

Measurements of Cerebral Blood Flow in Delayed Carbon Monoxide Sequelae Using Xenon Inhalation CT Scan

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The regional cerebral blood flow of four patients with delayed carbon monoxide sequelae and four age matched controls was measured, using a xenon inhalation CT scan (GE 9800). Variable patterns of decreased cerebral blood perfusion according to the clinical state of the patient were noted among the patients. Follow up studies, 2 months later, indicated that there was a correlation between the fluctuation of symptoms and the changes in regional cerebral blood flow. It is suggested that the impairment of cerebral perfusion may play a critical role in delayed carbon monoxide sequelae.

Key Words: Delayed carbon monoxide sequelae, cerebral blood flow, xenon inhalation CT scan.

In Korea, coal is used as a fuel for cooking and heating, and as a result the annual incidence of acute carbon monoxide intoxication is estimated to be more than one million cases (Song 1985; Yun 1985).

The survival rate for acute carbon monoxide intoxication is about 60 to 75% (Ginsberg and Romano 1976; Remick and Miles 1976), and 2.7 to 45% of the survivors develop neuropsychiatric sequelae. The delayed sequelae usually develop after 1 to 3 weeks of the pseudorecovery phase (Ginsberg 1978; Choi 1983).

The diverse neurological features of the delayed sequelae develop abruptly and are heralded by apathy, disorientation, amnesia, akinesia, abulia, double incontinence, bizarre behavior, or parkinsonian features (Plum *et al.* 1962; Ringer and Klawans 1972; Jefferson 1976; Ginsberg 1985; Min 1986). Although there is no known specific therapy for these patients, approximately 75% of the patients recover completely or with minimal deficit (Choi 1983).

The main pathologic changes that have been

described to date are conspicuous demyelination of the white matter and symmetrical necrosis of the globus pallidus. In some cases the presence of laminar necrosis at the second, third, fifth, or sixth cortical layer is also noted (Ginsberg 1979; Brierley and Graham 1984).

The vulnerability of the white matter to hypoxia (Welsh *et al.* 1978), direct carbon monoxide toxicity to the white matter (Gillen 1977), deep cerebral venous stagnation (Hassler 1966), and other events have been proposed as factors which contribute to the pathogenesis of the demyelination of the white matter. Also there is controversy as to whether the pathologic changes of the blood vessels play a critical role in the development of delayed sequelae (Courville 1957; Ginsberg 1979).

To further investigate this, the authors measured the changes in the regional cerebral blood flow in the patients with delayed carbon monoxide sequelae.

CASE REPORTS

The mean age of the two men and two women in this study was 58. There was no previous history of chronic disease or medication, and no evidence of attempted suicide.

The common findings were that each patient had slept in a poorly ventilated, coal-heated room and was found unconscious along with the other occupant of

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the room.

In each case, the following tests were performed after admission to Yonsei University Medical Center to rule out other metabolic diseases; complete blood count with morphology, urinalysis, chest PA, ECG, serum electrolytes, blood chemistry for liver and kidney function, stool examination, and arterial gas study. All results were within normal limits.

Case 1.

A 55-year-old woman and her husband suffered acute carbon monoxide intoxication on March 13, 1987. They had been in good health up to that time. She regained her previous mental state after 6 days.

On April 13, 1987, she developed progressive pathologic laughing, dressing apraxia, restlessness and memory loss, and was admitted to Yonsei University Medical Center.

On admission, her blood pressure was 120/80 mmHg and physical examination revealed no abnormalities. Although she showed minimal rigidity and retropulsion, she was able to walk without assistance. The glabellar, palmomental and grasp reflexes and

other focal neurological deficits were not noted. A spinal tap was performed, which showed an opening pressure of 165mmCSF, one RBC/cubic mm, one WBC/cubic mm, 25 mg/dL of protein and 100 mg/dL of sugar concentraion. An EEG showed generalized synchronous theta to delta waves.

On April 14, 1987, a brain CT scan and xenon inhalation brain CT scan were performed (Fig. 1, Left). After admission, her condition deteriorated rapidly to the bed ridden state. She showed minimal purposeful voluntary movement and double incontinence.

On June 26, 1987, follow up brain CT and xenon inhalation brain CT scans were performed (Fig. 1, right).

Case 2.

A 60-year-old novelist, the husband of the patient in Case 1, was found unconscious in a coal-heated room with his wife, on March 13, 1987. After 4 days, he became communicable.

He developed mutism and double incontinence on March 28, 1987. Two days after the onset of such symptoms, he was admitted to Yonsei University

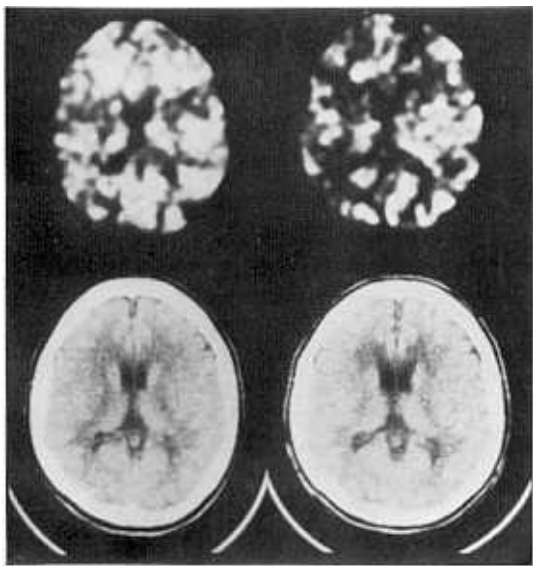


Fig. 1. Left, brain CT scan and xenon inhalation CT scan for case 1, performed at the time of onset. Right, follow up brain CT scan and xenon inhalation CT scan performed 2 months later.

Follow up study revealed fewer areas of enhancement in the xenon inhalation CT scan and low density areas around the frontal horn of the lateral ventricle along with symptomatic deterioration.

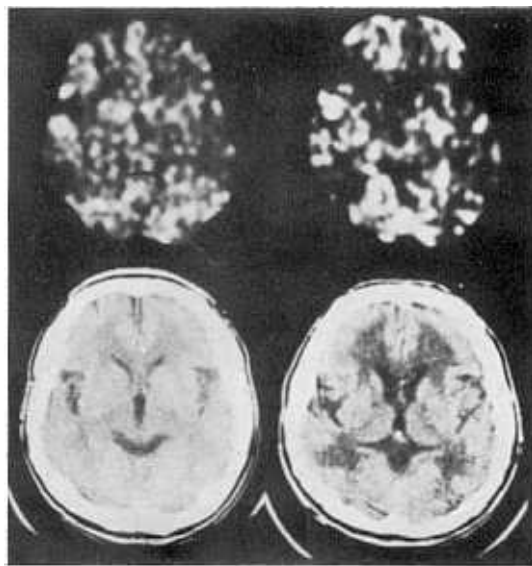


Fig. 2. Left, brain CT scan and xenon inhalation CT scan for case 2, performed at the time of severe deterioration. Right, brain CT scan and xenon inhalation CT scan repeated 2 months later.

Follow up brain CT scan revealed periventricular low density area but more enhanced areas in the xenon inhalation CT scan along with symptomatic improvement.

Medical Center. His blood pressure was 110/80mmHg, other vital signs were normal and physical examination revealed no definite abnormality. On neurologic examination, he exhibited masked face, hypokinesia, glabellar reflex, and was unable to walk alone, but no other focal neurologic deficits were detected. A spinal tap revealed an opening pressure of 150mmCSF, 73mg/dL of sugar, 30mg/dL of protein, and neither RBC nor WBC were detected. An EEG revealed bilateral synchronous delta waves.

He became bed-ridden soon after admission, stared at the ceiling and had no purposeful movement. He exhibited decorticate posture and there was severe rigidity in all extremities.

On April 14, 1987, a brain CT scan and xenon inhalation brain CT scan were done (Fig. 2, left).

After that, some improvements in rigidity and facial expression were noted, but he was still bed-ridden. On June 26, 1987, follow up brain CT and xenon inhalation brain CT scans were performed (Fig. 2, right).

Case 3.

A 50-year-old teacher and his companion suffered

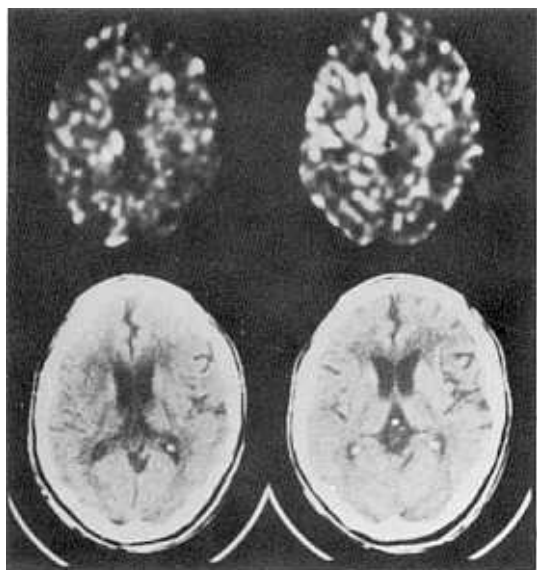


Fig. 3. Left, brain CT scan and xenon inhalation CT scan for case 3, performed at the time of full symptomatic progression. Right, brain CT scan and xenon inhalation CT scan repeated 2 months later after marked symptomatic improvement. Xenon inhalation CT scan revealed more enhanced areas and CT brain scan showed a periventricular low density area.

acute carbon monoxide intoxication in a coal-heated room on the morning of February 16, 1987. After 2 days, he became alert.

On March 28, 1987, he exhibited double incontinence, memory impairment, tactile hallucination, pathologic laughing, and rejection. On the next day, he became mutistic and akinetic.

On March 30, 1987, he was admitted to Yonsei University Medical Center. On physical examination, his blood pressure was 120/80mmHg and other physical findings were normal. Neurologic examination revealed glabellar sign, grasp reflex, masked face, retropulsion, normoactive deep tendon reflexes and minimal rigidity in the extremities. He could not walk without assistance and exhibited retropulsion and a short step gait. Permission was not given for a spinal tap. The EEG revealed generalized frequent theta to delta waves.

After admission, his condition deteriorated rapidly, and within a few days, he was bed-ridden and displayed abulia.

On April 14, 1987, a brain CT scan and a xenon inhalation CT brain scan were performed (Fig. 3, left).

During May, his symptoms improved notably, he was able to walk without assistance, and the double incontinence disappeared. He said 'Hello' to doctors and tried to write his name.

A follow up brain CT scan and a xenon inhalation CT brain scan were done on June 12, 1987 (Fig. 3, right).

Case 4.

A 68-year-old house-wife was found unconscious in a coal-heated room on November 14, 1986. However she received no specific treatment.

She became mutistic, exhibited bizzare behavior and double incontinence. She was admitted to the psychiatric ward of Yonsei University Medical Center on January 26, 1987, under the impression of delayed carbon monoxide sequelae. She showed some symptomatic improvement and was discharged on February 4, 1987.

The next morning she was found unconscious in that same room and was brought to Yonsei University Medical Center again. At that time, the carbon monoxide hemoglobin concentration was 28%. Neurologic examination revealed hyperactive deep tendon reflexes in all extremities, bilateral Babinski signs, but no other focal neurologic deficits were found. A spinal tap revealed an opening pressure of 100mmCSF, 30mg/dL of protein, 69mg/dL of sugar and neither RBC nor WBC were detected. The EEG show

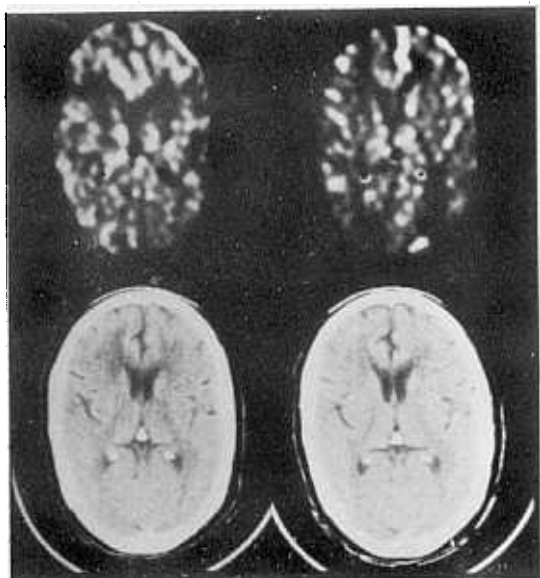


Fig. 4. Left, brain CT scan and xenon inhalation CT scan for case 4, performed at the time of improvement after the first delayed sequelae. Right, the follow up study, performed after the reappearance of rigidity, revealed less enhanced areas in xenon inhalation CT scan and normal brain CT scan.

ed frequent regular theta to delta waves in both hemispheres and the brain CT scan showed no gross abnormality. She became alert on the second hospital day, but after a few days, she became mutistic, and could not walk. She exhibited double incontinence, aggravated rigidity, and then became bed-ridden. With time, there were some symptomatic improvements such as the recognition of her family, walking without assistance, and the disappearance of double incontinence. On April 14, 1987, a xenon inhalation CT brain scan was taken (Fig. 4, left), and she was discharged with some improvement on April 29, 1987.

But she was admitted to the hospital a third time on May 28, 1987, due to drooling and increased rigidity. At that time, she showed a masked face, and then became completely bed-ridden with minimal purposeful movement. On June 12, 1987, a follow up brain CT scan and xenon inhalation CT brain scan were performed (Fig. 4, right).

METHOD

The regional cerebral blood flow of the four pa-

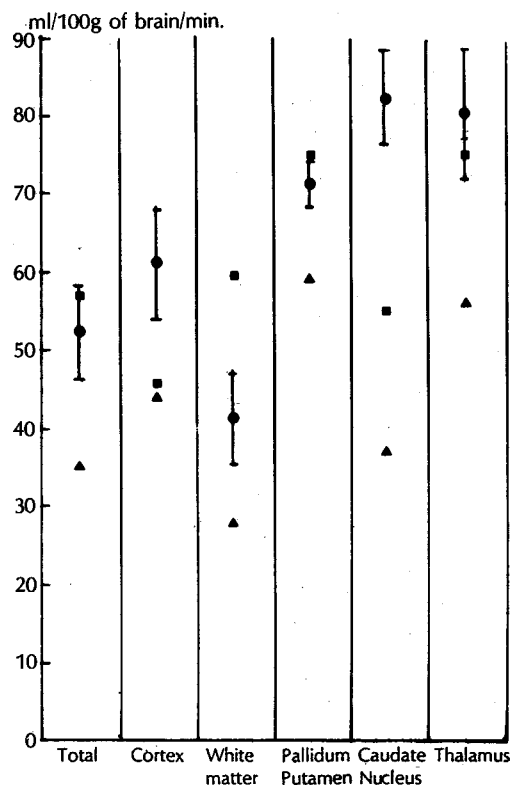


Fig. 5. Measurements for case 1, showing increased cerebral perfusion in the white matter in the first study which was performed at the time of onset. The follow-up study performed 2 months later, after symptomatic deterioration. The follow-up study showed decreased cerebral perfusion in all measured areas.

● Mean of the control group \pm S.D.

■ First measurements

▲ Follow up measurements

tients and four normal age matched controls was measured with the GE 9800 CT scanner and xenon inhalation system. Before starting this study, body temperature, blood pressure, and hematocrit were measured, and arterial P_{CO_2} were recorded. All recordings were normal with hematocrit of greater than 37%. Room temperature was maintained between 18-22°C.

A gas mixture of 35% xenon was prepared, and the level of the CT scan was adjusted to include the basal ganglia. The studies were begun immediately after the inhalation of the gas mixture and were concluded when the expired concentration of xenon exceeded 22% and attained a plateau.

The regional cerebral blood flow was estimated

by the computer system contained within the CT scanner. No remarkable complication were experienced during and after the studies.

RESULTS

The four patients in this study presented variable clinical courses.

In case 1, the first xenon study, made at the onset of the deterioration, revealed a hypoperfusion in the caudate nucleus and cortex, and hyperperfusion in the white matter. The follow up study was made after marked deterioration occurred. When considering the results of the first study, there was markedly decreased cerebral perfusion in the white matter, but the caudate nucleus showed the largest decrement in relation to the control data (Fig. 5).

The initial studies in cases 2 and 3 were made after severe symptomatic deterioration had occurred, and the follow up studies were conducted after symptomatic improvement had taken place. The cortex, caudate nucleus, and pallidum of case 2, which had been hypoperfused in the initial study, showed improved perfusion along with symptomatic improvement. However there was little alteration of perfusion in the white matter regardless of symptomatic improvement (Fig. 6).

Case 3 presented a similar clinical course and alterations of cerebral perfusion to case 2 (Fig. 7).

Case 4, which presented a fluctuating clinical course due to recurrent intoxications, revealed hypoperfusion in all areas. Although there was little difference, all measured areas except the caudate nucleus exhibited decreased perfusion along with the

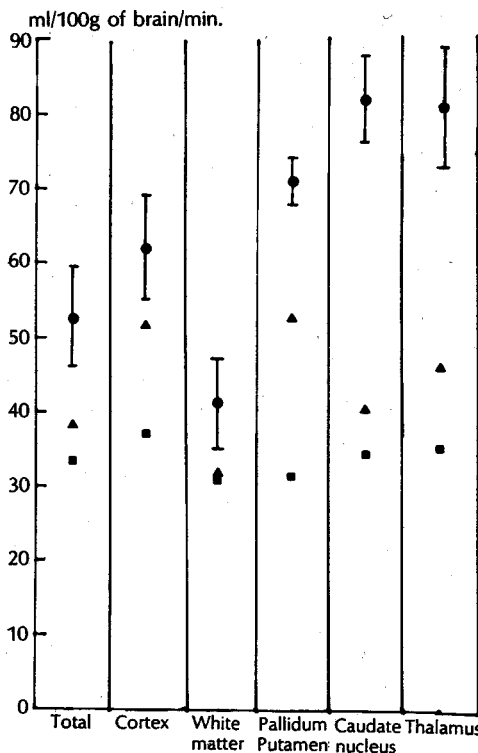


Fig. 6. Measurements for case 2. The follow-up study, which was made after symptomatic improvement showing improved regional cerebral perfusion in all measured areas, especially in the cortex and deep nuclei.

- Mean of the control group \pm S.D.
- First measurements
- ▲ Follow up measurements

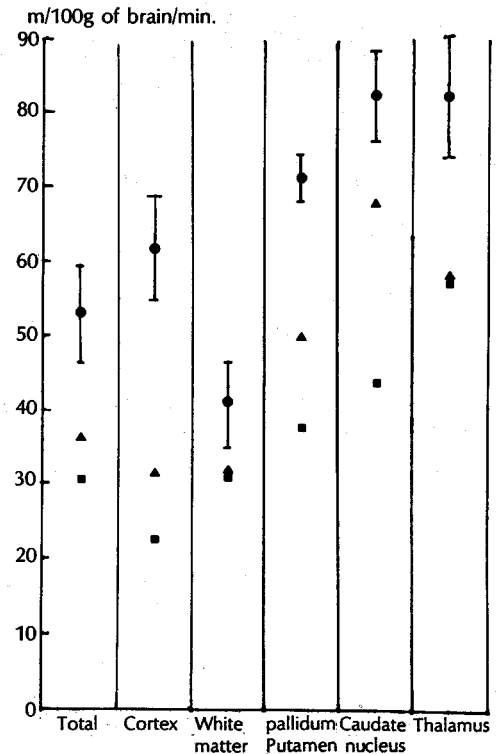


Fig. 7. Measurements for case 3, which exhibited a similar clinical course to case 2, revealed a similar pattern of increased cerebral blood perfusion in the follow-up study. In the first study there was marked perfusion impairment in the cortex.

- Mean of the control group \pm S.D.
- First measurements
- ▲ Follow up measurements

deterioration of the symptoms (Fig. 8).

However, the above findings could be summarized as follows.

- 1) When the scan was performed at the onset of deterioration, as in case 1, the presence of both hypoperfusion and hyperperfusion was noted.
- 2) When the scan was conducted after severe deterioration had occurred, as in cases 2 and 3, the cortex and deep gray nuclei were more hypoperfused than the white matter. But they increased more quickly than the white matter with symptomatic improvement.
- 3) In the case of a fluctuation of symptoms due to recurrent intoxication, as in case 4, both the white and gray matters were hypoperfused, and more perfusion defects were detected in all measured areas when the symptom worsened.

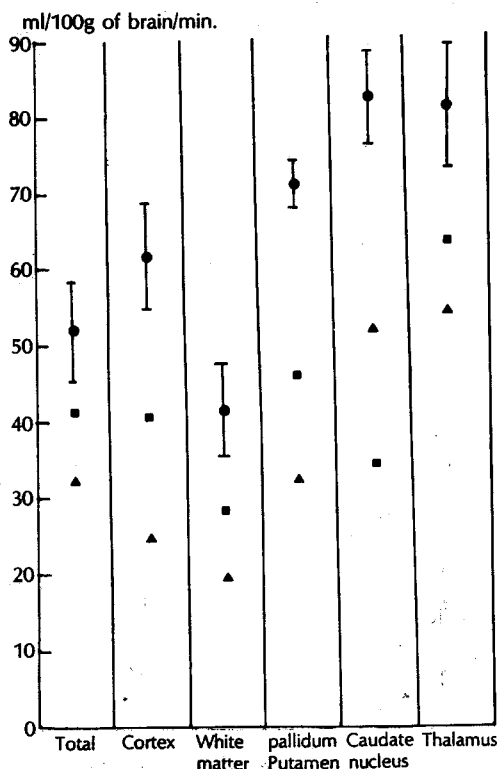


Fig. 8. Measurements for case 4, showing more impairment of regional cerebral perfusion in all measured areas except the caudate nucleus along with symptomatic deterioration.

● Mean of the control group \pm S.D.

■ First measurements

▲ Follow up measurements

DISCUSSION

Since Cramer first called attention to the white matter changes in 1891, much has been written in the literature about delayed carbon monoxide sequelae. But as yet no unique neuropathological alteration has been described and its pathogenesis is still in doubt (Courville 1957).

The majority of the reports have mainly described changes in the white matter. The pathologic changes are somewhat selective for myelin, and the axis cylinders are relatively preserved. Vacuolation in the myelin is followed by patchy demyelination, which becomes confluent, leading to generalized demyelination (Courville 1957; Brierley and Graham 1984).

Several possible etiologic mechanisms for delayed demyelination such as brain edema (Jacob 1940; Brucher 1967), venostasis (Hassler 1966; Lapresle and Fardeau 1966; Gillen 1977), direct cytotoxic effect (Ginsberg and Myer 1974; Gillen 1977), hypotension and lactic acidosis (Ginsberg 1974; Dooling and Richardson 1976; Ginsberg *et al.* 1976), less redundant arterial supply of the white matter (Ginsberg and Romano 1976), and vulnerability of the myelin to hypoxia (Welsh *et al.* 1978) have been suggested without confirmation.

Brain edema was thought to play a role because the distribution pattern of the edema was similar to that of demyelination (Jacob 1940). But there is no evidence of delayed demyelination following experimentally induced cerebral edema (Plum *et al.* 1962).

The presence of markedly dilated vessels in the brain and other viscera, and the preservation of the subcortical U fiber suggest that venostasis may play a role in the development of delayed sequelae (Hassler 1966; Dooling and Richardson 1976; Ginsberg 1979; Brierley and Graham 1984).

Early workers thought that the relative sparing of the gray matter meant that mechanisms other than hypoxia might be responsible, such as the direct cytotoxic effect of carbon monoxide. It was thought that the vulnerability of the white matter might depend on its low content of cytochrome oxidase (Ginsberg and Romano 1976). But this was disputed because the same alteration readily followed other metabolic diseases such as hypoglycemia, cardiac arrest, hepatic encephalopathy and head injury (Plum *et al.* 1962; Choi 1983).

With regard to systemic factors, the severity of the lactic acidosis and hypotension were correlated well

with the severity of demyelination (Ginsberg and Myer 1974; Ginsberg 1979).

Decreased blood flow to the globus pallidus due to compression of the vessels by brain edema was suggested to play a role in the development of lesions in the globus pallidus (Dutra 1952; Garland and Pearce 1967; Song *et al.* 1983).

In 1928, Meyer postulated that vascular smooth muscle might be altered by carbon monoxide, and that distorted regional cerebral circulation is responsible for the lesions in the pallidum and white matter. Someone refuted this notion, because it was thought that the pathologic changes in the vessels were not sufficient to account for the diffuse, conspicuous softening of the white matter (Ginsberg and Myer 1976; Jefferson 1976). Also if hypoperfusion was to play a role, why was the cerebral white matter, which need only one fifth as much oxygen as the gray matter, predominantly damaged (Brucher 1967; Ginsberg and Myer 1974; Ginsberg 1979).

However recent data in several experimental models has suggested that white matter was preferentially vulnerable to incomplete ischemia (Welsh *et al.* 1978). The suggested sequence of these vascular changes was functional vasospasm followed by secondary degenerative changes of the arteries and the capillaries in the necrotic foci (Courville 1957).

Thus the abnormalities of regional cerebral perfusion were thought to play a critical role in determining the extent and intensity of neuropathological alterations of the white matter (Ginsberg 1979).

As above, many authors have tried to explain the pathogenesis of white matter changes, but white matter changes were not necessarily correlated with clinical deterioration, and white matter changes might not be present in some patients (Brucher 1967, Ginsberg 1979).

If it is not enough to explain the diversity, severity, and reversibility of clinical manifestations of delayed carbon monoxide sequelae with pathological changes alone, other functional changes such as hypoperfusion could be considered to be contributing factors (Kangstrom *et al.* 1984).

The blood pressure and lumbar CSF pressure were normal in our patients and the viscosity of the blood in delayed carbon monoxide sequelae was not changed. Thus the hypoperfusion is thought to be due to vasomotor dysfunction or decreased demands.

However there were correlations between the changes in the regional cerebral blood perfusion and fluctuations of the symptoms in this study.

As a preliminary conclusion, the alteration of cerebral blood perfusion plays a critical role in delayed

carbon monoxide sequelae.

Further study is needed to define the pathogenesis of decreased cerebral blood perfusion for the prevention of delayed neurologic sequelae.

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