPM (18).

The clinical manifestations of CPM vary from minimal symptoms to a complete locked-in syndrome or coma, depending upon the extent of the lesions. During the last years it has become evident that the CPM is not invariably fatal; some patients survive and show a marked improvement of their neurologic disorders.

In CPM, there is usually a single, symmetrical lesion in the central part of the basis pontis. The myelinolysis can be extensive, occupying the whole basis pontis, with the exception of a small outer rim, or it may be quite limited and appear as a very small central lesion. Histologically, there is severe or complete loss of myelin in the lesion, with a concomitant loss of oligodendrocytes. The axons are mostly well preserved.

In CPM, MR shows the typical lesion in the basis pontis (Fig. 12). The MR abnormalities gradually disappear in cases that show clinical improvement, but a lesion remains visible for a long time. Extrapontine myelinolysis preferentially involves the cerebellar white matter; the mammillary bodies; the tegmentum of the midbrain; the lateral geniculate bodies; the thalamus; the basal ganglia; the internal, external, and extreme capsules; the anterior commissure; the fornix; and the deep layers of the cerebral cortex.

Hepatocerebral Syndromes

Hepatocerebral syndromes manifest by atrophy, by changes in signal intensity in the basal ganglia, and by T1 shortening of the white matter (particularly in infants and children). ^{1}H MR spectroscopy has shown a change in the glutamate/glutamine complex and in myoinositol (19–24). Most investigators believe that ammonia plays a key role in hepatic encephalopathy. Ammonia appears to cause neurotoxicity by interacting with the glutamate/glutamine metabolism. Apart from its other roles in metabolism, glutamate is the most important excitatory neurotransmitter. Hyperammonia stimulates glutamine synthesis via glutamine synthetase. It may also inhibit glutaminase and inhibit glutamate re-uptake by the astrocytes. Thus, hyperammonemia acts to increase the concentration of glutamine. Pathways of glutamate include transamination, dehydrogenation, deamination, and decarboxylation to γ-aminobutyric acid (GABA). GABA is the most important inhibitory neurotransmitter. However, the relation between these phenomena and the T1 shortening as seen on MR is not clear.

Other explanations for the T1 shortening of the basal ganglia have been suggested, such as accumulation of manganese or of lipid particles. McConnel et al (25) demonstrated intracytoplasmatic glial lipid accumulation in the caudate nucleus and putamen. According to Zeneroli et al (26) short-chain fatty acids accumulate in the blood and may play a role in the pathogenesis of hepatic encephalopathy.

In T1 MR images, T1 shortening in the basal ganglia can make the basal ganglia indistinguish-

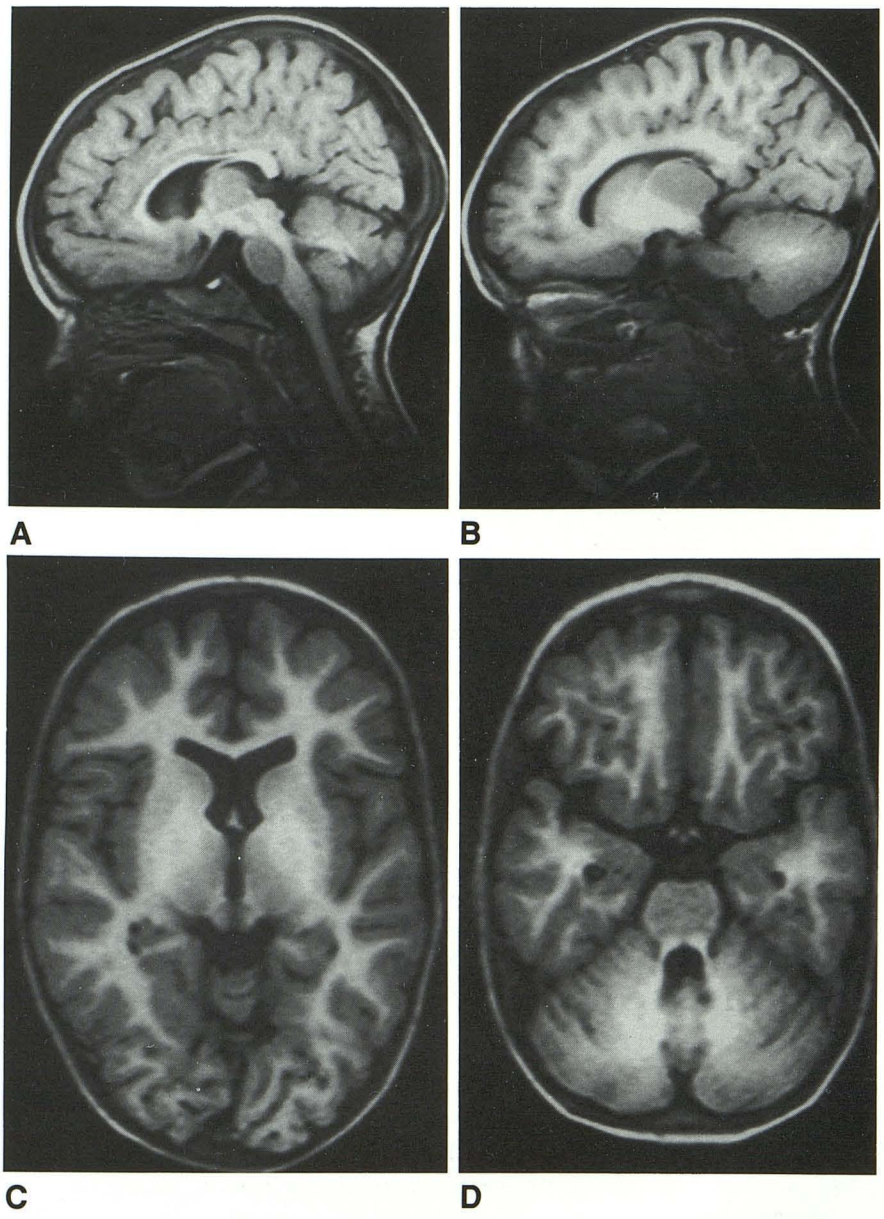


Fig. 13. Hepatic encephalopathy; 3-year-old boy, status post multiple surgical procedures for Hirschsprung disease, with many postoperative complications, hepatic failure, and hepatic encephalopathy. Midsagittal (*A*) and parasagittal spin echo MR (*B*) and T1 inversion recovery MR (*C* and *D*) show a high signal intensity in all cerebral and cerebellar white matter, especially the basal ganglia. The changes are most pronounced in the globus pallidus. The basis pontis is typically spared.

able from white matter (Fig. 13). At the same time, there is T1 shortening in the white matter, typically sparing the pons, but including the arcuate fibers. In older patients, this spread of T1 shortening over the white matter is less clear.

The T1 shortening of gray and white matter may be observed with a number of toxic-metabolic conditions, not just hepatic encephalopathy. Thus, we have seen this phenomenon in a child with a hemorrhagic shock encephalitis (Fig. 14). It may be that the glutamate/glutamine complex is involved via another metabolic pathway, but we cannot identify any specific cause for the T1 shortening.

Endogenous TE

The endogenous forms of TE are its smallest group. A number of inborn errors of metabolism should be included here, because their effects are mediated by a toxic product. This is the case in phenylketonuria (27), maple syrup urine disease, and globoid cell leukodystrophy (Krabbe disease).

Krabbe Disease

Krabbe disease or globoid cell leukodystrophy, is one of the lysosomal storage disorders (Fig. 15) (28). The primary defect in Krabbe disease is galactocerebroside-β-galactosidase, an enzyme

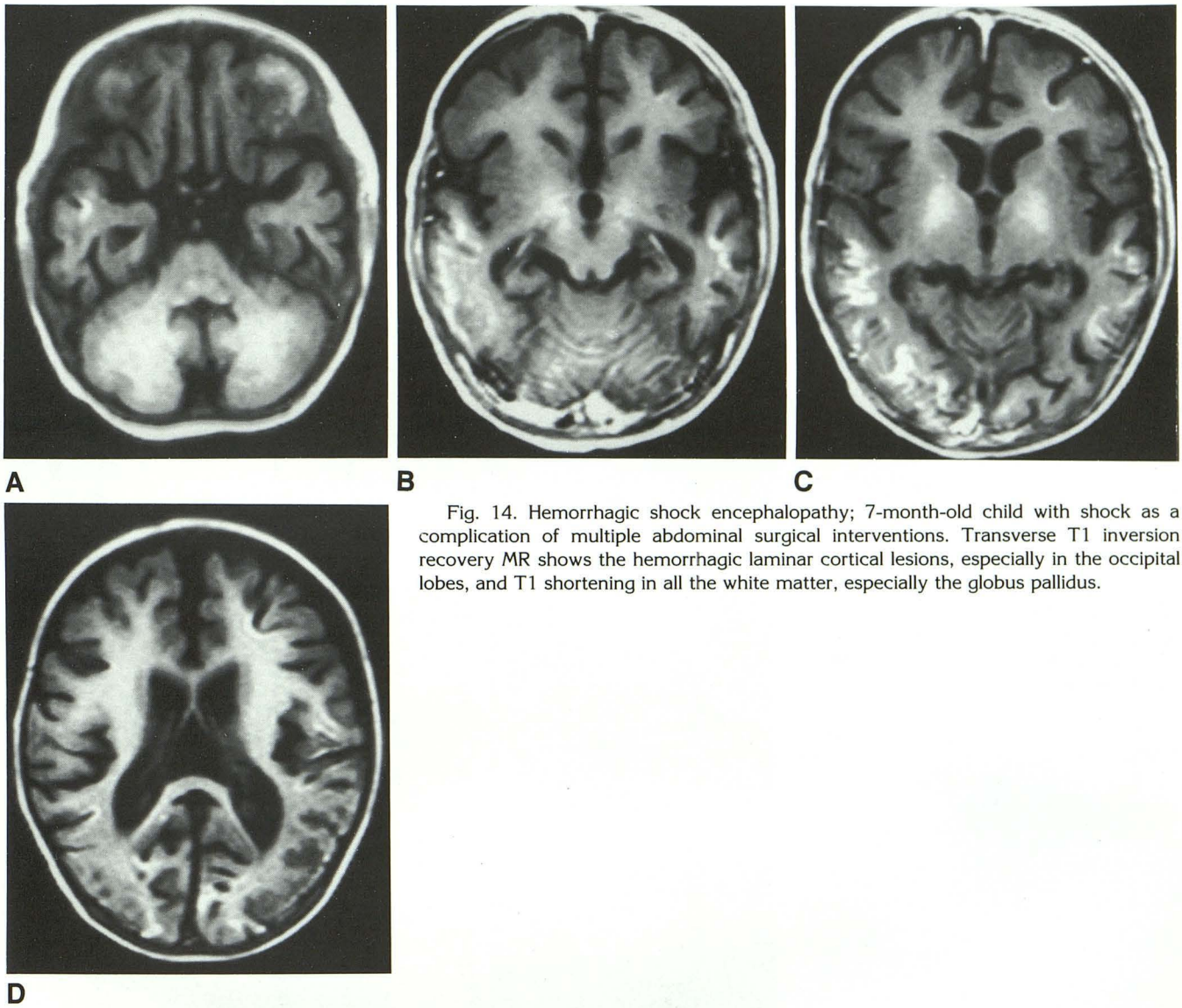


Fig. 14. Hemorrhagic shock encephalopathy; 7-month-old child with shock as a complication of multiple abdominal surgical interventions. Transverse T1 inversion recovery MR shows the hemorrhagic laminar cortical lesions, especially in the occipital lobes, and T1 shortening in all the white matter, especially the globus pallidus.

that has 2 functions: 1) it normally degrades cerebroside into galactose and ceramide and 2) it normally hydrolyzes psychosine (galactosyl sphingosine). Psychosine is a toxic metabolite that is essentially nonexistent in normal brain. Psychosine causes early, very rapid, almost complete death of the oligodendroglia. The oligodendroglia normally make myelin. Cerebroside is localized predominantly in myelin. Because Krabbe patients cannot break down cerebroside, one would normally expect an abnormally high concentration of cerebroside within their white matter. However, patients with Krabbe disease always show less cerebroside in the white matter than do normal individuals, because early death of the oligodendroglial cells terminates the synthesis of cerebroside. Krabbe patients do show an abnormally high ratio of cerebroside to sulfatide, which is indicative of abnormal accumulation of cerebroside, but this accumulation is in no way comparable to the extreme storage of sulfatide seen in metachromatic leukodystrophy.

Fetal Syndromes

The toxic substance interfering with fetal development can be considered an exogenous-external intoxication, reaching the unborn child via the mother. The fetal syndromes are unique, because the effect of the toxin depends upon the stage of development the child has reached, as well as upon the nature of the toxin, the concentration of the toxin, and the duration of the exposure (29, 30).

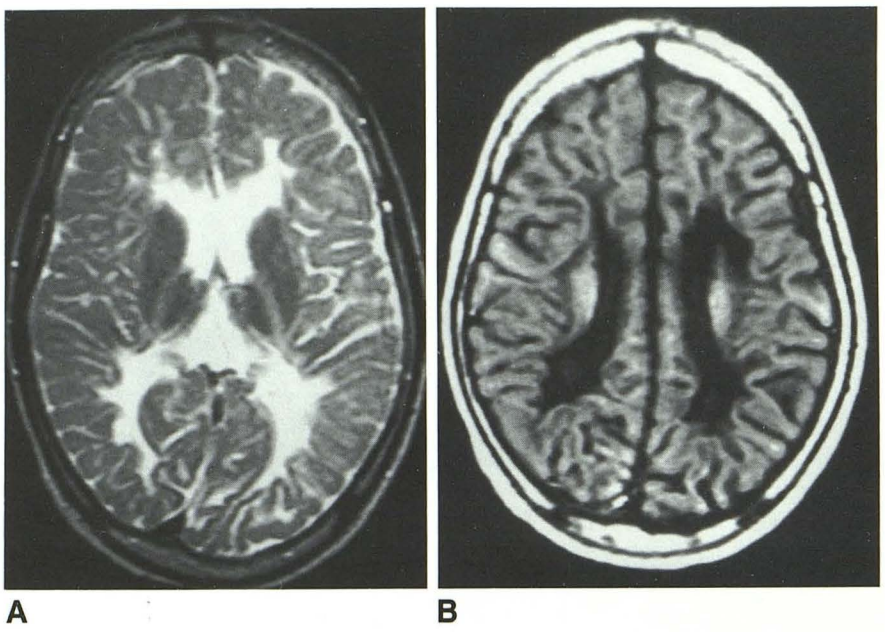


Fig. 15. Late-onset form of Krabbe disease; 14-year-old girl with a progressive neurologic syndrome. T1 MR (*A*) and T2 MR (*B*) show the general involvement of the white matter, with some atrophy. The deep infolding of the gray matter over the white is more conspicuous in *B*.

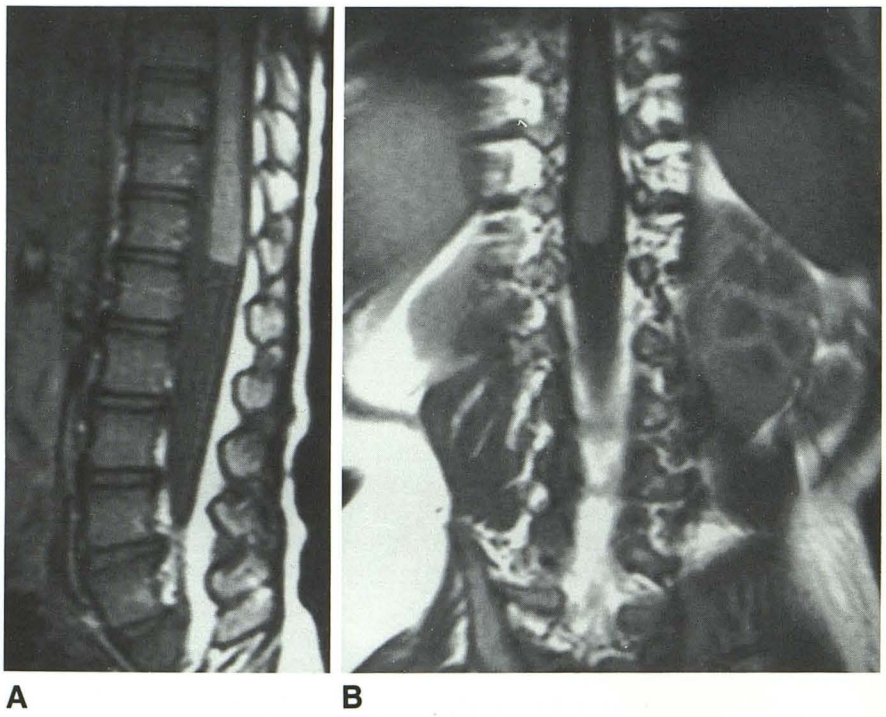


Fig. 16. Caudal regression syndrome; 4-month-old child of a diabetic mother.

A, Sagittal T1 MR. The abrupt cutoff and high position of the conus medullaris are characteristic of this syndrome.

B, Coronal T1 MR again shows the blunted termination of the conus. The sacrum ends at S2.

Toxic or teratogenic substances have a great impact on the developing fetus. The effects are often widespread and involve multiple parts of the body or the whole body, in addition to the brain. The gamut of possible dysgeneses is extensive and ranges from lethal malformation with early spontaneous abortion to mild alteration in morphology and function. The sources of the toxins include:

1. Iatrogenic—Syndromes can result from the use of established drugs prescribed to the mother, but taken during the pregnancy; most such cases are accidental. A few arise when drugs are given knowingly in desperate cases (30, 31). Antiepileptic drugs are known to cause developmental damage, resulting for example in the fetal hydantoin syndrome and the fetal valproate syndrome.

2. Alcohol and drug abuse—The most important cause of fetal dysgenesis is the use of drugs or alcohol during the pregnancy. The fetal alcohol syndrome has been reported extensively in the literature (32). These children are growth re-

tarded, have short palpebral fissures, a low nasal bridge, epicanthus, a long convex upper lip, and mental retardation. The numerous CNS anomalies of the fetal alcohol syndrome include: malformation of neuronal and glial migration, microcephaly, hydrocephaly, porencephaly, agenesis of the corpus callosum, meningomyelocele, and Dandy Walker malformation.

3. Metabolic disorders of the mother—Fetal development may suffer from a metabolic disorder of the mother. Diabetes mellitus may be one causative factor in the caudal regression syndrome, a complex abnormality of the caudal end of the embryo with anal atresia, sacral dysgenesis or agenesis, high position of the conus medullaris, and diverse urologic, neurologic, and orthopedic disorders (Fig. 16).

4. Physical events—Hyperthermia, radiation, amnionic bands, and mechanical trauma are all potentially considered hazardous to the developing fetus, possibly causing fetal dysgenesis. Strictly speaking, this category does not fall under the heading of toxic encephalopathy.

5. Teratogens—Compounds with teratogenic action are now listed in a reference manual (33). Their discussion exceeds the scope of this communication.

In most of the fetal syndromes the direct role of neuroradiologic imaging methods are limited; indirectly, of course, ultrasound, CT, and MR can depict congenital malformations, dysgyria, retarded myelination, and myelodysplasias.

Conclusion

Imaging modalities, in particular MR, play a modest, but sometimes very important role, in the diagnosis of toxic encephalopathy. The field offers another example of the way the MR reader should get involved in the pathophysiologic and pathomorphologic backgrounds of the observed lesions. The concepts of selective vulnerability and topistic (topographic) areas is helpful in understanding the patterned involvement of symmetrical areas in the brain with specific characteristics. Recognition of these patterns may lead to correct diagnosis.

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