White Matter Changes Caused by Chronic Solvent Abuse

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PURPOSE: To examine the brain damage of solvent abusers in Japan, where pure industrial toluene is frequently abused. **METHODS:** Twenty solvent abusers 17 to 33 years of age with 7.2 ± 4.0 years of abuse were examined with a 1.5-T MR imaging system. **RESULTS:** White matter hyperintensities in cerebrum, brain stem, and cerebellum on T2-weighted images were found in seven cases. The extent of white matter change was most clearly shown on proton density–weighted images. The patients with restricted white matter change and intermediate white matter change showed white matter hyperintensities in the brain stem and cerebellum on T2-weighted images, in some cases, with additional hypointensities in the corresponding T1-weighted images. These patients had mainly abused pure toluene. The patients with diffuse white matter change showed obvious brain atrophy, including hippocampal atrophy and thinning of the corpus callosum. These patients had mainly abused lacquer thinner. **CONCLUSION:** There are some patients with restricted but severe enough change to cause the neurologic symptoms in specific regions, such as the brain stem and/or cerebellum, before the brain atrophy becomes apparent. This suggests that the restricted white matter change represents not only an early change of diffuse white matter change, but at least in some cases also represents a qualitatively different change than that of diffuse white matter change. We suggest that pure toluene has a possible relation to this qualitative difference.

Index terms: Brain, effects of toxic substances on; Brain, magnetic resonance; White matter, abnormalities and anomalies

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Chronic organic solvent abuse is known to cause toxic encephalopathy (1) with neurologic signs including cognitive, pyramidal, cerebellar, and brain stem/cranial nerve findings (2). Neuroimaging studies with magnetic resonance (MR) have revealed atrophy and diffuse white matter change (WMC) in the central nervous system (CNS) (3–6). These results were reported from studies in which the abusers had inhaled glues, spray lacquer, or spray paint that contain some organic solvents in which toluene is considered to be the main cause of the CNS damage.

In Japan, organic solvents and methamphetamine are the most abused substances, and other drug abuse is rare. The National Police Agency reported that of 38 000 people arrested for illicit drugs in 1992, 55% were for organic solvents, 40% for methamphetamine, 4% for marijuana, and only 1% for others, including morphine and cocaine. Illegally traded pure industrial toluene frequently is abused. A multiinstitutional study of 138 outpatients and inpatients with solvent dependence reported the organic solvents abused were "thinner" (a word often used as a general term for organic solvents for abuse), 69.6%; pure toluene, 40.6%; and glues, 39%, with multiple replies (7). The purpose of this study was to summarize the CNS findings of Japanese abusers with 1.5-T MR and to compare them with previous studies.

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Subjects and Methods

We studied 15 men and five women with a history of solvent abuse for at least 1 year. Informed consent was obtained from each patient before the examinations. The diagnoses were confirmed by histories carefully taken from patients and their families. Although a cerebrospinal fluid analysis was not done, multiple sclerosis and other hereditary white matter diseases were excluded by their characteristic appearance of white matter abnormalities and family history. All but 1 had a history of hospitalization for solvent dependence. Patients with other drug dependencies or psychiatric disorders were excluded. The mean age in the sample was 21.8 ± 4.5 SD (range, 17 to 33) years. The duration of abuse was 7.2 ± 4.0 SD (range, 1 to 16) years. The duration was defined as the period between the age of first abuse and the age at the examination. Most of the subjects inhaled various compounds containing toluene during the long time of abuse, such as pure industrial toluene, lacquer thinner, glues, and tire repair spray. Most patients abstained from solvents at least 3 weeks before examinations to exclude the acute effect of solvent. Neurologic abnormalities were seen in 10 (50%) patients. Cerebellar signs (ie, ataxic gait and upper limb ataxia) were seen in 7 (35%). Sensory disturbance with glove and stocking pattern was seen in 2 (10%). Finger tremor with slight rigidity was seen in 1 (5%).

MR was performed using a Signa system (General Electric Medical Systems, Milwaukee, Wis) with a superconducting magnet operating at 1.5 T. Four series of study were performed: (*a*) sagittal T1-weighted imaging with multiplanar GRASS (gradient recalled acquisition in a steady state; MPGR) method (200/5/2 [repetition time/echo time/excitations]; flip angle, 60°; section thickness, 5 mm); (*b*) axial T2-weighted imaging and proton density–weighted imaging with variable echo method (3000/30,100/0.75 or 3000/17,102/1; section thickness, 5 mm; intergap measurement, 1.5 mm); (*c*) axial T1-weighted imaging using three-dimensional spoiled GRASS (SPGR) method (25/5/1, flip angle 35°; or 24/5/1, 30°), with a 3.5-mm section thickness; and (*d*) coronal T1-weighted imaging using the same 3-D spoiled GRASS method with 1 excitation, 30° flip angle, and a 3-mm section thickness. In all sequences, field of view was 20 cm, and matrix size was 256 × 192.

Results

The following abnormalities were found on MR: (*a*) hyperintensities on T2-weighted images in deep cerebral white matter including the centrum semiovale; periventricular white matter; posterior limb of the internal capsule; and ventral part of pons, middle cerebellar peduncles, and cerebellar white matter surrounding the dentate nuclei (n = 7); (*b*) hyperintensities on proton density–weighted images in white matter (n = 7) (this finding most clearly depicted the extent of the white matter change); (*c*) hypointensity in the thalami on T2-weighted and proton density–weighted images (n = 6); (*d*) cerebral cortical atrophy and dilatation of the ventricles including inferior horns of lateral ventricles that indicate hippocampal atrophy (atrophy also was seen in the brain stem and cerebellum, sometimes so mild that it was hard to count the number of the patients with this finding, found in patients both with and without abnormal signal intensity); and (*e*) thinning of the corpus callosum (n = 2).

According to the hyperintensities on proton density–weighted images, white matter change was characterized as follows: (*a*) restricted white matter change (ie, white matter change restricted to periventricular portion, and the demarcation between gray and white matter was preserved) (Fig 1) (n = 4); (*b*) diffuse white matter change (ie, white matter change more widespread, and the demarcation between gray and white matter was lost) (Fig 2) (n = 2); and (*c*) intermediate white matter change (ie, demarcation between gray and white matter lost in some portions) (n = 1).

The Table shows the combination of each finding and the clinical aspects of the patient with white matter change. The cases with restricted white matter change showed the white matter hyperintensity on T2-weighted images in brain stem, middle cerebellar peduncles, and cerebellar white matter surrounding dentate nuclei (Fig 3). Some of them showed additional hypointensities in the corresponding T1-weighted images (Fig 4). The cases with diffuse white matter change showed obvious brain atrophy including thinning of the corpus callosum and hippocampal atrophy (Fig 5). Hypointensity in the thalami was found in both types (Figs 1 and 2). All seven patients with white matter hyperintensity showed neurologic symptoms including cerebellar ataxia, tremor, and pyramidal signs. The patients with diffuse white matter change mainly abused lacquer thinner for longer periods than did the patients with restricted white matter change and intermediate white matter change, who mainly abused pure toluene.

Discussion

The MR findings of this study, such as loss of gray/white differentiation, white matter hyperintensities, hypointensity in thalami, and diffuse

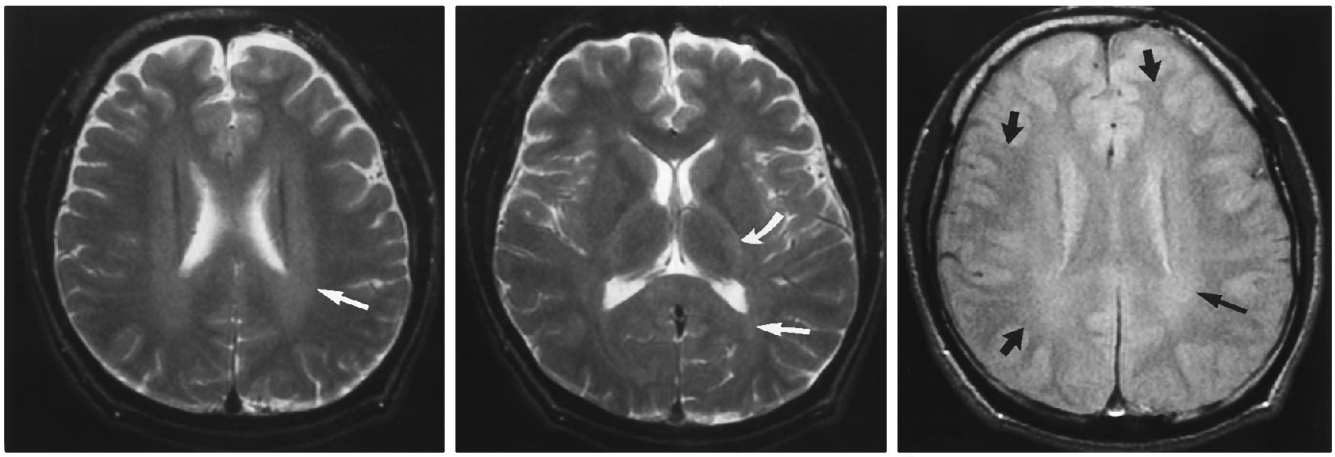

Fig 1. Restricted white matter change (patient 5).

A and *B*, Axial T2-weighted images (3000/100/0.75) show hyperintensities in the white matter surrounding lateral ventricles (*arrows*) and in posterior limb of internal capsule (*curved arrow*). The frontal lobe is slightly atrophic.

C, Axial proton density–weighted image (3000/30/0.75) corresponding to A. The white matter hyperintensities are restricted to the regions surrounding the lateral ventricles (*arrow*). This restriction causes the demarcation between gray and white matter to be preserved (*small arrows*) and distinguishes this from diffuse white matter change.

brain atrophy, including thinning of the corpus callosum and hippocampal atrophy, were essentially the same as those of previous studies (3–6). The main MR finding in the CNS of the chronic solvent abuser was the white matter change on T2-weighted and proton density–weighted images. This finding is considered to represent the damage in myelin, such as demyelination (8, 9) or myelin pallor (3), reported in histopathologic reports. In addition, we suggest the gliosis may be relate to these changes. Some histopathologic studies (8, 9) reported gliosis in white matter, which is a possible cause of T2 prolongation.

The most remarkable finding of this study was that there were two types of white matter change, restricted white matter change and diffuse white matter change. We were able to discriminate by the extent of hyperintensity on the proton density–weighted images. There were some differences in other MR findings between the two types. The cases with restricted white matter change showed the white matter hyperintensity on T2-weighted images in the middle cerebellar peduncles and cerebellar white matter surrounding the dentate nuclei that consist of the afferent system to the cerebellum and are possibly related to the cerebellar symptoms. In addition, some cases with restricted white matter change showed changes on T1-weighted images in addition to the corresponding T2-weighted images in these regions. The cases with diffuse white matter change showed equivocal white matter hyperintensity on T2-weighted images with no hypointensities on T1-weighted images in these regions.

MR studies on the myelinating process in infancy (10–13) are informative in considering what causes the T1 and T2 changes. The 1-month-old infants who were examined showed high signal intensity on T1-weighted images in the brain stem, cerebellar peduncles, posterior limb of the internal capsule, and corona radiata in the region of the rolandic fissure. After the spreading of this high signal intensity on T1-weighted images occurred, decrease in signal intensity on T2-weighted images followed. T1 shortening is considered to indicate the increase in cholesterol and glycolipids in the outer layer of myelin with myelin formation. T2 shortening correlates with the decrease in water content, which is at least partly caused by the increase in phospholipids in the inner layer with the tightening of the spiral of myelin around the axon (ie, the maturation of the myelin sheath) (12). If demyelination would follow the reverse process, T1 prolongation suggests a more severe change in white matter than does T2 prolongation.

Another difference in MR findings between the two types was the severity of the brain atrophy. The cases with restricted white matter change showed mild atrophy, whereas the cases with diffuse white matter change showed

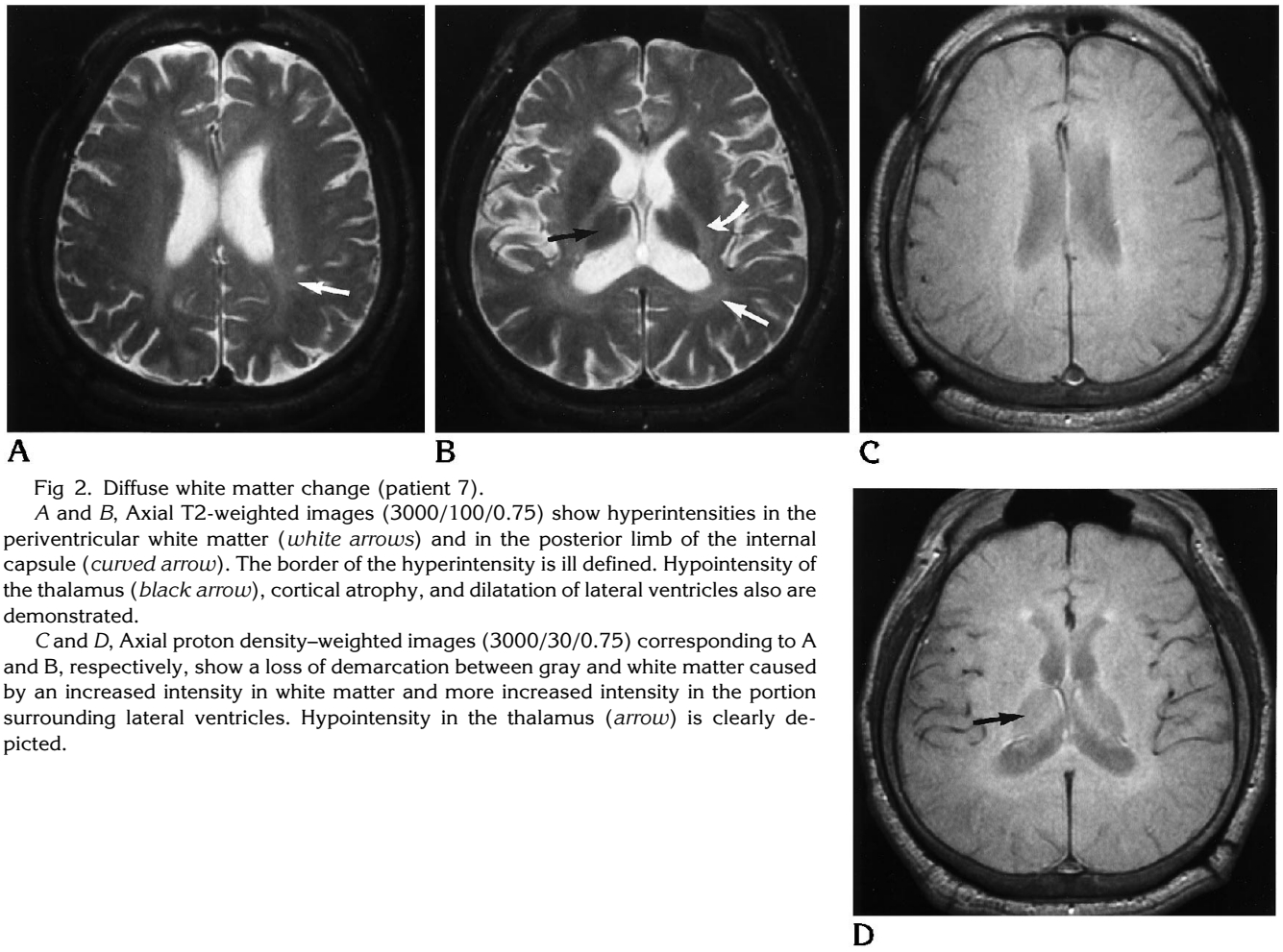

Fig 2. Diffuse white matter change (patient 7).

A and *B*, Axial T2-weighted images (3000/100/0.75) show hyperintensities in the periventricular white matter (*white arrows*) and in the posterior limb of the internal capsule (*curved arrow*). The border of the hyperintensity is ill defined. Hypointensity of the thalamus (*black arrow*), cortical atrophy, and dilatation of lateral ventricles also are demonstrated.

C and *D*, Axial proton density–weighted images (3000/30/0.75) corresponding to A and B, respectively, show a loss of demarcation between gray and white matter caused by an increased intensity in white matter and more increased intensity in the portion surrounding lateral ventricles. Hypointensity in the thalamus (*arrow*) is clearly depicted.

obvious brain atrophy, including thinning of the corpus callosum and hippocampal atrophy. Thinning of the corpus callosum also is found in cases with multiple sclerosis, a representative white matter disease, especially in longstanding and clinically severe cases (14, 15). Hippocampal atrophy has been reported in human studies (16). In addition, the increase in glial fibrillary acid protein that represents neural damage and gliosis is reported in the hippocampus of rats with toluene exposure (17).

Hypointensity in thalami on T2-weighted images was common to both types. Reduced signal intensity in putamina and thalami with white matter change also is reported in the patients with multiple sclerosis and is felt to be attributable to the redistribution of ferritin originally contained in oligodendroglia (18). Some researchers suggested this iron deposition, caused by demyelination, might be the cause of this finding in glue sniffers (6). However, Kojima et al reported the degree of this finding was not in proportion to that of the white matter change (19). Recently, Unger et al suggested that partitioning of toluene into the lipid membranes of cells may be responsible for this finding (20).

The difference in the changes in brain stem and cerebellum mentioned above suggests that restricted white matter change represents a qualitatively different change than that of diffuse white matter change. On the other hand, there is a possibility that restricted white matter change may represent an early stage of diffuse white matter change. The cases with diffuse white matter change had a longer duration of abuse and obvious brain atrophy. The intermediate case may represent the process of expansion from restricted white matter change to diffuse white matter change. Also, diffuse white matter change that causes loss of gray/white differentiation may obscure the focal changes in brain stem and cerebellum in the cases with

Patients with white matter change

Patient	1	2	3	4	5	6	7
Sex/Age, y	F/17	F/19	M/18	F/20	M/23	M/22	M/26
Duration of abuse, y	4	4	5	7	9	9	9
Mainly abused substance	Toluene	Toluene	Toluene	Toluene	Toluene	Lacquer thinner	Lacquer thinner
Neurologic findings							
Cerebellar signs	+	+	+	+	+	+	+
Pyramidal signs	+/−	−	+/−	−	−	−	+
MR findings							
Hyperintensities on T2-weighted images							
Periventricular white matter	+	+	+	+	+	+/−	+
Internal capsule	+	+/−	+	+	+	+/−	+
Brain stem	+	−	+	+/−	+	+/−	+/−
Middle cerebellar peduncles–cerebellum	+	+	+	+	+	+/−	+/−
Hypointensities on T1-weighted images							
Middle cerebellar peduncles–cerebellum	+/−	+/−	+	+	+/−	−	−
Hyperintensities on proton density–weighted images	Intermediate	Restricted	Restricted	Restricted	Restricted	Diffuse	Diffuse
Hypointensity in thalami	+	−	+	+	+/−	+	+
Atrophy							
Cortex	+/−	+/−	−	+/−	+/−	+	+
Corpus callosum	−	−	−	−	−	+	+
Cerebellum	−	−	+/−	−	−	+/−	+
Ventricular dilatation	−	+/−	+/−	+/−	−	+	+

Note.—+ indicates present; −, absent.

diffuse white matter change. Rosenberg et al (21) reported the prolongation of both T1 and T2 in cerebellar white matter in the patients whom we considered to have our diffuse white matter change. However, even if the cases with diffuse white matter change may have the same change in these regions, our study suggests that there are some patients with restricted but severe enough changes to cause the intractable neurologic symptoms in the specific regions such as the brain stem and/or cerebellum before diffuse white matter change occurs or brain atrophy becomes apparent.

One possible hypothesis for the qualitative difference is that the different substances abused cause the different changes. Pure toluene may cause the neurologic symptoms with restricted white matter change but lacquer thinner or glues may cause neurologic symptoms only after the diffuse white matter change occurs. Our patients with restricted white matter change mainly abused pure toluene, and the

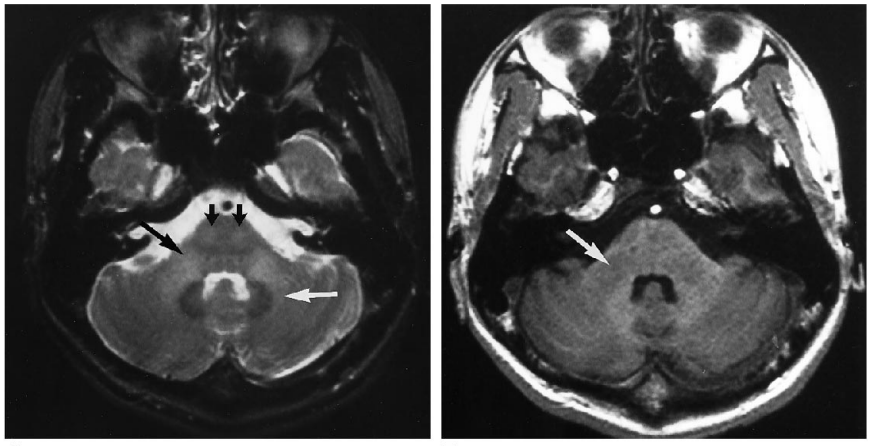

Fig 3. White matter hyperintensities in the brain stem and cerebellum on T2-weighted images in restricted white matter change (patient 5).

A, Axial T2-weighted image (3000/100/0.75) shows hyperintensity in the ventral part of pons (*small arrows*), middle cerebellar peduncles (*black arrow*), and cerebral white matter surrounding dentate nuclei (*white arrow*).

B, Axial T1-weighted image (25/5; flip angle, 35°) corresponding to A shows slight hypointensity of middle cerebellar peduncles (*arrow*).

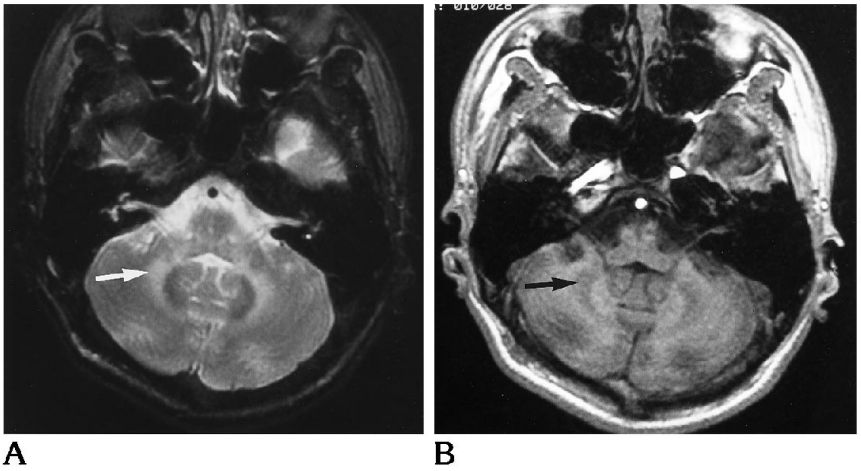

Fig 4. White matter hyperintensity in the cerebellum with corresponding hypointensities on T1-weighted images (patient 3).

A, Axial T2-weighted image (3000/100/0.75) shows hyperintensity in cerebellar white matter surrounding the dentate nucleus (*arrow*).

B, Axial T1-weighted image (25/5; flip angle, 35°) corresponding to C show hypointensity in the same region (*arrow*).

patients with diffuse white matter change mainly abused lacquer thinner. In one case with restricted white matter change (patient 2), the substance was proved to be pure toluene by a gaschromatographic analysis.

Restricted white matter hyperintensity in the brain stem and cerebellum has been reported in Japan (19, 22–27). In the United States, the loss of gray/white differentiation was reported (5). In the United States, other drugs are more prevalent. Therefore, pure toluene rarely is abused. Many abusers mentioned that pure toluene caused fewer unpleasant side effects such as nausea and headache than lacquer thinner or glues. The other components beside toluene that are included in lacquer thinner or glues may have harmful effects on the CNS and may cause diffuse changes with obvious brain atrophy. Also, the rarity of unpleasant side effects with pure toluene abuse may cause the rise in the concentration of toluene in blood and brain, and this may induce the restricted change in the vulnerable portions of the brain after a shorter duration of abuse. Moreover, the starting age of abuse may affect the changes. Because myelination in the CNS is known to be still occurring in adolescence (28), the early starting may possibly cause restricted white matter change in vulnerable portions of the brain. The parameters of abuse such as quantity of solvent, frequency of abuse, and the methods of inhalation also are important factors. However, it was hard to investigate these factors with accuracy. To determine which factor(s) plays a major role, the study of more cases is needed.

We attempted a composition analysis of solvents, although we were successful in only one case. Our inability to perform a more thorough composition analysis was partly because the possession of solvents for the purpose of inhalation is prohibited by the poisons and deleterious substance law in Japan. The abusers stated that they

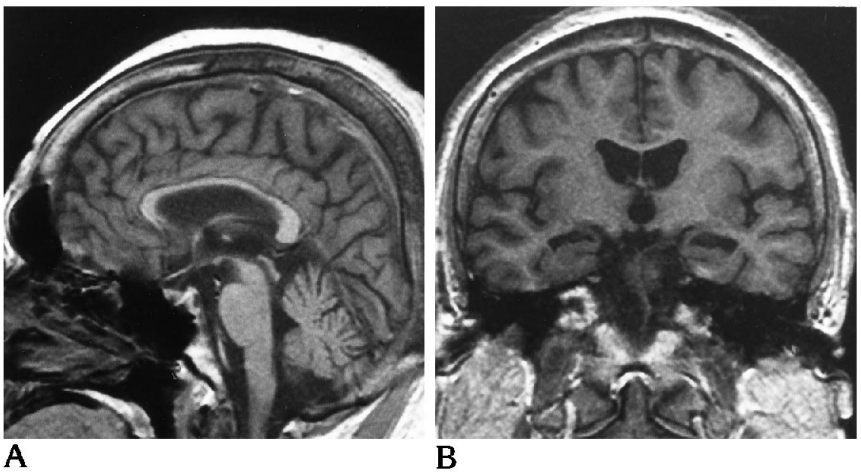

Fig 5. Thinning of corpus callosum and hippocampal atrophy in diffuse white matter change (patient 7).

A, Sagittal T1-weighted image (200/5; flip angle, 60°) shows thinning of the corpus callosum and dilatation of the fourth ventricle.

B, Coronal T1-weighted image (25/5; flip angle, 35°) shows thinning of the corpus callosum, cortical atrophy, dilatation of the lateral ventricles and third ventricle, and hippocampal atrophy.

can distinguish pure toluene from the other solvents according to its "taste." In addition, the composition analysis at the time of examination does not reveal the solvents used in the past. We believe we can trust their statements about what substances they mainly abused when we take into account their economic conditions and the information from their families.

So far, whether diffuse white matter change is caused by the spreading of restricted white matter change is not clear, neither is the reversibility of the white matter change. Also, the difference in the reversibility of the neurologic symptoms between the two types is an important but unanswered question. Further studies are needed, including a follow-up study of the cases with white matter changes.

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