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Chronological changes of MRI findings on striatal damage after acute cyanide intoxication: pathogenesis of the damage and its selectivity, and prevention for neurological sequelae: a case report

Kimihiro Kasamo[1], Yoshitaka Okuhata[2], Ryuji Satoh[1], Mori Ikeda[1], Sakae Takahashi[1], Rikisaburo Kamata[2], Yoshimi Nogami[1], and Takuya Kojima[1]

[1]Department of Neuropsychiatry, Nihon University School of Medicine, 30-1 Oyaguchi Kamimachi Itabashi-ku Tokyo 173, Japan
[2]Department of Radiology, Nihon University School of Medicine

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Summary. A 31-year-old male technician in an electroplating factory, who had been suffering from the temporal lobe epilepsy for 24 years and from hypertension for 2 years, took an unknown amount of potassium cyanide apparently over the lethal dose, in an attempt to commit suicide. He was treated successfully and survived without any neurological sequelae. The electroencephalograms and the nature of the seizures were not different before and after the poisoning. The T2-weighted magnetic resonance images at 9 and 51 days after the poisoning showed bilateral elevation of signals in the caudate nuclei and the putamina. At the 143th and 286th days, T2-weighted high-resonance areas were restricted to the lateral portion of the putamina. The T1-weighted images at the 51st day showed abnormal signal elevations in both putamina, while those of 9th, 143th and 286th days were mainly normal. Selective vulnerability of the putamen and the caudate nucleus may be due to their specific structural properties of high oxygen and glucose utilization, and enzyme distribution. Both chronological changes of striatal damage and the absence of neurological sequelae in this patient suggest the possibility that anti-epileptics and a calcium antagonist played a neuroprotective role in the acute cyanide intoxication.

Key words: Cyanide – basal ganglia – anti-epileptic drugs – calcium antagonist – MRI

Introduction

The average lethal dose of potassium cyanide is 250–300 mg. Death usually occurs in less than 1 h [12]. Because of the high mortality, the number of reports on surviving patients is small.

After magnetic resonance (MR) images became available, four English language reports on MR images of the brain after cyanide intoxication have been published [6, 9, 16, 20]. All reported patients showed parkinsonism or dystonia and the MR-detectable basal ganglial involvement. However, details of chronological changes of the damage and of factors contributing to the selective vulnerability of basal ganglia in cyanide intoxication were not discussed in these reports.

In the present patient, basal ganglial damage was reversible. Furthermore, he did not exhibit apparent extrapyramidal signs or symptoms. These phenomena suggest a hypothesis for preventing the occurrence of neurological sequelae after acute cyanide intoxication.

This is the first report on the chronological changes and on the hypothesis for preventing or decreasing neuronal damages.

A case report

A 31-year-old male electroplating technician took an unknown amount of potassium cyanide, apparently over the lethal dose, in a suicidal attempt. He dissolved 20–40 g potassium cyanide in 200 ml of milk, and drank all of this liquid. He became comatose and apneustic, and manifested severe metabolic acidosis. Emergency treatments with amyl nitrate, sodium thiosulphate and other intensive supportive therapies were started 30–60 min after the fluid had been taken. An analysis of gastric aspirates from the patient confirmed the presence of cyanide. Spontaneous breathing returned 2 h after the start of the treatment. His consciousness became clear in 8 h. Computed tomograms of the brain (B-CT) obtained

Correspondence to: Kimihiro Kasamo

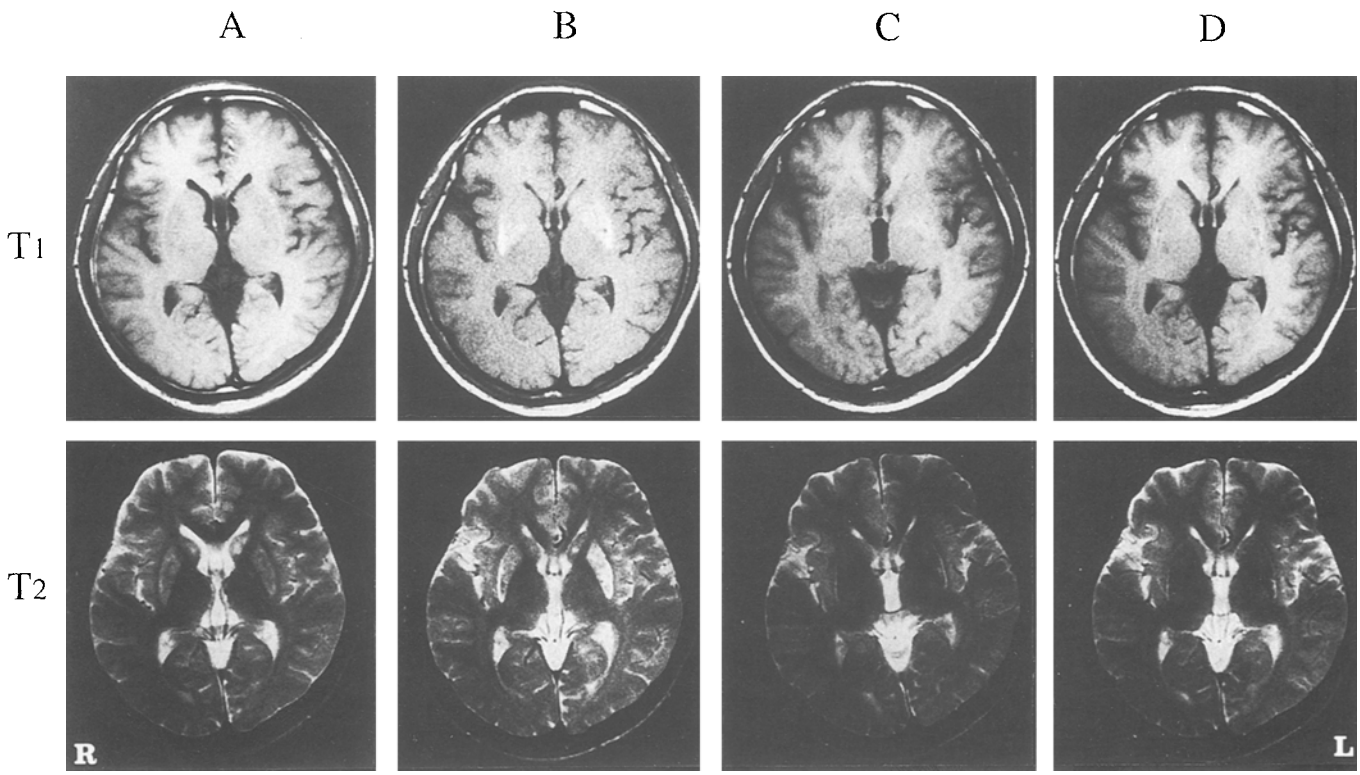

Fig. 1. Magnetic resonance (MR) images of the brain. *Upper rows;* T1-weighted (TR/TE 600/19 ms). *Lower rows;* T2-weighted (TR/TE 2500/80 ms except B which is 2000/80 ms) images. Upper and lower images in each column were obtained in the same day. **A** 9th, **B** 51st, **C** 146th and **D** 286th days after poisoning. In T1-weighted images, **A** largerly normal. **B** High signal intensity areas were seen in the bilateral putamina. **C** and **D** largely normal. In T2-weighted images, **A**, multiple punctate foci of high signal intensity were seen bilaterally in the putamina and in the heads of caudate nuclei. **B** Hyperintensity in the putamina became more significant while that of the caudate nuclei decreased. **C** Abnormal signals in the heads of caudate nuclei disappeared. High signal intensity areas were restricted to the posterio-lateral portion of the putamina. **D** same as **C**

2 h after his admission did not show any pathological changes. After the recovery, even at 1.5 years after the poisoning, he did not show signs or symptoms of sequelae of the cyanide intoxication. He also had been suffering from temporal lobe epilepsy for 24 years and from hypertension for 2 years. The frequency and the sign of the seizure, EEG findings, and blood pressure were not significantly different before and after the poisoning. Drugs and their daily doses prescribed at the time of the poisoning were sodium valproate (VPA) 1200 mg, carbamazepine (CBZ) 1200 mg, phenobarbital (PB) 78 mg, phenytoin (PHT) 225 mg and nifedipine 40 mg.

The T1-weighted MR images obtained 9 days after the poisoning were normal, those at the 51st day revealed almost symmetrical high-signal intensity areas in both putamina. These regions became iso-intense to white matter on the 146th and 286th days. (Fig. 1 upper rows)

On the T2-weighted images at 9 and 51 days after the poisoning, bilaterally symmetrical high-signal intensity areas were observed in the putamina and the heads of the caudate nuclei. While the size and the signal intensity of the putaminal lesions became larger and higher at the 51th day than at the 9th day, those of the caudate nuclei lesions decreased. The T2-weighted images of the 146th and 286th days revealed that high-signal intensity areas were restricted to the lateral portion of the putamina. (Fig. 1 lower rows)

MR images did not reveal hippocampal or cortical damage. Memory and intelligence were unaffected.

MR studies were performed on a 1.5T superconducting system (Philips Gyroscan S15HP).

Discussion

Factors contributing to selective vulnerability

In this patient, the putamen and the caudate nucleus were selectively affected. Also, in many reports on experimental animals [13] or on humans [6, 9, 10, 16, 20, 22], basal ganglia have been shown to be vulnerable to acute cyanide intoxication. Brierly [3, 4] has reported that the striatal damage is probably due to a combination of arterial hypotension and elevated central venous pressure, leading to ischemia and/or hypoxic hypoxia, and that there is no evidence for hypoxic neuronal damage of purely histotoxic type. Is the selective vulnerability of the striatum sufficiently explained by Brierly's idea alone?

This notion is supported by the evidence that oxygen and glucose are highly utilized in the striatum, the caud-

ate nucleus and the putamen [8]. Further support is provided by the fact that the cerebral and the cerebellar cortices, which have been reported to be the high oxygen utilizing structures [8], are also vulnerable to cyanide intoxication [5, 6, 10]. However, there are some contradictory observations.

Memory disturbance does not often occur after acute cyanide intoxication. Among six patients previously reported [6, 9, 10, 16, 20], only one [9] exhibited impaired memory. Post-mortem histological examinations have revealed that the hippocampi are unaffected [1, 22]. In experimental cyanide encephalopathy, the incidence of lesions in the hippocampus is smaller than that in the striatum [13]. Messing [15] has reviewed several reports on experimental and human cyanide encephalopathy, nine on human and seven on animals. Hippocampal damages were not mentioned in these reports. However, the putaminal, the globus pallidal or the caudate nucleic lesions were significant in these reports. These findings indicate that the hippocampus is less susceptible to cyanide intoxication than the basal ganglia, in spite of the fact that the hippocampus is the most vulnerable structure for ischemia [24]. Thus, it is unlikely that ischemia of the whole brain and/or hypoxic hypoxia is the one and only crucial factor in the genesis of the selective vulnerability of the striatum.

Histotoxic effects of the cyanide ion are due to the inhibition of the activity of cytochrome oxidase, the terminal enzyme in the respiratory electron transport chain. Neurons exposed to the cyanide ion should predispose to the hypoxic condition. The striatum is the structure with the highest distribution of cytochrome oxidase, which is followed by the cerebellar and cerebral cortices, the globus pallidus and the hippocampus [8]. Obviously, cyanide could affect the cytochrome oxidase-rich structures more severely than the poor ones. Furthermore, the distribution of the intrinsic cyanide detoxicating enzyme, rhodanese, is lower in the caudate and the putamen than in the hippocampus [18]. These facts indicate that the selective vulnerability of the striatum to cyanide might be based not only on the high utilization of both oxygen and glucose, but also on the structural properties of both the high levels of cytochrome oxidase and the low level of cyanide detoxicating enzyme. These properties should facilitate hypoxic insults caused by the cyanide intoxication. Thus, in addition to ischemic-hypoxic events in the whole brain, the characteristic distribution of these enzymes are also likely to be crucial factors in the genesis of the selective vulnerability of the striatum.

Pathology and pathogenesis of striatal damages

The T1- and T2-weighted MR studies 51 days after the poisoning in our patient showed high-signal abnormalities in both putamina. These findings indicated the existence of edema, inflammatory vasculitis and/or hemorrhagic infarction. Heterogeneous signal elevations on T2-weighted images in the putamina and in the caudate nuclei might reflect mutliple, punctate bland infarcts foci [2], which is supported by reports of post-mortem histological examinations [1, 22].

These MR findings on the 51st day are consistent with those of four previous reports [6, 9, 16, 20]. However, hyperintensity on T2-weighted images in the putamina of the present patient decreased gradually and was restricted to the lateral portion after the 51st day. A high-signal abnormality on T2-weighted images in the heads of the caudate nuclei disappeared before the 146th day. In contrast, abnormal findings on MR images of four cases previously reported did not show remarkable improvements [6, 9, 16, 20]. Furthermore, in these four patients, extrapyramidal signs manifested at least 3 weeks after the intoxication [6, 9, 16, 20], while our patient does not exhibit any neurological signs or symptoms as the consequence of the cyanide intoxication 1.5 years after the intoxication. The absence of neurological sequelae, and chronological changes of MR findings in our patient suggest that his basal ganglial damage was milder than that of the four patients.

Three reasons why his basal ganglial damages were milder are possible. Firstly, he took cyanide with milk. It inhibited absorption of cyanide and kept his serum concentration of cyanide at a lower level than those of these four patients. Secondly, he did not manifest brain edema, which suggested hypoperfusion of the brain was mild. Thirdly, he had been taking medication for epilepsy and hypertension. These drugs disturbed the development of basal ganglial damage.

Considering the time course from the intoxication to the start of emergency treatment, his general condition at admission and the amount of potassium cyanide he took, the first reason appears to be impossible. The second reason is possible, since cyanide intoxication often causes severe cerebral edema [23], which should produce brain hypoperfusion.

Assessing the third reason may provide some information concerning the prevention of neurological sequelae.

In cases of rapid death after cyanide poisoning, no specific lesion in the brain has been observed [5, 23]. The earliest occurrence of basal ganglial damage so far demonstrated is 36 h after taking the poison [5]. The time course of the earliest development of the damage is almost identical with that of the delayed neuronal death in the striatum [21]. However, in the present case, the damage of the putamen progressed slowly for at least 2 months. Also, in the previous reports [6, 11, 16, 18], it took from a few weeks to several months for extrapyramidal signs to appear, or for the damage of the putamen to be detectable in B-CT or MR. The time course of the slow progression is consistent with the feature of ischemia-induced slowly progressive neuronal damage reported by Nakano et al. [19]. Thus, the occurence of putaminal damage in cyanide intoxication is considered to be based on the mechanism in which delayed neuronal death and/or ischemia-induced slowly progressive neuronal damage is involved. Generation of delayed neuronal death and slowly progressive neuronal damage has been reported to be based on excessive release of excitatory amino acids, high calcium influx to neurons and the increase of neuronal activity [17, 19]. These phenomena result in the accumulation of calcium ions in

neurons, which plays an important role in neuronal damage [17].

Preventing neurological sequelae: a hypothesis

Our patient had been taking PHT, VPA, CBZ, PB and nifedipine with good compliance to treat epilepsy and hypertension before and after the intoxication. PHT and CBZ inhibit neurotransmitter release [7]. VPA enhances post-synaptic GABA responses [14] and attenuates N-methyl-D-aspartate (one of excitatory amino acids) receptor-mediated neuronal excitation [25]. PB would suppress neuronal excitability by limiting calcium influx through L- and T-channels [17]. Calcium antagonist, nifedipine, one of the dihydropyridines, inhibit calcium influx through L-channels [17].

Taken together, these facts and ideas suggest the hypothesis that, through limiting the accumulation of calcium ions in neurons, these anticonvulsants and nifedipine prevented the development of striatal damge in our patient. The possible value of this hypothesis should not be ignored. Thus, it is considered to be worth trying the administration of PHT, CBZ, PB, VPA or calcium antagonist after cyanide poisoning in order to prevent the occurrence of neurological sequelae.

Conclusion

Structural properties of the striatum, high oxygen and glucose utilization, high distribution of cytochrome oxidase and low distribution of endogeneous cyanide detoxication enzyme are considered to be the crucial factors in the genesis of the high susceptibility of the striatum to cyanide. The striatal damage and the sequelae after the acute cyanide intoxication seem to reflect the development of delayed neuronal death and/or slowly progressive neuronal damage. Administration of PHT, CBZ, PB, VPA or calcium antagonist immediately after the cyanide poisoning is suggested as worth trying for prevention of neurological sequelae.

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