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The role of Medical Imaging in the Investigation of Nitrous Oxide Toxicity

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Nitrous oxide (N_20) is a colourless, non-irritating gas initially described in medical practice in 1844, and is currently utilised as a safe, inhaled anaesthetic agent in dentistry and during labour to relieve pain. The term "laughing gas" is often coined to describe N_20 due to its euphoric and hallucinogenic effects. Adverse neurological effects of N_20 abuse were first described in 1978 in 14 dental practitioners[1]. The recreational use of N_20 is a growing public health concern, and has become increasingly popular in recent years, especially at parties and festivals to achieve a legal "high", with its use amongst Irish youths magnified in recent months due to repeated reports in the domestic media of related adverse health outcomes. N_20 is widely used in the catering industry as a propellant for whipping cream and can be legally purchased from catering outlets and on the Internet, with this ease of access an important factor in the rising incidence of its recreational abuse. Such has been the explosion in use amongst youths in recent years, N_20 is now reported to be the second most popular recreational drug in the UK[2] and it has become common place to see empty cannisters discarded on roadsides, playgrounds and other urban areas throughout the country.

N_20 is commonly inhaled through a balloon or bulb, with a rapid sensation of euphoria occurring within seconds. There is no associated hangover effect after consumption and normal functioning quickly returns after inhalation[3], additional factors adding to its popularity and abuse. Although not physically addictive, repetitive use can lead to psychological dependence, with chronic exposure leading to potentially serious consequences. Rarely, N_20 toxicity can occur acutely in the setting of acute exposure and pre-existing vitamin B_{12} deficiency. N_20 toxicity stems from its interaction with vitamin B_{12}, which it renders functionally inert, thus inducing a physiological state resembling that of a true vitamin B_{12} deficiency with resultant demyelination and gliosis in both the central and peripheral nervous systems. Clinical manifestations of N_20 toxicity are generally related to chronic high level exposure, with neurological sequelae most commonly reported including subacute combined degeneration of the spinal cord (N_20-SACD), myelopathy and peripheral neuropathy. The lower limbs more commonly affected than the upper limbs[4]. Demyelination of the dorsal columns of the cervical and thoracic cord appear to be the earliest manifestation of vitamin B_{12} deficiency and it is considered to be a reversible pathological stage, thus prompt diagnosis (both clinically and radiologically) and treatment is essential if suspected[5]. A Global Drug Survey in 2016 including over 100,000 participants found that 4% of those who used N_20 recreationally had experienced neurological symptoms[6]. There are no universally established treatment guidelines for

myeloneuropathy caused by N_20 toxicity, however treatment generally involves intra-muscular injections of hydroxocobalamin, with this treatment regimen derived from the standard vitamin B_{12} treatment course for traditional subacute combined degeneration of the spinal cord[7].

The increased incidence of N_20 abuse and subsequent toxicity amongst Irish youth has led to a significant increase in demand for imaging to accurately confirm the diagnosis and assess for potential adverse sequelae. MRI is the imaging modality of choice in assessing for spinal cord changes related to N_20-SACD. It is important to note that MRI may be normal despite clinically convincing symptoms[8] however spinal cord signal changes have been reported in 50-100% of patients presenting with N_20-SACD (7). Although imaging protocols vary based on institute, from our experience, whole spine sagittal T1, T2 and STIR sequences and T2/STIR axial sequences are sufficient to maximise diagnostic yield. MRI brain is not recommended unless there is a strong clinical suspicion of an alternative diagnosis, as is supported by current literature[7,9]. Unsurprisingly given the underlying pathophysiology, MRI features are identical to those of subacute combined degeneration of the spinal cord secondary to vitamin B_{12} deficiency. Axial sequences are most useful and classically demonstrates T2/STIR signal hyperintensity in the dorsal columns of the cord spanning multiple levels, with an “inverted V” or “inverted rabbit ears” appearance. The “inverted V” sign is caused by subacute, symmetrical, combined degeneration of the dorsal columns of the cervicothoracic spinal cord and is a specific finding associated with vitamin B_{12} deficiency[5]. On sagittal T2/STIR sequencing, longitudinal T2 signal hyperintensity is seen along the dorsal columns of the spinal cord. The lateral spinothalamic tracts are rarely involved. The cervical and upper thoracic cord are most commonly affected. Spinal cord lesions usually involve three or more spinal segments, with C3-C5 most commonly affected[10]. Rarer imaging features include mild cord swelling/oedema and subtle linear enhancement of the dorsal columns[9]. Given the increasing incidence of N_20 abuse in adolescents and young adults, awareness of the pathological manifestations of toxicity has increased, however MRI can also add significant value in ruling out other potential pathologies which can mimic this spinal cord syndrome. Unfortunately, MRI lacks specificity in determining the exact underlying pathological process responsible for the these spinal cord changes, with the findings of subacute combined degeneration of the spinal cord shared by other conditions, for example myelopathy caused by HIV infection, copper deficiency and vitamin E deficiency. MRI also lacks the ability to differentiate traditional subacute combined degeneration caused by a true vitamin B_{12} deficiency from N_20 toxicity induced spinal cord demyelination[7].

The increasingly prevalent recreational abuse of N_20 by Irish youths and adolescents is rapidly becoming a major public health issue due to its potential to cause significant neurological damage. Patients often conceal their recreational use of N_20 for various reasons, meaning a high clinical suspicion is necessary to make a timely diagnosis and thus treat and reverse potentially devastating neurological complications. It is important for both the treating Physician and Radiologist to be aware of the role, value and limitations of MRI in the diagnostic algorithm to ensure prompt diagnosis is made and timely treatment initiated.

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