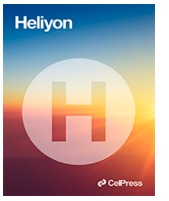
Heliyon 9 (2023) e13473

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon



Case report

Nitrous oxide inhalation-induced cerebral venous sinus thrombosis in a 20-year-old man: A case report

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ARTICLE INFO

Keywords:
Nitrous oxide
Cerebral venous sinus
Thrombosis
Case report

ABSTRACT

Nitrous oxide is increasingly abused in the young population and has been verified to induce neuropathy, myelopathy, encephalopathy, and thrombosis. Nitrous oxide-related thrombosis was identified in the coronary artery, ascending aorta, pulmonary artery, and deep vein in the lower extremities. Cases with nitrous oxide abuse-related thrombosis in cerebral veins or cerebral venous sinus have rarely been reported, and confounding risk factors for thrombosis other than nitrous oxide exist in previous cases. Here, we report a case of probable nitrous oxide abuse-related cerebral venous sinus thrombosis without common confounding risk factors for thrombosis except for nitrous oxide.

1. Introduction

Nitrous oxide is commonly used as a food aerosol propellant, inhalational anesthetic and engine accelerant [1]. Nitrous oxide abuse has become common in the young population for recreation, as it can cause euphoria, analgesia and hallucinations [2]. During its history, nitrous oxide has been found to induce neuropathy, myelopathy, skin hyperpigmentation, and anemia, mainly due to acquired deficiency in cobalamin metabolism [3]. In recent years, several clinical cases of nitrous oxide abuse have been associated with thrombosis both in veins and arteries [1,4,5]. Here, we report a case of probable nitrous oxide abuse-related cerebral venous sinus thrombosis.

2. Case report

A 20-year-old man presented to the Department of Emergency and reported a history of repetitive paroxysmal convulsions within 1 day. The patient developed the first typical tonic-clonic seizure like gazing upward with both eyes and foaming at mouth immediately after quarreling, which lasted for approximately 3 minutes and ceased spontaneously. The second tonic-clonic seizure occurred in the emergency room approximately 1 hour after the first seizure and lasted for more than 5 minutes. The second seizure was stopped by diazepam (10 mg, intravenously), and then the patient presented uracratia and transient delirium. The patient's mother reported that the patient began to inhaled nitrous oxide 3 months ago, but the frequency and volume of nitrous oxide inhalation were unclear. An emergent computed tomography (CT) scan found hypointensity in the left temporal lobe with nodal hyperintensity inside (Fig. 1A).

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https://doi.org/10.1016/j.heliyon.2023.e13473
Received 21 August 2022; Received in revised form 6 January 2023; Accepted 31 January 2023
Available online 7 February 2023

The patient was transferred to the Department of Neurosurgery, and neurological examination revealed no abnormal signs. Three days after seizure, Patient received magnetic resonance imaging (MRI), magnetic resonance venogram (MRV) and digital subtraction angiography (DSA), MRI reported infarction in the left temporal lobe with nodal hemorrhage inside (Fig. 1B C&D), MRV and DSA revealed a thrombus in the superior sagittal sinus, left transverse sinus, and left sigmoid sinus (Fig. 1E&F). The patient was then transferred to the Department of Neurology and received lumbar puncture, which revealed an intracranial pressure of more than 200 mmH_2O, normal leukocyte counts, protein levels, and IgG indexes in the cerebrospinal fluid. Blood tests found elevated serum homocysteine (26.3 μmol/l, normal range: <15 μmol/l) levels, normal serum vitamin B12 (243 pg/ml, normal range: 180–914 pg/ml) and folic acid (4.87 ng/ml, normal range: 3.2–18.5 ng/ml) levels, and slightly elevated D-dimer (1.31 mg/l, normal range: <0.55 mg/l) levels. Routine blood, hepatic and renal function, toxicological screening, thyroid function, tests for anticardiolipin antibodies and tests for antibodies against human immunodeficiency virus and syphilis were all negative. The electroencephalogram was normal.

We gave the patient warfarin (2.5 mg, orally, once per day), mannitol (25 g, intravenously, once per 8 hours), mecobalamine (0.5 mg, orally, three times per day), folic acid (5 mg, orally, three times per day), and valproic acid (500 mg, orally, twice per day). During the 9 days in the hospital, no more seizures occurred, and the patient did not complain of headache from onset to discharge.

Six and nine months after onset, the patient received a follow-up MRV examination, and MRV showed that the previous intracranial venous sinus thrombosis did not dissipate or relapse. After discharge, there were no recurrent seizures or neurological impairments. The level of homocysteine in the patient's blood reached the normal level (14.2 μmol/l, normal range: <15 μmol/l).

3. Discussion

Before this report, only 2 patients presented with intracranial thrombi, one in the isolated cortical vein [6] and the other in the venous sinus [7]. The patient with an isolated cortical vein presented motor aphasia and slight paralysis in the right face, right half of

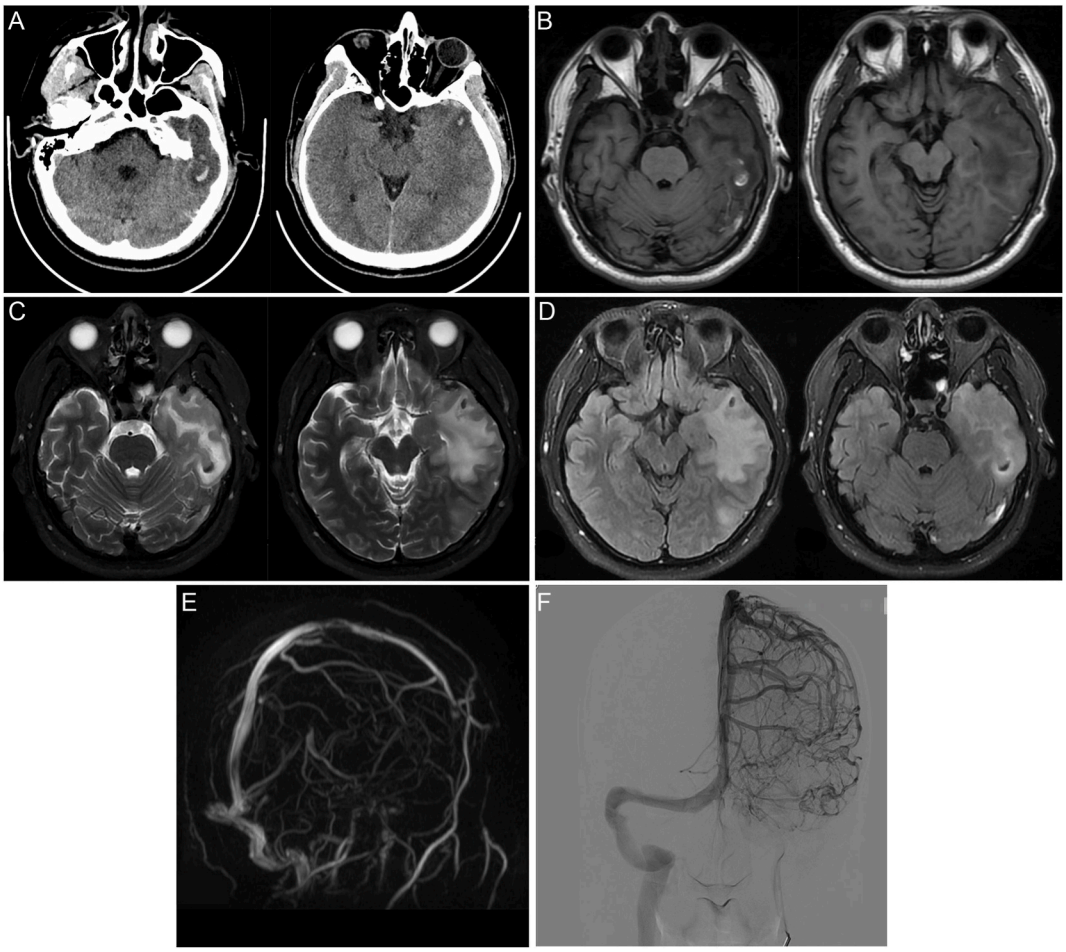

Fig. 1. Imaging of the patient showed cerebral infarction with hemorrhage inside the left temporal lobe and thrombus in the posterior part of the superior sagittal sinus, left transverse sinus, and left sigmoid sinus. (A) Computed tomography; (B) T1-weighted magnetic resonance imaging (MRI); (C) T2-weighted T2 imaging; (D) Fluid attenuated inversion recovery sequence imaging; (E) Magnetic resonance venogram; (F) Digital subtraction angiography.

the tongue, and right upper extremity after inhaled nitrous oxide for 1 week. However, this patient also took contraceptive drugs 10 days before onset [6], which is known as a risk factor for cerebral venous thrombosis [8]. The other patient with thrombi in the transverse sinus, sigmoid sinus, and jugular vein presented confusion, hallucinations, leg paralysis and falls after abusing nitrous oxide for several weeks. However, this patient was 11 weeks pregnant [7], which is also known as a risk factor for cerebral venous thrombosis [8]. Therefore, the association between nitrous oxide abuse and intracranial thrombus in the 2 previous cases was not very credible. In this report, the patient had no other known common risk factor for thrombosis, linking nitrous oxide abuse to intracranial thrombosis more likely.

In addition to intracranial thrombosis, nitrous oxide abuse was also reported to induce thrombosis in other vessels, including the coronary artery [4], ascending aorta [5], pulmonary artery [1], and deep vein in the lower extremities [1]. In one case, the nitrous oxide abuse-induced aortic thrombus caused embolism in the axillary artery and right middle cerebral artery [5].

The mechanism by which nitrous oxide induces thrombosis has seldom been discussed. Although previous studies attributed nitrous oxide-induced neuropathy, myelopathy, encephalopathy, and anemia to acquired deficiency in cobalamin metabolism [1,3], the cause of nitrous oxide-induced thrombosis is unclear. Most existing studies have speculated that nitrous oxide causes thrombosis by hyperhomocysteinemia [1,9], possibly due to atherogenesis [10]. However, atherogenesis may not explain most cases of nitrous oxide-induced thrombosis, as these patients are relatively young without definite evidence of atherosclerosis and present acute onset [1,4–7].

Moreover, nitrous oxide-induced thrombosis may also be attributed to acquired methylenetetrahydrofolate reductase (MTHFR) deficiency [1]. A patient with genetic MTHFR deficiency was reported to have deep vein thrombosis of the upper extremity and retinal vein without nitrous oxide [11], and pediatric retinoblastoma patients with MTHFR gene mutation were more likely to suffer choroidal infarction after nitrous oxide induction and subsequent ophthalmic artery chemotherapy [12]. Notably, one of the previous cases of nitrous oxide-induced intracranial thrombosis also had MTHFR mutations [6]. These findings indicate that patients with genetic MTHFR deficiency may have a tendency toward thrombosis; therefore, it is possible for nitrous oxide-induced acquired MTHFR deficiency to cause thrombosis. Regrettably, MTHFR and its gene polymorphsim were not tested on the reported patient because those are not routine tests in our hospital and the patient was not willing to take them when he was informed it might not impact his interventions. Additionally, hyperhomocysteinemia-induced inhibition of the anticoagulation system and promotion of the coagulation system may also be possible reasons for nitrous oxide-induced thrombosis. However, more evidence is needed to further illustrate the effect of hyperhomocysteinemia on coagulation in detail.

In all 2 previous cases [6,7] and this case of possibly nitrous oxide-induced intracranial thrombosis, the patients presented a favorable outcome after anticoagulative therapy accompanied by vitamin B12 and folic acid supplementation.

Nitrous oxide abuse might induce thrombosis, including intracranial thrombosis. Although treatment with anticoagulative drugs presented favorable results in existing patients, avoiding nitrous oxide abuse may be a cost-effective and effective way to prevent this problem. The possible mechanism between nitrous oxide and thrombosis is unclear, and hyperhomocysteinemia and MTHFR deficiency may play roles in it.

Author contribution statement

All authors listed have significantly contributed to the investigation, development and writing of this article.

Funding statement

The present study was supported by the Sichuan Science and Technology Program (2019YFH0196); 1·3·5 project for disciplines of excellence–Clinical Research Incubation Project, West China Hospital, Sichuan University (2018HXFH022); and the National Natural Science Foundation of China (81500959).

Data availability statement

Data included in article/supp. material/referenced in article. Some or all data, models, or code generated or used during the study are available from the corresponding author by request.

Declaration of interest's statement

The authors declare no competing interests.

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