Delayed Encephalopathy after Carbon Monoxide Intoxication - Long-Term Prognosis and Correlation of Clinical Manifestations and Neuroimages

Cheng-Lung Hsiao, Hung-Chou Kuo, and Chin-Chang Huang

Abstract- In order to understand the correlation between the clinical and neuroimaging manifestations and the long-term prognosis in delayed encephalopathy after carbon monoxide (CO) intoxication, we retrospectively reviewed 12 patients who had delayed encephalopathy from 89 patients with CO intoxication. There were 8 men and 4 women, with a mean age of 54.4±17.2 years (range: 11-79 years). All patients had prominent consciousness disturbance in the acute stage and received high flow of O_2 or hyperbaric oxygen therapy. All of them regained consciousness within 1-7 days, but subsequently developed delayed encephalopathy.

The delayed encephalopathy occurred from 14 to 45 days after recovery from the acute stage. The clinical manifestations included cognitive impairment, akinetic mutism, sphincter incontinence, gait ataxia and extrapyramidal syndromes such as chorea, dystonia, and parkinsonism. Brain MRI revealed multiple lesions in the subcortical white matter and basal ganglia, mostly in the globus pallidus, and to a lesser degree in the putamen, and caudate. In the follow-up period, sphincter incontinence first disappeared. The cognitive impairment improved greatly in the following few months, but the involuntary movements were improved only slightly. Some patients had persistent neurological sequelae, such as dystonia. Similary, the follow-up brain MRI showed a steady improvement. In conclusion, the delayed encephalopathy usually developed 2 weeks to 1.5 months after the acute phase of CO intoxication. Globus pallidus and subcortical white matter were commonly involved. The neurological manifestations improved and correlated roughly with the neuroimaging changes.

Key Words: Carbon monoxide, Delayed encephalopathy, MRI, Neurotoxic disease, Basal ganglion, Subcortical white matter

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INTRODUCTION

Acute carbon monoxide (CO) intoxication may induce hypoxic encephalopathy with variable degrees of brain damage, ranging from confusion to deep coma[1,2]. Approximately one-third of the patients succumb during

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the acute intoxication, most of the remaining patients can recover completely from the first episode[3]. However, 0.2-40% of the survivors develop delayed encephalopathy within 2-4 weeks after this pseudorecovery[4-7]. Several reports have described serial changes in the neuroimaging findings, time course of recovery, and long-term prognosis in delayed encephalopathy[6-10]. However, the possible mechanisms of delayed encephalopathy in humans and even in experimental animals are not fully understood[6,10,11]. In Taiwan, acute CO intoxication is not uncommon, but the data on delayed encephalopathy are still lacking[12,13]. The purpose of this study was to understand serial brain neuroimaging changes, the clinical course and the long-term prognosis of delayed encephalopathy in Taiwan.

MATERIALS AND METHODS

We retrospectively reviewed 89 patients who were admitted and diagnosed as acute CO intoxication from January 1985 to December 2000 in the emergency department. The inclusion criteria of delayed encephalopathy after CO intoxication included a definite clinical history and/or high CO-hemoglobin level, disturbance of consciousness in the acute stage, total or nearly total recovery of consciousness within days and the delayed neurological deterioration after a period of pseudorecovery[3-6]. We excluded 2 patients who had acute myocardial infarction and one patient who had also suffered from a traumatic intracranial hemorrhage in addition to CO intoxication. Nineteen patients had fulfilled the criteria but 7 of them did not have regular follow-ups. Therefore, only 12 patients were included in the study. There were 8 men and 4 women. All patients had received high concentrations of O_2 or hyperbaric oxygen treatment in the acute stage. The clinical features and the neuroradiological studies with brain MRI were carefully recorded. Because patients were unable to receive the Mini-Mental test or other cognitive tests, particularly in the early stage of delayed encephalopathy, cognitive functions were primarily evaluated by neurological examinations. Most of the patients received long-term monthly follow-up in the outpatient clinic by one of the authors (C-C Huang) for more than 1 year. Six patients had serial brain MRI studies.

RESULTS

Clinical manifestations

The current ages of 12 patients ranged between 11 and 79 years (mean: 54.4±17.2 years). The incidence of delayed encephalopathy after CO intoxication was 13.5%. The mean age at onset was 50.5±17.6 years (from 5 to 76 years). The main clinical features of acute CO intoxication were consciousness disturbance, including deep coma (4), semi-coma (1), stupor (1), delirium (1), drowsiness/somnolence (2), and confusion (3). Consciousness returned to nearly normal from 1 day to 7 days after the onset in all patients except for patient 1, who still had a disorientation to time. However, delayed encephalopathy developed from 14 days to 45 days after acute first episode. Table 1 shows the demographic data and clinical manifestations in the acute stage and delayed phase. The clinical manifestations of delayed encephalopathy included cognitive dysfunction (11), sphincter incontinence (9), akinetic mutism (6), and extrapyramidal features (10), such as rigidity (6), bradykinesia (5), dystonia (5), masked face (5), chorea (1), and resting tremor (1). Other neurological signs were cerebellar ataxia (2), dysmetria/dyssynergia (1), athetosis (1), small step gait (1), amnesia (1), acalculia (1), and hallucination (1).

Clinical follow-ups

All patients had clinical follow-up from 1 to 3 years. During the follow-up period, most of the cognitive dysfunctions improved continuously, although confusion, disorientation, and memory impairment still persisted in 9 patients for a period of within 3 months. One year later, the cognitive dysfunction had completely disappeared in 6 patients. Although cognitive impairment was still present in 5, the severity of cognitive dysfunction had improved. Regarding sphincter dysfunction, urine incontinence disappeared within 3 months in 6 patients. At one year, occasional sphincter dysfunction was still present in one patient. Concerning speech function, mutism was noted in 6 initially, and had disappeared in 5 patients 3 months later. One year later, akinetic mutism

Table 1. *Demographic data, neurological features, and brain MRI findings of 12 patients with delayed encephalopathy after CO intoxication*

Patient	Age at onset (yr)/sex	Duration of the occurrence of delayed encephalopathy(d)	Neurological features		Brain MRI lesions
			Acute phase	Delayed phase	Delayed phase
1	61/M	22	Disorientation to time, place, and person, incoherent speech, sphincter incontinence	Disorientation, urine incontinence, mutism, masked face, rigidity	GP
2	51/M	23	Consciousness disturbance, vomiting	Confusion, urine and stool incontinence, akinetic mutism, masked face, ataxia,	GP, SWM
3	66/F	20	Coma, vomiting	Cognitive dysfunction, hallucination, urine incontinence, bradykinesia, rigidity, dystonia, small step gait	GP, SWM
4	5/M	45	Consciousness disturbance	Mutism, chorea, dystonia, ataxia, dysmetria, dyssynergia	Putamen, caudate, SWM
5	76/M	14	Stupor, vomiting, neck stiffness	Disorientation to time, cognitive impairment, bad tamper, memory impairment	GP (R)
6	51/F	16	Semi-coma	Confusion, urine and stool incontinence, masked face, axial rigidity, resting tremor	GP, VE
7	64/F	29	Drowsy	Confusion, memory impairment, urine incontinence, athetosis, dystonia, bradykinesia	Putamen (L), SWM
8	48/F	19	Delirium, vomiting	Confusion to time, place, and person, urine incontinence, akinetic mutism, rigidity, bradykinesia, dystonia	GP, SWM, cortex, midbrain
9	49/M	17	Coma, vomiting	Confusion to time, place, and person, memory impairment, behavior changes, urine incontinence, rigidity, bradykinesia	GP, SWM
10	40/M	25	Coma	Confusion to time, place, and person, mental changes, urinary incontinence, rigidity, bradykinesia, stooped posture, turning block	GP, SWM
11	47/M	20	Somnolence, confusion	Confusion to time, place, and person, acalculia, amnesia, akinetic mutism, masked face	GP, SWM
12	48/M	23	Coma	Stupor, urine and stool incontinence, mutism, masked face, dystonia	GP (R > L), SWM (R > L)

CO: carbon monoxide; M: male; F: female; yr: year; d: day; MRI: magnetic resonance images; GP: globus pallidus; SWM: subcortical white matter; VE: ventricular enlargement; R: right; L: left.

was no longer observed. In 10 patients with extrapyramidal features, rigidity and bradykinesia were improved in 3 months later but still presented in 3 patients one year later. In 5 patients with dystonia, the symptom disappeared in two months later, and still presented partially in two, 1 year later. During the follow-up period, 2 patients with parkinsonian features received a short course of treatment with levodopa/carbidopa 300/75 mg daily, but none of them had a significant improvment. Patient 6 also had diabetes, chronic subdural hematoma after an accident, and several episodes of hypoglycemia in the follow-up period. Figure 1 summarizes the clinical improvement in various clinical manifestations during the follow-up period.

Brain neuroimaging findings

The initial brain MRI, performed in the first week, revealed multiple hyperintensity lesions on T2 weighted images, mainly in the basal ganglia (12), subcortical white matter (9), and even in the midbrain (1). Rarely, cerebral cortical atrophy (1) and ventricular enlargement (1) were observed. (Table 1) The thalamus was spared in all patients. In the subcortical white matter, the lesions were usually symmetric in 8 patients and asymmetric in 1. In the basal ganglia, the globus pallidus was involoved in 10, the putamen in 2, and the caudate in 1. In the globus pallidus, the involvement was moderate in 8 (symmetric in 7 and asymmetric in 1) and mild in 2 (symmetric involvement in 1 asymmetric in 1). The involvement of the putamen and the caudate was usually mild, and present only in 2. In the brainstem lesions, midbrain was affected in patient 8. Damage in the cerebellum was not observed.

Six patients underwent serial brain MRI studies,

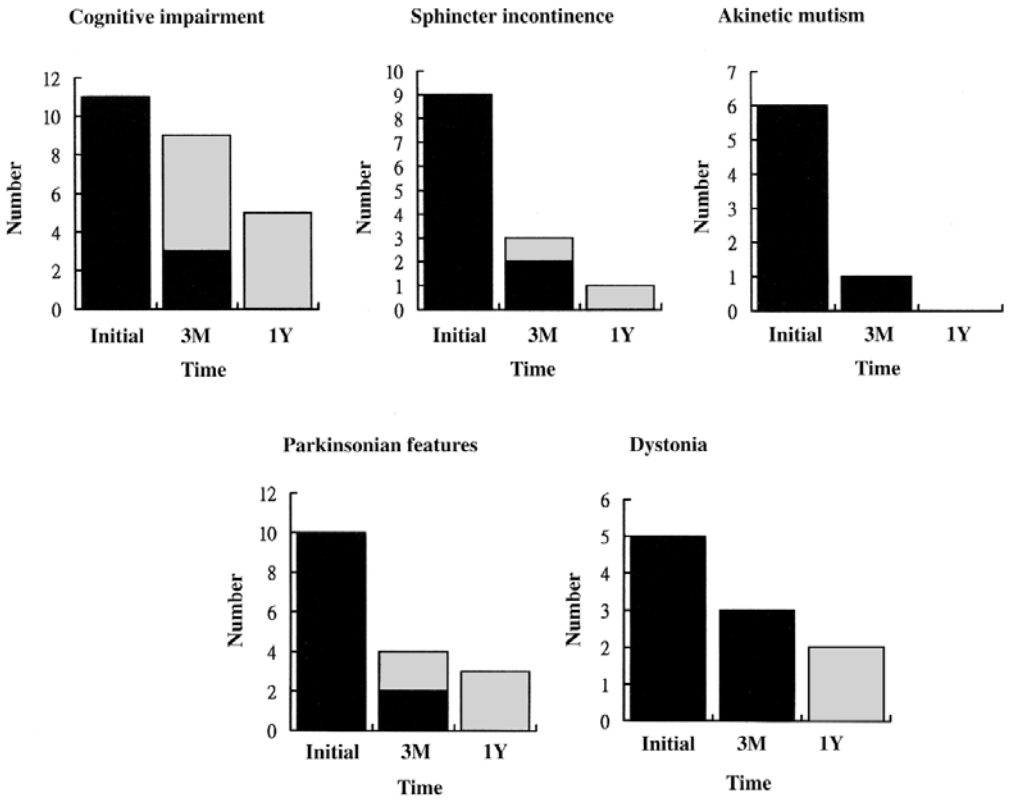

Figure 1. Serial clinical changes of 12 patients with delayed encephalopathy after CO intoxication revealed a steady improvement in various items including cognitive impairment, sphincter incontinence, akinetic mutism, parkinsonian features, and dystonia in the follow-up period (initial: at the initial stage, 3M: 3 months later, 1Y: 1 year later, ■ : persistent symptom, □ : partial improvement).

which revealed a prominent improvement in the subcortical white matter and globus pallidus lesions in all 6 patients (Table 2). The improvement was also noted in the putamen and caudate lesions of patient 4. In patient 10, serial brain MRI changes revealed a steady improvement in the subcortical white matter and globus pallidus lesion indicating that the delayed encephalopathy is a potentially reversible disorder (Fig. 2).

DISCUSSION

This study demonstrates the clinical course and neuroradiological changes in 12 patients with delayed encephalopathy after acute CO intoxication. In this report, the incidence of delayed encephalopathy is approximately 13.5%. In the previous studies, the ranges of the incidence are between 0.2% and 40%[3-9]. The main reasons for large variations are possibly due to different population and variability in choosing patients. In our report, the high incidence may be partly due to a retrospective study and data were collected only from the admitted patients. However it was similar to 11.8% for admitted patients by Choi[5]. The common clinical features included cognitive changes, sphincter incontinence, akinetic mutism, parkinsonism, and dystonia which were compatible with several previous studies[2,3,5,9,14-17]. All patients had a prominent improvement in all clinical features, particularly in sphincter incontinence and akinetic mutism. Although some sequelae such as dystonia and cognitive impairments persisted, the clinical severity was also improved during the follow-up period. The clinical presentations indicated that the frontal lobe dysfunction recovered faster than the extrapyramidal features.

The common neuroimaging changes were hyperintensity lesions in the basal ganglia, particularly in the

Table 2. *Serial brain MRI findings in 6 patients with delayed encephalopathy after CO intoxication*

Patient	3		4		9		10			11		12	
Time	1M	1.5Y	4D	4.5M	1.5M	1Y	2M	5M	1Y	2M	6M	1.5M	7M
Cerbral cortex	−	−	−	−	−	−	−	−	−	−	−	−	−
Subcortical white matter	+	−	++	+	++	+	++	+	−	++	+	++ (R > L)	+ (R > L)
Basal ganglia													
Putamen	−	−	+	−	−	−	−	−	−	−	−	−	−
Caudate	−	−	+	−	−	−	−	−	−	−	−	−	−
Globus pallidus	++ (B)	+ (B)	−	−	++ (B)	+ (B)	++ (B)	++ (B)	+ (B)	++ (B)	+ (B)	++ (R > L)	+ (R > L)
Thalamus	−	−	−	−	−	−	−	−	−	−	−	−	−
Brain stem													
Midbrain	−	−	−	−	−	−	−	−	−	−	−	−	−
Pons	−	−	−	−	−	−	−	−	−	−	−	−	−
Medulla	−	−	−	−	−	−	−	−	−	−	−	−	−
Cerebellum	−	−	−	−	−	−	−	−	−	−	−	−	−
Ventricular enlargement	−	−	−	−	−	−	−	−	−	−	−	−	−

MRI: magnetic resonance images; CO: carbon monoxide; Y: year; M: month; D: day; B: bilateral; R: right; L: left; ++: moderate abnormality; +: mild abnormality; −: normal.

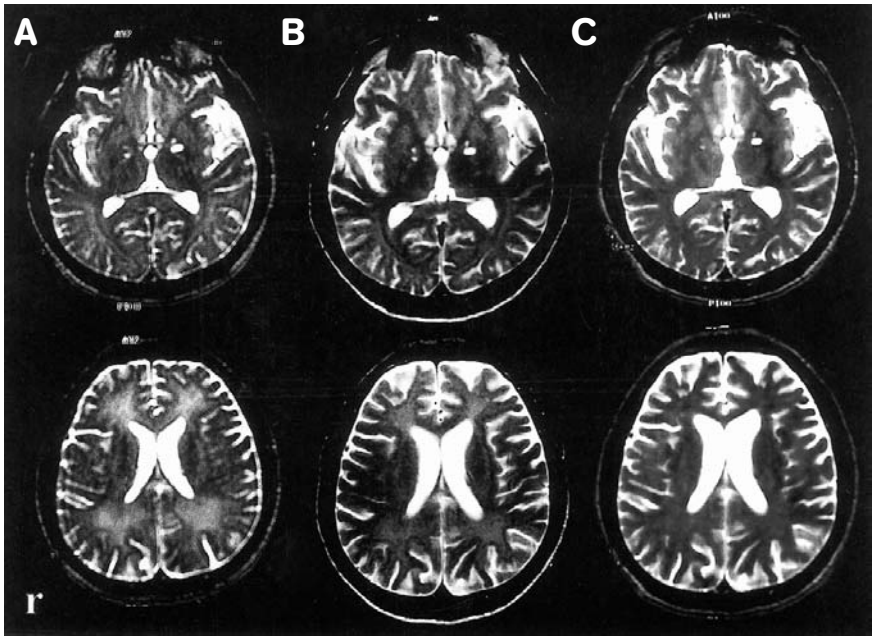

Figure 2. Serial brain MRI studies revealed a steady improvement in the subcortical white matter and to a lesser degree of improvement in the globus pallidum in patient 10. (A: at 2 months B: at 5 months, C: at 1 year)

globus pallidus and subcortical white matter. Serial brain MRI studies also demonstrated a steady improvement in the basal ganglia and subcortical white matter. The morphologic changes, including necrosis, ischemia or demyelination in the globus pallidus and cerebral white matter after acute CO intoxication, have been well documented[1,6-9,18,19]. In addition, spongy changes in the cerebral cortex and necrosis of the hippocampus were also noted[5,9,18,19]. In the delayed encephalopathy after CO intoxication, the characteristic findings were small necrotic foci and demyelinating changes in the cerebral white matter and globus pallidus[5,9,18]. Demyelination

with relative preservation of the axons was prominent in the frontal lobes of patients with delayed encephalopathy[2,9,20,21]. In our patients, early recovery of frontal lobe dysfunctions indicated a demyelinating process. The pathogenesis for the predominant involvement in the globus pallidus remains unclear, but ischemic changes were noted in some patients who died from CO intoxication[9,18-21]. In addition, this ischemia may precede irreversible changes[1].

In the present study, the clinical manifestations and courses were roughly correlated with the improvement in the MRI. The good recovery of cognitive functions and the subcortical white matter involvement indicated a reversible demyelination, rather than an irreversible necrosis. In contrast, the persistence of parkinsonism and/or dystonia for a longer period indicated that the lesions of the globus pallidus might have an irreversible necrosis in some patients. Intriguingly, patient 4 had no lesion in the putamen and caudate 4.5 months after the onset of delayed encepalopathy, but still presented with dystonia and chorea. The data indicated that sometimes the extrapyramidal features might not well correlate with the basal ganglion lesions, but also correlate with the subcortical white matter lesions.

In summary, cognitive dysfunction had a marked improvement after CO intoxication, while the parkinsonism, and dystonia might persist for more than 1 year in some patients. The most common MRI lesions in delayed encephalopathy after CO intoxication were in the subcortical white matter and globus pallidus. Both lesions improved gradually. However, the white matter lesions recovered faster than the globus pallidus lesions. The correlation between clinical presentations and neuroimaging changes in CO intoxication was roughly good.

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