SCIENTIFIC LETTERS

Acute ataxia induced by nitrous oxide abuse in young adults during the COVID-19 pandemic

Ataxia aguda inducida por el abuso de óxido nitroso en adultos jóvenes durante la pandemia de COVID-19

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Nitrous oxide (N_2O) is a gas used as an anesthetic agent[1]. Sometimes, its use is deviated for recreational purposes to induce a short-lasting euphoric sensation. Consumers inhale the gas from prefilled balloons that they legally and inexpensively purchase from food shops and the internet[2]. N_2O-induced toxicity has already been described in clinical practice and recreational use[3]. However, the incidence of N_2O-induced neurotoxicity has sharply increased all around the world, particularly during the COVID-19 pandemic[4-6]. Patients are usually referred to the Emergency Room (ER) where physicians are confronted with the diagnostic difficulty since the symptoms are often confused with Guillain-Barré syndrome (GBS). Although N_2O-induced neurotoxicity is becoming under scrutiny, its diagnosis remains challenging. Emergency doctors need clinical clues to diagnose it, especially when neurologists are not available. Herein, we report a series of patients with N_2O-induced neurotoxicity whom we compared with GBS patients. We also analyzed their relative frequencies during the COVID-19 pandemic.

The ER of Henri Mondor University Hospital receives 160 patients per day. A neurologist is present 24 hours a day and assesses each patient who presents acute neurological symptoms resembling those of GBS. We retrospectively included all consecutive patients initially suspected as GBS cases and finally diagnosed as N_2O-induced neurotoxicity from January 2020 to September 2021. N_2O-induced neurotoxicity was defined as neurological symptoms in a patient who admitted having consumed N_2O. They were compared with GBS patients diagnosed over the same period. We collected all clinical data and laboratory investigations of patients with GBS and N_2O-induced neurotoxicity. We compared the relative frequencies of N_2O-induced neurotoxicity and GBS with the incidence of COVID-19 in France based on the national register of positive Sars-Cov2 PCR7. We performed statistical analysis with IBM SPSS Statistics 23. The Henri Mondor institutional review board approved this study (IRB 00011558: 2022-131).

To the best of our knowledge, no case of N_2O-induced neurotoxicity was diagnosed before January 2020. From January 2020 to September 2021, 26 patients presented to our ER for N_2O-induced neurotoxicity (Figure 1): the first two cases over the first lockdown (March to May 2020), the third one at the end of the second lockdown (December 2020), and four patients over the third lockdown (April 2021). After the end of the last lockdown, we observed a steady increase of cases, with an average rate of four patients per month. From January 2020 to September 2021, we counted 21 GBS (Figure 2). If we focus on the period between April 2021 and September 2021, we witnessed 21 patients with N_2O-induced neurotoxicity compared with eight GBS cases. The median age of patients with N_2O-induced neurotoxicity was 22.7 years [range: 18.5-37.0]. Their mean N_2O consumption duration was 8.3 months for a mean amount of 9,380g/week [80-44,800], i.e., around 1,200 cartridges per week. Fifteen patients reported daily abuse of N_2O. The onset of neurotoxicity was mostly acute (Table 1). The chief complaint was gait disturbance or isolated paresthesia. Neurological examination often revealed ataxia associated with steppage. Three patients were wheelchair-bound. Patients with N_2O-induced neurotoxicity were usually younger than those with GBS (23 vs. 54 years, $p < .001$). Few of them exhibited upper limb weakness (1 vs. 18, $p < .001$) and proximal lower limb weakness (8 vs. 20, $p < 0.001$), and none had cranial nerve involvement (0 vs. 10, $p < .001$). A summary of the additional investigations is shown in Table 1. Moreover, we consistently found an increased serum homocysteine level in all of the ten tested

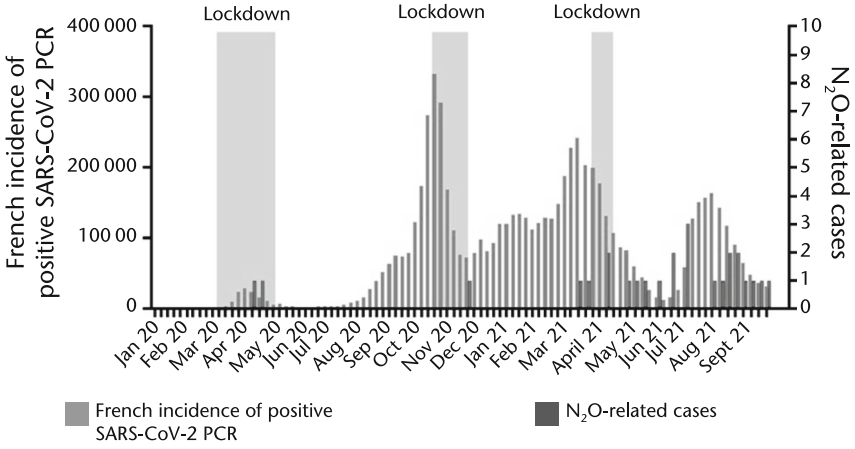

Figure 1. The sharply increased frequency of recreational nitrous oxide (N2O)-induced neurotoxicity during the COVID-19 pandemic.
This chart shows the incidence of positive SARS-Cov2 PCR (blue) in France from January 2020 to September 2021. The first patients with N_2O-induced neurotoxicity (red) seen at our Emergency Room in each of the three lockdowns we had in France (grey). Interestingly, the distribution of patients with N_2O-induced neurotoxicity differed after the third lockdown from the trend we observed before. The difference highlights the perpetuation of this emerging substance abuse and emphasizes the importance of recognition and early diagnosis.

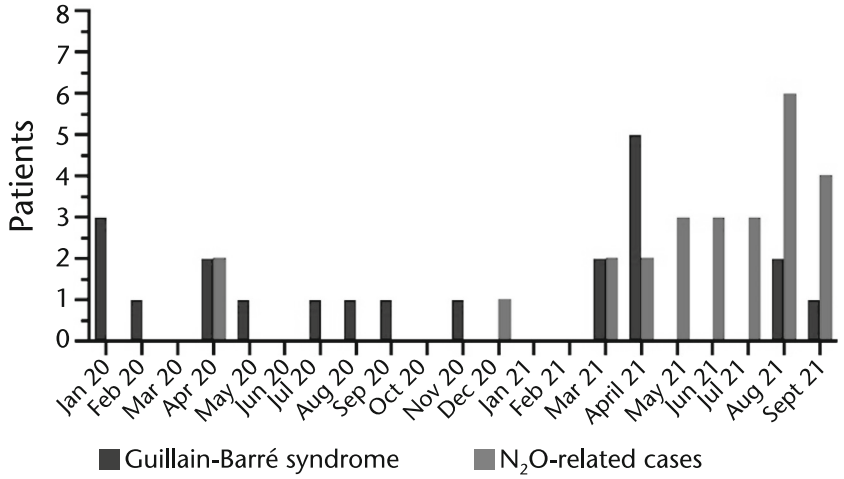

Figure 2. Comparative frequencies of N_2O-induced neurotoxicity and Guillain-Barré syndrome from January 2020 to September 2021.

patients, with a mean level of 93.7 ± 55.3 µmol/L (Normal < 15). All patients were put on vitamin B12 supplementation and advised to stop N_2O intake. The follow-up was available for nine patients with a mean duration of 5 months [1-12]. One patient did not stop N_2O recreational use and was stable three months after. All remaining patients reported persistent paresthesia.

We herein report a series of patients with N_2O-induced neurotoxicity and highlight its sharply emerging incidence over the COVID-19 pandemic. Its clinical presentation can be confounded with that of GBS, which is comparatively less frequent. Typically, the patient is a young adult exhibiting myelopathy characterized by acute areflexic ataxia with paresthesia often associated with distal predominant motor neuropathy. This new critical illness is recognizable and diagnosable in the ER. Acute ataxia should incite doctors to enquire about N_2O consumption and order homocysteine concentration level, which systematically increases in such conditions. Briefly, N_2O oxidizes vitamin B12, which impairs its pathway, and prevents homocysteine conversion to methionine, resulting in hyperhomocysteinemia[3]. However, homocysteine level measurement is often beyond the ER lab capacity. Other clues may help to distinguish N_2O-induced neurotoxicity from other acute neurological conditions. In GBS, we commonly observe upper limbs weakness, proximal lower limbs weakness, and cranial nerve involvement. Acute myelitis may be presented as acute areflexic ataxia8, however it is often associated with sphincter disturbances, and spinal MRI typically shows T2 hypersignal not limited to the posterior column with T1 gadolinium enhancement. Overall, in the context of acute ataxia or paresthesia, we can assume N_2O-induced neurotoxicity with confessed N_2O consumption and hyperhomocysteinemia. Eventually, the earlier N_2O-induced neurotoxicity is diagnosed, the better management would be to avoid sequelae. To date, there is no guidelines to treat neurological consequences of N_2O-induced neurotoxicity. We recommend N_2O interruption and vitamin B12 supplementation. Abstinence is crucial because, despite B12 supplementation, functional B12 deficiency will last with persistent N_2O intake[9]. Interestingly, the relative frequency of N_2O-induced neurotoxicity has dramatically increased during the COVID-19 pandemic and seems higher than that of GBS. The incidence of COVID-19 in the area of our ER matches the national incidence7. GBS incidence did not increase at the beginning of the COVID-19 pandemic10, probably because lockdown measures reduced the transmission of GBS-inducing pathogens, but could secondarily increase with both SARS-Cov-2 infection[11] and vaccines[12]. Noteworthy, the monocentric recruitment did not allow us to calculate the real incidences of N_2O-induced neurotoxicity and GBS. We only analyzed their relative frequencies. Additionally, we only described the retrospectively recruited patients with N_2O-induced neurotoxicity assessed by a neurologist. Some patients with mild clinical symptoms could have been missed by neurological expertise, which underestimates the disease real incidence. However, nowadays, N_2O-induced neurotoxicity is more prevalent, and all practitioners should be aware of its drastic worldwide increase[4-6]. The COVID-19 pandemic has shaken the society and is still an ongoing challenge, especially for the youth[13]. Lockdowns induced anxiety and lifestyle changes that encourage substance abuse, which could partly explain the increased incidence of N_2O-induced neurotoxicity in France[14]. Although our first cases emerged during the lockdowns, we

Table 1. Clinical and paraclinical features of patients with N_2O-induced neurotoxicity

Features	N = 26 n (%)
Progression phase duration	
Acute (< 1 month)	24 (92)
Subacute (1-3 months)	1 (4)
Chronic (>3 months)	1 (4)
Core complaint	
Walk impairment	16 (62)
Isolated limb paresthesia	10 (38)
Symptoms	
Unsteady gait	16 (62)
Limb paresthesia	23 (88)
Memory impairment	5 (19)
Neurological examination	
Ataxia	18 (69)
Steppage	8 (31)
Muscle weakness	16 (62)
Absent or decreased deep tendon reflexes	17 (65)
Babinski sign	2 (8)
Absent or decreased vibration sense	20 (77)
Spinal MRI	
Posterior T2 hyperintensity	12/16 (75)
Nerve conduction study	
Abnormal examination	12/15 (80)
Both axonal and demyelinating pattern	7/15 (47)
Isolated axonal pattern	5/15 (33)
Laboratory examination	
Anemia	3/18 (17)
Decreased blood vitamin B12 level	8/18 (44)
Decreased blood vitamin B9 level	2/13 (15)
Increased blood homocysteine level	10/10 (100)
Increased urinary methylmalonic acid	4/5 (80)

are concerned by the perpetuation of the phenomenon after the last lockdown. The Spanish National Drug Plan survey did not analyze N_2O recreational use, which merits reconsideration given that tourists may introduce it in party areas[15]. The easy access to N_2O and its inexpensiveness promote its consumption and trafficking. In 2019, the Global Drug Survey estimated that as much as 23% of the general population have already consumed N_2O in their lifetime[2]. However, it usually consists of intake of some cartridges during parties[2]. In our patients, N_2O was consumed on daily basis and at high doses, which might reflect the loss of control of initial festive consumption. Some authors reported a correlation between N_2O consumption and the clinical severity at the onset[5]. Therefore, we suggest referring N_2O regular users to addictology clinics.

Recreational N_2O-induced acute ataxia has risen during the COVID-19 pandemic and is apparently becoming more common to see than GBS in the ER. Early recognition leads to better management and might avoid sequelae. This perpetuating substance abuse is an emerging public health issue in the youth.

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