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Cognitive sequelae of methanol poisoning involve executive dysfunction and memory impairment in cross-sectional and long-term perspective

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ABSTRACT

Methanol poisoning leads to lesions in the basal ganglia and subcortical white matter, as well as to demyelination and atrophy of the optic nerve. However, information regarding cognitive deficits in a large methanol sample is lacking. The principal aim of the present study was to identify the cognitive sequelae of methanol poisoning and their morphological correlates. A sample of 50 patients (METH; age 48 ± 13 years), 3–8 months after methanol poisoning, and 57 control subjects (CS; age 49 ± 13 years) were administered a neuropsychological battery. Forty-six patients were followed in 2 years' perspective. Patients additionally underwent 1.5T magnetic resonance imaging (MRI). Three biochemical and toxicological metabolic markers and a questionnaire regarding alcohol abuse facilitated the classification of 24 patients with methanol poisoning without alcohol abuse (METHna) and 22 patients with methanol poisoning and alcohol abuse (METHa). All groups were compared to a control group of similar size, and matched for age, education, premorbid intelligence level, global cognitive performance, and level of depressive symptoms. Using hierarchical multiple regression we found significant differences between METH and CS, especially in executive and memory domains. METHa showed a similar pattern of cognitive impairment with generally more severe executive dysfunction. Moreover, all METH patients with extensive involvement on brain MRI (lesions in ≥2 anatomical regions) had a more severe cognitive impairment. From a longitudinal perspective, we did not find any changes in their cognitive functioning after 2 years' follow-up. Our findings suggest that methanol poisoning is associated with executive dysfunction and explicit memory impairment, supposedly due to basal ganglia dysfunction and disruption of frontostriatal circuitry proportional to the number of brain lesions, and that these changes are persistent after 2 years' follow-up.

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1. Introduction

Methanol is an industrial solvent that acts as a neurotoxin when ingested. A mass methanol poisoning is often the result of its use as a cheap substitute for ethanol (Hovda et al., 2005; Paasma, Hovda, Tikkerberi, & Jacobsen, 2007; Zakharov, Pelclova, Urban, et al., 2014). This was the case in the Czech Republic, where from September 2012 to January 2013 a total of 121 subjects were intoxicated by methanol sold in adulterated alcoholic beverages containing a mixture of 20–50% methanol and 50–80% ethanol (Zakharov, Pelclova, Urban, et al., 2014). Empirical evidence related to the effect of methanol poisoning on the brain and behavior is limited (Paasma et al., 2007), with only a small number of case reports or studies on small cohorts of patients (Airas, Paavilainen, Marttila, & Rinne, 2008; Anderson, Shuaib, & Becker, 1987; Bezdicek, Klempir, et al., 2014). A cross-sectional study based on a large cohort of patients with methanol poisoning and without concomitant chronic alcohol abuse is so far lacking.

The pathophysiological mechanisms of methanol poisoning are well known (Zakharov, Pelclova, Navratil, et al., 2014; Zakharov, Pelclova, Urban, et al., 2014). Methanol poisoning has toxic effects due to its metabolite formic acid, preponderantly on the retina, optic nerve, and other parts of the central nervous system (CNS) (Jacobsen & McMartin, 1986; Kraut & Kurtz, 2008; Mégarbane, Borron, & Baud, 2005; Sanaei-Zadeh, Zamani, & Shadnia, 2011). The accumulation of formic acid results in metabolic acidosis, damage to the basal ganglia (BG), and visual impairment when the concentration of formic acid is higher than 9.0–11.0 mmol/L (McMartin, Martin-Amat, Makar, & Tephly, 1977; Osterloh, Pond, Grady, & Becker, 1986; Sanaei-Zadeh, Esfeh, et al., 2011; Sejersted, Jacobsen, Ovrebø, & Jansen, 1983; Zakharov, Nurieva, et al., 2014). Thus, methanol poisoning leads to metabolic changes and lesions in specific sites in the CNS, especially in the BG, and primarily in the putamen. The putamen is affected by hemorrhage and subsequent necrosis. To a lesser extent, subcortical white matter (SWM) lesions and demyelination or even atrophy of optic nerve occur (Arora et al., 2007; Blanco, Casado, Vásquez, & Pumar, 2006; Singh, Paliwal, Neyaz, & Kanaujia, 2013; Vaneckova et al., 2014, 2015). Moreover, methanol is the metabolic precursor of formaldehyde (FA). FA at low concentrations can, in animal models, directly induce tau aggregation and amyloid β (Aβ) peptide deposits *in vitro* (Su, Monte, Hu, He, & He, 2016).

From previous findings, we hypothesize that methanol poisoning leads to a disruption of the functional architecture of frontostriatal circuitry (Alexander, DeLong, & Strick, 1986; DeLong & Wichmann, 2007; Owen, 2004) and cognitive decline (Su et al., 2016). The presumable assessment of "cognitive" impairment due to methanol poisoning should, therefore, include 1) assessment of executive function and working memory (WM), due to interconnection of the BG with the frontal lobes via the basal ganglia-thalamocortical circuits (Alexander & Crutcher, 1990); 2) assessment of motor speed due to possible loss of connectivity as a result of SWM lesions (Vaneckova et al., 2014, 2015); and 3) long-term memory assessment due to a general toxic and apoptotic effect on the CNS and also an examination of visual scanning and sustained visual attention due to atrophy of the optic nerve (Bezdicek, Klempir, et al., 2014; Su et al., 2016; Vaneckova et al., 2014, 2015).

Furthermore, based on an *a priori* assumption, we hypothesized that chronic alcohol abusers are a subgroup of methanol-poisoned patients and may have a different type of cognitive impairment than "pure" methanol-poisoned patients (Pfefferbaum, Sullivan, Mathalon, & Lim, 1997; Sullivan, Harris, & Pfefferbaum, 2010). We performed, therefore, a classification of methanol poisoning to methanol poisoning with no alcohol abuse and methanol poisoning with alcohol abuse on the basis of biochemical and addictological analyses. The primary objective of the present study was to show how well the methanol poisoning predicts possible cognitive deficits in a cross-sectional analysis and show their evolution in a long-term perspective. Second, we tried to disentangle the "pure" cognitive deficit induced by methanol poisoning with respect to deficits caused by chronic alcohol abuse and concomitant methanol poisoning. Third, we aimed to describe morphological correlates based on MRI that corroborate or refute the frontostriatal circuitry and cognitive deficit hypothesis.

2. Materials and methods

2.1. Study participants

Mass methanol poisoning occurred in the Czech Republic between September 2012 and January 2013. From a total of 121 intoxicated subjects, 20 died outside the hospital, and 101 were hospitalized. Among hospitalized subjects, 60 survived without and 20 with visual/CNS sequelae, whereas 21 died (Zakharov, Pelclova, Urban, et al., 2014). The patients were treated with an antidote (ethanol or fomepizole), alkalization, folate substitution, and intermittent or continuous hemodialysis (Zakharov, Navratil, & Pelclova, 2014; Zakharov, Nurieva, et al., 2014). All 80 surviving patients were confirmed to have methanol poisoning by toxicological analysis (methanol in blood serum) and were invited to participate in the cross-sectional study following their discharge from the hospital. One patient was further excluded due to incomplete information on admission, laboratory data, and clinical manifestations. Protocols established during the Norwegian methanol outbreak for the prospective collection of diagnostic and treatment information were used (Hovda et al., 2005; Zakharov, Pelclova, Urban, et al., 2014). The discharge reports of all hospitalized patients with a confirmed diagnosis, as well as the results of neurological and ophthalmological examinations on admission, during hospitalization, and on discharge were collected and analyzed at the Czech Toxicological Information Center. A detailed clinical history was obtained either directly from the patients or the relatives of critically ill patients on admission (Zakharov, Pelclova, Urban, et al., 2014), and included information regarding the onset and character of ocular manifestations and systemic toxicity; these patients were followed and examined in 2 years' perspective (Zakharov et al., 2015). Laboratory investigations on admission and other medical interventions are described in detail elsewhere (Vaneckova et al., 2014; Zakharov, Nurieva, et al., 2014; Zakharov, Pelclova, Urban, et al., 2014; Zakharov et al., 2016).

Fifty patients were followed up during a 3–8-month period after methanol poisoning (i.e., some may have had a longer time to recover). Assessment included neurological examination, neuropsychological assessment, and magnetic resonance imaging (MRI), or in some cases, computed tomography (CT). The remainder of the 80 methanol-poisoned survivors, i.e., the 30 patients rejected to participate in the study, were excluded for: complete blindness (2 patients), unwillingness to go to Prague from their place of residence, feeling of "enough doctors and hospitals" or of "being ashamed"; most of the persons did not want to explain the reason for their unwillingness. We followed these patients with the same protocol, and 46 of those 50 patients were examined after a 2-year period (Table 1). In 2015, the data collection took 2 months to reduce the variability of assessments in 2013; four patients from the overall 50 in 2015 died or refused to participate (8% attrition). Neurological deficits were measured by NNIPPS-PPS (Natural History and Neuroprotection in Parkinson Plus Syndromes-Parkinson Plus Scale, a clinical rating scale with the total score 0–309; Table 1) (Payan et al., 2011). Only 42 patients underwent MRI on a Gyroscan Phillips 1.5-T system using a standard imaging protocol