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Case Report

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Hilarious Gas Poisoning in Emergencies: An Atypical Case of Nitrous Oxide Poisoning

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Abstract

Background: Chronic nitrous oxide poisoning induces irreversible inactivation of vitamin B12, affecting two biochemical reactions that are essential for the proper functioning of the body. The prognosis is excellent when treated quickly and adequately. We present a case of a 23-year-old Caucasian woman with symptomatology due to chronic nitrous oxide inhalation.
Case presentation: A 23-year-old Caucasian woman was admitted into the emergency department with confusion and gait disturbance. Following the in-depth history and laboratory tests, chronic nitrous oxide poisoning was confirmed, and vitamin B12 supplementation was started promptly.
Conclusion: Our case demonstrated a clinical presentation and biological abnormalities typical of nitrous oxide (N2O) poisoning. The misuse of N2O is easy to access, the cylinders are over the counter, and there has been an appearance for a few years of mega-conditioning. The recreational misuse of nitrous oxide is mainly observed in young populations. It is important to raise the awareness of the nursing staff on the increase in their consumption. The treatment is based on vitamin B12 supplementation and long-term addiction monitoring.

Keywords

poisoning, nitrous oxide, vitamin B12

Background

Cobalamin or also called vitamin B12 is a water-soluble substance not synthesized by the human body, but which plays an essential role during DNA synthesis and hematopoiesis. It acts as a cofactor in two essential biochemical reactions. Nitrous oxide is a toxic substance which will induce the irreversible inactivation of vitamin B12. We decided to publish this case report because of the rarity of this pathology and given the observation, caused in part by some publicity on social networks, of the increase in the consumption of nitrous oxide in the young population of our western countries. It is a medical emergency whose anamnesis and biological examinations are characteristic, will allow a rapid diagnosis, and with appropriate treatment (vitamin supplementation) will lead to a favorable prognosis.

Case Presentation

A 23-year-old Caucasian patient was admitted to the emergency department with confusion and gait disturbances.

The anamnesis was not very helpful; the patient's sister-in-law reports having found her in a deplorable state of hygiene and with delusional remarks (vision of non-real people, etc.) in a depressive context due to a romantic separation. The patient complains of pain in the left calf and feels dyspneic. During the interrogation, she did not reveal any history and did not take any medication. She has no alcohol and smoking addiction.

On admission, blood pressure was 114/62mmHg, heart rate 100 beats per minute, respiratory rate 22 breaths per minute, oxygen saturation 100% on room air, and core temperature 38 .4°C.

On clinical examination, she has deplorable hygiene, and is mentally brady and dehydrated. Cardiopulmonary and abdominal examinations are normal. In the lower limbs, the patient has pain, redness in the left calf, and multiple abrasion-type wounds with signs of erysipelas. Neurological examination shows confusion and painful paraparesis with hypoesthesia under L1 of the left lower limb.

Faced with this clinical picture, the following additional examinations are carried out. Blood gas analysis revealed pH 7.50 (7.35-7.45), pCO 25mmHg (35-45 mmHg), pO2 128mmHg (75-90 mmHg), HCO3 19mmol/L (22.0 –29.0 mmol/L), base excess (BE) 2mmol/L (−2 to 2 mmol/L), SaO2 97.4% (95–99%) and lactate 1 mmol/L (0.50 – 2.00 mmol/L).

Biology shows hemoglobin at 7.5 /dL (11.5-15g/dL), leukopenia at 2.12 10^3/microL (3.8-11.4 10^3/microL) with neutropenia at 0.17 10^3/microL (1.4-7-7 10^3/microL), thrombocytopenia at 133000 (150-455 10^3/microL), disturbed coagulation with PTT and INR outside the norms, increased D-dimers, CRP at 316 mg/L (0-5 mg/L), no ARF and no ionic disorders. Urinary toxicology came back negative. The entire bacteriological map (EMU, blood cultures) is sampled.

The electrocardiogram revealed sinus tachycardia. A radiological assessment with a cerebral scanner and a thoraco-abdominal scanner is carried out. A right lower lobar and segmental postero-basal pulmonary embolism of the left lower lobe is highlighted.

Carrying out an additional biological assessment with an anemia assessment which highlights a collapsed vitamin B12 and a thrombophilia assessment with a markedly increased homocysteine.

Given the pancytopenia, the pulmonary embolism, and the neurological state, it was decided to carry out monitoring in the intensive care unit.

According to hematological advice, given severe pancytopenia, an emergency marrow puncture should be performed to rule out any acute leukemia.

When she arrived in intensive care, an in-depth hetero anamnesis was taken, the sister-in-law told us that she had found empty nitrous oxide canisters in the apartment.

Given the high suspicion of nitrous oxide poisoning, an introduction of intravenous supplementation with folic acid, vitamin B12, and at the level of admission biology, the dosage of methylmalonic acid was added and subsequently methylmalonic acid came back positive with a high level.

On the neurological level, a cerebral MRI and a spinal MRI were performed and came back reassuring. A lumbar puncture shows no abnormalities, and electromyography shows conduction blocks.

The diagnosis of chronic nitrous oxide poisoning was confirmed, and treatment with vitamin supplementation was instituted. We see a gradual improvement in pancytopenia and encephalopathy.

The patient was transferred to neurological rehabilitation for multidisciplinary care. Despite the rehabilitation, there are still sequelae with the need to use orthoses because the lady maintains a paresis of the elevator muscles of the feet.

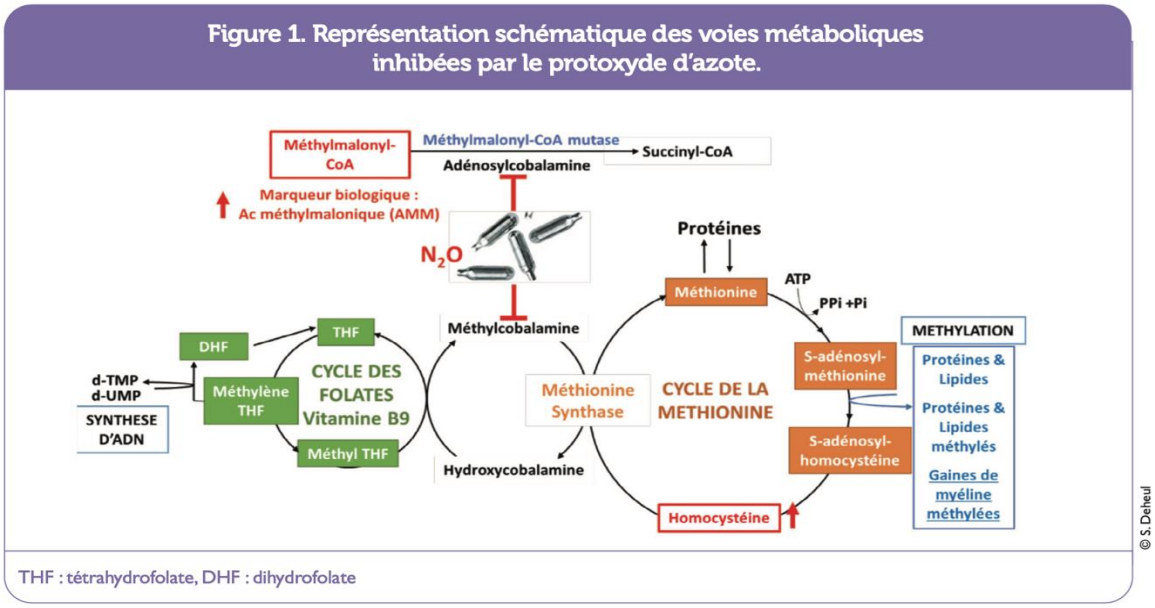
Discussion

Vitamin B12, also called cobalamin, is a water-soluble substance not synthesized by the human body, but which plays an essential role during DNA synthesis and during hematopoiesis [1].

It acts as a cofactor in two essential biochemical reactions: in the form of methyl-cobalamin (MeCbl), cofactor of cytoplasmic methionine synthase, and in the form of adenosylcobalamin, cofactor of mitochondrial L-methyl-malonyl-CoA mutase [2] [3].

Methionine synthase allows the cytoplasmic formation of methionine and tetrahydrofolate (THF, which is the reduced and active form of folic acid) from methyl-THF and homocysteine. The THF is then transformed into N5, N10methylene-THF, which is involved in the synthesis of DNA by promoting the methylation of deoxyuridine-5'-monophosphate (dUMP) into deoxythymidine-5'-monophosphate (dTMP). The generation of S adenosyl methionine from methionine is involved in various methylation reactions, including those involved in the synthesis of myelin components [4]. Methylmalonyl-CoA mutase allows the mitochondrial generation of succinyl-CoA, which enters the Krebs cycle and is involved in energy and cellular metabolism. (Fig.1)

Figure 1. Représentation schématique des voies métaboliques inhibées par le protoxyde d'azote.



THF : tétrahydrofolate, DHF : dihydrofolate

Inhalation of nitrous oxide induces irreversible inactivation of vitamin B12 by oxidation of the cobalt atom [5] and blocks the conversion of homocysteine into methionine and the conversion of methyl-malonyl-CoA into succinyl-CoA. This effect appears after 45 minutes in humans exposed to concentrations above 400 ppm [5]. In general, the clinical signs of a vitamin B12 deficiency (secondary to a deficiency in intake, absorption, etc.) only develop late, a few years (5 to 10 years) after the onset of the disease. cobalamin deficiency when hepatic reserves are depleted [6]. This could explain the condition of chronic exposure to N2O to see symptoms associated with vitamin B12 deficiency. Clinical manifestations may appear early after inhalation of N2O in patients with low vitamin B12 reserves [4]. In our case, the patient had recent emotional problems (breakup) and would have been found with several 2 kg canisters around her, which suggests a clinical and biological alteration

secondary to acute nitrous oxide poisoning. Indeed, there are a large number of packaging of nitrous oxide cylinders that are available over the counter, which promotes access, especially to young people.

The clinical picture related to vitamin B12 deficiency secondary to nitrous oxide poisoning includes neurological, psychological, and hematological damage.

On the neurological level, the inhibition of myelin synthesis leads to demyelination, swelling of the axons, and ultimately to a loss of substance [7]. The clinical presentation could correspond to demyelinating polyneuropathy, axonal neuropathy, or posterior cord syndrome [8] [5]. Electromyography makes it possible to differentiate between demyelinating polyneuropathy and axonal neuropathy. The posterior cord syndrome is characterized by a so-called "inverted V" T2 hypersignal on magnetic resonance imaging [5].

On the hematological level, the abnormalities frequently observed are macrocytosis, anisocytosis, hyper-segmentation of neutrophils, non-regenerative macrocytic anemia, thrombocytopenia, leucopenia and pancytopenia [6] [9].

At the psychiatric level, the mechanism by which N2O inhalation induces psychoses is unclear. Among the hypotheses mentioned, the appearance of the symptomatology would be secondary to cerebral anoxia, methemoglobinemia, and acidosis secondary to the inhalation of N2O or the action of N2O on the synthesis of monoamine neurotransmitters, such as dopamine, by increasing the synthesis of BH4 (tetrahydrobiopterin) [10] or finally by hypovitaminosis B12. Clinical manifestations include memory loss, depression, hypomania, dementia, paranoid psychosis with auditory, visual hallucinations and "megaloblastic madness"[7].

Hyperhomocysteinemia resulting from the inactivation of cobalamin represents a risk factor for the occurrence of thromboembolic events [11] [8].

The clinical picture described above is compatible with that presented by our patient. If the hypothesis of N2O poisoning had been mentioned on admission to the emergency room, performing an invasive procedure (marrow puncture, lumbar puncture) or costly procedure (cerebral MRI) could have been avoided.

The diagnosis of nitrous oxide poisoning is very often made with a certain delay because patients are generally admitted to the emergency room with an altered neuropsychiatric state, which does not allow a reliable anamnesis, as was the case for our patient. It is therefore important to make emergency physicians aware of this scourge (clinical presentation, diagnostic method, and therapeutic management) which is increasingly common in our society.

Faced with a clinical picture suggesting nitrous oxide poisoning, the search for a vitamin B12 deficiency must be systematic. However, plasma cobalamin levels may be normal because plasma vitamin B12 cannot differentiate between active vitamin B12 and its inactive oxidized form [4]. The markers of choice for all-cause cobalamin deficiency are homocysteine and methylmalonic acid (substrates of reactions catabolized by vitamin B12).

Homocysteine is less specific because it also increases in cases of vitamin B9 and B6 deficiency, kidney failure, and very rare hereditary metabolic diseases, and it can also be influenced by certain dietary parameters (alcohol, coffee) [4] [12]. Nevertheless, a study carried out by Redonnet-Vernhet et al. on 12 cases of patients admitted to the emergency room of the Bordeaux University Hospital after N2O poisoning showed that only two patients had a vitamin B12 level below normal but that all presented moderate to severe hyperhomocysteinemia, he recommends, in conclusion, a systematic measurement of homocysteine in case of suspicion of N2O poisoning [13].

The reaction catalyzed by methylmalonyl CoA mutase is not affected by other vitamins; therefore, methylmalonic acid (MAA) is considered a more specific marker of vitamin B12 deficiency [3]. A plasma increase in the MA level can be observed in the event of renal failure, intestinal infections, or in the event of MMA-CoA-mutase deficiency and is therefore not specific to N2O poisoning [14] ... It should be noted that the plasma MA level may be normal in the event of chronic N2O poisoning, unlike the homocysteine level, which remains high in a patient who takes vitamin B12 preventively [14].

In the case of our patient, the plasma level of vitamin B12 achieved in the context of pancytopenia had collapsed, the homocysteine level achieved as part of a thrombophilia assessment was high. The methylmalonic acid level, measured late on the admission biology to avoid being distorted because vitamin B12 supplementation had already been initiated, was high. All the biological and clinical criteria were therefore met to conclude that N2O poisoning was present in the absence of other pathologies demonstrated.

To date, in the literature, there are no specific recommendations for therapeutic management of patients admitted for nitrous oxide poisoning. Nevertheless, a complete eviction of this gas is essential. Vitamin B12 supplementation is done according to the scheme proposed in case of absolute deficiency [5]. Our patient received 1mg of cyanocobalamin intravenously for 10 days, followed by oral maintenance once a day for a total of two months. Partial clinical and biological improvement of the patient were quickly observed. At the end of her hospitalization, the patient benefited from neurological rehabilitation for persistent painful paraparesis with hypoesthesia and dysesthesia under L1 of the left lower limb, for one month.

After a follow-up of eight months, we observe in the patient persistence of a paresis of the elevator muscles of the foot in slow improvement, despite a complete eviction of laughing gas, vitamin B12 supplementation, and well-conducted physiotherapy. The patient has been off work since her hospitalization. This strongly calls into question the long-term impact of N2O poisoning both on the health of patients and on the socio-economic level (in an increasingly aging society).

Conclusion

Ultimately, the problem related to N2O poisoning is secondary to its recreational use by mostly young patients. The availability of this gas over the counter and its addictive nature are the main factors favoring its misuse. It is important to make young people aware of the consequences and their long-term impact in the event of acute or chronic N2O poisoning. It is also important to raise the awareness of the nursing staff, mainly the emergency physicians, of the clinical presentation and the biological abnormalities found in the event of nitrous oxide poisoning. This

would limit diagnostic delays and perhaps reduce the risk of persistent sequelae in the long term. This could also help reduce the socio-economic impact by limiting, for example, the costs induced by the overall care of these patients.

Competing interests: not applicable

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