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Nitrous oxide misuse: a clue not to be missed in young patients with venous thromboembolism

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ABSTRACT

A 27-year-old man presented with altered mental status and unilateral right lower limb swelling. Brain imaging and cerebrospinal fluid analysis were unremarkable. He reported history of nitrous oxide misuse after he recovered from his delirium. The diagnosis of drug induced psychosis was made. The right lower limb swelling was found to be due to extensive deep vein thrombosis. In another case, a 21-year-old woman presented with headache, vomiting and dipoplia. Brain imaging showed extensive cerebral venous sinus thrombosis. She also misused nitrous oxide. Both cases had low-normal vitamin B12 and elevated methylmalonic acid, consistent with nitrous oxide misuse. The woman was found to have elevated homocysteine because of functional vitamin B12 deficiency. Homocysteine was not measured in the man. Raised homocysteine is associated with increased thrombosis risk. Fourteen cases of nitrous oxide misuse associated arterial and venous thrombosis have been reported. These two cases highlighted the importance of inquiring about recreational drug use in young patients who presented with apparently unprovoked venous thromboembolism.

KEYWORDS: nitrous oxide, venous thromboembolism, thrombosis

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Introduction

In the COVID-19 era, we ought to consider the possibility of COVID-19 infection related thrombosis in young patients presenting with venous thromboembolism (VTE). This is especially true if the patient has no other thrombosis risk factors. In places where adenovirus-based COVID-19 vaccine is used, vaccine-induced immune thrombotic thrombocytopenia (VITT) is another consideration. More commonly, illicit drug users especially intravenous drug users present with VTE. Nitrous oxide misuse (NOM) via inhalation (Fig 1), which is not uncommon among the young adults, has also been associated with venous and arterial thrombosis.[1] We report two cases of NOM related VTE to highlight its presentations and the importance of including NOM as part of a comprehensive history taking in young patients presenting with clinical features suggestive of VTE.

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Case presentation

Case 1

A 27-year-old man with no significant past medical history (PMHx) presented with 1 week of confusion, hallucination and right lower limb swelling. He was first treated as a case of meningoencephalitis with ceftriaxone and acyclovir. His subsequent investigations including the cerebrospinal fluid analysis, magnetic resonance imaging (MRI) and magnetic resonance venogram (MRV) of brain showed no intracranial abnormalities. After he recovered from the delirium a few days after his admission, he reported a history of NOM over the past 1 year. A diagnosis of drug-induced psychosis was made. He underwent a duplex venous ultrasonography (US) for the right leg swelling. It showed a deep vein thrombosis (DVT) from the distal iliac vein to popliteal vein. A computed tomography (CT) of abdomen and pelvis showed extension of thrombus into the inferior vena cava and no evidence of malignancy. His thrombophilia screen performed during the acute phase was grossly normal. The slightly low anti-thrombin was likely the result of low molecular weight heparin (LMWH) treatment. During his stay, he was also found to have bilateral lower limb sensory loss secondary to severe functional vitamin B12 deficiency without macrocytosis. His MRI spine showed features consistent with subacute combined degeneration of spinal cord (SCDSC). He was treated with rivaroxaban and vitamin B12 replacement. He was discharged well but has not attended for thrombosis clinic follow-up. (See Table 1 for investigation results.)

Case 2

A 21-year-old woman presented with 1 month of headache, vomiting and dipoplia. She had no significant PMHx. Further inquiry revealed NOM (2–4 canisters daily) for the past 1 month to help relieve the headache. Her examinations were unremarkable. A plain CT of brain showed features suggestive of cerebral venous sinus thrombosis (CVST), which was confirmed subsequently by a CT venogram and MRV. Her thrombophilia screen was unremarkable other than the elevated homocysteine secondary to functional B12 deficiency. There was no macrocytosis. She was treated with LMWH then switched to rivaroxaban. She was discharged well but did not attend for thrombosis clinic follow up. (See Table 1 for investigation results.)

Table 1. Summary of investigations results during early phase of admission

Investigations	Case 1	Case 2	Reference range
Homocysteine total	Not done	58.2 umol/l	0–15 umol/l
Active B12	36	63 pmol/L	25–108 pmol/L <25: B12 deficiency 25–70: possible B12 deficiency >70: B12 depleted
Methylmalonic acid	11,427	675 nmol/L	0–280 nmol/L High level suggests functional vitamin B12 deficiency at the tissue level
Anti-phospholipid syndrome screen	Negative	Negative	
Protein C activity	114.1 iu/dL	121.9 iu/dL	81.1–146.3 iu/dL
Free protein S antigen	116.6 iu/dL	Not done iu/dL	80.2–137.4 iu/dL
Anti-thrombin activity	51.6 iu/dL	107.2 iu/dL	87–124.5 iu/dL
Prothrombin 20210	Normal	Normal	
Factor V Leiden	Not done	Normal	
JAK2 V617F	Not detected	Not done	

Discussion

According to the UK Office for National Statistics data for 2020, N_2O was the second most prevalent drug used among young adults aged 16–24 years.[2] The Global Drug Survey 2021 report showed 9.7% of the 32,022 participants have used N_2O in the last 12 months.[3] Its popularity is due to its low cost, widespread availability (eg it is found in whipped cream canisters in the food industry), legal status and perceived harmlessness.[1,4] It causes euphoria seconds after inhalation and the effects disappear within minutes.[1]

In one study, among NOM patients who sought medical attention, 80% presented with neurological complaints like numbness, paraesthesia and weakness.[5] Myeloneuropathy, SCDSC, peripheral neuropathy or polyneuropathy and myelopathy are some commonly reported neurological sequelae.[5] Other presentations include delirium, delusion, pneumomediastinum, skin hyperpigmentation and cytopenia.[5]

It was not until 2017 NOM was reported to be associated with thrombosis.[1] Fourteen cases of NOM related venous and arterial thrombosis have been reported so far.[1] The implicated thrombosis included extensive DVT, pulmonary embolism (PE), atypical site thrombosis such as CVST, mesenteric vein thrombosis, aortic arch thrombosis, ischemic stroke, myocardial infarction, and peripheral artery disease.[1]

N_2O impairs methyl-cobalamin function by oxidation.[1] Without functional methyl-cobalamin, homocysteine will accumulate as it cannot be converted to methionine.[1] The elevated homocysteine level is believed to be associated with increased venous and arterial thrombosis risk.[1] The inactive methyl-cobalamin displaces adenosyl-cobalamin (another form of B12) from mitochondria and leads to accumulation of methylmalonic acid (MMA).[1]

In NOM cases, cobalamin level is usually low or low-normal (as in our cases) but could be normal.[5] Raised MMA (as in our cases) and homocysteine level may be more accurate, but these may not be readily available, especially at the emergency department. Due to its short half-life and rapid elimination through lungs, it is

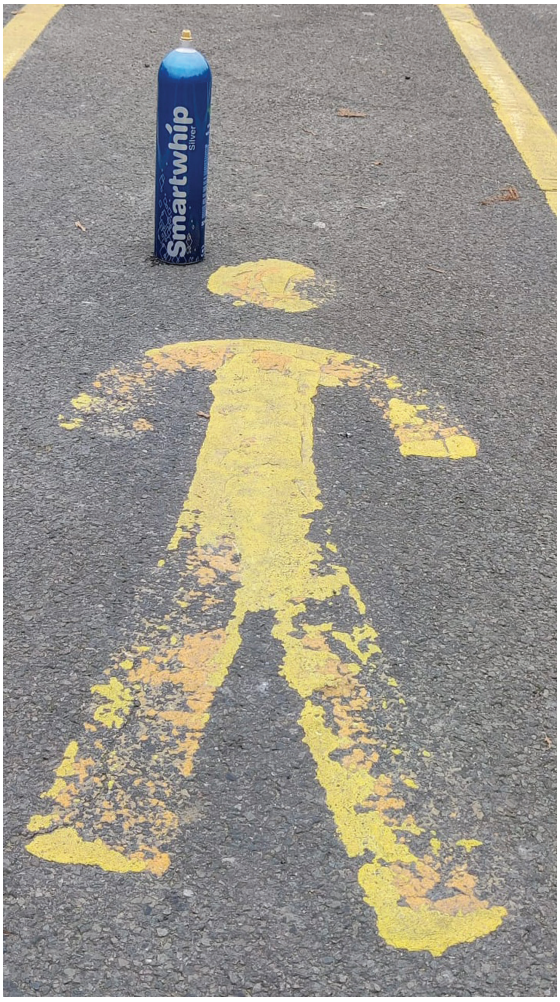

Fig 1. Nitrous oxide canister found in a neighbourhood park.

also difficult to screen for NOM, though blood and urine testing is possible.[5] The history of N_2O use is therefore of paramount importance in making the diagnosis of NOM associated thrombosis. In addition to NOM history, it is important to assess for active or recent COVID-19 infection in young patients who present with suspected VTE. In places where adenovirus-based COVID-19 vaccine is used, VITT needs to be considered. Onset of symptoms is usually 5–30 days (up to 42 days for isolated PE/DVT) post vaccine in VITT.[6] Failure to identify a history of NOM may result in unnecessary extended anticoagulation for mistakenly classified unprovoked VTE.

Treatment is abstinence, B12 replacement and anticoagulation. Anticoagulation duration of DVT and PE is generally 3 months as per provoked VTE cases.[7] For CVST, the anticoagulation duration is less well defined, generally between 3–12 months.[7]

Conclusion

NOM is associated with both arterial and venous thrombosis. It is important to consider NOM associated thrombosis in those who are young and have no additional thrombosis risk factors in addition to COVID-19 infection related thrombosis. VITT is another possibility in places where adenovirus based COVID-19 vaccine is used. Patients often present to the acute care facilities and acute physicians are reminded to include NOM in their history taking. Prevention is better than cure so better public education about the harm of NOM is vital. ■

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