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Occupational prolonged organic solvent exposure in shoemakers: brain MR spectroscopy findings

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Abstract

Our purpose was to investigate, by magnetic resonance (MR) spectroscopy, the metabolite changes in the brains of subjects in the shoemaking industry who had been chronically exposed to organic solvents. A total of 49 male subjects and 30 age-matched healthy volunteers underwent detailed neurological and psychiatric examinations. All subjects had long-echo [repetition time (TR) 2000 ms, echo time (TE) 136 ms] single-voxel MR spectroscopy. Voxels ($15 \times 15 \times 15$ mm^3) were placed in the parietal white matter, thalamus, and basal ganglia. N-acetylaspartate (NAA)/creatine (Cr) and choline (Cho)/Cr ratios were calculated. There was no significant difference between the study subjects and the control group in NAA/Cr ratios obtained from thalamus, basal ganglia, and parietal white matter. Cho/Cr ratios in thalamus, basal ganglia, and parietal white matter were found to be significantly increased compared to controls. There was a positive correlation between basal ganglia Cho/Cr ratio and duration of exposure ($r = 0.63$). MR spectroscopy should be performed to reveal metabolite changes and determine the degree of brain involvement in solvent-related industry workers.

Keywords: Occupational exposure; Solvents; Magnetic resonance spectroscopy

1. Introduction

Exposure to occupational organic solvents, which are used for extracting, dissolving, or suspending materials not soluble in water, poses an important health problem that differs from country to country for workers in industries involved with paints, adhesives, surface cleaning, dry cleaning, printing, plastics, pesticides, and chemicals [1–4]. The risk of solvent exposure, even at low doses, is increased in workers handling glues and adhesives used in shoe manufacturing [5–7]; toluene is the main component of organic solvents used in this industry [1,8–14]. Organic solvents constitute a large group of volatile chemicals, mainly hydrocarbons and their derivates. Through inhalation of the vapor and absorption through the skin, significant amounts of solvents are carried into the body [15]. Since solvents are lipophilic, they have an affinity to neuronal tissue that may lead to various neuropsychiatric findings [2,3,15,16].

In the autopsy studies involving people who were chronically exposed to organic solvents, reported changes were consistent with a demyelinating process, namely widespread loss of myelin, mild loss of axons, reduction in numbers of oligodendroglia, and gliosis [17–19].

Magnetic resonance spectroscopy (MRS) is a rather new, noninvasive, imaging modality used to study changes of the tissue metabolite composition in different brain diseases. It could provide significant additional information on brain metabolism induced by organic solvents. Our aim was to examine the cranial MR imaging (MRI), MRS, and neuropsychiatric findings in a series of subjects who were chronically exposed to organic solvents in the shoemaking industry.

2. Materials and methods

A total of 49 male shoemakers who had been exposed to mixtures of organic solvents (e.g., toluene and thinner) to

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clean, degrease, and dye-finish products; ingredients in glues; and adhesives, having worked in the shoe manufacturing industry between the ages of 14 and 58 (mean age: 31.4 ± 9.6 years), were included in our study. A total of 30 healthy male volunteers (mean age: 32.8 ± 8 years) who were not exposed to organic solvents and did not abuse any kind of substance constituted the control group. Ethics Committees of our institution approved the study protocol and informed consent was obtained from subjects and their employer.

The workers were interviewed thoroughly about overall job history with an emphasis on the duration of previous use of organic solvents, duration of long-term breaks (e.g., due to unemployment, disease, accident, and military service). All workers had a several-year history of essentially continuous exposure to solvents vapor throughout their working hours (more than 8 h/day and for more than 25 days/month). The subjects were gathered from the same shoe factory. The workplaces of shoemakers were visited by the investigators. The ventilation of the workplaces where gluing and polishing occur was found to be insufficient. Since glue containers were open all the time, there was an intense odor. No quantitative exposure data were available. The mean duration of exposure to organic solvents was 15.4 ± 8.9 years (range: 3–34).

All study participants underwent detailed neurological and psychiatric examinations administered by the respective specialists. Psychiatrically, all subjects and controls were evaluated according to the DSM IV (Diagnostic and Statistical Manual of Mental Disorders, American Psychiatric Association, 1994) criteria from the points of alcohol and substance abuse and addiction based on interviews and self-reported information. In the past, this examination has not revealed alcohol and substance abuse in subjects and controls together with neuropsychiatric disorders such as depression, schizophrenia, and bipolar disorder.

The MRI examination consisted of routine imaging and single-voxel spectroscopy (SVS). MRI was performed on a 1.5-T system (Philips, Gyroscan Intera Master, Best, Netherlands). T_1-weighted images (TR: 560, TE: 15) were obtained in the axial and sagittal planes. T_2-weighted images (TR: 4530, TE: 100) were obtained in the axial, sagittal, and coronal planes. Subjects and the healthy volunteers were studied during the same time period.

SVS was performed in all study participants by using a point-resolved spectroscopy sequence (PRESS; TR: 2000, TE: 136 ms) with 128 averages; voxel sizes of 15 × 15 × 15 mm^3 were used. Voxels were placed in basal ganglia, thalamus, and parietal white matter [9,10,20,21]. Prior to MRS, shimming was performed to optimize field homogeneity and water suppression was optimized using automated routines provided by the manufacturer. The water signal was suppressed by a chemical-shift selective saturation pulse. A spectral sweep width of 1000 Hz was used with data size of 1024 points. The spectra were processed automatically using baseline correction and curve-fitting procedures to determine the resonance areas of N-acetylaspartate (NAA), creatine (Cr), and choline (Cho). Analysis of the spectra was performed with the manufacturer-supplied spectroscopy software package of the MR system. The spectrum was referenced to Cr peak. Resonances were assigned as follows: NAA, 2.0 ppm; Cr, 3.02 ppm; and Cho, 3.2 ppm. Peak area metabolite ratios (NAA/Cr and Cho/Cr) were calculated. MRI and MRS findings were evaluated by the same investigators (A.A., R.K., and K.S.).

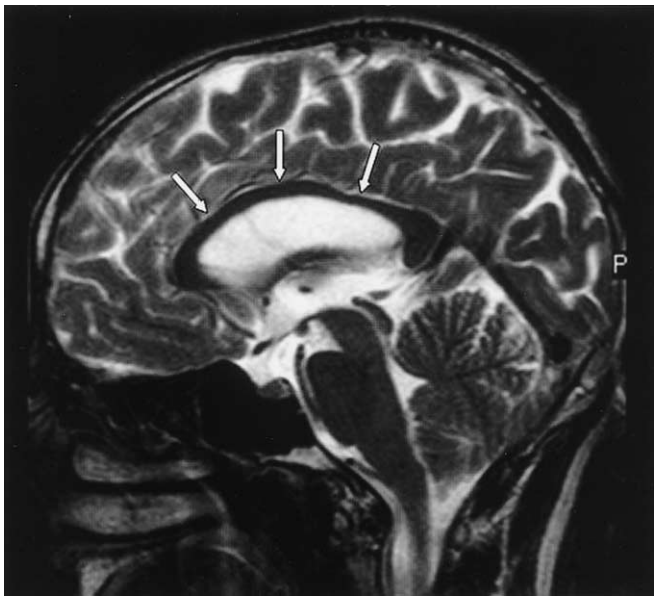


Fig. 1. Sagittal T_2-weighted image (4530/100) shows diffuse thinning in the corpus callosum (arrows) and atrophic dilatations in cortical sulci.

All statistical analyses were performed using a commercially available SPSS version 10.0 software package (SPSS Inc., Chicago, IL, USA). The results are presented as mean ± standard deviation to facilitate comprehension of the tables. Independent samples *t* test was used for the assessment of any difference in the metabolite ratios of parietal white matter, basal ganglia, and thalamus between the

Table 1
Neurological findings in 49 subjects

Finding	*n* (%)
Anosmia	12 (24.4)
Decrease in visual acuity	20 (40.8)
Brain stem	
Vertigo	35 (71.4)
Tinnitus	24 (48.9)
Diplopia	9 (18.3)
Cerebellar	
Nystagmus	6 (12.2)
Ataxia	21 (42.8)
Dysarthria	19 (38.7)
Intentional tremor	19 (38.7)
Dysdiadochokinesis	2 (4.08)
Extrapyramidal	
Tremor	35 (71.4)

Table 2
Metabolite ratios of three different locations obtained from organic solvent–exposed subjects and control subjects

Metabolite ratio	Location	Organic solvent–exposed subjects (n = 49)	Control subjects (n = 30)
NAA/Cr	White matter	1.84 ± 0.23	1.87 ± 0.12
	Basal ganglia	1.27 ± 0.13	1.27 ± 0.14
	Thalamus	1.75 ± 0.17	1.75 ± 0.09
Cho/Cr	White matter	1.21 ± 0.16*	0.97 ± 0.10
	Basal ganglia	1.06 ± 0.16*	0.74 ± 0.14
	Thalamus	1.14 ± 0.16*	0.94 ± 0.10

* $p < 0.05$ overall vs. control.

healthy control and solvent-exposed subjects. Pearson's correlation test was used to assess whether there is a correlation between the duration of exposure and metabolite changes in parietal white matter, basal ganglia, and thalamus. A p value below 0.05 was considered statistically significant.

3. Results

There was no significant difference in age between subjects exposed to organic solvents and control subjects. Psychiatric examinations did not reveal any clinical pathologic findings.

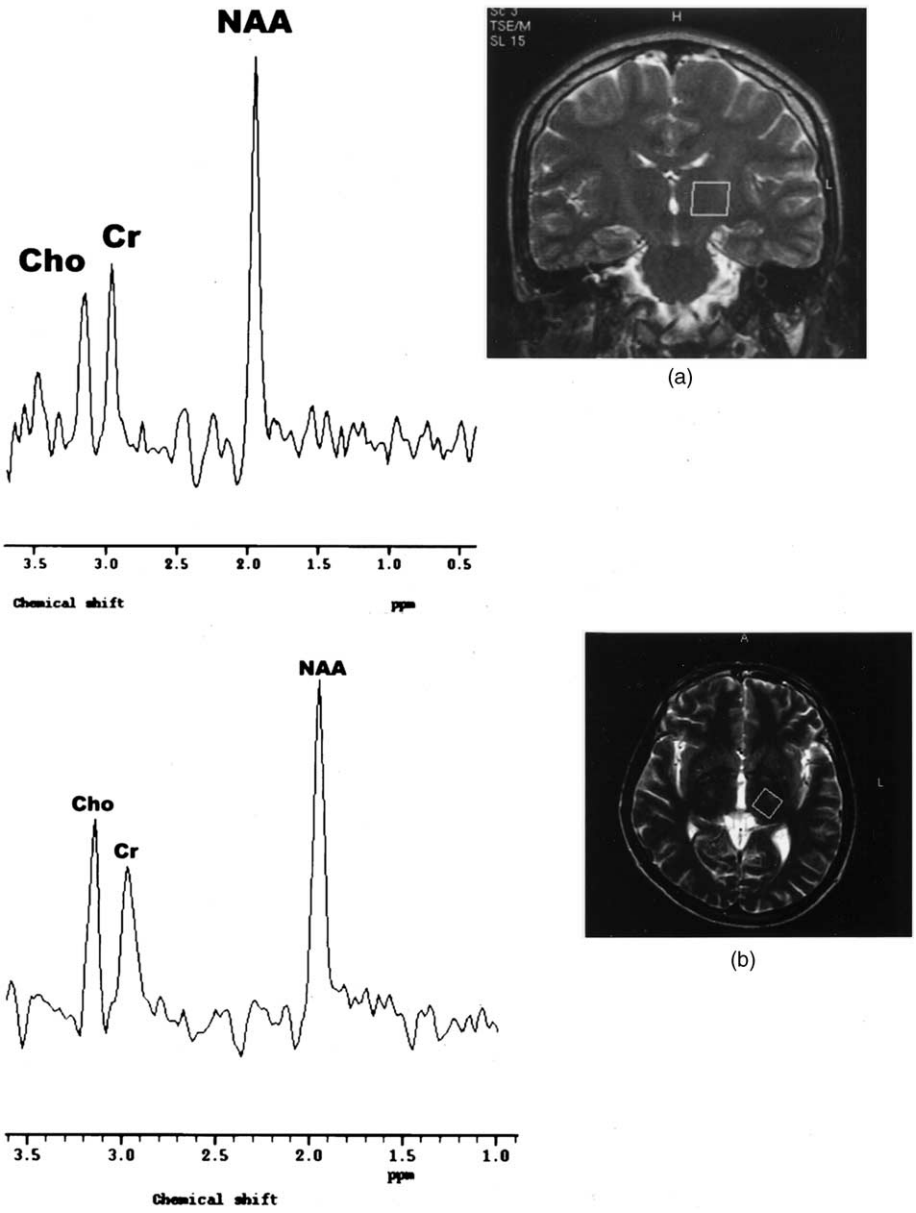


Fig. 2. (a) A 22-year-old man with 5 years of exposure to organic solvents; MR spectrum (PRESS; 2000/136) obtained from the left thalamus shows normal metabolite peaks. (b) A 30-year-old man with 10 years of exposure to organic solvents; MR spectrum (PRESS; 2000/136) obtained from the left thalamus shows normal NAA/Cr and increased Cho/Cr ratios that may indicate demyelination.

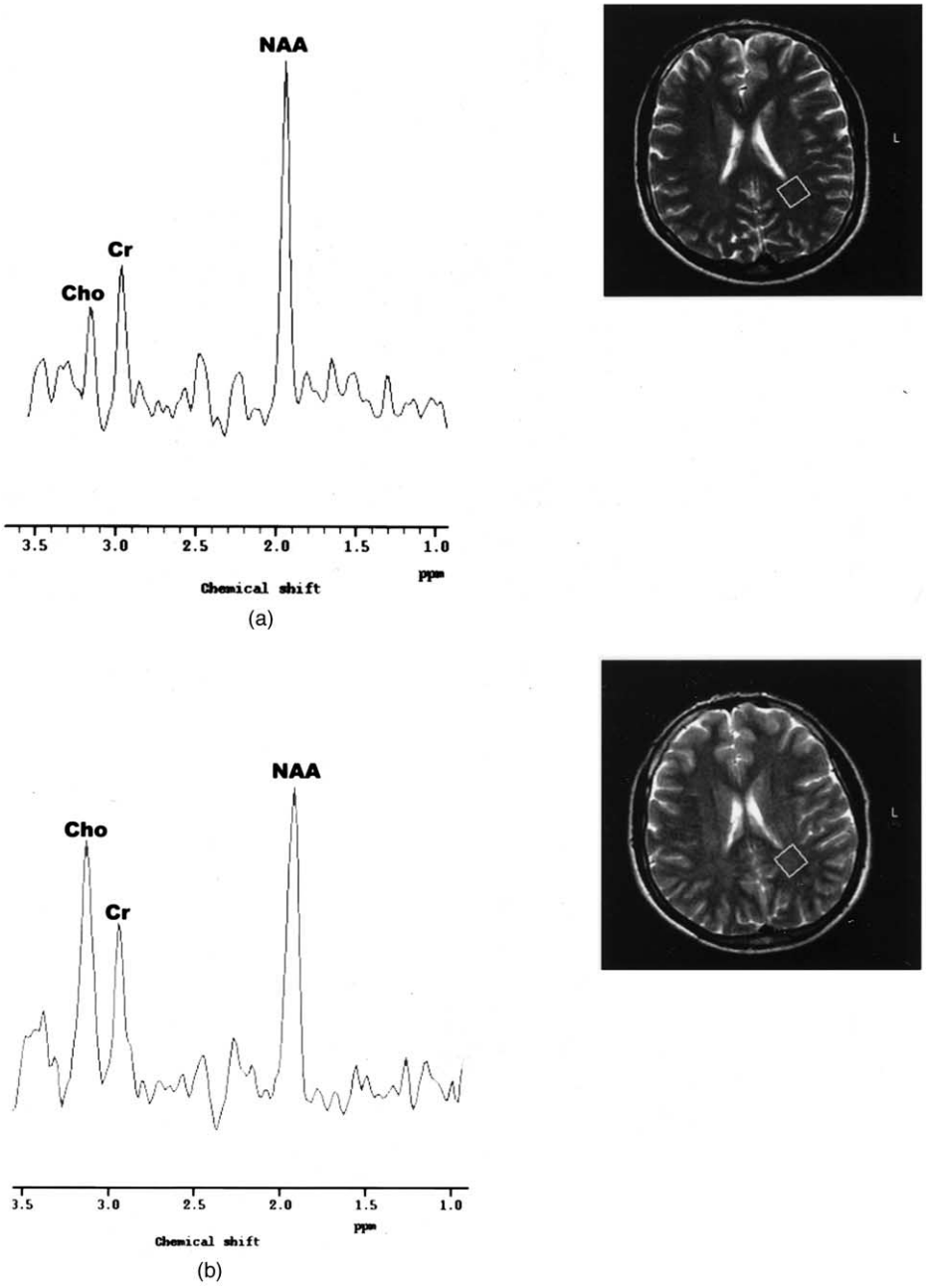
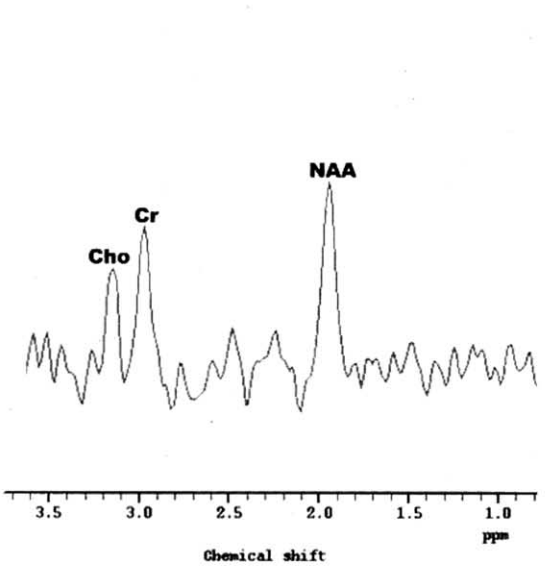


Fig. 3. (a) A 21-year-old man with 4 years of exposure to organic solvents; MR spectrum (PRESS; 2000/136) obtained from parietal white matter shows normal metabolite peaks. (b) A 47-year-old man with 30 years of exposure to organic solvents; MR spectrum (PRESS; 2000/136) obtained from parietal white matter shows normal NAA/Cr and significantly increased Cho/Cr ratios that may reveal demyelination.

Cranial MR imaging revealed mild cerebral and cerebellar atrophy ($n = 11$, 22.4%); thinning of corpus callosum ($n = 8$, 16.3%); and hypointensity (on T_2-weighted images) in basal ganglia ($n = 7$, 14.2%; Fig. 1). Headache (87.7%), vertigo (71.4%), tremor (71.4%), tinnitus (48.9%), and ataxia (42.8%) were among the most common neurological findings (Table 1).

Fig. 4. (a) A 22-year-old man with 4 years of exposure to organic solvents; MR spectrum (PRESS; 2000/136) obtained from the left basal ganglia shows normal metabolite peaks. (b) A 30-year-old man with 13 years of exposure to organic solvents; MR spectrum (PRESS; 2000/136) obtained from the left basal ganglia shows normal NAA/Cr and moderately increased Cho/Cr ratios. (c) A 58-year-old man with 34 years of exposure to organic solvents; MR spectrum (PRESS; 2000/136) obtained from the left basal ganglia shows normal NAA/Cr and prominently increased Cho/Cr ratios that may reveal significant demyelination after long-duration exposure to solvent.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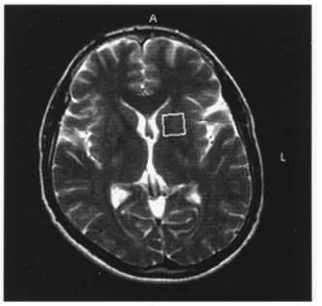
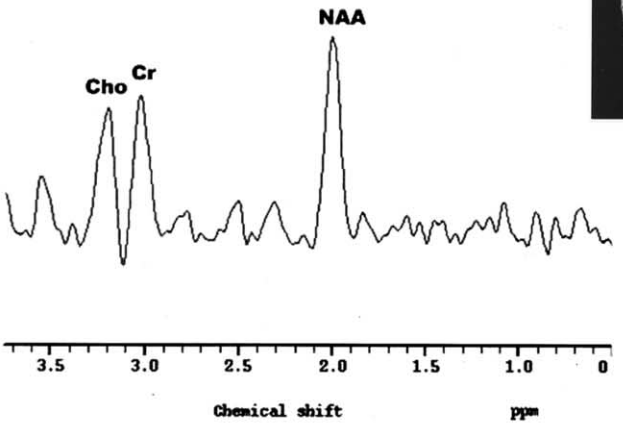


(a)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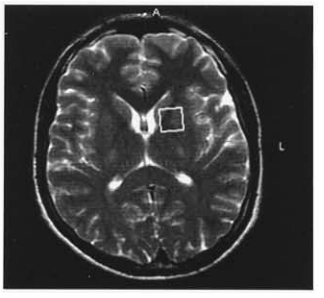

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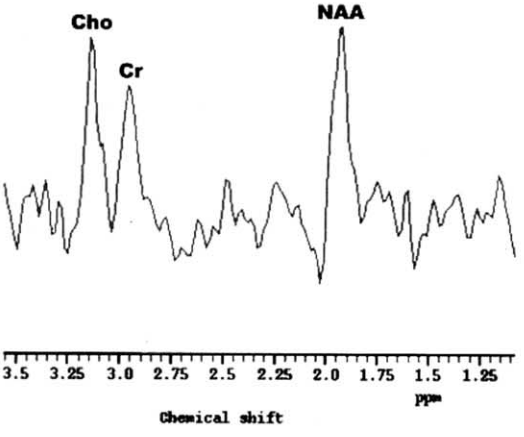
Cho
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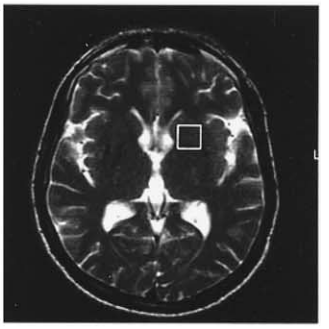

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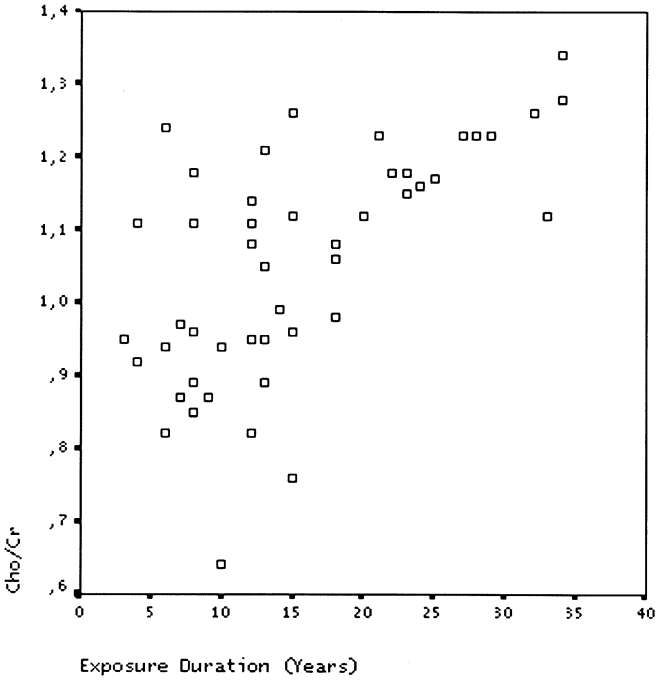

Fig. 5. Scatter-plot graph shows the increase of Cho/Cr ratio in basal ganglia as the duration of organic solvent exposure increases (r = 0.63).

Metabolite ratios obtained from parietal white matter, basal ganglia, and thalami of all study participants are presented in Table 2. There was no significant difference between subjects exposed to organic solvents and control subjects in NAA/Cr ratios obtained from thalami, basal ganglia, and parietal white matter. Cho/Cr ratios obtained from parietal white matter, basal ganglia, and thalamus were significantly increased in solvent-exposed compared to control subjects [$p = 0.0001$; Figs. 2 (a), 2(b), 3 (a), and 3(b)]. There was a positive correlation between basal ganglia Cho/Cr ratios and the duration of exposure [r = 0.63, $p = 0.0001$; Figs. 4 (a–c) and 5].

4. Discussion

Widespread usage of organic solvents still is an important occupational health hazard, even in developed countries where there are strict rules and regulations about workplaces and working conditions. In acute solvent intoxications, there is clear evidence of an exposure-effect relationship, but long-term, low-level occupational exposure to solvents is more difficult to detect. Prolonged exposure to these solvents could lead to chronic toxic encephalopathy in people working in these environments [1,2,16]. It has been reported that prolonged exposure to organic solvents causes the chronic and often irreversible neurobehavioral deficits that are labeled chronic toxic encephalopathy [2]. This type of encephalopathy, reported to cause cerebellar symptoms and signs such as ataxia, tremors, dysarthria, nystagmus, cognitive impairment, spasticity, Parkinson's disease, subjective symptoms (like headache, tiredness, memory disturbances, and dizziness), psychiatric disorders, and general neuroasthnenic signs [10,15,22–25]. Tremor ($n = 35$, 71.4%) and headache ($n = 43$, 87.7%), tinnitus ($n = 24$, 48.9%), dysarthria ($n = 19$, 38.7%), and intentional tremor ($n = 19$, 38.7%) were among the most common neurological findings in our study. Although our subjects demonstrated sparse neuropsychiatric findings, none of the presented signs and symptoms were significant to make the diagnosis of clinically important toxic encephalopathy.

The reported cranial MRI findings of chronic solvent encephalopathy include mild cerebral cortical atrophy, mild cerebellar atrophy, thinning of corpus callosum, hypointensity in thalamus and basal ganglia, parietal white matter changes, and loss of demarcation between gray and white matter [10,19,22,26]. All these MRI findings have been attributed to the demyelination and gliosis (due to penetration of organic solvents into the myelin sheath) in the cerebral and cerebellar white matter histologically. On the other hand, hypointensity in thalami and basal ganglia was thought to represent the deposition of iron due to demyelination and axonal loss [9,10,22,26–28]. There were no visible white matter changes and loss of demarcation between gray and white matter on MRI in any of our subjects. The lower frequency of such MRI findings in our study could be related to chronicity and the level of exposure to organic solvents.

In contrast to conventional MRI, MRS could provide information on neuronal/axonal viability, cellular energetics, and cellular membrane status. With increasing use and application in different diseases of the central nervous system, MRS would aid in the diagnosis and clinical management of various pathological processes [29–31]. The prominent resonances detected on MRS in normal brains include NAA, Cho, and Cr. Since NAA is a neuroaxonal marker, abnormalities of neuronal structures like reduced neuronal density or viability lead to reductions in NAA. Therefore, it is an important predictor of neuronal dysfunction. Creatine plays an important role in the cellular energy metabolism. It is more concentrated in glia than in neurons. Except in trauma, stroke, tumor, and Cr deficiency syndromes, Cr levels tend to remain relatively unchanged. Therefore, Cr is often used as a putative internal standard against which the other metabolites can be compared [29]. In our study, NAA/Cr ratios in thalami, basal ganglia, and parietal white matter of subjects exposed to organic solvents were normal compared to control subjects, which could indicate an absence of neuroaxonal loss.

Major components of the Cho resonance are choline-containing compounds with small molecular weight, such as phosphocholine and glycerophosphocholine, that form a pool involved in membrane synthesis and degradation. The increase in the Cho/Cr ratio might point to an inability to properly incorporate Cho-containing molecules into myelin. Also, loss or disruption of normal myelin increases the level of Cho-containing compounds. Thus, an increase in Cho/Cr ratio could indicate demyelination [29–31]. In our study,

MRS revealed important metabolite changes in parietal white matter, basal ganglia, and thalami. In all organic solvent–exposed subjects in our study, Cho/Cr ratios were significantly increased in these regions compared to control subjects. Our study indicated significant increases in Cho/Cr ratios in all organic solvent–exposed subjects, which could implicate severe demyelination that is not visible by MRI. Futhermore, the Cho/Cr ratio increase in the basal ganglia showed a linear correlation ($r = 0.63$) with the duration of the exposure, which could indicate a duration-related demyelination increase.

5. Conclusion

Chronic toxic encephalopathy due to occupational organic solvent exposure in underdeveloped or developing countries, where the workplaces are less regulated and periodic health controls are lacking, is still an important health problem. While the effects of prolonged, low-level exposure to organic solvents leading to subtle neuropsychiatric findings may not be apparent on conventional MRI, it is easy to detect them with MRS. Therefore, MRS could be used in the evaluation of these subjects in addition to neuropsychiatric examination and MRI.

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