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Imaging findings after methanol intoxication (cohort of 46 patients)

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Abstract

OBJECTIVES: Our goal is to demonstrate the variability of imaging findings, primarily in the MRI, in 46 patients who survived acute methanol poisoning. This cohort of patients is the largest such sample group examined by MRI.
METHODS: Patients were examined by means of imaging methods (42 patients by MRI and 4 by CT). All had an identical protocol of MR examination (T2WI, FLAIR, T1WI with or without application of contrast medium and T2WI/FFE, DWI in the transversal plane of the scan, and with focus on the optic nerves in the coronal plane of the scan in T2WI-SPIR).
RESULTS: Imaging methods revealed a positive finding associated with methanol intoxication in 21 patients (46%). These consisted of symmetrical lesions in the putamen – 13 patients (28%), haemorrhage – 13 cases (28%), deposits in white matter with localization primarily subcortically – 4 cases (9%), lesions in the region of the globus pallidus – 7 cases (15%) (in 6 cases without combination with the lesions in the putamen), lesions in the brainstem afflicted 6 patients (13%),

ORIGINAL ARTICLE

and lesion in the cerebellum was found in one case. A pathological finding was found only in the patients examined by MRI.

CONCLUSION: Almost half of the patients who survived acute methanol poisoning had pathological findings by MRI. The most common finding concerned an affliction of the putamen, which is a predilection area. An interesting finding was the relatively frequent occurrence of selective lesion of the globus pallidus, which is more usually associated with other types of intoxication.

Abbreviations:

CNS	- central nervous system
CT	- computer tomography
DWI	- diffusion weighted image
FA	- flip angle
FFE	- fast field echo
FLAIR	- fluid attenuated inversion recovery
MRI	- magnetic resonance imaging
SPIR	- spectral presaturation with inversion recovery
THK	- slice thickness
TE	- time to echo
TR	- time to repetition

INTRODUCTION

At present, The Czech Republic is immersed in the aftermath of the methanol affair, in which more than 120 cases of poisoning by methyl alcohol were recorded from September 2012 onwards (Zakharov *et al.* 2014 a). Methanol is a clear, colourless, highly toxic substance, which in its flavour and aroma is similar to ethanol. It is contained in cleaning products, varnishes, paints, antifreeze compounds, fuel compounds and, in cases of fraudulent adulteration, also in alcoholic beverages. Its quantity is strictly regulated in alcoholic spirits, according to valid state standards. Poisonings may occur, beyond suicide attempts, especially in the cases of replacement of ethanol by methanol. Intoxication with methanol leads to metabolic acidosis and affection of the central nervous system (CNS), primarily of the optic nerves, and there is a predilection in affection of the basal ganglia, in the most severe cases causing death of the patient (Arora *et al.* 2007; McLean *et al.* 1980).

Tab. 1. Basic descriptive statistics of the group intoxicated with methanol (N=46).

	median	SD	(min–max)
Age (years)	47	13.42	(25–73)
MetOH (mg/l)	833	1497	(85–7307)
pH	7.25	0.226	(6.69–7.46)
pCO_2 (kPa)	3.99	1.199	(1.47–6.10)
Formic acid (mg/l)	578	372.3	(0–1400)
Time to diagnosis and treatment (hours)	24	21	(1–96)

The latent period following consumption of methanol is usually 12–24 hours, which corresponds with the biotransformation of methyl alcohol to formaldehyde and finally to formic acid. Both of these substances are more toxic than methanol itself, with the highest toxicity caused by formic acid (Blanco *et al.* 2006). Acute symptoms that are regularly described include disorders of vision, headache, nausea, and fatigue. In more severe conditions seizures, stupor, or coma may occur, resulting frequently in the death of the patient. In addition to affliction of the CNS there are also frequent gastrointestinal symptoms. Biochemical analysis proves metabolic acidosis; the level of methanol in the blood may be measured, as well as that of formic acid (Zakharov *et al.* 2015a). Optic nerve demyelination, as a secondary to the myelinoclastic effect of formic acid, has been suggested as being responsible for optic nerve damage with or without axonal loss (Blanco *et al.* 2006; Gaul *et al.* 1995). In the brain tissue, the severe damage is shown in the basal ganglia, primarily the putamen. Necrosis, frequently complicated by haemorrhage, may be seen. Further predominant localization is in the subcortical part of white matter. Lesions in the brainstem, cerebellum and in the nucleus caudatus are observed less commonly (Gaul *et al.* 1995; Zakharov *et al.* 2014b). All the pathological changes described above can be well displayed by magnetic resonance imaging (MRI), where the presence of certain findings (e.g. haemorrhage) is also of prognostic significance (Arora *et al.* 2007; McLean *et al.* 1980; Blanco *et al.* 2006; Zakharov *et al.* 2015a; Gaul *et al.* 1995; Zakharov *et al.* 2014b; Singh *et al.* 2013; Jain *et al.* 2013; Kuteifan *et al.* 1998; Srivastava & Kadam 2013; Sharma *et al.* 2009).

MATERIALS AND METHODS

During and after the methanol outbreak in the Czech Republic in 2012, a total of 46 patients were examined by imaging methods in a study focused on the sequel to methanol poisoning. MR examination was conducted in 42 patients using the standard protocol, whereas 4 patients had a native computer tomography (CT) examination because of contraindication for MRI. The patients were examined at a time interval of 2–8 months after the acute intoxication. The observed group had 39 men and 7 women; the median age was 47 years (range 25–73 years). The median serum concentration of methanol upon intoxication was 833 mg/l, with a markedly wide range (85–7307 mg/l), formic acid 578 mg/l (0–1400 mg/l) (this was measured in 30 patients in the group), the median pH value was 7.25 (6.69–7.46) and pCO_2 was 3.99 kPa (1.47–6.10 kPa). The mean time from the onset of the initial symptom of intoxication to the first contact with medical doctors was 24 hours (1 hour to 96 hours, see Table 1). All patients in the study provided informed consent which was approved by the General University Hospital Ethics Committee.

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All 42 patients underwent MRI on a Gyroscan Philips 1.5 T system with the following protocol: axial T2WI with slice thickness (THK) 6.0/0.6 mm through the whole brain, with the following parameters: repetition time (TR) 4241 ms, time to echo (TE) 100 ms, flip angle (FA) 90°, FLAIR (fluid attenuated inversion recovery): TR 11000 ms, TE 140 ms, inversion time (TI) 2800 ms, FA 90°, T1 weighted image: TR 569 ms, TE 15 ms, FA 69°, T2 weighted image – fast field echo (FFE): TR 665 ms, TE 23 ms, FA 18°, single shot diffusion weighted image (DWI) : TR 2901 ms, TE 75 ms, FA 90°, T1WI after administration of gadolinium and in coronal images centred to the orbital region T2WI with suppression of fat (spectral presaturation with inversion recovery – SPIR): TR 5506 ms, TE 100 ms, FA 90°. CT was conducted on 4 patients using a Siemens Emotion 16 instrument within the standard scope from the vertex to the cranial base, without administration of a contrast medium. Pathological findings were described by two independent neuroradiologists, with high qualification in neuroradiology on MRI, in connection with intoxication, as well as some secondary pathological findings without an unequivocal connection.

Statistics: Continuous variables were expressed as the means, standard deviations, medians and ranges, categorical variables as percentages. The patients were divided into two groups: those with pathological MR findings due to methanol intoxication and those without. These two groups were compared from the perspective of the different levels of formic acid, pH and pCO_2 and logarithmic values of methanol found on admission to hospitals; one-tailed t-tests for equality or none quality means were used and alternatively Mann-Whitney tests (especially for not normally distributed values of methanol).

RESULTS

In 21 patients (46%) the imaging methods revealed a positive finding that could be associated with methanol intoxication. Most frequently this concerned bilateral lesions in the putamen, which afflicted 13 patients (28%); none of them had unilateral damage (Figures 1 and 2). Deposits in white matter with primarily subcortical localization occurred in 4 cases (9%), lesions in the region of the globus pallidus were found in 7 patients (15%), lesions in the brain stem were determined in 6 cases (13%), and lesions in the cerebellum in one case (Table 2) (Figures 3–6). Haemorrhage was detected in 13 patients (28%). Of the patients who had a pathological finding in the region of the putamen, haemorrhagic necrosis was detected in 7 cases, whereas in 6 patients no haemoglobin breakdown products were displayed even in sequence T2W FFE. In all the patients with subcortical lesions, there were bilateral lesions present in the putamen. Haemorrhage in the subcortical white matter deposits was found in 4 patients. Of those patients who had lesions in the globus pallidus, haemorrhagic necrosis appeared in this region in 4 cases. In one patient we found lesions in both the globus pallidus and the putamen (haemorrhagic necrosis was not present), in the other 6 patients with deposits in the globus pallidus the putamen was not afflicted, and one patient had a lesion also in the nucleus dentate. Atrophy of the optic nerve was detected by MRI examination in 3 patients, in one of them this concerned an isolated affliction with a negative intracerebral finding (Table 2). In 7 cases atrophy of the brain was determined: in one case an affliction typical in individuals with increased abuse of ethanol was displayed (symmetrical lesions of high signal intensity near the third ventricle) and evaluated as Wernicke's encephalopathy. In 4 cases non-specific changes were determined in the white matter, which were evaluated as leukoaraiosis; one patient had an arachnoid cyst, one patient had a cavernoma, and another one had a subdural hematoma. On DWI imaging, restriction of diffusion was not evident in any of the patients. Enhancement following administration of the contrast medium was not evident in any patient. Of the patients examined by CT, none had a pathological finding that would have an unequivocal connection with intoxication by methanol (two had a cortical atrophy, one an atrophy of the cerebellum and one an entirely negative finding). If we detach the group of patients examined by MR from the entire group of patients examined by imaging methods, a pathological finding in connection with intoxication was detected in 21 patients, thus in 50% of cases.

The patients with pathological findings by imaging methods had significantly higher serum methanol concentration on admission (for logarithmic values of methanol $t[42]=2.086$; $p=0.022$; after application of Mann-Whitney test $p=0.021$). The median serum concentration of methanol in the group of patients with a pathological MRI finding was 1362 mg/l (range 87–7307 mg/l), in the patients with a negative finding on the imaging methods this was 694 mg/l (range 85–4100 mg/l) (in 2 patients the serum methanol level was not determined, one from each group). Similarly, statistical significance was determined by comparison of both groups, depending on the level of formic acid

Tab. 2. Localization of pathological MRI findings due to methanol intoxication and localization of haemorrhagic necrosis.

	Localisation	Haemorrhagic necrosis
putamen	13	7
globus pallidus	7	4
subcortical white matter	4	4
cerebellum	1	0
brainstem	6	0
n. opticus	3	0

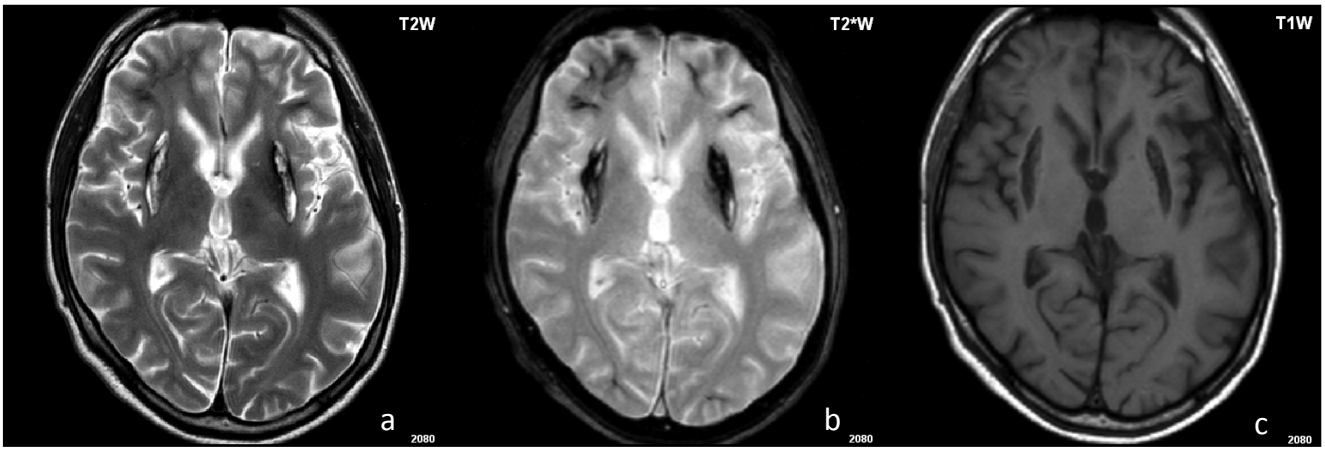

Fig. 1 a, b, c. 33 year old male with intoxication by methanol. The interval from the initial symptom to the first contact with a doctor was 34 hours, the blood methanol level was 927 mg/l, zero ethanol level, the formic acid level was 693 mg/l, pH 6.72, pCO_2 3.16 kPa. MR was conducted 6 months after intoxication. Bilateral lesions of a mixed signal are evident in the T2W image in the area of the putamen, as well as in the white matter frontally, to a lesser degree also occipitally, which corresponds to haemorrhagic necrosis (**a**, **b**). In the T1W image the lesions are primarily hyposignal in the region of the putamen (**c**).

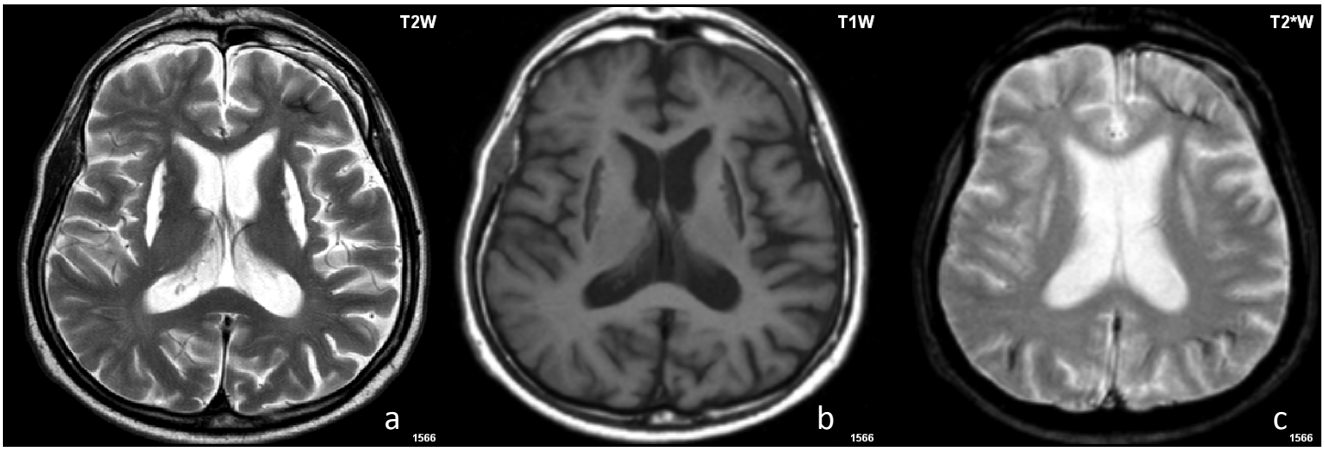

Fig. 2 a, b, c. 58 year old male patient brought in by ambulance service, comatose state (unknown time of onset of initial symptoms), methanol level 3600 mg/l, zero ethanol level, formic acid level not measured, pH 6.79 and pCO_2 2.77 kPa. Symmetrical high-signal-intensity in the putamen in the T2W image, a low signal intensity is evident subcortically on the frontal left side, which corresponds to haemorrhagic necrosis (**a**), upon use of sequence T2W/FFE haemorrhage is evident also frontally contralaterally and bilateral occipitally (**c**). In the T1W image low signal intensity are evident in the putamen bilaterally (**b**). A secondary finding is subdural hematoma on the frontal left side.

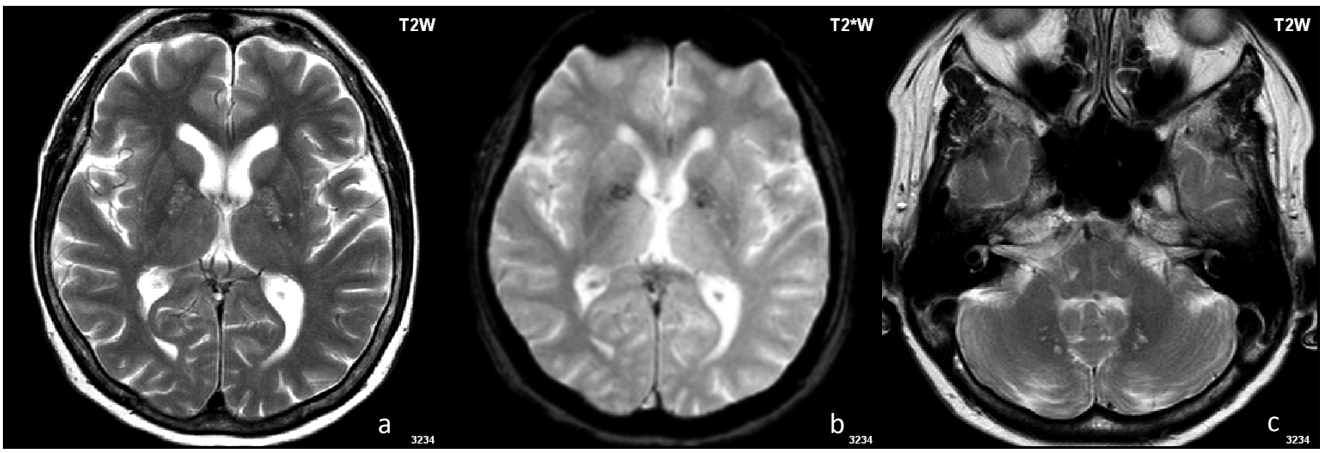

Fig. 3 a, b, c. 62 year old female, hospitalized 12 hours after consumption of methyl alcohol, level of methanol was 1760 mg/l, ethanol 510 mg/l, formic acid 765 mg/l, pH 7.085, pCO_2 2.66 kPa. Symmetrical high signal intensity foci in the pallidus bilaterally (**a**), in T2W/FFE minor deposits of haemorrhage are evident in the pallidus (**b**). Multiple lesions with high signal intensity in cerebellum, in the region of the nucleus dentatus (**c**).

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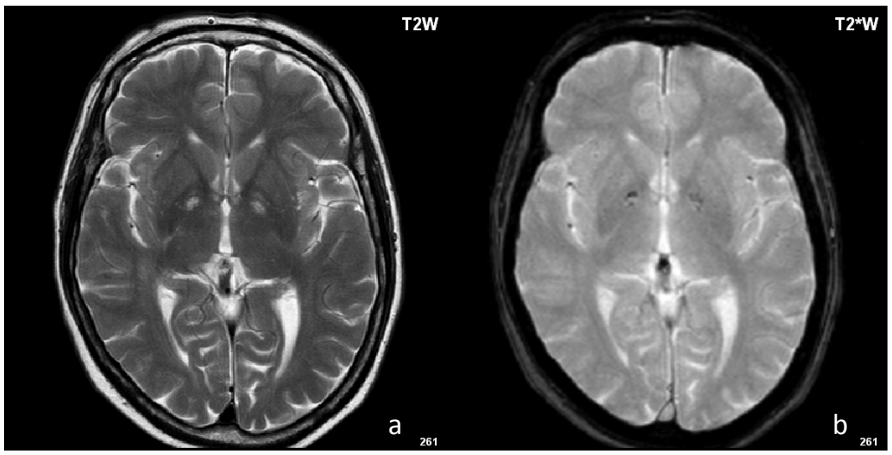

Fig. 4 a, b. 23 year old female, interval from initial symptom to first contact with doctor was 14 hours, methanol level was 87 mg/l, zero ethanol level, formic acid level not determined, pH 7.42, pCO_2 4.39 kPa. Symmetrical hypersignal lesions in pallidum (**a**), with very small deposits of haemorrhage (**b**).

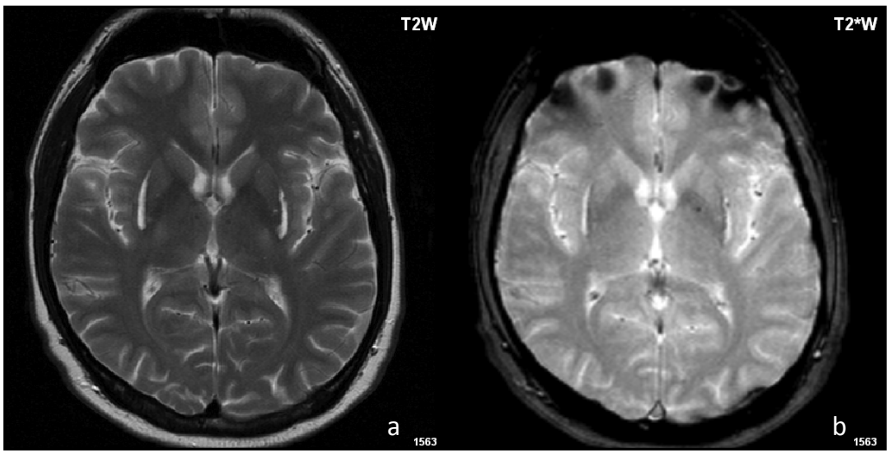

Fig. 5 a, b. 38 year old male, interval from initial symptoms to first contact with doctor was 48 hours, methanol level was 1380 mg/l, zero ethanol level, formic acid level not determined, pH was 6.69, pCO_2 was 3.17 kPa. Symmetrical high signal intensity in laterodorsal parts of putamina in T2W image (**a**), upon use of gradient sequence evident hyposignal in places, corresponding to haemorrhagic necrosis (**b**).

Tab. 3. Group of patients with a pathological MRI finding due to methanol intoxication and with negative MRI findings.

	Patients with a pathological MRI findings			Patients with negative MRI findings		
	median	SD	(min–max)	median	SD	(min–max)
MetOH (mg/l)	1362	1844	(87–7307)	694	976	(85–4100)
pH	7.01	0.25	(6.69–7.42)	7.34	0.12	(7.06–7.46)
pCO_2 (kPa)	3.16	1.13	(1.47–5.20)	4.14	1.25	(1.50–6.10)
Formic acid (mg/l)	693	284	(94–1012)	314	390	(0–1400)

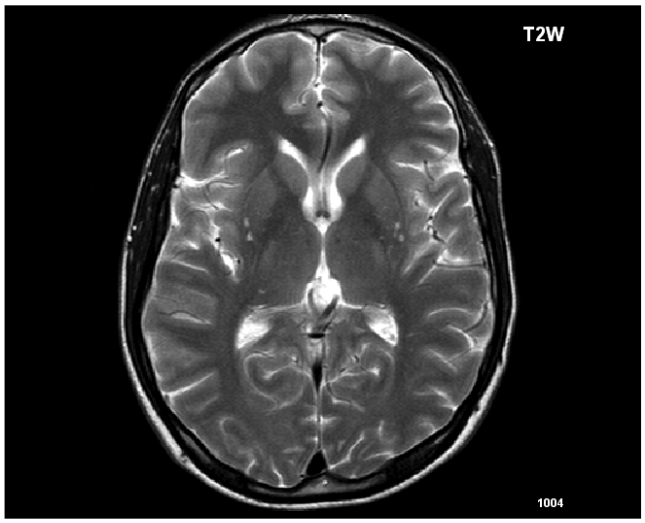

Fig. 6. 38 year old male, interval from consumption (which, however, according to anamnesis persisted for several days continuously) until medical intervention 3 hours, methanol level was 7307 mg/l, ethanol100 mg/l, formic acid level 1012 mg/l, pH 7.02, pCO_2 1.98 kPa. Discrete MR finding – symmetrical bilateral minor lesions in laterodorsal part of putamina.

(the level was not determined in 16 patients, 8 from each group) (t[28]=2.238; p=0.017) The median level of formic acid in patients with a positive finding by MRI was 693 mg/l, compared with 314 mg/l in patients with a normal MRI finding. Comparing the arterial blood pH on admission the group of patients showing a pathological MRI finding with the group having a negative finding, the value of p<0.001 was obtained. In the group with a positive finding the median pH value was 7.01 (range 6.69–7.42) and in the group with a negative finding the median pH value was 7.34 (range 7.06–7.46). The two groups of patients, with a negative finding and with a pathological finding by imaging methods, did not show statistically significant difference in the level of arterial blood pCO_2 (p=0.172 for 1-tailed t-test) (Table 3).

DISCUSSION

The group of patients examined in our study represents the largest sample of pathological MR findings in patients with acute methanol poisoning. Publications to date usually demonstrate individual cases of intoxication (Arora *et al.* 2007; Blanco *et al.* 2006; Jain *et al.* 2013; Sharma *et al.* 2009). In terms of the number of patients, of interest is the study by Sefidbaktov, who described radiological findings in nine individuals following intoxication by methanol and at the same time summarized the MRI findings from several studies with a description of individual case reports. Necrosis of the putamen was described in five cases, three of these also had a lesion of the globus pallidus, in two cases a haemorrhage was present, and in one case the putamen was afflicted together with a diffusion lesion of white matter. CT demonstrated subarachnoid haemorrhage and a diffuse reduction of density of the brain parenchyma in one patient: the finding was interpreted as oedema of the brain – the patient was in a coma and later died. In two subjects an enhancement was described following administration of a contrast medium. Non enhancement was present in the group we observed, which could be explained by the longer time interval between the examination and intoxication. The same reason most probably explains the absence of restriction of diffusion on DWI (Sharma *et al.* 2009 Server *et al.* 2003).

In the present group of patients a pathological finding occurred most frequently in the region of the putamen (in 13 cases, 28%); in all cases the lesions were bilateral; the extent of the affliction fluctuated from partial changes, most often localized laterodorsally, to haemorrhagic necrosis with affliction of the putamen in its full extent. Selective lesion of the putamen may be explained by a number of reasons (Feaney *et al.* 2001; Glazer & Dross, 1993). One is a reduction in the blood flow through the basal veins of Rosenthal upon secondary hypotension (Hubacek *et al.* 2015). Another possible explanation is the direct toxic effect of formic acid, which accumulate in the putamen more often than in other regions, together with a greater sensitivity of the neurons of the striatum to the toxic damage of metabolites of methanol (Sefidbakht *et al.* 2007). The basal ganglia and the optic nerve have a relatively high susceptibility to anoxia and ischemia, which occur due to the inhibition of cytochrome c oxidase by the formic acid, which leads to hypoxia, metabolic acidosis and other metabolic abnormalities (Arora *et al.* 2007).

In the group of patients with pathological findings, the level of methanol and formic acid was higher compared to the subjects with a physiological finding (p=0.022, p=0.017). However, substantial dispersion of values was found in both groups: for example patients with a very high level of methanol (e.g. 3000 mg/l, or 4100 mg/l) had a negative finding on MRI and the patient with the highest level of methanol (7307 mg/l) had only a very slight finding on MRI (minor symmetrical lesions in the putamen without the presence of haemorrhagic necrosis) (Figure 6). A possible explanation could be early medical intervention. However the patient with the highest level of methanol also had a very high level of formic acid at 1012 mg/l, which indicates that the severity of the damage might be influenced by individual lack of sensitivity to the noxious substance, which can be explained by certain genetic predispositions (Hubacek *et al.* 2015).

On comparison of the patients in Figure 1 with Figure 2, a typical affliction of the putamen is visible (in the patient in Figure 1 with the presence of hemorrhagic necrosis); in both patients there was extensive damage in the white matter, primarily subcortically, with the presence of haemoglobin breakdown products. An interesting finding was the fact that one patient had a serum methanol level 3.9 times higher than the other patient; nevertheless the MR finding was analogous. In the patient with a lower methanol level (Figure 1) the long interval between the first clinical symptoms and the beginning of treatment, when the methanol was most probably largely metabolized, can be offered as an explanation. CT imaging was performed acutely in both patients with a non-specific finding; only oedema was manifested. MRI examination six months after the intoxication displayed a typical image for intoxication by methanol (Vaneckova *et al.* 2014).

Upon a comparison of patients with a pathological finding in connection with intoxication by methanol with patients with a negative finding, a statistically significant difference was found in the serum level of methanol, formic acid and arterial blood pH. Some studies have not found any statistically significant association between the level of methanol and the severity of the affliction (Meyer *et al.* 2000). This may be due to a range of factors e.g. the level of ethanol during the treatment of intoxication or the long interval from the beginning of the symptoms until hospitalization, when the level of methanol could be already lower due to its biotransformation to formic acid (Hovda *et al.* 2004; Zakharov *et al.* 2015 b).

Bilateral symmetrical pathological change of the signal in the putamen is typical of intoxication by methanol, but is not specific. This occurs also in the case of Wilson's disease, Kearns-Sayre syndrome, Leigh's syndrome, carbon monoxide poisoning, hypoxia, hypoglycaemic encephalopathy, haemolytic-uremic syndrome, hepatocerebral encephalopathy, in osmotic demyelization syndrome and in the case of extrapontine myelinolysis (Kim *et al.* 2006; Osborne *et al.* 2010; Burgetova *et al.* 2008). Pathological changes of the signal in the region of the basal ganglia occur also in the case of acute intoxication by cyanide or by ethylene glycol. In addition there may be haemorrhage in the region of the putamen in the case of abuse of psycho-stimulants (cocaine and amphetamine) (Rachinger *et al.* 2002; Beltz & Mullins 2010, Caparros-Lefebvre *et al.* 2005). An increased signal in the region of the basal ganglia

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also occurs in the case of Creutzfeldt-Jakob disease or Huntington's disease (Osborne *et al.* 2010; Beltz & Mullins 2010).

In 7 patients (15%) there were lesions in the globus pallidus. In only one of these patients were there also lesions in the putamen; the others had an isolated affliction and one patient also had lesions in the nucleus dentatus. Cases of affliction of the globus pallidus are reported in the literature. However, with the exception of one case report, these are not isolated, but occur always in combination with a pathological finding in the putamen (Sefidbakht *et al.* 2007; Osborne *et al.* 2010). The variable duration of the interval from the onset of the symptoms until medical intervention is offered as an explanation. Some patients underwent urgent medical intervention at a time when the methanol was only partially metabolized into formic acid (Bhatia *et al.* 2008). A case report describing isolated localization of the affliction in the globus pallidus focuses primarily on the retrospective correlations of the finding by MRI. This MRI was originally erroneously evaluated as normal and as late as six months after intoxication the diagnosis of intoxication by methanol was correctly determined by an ophthalmologist and the images were reinterpreted as symmetrical hemorrhagic isolated lesions of the globus pallidus. Examination in a gradient sequence, which is more sensitive to haemoglobin breakdown products, proved to be of great benefit. This particular case points to potential problems with the interpretation of the finding by imaging methods, which could occur primarily in those patients where intoxication was of rather a mild degree. In this case, the finding could have been interpreted as normal, which could lead to an erroneous diagnosis and thus a poorly chosen therapy: the patient's condition was interpreted as bilateral optic neuritis (Halavaara *et al.* 2002). The presented group of patients demonstrates that selective affliction of the globus pallidus may occur far more often than previously assumed and far more than has been demonstrated in the case reports published hitherto. As a result, radiologists should be familiarized with this possibility and the gradient sequence, which is more sensitive to the detection of haemoglobin breakdown products and can help in the case of discrete findings, should always be included in the protocol. Within the framework of differential diagnosis of selective affliction of the globus pallidus in MRI, in addition to the above-mentioned CO intoxication, it is also necessary to consider the relatively rare degenerative disorders – neurodegenerations with brain iron accumulation – among which is pantothenate kinase-associated neurodegeneration, characterized by "tiger's eyes" in the region of the globus pallidus. This symptom may also occur in other neurodegenerative disorders: corticobasal degeneration, Parkinson's disease, progressive nuclear paralysis, and multiple system atrophy (Guillerman 2000; Chang *et al.* 2009). The neurodegenerative disorders in which changes of the signal in the basal ganglia may occur include neuroferritinopathy (McNeill *et al.* 2008).

Imaging methods in the acute stage could not contribute to the diagnosis of intoxication by methanol: CT may acutely display only brain oedema, but on the other hand it eliminates a range of other clinical units which could be the cause of a severe clinical condition. The occurrence of bilateral haemorrhagic necrosis of the putamen and caudate, subcortical necrosis and symmetrical bilateral necrosis of the tegmentum and the optic nerves have a negative prognostic significance in MRI (Gaul *et al.* 1995).

CONCLUSIONS

This study shows typical MR findings 2–8 months after acute methanol poisoning. Such findings which, in the case of unclear diagnosis in the acute stage and in the case of long-term sequel, in particular those afflicting the optic nerve, may indicate the possibility of intoxication by methanol and potentially lead to a subsequent determination of the source of intoxication and prevention of intoxication of further individuals. In contrast with the literature data presented hitherto, selective affliction of the globus pallidus is relatively common and in the case of a lesion thereof it is necessary to consider the possibility of intoxication by methanol.

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Conflict of interest *We declare that we have no conflict of interest.*

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