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# A Clinical Observation of Delayed Neurologic Deterioration Following Carbon Monoxide Poisoning†

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= Abstract = **Some patients with anoxic exposure develop new neurologic deficits after periods of delay when they recover from the initial anoxia. This Delayed Neurologic Deterioration(DND) is most commonly seen following carbon monoxide(CO) poisoning. This study was done to further describe the clinical features of this interesting but rare entity. We reviewed the records and brain scans of 37 patients who were admitted to Seoul National University Hospital because of DND following CO poisoning during the period January 1980 to December 1986. On reviewing the data, we were able to see certain patterns. Age may be important in the development of DND. Most patients were in their 40's to 60's. Patients with severe CO poisoning may be at higher risk of developing DND. However many patients with DND had brief periods of unconsciousness during acute poisoning. The lucid interval was usually 1-4 weeks. Long lucid interval may predict good prognosis. Global encephalopathy was the most common. Post-CO Parkinsonism was diagnosed in 5. Parkinsonism was part of global encephalopathy. They improved with L-dopa better than with anticholinergics. Low density in the globus pallidus may not be associated with Parkinsonism. Diffuse brain atrophy was the most common radiological finding.**

Key Words; *Carbon monoxide, Delayed neurologic deterioration, Parkinsonism, Pathoclisis*

## INTRODUCTION

Carbon monoxide(CO) poisoning is a worldwide problem. In Korea, it is especially important because coal is widely used as a domestic fuel for cooking and heating. Even though rapidly decreasing as a result of changes in heating systems, it still continues to pose a major health hazard to a large population.

CO binds to hemoglobin, and interferes binding and release of oxygem. The importance of binding to iron containing proteins as cytochrome C oxidase and myoglobin is not clear. As a result, CO poisoning produces a form of anoxia. It causes myocardial depression with hemodynamic change. The ischemic component is believed to play an important role in the pathophysiology. CO poisoning can directly and indirectly produce various neurologic complications. Of interest is Delayed Neurologic Deterioration(DND) which manifests itself after

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a lucid interval when a victim maintains an apparently normal life after initial CO poisoning. It can be seen in other clinical situations of anoxia-ischemia, but is most often seen in CO poisoning. It is a well recognized entity, but rare. The largest series was reported by Choi (1983), but did not get much attention in the references. This paper is to further describe the clinical and radiological patterns of this entity. Pathophysiology will be reviewed and discussed with special reference to selective neuronal vulnerability and delayed appearance of this syndrome.

## MATERIALS AND METHODS

An examination was completed of the charts and brain scans of patients who were admitted to Seoul National University Hospital during the period of January 1980 through December 1986. The patients were victims of CO poisoning, documented by clinical history and carboxyhemoglobin level in most cases. Only adult patients older than 15 years of age were included.

They had various neurologic complications, but this paper concerns DND only. DND was defined as a new neurologic deterioration after a lucid interval when the patient maintains an apparently normal neurological function after he recovers from an acute CO poisoning. We studied the clinical features including coma duration in the acute stage, lucid interval, symptoms and signs, and radiological findings.

The total number of patients in the investigation was 204.179 were admitted to our hospital during the acute poisoning, and 37 were admitted because of DND. Out of 37 patients with DND, 12 were admitted to this hospital during acute CO poisoning, and others were seen at other hospitals. Patients were included in the vegetative category if they were mutistic, dysphagic to aphagic, quadriparetic and incontinent sometime during the course. The best response to noxious stimuli was grumbling or grimacing. Eight patients were included in the vegetative and 29 in the nonvegetative group by these criteria.

## RESULTS

Demographic data of the patients are listed in Table 1. Age distribution of patients with acute CO poisoning reflected that of the general population. Ages of DND patients ranged from 25 to 74 with a mean of 55.2 which is older than that of patients with acute CO poisoning (39.4). Only one DND patient was younger than 40. Ages of vegetative DND patients ranged from 53 to 73 with a mean of 61; and that of nonvegetative patients, from 25 to 74 with a mean of 53.6.

The duration of coma during the acute CO poisoning is in Table 2. 70% of the total patients (26 out of 37) were comatose for less than one day, and 30% (11 out of 37) were comatose for 1-5 days. 49% (18 out of 37) were comatose for less than 12 hours, and 2 developed vegetative DND. Average duration of coma in the vegetative group was 1.9 days

**Table 1.** Age distribution of the patients

| Age | Acute poisoning | DND* | | |
|---|---|---|---|---|
| | | Vegetative | Nonvegetative | Total(%) |
| 15- | 23 | 0 | 0 | 0 ( 0) |
| 20- | 57 | 0 | 1 | 1 ( 2) |
| 30- | 25 | 0 | 0 | 0 ( 0) |
| 40- | 16 | 0 | 8 | 8 (50) |
| 50- | 26 | 4 | 9 | 13 (50) |
| 60- | 22 | 3 | 10 | 13 (59) |
| 70- | 8 | 1 | 1 | 2 (25) |
| 80- | 2 | 0 | 0 | 0 ( 0) |
| Total | 179 | 8 | 29 | 37 (21) |

* See text for legend

**Table 2.** Coma duration in DND

| Coma duration | Vegetative(%) | Nonvegetative(%) | Total(%) |
|---|---|---|---|
| -0.5 day | 2 (25) | 16 (55) | 18 (49) |
| -1 | 2 (25) | 6 (21) | 8 (22) |
| -2 | 1 (13) | 2 ( 7) | 3 ( 8) |
| -3 | 2 (25) | 3 (10) | 5 (14) |
| -4 | 1 (13) | 1 ( 3) | 2 ( 5) |
| -5 | 0 (10) | 1 ( 3) | 1 ( 3) |
| Total | 8(100) | 29(100) | 37(100) |

compared with 1.2 days in the nonvegetative group.

Lucid interval was usually between 1-4 weeks (range 7-60 days) (Table 3). Average lucid interval in the vegetative group was 15.4 days compared with 32.2 days in the nonvegetative group.

Two of the vegetative group deteriorated; two remained stationary; and four improved over several months with significant residual neurologic impairment. In contrast, all patients in the nonvegetative group improved over months to years, however, with residual impairment.

In the nonvegetative group, presenting symptoms were abnormal behavior in 9, confusion in 6, movement disorder in 5, and urinary incontinence in 1. Their full-blown symptoms and signs are summarized in Table 4. Common psychic symptoms were apathy, personality change, irritability, silly smile, psychomotor retardation, emotional flattening, delusion, hallucination and echolalia in this order of occurrence. Mental deterioration ranged from mild to severe dementia. Speech disturbances ranged from mumbling, dysarthria and anarthria. Bradykinesia and masked faces were common.

**Table 3.** Lucid interval in DND

| Lucid duration | Vegetative(%) | Nonvegetative(%) | Total(%) |
|---|---|---|---|
| - 7 day | 0 ( 0) | 1 ( 3) | 1 ( 3) |
| 8-14 | 3 (38) | 4 (14) | 7 (19) |
| 15-21 | 5 (63) | 6 (21) | 11 (30) |
| 22-28 | 0 ( 0) | 12 (41) | 12 (32) |
| 29-35 | 0 ( 0) | 4 (14) | 4 (11) |
| 36- | 0 ( 0) | 2 ( 7) | 2 ( 5) |
| Total | 8(100) | 29(100) | 37(100) |

**Table 4.** Clinical features of 29 patients with nonvegetative DND

| Clinical | No. | (%) |
|---|---|---|
| Psychiatric | 29 | 100 |
| Cognitive | 27 | 93 |
| Speech | 7 | 24 |
| Pyramidal | 16 | 55 |
| Extrapyramidal | 23 | 79 |
| Gait | 13 | 45 |
| Incontinence | 23 | 79 |

Action tremor and chorea were seen in one case each. Gait disturbances included short steps, festination, retropulsion, and wide based gait. Many were incontinent. Post-CO Parkinsonism was diagnosed in 5. They were more rigid and apastic than tremulous. All had dementia and incontinence. They were treated with anticholinergics and L-dopa with moderate improvement, better with L-dopa.

In the vegetative group, 8 CT and 1 MRI scans were obtained in the follow-up stage. Seven of the 8 CT scans showed diffuse brain atrophy; 2, low density in the globus pallidus; and 1, low density in the deep parietal area. The MRI scan showed increased T2 signal in the periventricular area. In the nonvegetative group, 15 CT and 2 MRI scans were done in the chronic stage. Six of the 15 CT scans showed diffuse brain atrophy; 4, periventricular low density; and 4, low density in the globus pallidus. Three scans were normal. One of the 2 MRI scans showed increased T2 signal in the periventricular area; and the other, in the frontal area. The brain CT scan was normal in the latter case. Of the 4 patients who showed low density in the globus pallidus, only 2 were diagnosed as post-CO Parkinsonism. Four CT scans were done in the 5 patients who were diagnosed as post-CO Parkinsonism. Two showed low density in the globus pallidus; 1, periventricular low density; and 1, diffuse brain atrophy.

## DISCUSSION

Epidemiological generalization should be drawn cautiously from this study. The method of patient collection makes it difficult for the patient groups in the study to be representative. Patients were included in the study simply because they were inpatients during the arbitrary period and may not eflect general population or patients. For acute poisoning group, we did not look at the patients who visited the ER during the 6 year period(more than 3,000), nor outpatients. As the scope of the work was not intended to be a systematic epidemiological

**Table 5.** CT findings in DND

| | Vegetative | Nonvegetative |
|---|---|---|
| No. of the scans | 8 | 15 |
| Diffuse brain atrophy | 8 | 16 |
| Periventricular low density | 1 | 4 |
| Low density in the globus pallidus | 2 | 4 |
| Normal | 0 | 3 |

study, we rather chose to simply look at 179 inpatients as a quick refernce realizing the problems in it. We do not have actual follow-ups of every 179 patients admitted during acute co poisoning. 12 patients developed DND and were admitted, and we are simply assuming that other 167 patients probably made a full recovery without neurological deficit. Many patients in the DND group(25 out of 37) did not come from the acute poisoning group. They were taken care of at other hospitals during acute poisoning, and were referred to us when they developed DND. As a result, the DND group is heterogeneous, and may not be compaprable to acute poisoning group. The same precaution should be paid to other results and conclusions for the same reason that this is not a population based study, but a collection of clinical data in patients seen in a single institution. However, because of the large number of patients which is more difficult to find in other areas than in Korea, we tried to make several generalizations from the data.

DND patients were older than the general group of patients with aute CO poisoning which tends to reflect the general population (55.2 vs. 39.4). Only one patient was younger than 40. Vegetative patients tend to be older than nonvegetative ones (61 vs 53.6). During the same study period, we had 16 patients who had persistent neurologic damage rendered by initial CO poisoning. Mean age was 36.1, and patients who were vegetative were older with a mean of 46. 6 compared with 27.9 in nonvegetative patients. It seems that age is an important factor in the development of DND and severity. However, it is noted that the risk of developing DND in the very aged patients over 70 did not follow the trend (Table 1). The number of the patients in the subsets might be too small to be significant and may not reflect true trend. Or there may be some other factors involved.

One pure speculation might be that the very aged patients are less likely to return to vigorous phisical activity. Even though not proven, early return to normal activity is thought to precipitate DND. However, it should be emphathised again that the data is based on a collection of patients in a single institution and not from epidemiological survey, thus the results and conclusions should be viewed with great caution.

Coma duration in the acute CO poisoning was longer (1.9 vs 1.2 days), and lucid interval was shorter (15.4 vs 32.2 days) in the vegetative DND patients than the nonvegetative group with great overlap. Even though there may be a positive correlation between level of consciousness on admission and later development of neuropsychiatric sequelae (Smith and Brandon 1973), it should be noted that 18 patients were comatose for less than 12 hours initially in our study. Two of the 18 patients developed vegetative DND. Even seemingly mildly affcted patients should be warned against the development of DND, especially in older patients (Beck 1927; Dancey and Reed 1936). All 8 vegetative DND patients had a lucid interval of less than 21 days compared with only 39% (11 out of 29) in non vegetative DND. Other 71% of nonvegetative DND develoled afte longer than 21 days of lucid interval. However, one nonvegetative DND patient had the shortest lucid interval of less than 7 days. Earlier development of DND after CO poisoning may not be quite predictive of bad prognosis, but longer lucid interval (> 3weeks) may predict good prognosis.

Clinical presentation was usually that of global encephalopathy and this was corroborated on clinical examination. Psychic and cognitive changes were the dominant clinical pictures. Psychiatric manifestation is believed to be due to diffuse encephalopathy. Even in patients with principal complaints of movement disorders, cognitive impairment was always

found on examination. Urinary incontinence was very frequent. Most patients were spastic and rigid.

Parkinsonism following CO poisoning is a well-described form of secondary Parkinsonism (Choi 1983; Grinker 1926; Klawans *et al.* 1982; Ringel and Klawans 1972). The Parkinsonian feature is more often part of diffuse encephalopathy, however, post-CO pure Parkinsonism has been described (Klawans *et al.* 1982; Ringel and Klawans 1972). In the report of Klawans *et al.* (1982), there was low density in the globus pallidus on the CT scan. The patient showed improvement with anticholinergics, but not with L-dopa. The authors argued that pallidal lesion caused Parkinsonism, and lack of response to L-dopa was due to absence of dopamine receptors in the globus pallidus. In this study, 5 patients were diagnosed as post-anoxic Parkinsonism. They were bradykinetic and rigid rather than tremulous. All showed evidence of global encephalopathy as cognitive impairment. Choi (1983) did not specificially mention dementia in patients with Parkinsonism, however, 98.5%(64 out of 65) of total DND patients had mental deterioration. Because we were aware of the paper by Klawans *et al.* (1982) that a post-CO Parkinsonian patient improved with anticholinergics but not with L-dopa, we did open trials several times. All showed better improvement with L-dopa than with anticholinergics. Only 2 of 4 CT scans in the 5 patients with post-CO Parkinsonism showed low density in the globus pallidus. Of the 4 patients with nonvegetative DND who had low density in the globus pallidus, only two were diagnosed as post-CO parkinsonism. Plum *et al.* (1962) observed necrosis of the globus pallidus at autopsy of a patient who showed no symptoms during life but gave a remote history of anoxic exposure, and suggested that no distinctive symptomatology may occur from these lesions. We also observed 2 patients, not included here, who showed low density in the globus pallidus after CO poisoning, and had no symptoms. In conclusion, post-CO Parkinsonism may not be attributed to lesions in the globus pallidus, and our experience suggests that Parkinsonian feature are part of a more diffuse encephalopathy.

Necrosis in the globus pallidus and white matter is a characteristic finding in CO poisoning. Necrosis in the globus pallidus develops in the acute stage, while whsite matter demyelination can develop in the chronic stage (Plum *et al.* 1962; Lapresle and Fardeau 1967). After reviewing the CT scans in 21 patients with acute CO poisoning, Sawada *et al.* (1980) reported that low density in the globus was correlated with poor prognosis. However, Miura *et al.* (1985) examined 60 patients with acute CO poisoning, and observed that the prognosis depended on the severity of white matter changes and not the extent of the low density in the globus pallidus. The CT scans in our study were done in the chronic stage. Brain atrophy was the most common finding. Low density in the periventricular area and globus pallidus was equally common. As the MRI scan is more sensitive for white matter changes, we expect to see more frequent white matter changes with MRI scans. Our limited experiences with MRI scans seems to confirm this. All the three MRI scans done showed changes in the white matter. One of the MRI scans had a normal CT scan. Three patients had normal CT scans, but had DND. A normal CT scan can be seen in patients with DND.

Pathophysiology and neuropathology of CO poisoning were extensively studied with special reference to selective necrosis of the globus pallidus, extensitve demyelination with sparing of axons in the cerebral white matter, and delayed neurologic deterioration. To explain selective necrosis of the globus pallidus, Vogt and Vogt(1937) suggested that there is an inherent tissue vulnerability based on the tissue's intrinsic metabolic properties and coined the term "pathoclisis". However, detailed neuropathological studies have shown that the lesion commonly extends into the adjacent internal capsule (Grinker 1926; Lapresle and Fardeau 1967) whose metabolic properties would be very different. The same pathology has been reported in other conditions of

hypoxia-ischemia (Dooling and Richardson 1976; Plum *et al.* 1962; Ginsberg *et al.* 1976). These suggest that the necrosis in the globus pallidus is not related to metabolic differences from other tissue or particular susceptibility to CO.

Grey matter has a far greater metabolic activity, and consumes 5 times more oxygen than white matter (Sholz 1949). Thus, infarction is usually severe, or limited to the cortex sparing the white matter. It is evident that more than anoxic mechanism is needed to explain selective white matter damage in CO poisoning. Based on clinical data(Ginsberg *et al.* 1976) and experimental study in the primates (Ginsberg *et al.* 1974), Ginsberg suggested that "hypoxic-ischemic leukoencephalopathy" was correlated with metabolic acidosis and systemic hypotension. Okeda *et al.* (1982) showed experimentally that hypoxia and subsequent hypotension are the two essential factors in the pathogenesis of hypoxic-ischemic leukoencephalopathy. They proposed that enormous vasodilation in the white matter induced by hypoxia and subsequent hypotension causes a more severe circulatory disturbance in the white matter which is supplied by more distal arterial branches than in the cortex, thus making the white matter more susceptible to hypoxia-ischemia. CO has a strong affinity for myoglobin, and causes early myocardial depression with attendant hypotension (Takano *et al.* 1981). This might explain why hypoxic-ischemic leukoencephalopathy is more often seen in CO poisoning than in other forms of hypoxia-ischemia.

The mechanism of delayed neurologic deterioration is not known. DND is seen in other forms of hypoxia-ischemia(Dooling and Richardson 1976; Plum *et al.* 1962), and can not be explained by any particular property of CO. There are two types of white matter pathology in CO poisoning and other hypoxia-ischemia (Lapresle and Fardeau 1967). One is multifocal or massive necrosis of the white matter seen in patients who died after the acute insult without improvement. The other is diffuse demyelination of white matter with sparing of axons (Grinker's myelinopathy) which is seen in patients who recovered initially and died of later neurologic deterioration. This Grinker's myelinopathy is considered to be a basic neuropathology in DND (Plum *et al.* 1962; Lapresle and Fardeau 1967). Plum *et al.* (1962) suggested that anoxic injury to oligodendrocytes with failure to continue to support axon is the mechanism of delayed deterioration. However, DND with necrosis of the deep grey matter sparing the white matter has been reported (Dooling and Richardson 1976), and argues against Plum's hypothesis.

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