SHORT REPORT

Neuronal damage in the interval form of CO poisoning determined by serial diffusion weighted magnetic resonance imaging plus $^1$H-magnetic resonance spectroscopy

T Murata, H Kimura, H Kado, M Omori, J Onizuka, T Takahashi, H Itoh, Y Wada

Abstract
In a patient with the interval form of carbon monoxide (CO) poisoning diffusion weighted MRI and proton magnetic resonance spectroscopy ($^1$H-MRS) were serially performed immediately after the appearance of delayed sequelae (the 23rd day after exposure). During the period in which few clear findings were evident on MRI T2 weighted images, a high signal area in the cerebral white matter and relative decrease in the apparent diffusion coefficient (ADCav) were already apparent on diffusion weighted images, with these findings thought to sensitively reflect the tissue injury associated with the onset of sequelae. The decrease in relative ADCav persisted until the 38th day after exposure. Subsequently, ADCav gradually increased, and in the cerebral white matter showed higher values in the 118th day after exposure than immediately after the onset of sequelae. During this period, on $^1$H-MRS choline containing compounds showed persistently high values throughout the course, with N-acetylaspartate depletion and the appearance of a lactate peak later in the course. These findings, with regional specificity in the cerebral white matter, reflect the developmental process of the white matter lesions in the interval form of CO poisoning in which demyelination progresses leading to neuronal necrosis. Serial diffusion weighted imaging plus $^1$H-MRS measurements are useful in determining the tissue damage and long term outcome of delayed sequelae associated with the interval form of CO poisoning.

Keywords: carbon monoxide poisoning; diffusion weighted MRI; proton magnetic resonance spectroscopy

The interval form of carbon monoxide (CO) poisoning characteristically shows disturbed consciousness in the acute phase, followed by recovery and an asymptomatic period (lucid interval) extending over several days to weeks, after which neurological or psychiatric sequelae recur. The underlying pathological lesion is thought to be progressive diffuse demyelination in the cerebral white matter. Once the demyelination, progressing from the initial period after exposure reaches a certain threshold an irreversible state is created at which point delayed sequelae become apparent. However, it is difficult to predict and diagnose such sequelae early, and the underlying pathogenic mechanism remains unexplained. Also, at present no clear marker helpful in predicting the prognosis of sequelae is available.

Since the first report of Moseley et al. in 1990 that diffusion weighted MRI, which can image the diffusion of water molecules in the in vivo state, can detect local brain ischaemia at an extremely early stage in an animal model, this modality has attracted attention as a diagnostic method to detect conditions such as cerebral infarction and multiple sclerosis. By measuring the apparent diffusion coefficient (ADC) in vivo, study of structural changes and function in living tissues becomes feasible. Hitherto, no studies have applied diffusion weighted imaging to the interval form of CO poisoning. On the other hand, proton magnetic resonance spectroscopy ($^1$H-MRS), which can non-invasively provide biochemical information about brain tissues, has been shown to provide useful markers for the evaluation of neuronal viability in the interval form of CO poisoning. In the present study, we serially performed diffusion weighted imaging and $^1$H-MRS immediately after the appearance of delayed sequelae in a patient with the interval form of CO poisoning.

Case report
A 57 year old man went fishing by himself on the evening of 4 May 1999. He burned charcoal in his closed car to roast fish that he had caught, and lost consciousness. The next morning, an estimated 12 hours later, he was found in a comatose state and taken to a nearby hospital. Arterial blood analysis showed a carboxyhaemoglobin concentration of 27.2%. Based on this high value and the situation at the scene of his discovery, a diagnosis of...
coma due to CO poisoning was made. Oxygen was immediately administered, and he recovered consciousness the second day after exposure. He was discharged from hospital after waiting for his general condition to improve. However, from the 20th day after exposure disorientation and lassitude became noticeable, and the interval form of CO poisoning was suspected, for which he was readmitted on 26 May (22nd day after exposure). On admission the patient was expressionless but conscious (Glasgow coma scale 14/15). He was disoriented to day and time, but could respond to simple questions such as those regarding his name. Neurologically, primitive reflexes (grasping, palmomental reflex) were noted, but no pathological reflexes or abnormal deep reflexes. He could stand, but walking was sluggish. Mild rigidity was present in his four limbs, and he was incontinent of urine and faeces. Feeding was possible with help. No particular blood biochemical abnormalities were found on admission.

From the day after admission he received oxygen under high pressure (8 l/minute, O₂ partial pressure about 600 mm Hg, for 6 hours/day). Various brain metabolism enhancing agents (citicoline (500 mg/day), meclofenoxate HCl (600 mg/day), cytochrome C (30 mg/day), ubidecarenone (30 mg/day), adenosine triphosphate (20 mg/day)) were also administered. Subsequently, the patient showed gradually progressive loss of initiative, and from about 10 June (the 37th day after exposure) manifested an apallic syndrome with no voluntary movement except for that of the eyes. At present, 600 days after exposure, the patient continues to show an apallic syndrome.

**SERIAL MAGNETIC RESONANCE IMAGING: METHOD AND FINDINGS**

Brain MRI was performed on the 23, 31, 38, 45, 79, and 118th days after exposure using a 1.5 Tesla MR unit (SIGNA, GE) and standard spin echo (SE) sequences for T1 weighted images; fast SE sequences for T2 weighted images and diffusion weighted imaging. Diffusion weighted imaging was performed using a multislice, single shot, SE planar sequence. The imaging measurements were echo time=3200 ms, matrix size 256×256, fields of view 220 mm, with a 5 mm slice thickness. Diffusion gradients were applied in each of the x, y, and z directions with four b values ranging between 0 and 1000 seconds/mm². The average apparent diffusion coefficient (ADCav) was calculated as ADCav=1/3(ADCx+ADCy+ADCz). To quantify changes in ADCav independent of tissue and gradient orientations, relative ADCav (as a ratio relative to the left thalamus) was calculated according to the method previously described. On the 23rd day after exposure, no abnormal findings were apparent on T2 weighted images (fig 1 A), whereas on diffusion weighted images (fig 1B) obtained on the same day dot-like hyperintense areas were noted mainly in the frontal lobe deep white matter. On the 38th day after exposure, slightly hyperintense areas were found in the frontal and parietal lobe white matter (fig 1 C), whereas on diffusion weighted imaging (fig 1 D), compared with the previous findings, enhancement of the intensity of the white matter hyperintense areas and a general increase in their extent were also noted. On the 118th day after exposure, on T2 weighted images (fig 1 E) an even greater enhancement of the intensity of the white matter hyperintense areas and slight
enlargement of the ventricles were seen. On diffusion weighted images (fig 1 F) obtained on the same day, attenuation of the intensity of the white matter hyperintense areas and a change in hypointensity in the central portions was seen. Figure 2 A shows the serial changes in the relative ADCav in the frontal lobe white matter and anterior cingulate gyri.

SERIAL PROTON MAGNETIC RESONANCE SPECTROSCOPY: METHOD AND FINDINGS

The magnetic resonance investigations were performed on a conventional 1.5 Tesla imager (SIGNA, GE) with a standard head coil. For 1H-MRS, two voxels, size 2x2x2 cm³, were selected in the left frontal lobe white matter around the anterior horn of the lateral ventricle and anterior cingulate gyri (fig 1 A). Magnetic resonance spectra were acquired using point resolved echo spectroscopy (PRESS) with a repetition time of 2000 ms and an echo time of 136 ms. The peak area ratios of N-acetylaspartate (NAA), total creatine (Cr), choline containing compounds (Cho), and lactate (Lac) were obtained from the spectra with a curve fitting method. The area ratios of each peak were expressed as the relative ratio to Cr in each spectrum, as it has been reported that these remain relatively stable even in the presence of rapid fluctuations in energy metabolism. Serial changes in the relative ratio of each peak to the Cr peak: Cho/Cr, NAA/Cr, and Lac/Cr are shown (fig 2 B: frontal lobe white matter; fig 2 C: anterior cingulate gyri).

Discussion

We speculated on the progressive process of brain injury in the interval form of CO poisoning from the serial measurements of the combination of diffusion weighted images and 1H-MRS. In the frontal lobe white matter, relative ADCav decreased until the 38th day after exposure, then slowly increased, and showed higher values in the 118th day after exposure than immediately after the appearance of sequelae (fig 2 A). Ischaemic brain tissue ADC values were low for several days after onset, but subsequently gradually increased until normal values—and still later high ones—were shown. This sequence is thought to reflect a series of pathological changes from cytotoxic oedema to vasogenic oedema, and destruction of the cell membrane, culminating in cell necrosis. In the present patient with the interval form of CO poisoning, in the period immediately after the appearance of sequelae when few clear findings were evident on T2 weighted images, a relative decrease in ADCav was found and persisted much longer than the few days after acute cerebral infarction. This suggests the possibility that after the appearance of sequelae acute cell necrosis such as seen in acute cerebral infarction did not occur but rather that tissue injury caused by factors such as slowly progressive cytotoxic oedema could be sensitively depicted by diffusion weighted images. During this period 1H-MRS showed persistently high Cho/Cr at the same site throughout the course, with progressively decreased NAA/Cr and increased Lac/Cr found with time (fig 2 B). Hitherto, decreased NAA has been considered as a marker reflecting neuron and axon drop out and degeneration, whereas the Cho peak has been reported to reflect the quantity of choline containing substances such as phosphocholine and glycerophosphocholine, which are involved in membrane metabolism. Also, under conditions such as ischaemia or hypoxia in which ATP cannot be adequately supplied, Lac production occurs in association with a compensatory enhancement of anaerobic glycolysis (inverse Pasteur effect). These findings are thought to reflect the developmental process of the white matter lesions in the interval form of CO poisoning in which demyelinating membrane destruction progresses leading to neuronal necrosis. In this patient, before the 1H-MRS study, citicoline administration was initiated. Babb et al reported a roughly 20% change in the Cho/Cr ratio in 1H-MRS after a single administration of 4000 mg citicoline. However,
Table 1 Serial neuroimaging study of white matter lesions in the interval form of CO poisoning

<table>
<thead>
<tr>
<th>Study</th>
<th>Methods</th>
<th>Age (a)</th>
<th>Lucid interval</th>
<th>Time of initial neuroimaging</th>
<th>Serial changes in white matter lesions and clinical outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hayashi et al.</td>
<td>CT</td>
<td>1</td>
<td>72</td>
<td>11 days after the onset of sequelae</td>
<td>A correlation between changes in CT abnormalities (a low density area in the white matter) and clinical presentation</td>
</tr>
<tr>
<td>Choi et al.</td>
<td>CT</td>
<td>13</td>
<td>37–78</td>
<td>Within 11 days after the onset of sequelae</td>
<td>No correlation between the CT findings and the outcome of delayed CO sequelae</td>
</tr>
<tr>
<td>Chang et al.</td>
<td>MRI</td>
<td>15</td>
<td>25–71</td>
<td>4–9 weeks after exposure to CO during the relapse of sequelae</td>
<td>A decrease in extent and signal intensity of white matter lesions accompanied by a reduction of clinical symptoms</td>
</tr>
<tr>
<td>Kamada et al.</td>
<td>H-MRS</td>
<td>1</td>
<td>55</td>
<td>9 days after the onset of sequelae</td>
<td>Lowered NAA/Cr and increased Cho/Cr immediately after the onset of sequelae recovered, reflecting clinical improvement</td>
</tr>
</tbody>
</table>

at a lower dose (500 mg, the same dose as used in our patient), no significant changes were seen. Therefore, the marked increase in Cho/Cr (about double the control value) may not be primarily caused by citicoline administration but may rather reflect the pathological condition of delayed sequelae of the interval form of CO poisoning.

In the anterior cingulate gyri, as in the frontal lobe white matter, after a persistent decrease in relative ADCav (until the 38th day after exposure) recovery to about the value immediately after the appearance of sequelae was seen, but thereafter no further increase occurred (fig 2 A). On 1H-MRS Cho/Cr showed persistently high values, and NAA/Cr was slightly decreased, and no Lac was seen at any time during the course (fig 2 C). We speculate from these findings that in the anterior cingulate gyri as well, demyelinating membrane destruction progresses, but unlike the frontal lobe, changes in white matter stop after a given point and thus do not result in neuronal necrosis. Lesions in cerebral white matter have been pointed out as the sites responsible for the interval form of CO poisoning, with the present diffusion weighted images and 1H-MRS findings supporting the contention that, compared with the cortex, more selective injury is found in the white matter. Table 1 shows previous neuroimaging studies that evaluated the association between serial changes in white matter and long term outcomes of delayed sequelae in the interval form of CO poisoning. In all these studies, neuroimaging examination was initiated after the onset of sequelae. To predict delayed sequelae and clarify their pathogenic mechanism, further neuroimaging studies on serial changes in the subclinical pathological condition during the lucid interval are necessary.

In conclusion, serial diffusion weighted imaging plus 1H-MRS measurements can be useful in determining the tissue damage and long term outcome of delayed sequelae associated with the interval form of CO poisoning. They delineate the progression of cytotoxic oedema and demyelination, and thereby provide markers of the neuronal degenerative process in this condition.

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