Case Report

Neurological Manifestation of Methyl Bromide Intoxication†

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Methyl bromide is a highly toxic gas with poor olfactory warning properties. It is widely used as insecticidal fumigant for dry foodstuffs and can be toxic to central and peripheral nervous systems. Most neurological manifestations of methyl bromide intoxication occur from inhalation. Acute toxicity characterized by headache, dizziness, abdominal pain, nausea, vomiting and visual disturbances. Tremor, convulsion, unconsciousness and permanent brain damage may occur in severe poisoning. Chronic exposure can cause neuropathy, pyramidal and cerebellar dysfunction, as well as neuropsychiatric disturbances. The first case of methyl bromide intoxication in Thailand has been described. The patient was a 24-year-old man who worked in a warehouse of imported vegetables fumigated with methyl bromide. He presented with unstable gait, vertigo and paresthesia of both feet, for two weeks. He had a history of chronic exposure to methyl bromide for three years. His fourteen co-workers also developed the same symptoms but less in severity. Neurological examination revealed ataxic gait, decreased pain and vibratory sense on both feet, impaired cerebellar signs and hyperactive reflex in all extremities. The serum concentration of methyl bromide was 8.18 mg/dl. Electrophysilogical study was normal. Magnetic resonance imaging of the brain (MRI) revealed bilateral symmetrical lesion of abnormal hypersignal intensity on T2 and fluid-attenuation inversion recovery (FLAIR) sequences at bilateral dentate nuclei of cerebellum and periventricular area of the fourth ventricle. This incident stresses the need for improvement of worker education and safety precautions during all stages of methyl bromide fumigation.

Keywords: *Methyl bromide, Intoxication*

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Methyl Bromide (MB) is a halogenated aliphatic hydrocarbon commonly used as an insecticide in the form of gas[1]. It is generally used for dry foodstuff and as a soil fumigant in green houses and fields for the control of nematodes, fungi and weeds[2]. Route of human exposure to MB is inhalation and dermal contact[3]. Signs and symptoms of inhalation exposure depend on the concentration and duration of exposure[3,4]. Target organs of intoxication include the nervous system, respiratory system, kidney, eye and skin[5,6]. Acute MB intoxication mainly involves the central nervous system (CNS) and is often related with poor outcome such as coma and seizures[6]. Chronic intoxication includes syndrome in acute exposure plus visual and hearing disorders, axonal polyneuropathy, ataxia and psychological symptoms[6,7]. Most of the cases of MB intoxication reported in the literature are due to acute intentional and accidental poisoning during fumigation or manufacturing[5,6,8,9]. In the present report, the first case of chronic MB intoxication in Thailand has been documented. Neuroimaging study, which has been rarely reported, was also described.

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Case Report

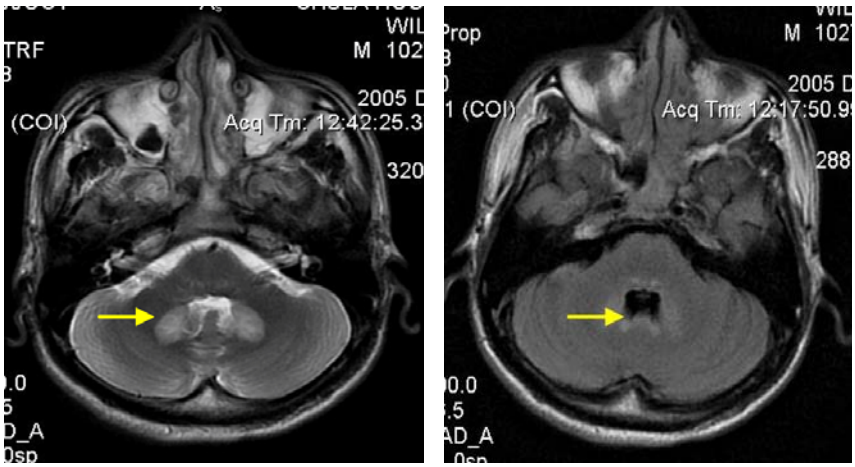
Two weeks before admission, a 24-year-old healthy man developed paresthesia of both legs,

progressive unstable gait and paroxysmal vertigo, which was not related to positional change. He had a 3-year history of working in a warehouse of imported vegetables, fumigated with MB. His 14 co-workers also developed the same symptoms but were less in severity. On admission, his vital signs and general physical examination were unremarkable. Neurological examination revealed normal mental status and cranial nerves. His motor power was normal but increased muscle tone and brisk deep tendon reflexes were noted in all extremities. Babinski's signs were plantar flexion bilaterally. Loss of pain and vibration sensation on both lower extremities and positive Romberg's test were observed. He had severe ataxic gait, impaired tandem walk as well as bilateral impaired finger to nose and heel to knee tests. Laboratory tests included complete blood count, serum electrolytes, plasma glucose, BUN/Cr and liver function tests were within normal limits. Sensory nerve conduction studies (NCS) including right median, ulnar, radial nerve and bilateral sural responses were unremarkable. Normal motor NCS on deep peroneal, tibial, median and ulnar nerves were observed on both sides. Segmental stimulation performed up to the Erb's point on both sides and F-wave latencies obtained on all of these motor nerves revealed no abnormalities. Normal H-reflexes to gastrocnemiussoleus muscles were documented on both sides. Needle electromyography of the selected proximal and distal muscles of the three limbs revealed no evidence of denervation or myopathic pattern. Magnetic resonance imaging (MRI) of the brain revealed normal T1 weighted image (T1WI). Bilateral symmetrical high signal intensity on T2 weighted image (T2WI) and fluid-attenuation inversion recovery (FLAIR) sequences were observed at bilateral arcuate-dentate nuclei of the cerebellum, periventricular area of the fourth ventricle (Fig. 1), inferior olivary nuclei, periaqueductal gray, superior and inferior colliculi. There was no detectable abnormality on diffusion weighted image (DWI) study. Post-gadolinium study depicted no enhanced lesions. MRI of the spinal cord was normal. Cerebrospinal fluid study revealed no abnormal profiles. Serum bromide level of 8.18 mg/dl was obtained (normal < 0.5 mg/dl). Toxic and nutritional causes of the neurological syndrome were ruled out by tests for serum lead, arsenic, folate and vitamin B12.

Termination of gas exposure, resulted in gradual improvement in ataxia, impaired finger to nose, heel to knee and Romberg's tests. After 3 months, only mild gait imbalance on tandem walking, paresthesia of lower extremities, reduced propioceptive pain, and touch sensation in the feet were detected.

Discussion

MB is a colorless and odorless volatile liquid with a boiling point of 3.6°C[1]. It is easily toxic because of poor olfactory warning properties[3]. Symptoms of acute mild MB poisoning are often non-specific and include headache, dizziness, abdominal pain, nausea, vomiting, visual disturbances and ataxia[10]. Tremor,



A B

Fig. 1 MRI of the brain: revealed bilateral symmetrical lesion of abnormal signal intensity on T2 (arrow) at dentate nuclei (A) and abnormal fluid-attenuation inversion recovery (FLAIR) sequences (arrow) at periventricular area of the fourth ventricle (B)

convulsion, unconsciousness and permanent brain damage are observed in severe poisoning[4,10]. The severity of intoxication depends on the dose and duration of exposure[4]. Chronic intoxication of low level MB exposure causes progressive neurological dysfunction, which may be difficult to diagnose[11,12]. The main symptoms include visual and hearing disturbances, axonal polyneuropathy, incoordination, ataxia[7] and psychological symptoms including loss of initiative, depressed libido, personality changes and hallucinations[13]. Symptoms generally disappear after the exposure is terminated, but numbness of the extremities and visual disturbances may persist for 2-5 months or more[7,8]. Measurable levels of the parent agent in the blood are rapidly reduced, probably as a result of direct tissue chemical reaction[8,10]. Therefore, it is often difficult to diagnose this condition without obtaining an occupational history of exposure, especially in chronic cases. Serum bromide level is also poorly correlated with toxic effects and asymptomatic high level is possible[11,12]. The clinical syndrome of the presented patient was compatible with chronic MB toxicity. History of exposure and high serum bromide level of 8.18 mg/dl (normal < 0.5) confirmed the diagnosis. After a complete electrophysiologic investigation, evidence of peripheral neuropathy had not been demonstrated. The neurological syndrome in this patient related to CNS intoxication has been demonstrated by MRI.

MRI findings of MB intoxication have been recently reported[14-16]. Rhinshu S. demonstrated symmetric T2 signal abnormalities in posterior putamen, subthalamic nuclei, restiform bodies, vestibular nuclei, inferior colliculi, and periaqueductal gray[14]. Howard L. reported symmetric brainstem and cerebellar MRI lesions at inferior colliculi, periaqueductal gray, dentate nuclei, dorsal pons, and inferior olives[15]. Kang K also depicted involvement of corpus collosum[16]. MRI in the presented patient revealed symmetric involvement of bilateral arcuate-dentate nuclei of cerebellum and periventricular area of the fourth ventricle, inferior olivary nuclei, periaqueductal gray, superior and inferior colliculi. Pathological abnormalities in an autopsy study following lethal MB intoxication included bilateral symmetrical hemorrhagic damages and peticheal hemorrhage of mamillary bodies, inferior colliculi and cerebellar dentate nuclei[17,18]. Nonlethal intoxication with the syndrome of ataxia and paralysis have been observed in laboratory animals and tissue degeneration included nasal tissue, adrenal glands and brains[19]. Changes in brain catecholamines and tyrosine hydroxylase activity were also documented in these animal models[19].

The pathology in the CNS after MB intoxication has some features resembling Wernicke's encephalopathology and Leigh's disease[15]. The exact mechanism of MB induced CNS toxicity is unclear and is proposed to be related to the disruption of enzymes involved in metabolic pathways responsible for the generation of energy[15,20,21]. MB intoxication should be classified as one of the energy deprivation syndrome (EDSs). EDSs are disorders with diverse etiologies i.e. toxic, genetic and nutritional. EDSs share a characteristic anatomic distribution of abnormalities with preferential damage to periventricular, cerebellar and brainstem areas[22].These areas appear to be selectively vulnerable to metabolic-energy derailment[22]. Well known nutritional and genetic EDSs are Wernicke's encephalopathy and Leigh's disease respectively[23]. These two disorders produce a similar distribution of brain abnormalities. In Wernicke's encephalopathy, a deficiency of thiamine which is a necessary cofactor in glycolysis, the lesions are commonly located at periventricular areas of thalamus, hypothalamus, brainstem, mammillary bodies, periaqueductal grey and cerebellar cortex[23]. In Leigh's disease, a mitochondrial disorder, neuropathological findings are similar to those of Wernicke's encephalopathy, except the sparing of mammillary bodies[24]. In the literature, there are two reported cases of MB intoxication with Wernicke-like brain MRI[24,25]. In Wernicke's encephalopathy prominent involvement of the inferior colliculi and periaqueductal area are usually detected in DWI[26,27]. However, MRI in MB intoxication revealed no abnormality in DWI at these areas and this pattern can be used to differentiate the two conditions[26,27]. In the last ten years, cases of acute and chronic MB intoxication have been reported and are summarized in Table 1.

Conclusion

A patient with MB intoxication who presented with signs and symptoms of cerebellar and brainstem abnormalities has been described. MRI of the brain showed bilateral symmetrical lesions of abnormal signal intensity on T2WI and FLAIR sequence at bilateral dentate nuclei of the cerebellum and periventricular area of the fourth ventricle. The patient gradually improved after termination of the exposure. Awareness of this syndrome and occupational history of MB exposure is necessary for the correct diagnosis. The MRI findings are characteristic for MB intoxication but must be differentiated from Wernicke's encephalopathy. The

Table 1. Case reports of acute and chronic MB intoxication in last ten years

Patient no. (Ref)	Sex/Age (yr)	Duration/ Route	Symptoms and signs	Serum bromide level (microgram/ml)	Neuroimaging
1 (3)	M/32	A/D	Dermal burns,vesicles, weakness-brisk deep tendon reflex, paresthesia lower extrimities, Babinski signs, ataxia	12	-
2 (4)	-	A/I	Seizure, fever, multiorgan failure, dead	270	-
3 (5)	F/12		Ataxia, severe action myoclonus, dysarthria	113.0	-
4 (8)	M/39	A/I	Dizziness, vomiting, myoclonus, akinetic mutism	72.9	-
5 (8)	F/34	A/I	Dizziness, vomiting, myoclonus, akinetic mutism, derilium, convulsion, behavioral changes	67.8	-
6 (8)	F/5	A/I	Dizziness, vomiting, myoclonus, convulsion	91.5	CT - enlarged sulci, cerebral atrophy
7 (14)	M/30	A/I	Paresthesia feet, unstable gait, blephaloptosis	43.7	MRI - high SI at putamen, subthalamic nuclei, dorsal medulla oblongata, inferior colliculi, periaqueductal gray
8 (15)	M/30	C/I	Ataxia, acral paresthesias, vertigo, horizontal diplopia, pain-vibratory sense loss, absent ankle reflexes	29	MRI - high SI on T2 and FLAIR in dentate nuclei, periaqueductal grey, dorsal midbrain, pons, inferior olives
9 (16)	M/31	C/I	Dizziness, vomiting, walking difficulty, urinary incontinence, paresthesia extremitie simpaired comprehension of language	-	MRI - high SI on T2 at splenium of corpus callosum
10 (16)	M/32	C/I	Dizziness, vomiting, headache, dysarthria, confusion, seizure	-	MRI - bilateral symmetric high SI on T2 in splenium of corpus callusum, globus pallidus, periaqueductal grey, pontine tegmentum, dentate nuclei, medulla oblongata
11 (28)	M/45	C/I	Visual disturbance, dysarthria, decreased muscle strength, gait disturbance, erectile dysfunction	11.2	-
12 (present case)	M/24	C/I	Vertigo, cerebellar ataxia, paresthesia, spasticity all extrimities	8.18	MRI - High SI T2wI FLAIR bilateral arcuate-dentate nuclei, periventricular of 4th ventricle, inferior olivary nuclei, periaquiductal gray, superior-inferior colliculi

A = acute, C = chronic, I = inhalation, D = dermal exposure, M = male, F = female, Ref = reference

presented case emphasizes the need for the improvement of worker education and safety precautions during all stages of MB fumigation.

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อาการแสดงทางระบบประสาทของการเกิดพิษจากสารเมททิลโบรไมด์: รายงานผู้ป่วย

กนกรัตน์ สุวรรณละออง, กัมมันต์ พันธุมจินดา

เมททิลโบรไมเป็นแก๊สซึ่งมีความเป็นพิษสูง มีคุณสมบัติการเตือนด้านกลิ่นที่ไม่ดี เมททิลโบรไมด์ เป็นสารที่ใช้อย่างแพร่หลายในการอบฆ่าแมลงและอบแห้งอาหาร และสามารถทำให้เกิดพิษได้ทั้งต่อระบบประสาทส่วนกลางและระบบประสาทส่วนปลาย อาการแสดงของการเกิดพิษต่อระบบประสาทส่วนใหญ่เกิดจากการสูดดมพิษเฉียบพลัน ได้แก่อาการปวดศีรษะ เวียนศีรษะ ปวดท้อง คลื่นไส้ อาเจียน และความผิดปกติด้านการมองเห็น อาการสั่น ชัก ไม่รู้สึกตัว และสมองถูกทำลายอย่างถาวรเกิดได้ในกรณีที่เกิดอาการเป็นพิษอย่างรุนแรง การได้รับสารพิษอย่างเรื้อรังสามารถทำให้เกิดอาการผิดปกติของปลายประสาท การเคลื่อนไหว การทรงตัว รวมถึงอาการทางจิตประสาท รายงานผู้ป่วยที่เกิดพิษจากเมททิลโบรไมด์รายแรกในประเทศไทย เป็นผู้ป่วยชายอายุ 24 ปีทำงานในโรงงานอบผักเพื่อส่งออกต่างประเทศ มาด้วยอาการเดินเซ เวียนศีรษะ และชาเท้า 2 ข้าง 2 สัปดาห์ก่อนมาโรงพยาบาล ผู้ป่วยมีประวัติสัมผัสกับสารเมททิลโบรไมด์เป็นเวลา 3 ปี เพื่อนร่วมงานของผู้ป่วยจำนวน 14 คน มีอาการคล้ายกับผู้ป่วย แต่ความรุนแรงน้อยกว่า การตรวจทางระบบประสาทพบ เดินเซ ความรู้สึกเจ็บ และสั่นสะเทือนของเท้า 2 ข้างลดลง การทรงตัวผิดปกติ และรีเฟร็กไวทุกระยางค์ ระดับเมททิลโบรไมด์ ในเลือด วัดได้ 8.18 มก./ดล. การตรวจเส้นประสาทและกล้ามเนื้อ ด้วยไฟฟ้าไม่พบความผิดปกติ ภาพคลื่นแม่เหล็กไฟฟ้าสมอง (เอมอาร์ไอ) พบรอยโรคที่มีความเข้มมากขึ้นในภาพที 2 และแฟลร์ทั้งสองข้าง และสมมาตรกันในบริเวณ เดนเตตนิวคลีไอของซีลีเบลลัม และบริเวณรอบเวนทริเคิล รายงานนี้กระตุ้นให้เห็นความสำคัญในการให้ความรู้แก่คนงาน และการป้องกันอันตรายที่จะเกิดขึ้นในทุกขั้นตอนของ การใช้เมททิลโบรไมด์เป็นสารอบฆ่าแมลง