Schizophrenia Research 208 (2019) 475–476

Contents lists available at ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

Letter to the Editor

Double-sidedness of "laughing gas" on the *N*-methyl-D-aspartate receptor: A case report of acute psychosis associated with nitrous oxide-induced hyperhomocysteinemia

Nitrous oxide (N_2O), also known as "laughing gas," is commonly used as an anesthetic in the medical and dental fields. As a non-competitive antagonist of *N*-methyl-D-aspartate (NMDA) receptors, N_2O inhibits excitatory glutaminergic transmission and yields an anesthetic effect (Sanders et al., 2008). Beyond its medical use, the unique recreational properties of N_2O, including euphoric and anxiolytic effects, encourage its misuse (van Amsterdam et al., 2015). The 2014 Global Drug Survey has reported that N_2O abuse is increasing worldwide (Kaar et al., 2016). In particular, the number of N_2O abusers is growing rapidly in Asian countries, especially among adolescents and young adults (Kwon et al., 2019; Lan et al., 2019).

Repeated inhalation of N_2O causes various medical and neurologic complications, including, in particular, myeloneuropathy (Garakani et al., 2016). Psychotic symptoms are also very common, with approximately 27.8% of N_2O users reporting hallucinations (Kaar et al., 2016). In this regard, an understanding of the neurobiological alterations following N_2O inhalation would provide novel insight into the pathogenesis of schizophrenia. We thus aimed to discuss the clinical and scientific importance of N_2O abuse in the field of psychiatry by examining a case of acute psychosis after heavy N_2O inhalation.

A 22-year-old Korean woman with no previous psychiatric history was admitted to a psychiatric inpatient unit with auditory hallucination, visual illusions, and affective lability that had started a month prior. The patient experienced continuous voices commenting on her daily routine, resulting in a loss of reality testing. She had first inhaled N_2O a year prior and began inhaling up to 500 balloons 2–3 times a week for 3 months. At that time, she experienced similar voice-commenting hallucinations, which gradually subsided when she quit N_2O use. A month before her hospitalization, she restarted recreational inhalation of N_2O. Her use at this time was excessive, as she was inhaling up to 250 balloons daily. Her last inhalation was 5 days prior to her hospitalization. No adverse life events or stressors were reported. Physical examination showed no abnormal physical symptoms or sign. She suffered tingling sensations in both of her feet, but her neurological examination revealed normal motor, sensory, and reflex functions. An in-depth psychiatric examination revealed that her consciousness was normal and that she was well-oriented. Although her delusion was not well-structured, she was perplexed by auditory hallucinations, visual illusions, and referential delusion with paranoia. Her affect was labile with sudden and inappropriate bouts of crying and laughing. Brain magnetic resonance imaging, electroencephalography, and electromyography were performed to rule out organic lesions, and the results of each were normal. Blood test results were in the normal range except for homocysteine (61.81 μmol/l, reference range: 0–12 μmol/l) and vitamin B_{12} (136 pg/ml, reference range: 211–911 pg/ml), suggesting a vitamin B_{12} deficiency.

The patient was treated daily with 5 mg of intravenous hydroxycobalamin, a precursor of vitamin B_{12}, for 10 days, after which the level of homocysteine normalized (5.06 μmol/l). Lorazepam (0.5 mg/day) was used to relieve anxiety and insomnia. The patient's total score on the Positive and Negative Syndrome Scale was 62 at baseline and was eventually down to 37 on the 15th hospital day (Fig. 1). When she was discharged after 17 days of hospitalization, her psychotic symptoms were in full remission.

Recent investigations suggest that the direct and indirect effects of N_2O on NMDA receptors may contribute to the emergence of psychotic symptoms. Like ketamine, N_2O can block NMDA receptors on inhibitory γ-aminobutyric acid interneurons and activate excitatory signaling pathways, including dopaminergic neurons (Sakamoto et al., 2006; Savage and Ma, 2014). The N_2O-induced increase in dopamine may be one potential mechanism of the hallucinogenic effect of N_2O, compatible with the NMDA receptor hypofunction hypothesis of schizophrenia.

Given, however, that the elimination half-life of N_2O is in minutes, its indirect effect on NMDA receptors via elevated homocysteine may play a more critical role in the development of psychosis. N_2O has an inhibitory effect on vitamin B_{12} by blocking the conversion of homocysteine to methionine, which ultimately causes hyperhomocysteinemia that lasts for more than a week, even after N_2O cessation (Savage and Ma, 2014). Accumulated homocysteine exerts neurotoxicity by enhancing the generation of reactive oxygen species and modulating NMDA

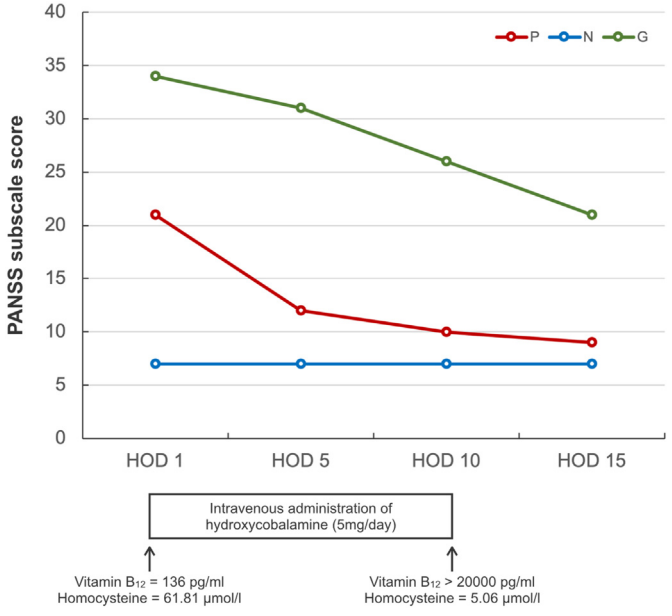

Fig. 1. Temporal changes in the severity of clinical symptoms and in the blood level of homocysteine in the presented patient. Abbreviations: PANSS, Positive and Negative Syndrome Scale; P, positive symptom subscale; N, negative symptom subscale; G, general psychopathology subscale; HOD, hospital day.

https://doi.org/10.1016/j.schres.2019.02.006

receptor activity (Savage and Ma, 2014). Homocysteine is known as an agonist at the glutamate site of NMDA receptors, while also acting as a partial antagonist at the glycine site (Lipton et al., 1997). Although the implications of this dual action in the emergence of psychotic symptoms remain unclear, previous research has shown that elevated homocysteine is a risk factor for schizophrenia (Muntjewerff et al., 2006). Our case, which describes a patient with a sustained increase in homocysteine after heavy N_2O use that fully recovered after its normalization, supports the hypothesis that disruption in homocysteine levels may be a causative factor in the development of psychotic symptoms.

In conclusion, clinicians should consider N_2O abuse in patients who present psychotic symptoms of unclear origin. Further investigations are required to understand how N_2O and homocysteine act on NMDA receptors and establish a neurobiological model to aid in our understanding of the pathogenesis of schizophrenia.

Contributors

S.E. Kim and M. Bang were responsible for the diagnostic evaluation and management of the patient. S.E. Kim managed the literature reviews and wrote the first draft of the manuscript. S.-H. Lee and M. Bang provided the critical revision of the manuscript. All authors contributed to and approved the final manuscript.

Conflict of interest

The authors have declared that they have no conflict of interest.

Acknowledgement

None.

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25 January 2019