

SUMMARY

Context: Acute methanol poisoning is a life-threatening condition. Methanol is metabolized in the organism to formaldehyde and then to formic acid, which inhibits cytochrome c oxidase in mitochondria and thus contributes to the development of oxidative stress.

Aim: To study the role of oxidative stress in the pathogenesis of acute neuronal damage to the central nervous system (CNS), in the development of long-term sequelae of methanol poisoning and chronic neurodegenerative processes in the years following acute methanol exposure.

Material and Methods: Methanol intoxication was confirmed analytically in 55 patients included in the study; their age at the time of poisoning was 46.7 ± 3.6 years (9 females and 46 males). All patients, together with 41 control subjects, were examined in a prospective longitudinal cohort study. At admission, during hospitalisation, and at regular intervals after discharge during the follow-up, the patients were sampled for serum concentrations of lipid oxidative damage markers 4-hydroxy-trans-2-hexenal (HHE), 4-hydroxynonenal (HNE), malondialdehyde (MDA), and 8-isoprostane, for nucleic acids oxidative damage markers 8-hydroxy-2'-deoxyguanosine (8-OHdG), 8-hydroxyguanosine (8-OHG), 5- (hydroxymethyl) uracil (5-OHMU), for proteins oxidative damage markers ortho-tyrosine (o-Tyr), nitrotyrosine (NOTyr), chlorotyrosine (Cl-Tyr), and for leukotrienes LTB₄, LTC₄, LTD₄, and LTE₄. The patients were examined 4.9 ± 0.6 , 25.0 ± 0.6 , and 49.9 ± 0.5 months after discharge. The clinical examination protocol included biochemical laboratory tests, ocular and neurological examinations, visual evoked potential measurements (VEP), optical coherence tomography (OCT) with retinal nerve fibers thickness (RNFL) measurements, magnetic resonance imaging (MRI) of the brain with image processing by volumetric software Morphobox.

Results: Patients with acute methanol poisoning had significantly higher concentrations of peripheral blood serum lipoperoxidation markers HHE, HNE, MDA, and leukotrienes than survivors examined two years after poisoning (all $p < 0.001$). During hospitalization, patients who survived intoxication had higher acute leukotrienes concentrations of LTB₄, LTC₄, LTD₄, LTE₄, and lipoperoxidation markers than the deceased subjects (all $p < 0.01$). Patients with toxic damage to basal ganglia had relatively lower acute serum concentrations of leukotrienes and lipoperoxidation markers than those who survived without CNS sequelae ($p < 0.05$). Two years after discharge from the hospital, there was no association between serum leukotrienes concentrations, markers of lipoperoxidation and CNS sequelae of methanol poisoning.

Only one of three measured acute markers of nucleic acids injury, 8-OHdG, was significantly elevated compared to subsequent concentrations ($p = 0.009$). Of observed acute markers of oxidative proteins damage, only o-Tyr concentration was elevated ($p < 0.001$). When comparing acute concentrations of nucleic acids and proteins oxidative damage markers, only the concentrations of two markers - 8-OHdG and 8-OHG - were significantly higher in the survivors than in the deceased ($p < 0.05$). The follow-up serum concentrations of oxidative damage markers of nucleic acids and proteins did not correlate with acutely measured concentrations and CNS sequelae of methanol poisoning.

Patients with the evidence of toxic brain damage on MRI had significantly lower volume of putamen, nucleus caudatus, and globus pallidus compared to the patients without CNS sequelae ($p < 0.05$). Basal ganglia volume in survivors correlated with acute leukotriene LTB₄ concentration ($p < 0.05$) and acute concentrations of markers of oxidative damage of lipids (MDA, 8-isoprostane) and proteins (o-Tyr). Positive correlation was demonstrated between basal ganglia volume and retinal nerve fibers thickness measured within the follow-up examinations.

Conclusion: Mechanisms of oxidative stress play an important role in the pathogenesis of toxic CNS damage in patients with acute methanol intoxication. These mechanisms can have both protective and destructive effects depending on the intensity and duration of acute oxidative stress caused by the direct toxic effect of formic acid. The interaction between early neuronal membrane lipoperoxidation and leukotriene-mediated neuroinflammation is involved in important neuroprotective mechanisms. Acute oxidative damage to nucleic acids and proteins in survivors was relatively mild and reversible. Survivors of acute methanol poisoning with sequelae of toxic brain damage had lower volume of the basal ganglia and retinal nerve fibers thickness, and these values correlated positively, demonstrating OCT RNFL as a suitable screening method for early diagnosis of long-term CNS sequelae of methanol poisoning.