Physical and Psychological Characteristics of Nitrous Oxide Abusers During the COVID-19 Pandemic: An Observational Study.

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Research

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Abstract

Background The coronavirus disease 2019 (COVID-19) was classified as a global pandemic by the World Health Organization. In addition to health effects, it has also brought about psychological problems due to its economic and social impact. Psychological effects have led to drug and alcohol abuse. To inform physician decisions, there is a need to characterize the physical and psychological characteristics of nitrous oxide abusers during the COVID-19 Pandemic.

Methods: We enrolled six nitrous oxide abusers who sought treatment at Taizhou Hospital of Zhejiang province between May 2020 and June 2020. Clinical data including socio-demographic, physical examination, laboratory examination, electromyography, neuroimaging, and psychological assessment were collected.

Results: The enrolled patients had a mean age of 22±4.3. Clinical presentations included varying degrees of limb numbness and an ataxic gait. Under laboratory examination, it was revealed that all the patients did not have pernicious anemia, 4 patients had decreased vitamin B12 while 3 patients exhibited elevated homocysteine levels. MR of the spinal cord revealed that 4 patients had abnormal signals in the cervical spinal cord. These signals were of high symmetry with splayed or inverted V sign after T2WI. Peripheral nerve damage was observed in 5 patients who were subjected to an electromyogram (EMG) test. The Symptom Checklist 90 (SCL-90) psychological evaluation indicated that all patients had severe anxiety, depression and psychosis. The psychological status of nitrous oxide abusers was significantly different from that of health controls. After treatment by vitamin B12, the patients' physical symptoms improved, and they were discharged from the hospital. For the evaluation of mental and psychological outcomes post-discharge, patients were asked to go to the psychological department for check-up and follow-up.

Conclusion: The enrolled 6 patients caused by abuse of nitrous oxide presented with symptoms of subacute combined with spinal degeneration. They had more serious psychological problems related to the COVID-19 pandemic. These problems require immediate attention and interventional approaches. The national government and other departments should take active measures to control abuse of nitrous oxide.

Trial registration: Not applicable.

Introduction

Coronavirus disease 2019 (COVID-19) was declared a global pandemic by the World Health Organization (WHO). This disease has caused 18.14 million morbidities and 691,000 mortalities as of 4th August 2020. The mortality rate has been estimated to be 3.81%[1]. To the infected and affected people, Covid-19 has had negative physical and mental health outcomes [2–4]. The psychological effects have led to drug and alcohol abuse.

Nitrous oxide is popularly abused, especially among the youth. It causes feelings of euphoria, calmness and relaxation[5,6]. However, long-term or heavy use of nitrous oxide can lead to bone marrow suppression, spinal cord damage, peripheral neuropathy, encephalopathy, pernicious anemia among other health defects[7–9].

It is important to characterize the physical and psychological outcomes of nitrous oxide inhalation in order to improve the clinical management of its adverse effects, especially during the COVID-19 pandemic period.

Materials And Methods

Data collection

Patients attending Taizhou Hospital of Zhejiang Province for care due to nitrous oxide addiction were consecutively enrolled. Clinical data including sociodemographic characteristics, physical examination, laboratory examination, electromyography, neuroimaging, and psychological assessment were obtained. The study was done between May 2020 and June 2020.

Magnetic Resonance Imaging (MRI)

An MRI scan of the cervical spine and brain was done to all patients. T1WI sequences included MRI sequences with and without gadolinium. Sagittal and axial images were obtained using T2-weighted MRI sequences. Data on the affected spinal cord segments (number of segments of the spine) and their positions on the sagittal image (cervical and thoracic vertebrae) were recorded.

Electromyogram (EMG)

Neurologic manifestations such as muscle weakness, sensory loss, and cognitive decline were recorded. Nerve conduction studies were performed on the median nerve, ulnar nerve, peroneal nerve, tibial nerve, and sural nerve depending on the clinical manifestations of patients. Compound muscle action potential (CMAP) amplitude, distal latency, sensory nerve action potential (SNAP) amplitude, and conduction velocity were detected using a full range functional EMG evoked potentiometer (Keypoint 9033A07, Denmark).

Psychological assessment

Using Symptom Checklist 90 (SCL-90), the mental state of the patients was assessed by a professional psychiatrist. The severity of symptoms is determined by the number of standard deviations of the dimension score from the norm group mean.

Statistical Analysis

Data were analyzed by the Statistical Package for Social Sciences (IBM SPSS 16.0). Descriptive statistics and one-sample t-test were performed for data comparison between groups. Statistical significance was set at $p \leq 0.05$.

Results

1. Sociodemographic and baseline characteristics of the study patients

From May 2020 to June 2020, 6 patients with nerve damage caused by nitrous oxide inhalation were admitted to our hospital and were enrolled. 6 patients attended Taizhou Hospital of Zhejiang Province for care due to nitrous oxide abuse The mean age of the 6 patients was 22±4.3. Four of the 6 patients were college students while 2 were high school graduates. There were 2 males and 4 females. The average duration of nitrous oxide abuse was 6.5±4.4 months. Three of the study patients began inhalation of nitrous oxide during COVID-19. After abstinence, one of the three had relapsed during the pandemic. The remaining 3 patients were noted to have increased their daily dose of nitrous oxide during the pandemic. Four patients exhibited low vitamin B12 levels while three had elevated homocysteine levels according to the normal reference range (vitamin B12 is 180.0-914.0 pg/ml; homocysteine is 5.0-20.0 μmol/L). SCD was diagnosed among all the six patients. Five patients had improved clinical outcomes after vitamin B12 and adenosine cobalamin injection therapies (Table 1).

2. Physical examination and EMG

All the study patients presented with limb numbness and varying degrees of walking instability. Mild memory loss was documented in 2 patients. Varying degrees of sensory impairment and sensory ataxia were exhibited among the patients. One patient had decreased muscle strength. There was no case of a positive pathological sign or obvious damage to the pyramidal tract (see supplementary materials).

EMG examination showed peripheral nerve damage in 5 patients. Two of the patients had multiple motor and sensory axonal damage and myelin sheath change. One patient was diagnosed with motor nerve damage, 2 patients were diagnosed with partial nerve damage. One of the patients did not exhibit any signs of nerve damage (Table 2).

3. Imaging results

Four patients had high symmetric signals in the cervical spinal cord after MR T2WI. They presented with splayed or inverted V signs. One of the patients exhibited a slightly high signal in cervical spinal cord T2WI while the other one did not exhibit any imaging abnormalities. In the first case, the cervical spinal

cord at 3-6 segments was slightly thickened and the signal was locally abnormal. In the second case, T2WI exhibited a slightly high signal. In the third case, 3-5 intervertebral disc degeneration and herniation was observed. In the fourth case, the cervical spinal cord signal was slightly abnormal at 2-5 segments. The 1-5 cervical spinal cord segment in case 5 was slightly thickened and the signal was locally abnormal. In the sixth case, the cervical 5/6 intervertebral disc was slightly inflated, the physiology curvature of cervical vertebra was slightly straight and degeneration in cervical 1-5 segment was observed (Figure 1).

Figure 1. Results of MR T2WI showing high symmetry signal in the cervical spinal posterior cord, presenting splayed or inverted V sign. On the left of each case is sagittal image and on the right is axial image. Red arrows indicate a clearly high signal. Yellow arrows indicate slightly higher or suspicious signals.

4. Mental states of the 6 nitrous oxide abusers

We used symptom checklist 90 (SCL90) to evaluate the mental status of 6 patients. The results showed that the total score of each case was more than 250 points, and all cases had various psychological problems as described: Case 1: severe depression, anxiety, hostility, phobia and psychosis; Case 2: Severe anxiety and psychosis; In case 3, all the somatization, interpersonal sensitivity, depression, anxiety, hostility, phobia, paranoid ideation and psychosis symptoms were serious except for obsessive compulsive symptoms. Case 4 exhibited severe somatic symptoms, anxiety, hostility, and psychosis; Case 5: Severe anxiety, depression and terror; Case 6: severe hostility and paranoid ideation. The major psychological manifestations were anxiety, depression, hostility and psychosis (Table 3).

To analyze the differences in the psychological status of nitrous oxide abusers and normal people, the SCL-90 score of patients and healthy controls during the pandemic[3] was compared. It was noted that the psychological status of nitrous oxide abusers in anxiety, hostility, depression, interpersonal relationships, paranoia, psychosis and other dimensions was significantly different from those of health controls (Table 4).

Discussion

Due to the COVID-19 pandemic, public psychological problems cannot be ignored. In addition to the heightened mental stresses among patients and healthcare workers during the COVID-19 pandemic, the mental health of healthy people was also affected. There was a drastic increase in public fear, a decline in social and economic activities that triggered psychosocial sequelae. Quarantined individuals exhibited depression, fear, guilt and anger[10]. Psychosocial stress due to social changes in response to COVID-19 infections enhanced mental problems. Studies have documented that more than 50 percent of SARS and MERS patients have suffered psychological distress [11,12]. In their study, Cuiyan Wang et al reported that a total of 53.4% of the respondents exhibited either moderate or severe psychological problems under

impact of the pandemic, 16.5% exhibited moderate to severe depressive symptoms, 28.8% had moderate to severe anxiety symptoms while8.1% had moderate to severe stress [2].

For more than 170 years, nitrous oxide has been used as an anesthetic in clinical practice. As a hallucinogen, it has been widely used in entertainment joints and youth gatherings in Europe and America[13]. Its inhalation causes feelings of euphoria, involuntary laughter, distorted voices and mild hallucinations. These feelings peak after about 20 seconds and then quickly disappear[6]. The user feels normal within 2 minutes of inhalation. A global drug survey (GDS2014) conducted in 17 countries involving 74,864 patients confirmed that the prevalence of nitrous oxide use as a recreational drug in the UK and US was 38% and 29.4%, respectively[13]. Incidences of nitrous oxide abuse in China are gradually increasing, with the majority of the abusers being the youth [14]. In this study, patients were aged between 17 and 28 years, among whom 4 were college students.

Case reviews in our hospital for the past three years showed that only 6 patients of nitrous oxide abuse were treated between October 2017 and December 2019. Comparison with recent cases shows that the proportion of nitrous oxide abuse during COVID-19 was high. Increased nitrous oxide abuse during the COVID-19 pandemic reflects psycho-social changes among young people. Literature has shown that nitrous oxide abuse can lead to a series of abnormal mental symptoms, including personality changes, mood disorientations (such as anxiety, depression, mania), impulsive and aggressive behaviors, hallucinations, delusions and other psychotic symptoms[8,15]. These factors increase mental obstacles and also affect compliance to therapy and its outcomes.

The risk factors for nitrous oxide abuse identified in this study included the lack of employment or study during the pandemic, a history of nitrous oxide abuse and relapse during the pandemic, boredom, curiosity and peer pressure. Psychological assessment detected varying degrees of anxiety and depression with 2 cases of severe depression and 1 case of obvious suicidal tendency. The SCL-90 score of the 6 patients was significantly higher compared to that of healthy individuals. In addition, they presented serious psychological problems (Table 3, 4).

Due to study limitations, the psychological test scores and mental state of patients before the pandemic could not be obtained. Therefore, the psychological impact of the pandemic on the patients as well as nitrous oxide abuse outcomes on the patients' mental state could not be verified. However, the number of patients seeking medical care for nerve injuries due to nitrous oxide increased. The frequency and inhalation amount increased during the pandemic. Aggravation of the disease indicated that the psychological problems of the patients were related to the pandemic. Therefore, while treating a patient's physical illness during a pandemic, their psychological state should also be monitored for timely intervention.

The adverse effects of exposure to nitrous oxide include slowed reaction rate, dizziness, nausea and vomiting. Inhalation of large quantities of nitrous oxide at a high pressure may lead to suffocation. Long-term adverse effects include nerve damage, vitamin B12 deficiency and cobalamin reactive psychosis [16].

Pernicious anemia and neurological damage caused by nitrous oxide are very common. Clinical manifestations of these conditions include paresthesia in limbs, gait instability or difficult walking, weakness, falls or balance disorders, Lhermitte's Sign and ataxia[17]. Occasionally there is cognitive impairment and optic atrophy [18,19]. In this study, all the 6 patients were recreational users of nitrous oxide, presenting with limb numbness and varying degrees of walking instability. Two patients presented with mild memory loss, 4 presented with increased T2 signal in cervical spinal cord (Fig. 1), 3 presented with extensive peripheral nerve damage (Table 2), while 1 exhibited mild anemia.

Damage to the nerve system by nitrous oxide is mainly due to vitamin B12 deficiency and homocysteine accumulation. Vitamin B12 is an important cofactor of cellular methionine synthase. Extremely low levels of vitamin B12 leads to methionine consumption and homocysteine accumulation. Methionine consumption leads to a decrease in downstream S-adenosine, which is required for myelin production and maintenance. Deficiency in vitamin B12 leads to demyelination and gliosis of the central nervous system (especially the dorsal spinal cord), as well as demyelination of peripheral nerves. Homocysteine accumulation increases the risk of stroke and peripheral neuropathy [19]. In this case series, vitamin B12 levels were lower than normal in 4 patients, and homocysteine levels were significantly elevated in 3 patients (2 patients not measured before treatment) (Table 1). The current therapies for nerve damage caused by nitrous oxide include cessation of exposure and supplementation with high doses of vitamin B12 [20]. We noted that after adenosine cobalamin injection, 5 patients exhibited symptomatic relief while 1 patient did not exhibit any symptomatic relief.

Nitrous oxide abuse has increased people's physical, psychological and socio-economic burden. This calls for immediate attention to the control of nitrous oxide abuse.

Disadvantage of this research: In this study, we failed to obtain the psychological assessment data of the patients before the pandemic and before they started abusing nitrous oxide. The causal relationships between the pandemic and psychological changes, and between nitrous oxide abuse and psychological changes could not be explained.

Conclusion

In this study, cases of nervous system diseases and psychological problems caused by abuse of nitrous oxide in the department of neurology of our hospital during COVID-19 pandemic were analyzed. Results showed that these 6 patients presented with symptoms of subacute combined with spinal degeneration. And they had more serious psychological problems related to the COVID-19 pandemic. This indicates that neurologists should provide comprehensive treatment of nervous system diseases caused by excessive nitrous oxide. In addition, our results show that focus should be directed at controlling the effects of novel Coronavirus on the psychological well-being of people. Governments should develop measures to control nitrous oxide and parents should spend time with their children during the pandemic period.

Declarations

Ethics approval and consent to participate

All data were anonymized to comply with the provisions of personal data protection. The patients have provided their consent to publish this research, and the consent procedure was approved by the Ethics Committee of Taizhou Hospital of Zhejiang Province. All procedures were performed according to the guidelines of the institutional ethics committee and the tenets of the Declaration of Helsinki were adhered to throughout.

Consent for publication

All co-authors have seen and agree with the contents of the manuscript and consent to publish this research.

Availability of supporting data

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Author Contributions

SZL conceived and designed the study. SSW, GW, TLW, ANY, YJW did data collection. SSW, GW performed data analysis. SZL provided resources. SSW and GW wrote the original draft. SZL reviewed and edited the manuscript. All authors read and approved the final manuscript.

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References

1. WHO. *Coronavirus disease (COVID-2019) situation reports*, <https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports> (2020).
2. Wang, C. *et al.* A longitudinal study on the mental health of general population during the COVID-19 epidemic in China. *Brain, Behavior, and Immunity* **87**, 40-48, doi:https://doi.org/10.1016/j.bbi.2020.04.028 (2020).
3. Tian, F. *et al.* Psychological symptoms of ordinary Chinese citizens based on SCL-90 during the level I emergency response to COVID-19. *Psychiatry research* **288**, 112992, doi:10.1016/j.psychres.2020.112992 (2020).
4. Zhu, Z. *et al.* The psychological status of people affected by the COVID-19 outbreak in China. *Journal of psychiatric research* **129**, 1-7, doi:10.1016/j.jpsychires.2020.05.026 (2020).
5. McGarvey, E. L., Clavet, G. J., Mason, W. & Waite, D. Adolescent inhalant abuse: environments of use. *The American journal of drug and alcohol abuse* **25**, 731-741, doi:10.1081/ada-100101889 (1999).
6. Randhawa, G. & Bodenham, A. The increasing recreational use of nitrous oxide: history revisited. *BJA: British Journal of Anaesthesia* **116**, 321-324, doi:10.1093/bja/aev297 (2015).
7. Keddie, S. *et al.* No laughing matter: subacute degeneration of the spinal cord due to nitrous oxide inhalation. *Journal of neurology* **265**, 1089-1095, doi:10.1007/s00415-018-8801-3 (2018).
8. Garakani, A. *et al.* Neurologic, psychiatric, and other medical manifestations of nitrous oxide abuse: A systematic review of the case literature. *The American journal on addictions* **25**, 358-369, doi:10.1111/ajad.12372 (2016).
9. Renard, D., Dutray, A., Remy, A., Castelnovo, G. & Labauge, P. Subacute combined degeneration of the spinal cord caused by nitrous oxide anaesthesia. *Neurological sciences : official journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology* **30**, 75-76, doi:10.1007/s10072-009-0013-2 (2009).
10. Brooks, S. K. *et al.* The psychological impact of quarantine and how to reduce it: rapid review of the evidence. *The Lancet* **395**, 912-920, doi:https://doi.org/10.1016/S0140-6736(20)30460-8 (2020).
11. Mak, I. W., Chu, C. M., Pan, P. C., Yiu, M. G. & Chan, V. L. Long-term psychiatric morbidities among SARS survivors. *General hospital psychiatry* **31**, 318-326, doi:10.1016/j.genhosppsych.2009.03.001 (2009).
12. Kim, H. C., Yoo, S. Y., Lee, B. H., Lee, S. H. & Shin, H. S. Psychiatric Findings in Suspected and Confirmed Middle East Respiratory Syndrome Patients Quarantined in Hospital: A Retrospective Chart Analysis. *Psychiatry investigation* **15**, 355-360, doi:10.30773/pi.2017.10.25.1 (2018).
13. Kaar, S. J. *et al.* Up: The rise of nitrous oxide abuse. An international survey of contemporary nitrous oxide use. *Journal of psychopharmacology (Oxford, England)* **30**, 395-401, doi:10.1177/0269881116632375 (2016).
14. Zheng, D. *et al.* The sharp rise of neurological disorders associated with recreational nitrous oxide use in China: a single-center experience and a brief review of Chinese literature. *Journal of neurology* **267**, 422-429, doi:10.1007/s00415-019-09600-w (2020).

15. Cousaert, C., Heylens, G. & Audenaert, K. Laughing gas abuse is no joke. An overview of the implications for psychiatric practice. *Clinical neurology and neurosurgery* **115**, 859-862, doi:10.1016/j.clineuro.2013.04.004 (2013).
16. Hathout, L. & El-Saden, S. Nitrous oxide-induced B□□ deficiency myelopathy: Perspectives on the clinical biochemistry of vitamin B□□. *Journal of the neurological sciences* **301**, 1-8, doi:10.1016/j.jns.2010.10.033 (2011).
17. Oussalah, A. *et al.* Global Burden Related to Nitrous Oxide Exposure in Medical and Recreational Settings: A Systematic Review and Individual Patient Data Meta-Analysis. *Journal of clinical medicine* **8**, doi:10.3390/jcm8040551 (2019).
18. Thompson, A. G., Leite, M. I., Lunn, M. P. & Bennett, D. L. Whippits, nitrous oxide and the dangers of legal highs. *Practical neurology* **15**, 207-209, doi:10.1136/practneurol-2014-001071 (2015).
19. Leishear, K. *et al.* Vitamin B12 and homocysteine levels and 6-year change in peripheral nerve function and neurological signs. *The journals of gerontology. Series A, Biological sciences and medical sciences* **67**, 537-543, doi:10.1093/gerona/glr202 (2012).
20. Al-Sadawi, M. *et al.* Inhaled Nitrous Oxide 'Whip-Its!' Causing Subacute Combined Degeneration of Spinal Cord. *American journal of medical case reports* **6**, 237-240, doi:10.12691/ajmcr-6-12-3 (2018).

Tables

Due to technical limitations, table 1, table 2, table 3 and table 4 are only available as a download in the Supplemental Files section.

Figures

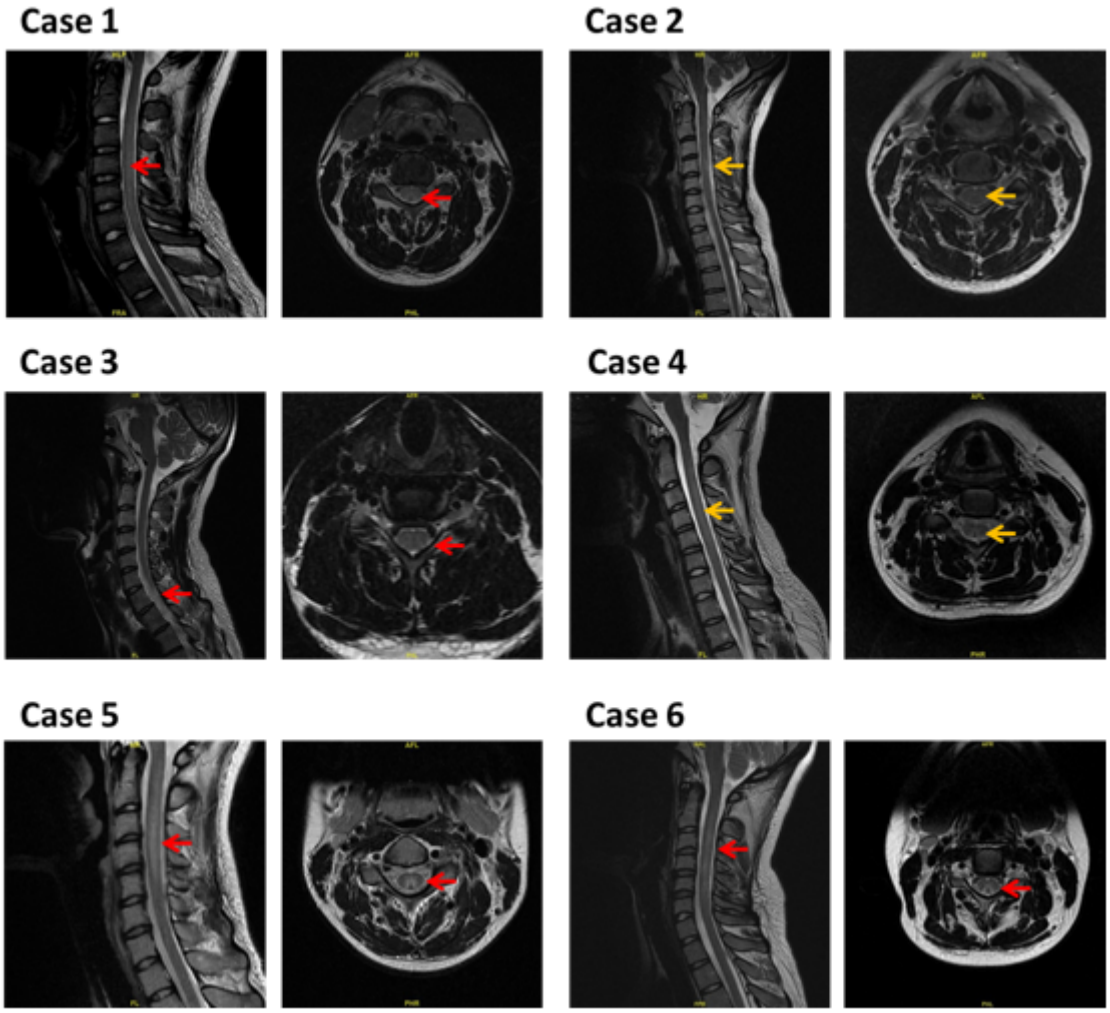

Figure 1

Results of MR T2WI showing high symmetry signal in the cervical spinal posterior cord, presenting splayed or inverted V sign. On the left of each case is sagittal image and on the right is axial image. Red arrows indicate a clearly high signal. Yellow arrows indicate slightly higher or suspicious signals.

Supplementary Files

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