Longitudinal study of carbon monoxide intoxication by diffusion tensor imaging with neuropsychiatric correlation

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Background: White matter damage is common after carbon monoxide (CO) intoxication, but in vivo follow-up studies about the mechanism of white matter damage are not possible in pathology series. Diffusion tensor imaging (DTI) and voxel-based morphometry (VBM) can quantify diffusion parameters and volumetric changes in white matter that can be correlated with neuropsychological performances in longitudinal studies. **Methods:** We examined 9 patients with CO intoxication using DTI, VBM and neuropsychologic tests at an average of 3 and 10 months after CO exposure. We used data from 18 age- and sex-matched controls for comparison. **Results:** We found that cognitive recovery at 10 months after CO intoxication was not significant, although it was after 3 months. The neuropsychologic tests correlated better for the fibre tract of the semicentrum ovale and not the periventricular fibres. Diffusion measures suggest increases in fractional anisotropy, mean diffusivity and axial eigenvalues over time, while increases in radial eigenvalue were evident at 3 months compared with controls. Periventricular white matter atrophy was observed 10 months after CO intoxication. **Limitations:** Our study included few cases, and the interpretation of the putative changes on neuroimaging findings cannot be confirmed by histology. **Conclusion:** Our study showed that the evolution of white matter injury in CO encephalopathy occurred over time. Cognitive recovery was not evident in the follow-up period because of white matter injuries.

Introduction

Carbon monoxide (CO) intoxication by charcoal burning has become the primary method of attempted suicide in Taiwan,¹ leading to an increase of more than 20% in the overall suicide rate.² Carbon monoxide intoxication can lead to acute and chronic neuropsychiatric complications. The pathophysiologic mechanisms of brain injury following CO exposure vary.³ One important factor is the inflammatory reaction after toxic exposure.⁴ Cortical and subcortical white matter damage have been reported to account for the neuropsychologic

deficits,⁵⁻⁷ but longitudinal follow-up of white matter damage is not possible in pathology series.

Voxel-based morphometry (VBM) is an unbiased, whole-brain quantitative method that can detect volume changes of grey⁸ and white matter. Diffusion tensor imaging (DTI)⁹ is a recently developed tool that uses magnetic resonance imaging (MRI) technology. Fractional anisotropy (FA) and mean diffusivity are 2 DTI-derived parameters that provide information about microstructure changes.¹⁰ Although the specifics are not well known, FA quantifies the directionality and coherence of the white matter tracts by factors such as

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myelination, axonal density and integrity.^{11,12} Analysis of axial and radial diffusivity may provide potential measures of the mechanisms of white matter changes because increased axial diffusivity has been reported to reflect axonal changes in trauma, whereas changes in radial diffusivity strongly correlate with myelin abnormalities.¹³ In this study, a combination of DTI and VBM were used to monitor CO-intoxicated patients over time. Their clinical parameters were compared with those of controls.

Methods

Patient enrolment

The neurology clinic at Kaohsiung Chang Gung Memorial Hospital recruited 9 CO-intoxicated patients from August 2006 to November 2008. We included 18 age-matched healthy participants from the normative database as controls for neuropsychologic testing and MRI comparison. The age of each control was within 2 years of the sex-matched CO patient. None of the control participants had a history of neurologic or neuropsychiatric disorders, and all had normal results of MRI scanning and basic blood tests (liver and renal function tests, electrolytes and complete blood cell counts).

Informed consent was obtained from all participants, and the Institutional Review Board of Chang Gung Memorial Hospital approved the study protocol.

Cognitive testing

We used a comprehensive battery of tests to assess the cognitive ability of all participants and the Mini-Mental State Examination (MMSE)¹⁴ to assess their general intellectual function. We evaluated cognitive severity using the Clinical Dementia Rating (CDR) Scale.¹⁵ We also assessed verbal and nonverbal episodic memory using the word-recognition test from the Alzheimer's Disease Assessment Scale–Cognitive (ADAS-Cog)¹⁶ and recollection of the Rey–Osterrieth complex figure¹⁷ after a 10-minute delay (maximal value = 17, normal value > 13.4). We chose CDR because it evaluates the functional capacity of the participant independent of physical disability, which may occur in patients with CO intoxication. The ADAS-Cog memory subset was chosen to investigate memory recall and registration ability because it has been extensively tested for its sensitivity and specificity in differentiating between patients with and without memory problems.

We adapted the test for memory-retrieval ability from the word-recognition test of ADAS-Cog. We evaluated the scores as follows: a hit (maximal value = 12, normal value > 9.5) was the recognition of a word that had appeared before; a false alarm was a response to a word that was not in the test list; a miss was a nonrecognition of a word that had appeared before; and a correct rejection (maximal value = 12, normal value > 8.5) was the recognition that a word had not appeared before. We used language screening tests including the 17-item Boston Naming Test¹⁸ (maximal value = 17, normal value > 16.5) and semantic verbal fluency (number of animals and vegetables in 1 min).

We assessed visuospatial ability by instructing participants to copy a modified Rey–Osterrieth complex figure (maximal value = 17, normal value > 16.3) and by use of the number–location test from the Visual Object and Space Perception Battery¹⁹ (maximal value = 10, normal value > 9.5). We also assessed the ability to perform 5 arithmetic calculations and digit forward span. We evaluated executive function using the digit backward span, reasoning and abstract thinking questions and design fluency test.²⁰ We used the Neuropsychiatric Inventory (NPI) to assess behavioural symptoms.²¹

Magnetic resonance imaging protocols

Scans were performed using a 3-T scanner (Excite; GE Medical System) equipped with echo-planar capability. The structural MRI sequences were as follows:

1. Axial fast spin-echo T_2 -weighted image: repetition time 4200 ms, echo time 102 ms, 2 acquisitions, field of view (FOV) 240 × 240 mm, 320 × 224 matrix, section thickness 5 mm.
2. Axial fluid-attenuated inversion recovery image: repetition time 8000 ms, echo time 100 ms, time for inversion 2000 ms, 1 acquisition, FOV 240 mm × 240 mm, 320 × 256 matrix, section thickness 5 mm.
3. T_1 inversion recovery–prepared 3-dimensional spoiled gradient-recalled acquisition in steady-state sequence: repetition time 8600 ms, preparation time 400 ms, FOV 240 mm × 240 mm, slice thickness 1 mm.
4. Diffusion tensor imaging: single-shot echo-planar sequence with gradients applied in 25 noncollinear directions. Axial images were acquired using the following parameters: repetition time 7000 ms, echo time 72 ms, FOV 240 mm × 240 mm, 128 × 128 matrix, which led to an in-plane resolution of 1.875 mm. Data were subsequently interpolated to 1 × 1 mm. Thirty contiguous slices of 5-mm thickness were obtained without gap. A b value of 1000 s/mm² was used.

We processed the imaging data on a personal computer using SPM 5 (www.fil.ion.ucl.ac.uk/spm/; Wellcome Department of Cognitive Neurology, London, UK) for VBM data and FSL version 4.0.1 (www.fmrib.ox.ac.uk/fsl/) for DTI data.

Voxel-based morphometry

The VBM protocol followed standard procedures.²² We created an ad hoc age-matched template image to optimize the spatial normalization. We applied affine and nonlinear transformations to spatially normalize the participants' images to the template. We sequentially performed normalization, segmentation into 3 classes of tissue (grey matter, white matter and cerebrospinal fluid), modulation and spatial smoothing of images with 8-mm full-width at half-maximum isotropic Gaussian kernel.

We compared data between the CO and control groups. Age and sex were considered covariates of no interest to exclude their possible effects on regional grey or white matter volume.²² The significance threshold was set at $p < 0.05$ and corrected for multiple comparisons across the whole brain (family-wise error).

Tract-based spatial statistics

The FA data from all participants were aligned into a common space using a nonlinear image registration toolkit.²³ We calculated FA from realigned diffusion tensor and then this projected onto a mean FA skeleton; the resulting data were used for voxel-wise comparisons across participants. We compared the FA data using permutation-based nonparametric inference on cluster size²⁴ and Randomize 2.0 software (www.fmrib.ox.ac.uk/fsl/randomise/index.html). We used a restrictive statistical threshold (threshold-free cluster enhancement threshold, $p < 0.05$, corrected for multiple comparisons). We identified abnormal white matter tracts on FA maps based on the atlas prepared at Johns Hopkins University.²⁵

After using the FA images to achieve nonlinear registration and stages of skeleton formation, we estimated the projection vectors from each individual participant onto the mean FA skeleton. The nonlinear warps and skeleton projections were then separately applied to the mean diffusivity, axial and radial eigenvalue images. We analyzed the resulting statistical maps at a threshold of $p < 0.05$ (corrected at cluster level for multiple comparisons).

Statistical analysis

We used the Kruskal–Wallis H test to compare neuropsychiatric performance between those in the CO and control groups because these data were not normally distributed. We used a paired t test to test for differences between the performance of patients at 3 and 10 months.

We performed further analyses on the axial and radial eigenvalues extracted from the aligned database for the regions showing differences in FA values between the CO and control groups. We evaluated the relation between diffusion parameters (FA, mean diffusivity, axial and radial eigenvalues) and cognitive domains in the CO group using nonparametric correlation analysis. The r values within the regions of interest against the cognitive scores were obtained by use of

SPSS (version 11.0 for Windows). We considered $p < 0.01$ statistically significant.

Results

Patients

The CO group comprised 4 male and 5 female patients (Table 1). Patients were diagnosed with CO intoxication based on a history of a charcoal burning suicide attempt and an elevated carboxyhemoglobin level ($> 10\%$) at the emergency department (mean 20.4%, range 15%–25%). All patients had an initial loss of consciousness and received normobaric oxygen therapy. None had a neurologic or neuropsychiatric history. Brain MRI and neuropsychologic examinations were performed after 3 months (mean 86, standard deviation [SD] 8, d) and 10 months (mean 312, SD 17, d).

Cognitive tests and clinical features

The cognitive data for CO patients and controls is summarized in Table 2. The CO group scores at both the 3- or 10-month follow-up visit were lower than those of controls in multiple domains, including visual and verbal memory, executive function, calculation and visuospatial function. Paired t tests did not reveal significant differences between the 3- and 10-month follow-up data in the CO group.

The CO group at 3 months had higher depression scores on NPI than controls (4.9 v. controls 1.45, $p = 0.01$, $t_{25} = -2.79$) and NPI total score ($p = 0.004$, $t_{25} = -3.13$; Table 1). The scores in the CO group were not significantly different from the control scores at 10 months. In the CO group, no NPI domain score was significantly different between 3 and 10 months.

Diffusion parameters at 3 months

The red voxels in Figure 1(A–D) show the areas where FA was reduced in the CO group. These regions include the

Table 1: Characteristics of the 9 carbon monoxide-intoxicated patients

Patient	Age, yr	Sex	Education, no. of yr	Duration of unconsciousness, hr	Initial clinical presentation	Important findings at presentation	Important findings at study enrolment
1	41	Female	12	8	Confusion	Ataxic gait with right lower leg weakness	Parkinsonism, apathetic, cognitive decline
2	57	Male	12	5	Headache, myalgia	Personality changes	Memory complaints, insomnia, parkinsonism
3	43	Male	9	12	No verbal output with dull response	Apathetic	Cognitive decline
4	41	Female	12	3	Dizziness and headache	Parkinsonism	Unsteady gait, memory complaints
5	26	Female	9	5	Dizziness and headache	Unsteady gait	Personality changes, depression
6	37	Female	16	12	Confusion	Insomnia, gait problem	Cognitive decline
7	24	Female	16	8	Confusion	Unsteady gait	Tremor, leg dystonia
8	63	Male	12	7	Tremor of lower limbs	Memory complaints	Topographic disorientation, parkinsonism
9	41	Male	12	10	Unsteady gait, dizziness, confusion	Memory complaints	Incontinence, depressed mood

anterior and posterior corpus callosum, orbitofrontal cortex, internal capsule, anterior region of the external capsule, thalamus and corona radiata. These regions overlapped with the regions with increased mean diffusivity in the CO group (Fig. 1E–H). Panels I and J in Figure 1 represent regions showing increased axial eigenvalue in the CO group, which are the anterior part of the external capsule and frontal corona radiata. Regions with increased radial eigenvalue overlapped with FA and mean diffusivity regions. No regions showed decreased FA, increased mean diffusivity, decreased axial eigenvalue or increased radial eigenvalue in the control group.

Diffusion parameters at 10 months

Figure 2(A–D) shows the regions where FA was reduced in the CO group compared with controls, including the anterior and posterior corpus callosum, orbitofrontal cortex, internal capsule, anterior region of external capsule, thalamus and corona radiata. Regions showing increased mean diffusivity in the CO group (Fig. 2E–H) were more extensive than the FA

map, which showed additional regions, such as cerebral peduncles, brain stem, cerebellar vermis and subcortical U fibres. Regions with increased axial eigenvalue in the CO group overlapped with regions of increased mean diffusivity (Fig. 2I–M), where there was more extensive cerebellar hemisphere white matter involvement (Fig. 2I). Regions with increased radial eigenvalue in the CO group (Fig. 2N–Q) overlapped with the mean diffusivity map, except with less involvement of the brain stem region. No regions showed decreased FA, increased mean diffusivity, decreased axial eigenvalue or increased radial eigenvalue in the control group.

Diffusion parameters at 3 and 10 months

Regions showing relatively decreased FA at 3 months (Fig. 3A–C) included the inferior fronto-occipital and inferior longitudinal fasciculus, corticospinal tract and superior longitudinal fasciculus. Areas with increased mean diffusivity at 10 months (Fig. 3D–G) included the anterior and posterior corpus callosum, right thalamus, superior longitudinal fasciculus

Table 2: Neuropsychologic comparisons of carbon monoxide–intoxicated patients 3 and 10 months after exposure and control participants

Neuropsychologic measure	Group; mean (SD)		
	CO patients, 3-month follow-up	CO patients, 10-month follow-up	Control participants
Mini-Mental State Examination ¹⁴	21.1 (7.1)*	21.0 (9.4)*	29.3 (0.4)
Clinical Dementia Rating ¹⁵	0.7 (0.4)*	0.9 (1.6)*	0
Verbal episodic memory ¹⁶ (maximal = 10)			
1st trial	3.8 (1.3)	3.7 (1.4)*	5.1 (1.3)
2nd trial	4.9 (1.7)*	5.2 (1.2)*	7.3 (0.8)
3rd trial	5.4 (1.8)*	5.6 (1.7)*	7.9 (1.4)
Delay recall	4.0 (2.2)*	4.5 (2.4)*	7.2 (1.8)
Visual memory ¹⁷			(1.8)
Modified R-O recall (maximal = 17)	5.9 (4.8)*	7.3 (5.4)	15.5 (2.1)
Modified R-O recognition (maximal = 1)	0.5 (0.5)*	0.9 (0.3)	1.0 (0)
Word-recognition test ¹⁶			
Hit	9.3 (1.9)	10.3 (1.3)	10.8 (1.3)
False alarm	0.2 (0.4)	0.3 (0.7)	0.4 (0.6)
Missed	2.4 (1.9)	1.2 (1.1)	1.8 (2.6)
Correct rejection	11.7 (0.4)	11.9 (0.3)	11.0 (2.6)
Language ability			
Boston Naming Test ¹⁸ (maximal = 17)	16.1 (0.7)	15.9 (0.7)	17 (0)
Semantic fluency: animal	10.8 (2.9)*	10.4 (2.9)*	16.6 (5.4)
Semantic fluency: vegetables	9.9 (2.6)*	11.3 (3.6)	15.2 (3.7)
Visuospatial ability			
R-O complex copy ¹⁷ (maximal = 17)	12.4 (7.4)	17.0 (0)	17.0 (0)
Visual Object and Space Perception Battery ¹⁹ (maximal = 10)	7.7 (3.1)*	7.7 (1.8)*	10.0 (0)
Calculation (maximal = 5)	3.8 (1.4)*	3.9 (1.2)	4.9 (0.2)
Executive function ²⁰			
Digit backward	3.3 (1.3)*	3.9 (1.1)*	5.4 (1.5)
Design fluency	4.4 (3.6)	5.8 (3.2)	8.3 (4.9)
Reasoning (maximal = 8)	6.4 (1.4)	7.6 (1.0)	7.4 (1.1)
Judgment (maximal = 12)	7.2 (2.0)*	7.4 (3.0)	10.5 (2.4)
Digit forward	7.7 (1.0)	7.7 (0.9)	8.0 (1.9)
Neuropsychiatric Inventory total scores ²¹	12.7 (12.6)*	6.4 (6.5)	3.82 (3.1)

CO = carbon monoxide; R-O = Rey–Osterrieth; SD = standard deviation.

**p* < 0.01 compared with controls.

Fig. 1: Clusters with significant differences (red) between the carbon monoxide group 3 months after exposure and controls. The clusters were overlaid on the mean fractional anisotropy skeleton map (green) (all $p < 0.05$, multiple correction at the cluster level). The background anatomic reference was the Montreal Neurological Institute 152 Image.

and inferior frontal occipital fasciculus. Panels H–L in Figure 3 show regions with decreased axial eigenvalue at 3 months, including the brain stem, anterior and posterior corpus callosum, orbitofrontal cortex, internal capsule, anterior region of external capsule, thalamus and corona radiata. No region showed

differences in radial eigenvalue between 3 and 10 months, and no region showed decreased FA, mean diffusivity or axial eigenvalue at 10 months compared with at 3 months.

Values of axial and radial eigenvalues were further extracted from the regions where FA was reduced at 3 months

Fig. 2: Clusters with significant differences (red) between the carbon monoxide group 10 months after exposure and controls. The clusters were overlaid on the mean fractional anisotropy skeleton map (green) (all $p < 0.05$, multiple correction at the cluster level). The background anatomic reference was the Montreal Neurological Institute 152 Image.

for further analysis (Fig. 4). The results showed that reduced FA resulted from changes of axial eigenvalue (Fig. 4A) rather than radial eigenvalue (Fig. 4B).

Voxel-based morphometry

Comparison between the CO group (at either 3 or 10 months) and the control group showed no voxels with significant differences in grey matter volume. A direct comparison between 3 and 10 months in the CO group also did not reveal any areas with significant differences.

Comparison between the CO group at 3 months and the control group did not reveal significant differences in white matter regions. However, there was significant atrophy in the periventricular white matter at 10 months when the CO group was compared with the control group (Fig. 5). These regions included the anterior and posterior corpus callosum and the white matter tract in the temporal-parietal subcorti-

cal regions. There were no significant differences in white matter volume between 3 and 10 months in the CO group.

Correlation between neuropsychologic testing and diffusion parameters

Relation between FA and cognitive domains

At 3 months, correlation between FA and cognitive domains showed that the MMSE score was correlated with left temporal parietal white matter ($r = 0.75$), bilateral high frontal regions (r left = 0.728, right = 0.767). The CDR score was inversely correlated with left temporal parietal white matter ($r = -0.894$), left lower corona radiata ($r = -0.827$) and right higher corona radiata ($r = -0.7$). Digit backward scores correlated with left temporal parietal white matter ($r = 0.789$) and right high corona radiata ($r = 0.77$), whereas verbal generation score correlated with left inferior frontal ($r = 0.804$), high frontal ($r = 0.751$), temporal parietal white matter ($r = 0.718$)

Fig. 3: Clusters with significant differences (red) between the 3- and 10-month follow-up images in the carbon monoxide groups overlaid on the mean fractional anisotropy skeleton map (green) (all $p < 0.05$, multiple correction at the cluster level). The background anatomic reference was the Montreal Neurological Institute 152 Image.

and right lower corona radiata ($r = 0.76$). Delayed memory scores correlated with left temporal parietal white matter ($r = 0.806$) and left lower corona ($r = 0.786$).

At 10 months, the digit backward scores were correlated with FA in the left inferior frontal ($r = 0.894$). Verbal generation score were correlated with left temporal parietal white matter ($r = 0.975$).

Relation between mean diffusivity and cognitive domains

At 3 months, both MMSE ($r = -0.85$) and CDR ($r = 0.783$) scores correlated with the mean diffusivity value of the right inferior frontal region. Scores of judgment were inversely correlated with the right high frontal mean diffusivity value ($r = -0.675$).

At 10 months, verbal fluency scores were inversely correlated with the right ($r = -0.975$) and left ($r = -0.975$) external capsule.

Relation between axial eigenvalues and cognitive domains

No domains showed correlation at 3 months with axial eigenvalues. At 10 months, axial diffusivity was inversely correlated with digit backward scores ($r = -0.894$), and the delay recall memory correlated with the right lower corona radiata ($r = -0.89$).

Relation between radial eigenvalues and cognitive domains

At 3 months, MMSE ($r = -0.833$) and CDR ($r = 0.894$) scores were highly correlated with radial eigenvalues. Digit backward score were inversely correlated with the left high corona radiata ($r = -0.912$). Verbal fluency scores were inversely correlated with the left lower corona radiata ($r = -0.73$), right lower corona radiata ($r = -0.876$) and left temporal parietal white matter ($r = -0.838$), whereas scores of calculation inversely correlated with the left ($r = -0.868$) and right corona radiata ($r = -0.806$). At 10 months, delay memory scores were inversely correlated with the left lower ($r = -0.89$) and high corona radiata ($r = -0.89$).

Discussion

Our study suggests that there were increased changes over time in the CO group, which is consistent with previous findings²⁶⁻²⁸ that neural damage continues variably between patients and structures. Furthermore, our findings may also provide a possible mechanism. Because diffusion indices such as FA and mean diffusivity are derivatives from the 3 tensor eigenvalues, our analysis corroborates the changes contributed by each eigenvalue and shows that extensive changes in the FA map at both 3 and 10 months in the CO group are contributed to initially by increases in radial eigenvalues. This longitudinal study shows that axial eigenvalues evolve during the follow-up period with accompanying atrophy of the white matter tract, which supports the results of increased mean diffusivity in the CO group.

Using an apparent diffusion coefficient map, Kim and colleagues²⁹ showed that reduced diffusivity developed in the white matter 25 to 95 days after CO intoxication; they interpreted this as slowly progressive cytotoxic edema.³⁰ The time window studied by Kim and colleagues²⁹ was earlier than in our study. Our study and one by Terajima and colleagues³¹ found a gradual increase of mean diffusivity after 3 months following CO exposure. In conjunction, values of mean diffusivity may initially be lower than controls and then increase, reaching a level higher than controls. A longitudinal increase in mean diffusivity suggests less restriction of water diffusion in all directions. One explanation for these changes may be tissue atrophy resulting from unrecovered white matter damage.^{26,31} Apparently, mean diffusivity values detected the changes earlier because our VBM result also detected the volume reduction after 10 months of follow-up.

This study also shows increases in radial eigenvalues at 3 months. One explanation for this phenomenon is that more free water diffuses across the myelin barrier, which may correspond to myelin damage.³² Because there were no interval

Fig. 4: Bar graph showing eigenvalues extracted from the significant regions between the 3- and 10-month follow-up images in the carbon monoxide (CO) group. (A) Axial eigenvalues in CO group show significant differences in the 6 regions ($p < 0.05$) between 3 and 10 months. (B) Values in radial eigenvalues were not different between 3 and 10 months in the CO group. Axial and radial eigenvalues are expressed in $103 \text{ mm}^2/\text{s}$. Data are means and standard deviations. T-P = temporoparietal.

changes in radial eigenvalues, our results suggest that disruption of myelin is persistent and recovery from damage does not occur after 10 months. From axial diffusivity analysis, only the anterior part of the external capsules and frontal corona radiata are affected at 3 months, with further increases in axial diffusivity in the deep white matter at 10 months. This indicates enlargement of affected regions by axonal injury from CO toxicity.^{33,34} Based on the changes of axial and radial eigenvalues, increasing FA values from 3 to 10 months are attributed to the axial eigenvalues changes, which should not be misinterpreted as recovery of fibre coherence.

From our comparison with age-matched controls, we can see that cognitive presentation, as quantified by neuropsychologic data, supports the cognitive sequel of CO. Cognitive presentations in CO intoxication can be partly explained by reduced connectivity between different cortical regions.^{35,36} Compared with the control group, the CO group had lower scores in digit backward and verbal fluency, which may be related to interruption of the frontotemporal circuits.^{37–39} Impairment in free recall rather than retrieval suggests that memory deficits may be due to subcortical deficits,⁴⁰ whereas

interruption of the temporal visual pathway results in visuospatial deficits.

From direct comparison of neuropsychologic data from the CO group at 3 and 10 months after exposure, it was evident that the recovery of cognition was not significant. In conjunction with analysis of diffusion parameters and atrophy in white matter, we speculate that the test scores at 10 months after exposure should be worse than at 3 month if white matter damage is a major predictor of outcome. Although the major white matter atrophy in this study was in the periventricular white matter, one possibility is that periventricular white matter is not a major determinant of cognitive deficits in CO encephalopathy. This is based on our cognitive test with FA correlation results, which showed that the semicentrum ovale rather than the deep white matter had better correlation with cognitive decline. This was also observed by Parkinson and colleagues,⁴¹ suggesting that the semicentrum ovale, not the periventricular areas, is significantly associated with cognitive decline. Another explanation is that even though white matter changes are commonly observed in CO encephalopathy, interpretation of neuropsychologic deficits

Fig. 5: Atrophy of white matter in carbon monoxide-intoxicated patients 10 months after exposure compared with controls by use of voxel-based morphometry. The anatomic reference was the white matter template specific to this study.

should also consider the effects of cortical involvement. From the grey matter VBM results, longitudinal atrophy in grey matter was not different from age-matched controls. The relative sparing of axonopathy on subcortical U fibres without grey matter atrophy may account for the undetected cognitive deterioration at 10 months in this study.

Limitations

There are several limitations to this study. First, we enrolled a small number of patients. A larger study group may be necessary to confirm our observations. Second, we cannot provide histologic proof in this study because this was a longitudinal study involving humans. Therefore, the interpretation of the pathological changes through neuroimaging findings (as reflected by changes in axial and radial eigenvalues) cannot be proved. Nonetheless, the results are consistent with those of previous pathology studies in which myelin damage was constant with or without axonal destruction.^{30,42} It is worth noting that a direct correlation between axial and radial diffusivity parameters and the microscopic pathology of white matter injury has not been conclusive. As such, interpretation of changes in axial or radial eigenvalues as demyelination or axonopathy^{43,44} should be treated with great care especially in regions where neuron fibres cross.⁴⁵

Conclusion

This in vivo human study showed the evolution of white matter diffusion changes and atrophy regions after CO intoxication. Diffusion measures were better correlated with cognitive decline on the fibre tract of the semicentrum ovale and not the periventricular fibres. Although changes in grey matter volume were not evident, neuropsychiatric deficits were persistent in the follow-up study, suggesting the importance of white matter integrity.

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