Chronic Toxic Encephalopathy in a Painter Exposed to Mixed Solvents

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This paper describes symptoms and findings in a 57-year-old painter who had been exposed to various organic solvents for over 30 years. He began to work as a painter at 16 years of age, frequently working in poorly ventilated areas; he used solvents to remove paint from the skin of his arms and hands at the end of each work shift. The patient and his family noticed impaired short-term memory function and changes in affect in his early forties, which progressed until after he stopped working and was thus no longer exposed to paints and solvents. After the patient’s exposures had ended, serial neuropsychological testing revealed persistent cognitive deficits without evidence of further progression, and improvement in some domains. Magnetic resonance imaging revealed global and symmetrical volume loss, involving more white than gray matter. The findings in this patient are consistent with chronic toxic encephalopathy and are differentiated from other demyelinating processes such as Alzheimer’s disease, multi-infarct (vascular) dementia, and alcoholic dementia. Previous descriptions in the literature of persistent neurobehavioral effects associated with chronic exposure to organic solvents corroborate the findings in this case.

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Case Presentation

A 57-year-old man was initially examined in our clinic because of current memory difficulties, disorientation, irritability, and insomnia. His wife recalled the appearance of subtle changes in affect and memory problems as much as 15 years before the patient was disabled enough to seek medical attention specifically for these problems. His condition had progressively worsened since his wife first noticed it, until he had to stop working. Subsequent examinations showed that there was no further progression of illness after the exposure to various paints and solvents ceased, but despite some improvement, many features of his disability remain severe after almost 4 years without further exposure.

Boston Occupational and Environmental Neurology Questionnaire

Work history. The patient began working as a painter at 16 years of age. He worked for the same company from age 16 to 21 years (1954–1959); during this time he primarily spray painted the exteriors of gasoline storage tanks. When necessary, he also assisted the metal alloy welders who made repairs to the insides of the tanks and spot-primed and painted the repaired metal. He did not use a respirator; his only protection from the paint fumes came from breathing through a rag that he wrapped around his face.

At 21 years of age, he began painting the interiors and exteriors of residential housing. From 22 to 24 years of age (1959–1962), he worked painting interiors of university buildings with a variety of oil-based paints. From 1962 to 1988, he painted the interiors of commercial buildings (stores and office buildings). He frequently painted the inside of poorly ventilated walk-in type refrigerators in grocery stores. To protect the employees and customers of the stores from becoming ill from the paint fumes, the job foreman often closed the door, thus forcing the patient and his co-workers to paint in an unventilated area without respirators for up to 2 hr. The patient and his co-workers often experienced nausea, dizziness, and staggering gait while painting in these confined spaces. Although none of the painters ever lost consciousness, their symptoms were often severe enough to necessitate leaving the refrigerator for relief.

Exposure history. For most of his career the patient used oil-based paints. He was forced to retire because of disability in 1995 at 57 years of age. Material safety data sheets (MSDS) provided by this employer indicated that the patient and his co-workers had been exposed to lead, titanium dioxide, creosote, and mixed solvents including ammonia, chlorine bleach, various alcohols (e.g., isopropanol and methanol), methyl ethyl ketone, methyl isobutyl ketone, formaldehyde, carbon tetrachloride, methylene chloride, ethylene glycol, propylene glycol, hexylene glycol, nitroethane, cyclohexane, acetone, xylene, toluene, benzene, and petroleum naphthas. The patient frequently used painter’s naphtha to clean off his hands, arms, and face at the end of his work shift; painter’s naphtha (also known as VM & P naphtha or benzine) is a petroleum derivative containing a mixture of C5–C11 hydrocarbons.

Past medical history of patient and family. The patient was born on 25 December 1938 in South Carolina to two apparently healthy parents. There was no family history of dementia, psychiatric disease, or other neurological illnesses, and neither the patient’s sister or parents suffered from any of these diseases.

Currently, the patient smokes 1–1.5 packs of cigarettes per day. Although he no longer drinks alcohol, in the past he consumed one to three drinks each evening for 20 years; he did not drink during work or on weekends, and he stopped drinking 10 years before presenting with his current complaints. His childhood medical history included German measles and pneumonia at 3 weeks of age. He experienced a mild head trauma at age 12; although he was dazed, he did not lose consciousness. He had gastrointestinal symptoms at age 49 (10 years before we examine him) that were diagnosed as a duodenal ulcer.

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Six years before the onset of his current and persistent neurobehavioral impairments he experienced episodes of dizziness and numbness of his right arm, often aggravated by painting with a brush. A computed tomography (CT) scan of his head was normal. He was referred to a cardiovascular specialist who diagnosed an occlusion of the right subclavian artery, resulting in a "subclavian steal syndrome"; surgery for this was not deemed necessary, as the blood flow to his arm and hand remained adequate.

**Present illness and current symptoms.** The patient continued painting for many years, despite occasionally experiencing episodes of dizziness and headaches, which were ameliorated when he was not exposed to paint fumes. At the high point of his career (1982–1984), the patient was considered a very capable and reliable worker; he was able to supervise others and schedule and assign tasks. He also gave the crew members directions about how to get to the various work sites where they were assigned on a particular day. During this time he also frequently mixed paints to create specific colors, a task at which he was considered to be quite skilled.

The patient began to notice changes in his mood and personality (he became more irritable), as well as problems with his memory (he began to have difficulty remembering the names of new workers). These symptoms progressed gradually over the next 15 years while he continued to work. By 1993, the patient began to experience severe anxiety attacks and depression. Symptomatic improvement was obtained from setraline hydrochloride and clonazepam during the 3 years before he stopped painting. He was forced to retire in 1995 at 57 years of age because of his memory problems, which by then were causing him to frequently forget the names of recently hired co-workers, his difficulty with mixing paints, and his difficulty in finding job sites (he frequently got lost).

He was examined by a neurologist for the first time in 1996. The patient reported that he frequently would get lost while driving his car and needed to write things down in order to remember them. In addition, he reported that his memory problems were making him irritable, defensive, and depressed. Currently, the patient requires Aeb from his wife to aid in his recall, he has difficulty dressing at times, he often has spatial disorientation problems, and he continues to need medication (fluoxetine hydrochloride and lorazepam) for his apparent frustration and reactive depression.

On examination, he was oriented to person, time, and place. There was no dysarthria and his conversational speech was fluent. He could read the notes that he used to recall specific items he wanted to talk about. His recall for recent events was labored, but significantly improved since he was first seen in 1996. His memory for past events was intact. He continues to have difficulty with visual memory, and he reports that he still gets lost when driving to and from unfamiliar places. He could not remember the color of his toothbrush, even after his wife had repeatedly reminded him. His wife stated that his visual memory impairment was manifested by his difficulty with object assembly tasks; he could still take things apart, but he could not remember how to put them back together. The patient stated that he had begun riding a bicycle for exercise and reported that he had no trouble finding his way around his neighborhood, but he could not remember when he started this exercise program. His mood and affect was improved. No overt gait disturbance was noted, as would be seen with a peripheral neuropathy or cerebellar dysfunction.

**Time–Exposure–Symptom Line**

A time-exposure–symptom line (Fig. 1) of the patient's past and current medical and exposure history was constructed from information obtained from the Boston Occupational and Environmental Neurology Questionnaire (1), a careful review of his medical and employment records, and from an interview with the patient and his wife.

**Physical examination.** A physical examination (10 January 1996) revealed a well-developed and well-nourished man whose physical condition matched his chronological age. His resting blood pressure was 120/80 and his pulse was regular. Auscultation of the carotid arteries revealed no bruits, nor were there any bruits over his subclavicular area. He was well oriented to person, place, and time. His free speech was fluent and his oral comprehension, repetition, and naming were intact. He had difficulty with reciting serial "7s" but he subtracted "3s" correctly. He was able to spell the word "world" forward and backward.

His extraocular eye movements were intact and there was no nystagmus. Pupils were equal and reactive to light and there was no evidence of papilledema. Facial sensation was intact symmetrically, the gag reflex was present, and there was no dysarthria. Motor examination revealed normal bulk, tone, and strength in the upper and lower extremities. Deep tendon reflexes were present and normal (2+); plantar reflexes were flexor. Sensory examination including testing of touch, vibration, and pain, and temperature sensation was normal. However, there was no hair on areas of his lower legs that were normally covered by socks. Performance on finger-to-nose, heel-to-toe, tandem gait were normal, and he was able to hop without difficulty.

**Biochemical diagnosis.** Although he was symptomatic when acutely seen, biological markers including urine hippuric acid were not obtained to document his exposure at that time. A heavy-metal screen done approximately 1 year after cessation of exposure to paint and painting materials revealed a blood lead level of 13 µg/dl and a

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**Figure 1.** Time–exposure–symptom line (TES-line) demonstrating the chronological relationship between the patient's history of exposures to paints and solvents and the progression of his neurobehavioral manifestations. Abbreviations: BPb, blood lead level; EEG, electroencephalogram; MRI, magnetic resonance imaging.
mercury level of 5 µg/l, and manganese was not detectable. A complete blood count and thyroid tests were normal. Liver function tests, including serum glutamicoxaloacetic transaminase, serum glutamic pyruvic transaminase, total bilirubin, alkaline phosphatase, albumin, and protein, were normal. Lyme titer was also negative.

Neurophysiological diagnosis. The electroencephalogram (EEG) of this patient done in 1996 was characterized by excessive theta activity. Low to medium voltage sharp activity was noted in the posterior (occipital) area. A moderate amount of beta (fast) activity was also seen superimposed over the background activity. Response to photic driving was normal, and no frank epileptiform activity was seen. Nerve conduction studies were not performed on this patient, who also had no clinical evidence of peripheral neuropathy.

Neuroimaging. Magnetic resonance imaging studies were made 6 months after the patient first sought medical attention for his cognitive deficits (1996). Symmetry and the general cerebral architecture were intact except for subtle findings related to a generalized volume loss. The sulcal markings were wider than expected for the patient’s age. This is best observed on the T2-weighted axial images (Fig. 2A). The amount of volume loss observed at the base of the brain was similar to that seen in the frontal and parietal lobes. The temporal horns of the lateral ventricles were well recognized, but did not appear out of proportion to the remainder of the ventricles. White matter tracts were symmetrical, but were qualitatively thinned throughout. The signal within the white matter was uniform and of normal intensity. The cortical ribbon in the supratentorial neocortex was uniform and normal in signal throughout, but thinner than expected for a patient of this age.

T1-weighted coronal images revealed that the medial temporal lobes were normal in signal and configuration and were not disproportionately atrophied (Fig. 2B). The hippocampal formations were of normal architecture and signal. Although the archicortex of the entorhinal structures had an apparently increased signal, a disproportionate change in volume was not noted. The deep nuclei had normal position and architecture. The head of the caudate was not atrophied, but did show an increased T2-weighted signal bilaterally. Similar symmetric findings were seen in the putamina. The globi pallidum were of normal structure and signal intensity. The images of the brainstem (mesencephalon, pons, and medulla) were normal in signal strength and size. On T1-weighted midsagittal images, the cerebellum appeared moderately atrophied, but this was not disproportionate to that seen in the cerebral cortex. (Fig. 2C)

The neuroimaging findings in this patient can be summarized as indicative of global and symmetric volume loss, involving more white than gray matter. The abnormal findings noted in the magnetic resonance imaging (MRI) of this patient (Fig. 2) are in stark contrast with the normal findings of the CT scan performed 8 years earlier. These findings can thus be chronologically related to the clinical progression of this patient’s cognitive deficits that were unremarkable 8 years earlier (in 1988), but which had reached maximum severity by the time the second neuroimaging study was performed (in 1996).

Neuropsychological diagnosis. Neuropsychological assessment (1996) revealed a full scale IQ of 93 (Verbal IQ = 96; Performance IQ = 91). Impaired performance was noted on tests of verbal (California Verbal Learning Test) and nonverbal memory (delayed reproduction of Rey-Osterreith complex figure). Performance on tests of attention and executive function (Trails A and B and Wisconsin Card Sort Test) was impaired as well. Visuomotor coordination (Grooved Pegboard Test) was also below expectation. Tests of mood and affect revealed anxiety and depression. Tests of language function, including confrontation naming (Boston Naming Test), were within normal limits.

A second neuropsychological assessment done 1 year later (in 1997) revealed a full scale IQ of 90 (Verbal IQ = 92; Performance IQ = 88). His performance was impaired on tests of attention and executive function (Trails A and B and Wisconsin Card Sort Test). His scores on tests of visuospatial planning and organization (copy of Rey-Osterreith complex figure; Hooper Test of Visual Organization) were below expectation. Deficits in visuomotor coordination (Grooved Pegboard Test) were also noted. Remote memory was intact, but his performance on tests of verbal (California Verbal Learning Test) and nonverbal memory (delayed reproduction of Rey-Osterreith complex figure) remained below expectation. Language functions including spontaneous speech and confrontation naming (Boston Naming Test) were intact. The findings of this follow-up assessment demonstrated a persistent impairment of cognitive function and supported the diagnosis of chronic toxic encephalopathy. Such static deficits on serial neuropsychological testing and the preservation of language function are not seen in progressive dementing processes such as Alzheimer’s disease and multi-infarct dementia, both of which are associated with marked worsening of performances on serial neurobehavioral assessments.

Discussion

Toxic effects of organic solvents. Painters are frequently exposed to mixtures of organic solvents, including naphtha, toluene, xylene, and n-hexane. Acute exposures to high concentrations of these solvents results in the immediate onset of symptoms of inebriation, dizziness, headache, nausea, and vomiting that can easily be related chronologically.

Figure 2. Magnetic resonance imaging studies in a patient (a former painter) with chronic toxic encephalopathy (1.5-tesla magnet). (A) T2-weighted axial image through the lateral ventricles demonstrating corticatal atrophy. (B) T1-weighted coronal image demonstrating diffuse cortical atrophy and that the temporal lobes and hippocampi are not disproportionately atrophied. (C) T1-weighted midsagittal image demonstrating proportional atrophy of the cerebellar vermis.
to the exposure situation (2). Unless the exposure concentrations were high enough to be fatal, these symptoms are usually transient and therefore are ameliorated by removal of the affected person(s) from exposure. Conversely, symptoms associated with chronic exposures appear gradually. Workers are often unaware of nonspecific symptoms, such as headache, irritability, and insomnia, which may indicate exposure to hazardous chemicals and that they are at risk of developing more persistent effects. Often, overt symptoms including poor attention, mood changes, memory problems, and delirium, and even inebriation with associated ataxia and incoordination, may be ignored by the affected person until they interfere with daily tasks. The affected worker may not seek medical attention even when these abnormal behaviors are pointed out by co-workers or family members.

Similar neurological signs and symptoms arise from the same principal neuroanatomical structures; thus, the symptoms of solvent exposure may resemble those of primary neurological diseases. A diagnosis of a neurotoxic syndrome following chemical exposure must be differentiated from a neurological disease of non-neurotoxic etiology that is not associated with chemical exposure. Idiopathic (nontoxic) neurologic disease usually follows a progressive course, with continued development of symptoms in the absence of any identified exposure to neurotoxins. The exact chemical exposures experienced by this patient who had been exposed to various oil-based and latex paints, paint thinners, and other solvent-containing materials, such as pit glaze and glue, cannot be ascertained. Determining the possible contribution of any particular solvent to this patient's illness requires consideration of the effect of the enhancement of metabolism associated with chronic exposure to a mixture of industrial solvents and ethanol. In this case, the effects of chronic exposure to the combinations of solvents that the patient had reportedly been exposed to was most likely "additive" because few of these solvents would have enhanced the toxicity of one another. One example is the competitive inhibition of toluene metabolism due to exposure to other benzene derivatives such as xylene. In such a case, the blood levels of both parent molecules would have been increased. However, the patient's chronic exposure to ethanol and other organic solvents that induce cytochrome P450 enzymatic activity would have had synergistic effects on the toxicity of carbon tetrachloride, which is metabolized to the trichloromethyl free radical (Cl3C•) (3,4). The contribution of free radicals to oxidative stress and cell membrane dysfunction is a well-recognized mechanism of neurotoxicity (5).

The possibility that this patient's current cognitive deficits are due to his exposure to toluene and other benzene derivatives, as well as the numerous aliphatic hydrocarbons to which he was exposed, is consistent with other published reports of the neurotoxic effects of these solvents. Acute effects of exposure to toluene include dimmed vision, headache, fatigue, confusion, light-headedness, inebriation, attention and memory deficits, disturbed equilibrium and coordination, and occasionally nausea, vomiting, or unconsciousness (6). Unrecognized acute effects of toluene exposure may be mistaken for mood and affective disorders, such as manic-depressive illness or schizophrenia (7).

Chronic toxic encephalopathy follows long-term exposure to toluene and is characterized by apathy, inattention, poor memory, and impaired performance of complex cognitive function. Mood swings, irritability, and anxiety attacks occur early, followed by memory impairments and problem-solving difficulties. The absence of anemia is a principal finding that differentiates a dementia due to toluene exposure from the progressive dementias such as vascular disease or Alzheimer's disease (8-10). Chronic exposure to toluene has been associated with significant central nervous system effects resulting in cerebral and cerebellar atrophy. Toluene-induced chronic toxic encephalopathy is associated with white matter changes (11); thus, in some cases, it may be difficult to distinguish it from multi-infarct vascular disease with related dementia. Because increasing duration of exposure is correlated with increasing age of the exposed workers, the effects of aging are a potential confounder in the diagnosis of chronic toxic encephalopathy. However, the symptoms associated with exposure to toluene and other industrial solvents typically stabilize or improve after cessation of exposure; although progression may be seen in some older individuals, such a progression is typically not as rapid as that seen in idiopathic progressive demening processes such as Alzheimer's disease (10).

Exposure to mixed organic solvents, including aliphatic hydrocarbons and benzene derivatives, has been associated with central and peripheral nervous system dysfunction (11,12-14). Organic solvents are lipophilic and are readily absorbed via pulmonary, gastrointestinal, and dermal routes; then they readily cross the blood–brain barrier. Many organic solvents are also metabolized to alcohols (e.g., hexanol and trichloroethanol). The alcohol metabolites of organic solvents are responsible for many of the acute narcotic effects associated with exposures to these chemicals. Further metabolism of the alcohol metabolites of organic solvents leads to the formation of aldehydes that can also react with cellular macromolecules, thereby disrupting cellular processes. Because these metabolites share common mechanisms of action, concurrent exposures to several organic solvents can have additive, synergistic, and/or potentiating effects on nervous system functioning.

Once absorbed, organic solvents are metabolized by enzymes such as cytochrome P450. These enzymes are located primarily in the liver but are also found, to a lesser extent, in other tissues including the brain. Simultaneous acute exposure to high concentrations of mixed organic solvents results in competition for drug-metabolizing enzymes and thus higher blood levels of the parent molecule. Conversely, chronic exposure to organic solvents, such as ethanol or commonly used pharmaceutical drugs such as phenobarbital, induces the activity of drug-metabolizing enzymes including cytochrome P450, which results in enhanced formation and excretion of metabolites (4,15). Solvents can be metabolically deactivated or activated by the cytochrome P450 monooxygenase system. Because not all metabolites are less toxic than the parent molecule, induction of drug-metabolizing enzymes can enhance the in vivo toxicity of an organic solvent or pharmaceutical drug. Metabolic activation by cytochrome P450 results in the formation of electrophilic alkylation agents (i.e., molecules containing an electron-deficient atom with a positive charge that can covalently bind with the nucleophilic centers of cellular macromolecules to form adducts) (16,17).

**Definition of toxic encephalopathy.** The neurobehavioral effects of exposure to neurotoxicants can be classified according to the clinical manifestations, temporal profile of the symptoms, and the nature of recovery or residual deficits (18). There are four categories of toxic encephalopathies:

- **Acute organic mental disorder:** mild, transient, and reversible symptoms of acute intoxication [for example, a brief exposure to volatile and aromatic substances, such as glue or varnish in a poorly ventilated area or ingestion of common ethyl alcohol (ethanol), produces an acute organic mental disorder]
- **Acute toxic encephalopathy:** associated with permanent residual cognitive impairment, which often occurs after an overwhelming acute exposure that in the worst cases can result in coma or death
- **Organic affective (mood) syndrome:** can develop insidiously with subacute or chronic exposures and can last from weeks to years. The symptoms of this syndrome are sometimes incorrectly attributed to primarily psychiatric disorders because they consist of mood...
disturbances and affect changes including depression, irritability, fatigue, and anxiety. Consideration of other concurrent findings on neurological examination along with the results of formal neuropsychological testing allows the clinician to reconcile discrepancies and corroborate the test results.

- Chronic toxic encephalopathy: describes patients who present with affective disturbances as well as cognitive deficits. The cognitive and affective disturbances seen in these patients interfere with performance of activities of independent daily living and gaining meaningful employment is often impossible. The neuropsychological test findings in chronic toxic encephalopathy are for the most part permanent, although some improvement may be seen in some cognitive domains following removal of the patient from the source of exposure (18).

Elofsson et al. (13) reported a similar neuropsychological profile with marked memory and manual dexterity performance deficits and intact verbal performance deficits among a group of 80 car painters, whose test scores were compared with those of 80 unexposed controls. An epidemiologic investigation of 3,303 Danish males 57–75 years of age (mean of 62.5 years) revealed an increased incidence of attention, memory, and psychiatric problems among workers who had been exposed to solvents for periods >5 years (19). The EEG findings seen in the patient presented here are consistent with findings reported in other workers exposed to mixed solvents. The EEG studies in 87 workers diagnosed with chronic toxic encephalopathy showed diffuse slow wave abnormalities but no epileptiform activity (20). The MRI findings in this patient are consistent with the neuroimaging (CT scans) reported by Arlend-Søborg et al. (12), who revealed diffuse cerebral atrophy in a group of house painters.

Differential diagnosis. The history and neuropsychological findings in the patient presented here are consistent with the insidious onset of an organic affective syndrome that gradually evolved, with his continued exposure to organic solvents, into a chronic toxic encephalopathy. The neuropsychological findings in this patient are atypical for the dementia of Alzheimer’s disease, given the absence of naming problems (anoma) and the lack of progression of the dementia. The possibility that these findings may be due to other dementing processes such as cerebrovascular disease (e.g., multi-infarct dementia) was also ruled out because of the stability of his performance over time.

The possibility of ethanol contributing to this patient’s current symptoms cannot be disregarded. Chronic intake of ethanol has been associated with neuroimaging and EEG abnormalities (21–23). However, the aforementioned findings are consistently associated with consumption of at least 60 g ethanol/day; this patient usually consumed only two to three drinks (approximately 24–36 g) per day. The amount of chronic ethanol intake seen in this patient is consistent with the definition of a moderate social drinker, and consumption of fewer than five alcoholic drinks per day would not put an adult male at an increased risk for cognitive deficits (24). Furthermore, removal from organic solvents, including ethanol, is typically associated with improvement or stabilization in cognitive functioning (22,25), whereas he cognitive symptoms reported by this patient had actually progressed since he stopped drinking. In contrast, his symptoms have improved since he retired and thus ended his exposure to industrial organic solvents; this further supports the diagnosis of chronic toxic encephalopathy due to his exposure to organic solvents. Furthermore, this patient does not show any marked concurrent clinical evidence of the peripheral neuropathy or cerebellar ataxia that would be expected with heavy alcohol intake. The absence of peripheral neuropathy also suggests that this patient’s cognitive symptoms are not due to malnutrition or diabetes, both of which are associated with peripheral neuropathy; the diagnoses of malnutrition and/or diabetes were also not supported by serial laboratory studies (26,27).

Diseases that may lead to similar MRI findings as in this case include cerebrovascular and neurodegenerative disorders and the chronic sequelae of anoxia, trauma, infection, and metabolic or toxic encephalopathy. A significant observation that is useful in making a differential diagnosis is the lack of a T2-weighted signal change, which is representative of demyelination or reactive gliosis. Chronic cerebrovascular disease is commonly associated with increased signal in the periventricular white matter. Often this pattern follows the general distribution of the deep border zone territory. This is seen in the “chronic small vessel diseases,” particularly microangiopathy of hypertension, lipohyalinosis, and amyloid angiopathy. These periventricular changes are often confluent, but may have focal, patchy areas of signal abnormality representative of small regional infarct. Without these white matter changes, it is difficult to diagnose cerebrovascular disease.

In the earliest stages, the neurodegenerative disorders may be difficult to recognize. As these diseases progress, however, characteristic changes become apparent. Noting the lobar distribution, such as the temporoparietal predominance in Alzheimer’s disease, may be helpful in the diagnosis. A frontotemporal distribution, with sparing of the posterior aspect of the superior temporal gyrus (striate cortex), is commonly seen in Pick’s disease. A medial temporal (rhinencephalon) wasting is also relatively common in these disorders. Loss of deep nuclear structures such as selective early loss of caudate mass or signal abnormality in the striatum are reflective of such diseases as Huntington’s chorea or Creutzfeldt-Jakob disease, respectively. Some neurodegenerative diseases have either a lack of or very subtle findings. Diseases in the spectrum of multisystem atrophy and chronic Wernicke’s encephalopathy, for example, can be quite difficult to detect. Volume loss specific to the midbrain is commonly described in multisystem atrophy, but in practice, these changes occur quite late in the disease and are often difficult to recognize because standard imaging measurements are not available for the midbrain (28). The T2 dark changes of chronic microhemorrhage in shrunken mammillary bodies, hypothalamus, and dentate nuclei are often overlooked in chronic Wernicke’s encephalopathy.

The differential diagnosis of chronic toxic encephalopathy depends on the exclusion of other possible etiologies, including the neurodegenerative diseases, and the chronological association of the exposure situation with the onset and progression of the clinical, neuropathological, neuropsychological, and neuroimaging findings in the patient. In this case the neuroimaging findings and neuropsychological test results could be related chronologically to the exposure events and to the progression of the patient’s illness. In addition, the neuroimaging and neuropsychological findings do not support an alternative diagnosis.

The patient’s chronic consumption of alcohol during most of his professional career would have induced enzymatic activity (e.g., cytochrome P450). Although this would have enhanced the neurotoxic potential of some of the solvents to which he was exposed, induction of drug metabolizing enzymes could also have had a protective effect by enhancing conjugation and thus excretion of the metabolites of these chemicals. Many of the solvents to which this patient was exposed (e.g., methyl ethyl ketone, methyl isobutyl ketone, formaldehyde, propylene glycol, chlorinated bleaches, toluene, benzene, and petroleum naphthas) are not metabolically activated. Therefore, this patient’s chronic consumption of ethanol throughout much of his working life would most likely have protected him from the effects associated with increased blood levels of those solvents, such as formaldehyde, that do not require metabolic activation to induce their toxic effects.
Nevertheless, the toxicity of some of the other solvents to which he was exposed, including methylene chloride, would have been enhanced by induction of cytochrome P450 activity. Methylene chloride is primarily metabolized to carbon monoxide (CO) in the liver. Increased blood levels of CO are associated with tissue hypoxia. In this case, the patient's habit of smoking up to one and one-half packs of cigarettes per day also contributed to his total exposure to CO. Therefore, although the contribution of CO-induced tissue hypoxia to this patient's neurologic illness should be considered, it was most likely minimal. If CO were to show abnormalities in the globus pallidus and demyelination in the centrum semiovale. In addition, the clinical neurologic picture would be expected to include features of parkinsonism (2).

**Conclusion and Prognosis**

The findings in this patient are consistent with chronic toxic encephalopathy due to solvent exposure and are atypical for Alzheimer's disease, given preservation of language skills, the absence of naming problems (anoma), and the lack of progression of the dementia. Based on the MRI studies and the stability of his performance over time, it is unlikely that these findings were due to other detaining processes such as cerebrovascular disease (e.g., multi-infarct dementia). The diffuse MRI findings and neuropsychological test results in this patient are consistent with reported cases of chronic toxic encephalopathy in house painters. The EEG findings for this patient are consistent with findings for other workers exposed to mixed solvents.

The prognosis for full recovery in this patient is poor. At follow-up examination (25 September 1998), the patient reported that he had stopped attending psychological rehabilitation therapy sessions because he was "frightened and was getting nowhere"; he also felt that the sessions were "not doing him any good." He is permanently disabled. His anxiety and depression may have been exacerbating his symptoms somewhat; thus, continued symptomatic anxiolytic and antidepressant therapy is necessary. Ongoing abstinence from alcohol and a significant reduction in caffeine intake was strongly encouraged. Assistance with the development of mnemonic strategies such as a structured memory logbook has been provided, but this patient's cognitive impairments, particularly his memory problems, do not allow him to learn or gain insight from such intellectual input.

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