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SCIENTIFIC LETTER

Multifocal neuraxial involvement in acute methanol intoxication: A series of two patients from rural India

Afectación multifocal del neuroeje en la intoxicación aguda por metanol: una serie de dos pacientes procedentes de la India rural

Dear Editor,

Methanol is a widely used industrial short-chain aliphatic alcohol with known neurotoxic properties.[1] Alcoholic beverage (beer, wine, and distilled spirits, among others) are people's main sources of exogenous methanol (also known as methyl alcohol).[1] Methanol is considered a poison in humans because it is slowly metabolized by alcohol dehydrogenase 1b (ADH1b) into toxic formaldehyde, which is further metabolized to formic acid.[1]

We herein report two patients with multifocal neuraxial involvement after acute methanol intoxication and the proper management of every one of them.

Case 1: A 22-year-old previously healthy man from rural West Bengal (India) presented with an acute-onset painless diminution of vision (DOV) for the last day. He got the news of the availability of "low-cost" unbranded liquor in a non-licensed hotel where he went. He was later found drunk and in a semiconscious condition. His past medical history was unremarkable, and there were no other symptoms. He also complained of burning sensations over both feet and palms and tingling/numbness in a stocking-glove pattern. Clinical examination revealed dilated pupils, which were very sluggishly reactive to direct and consensual light, and bilateral relative afferent papillary defect (RAPD). Fundoscopic examination revealed clear ocular media, hyperemic discs, and bilateral papilledema. Visual acuity was reduced to the perception of light in both eyes. Bilateral knee- and ankle-deep tendon reflexes were absent. He had reduced perception of all the sensory modalities below knee level. The rest of the neurological examination was normal.

Complete blood cell count and renal, thyroid, and liver function tests disclosed mild neutrophilic leukocytosis, raised erythrocyte sedimentation rate, and moderately increased transaminases and gamma-glutamyl transferase. A serum creatine phosphokinase level was raised (1080 UI/L). Arterial blood gas analysis revealed high-anion gap metabolic acidosis (HAGMA). Visual evoked potential (VEP) showed prolonged P100 latency involving both eyes (right more than left). A nerve conduction study revealed a sensorimotor (sensory more than motor) polyneuropathy (lower limbs more than upper limbs). Magnetic resonance imaging (MRI) of the brain on day five of admission revealed bilaterally symmetrical hyperintense lesions on T2-weighted imaging and FLAIR sequences involving lentiform nucleus and hypointense lesions over the corresponding areas on T1-weighted imaging; a contrast study revealed focal peripheral nodular enhancement (Fig. 1).

The patient was prescribed high-dose intravenous methylprednisolone (1 g/day for five days) and high-dose parenteral vitamin B1, B6, B12, and folic acid therapy and was subjected to visual rehabilitation therapy without any significant improvement. In the third month of follow-up, he complained of insidious onset, gradually progressive slowness of movements, stiffness of the body, tremulous limbs (pronounced at rest), and changes in speech. Neurological examination revealed symmetrical parkinsonism (appendicular more than axial rigidity, resting tremor, bradykinesia, hypomimia, apathy, and shuffling gait with decreased arm swing) and a mild persistent length-dependent polyneuropathy. The MDS-UPDRS score was 82/199 (the motor examination sub-score was 53/108). He was prescribed levodopa-carbidopa combination therapy (625 mg/day), pramipexole (2 mg/day), and trihexyphenidyl (2 mg/day) in a gradually escalating fashion. In the fifth month of follow-up, his MDS-UPDRS score improved to 20/199.

Case 2: A 31-year-old man from rural West Bengal (India) with a history of chronic alcoholism and tobacco abuse was referred to our clinic (on March 20th, 2021) with complaints of acute-onset static (somewhat spontaneously improved) bilateral painless DOV in the last month. History revealed recurrent bouts of nausea, vomiting, and hiccoughs since morning hours on February 16th, 2021, followed by sudden-onset painless bilateral DOV after binge drinking unbranded alcohol at midnight on February 15th, 2021. No other neurological deficits were reported. Neuro-ophthalmologic examination displayed bilaterally mid-dilated pupils, which were very sluggishly reactive to direct and consensual light,

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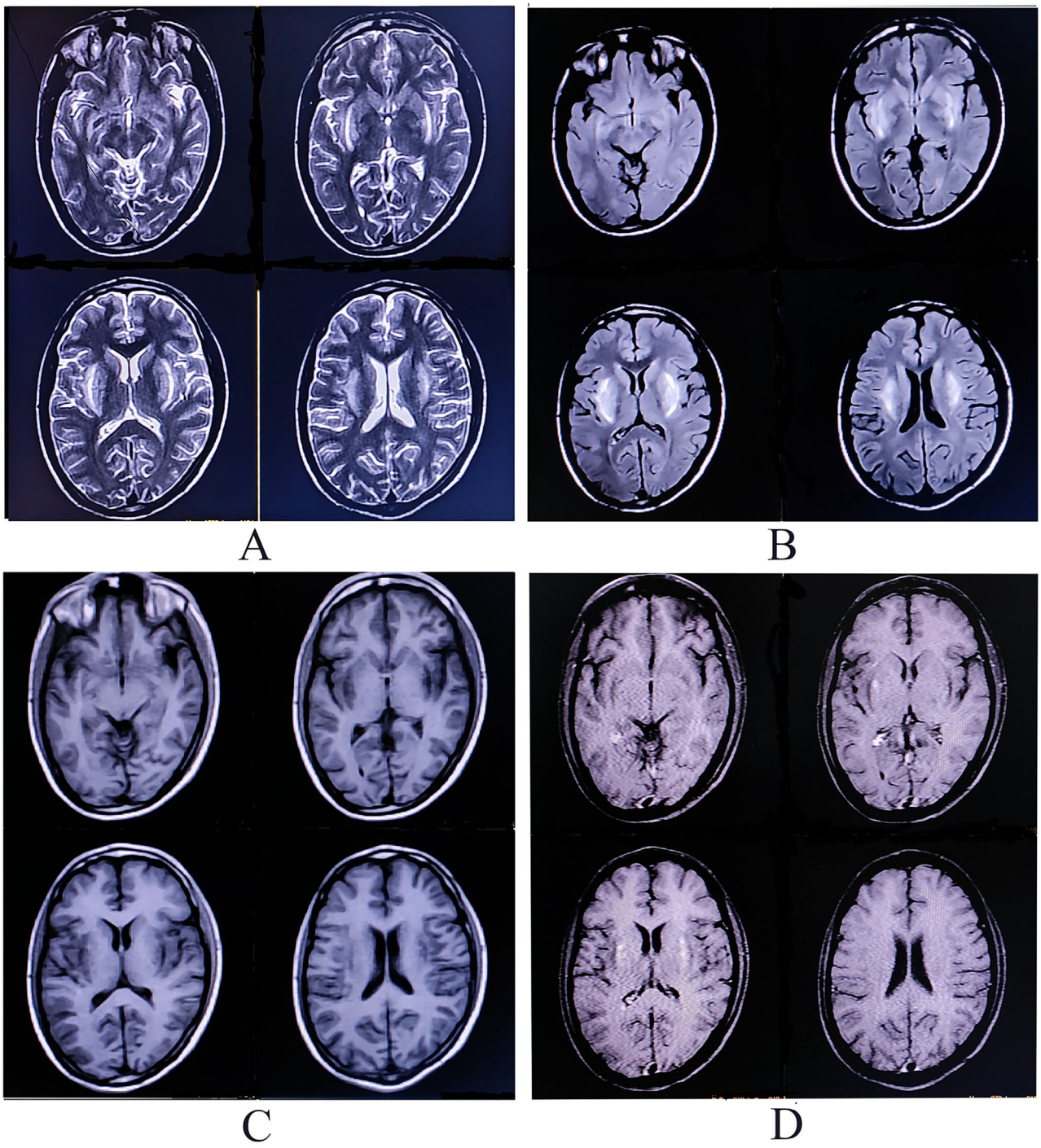

Fig. 1 MRI of the brain on day five of admission revealed bilaterally symmetrical hyperintense lesions on T2-weighted imaging (A) and FLAIR sequences (B) involving lentiform nucleus and hypointense lesions over the corresponding areas on T1-weighted imaging (C); contrast study (D) revealed focal peripheral nodular enhancement.

and no RAPD. Funduscopic examination revealed bilateral optic atrophy. Visual acuity was reduced to the perception of hand movements in both eyes. The rest of the neurological examination was normal. Complete blood cell count and renal, thyroid, and liver function tests only disclosed moderately raised transaminases and gamma-glutamyl transferase. Arterial blood gas analysis was normal (no HAGMA). VEP showed prolonged P100 latency involving both eyes (left more than right). MRI of the brain on day six of admission revealed bilaterally symmetrical contrast-enhancing lesions hyperintense on T2-weighted imaging and FLAIR sequences involving lentiform nucleus and hypointense lesions over the corresponding areas on T1-weighted imaging with blooming in GRE sequences (Fig. 2).

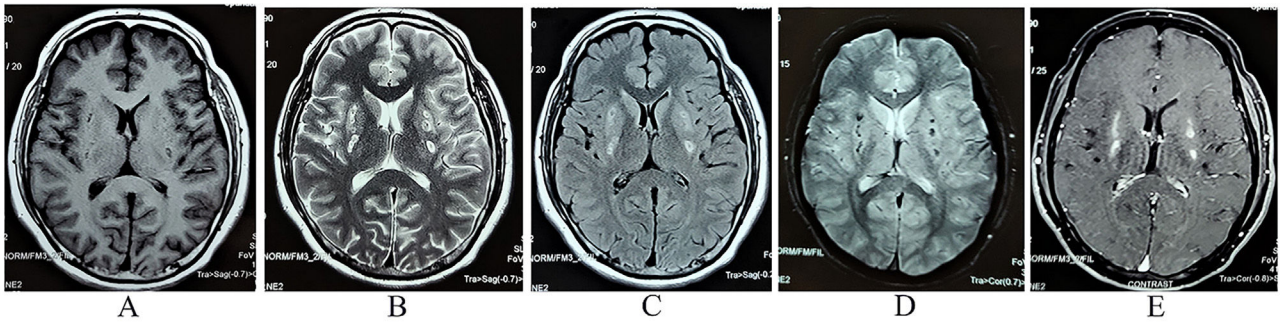

Fig. 2 MRI of the brain on day six of admission revealed bilaterally lesions involving the lentiform nucleus on T1-weighted imaging (A), which were hyperintense on T2-weighted imaging (B) and FLAIR sequences (C) with blooming in GRE sequences (D) and symmetrical contrast-enhancing (E).

The patient was prescribed high-dose intravenous methylprednisolone (1 g/day for five days) and high-dose parenteral vitamins B1, B6, B12, and folic acid therapy and was subjected to visual rehabilitation therapy without any significant improvement.

In both cases, blood glucose profile, lipid profile, and serum electrolytes were within normal range, hepatitis B, C, and HIV (1,2) serologies were negative. Cerebrospinal fluid analysis showed no abnormalities (including IgG index and oligoclonal bands). Serum and cerebrospinal fluid studies for relevant neuro infections and lactate levels were also non-contributoryfg. AQP4 and MOG antibodies were negative in both cerebrospinal fluid and serum. Targeted tests for Wilson disease and neurodegeneration with brain iron accumulation were negative. Autoimmune and connective tissue profiles, vasculitis, and paraneoplastic profiles were unyielding. Serum angiotensin-converting enzyme was normal. And so was the high-resolution tomographic scan of the thorax. The serum methanol level could not be tested due to insufficient infrastructure support. A provisional diagnosis of acute methanol intoxication was made.

After 12 to 24 h, methanol is converted to its toxic metabolites (formic acid and formaldehyde), leading to severe metabolic acidosis.[1] Formic acid inhibits mitochondrial cytochrome oxidase, resulting in tissue hypoxia; this effect is enhanced when the pH is low.[1] Notably, formic acid injection per se leads to optic disk damage, independently of acidosis; the ocular effects associated with methanol poisoning appear to be due to hypoxia in areas of the cerebral and distal optic nerves.[3] Formaldehyde and formic acid cause severe toxic effects on the central and peripheral nervous systems, but above all, on the basal ganglia and optic nerves.[1,2]

Methanol poisoning or deaths are frequent in India. The symptoms can range from mild to severe, depending on exposure and presentation time. A recent retrospective descriptive study of acute methanol toxicity reported that the majority of patients had onset of symptoms between 12 and 24 h; all patients had gastrointestinal symptoms, 97% of patients had visual disturbances, 91% had central nervous system manifestation, while frank coma was observed in 15%.[3] Regarding the peripheral nervous system, in a 6-year prospective longitudinal cohort study, no association was found between the severity of acute methanol poisoning and the prevalence of polyneuropathy.[4]

Methanol-induced optic neuropathy is a serious condition that may result in irreversible visual impairment or blindness related to damage and loss of function of the optic nerve and retina.[5,6] Despite the development of therapeutic approaches, visual sequelae are seen in up to 40% of survivors.[7,8] Thus, it continues to be a significant problem for healthcare systems worldwide.[5,6]

There is no clear explanation for why formic acid affects the retina, optic nerve, and basal ganglia (putamen) but does not involve other brain areas. Accumulating formic acid in high amounts in these areas has been suggested to lead to damage.[6–9] A possible explanation for this may be the expression of aquaporins, especially 1, 3, and 4, which are essential for the water and osmotic balance of brain cells and the optic nerve, which are not only responsible for transporting water but also polar molecules such as glycerol or methanol to these tissues.[6–9]

Early recognition, treatment, and occupational safety protection are crucial in methanol toxicity.[10] The treatment of acute methanol intoxication usually aims to prompt the elimination of methanol and prevent complications.[10] Ethanol and fomepizole competitively inhibit alcohol dehydrogenase and impede ethanol metabolism and accumulation of its metabolites.[10] Folic acid and folinic acid metabolize toxic formic acid to non-toxic carbon dioxide and water.[10] Given the relative safety of folate, it should be considered an adjunctive treatment in methanol poisoning, especially in patients with an anion gap metabolic acidosis.[11] Because folic acid may decrease cobalamin reserves, treatment with vitamins B6 and B12 is recommended for up to one month.[10,12] Supportive measures include managing acidosis, coma, seizures, encephalopathy (e.g. vitamin B1), and airway maintenance.[10,12] Hemodialysis is used ultimately when other therapeutic measures fail.[10,12] Complications such as optic neuritis, polyneuropathy, and parkinsonism warrant special attention. Funduscopy and MRI of the brain should be performed to look for these potential complications. High-dose steroids are generally used for treating optic neuritis, while levodopa has been tried in cases of methanol-induced parkinsonism.[6]

Parkinsonism has rarely been reported as a long-term consequence of methanol intoxication. In 2012, a case of acute methanol intoxication with metabolic acidosis, bilateral optic neuritis, and involvement of the central and peripheral nervous system was reported.[13] MRI findings were consistent with bilateral putaminal necrosis.[13] Two years later, a young male developed acute onset parkinsonism,

optic neuritis, and peripheral neuropathy with evidence of putaminal necrosis following methanol poisoning[6]. In 2019, another case of methanol poisoning-induced parkinsonism with optic neuritis was reported.[7]

In our series, case 1 developed bilateral irreversible optic neuropathy, axonal sensorimotor polyneuropathy, and parkinsonism, reporting for the first time the co-occurrence of all these features in a single methanol poisoning case. Case 2 presented much later without acute revealing features but finally with bilateral irreversible optic neuropathy and confirmed hemorrhagic putaminal necrosis.

When facing a patient with bilateral putaminal necrosis, optic neuropathy, polyneuropathy, and parkinsonism, along with unexplained HAGMA, acute methanol intoxication should be suspected, even in the absence of suggestive medical history. Methanol intoxication still constitutes a serious problem in developing countries like India. This case series study describes the neurological consequences of methanol intoxication involving the central and peripheral nervous systems. It highlights the importance of early diagnosis and prompt treatment of this challenging life-threatening condition. Active case finding, timely intervention, complete cessation of alcohol consumption, and awareness and supervision of commercial alcohol use are key factors in reducing mortality and morbidity among these patients.

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Disclosures

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Ethics statement

Written informed consent was obtained from the patients to publish this case report and any accompanying images.

Author contributions

All authors contributed significantly to the creation of this manuscript; each fulfilled criterion as established by the ICMJE.

Conflicts of interest

The authors declare that they have no conflict of interest.

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