—Case Reports—

A Case of Fever, Impaired Consciousness, and Psychosis Caused by Nitrous Oxide Abuse and Misdiagnosed as Acute Meningitis

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Nitrous oxide (N_2O) is readily available, and its abuse for recreational purposes has become a social problem. In Japan, where N_2O is strictly prohibited for non-medical use, abuse is often overlooked due to a lack of experience in the field. N_2O abuse causes various long-term symptoms, including vitamin B_{12} deficiency, myelopathy, myeloneuropathy, subacute combined degeneration, mood changes, and psychosis. The diagnosis of N_2O abuse is difficult due to the compound's short half-life and rapid elimination through the lungs. This report describes a case of fever and impaired consciousness in a patient with a history of N_2O abuse. (J Nippon Med Sch 2023; 90: 404–407)

Key words: substance use disorder, N_2O, impaired consciousness

Introduction

Nitrous oxide (N_2O), commonly known as laughing gas, is broadly used as an anxiolytic and local anesthetic agent. It produces a state of analgesia, depersonalization, derealization, dizziness, euphoria, and auditory distortions. N_2O abuse among dentists was reported as early as the late 1970s[1].

The earliest report of N_2O abuse was published in 1961[2]. The 2016 Global Drug Survey indicated that N_2O abuse was rapidly spreading worldwide, and N_2O was the seventh-most popular recreational drug[3]. The total prevalence of lifetime N_2O use was 4.7% (ages 12-17: 0.6%; 18-25: 4.4%; ages ≥26: 5.3%) in the USA[2], where N_2O is among the top five most-common inhalants abused by adolescents[4]. N_2O abuse symptoms include vitamin B_{12} deficiency, myelopathy, myeloneuropathy, subacute combined degeneration, mood change, and psychosis[2,5,6].

In Japan, the prevalence of N_2O abuse is extremely low under strict drug regulations beginning in 2016. Thus, it is likely to be underdiagnosed because physicians have little experience diagnosing and treating such cases. We describe the case of a 36-year-old Japanese male who presented with impaired consciousness and fever. Although his symptoms mimicked meningitis, they were eventually attributed to chronic N_2O abuse.

Case Report

A 36-year-old Japanese male with no significant medical history (including mental illness, depressive state, or schizophrenia), medications, or allergies presented to the emergency department with fever and disorientation. He did not have a smoking history and mostly consumed beer (1.0-1.5 L/week). There was no family history of mental disorders. He had taken an engineering job in Vietnam the year before. A month later, he started inhaling N_2O due to stress. The quantity and frequency of use were unknown. He was dismissed from his job and returned to Japan 3 days before admission, which corresponded with his last administration of N_2O. By that time, he had also started experiencing hallucinations, such as hearing voices, perceiving electricity falling from the ceiling, and believing his thoughts were being read by other people.

Upon admission, he presented with fever, disorientation, dyspnea, muscle weakness, and numbness in both upper and lower extremities. On examination, he scored 2 points on the Japanese Coma Scale and E4V4M6 on the

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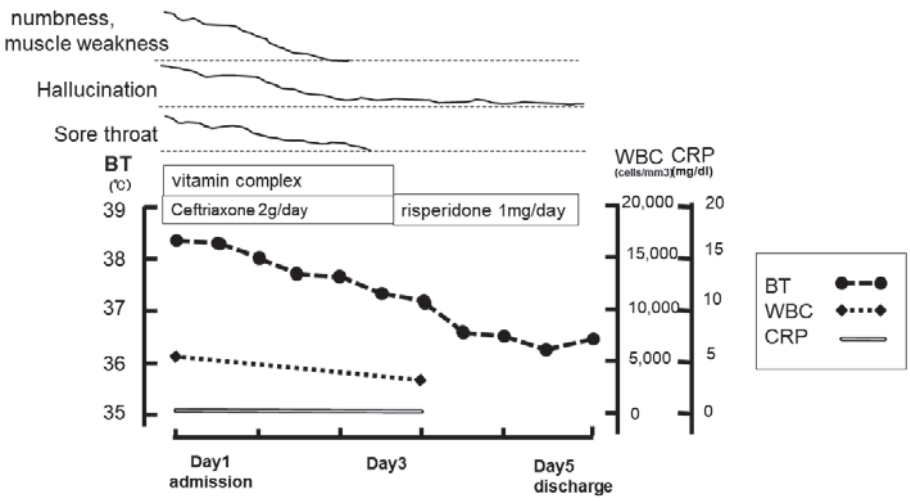

Fig. 1 BT: body temperature (°C) WBC: white blood cell count (cells/mm^3) CRP: C-reactive protein (mg/dL)

Glasgow Coma Scale. His respiratory rate was 34 breaths/min, blood pressure was 131/81 mmHg, heart rate was 90 bpm, SpO_2 was 96%, and body temperature was 38.7°C. Physical examination revealed no palpable neck lymphatic nodes; however, he had a sore throat with lymphoid follicles and no tonsillar enlargement. His chest and abdominal examinations were unremarkable. Neurological examination revealed intact cranial nerve function, intact motor strength, intact tendon reflex, no neck stiffness, and a positive Kernig's sign.

Complete blood count revealed a white blood cell count of 5,100 cells/mm^3, hemoglobin level of 14.7 g/dL, and platelet count of 238×10^9/L. The mean corpuscular volume was 90.3 fL. Blood chemistry revealed no abnormal findings except for C-reactive protein (CRP) levels of 0.40 mg/dL. Infectious disease screenings for HIV, hepatitis B, hepatitis C, and syphilis were all negative. Cerebrospinal fluid examination showed 2 cells/μL, total protein level of 39 mg/dL, and glucose level of 80 mg/dL. Thoracic radiography, computed tomography of the neck, chest, abdomen, and pelvic regions, as well as cranial magnetic resonance imaging findings, were unremarkable.

His initial diagnosis was meningitis based on observations of high fever and impaired consciousness. The lumbar puncture result was negative for meningitis. As the patient had returned from Vietnam, imported infectious diseases, especially those caused by *Salmonella typhi*, were suspected. The patient was hospitalized with the presumptive diagnosis of *S. typhi* and treated with ceftriaxone 2 g q24. He was intravenously administered a vitamin complex, which included vitamin B_{12} dose of 1,000 μg. The clinical course is presented in **Figure 1**.

The following day, his body temperature was <38°C but upper respiratory symptoms, such as sore throat and dyspnea, persisted. Given his negative blood cultures, slightly elevated white blood cell count, negative procalcitonin, and slightly elevated CRP, he was diagnosed with an upper respiratory infection, and ceftriaxone administration was stopped on day 3.

On day 3 of hospitalization, the numbness and muscle weakness completely subsided, and his hallucinations were abated. The presumptive psychiatric diagnosis was acute and transient psychotic disorder (brief psychotic disorder), or delirium. The patient was treated with risperidone (1 mg/day), and his hallucinations continued to abate. The patient was discharged on day 5 and returned home, continuing treatment at a local psychiatric hospital. Six months after discharge, a final diagnosis of N_2O-related psychosis with an upper respiratory infection was made, and risperidone was subsequently discontinued.

Discussion

N_2O can cause vitamin B_{12} deficiency because it inactivates vitamin B_{12} through the oxidation of its cobalt core[3,6,7]. This impairs fatty acid synthesis and causes subacute combined degeneration of the spinal cord[8]. The precise pathophysiology of psychiatric abnormalities related to N_2O users remains unclear. Psychiatric symptoms may occur with or without neurological and hematological symptoms[2,7,9].

Garakani et al.[2] reported that the amount of N_2O inhalation to onset was undetermined because the amount of

inhalation and the duration varied. However, most previous reports did not provide this information[2]. The common neurologic sequelae of N_2O abuse are numbness, paresthesia, and weakness, and the common diagnoses are myeloneuropathy, subacute combined degeneration, peripheral neuropathy or polyneuropathy, and myelopathy[2]. The common psychiatric sequelae of N_2O abuse are delusion and delirium, but the symptoms may vary from depression, confusion, and paranoia to bizarre behavior[2,4]. In the current case, since the psychiatric symptom was transient hallucinatory behavior after N_2O abuse, we considered this to be psychosis due to N_2O abuse.

Moreover, in the aforementioned study by Garakani et al.[2], the laboratory test results varied in each case. The vitamin B12 level was low to high, while the mean corpuscular volume, as well as the homocysteine and methylmalonic acid levels, were normal to elevated. Nerve conduction studies were positive (or partially positive) in 87.5% of cases. Neuroimaging results were positive in 78% of cases[2].

There is no standard treatment for N_2O-induced psychosis, but the termination of N_2O inhalation and short-term supplementation with cobalamin (typically 1,000 μg/day for 1 week) can exert therapeutic effects[9]. In patients with psychiatric problems, antipsychotics may also be used. Treatment results are mostly favorable, and patients are usually free from psychiatric symptoms following treatment[9].

The diagnosis of N_2O abuse is challenging because of its wide-ranging symptoms[2,9] and difficulty in determining the amount of N_2O inhaled. Patients are usually dishonest concerning the substance use, potentially leading to delayed or missed diagnoses. The presence of N_2O is also difficult to screen because of its short half-life and rapid elimination[2]. As there is no formal screening for N_2O, it is rarely considered a possible cause in the emergency department or other settings[2].

Potential complications of N_2O abuse are relatively rare, but awareness is critical and may contribute to differential diagnosis when young patients develop unusual and otherwise unexplained symptoms[10]. General physicians in Japan may encounter patients with histories of N_2O abuse who present with fever and unexplained symptoms, such as impaired consciousness, shortness of breath, muscle weakness, and numbness in the extremities. Practitioners of Japanese general medicine should understand that N_2O abuse may have various consequences, including psychiatric adverse effects.

There are several limitations to this report. First, the patient regularly consumed alcohol, and there was a possibility he was experiencing alcohol withdrawal symptoms. We could not differentiate the diagnosis between alcohol withdrawal and N_2O-induced psychosis. Second, we did not measure vitamin B12, homocysteine, or methylmalonic acid levels owing to the premature closure. Since the fever and hallucination improved quickly, we did not suspect the effects of N_2O abuse.

Informed consent was obtained from the patient orally.

Conclusions

General practitioners should consider the possibility of N_2O abuse whenever they observe inexplicable neurological, psychiatric, or hematological symptoms.

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