METHYL BROMIDE POISONING: A REPORT BASED ON FOURTEEN CASES

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メチルブロマイド中毒症の臨床的研究

(3) 自験例 14 症例の検討

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Preface

Methyl bromide, CH₃Br, has been widely used in Japan as a fumigant in disinfestation of grains and woods because of its effective penetrating ability and absence of fire hazard. Unfortunately, it is highly toxic and poisonings readily occur following accidental or repeated exposures. The first case of methyl bromide poisoning was reported in 1899 by Schuler.¹⁾ Severe and fatal cases occurred mostly in German industries and the British Navy up to 1945. In 1946, von Oettingen²⁾ listed 28 fatalities, 150 non-fatal cases and 32 cases with skin injury alone. Today, chronic poisoning seems to be prevalent following repeated exposures to the vapour of low concentrations^{3,4)}.

This paper describes clinical features of methyl bromide poisoning, based on the present authors' study of the fourteen cases during the years 1964—1970.

Case summaries

Case 1. A 28-year-old government officer was accidentally exposed for twenty minutes to methyl bromide vapour which had leaked from a crevice of a warehouse under fumigation. He complained of nausea, headache and loss of leg control. An hour later he was admitted to a hospital, when hand tremor and mild speech disturbances were noticed, and fell asleep for four hours. Next morning he had severe headache. Hand tremor persisted for several days. He admitted to one of our hospitals

for further examinations, ten days after the onset. Red perimetry disclosed a contracted visual field. The outcome was favorable; ataxia of gait disappeared sixteen days after the exposure.

Case 2. A 28-year-old man had been employed in fumigation for four years when he began to have blurred vision, dysarthria, coolness and numbness of the leg, unsteadiness of gait and memory disturbances. Physical examinations disclosed positive Romberg's sign, sluggish knee and ankle jerks and elevated blood pressure (152/94 mmHg). Red perimetry showed contracted visual field. Six months after the admission to the hospital, ataxia of gait improved, but heaviness of the head remained persistent.

Case 3. A 32-year-old man had been employed in fumigation for four years when he had dizziness, dimness of sight and unsteadiness of gait. He returned to work with complete recovery three months after leaving the job. Four months later, he began to have heaviness of the chest, shortness of breath, headache, insomnia, memory disturbances, dysarthria, ataxic gait and numbness of the lower extremities. Physical examinations disclosed exaggerated knee and ankle jerks. White and red perimetry showed contracted visual field. The electroencephalogram showed diffuse fast wave of low amplitudes with sporadic sharp activities. He resumed normal gait six months after the admission and returned to work. Exaggerated deep reflexes did not improve. He often complained of easy fatigability.

Case 4. A 48-year-old man had been employed in fumigation for eight years when he began to have dizziness, general malaise, depression, irritability, loss of libido and unsteadiness of gait. Physical examinations revealed elevated blood pressure (180/110 mmHg), contracted visual field (red perimetry) and downward sloping audiogram. He returned to work with a subjective improvement eight months after leaving the job. After the next thirteen months, he

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began again to have ataxia of gait, paresthesia, impaired superficial and deep sensations, hand tremor and positive Romberg's sign as well as neurasthenic state. Those findings remained unchanged over a year.

Case 5. A 38-year-old fumigator experienced transient methyl bromide poisoning five times in seven years. He complained of headache, nausea, vomiting and shivering ten minutes after completing work in a fumigated warehouse. Next morning, numbness of the extremities, unsteadiness of gait, forgetfulness and irritability developed. Physical examinations revealed muscular weakness, exaggerated deep reflexes, impaired superficial sensation in the left upper extremity, incoordination of all the extremities, positive Romberg's sign, memory disturbances and skin rash. White and red perimetry showed contracted visual field. Sensory disturbances persisted for seven months after leaving the work.

Case 6. A 36-year-old man had been employed in fumigation for eight years when he showed paresthesia of the lower extremities, ataxia of gait, exaggerated deep reflexes, ankle clonus, incoordination of all the extremities and contracted visual field (red perimetry). He returned to job with subjective improvement two months after leaving work. Deep reflexes were still exaggerated.

Case 7. A 51-year-old harbor worker had an accidental exposure to methyl bromide while loading in a warehouse. An hour later, he complained of headache, nausea and vomiting. Five more hours later, he became chilly and fell asleep. Next morning, he could not stand up due to loss of leg control. Headache, anorexia and asthenopia were severe. Nephritis was suspected by a physician because of elevated blood pressure and proteinuria. On the tenth day of illness, physical examinations disclosed speech disturbance, hand tremor, positive Romberg's sign and hearing loss with a dip at 4000 Hz. White and red perimetry showed contracted visual field. Spinal tap showed a protein content of 62 mg/dl. The electroencephalogram showed a slow α rhythm; hyperventilation test induced θ waves. Dilatation of the lateral and third ventricles was noted on the pneumoencephalogram. Blood pressure was 174/100 mmHg on admission and gradually fell to the normal level (130/80 mmHg) in a month without administration of antihypertensive drugs. On physical examinations prior to the exposure, he was normotensive. Mild ataxic gait and headache were noticed a month after the onset.

Case 8. A 34-year-old man had been employed in fumigation for fourteen years when he had dizziness

and unsteadiness of gait several minutes after fumigation. Palpitation and exertional dyspnea were also noticed. Physical examinations disclosed horizontal nystagmus, incoordination of all the extremities, sluggish knee and ankle jerks, paresthesia of the lower limbs, positive Romberg's sign and high blood pressure (184/100 mmHg). He returned to work with mild ataxia of gait and normal blood pressure twenty days after the onset.

Case 9. A 54-year-old man had been employed in fumigation for four years when he had general malaise, hypesthesia of the hands and unsteadiness of gait several hours after completing work. Until this time, he had experienced the attack of transient methyl bromide poisoning more than five times. Physical examinations showed high blood pressure (188/112 mmHg), nystagmus, ataxia of gait, incoordination of all the extremities, contracted visual field (red perimetry), high pitch hearing loss and memory disturbances. The electroencephalogram was at borderline; the pneumoencephalogram showed slight dilatation of the lateral ventricles. Blood pressure was normal (150/90 mmHg) twenty days later. He returned to work with headache, dyspnea and mild ataxia of gait nine months after the onset. He was again hospitalized because of aggravation of dyspnea and died of heart failure on the thirty-third hospital day. Postmortem examination showed atrial stenosis with remarkable congestion of the lungs, liver and brain.

Case 10. A 37-year-old fumigator had headache, dizziness and paresthesia of the lower extremities an hour after the administration work of methyl bromide in a sealed warehouse. Until this time, he had been employed for three months. He returned to work with subjective improvements twenty days later.

Case 11. A 27-year-old steward lost consciousness following exposure to methyl bromide in a fumigated warehouse. A week later he was alert. Two months later, physical examination revealed loss of visual acuity, central scotoma, horizontal nystagmus, hand tremor, exaggerated knee and ankle jerks, impaired superficial sensation and paresthesia of the lower extremities. Nystagmus and sensory disturbances remained unchanged sixteen months after the onset.

Case 12. A 33-year-old man had been employed in fumigation for nine months when he began to have headache, ataxic gait, muscular weakness and atrophy. The electromyogram was abnormal with an evidence of lower motor neuron involvements. Gradual improvement was noted. He returned to work six months after the admission.

Fig. 1 Electroencephalogram showing marked photomyoclonic responses induced by photic stimulation (5 Hz) in Case 13.

Case 13. A 62-year-old chemist had been engaged for seven weeks in a manufactory of tribromosalicylanilide. During this chemical process methyl bromide gas was generated in a moderately high concentration, the value of which was afterwards determined by Prof. Y. Yamamura of Jikei college of medicine.⁵⁾ The chemist experienced temporary headache, diplopia and unsteadiness of gait. Seventeen days later, he noticed twitching of the third, fourth and fifth fingers of the right hand while at work. Generalized convulsions occurred three hours later, followed by coma and respiratory distress. He was unconscious for one week. On regaining consciousness he had intention tremor, muscular weakness and ataxic gait. Four years later, he admitted to our hospital because of emaciation and physical disability. Physical examinations showed ataxia of gait, intention tremor, incoordination of all the extremities, scanning speech, illegible handwriting, spastic paresis, pathological reflexes, mild muscular atrophy and hepatomegalia. The electroencephalogram showed fast waves with diffuse low amplitude followed by sporadic spikes and θ waves; bemegride activation test induced θ bursts with irregular

spikes and waves. Photic stimulation test induced marked photomyoclonic response (Fig. 1). In addition, the following findings were noted: central deafness with high pitch hearing loss, neurogenic EMG at the upper extremities and creatinuria. Liver function tests were all normal. Diazepam was symptomatically effective. His signs and symptoms have remained unchanged over five years. Muscle twitching of all the extremities occurs readily following strong exercises.

One of his colleagues, 23-year-old chemist, had also engaged in the same chemical process for twenty days when he experienced unsteadiness of gait and diplopia. Complete recovery was noted a few days after the admission.

Case 14. A 22-year-old fumigator was admitted to the hospital because of unsteadiness of gait and numbness of the lower extremities lasting two months. During three years before admission, he was engaged in fumigation work using methyl bromide. Seven months previously, he suffered from transient headache, dizziness, vomiting and unsteadiness of gait. Physical examination on admission revealed ataxia of gait, incoordination of the lower and left

Table 1 Symptoms of our fourteen cases

Symptom	Number of cases	%
Gait disturbance	12	86
Headache	11	79
Numbness of the extremities	9	64
Dizziness	7	50
Nausea, Vomiting	5	36
Speech disturbance	5	36
Blurred vision	3	21
Forgetfulness	3	21
Irritability	2	
Insomnia	2	
Emaciation	2	
Double vision	1	
Chills, Shivering	1	
Loss of libido	1	
Depression	1	
Anxiety	1	
Asthenopia	1	
Total	14	100

upper extremities, impaired superficial and vibratory sensations, absent ankle jerk and positive Romberg's sign. Laboratory tests disclosed mildly elevated ESR, positive CRP reaction and neurogenic EMG at the left upper and lower extremities. Ataxia of gait was gradually alleviated. Dysesthesia of the legs and absent ankle jerk remained unchanged five months after the onset.

Review of the cases

All the cases were men being comprised of ten fumigating men, a government officer, a harbor worker, a steward and a chemist. All but one became ill associated with fumigation, while the other with the manufacture of tribromsalicylanilide. Length of work of fumigating men was 3 months to 14 years with the average of 5 years. Frequency of the previous attack was from once to 14 times for each man. Mean age was 38, with a range of 26–62.

There was a latent period of several minutes to several hours before the onset of initial symptoms (Cases 1, 5, 7, 8, 9, 10 and 14). It elapsed the following several up to twenty hours until major neurological symptoms were manifested during the attack (Cases 1, 5, 7, 9, 13 and 14).

Initial symptoms were headache, dizziness, nausea and vomiting in most cases. Cardinal symptom

Table 2 Signs manifested in our fourteen cases

Sign	Number of cases	%
Ataxia of gait, Incoordination	11	79
Contracted visual field (red perimetry)	8	57
Positive Romberg's sign	6	43
Exaggerated deep reflexes	6	43
Transient hypertension	5	36
Impaired superficial sensation	5	36
Hearing loss	4	29
Nystagmus	4	29
Muscular weakness	4	29
Hand tremor	4	29
Coma	2	
Intention tremor	2	
Impaired deep sensation	2	
Sluggish deep reflexes	2	
Muscular atrophy	2	
Inability to fix	2	
Skin rash	2	
Generalized convulsion	1	
Pathological reflexes	1	
Total	14	100

was ataxia of gait. Numbness of the extremities and speech disturbance were also common (Table 1). Physical signs were multiple, *i. e.*, ataxia of gait, constriction of visual field, exaggerated tendon reflexes, positive Romberg's sign, impaired superficial sensation, transient hypertension, hearing loss, nystagmus, muscular weakness and hand tremor in the order of frequency. Coma, generalized convulsion, intention tremor, impaired deep sensation and pathological reflexes were also noticed (Table 2). Unilateral nerve signs such as anesthesia and incoordination of the extremities were noted in three cases (Cases 4, 5 and 14). Neurasthenic reactions were observed in such cases which had a history of frequent episodes of acute poisoning (Cases 2, 3, 4, 5 and 9). It is worthy of mention that transient hypertension, *i. e.* above 160 mmHg systolic or 90 mmHg diastolic, was noted in five cases (Cases 2, 4, 7, 8 and 9).

Abnormalities in electroencephalogram were found in three out of eleven cases examined, *i. e.* fast waves of diffuse low amplitude (Cases 3 and 13) and slow α pattern (Case 7), (Table 3). The pneumoencephalogram disclosed dilatation of the cerebral ventricles in two cases (Cases 7 and 9). The cerebro-spinal fluid was abnormal in only one case

Table 3 Laboratory data in our fourteen cases

Laboratory data	Number of cases
Abnormal electroencephalogram	3 (11)
Flat EEG pattern: flat with fast	2
θ -slow α -pattern	1
Abnormal pneumoencephalogram	2 (2)
Dilatation of the lateral and third ventricles	1
Dilatation of the lateral ventricles	1
Abnormal cerebrospinal fluid	1 (8)
Elevated total protein	1
Loss of visual field	9 (14)
Contracted peripheral visual field (red perimetry)	8
Contracted peripheral visual field (white perimetry)	3
Central scotoma	1
Hearing loss	4 (4)
High tone hearing loss (abrupt form)	2
High tone hearing loss (gradual form)	1
A dip at 4000 cps	1
Abnormal electromyogram	3 (3)
Neurogenic	3

Number of cases examined are shown in parentheses.

Table 4 A Clinical Classification of Methyl Bromide Poisoning
(ARAKI, S., USHIO, K. and ABE, A., 1971)

Clinical type		Latent period	Clinical manifestations	Outcome
Acute poisoning	Transient type	Several minutes to several hours	Initial symptoms: headache, dizziness, nausea and vomiting Unsteadiness of gait	Complete recovery (within one month)
	Severe type	Several hours	Coma, generalized convulsion ataxia of gait <i>etc.</i>	Sequelae are usual
	Fulminant type	Within several hours	Acute pulmonary edema	Death (within 48 hours)
Chronic poisoning		Over several months (repeated exposures)	Ataxia of gait <i>etc.</i>	Improvement (more than several months later)

among eight cases examined, *i. e.* slightly elevated proteins (Case 7). The electromyogram was neurogenic in three cases (Cases 12, 13 and 14). There were no findings suggesting renal or hepatic involvement on routine laboratory examinations. The Wasserman test of cerebro-spinal fluid was negative in all the cases. Unfortunately, blood bromide levels could not be measured.

Nine cases were hospitalized and five cases were treated on the outpatient basis. Vitamins B₁, B₆, and B₁₂, and other drugs were administered to all

the cases with little effects. None of the cases received B. A. L.

Two cases recovered completely within a month (Cases 1 and 10). All of the others were still ataxic one to three months after the onset. Four cases could not be followed up any further. Six cases resumed normal gait at sixth to eighth month after the onset (Cases 2, 3, 5, 9, 11 and 12). Two cases seemed to have permanent sequelae (Cases 4 and 13), one of which with severe cerebellar and pyramidal-tract symptoms has been followed up for five

years.

Discussion

Methyl bromide poisoning is characterized by little awareness of exposure, latent period, multiplicity of clinical manifestations and slow recovery.

As the vapour is odourless in dilute concentrations, it is possible to experience a fatal poisoning without awareness of exposure. In addition, protean neurological manifestations and the latent period might mislead into an erroneous diagnosis if the suspicion of this poisoning is not entertained, *i.e.* cerebrovascular accidents, multiple sclerosis, subacute combined degeneration of the cord, polyneuritis *etc.*

Occurrence of convulsions does not always indicate a fatal outcome; we have a doubt on the suggestion that a sudden exposure to large concentrations following continuous slight exposure does not result in pulmonary edema (Rathus and Landy, 1961),⁶⁾ which may be the result of massive exposure.

A transient acute rise in the blood pressure may be observed with all convulsant poisons (Moeschlin, 1965)⁷⁾. It is to be mentioned that all the cases with transient hypertension were neither acutely severe nor followed by convulsion in our series.

Unilateral nerve signs were also described in other reports, such as intention tremor, myoclonus, incoordination, Jacksonian convulsions, cogwheel rigidity, scotoma *etc.* (Rathus and Landy, 1961; Longley and Jones, 1965; Hine, 1969)^{6,8,9)}. Skin lesions arise through contact with the liquid or vapour. Uremia (Benatt and Courtney, 1948; Prain and Smith, 1952)^{10,11)} and jaundice (Hine, 1969)⁹⁾ have been reported.

The main clinical manifestations of methyl bromide poisoning are: ataxia of gait in mild cases as well as in chronic ones; generalized convulsion and coma in acute severe cases; acute pulmonary edema in fulminant cases. The latent period and outcome seem to be related to the quantity and the duration of exposure. Table 4 illustrates our clinical classification of methyl bromide poisoning (Araki *et al.*, 1971)⁴⁾, which may simplify complicated clinical pictures due to this poisoning.

In our series, four cases were classified into acute transient type (Cases 1, 7, 8 and 10), two cases acute severe type (Cases 11 and 13), eight cases chronic type (Cases 2, 3, 4, 5, 6, 9, 12 and 14).

自験例14症例について検討を加えた。燻蒸作業に関連して発症したものが13例で、薬品製造が1例である。臨床症状は多彩で大脳皮質、小脳、脳神経(第2, 3, 4,

Summary

A clinical analysis was made of fourteen cases of methyl bromide poisoning. Thirteen cases occurred in relation to fumigation of foodstuff or wood, the remaining one to preparation of a chemical. Transient hypertension was observed in five cases, contracted visual field in eight, and unilateral nerve signs in three. Five cases resumed normal gait six to eight months after the onset. Eight cases were included in the chronic type, four in the transient type and two in the severe type.

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6, 8 脳神経), 末梢神経, 錐体路, および後索の障害が疑われた。主症状は慢性中毒と軽症急性中毒では歩行失調, 重症型急性中毒では全身攣瘳と昏睡であった。一過

性高血圧が5例，周辺視野狭窄が8例，および片側神経障害が3例にみられた．回復は遅く，2例では半永久的な後遺症が残り，5例は歩行失調が消失するまで6～8

か月を要した．著者らの分類法に従うと，14症例中軽症型急性中毒が4例，重症型急性中毒が2例，および慢性中毒が8例であった．