Spectrum of nitrous oxide intoxication related neurological disorders in Korea: a case series and literature review

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Background: Nitrous oxide (N2O) is used in surgery and dentistry for its anesthetic and analgesic effects. However, neurological and psychiatric manifestations of N2O abuse have been increasingly reported among Korean adults. The aim of this study was to demonstrate laboratory findings of N2O abuse in Korean patients.

Methods: Patients diagnosed with N2O-induced neuropathy or myelopathy from August 2018 to December 2019 were enrolled. Their clinical presentations and laboratory and imaging findings were analyzed.

Results: Sensory changes and limb weakness were present in nine of the enrolled patients. The laboratory findings revealed that seven patients had high homocysteine levels and five had high methylmalonic acid levels in their blood. Nerve conductions studies indicated that axonal neuropathy was present in four cases and longer F-wave and Hoffman’s-reflex latencies were present in two cases. Signal changes in cervical spine imaging occurred in five patients, while two had normal results.

Conclusions: Chronic N2O abuse can cause neurological damage or psychiatric problems. Because N2O is illegal for recreational use in Korea, patients tend to hide their history of use. Even though the spinal imaging results were normal, clinicians should consider the possibility of N2O use, and further electrophysiological tests should be applied for precise evaluations.

key words: Nitrous oxide; Neuropathy; Spinal cord; Subacute combined degeneration; Homocysteine
INTRODUCTION

Nitrous oxide (N₂O) is a colorless and nonflammable gas that is used in surgery and dentistry due to its anesthetic effects. N₂O has recently been misused for recreational purposes due to its euphoric effects when inhaled. The recreational use of N₂O is currently prohibited in Korea due to its negative clinical effects, such as inducing vitamin B₁₂ deficiency or mechanisms that lead to thrombosis. However, N₂O is still available in whipped-cream canisters or small bulbs that are predominantly used for recreation by young people. Reported cases of neurological and psychiatric manifestations of N₂O abuse have recently increased among adults in Korea.

The neurological complications associated with N₂O abuse usually manifest as subacute combined degeneration (SCD) of the spinal cord. N₂O deactivates the enzyme methionine synthase by inactivating methylcobalamin and impairing the methylation of myelin sheath proteins, leading to spinal cord degeneration and myelopathy. These processes can also cause peripheral nervous polyneuropathies. Several clinicians in Korea have reported various clinical symptoms and abnormal findings in tests after N₂O inhalation, such as in electrophysiological examinations and magnetic resonance imaging (MRI). Additionally, vitamin B₁₂ deficiency tends to the induction of hyperhomocysteinemia, which in turn induces thrombosis. There are numerous previously reported cases of hyperhomocysteinemia inducing deep vein thrombosis or pulmonary thromboembolism (PTE).

The use of illegal drugs such as cocaine, heroin, methamphetamine, and cannabis is reportedly lower in Korean than in other countries. Illegal drug usage is therefore considered by Korean clinicians less when they are determining symptom etiology. Since it is rare for patients to report their N₂O use, diagnosing patients with atypical clinical manifestations is also difficult. A good understanding of the clinical manifestations of N₂O usage is therefore important. Here we report nine patients with neurological manifestations and abnormal laboratory findings following N₂O abuse.

MATERIALS AND METHODS

Patient sample and clinical measurements

We retrospectively analyzed clinical data from nine patients diagnosed with N₂O-induced neuropathy or myelopathy. This hospital-based case-series study investigated patients who presented at the Hanyang University Hospital (a tertiary referral medical center) in Seoul, Korea from August 2018 to December 2019. All patients underwent routine laboratory tests including a complete blood count, coagulation test, electrolyte test, and routine urine analysis. Considering the effects of N₂O on vitamin B₁₂ metabolism, serum methylmalonic acid (MMA), homocysteine, and vitamin B₁₂ levels were also examined. Electrophysiological tests such as a nerve conduction study (NCS) or electromyography were applied to eight patients. Spinal cord MRI, computed tomography (CT) scan with contrast enhancement, and chest CT angiography had been performed on seven, one, and one patient, respectively. Neurological examinations were performed, with the motor power of all four limbs measured according to the Medical Research Council grading system. Ethical approval was obtained for this study from the Institutional Review Board of the Hanyang University Hospital (IRB No. 2020-03-008).

Electrophysiological examinations

Standard motor and antidromic sensory NCSs were performed bilaterally on four motor nerves (median, ulnar, posterior tibial, and fibular) and three sensory nerves (median, ulnar, and sural) of eight patients. This analysis evaluated the terminal latency, compound muscle action potential amplitude (CMAP), and conduction velocity of each nerve. We defined abnormal results as changes of at least 20% from the lower conduction velocity and CMAP limits, and from the upper terminal latency limit. Demyelinating NCS patterns were defined according to the guidelines from the American Association of Neuromuscular and Electrodiagnostic Medicine. F-wave latency was measured after supramaximal motor nerve stimulation, which identified ten F-waves. Hoffman’s reflex (H-reflex) was recorded from the soleus when stimulating the tibial nerve.

Literature review

Literature searches were performed of the MEDLINE and PubMed databases using the search terms “neuropathy N₂O” and/or “myelopathy N₂O” and including case reports published between 2006 and 2019 in South Korea. The reference lists of these reports were considered secondary.
### Table 1. Clinical features and laboratory findings of nine patients with neurological effects from (N₂O) intoxication

| Pt no. | Age (years) | Sex | Duration$^a$ | Initial symptoms | Neurological examination | Laboratory data | Spinal cord MRI | Other findings |
|--------|-------------|-----|--------------|-------------------|--------------------------|----------------|----------------|----------------|
| 1      | 28          | M   | 3 weeks      | Weakness in both limbs, Paresthesia in both legs (proximal→distal) | Quadriplegia (grade IV), Hypoesthesia below C5, Tandem gait (-), Romberg’s sign (+) | Hb 12.2$^b$, MCV 100.3$^b$, D-dimer 1.83$^b$, aPTT 31 | Vit B₁₂ 382.2, HCY 56.7$^b$, MMA 12.27$^b$ | T2-weighted hypointensity at the posterior column (C2-C5) | Pulmonary artery thromboembolism on chest CT |
| 2      | 27          | F   | 3 weeks      | Gait disturbance, Acroparesthesia, Dyspepsia | Decreased dorsiflexion (grade IV), Stocking-glove hypoesthesia, Tandem gait (-), Romberg’s sign (+) | Hb 13.2, MCV 103.2$^b$, D-dimer 0.09, aPTT 38 | Vit B₁₂ 267.7, HCY 45.4$^b$, MMA 9.44$^b$ | T2-weighted hypointensity at the posterior column (upper cervical cord) |
| 3      | 24          | M   | 16 weeks     | Weakness in both leg, Numbness in both legs | Decreased dorsiflexion (grade IV), Hypoesthesia in both legs, Tandem gait (-), Romberg’s sign (+) | Hb 14.7 MCV 97.5, D-dimer 0.20, aPTT 33 | Vit B₁₂ > 2,000, HCY 10.7$^b$, MMA 1.00 | Not checked |
| 4      | 23          | F   | 4 weeks      | Weakness in both limbs (distal→proximal), Acroparesthesia | Decreased dorsiflexion (grade III), Quadriplegia (grade IV), Stocking-glove hypoesthesia, Hypoactive DTR, Decreased anal tone, Tandem gait (-), Romberg’s sign (+) | Hb 11.5$^d$, MCV 106.1$^b$, D-dimer 0.52$^b$, aPTT 27 | Vit B₁₂ > 2,000, HCY 25.0, MMA 2.63 | T2-weighted hypointensity at the posterior column (C2-C6) |
| 5      | 28          | M   | 2 weeks      | Weakness in both ankles, Acroparesthesia | Decreased dorsiflexion (grade IV), Stocking-glove hypoesthesia, Hypoactive DTR, Decreased anal tone, Tandem gait (-), Romberg’s sign (+) | Hb 16.9, MCV 100.6$^b$, D-dimer not checked, aPTT 36 | Vit B₁₂ 201.6, HCY 45.6$^b$, MMA not checked | No signal change |
| 6      | 24          | M   | Unknown      | Weakness in both legs (distal→proximal), Paresthesia in both legs | Quadriplegia (proximal, grade IV; distal, grade II), Stocking-glove hypoesthesia, Areflexia, Tandem gait (-), Romberg’s sign (+) | Hb 16.9, MCV 100.6$^b$, D-dimer not checked, aPTT 37 | Vit B₁₂ 414.5, HCY 45.5$^b$, MMA 5.86$^b$ | Not checked |
| 7      | 26          | F   | 2 weeks      | Numbness in both legs (distal→proximal) | Vibration loss in both legs, Hypoactive DTR, Tandem gait (-), Romberg’s sign (+) | Hb 11.3$^b$, MCV 102.5$^b$, aPTT 27, D-dimer 0.14 | Vit B₁₂ 162.1$^b$, HCY 49.1$^b$, MMA 4.87$^b$ | No signal change |
Table 1. Continued

| Pt no. | Age (years) | Sex | Durationa | Initial symptoms | Neurological examination | Laboratory data | Spinal cord MRI | Other findings |
|--------|-------------|-----|-----------|------------------|--------------------------|-----------------|-----------------|---------------|
| 8      | 22          | F   | 12 weeks  | Acroparesthesia  | Stocking-glove hypesthesia | Hb 13.5 MCV 101.6b | Vit Bl2 1,456 | T2-weighted hyperintensity at the posterior column (C2 and C3) |
|        |             |     |           | Tandem gait (-), Rombberg’s sign (+) | D-dimer 0.08 aPTT 33 | HCY 11.2 | MMA 3.32 | |
| 9      | 35          | F   | 12 weeks  | Weakness in both legs | Paraparesis | Hb 11 MCV 1071 | Vit Bl2 2221 | T2-weighted hyperintensity at posterior, anterior, and lateral column (C7 to conus medullaris) |
|        |             |     |           | Paresthesia in both legs | Vibration loss in both legs | D-dimer 1.1 aPTT 31 | HCY 76.4 | MMA not checked | |
|        |             |     |           | | Hyperactive DTR, Babinski sign (+) | | | Chest CT angiography showed no specific lesions | |

Pt, patient; MRI, magnetic resonance imaging; M, male; Hb, hemoglobin (normal range = 12-18 g/dL); MCV, mean corpuscular volume (normal range = 80-99 fl); D-dimer (normal range = 0-0.24 mg/L); aPTT, activated partial thromboplastin time (normal range = 25-39 seconds); Vit Bl2, vitamin Bl2 (normal range = 197-771 pg/mL); HCY, homocysteine (normal range = 0-15 μmol/L); MMA, methylmalonic acid (normal range = 0.01-3.76 mg/g); CT, computed tomography; F, female; DTR, deep tendon reflex.

aInterval between time of last N2O inhalation and symptom onset as reported by the patient; bAbnormal laboratory findings.

sources. Cases without postmortem analyses or NCS results were excluded.

RESULTS

Nine patients aged between 23 and 35 years visited our hospital from August 2017 to December 2019 (Table 1). All patients had a history of N2O inhalation during the 6 months prior to admission. The interval between the last N2O inhalation and symptom onset varied from 2 weeks to 4 months, while the interval between symptom onset and hospital visit varied from 3 days to 1 month, with the majority of patients visiting 1 week after symptom onset. Five patients were female. Sensory change was the initial symptom of all patients. These sensory symptoms varied between patients and included an ascending tingling sensation in both legs (patient no. 1), numbness in both legs (patient no. 3 and 7), and acroparesthesia (patient no. 2, 4, 5, 8, and 9). Five patients experienced muscle weakness, three of which only had lower limb weakness (patient no. 3, 6, and 9), and two had both upper and lower limb weakness (patient no. 1 and 4). Muscle weakness only in the ankles was found in patient no. 5. One patient had dyspepsia. None of the patients were vegetarians or had previously received gastrointestinal surgery.

Neurological examinations indicated that seven of the nine patients had limb paresis. Three had mild weakness in ankle dorsiflexion and the other four had quadripareisia. Sensory changes were detected in patient no. 1, while patient no. 7 and 9 had a loss of vibration sensation in both legs. Among the other patients, six had stocking-glove hypesthesia (patient no. 2, 4, 5, 6, 8, and 9). Hypoactivity of the deep tendon reflex (DTR) occurred in four cases (patient no. 4, 5, 6, and 7), four had normoactive DTR, and one had hyperactive DTR (patient no. 9). Patient no. 2 had dysmetria of the upper limbs and all patients except no. 5 showed abnormal results in the Romberg test. All patients had an impaired tandem gait. Digital rectal examinations indicated that patient no. 4 had decreased anal tone.

Laboratory findings revealed low hemoglobin levels and large mean corpuscular volumes in four and six patients, respectively. Only one patient had a low serum vitamin Bl2 level (patient no. 7). Elevated serum homocysteine levels were indicated in seven cases (patient no. 1, 2, 3, 5, 6, 7, and 9), and five patients had high blood MMA levels.

NCSs were performed on eight patients (Table 2). Among them, four had axonal neuropathies (patient nos. 3, 4, 5, and 6) and one had longer F-wave and H-reflex latencies in both lower limbs (patient no. 7). Seven patients had a decreased sural nerve conduction velocity or longer H-reflex latency.
Most patients had more abnormalities in the lower limbs than in the upper limbs, distal limb regions were affected more than were proximal regions, and sensory nerves were involved more frequently than were motor nerves. Demyelination was not observed in any patient. The reference values and raw data of patients’ nerve conduction study are shown respectively on Supplementary Table 1, 2.

Seven patients received spinal MRI, five of whom had signal changes in the dorsal column of the cervical spine, as indicated in T2-weighted images (Fig. 1). Patient no. 9 had concurrent hyperintensity lesions in the anterior, lateral, and posterior spinal column (Fig. 2). Two patients (patient no. 5 and 7) showed normal results in spinal MRI.

All patients received hydroxocobalamin as a vitamin B12 supplement. Three patients received additional steroid therapy. Intravenous immunoglobulin G was administered to one patient (patient no. 5) due to their observed clinical features being similar to those associated with early Guilliain-Barre syndrome. Patient no. 1 suffered from N2O addiction and depression, so they received psychiatric consulting.

A literature search identified five articles describing SCD attributed to recreational N2O abuse, including three male

Table 2. Abnormal findings in NCSs of nine patients

| Pt no. | Median nerve (motor) | Median nerve (sensory) | Ulnar nerve (motor) | Ulnar nerve (sensory) | Posterior tibial nerve (motor) | Fibular nerve (motor) | Sural nerve (sensory) | H-reflex latency | Conclusion |
|-------|----------------------|------------------------|--------------------|----------------------|-------------------------------|----------------------|---------------------|-----------------|------------|
| 1     |                      |                        |                    |                      | F-wave latency ↑ (Rt)          | CMAP ↓ (both)        | CV ↓ (both)        |                 | Sensorimotor polyneuropathy in leg |
| 2     |                      |                        |                    |                      | F-wave latency ↑ (both)        | F-wave latency ↑ (both) | CV ↓ (both)        | H-reflex latency ↑ (both) | Sensoimotor polyneuropathy |
| 3     | CV ↓ (both)          | CV ↓ (Lt)              | F-wave latency ↑ (Lt) |                      | CMAP ↓ (both)                 | CV ↓ (Lt)            | CV ↓ (both)        | H-reflex latency ↑ (both) | AMSAN      |
| 4     | CV ↓ (Lt)            | CV ↓ (both)            | CV ↓ (Rt)          | F-wave latency ↑ (both) | CMAP ↓ (both)                 | CV ↓ (both)          | CV ↓ (both)        | H-reflex latency ↑ (both) | AMSAN      |
| 5     | CV ↓ (both)          | CV ↓ (Lt)              | CV ↓ (both)        |                      | CMAP ↓ (both)                 | TL ↑ (Rt)            | No CMAP ↓ (both)   | CV ↓ (Rt)        | H-reflex latency ↑ (both) | AMSAN      |
| 6     | CMAP ↓ (Lt)          | CV ↓ (both)            | TL ↑ (Rt)          | CV ↓ (both)          | No CMAP ↓ (both)              | No CMAP ↓ (both)     | CV ↓ (Lt)          | No H-reflex latency ↑ (both) | AMSAN      |
| 7     |                      |                        |                    |                      | F-wave latency ↑ (both)        | F-wave latency ↑ (both) |                    | H-reflex latency ↑ (both) | Normal     |
| 8     | CV ↓ (Rt)            | CV ↓ (both)            |                    |                      | CMAP ↓ (Lt)                   | F-wave latency ↑ (both) | CV ↓ (both)        | H-reflex latency ↑ (both) | Sensory dominant polyneuropathy |
| 9     | Not checked          |                        |                    |                      |                               |                      |                    |                 |            |

Undocumented findings were normal.

NCSs, nerve conduction studies; H-reflex, Hoffman’s reflex; Rt, right; CMAP, compound motor action potential amplitude; CV, conduction velocity; Lt, left; AMSAN, acute motor-sensory axonal neuropathy; TL, terminal latency.
and seven female cases. All of these cases had gait disturbances or sensory changes as initial symptoms accompanied by signal changes in cervical MRI. NCSs indicated neuropathic patterns or early-stage polyneuropathy. One patient presented with incidental PTE and lung infarction. Table 3 summarizes the details of the published cases.5,9,10

**DISCUSSION**

N₂O is known to selectively oxidize folate and vitamin B₁₂, rendering them inactive and unable to degrade homocysteine into methionine, which is required for normal myelin production.11 Active vitamin B₁₂ is also required to convert MMA into succinyl-CoA. Serum levels of both homocysteine...
| Year  | Ref.          | Age<sup>a</sup>/sex | Symptoms                                      | Neurological examination          | Laboratory findings               | MRI changes                     | NCS                          | Others                        |
|-------|---------------|----------------------|-----------------------------------------------|-----------------------------------|-----------------------------------|---------------------------------|-------------------------------|--------------------------------|
| 2019  | Lee et al.    | 32/F                 | Gait disturbance                              | Romberg’s sign (+), sensory ataxia | Low Vit B<sub>12</sub>             | Posterior column of C1 and C2   | Not mentioned                 |                                |
| 2018  | Kang et al.   | ?/F                  | Progressive limb paralysis                    | Motor weakness in lower extremities | Increased MCV                    | Posterior column of cervical cord| Demyelinating polyneuropathy  |                                |
|       |               | ?/F                  | Progressive limb paralysis, paresthesia       | Romberg’s sign (+), motor weakness in lower extremities, hypesthesia to vibration, position | Increased MCV                    | Posterior column of cervical cord| Demyelinating polyneuropathy  |                                |
|       |               | ?/F                  | Progressive limb paralysis, paresthesia       | Romberg’s sign (+), motor weakness in lower extremities, hypesthesia to vibration, position | Increased MCV                    | Posterior column of cervical cord| Normal                       |                                |
| 2018  | Kwon et al.   | 22/F                 | Gait disturbance, progressive paresthesia in legs and hands | Paraparesis (MRC grade III)<sup>b</sup>, Romberg’s sign (+), decomposition, hypesthesia to vibration, tactile | Increased MCV                    | Posterior column of cervical cord| Axonal motor neuropathy       | Incidental PTE with lung infarction |
|       |               | 33/M                 | Gait disturbance, progressive numbness in legs | Romberg’s sign (+), sensory ataxia, hypesthesia to vibration, position, hyporeflexia | Increased MCV                    | Posterior column of cervical cord| Axonal motor neuropathy       |                                |
| 2018  | Choi et al.   | 24/M                 | Gait disturbance, paresthesia in all limbs, voiding difficulty | Romberg’s sign (+), gait ataxia, hypesthesia, paresthesia to tactile, hyperreflexia | Increased MCV                    | Posterior column of cervical cord| Sensorimotor polyneuropathy in lower limbs |                                |
|       |               | 22/F                 | Progressive leg paralysis, voiding difficulty, paresthesia in legs | Paraparesis (MRC grade II), hypesthesia to tactile, areflexia | Low Vit B<sub>12</sub>             | C2-CS                           | Sensorimotor polyneuropathy in lower limbs |                                |
| 2006  | Kwoun et al.  | 40/M                 | Gait disturbance, numbness in hands and feet | Hypoesthesia to pain, vibration, position, Romberg’s sign (+), gait ataxia, hyperreflexia | Microcytic hypochromic anemia     | Posterior column and lateral column of cervical cord | Demyelinating polyneuropathy |                                |

Ref, reference number; MRI, magnetic resonance imaging; NCS, nerve conduction study; F, female; Vit B<sub>12</sub>, vitamin B<sub>12</sub>; MCV, mean corpuscular volume; PTE, pulmonary thromboembolism; MRC, Medical Research Council; M, male.

<sup>a</sup>All patients were aged 21-36 years; <sup>b</sup>Active movement against gravity.
vitamin B12 prior to visiting our hospital. A previous case re-
expression).14
symptoms (including impaired memory function and de-
expression).14
illegality of recreational N2O use in Korea, most patients with
port indicated that homocysteine and MMA levels could be
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as numbness in the extremities, ataxia, and psychomotor
symptoms (including impaired memory function and de-
There were marked variations in clinical symptoms, labo-
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This interference with vitamin B12 metabolism could lead to demyelination in the central or peripheral nervous system and also to megaloblastic anemia. These pathophysiological mechanisms result in N2O intoxication being associated with clinical features such as numbness in the extremities, ataxia, and psychomotor symptoms (including impaired memory function and de-
and MMA are elevated during vitamin B12 deficiency. Previ-
asymptomatic spinal cord. This specific finding is known as the “inverted-V sign.” In the present case series, the MRI findings of about half of the patients were compatible with SCD. However, two patients who had no detected MRI signal changes had abnormal NCS results, which represents the first report of
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principally among adolescents and young adults. Due to the
symptomatic spinal cord. This specific finding is known as the “inverted-V sign.” In the present case series, the MRI findings of about half of the patients were compatible with SCD. However, two patients who had no detected MRI signal changes had abnormal NCS results, which represents the first report of
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This phenomenon in Korea. One patient also had concurrent involvement in the anterior, lateral, and posterior spinal col-
and MMA are elevated during vitamin B12 deficiency. Previ-
and MMA are elevated during vitamin B12 deficiency. Previ-
There have been several reports of the deleterious effects of N2O abuse in Korea. Kwoun et al.7 reported the first case of myeloneuropathy following chronic N2O abuse in 2003. In that report, the patient had paresthesia in both distal limbs and ataxia. Spinal MRI indicated high signal intensities from segments C2 to C5 on a T2-weighted image. Furthermore, NCSs indicated a demyelinating neuropathic pattern. Serum vitamin B12 levels were low and those of homocysteine were high. Two other cases of SCD caused by N2O gas were reported by Kwon et al.18 in 2019. Both patients had sensory changes in their limbs and the inverted-V sign was visible in T2-weighted spinal MRI. NCSs indicated axonal motor polyneuropathy in that case. In all previous cases of N2O intoxication in Korea, spinal cord MRI indicated signal changes similar to those observed in SCD. Unlike previously reported cases, we found two patients who had abnormal NCS results despite having normal spinal MRI results. We therefore sug-
and MMA are elevated during vitamin B12 deficiency. Previ-
and MMA are elevated during vitamin B12 deficiency. Previ-
addressing this issue requires treatments for neuro-
Currently illegal to use N2O gas for recreational purposes in Korea. It was therefore difficult to evaluate the correlations

https://doi.org/10.14253/acn.2021.23.2.108
http://www.e-acn.org
between clinical features and the exact amount and duration of N₂O inhalation.

The clinical manifestations of N₂O intoxication related to neurological disorders varied between the included patients, but had a general commonality. Several clinical indicators may include young adults with progressive subacute weakness and lower-extremity-dominant sensory changes. Increased serum MMA, homocysteine, axonal-type sensorimotor polyneuropathy patterns in electrophysiological tests, and predominant posterior column involvement observed in MRI may indicate the presence of N₂O intoxication related to neurological disorders. Careful evaluations of the clinical history of N₂O abuse are therefore warranted when these clinical findings are observed.

Conflicts of Interest
The authors have no conflicts to disclose.

Acknowledgements
This work was supported by the research fund of Hanyang University (HY-202110000001136).

Supplementary Material
Supplementary Materials can be found with this article online https://doi.org/10.14253/acn.2021.23.2.108.

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