Clinical Neurology and Neurosurgery 115 (2013) 859–862

Contents lists available at ScienceDirect

Clinical Neurology and Neurosurgery

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

Review

Laughing gas abuse is no joke. An overview of the implications for psychiatric practice

Céline Cousaert*, Gunter Heylens, Kurt Audenaert

Department of Psychiatry and Medical Psychology, University Hospital Ghent, De Pintelaan 185, B-9000 Ghent, Belgium

ARTICLE INFO

Article history:
Received 20 June 2012
Received in revised form 20 March 2013
Accepted 3 April 2013
Available online 1 May 2013

Keywords:
Nitrous oxide
Psychiatric symptoms
Psychosis
Cobalamin

ABSTRACT

Abuse of nitrous oxide – also known as laughing gas – can lead to a number of well-known neurological symptoms but also to less documented psychiatric symptoms. Studies show abuse prevalence rates ranging from 12% to 20% among youngsters and thereby classify nitrous oxide as one of the five most frequently used inhalants. Its abuse still remains unrecognized in psychiatric settings, however. Since treatment is straightforward, it is important to raise the awareness of clinicians with respect to typical signs and symptoms. This paper presents a case report and gives an overview of the existing literature on psychiatric symptoms and therapy.

Contents

1. Introduction

Nitrous oxide (N_2O), commonly known as laughing gas, is used in medicine as a volatile anesthetic. In addition to its medical use, it has many applications in the food and car industries. In these contexts it is used as a propellant in whipped cream dispensers, as an engine accelerant and as an oxidizer in rocket engines. Whipped cream cans or gas cartridges make N_2O available to a larger public and they can be purchased in most supermarkets under the name "whippits" for about 15 euro for 50 bulbs [1]. The cartridges may be opened by puncturing the end and capturing the escaping gas in a large container or in an inflatable object such as a balloon, thus making nitrous oxide ready for inhalation [2]. Cases are described where the patients discharge the "whippits" into a container and then directly inhale via a facial mask [3,4].

After the first report of its kind in 1978, [5] attention for N_2O abuse increased. An anonymous questionnaire of 1979 [6] in the USA revealed that up to 20% of medical and dental students had at one time inhaled nitrous oxide for recreational purposes. A questionnaire-based study of 2003 [7,8] at the University of Auckland, New Zealand showed in more detail that 12% of the first-year students used the substance recreationally and 3% inhaled it at least monthly.

The purpose of this paper is to present an overview of the psychiatric effects of N_2O inhalant use and raise clinical awareness by means of case reports in which the psychiatric symptoms are prominent. The implications for psychiatric practice in terms of the screening and assessment aimed at these substance-using populations will be documented and discussed.

2. Case report

A 24-year-old, Caucasian male with no psychiatric history was brought to the emergency department (University Hospital Gent,

* Corresponding author. Tel.: +32 09 332 4395; fax: +32 09 332 4989.
E-mail address: celine.cousaert@ugent.be (C. Cousaert).

0303-8467/$ – see front matter © 2013 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.clineuro.2013.04.004

Belgium) by his parents because of his altered mental status and bizarre behavior. His confusing story about turning the world into a better place was colored with paranoia. The parents reported that the patient had never had similar thoughts or delusions in the past. He worked as a technician in a nuclear plant and ruled out occupational exposure to any toxic substance. He was not in a relationship and lived alone in an apartment. He initially denied using any recreational drugs and alcohol, but further in-depth interviewing led to the admission of excessive use of inhalants, more particularly nitrous oxide. He and his friends had bought several cases of nitrous oxide bullets from a grocery store which they had repeatedly inhaled using balloons. He denied having had any psychiatric symptoms in the past. Sleep and appetite were reported as normal and the patient was eating a balanced diet. No specific life-events and stressors could be identified.

Physical inspection revealed a young man with a pale color and no apparent pathological physical signs or symptoms. Psychiatric examination demonstrated that he was oriented in person and place, but disoriented in time. Consciousness was normal, but he showed short episodes of reduced responsiveness to the interviewer. He demonstrated unstructured thoughts and his ideas were hard to follow. His mood was euthymic and he was only marginally disturbed. He denied any suicidal ideations. Neurological examination showed symmetric deep tendon reflexes, a neutral plantar response and normal motor and sensory system responses to vibration, pain, touch, temperature, position and proprioception, but the patient had discrete spastic tonus with asterixis. Electroencephalography was normal. Brain scans, including CT scan and magnetic resonance imaging (MRI) were normal. Blood tests showed an INR of 2.76 (0.9–1.1), increased bilirubin levels (total bilirubin of 1.8 mg/dL, direct bilirubin of 0.49 mg/dL, indirect bilirubin of 1.28 mg/dL); the vitamin B_{12} level two days after admission was 171 pg/mL (reference range 197–866). A blood toxicology test was performed and turned out to be negative for amphetamines, cocaine and opiates. Only marginal blood levels of cannabinoids (THC) were found. The patient was treated with 1000 micrograms of vitamin B_{12} intramuscularly every day for one week. His neurological and psychiatric symptoms improved rapidly. By the day of discharge, one week after his presentation to our hospital, his mental status had been normalized. His hallucinations had resolved and he felt better. Seven weeks later, he returned to the outpatient clinic for a follow-up session. He was in a normal mental and neurological condition and his blood results were normalized.

3. Method

We used the search engine PUBMED to find relevant papers on nitrous oxide and psychiatric symptoms by using the search words “nitrous oxide” and “psychiatric symptoms”. This yielded 23 results. In addition, the references cited in the papers found were symptomatically checked for relevance to this paper.

4. Discussion

Despite the fact that there are a number of case studies that report clinical findings of sensory and motor dysfunction, we will concentrate on the only cases found in the literature until now that describe psychiatric symptoms (e.g. psychosis and conversion disorder) as prominent.

Sethi et al. [3] describe the case of a 33-year-old, unemployed Indian–American male with no past psychiatric history, who was brought to the hospital because of his bizarre behavior and paranoid delusions. The patient and his wife reported that he had no previous history of similar thoughts or delusions. He had worked as a medical technologist in the past and ruled out occupational exposure to any toxic substance. He initially denied using any recreational drugs and alcohol, but after further intensive questioning he admitted to the excessive use of inhalants, more particularly nitrous oxide. He had bought several packages of nitrous oxide containers from a cookware store. Using a plastic container fitted with an airtight facemask, he had inhaled the nitrous oxide gas on a daily basis for nearly 4 weeks prior to his current hospitalization. He showed bizarre paranoid behavior and delusions, but denied any auditory or visual hallucinations. The neurologic examination was normal, and a negative urine toxicology screen test did not indicate any other commonly abused drugs. He was treated intramuscularly with 1000 micrograms of vitamin B_{12} daily for one week and with low-dose quetiapine. At the time of discharge, 2 weeks after his presentation to the hospital, his delusions were resolving and he felt generally better.

A 55-year-old unemployed man was brought to the emergency room in a New York hospital because of an altered mental state and problems with his gait. He was agitated, confused, and paranoid. His past medical history was notable for obsessive compulsive disorder and vitamin B_{12} deficiency diagnosed many years before. His vitamin B_{12} level on the day of admission was 121 μg/L (reference rang 190–930). He denied following a vegetarian diet, or suffering from alcohol abuse or illicit drug use. His imaging studies, including MRI, were unremarkable and the urine toxicology test was negative. After the discovery of commercial metal gas containers and a balloon in his home, the patient admitted to having inhaled nitrous oxide for many years in order to be able to ‘sleep’. His symptoms rapidly improved after starting treatment with vitamin B supplements and folic acid. By the day of discharge he was able to walk unassisted and his mental status had improved [4].

The neurological and psychiatric symptoms that were described in the case reports, including those in this paper, were all associated with low vitamin B_{12} (cobalamin) levels. Clinical neurological symptoms related to vitamin B_{12} deficiency include central nervous system manifestations and peripheral nervous system manifestations [9,10]. The following neurological symptoms were described: spastic tonus, increased reflexes, decreased vibration sensitivity and proprioception, reduced intellectual function, global dementia or amnesia, paralysis, optic neuropathy and ophthalmoplegia [3,4,11]. Patients with vitamin B_{12} deficiency may also present hematological manifestations, such as macrocytic anemia. These symptoms are, unlike the psychiatric symptoms, well-described in the literature and beyond the aim of this review. The relationship of vitamin B_{12} deficiency to psychiatric symptomatology is far more controversial. However, a psychiatric presentation with prominent psychiatric symptoms may be the first presenting symptom of vitamin B_{12} deficiency, and can occur in the absence of the well-known neurological and hematological changes [12]. Patients may present violent behavior or more subtle personality changes [13]. Anything from a mild mood disorder to grossly psychotic behavior may be encountered (confusional state, depression, hypomania, severe agitation and florid psychosis) [14]. Also, vague complaints such as fatigue, generalized weakness and loss of memory have been documented [9]. A poor diet status among a certain group of psychiatric patients makes them prone to vitamin B_{12} deficiency. One study [15] reported a 15% incidence of vitamin B_{12} deficiency among patients with psychiatric disorders.

Nitrous oxide has been documented as a known cause of deficiency of vitamin B_{12}, [16] and the enzymes in which it is a cofactor, [3] through the inactivation of vitamin B_{12} in vivo as a result of irreversible oxidization of its cobalt ion. This results in the incorporation of abnormal fatty acids into the myelin sheath [17–19] and decreased DNA formation [20].

In addition to the vitamin B_{12}-related explanation, it can be hypothesized that the psychomimetic effects of N_2O, such as hallucination, agitation and disorientation may be due to the