

Medical Sciences

Brain Structural-Haemodynamic Changes Caused by Methcathinone (Ephedron) Abuse

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ABSTRACT. Purpose: The aim of the study was to assess brain structural and haemodynamic findings in Methcathinone chronic users. This addictive psychoactive substance is derived via the oxidation of ephedrine with potassium permanganate.

Materials and Methods: In 2006-2013 years 41 patients (35 male and 6 female) with the history of chronic intravenous use of manganese based drugs were investigated. Patients age ranged from 23 to 54 years (mean 37.9y); All patients underwent brain MRI (1.5T, 3T), MR-angiography and Color Doppler of extra-intracranial vessels, neurologic and neuropsychological examinations. Cerebrovascular reactivity (CVR) by TCD test was also evaluated;

Results: In majority of abusers 32(78%) extrapyramidal disorders similar to Parkinson's disease: bradikinesia, postural disturbance, araxia, tremor, muscular dystonia was noted. Pseudobulbar syndrome or personal abnormalities was comparatively rare. Two cases of stroke was diagnosed. In 34y. old male patient severe dissection and thrombosis of the ICA was marked, and in 41y. old male- thrombosis of the MCA. MR images revealed T1 hyperintense lesions in 35(85%) cases, predominantly in globus pallidum (30/74%), substantia nigra (28/68%), nuclei dentatus of cerebellum (23/55%), anterior pituitary lobe (16/40%) and the white matter (4/10%). In 16(40%) cases neuroimaging revealed atrophy of the hippocampus, cerebellum. Study demonstrated diffuse areas of decreased fractional anisotropy within white matter, particularly in more anterior tracts; The development of brain changes were significantly associated with duration of abuse. At MRA moderate to severe vessel irregularity consistent with vasoconstriction and vasodilation was present in 28 (68%)case. TCD revealed reduced blood flow in MCA and ACA. The abusers also had significantly increased pulsatility index (PI) values and impaired CVR. No gender or side-to side difference was observed for blood flow velocities or PI. The severity of TCD changes was significantly associated with duration of abuse longer than 1 year.

Conclusion: Our results suggest, that MRI demonstrate systematic brain structural deficits in Methcathinone abusers. DTI identifies areas of disruption in white matter tracts. Slowed cerebral blood flow velocity with the increased pulsatility and impaired CRV in abusers indicate increased cerebrovascular resistance due to the vasoconstriction of small cortical vessels. © 2016 Bull. Georg. Natl. Acad. Sci.

Key words: Methcathinone, abuse, MR-tomography, brain haemodynamics

Toxic encephalopathy (TE) is a degenerative neurologic disorder caused by exposure to toxic substances like organic solvents. Exposure to toxic substances can be presented with wide range of neurologic abnormalities. Toxic encephalopathy can be caused by various chemicals, some of which are commonly used in everyday life. Toxic encephalopathy can permanently damage the brain and currently, treatment is mainly just for the symptoms.

Manganese (Mn) is an essential trace metal, present in most tissues. Mn binds to and/or regulates many enzymes throughout the body. Mn is a required co-factor for arginase, which is responsible for urea production in the liver, superoxide dismutase, which is critical to prevent against cellular oxidative stress and pyruvate carboxylase, an essential enzyme in gluconeogenesis. In brain, about 80% of Mn is associated with the astrocyte-specific enzyme glutamine synthetase, here Mn plays a regulatory role, although it is not a required co-factor [1, 2].

Mn is widely used in industry and is found in commercial products and industrial settings. Occupational inhalational exposure, especially in mining, smelting, and welding, has been the main cause of human Mn intoxication. The symptoms of chronic Mn intoxication were first reported in workers inhaling "black oxide of manganese" as a difficulty of movement, paraplegia, accompanied by lack of facial expression, drooling, and impaired speech [1-3].

On the other hand, intoxication due to chronic parenteral use of manganese in psychoactive substances is increasingly encountered as a problem that causes serious neurological impairment. Mn based synthetic drug, methcathinone hydrochloride, known as ephedron in Europe, is widely used psychoactive stimulant. Ephedron is derived via the oxidation of ephedrine/pseudoephedrine with potassium permanganate and acetyl salicylic acid and is administered intravenously. This psychostimulant mixture is known as a 'Russian Cocktail', "Cat", "Jeff", "Mulka". The first report of Mn intoxications in substance-dependent individuals was published more than 20

years ago in Russia. Within the last few years literature reported cases of ephedron encephalopathy in Eastern Europe, Western Europe and Canada [2,4,5].

Long-term parenteral use of ephedron by recreational psychoactive substance users can lead to progressive, permanent, neurodegenerative damage, resulting in syndromes similar to idiopathic Parkinson's disease, known as manganism.

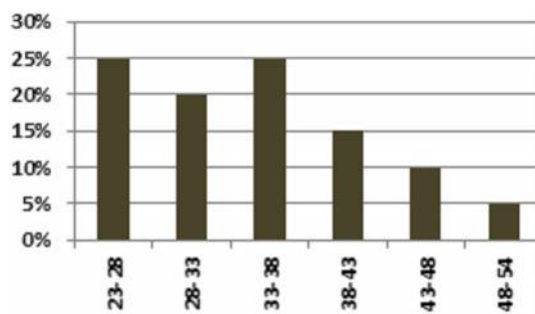
This condition, which is caused by manganese, is reported to be resistant to levodopa and to cause permanent damage. As the stable psycho-somatic disorders nowadays it represents not only medical, but a social problem as well.

Purpose: The aim of our study was to assess the neuroradiologic and haemodynamic findings in patients using synthetic (self-made) manganese based psychoactive substances (Methcathinone). The goal of this study was to present a typical brain MRI pattern as a result of chronic ephedrine abuse, and correlation with clinical symptoms.

Materials and methods: In 2007-2014 years 41 patients (35 male and 6 female) with the history of chronic intravenous use of manganese based drugs were investigated at the Research Institute of Clinical Medicine. Patients age ranged from 23 to 54 years (mean 37.9y); age distribution is described in the Table 1. Each patient admitted taking intravenous ephedron injections for at least 6 months (from 6 month to 5 years). Mean duration of abuse was 1,5 year The control group consisted of healthy 20 subjects (mean age 52 years \pm 9y).

All patients underwent brain MRI (1.5T, 3T), MR-angiography and Color Doppler of extra-intracranial vessels, neurologic and neuropsychological examinations. Blood flow parameters of the anterior and middle cerebral arteries (ACA, MCA) was measured by transcranial Color Doppler. Cerebrovascular reactivity (CVR) by TCD test was also evaluated;

Brain MRI scans were performed in all the patients using a Siemens Verio 3.T, and Siemens Aera 1.5T system. Acquired sequences included T1-weighted images in sagittal and axial planes (SE,

Table. 1 Distribution of patients by age

TR=596 ms, TE=15 ms, NAS=2, slice thickness 5 mm, pitch 1 mm), T2-weighted images in coronal planes (TSE, TR=5058 ms, TE=100 ms, slice thickness 5 mm, pitch 1mm) and axial FLAIR sequence (TR=11000 ms, TI=2800 ms, TE=140 ms, NAS=2, slice thickness 5 mm, pitch 1mm). Signal intensity measurements on T1-WI were acquired in order to ensure objective assessment of visible lesions or suspicious areas. Evaluation of intracranial vessels was performed with Tof-fl3d-sequence - TR 56ms. TE 10.4ms. FA40; for the extracranial vessels tof -fl2d-was used - TR 52ms, TE 10ms, FA70. Contrast enhancement by 5% Magnevist (Schering) was used.

Color Doppler ultrasonography (CDUS) of the extracranial carotid and vertebral arteries was performed on the unit Toshiba Aplio XG and Toshiba ... artery disease was assessed and defined according to standardized criteria. Transcranial Doppler sonography (TCD) was performed on the same Aplio 500 and Toshiba Aplio XG unit with 2.1MHZ probe.

Examination of vessels of the circle of Willis was performed as described by Aaslid et al. Blood flow velocities (Vcm/s) in the middle, anterior, posterior cerebral arteries (MCA, ACA, PCA) and pulsatile indexes (PI) were measured. The patency of major collateral vessels, namely OA, anterior (ACoA), and posterior (PCoA) communicating arteries, was evaluated.

Results: Following the patients examination in 30(73%) abusers were revealed various psychological changes, such as memory impairment (verbal and

non-verbal), irrational thinking, personality changes - aggressiveness, obsessive, destructive. In 27(66%) cases euphoria, hyperactivity, logorrhea, increased libido, tachicardia, parestesia - were noted.

Substance abuse was associated with stable neurological disabilities. Most patients 31(76%) had the combination of extrapyramidal disorders (parkinsonism, muscular dystonia, tremor, myoclonia) with mild cognitive abnormalities (bradyphrenia, attenuated attention, reduced working capacity, decreased phonetic verbal fluency, tendency to impulsivness).

Horizontal and vertical eye movements were recorded in 27 (66%) EP, using standardized oculomotor tasks EP patients showed slow and hypometric horizontal saccades, an increased occurrence of square wave jerks, long latencies of vertical antisaccades, a high error rate in the horizontal antisaccade task, and made more errors than controls when pro- and antisaccades were mixed.

Majority of patients 34(82%) manifest clinical features, notable as levodopa-resistant form of Parkinsonism, particularly with bradykinesia, oligokinesia, bradymimia (mask-like face), tremor, retro and anteropulse.

In severe cases signs of Mn neurotoxicity include muscular dystonia mostly of face and lower extremities with tremor and characteristic gait so-called "cock walk". Patients walk with a cockwalk gait, characterized by the feet not completely contacting with the ground; patient walks on their toes and there is a tendency to fall while walking backwards. This type of walking found similar to a cock's walk because of the heels being up in the air, and the special posture of the trunk and arms, is characteristic of manganese parkinsonism.

The patients reported that the onset of their first neurologic symptoms (gait disturbance in 20(49%) and hypophonia in 3(7%)) occurred after a mean of 8 months of methcathinone use. At the time of neurologic evaluation, all 41 patients had gait disturbance and 32 (78%) had difficulty walking backward; 19(46%) patients were falling daily, and 3 of these

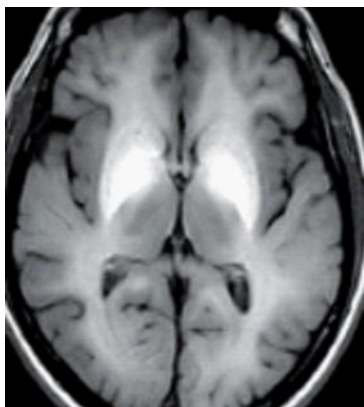


Fig. 1. Brain MRI T1-WI axial plane of a patient with ephedrone encephalopathy: symmetrical signal increase in globi pallidi.

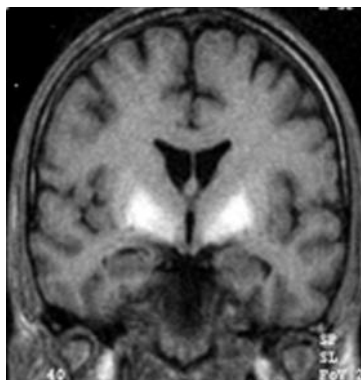


Fig. 2. Brain MRI T1-WI coronal plane of abuse patient: symmetrical signal increase in globi pallidi.

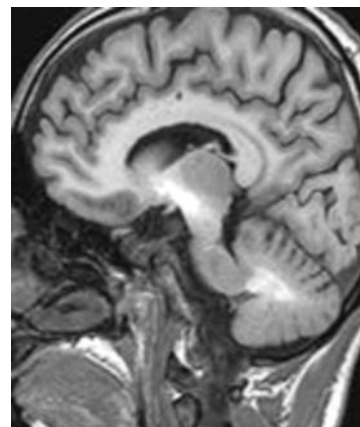


Fig. 3. Brain MRI T1-WI sagittal plane of a patient with ephedrone abuse moderate signal intensity increase in cerebellar hemisphere white matter and significant signal intensity increase in globus pallidus.

patients used a wheelchair. 31(76%) patients had hypophonic speech in addition to gait disturbance, and one of these patients was mute.

In our study we analyze lesions observed in brain Magnetic resonance imaging (MRI) in a series of active abuse patients and former users. Magnetic resonance imaging of the brain in active ephedrone users revealed abnormalities in 35(88%) cases. MRI showed symmetrical hyperintensity on T1-weighted images mostly in the globus pallidus (24/75%) and substantia nigra (22/69%). Less frequently involved structures were nucleus dentatus of cerebellum (18/56%), anterior pituitary lobe (11/39%), white matter (3/9%). In former users, the signal increase was less intense and not so widespread. MRI was already normal 6-8 months after the last exposure to ephedron, but clinical signs remained unchanged (Figs. 1-3).

In active abusers two cases of acute stroke was diagnosed: Male patient, 41y. old, with abuse period of 2.5y, received in our clinic with acute thrombosis of left middle cerebral artery (MCA) and ischemia of left MCA territory area of extended posteriorly to the occipital lobe;

Another stroke was described in 34y. old man, abuse period 3.5y. with acute spontaneous dissection of the left Internal Carotid artery, and infarction

of left MCA supply area.

artery presented a flame-like occlusion, typical of an acute dissection (Fig. 4).

For the evaluation of changes in brain haemodynamics we have studied by Transcranial Color Doppler sonography (TCCD) blood flow parameters in abusers and in control ones. Blood flow velocities (Vcm/s) in the middle, anterior, posterior cerebral arteries (MCA, ACA, PCA) and resistive (RI) and pulsatile indexes (PI) were measured. Our study revealed significantly decreased flow velocity parameters (V_{sis}, V_{mean}, V_{dias}) for the MCA and ACA in abusers compared to control subjects (Fig. 5). There were no significant gender interactions.

Evaluation of vascular resistivity showed, that the abusers also had significantly higher PI values than the control subjects. In abusers mean PI MCA-0.98, PIACA-0.91, In control persons mean PI MCA-0.86, PIACA-0.83. The severity of TCD changes was significantly associated with duration of abuse longer than 1 years.

Pathologies of the brain vasculature was revealed also by the intracranial Mr-angiography study. At the intracranial TOF-and SSD MR-angiography images moderate to severe vessel irregularity consistent with vasoconstriction and vasodilatation

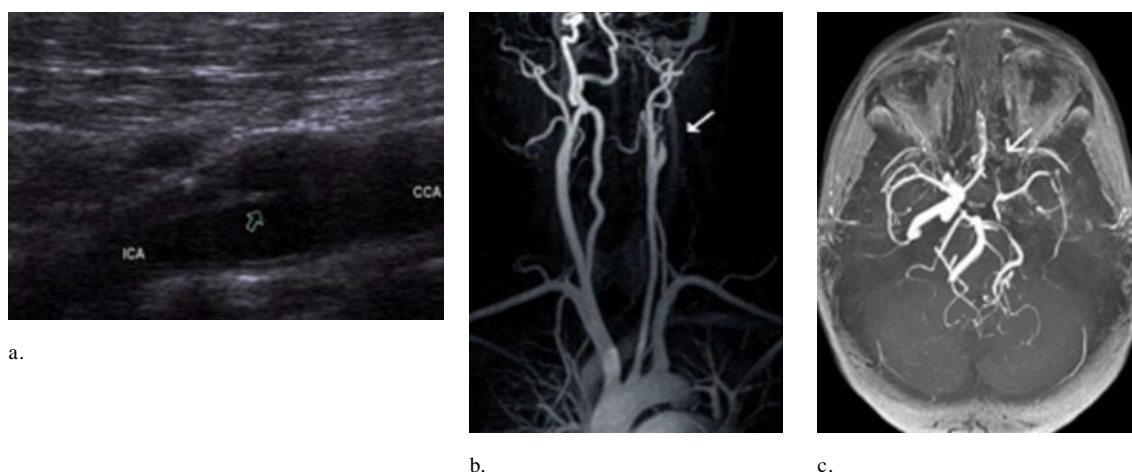


Fig. 4. Spontaneous dissection of the left ICA.

a. B-mode ultrasound image. The free floating intimal flat in the ICA lumen.

b. Extracranial MR-angiography, Tof-fl-2d-MIP. Occlusion/ thrombosis of the ICA .

c. intracranial MR-angiography, Tof-fl-2d-MIP. Decreased signal intensity from the left MCA.

was present in 27 (66%) cases.

TCD is an ideal functional test for detecting rapid changes in cerebral perfusion. The assessment of cerebral vasoreactivity can provide information regarding the reserve capacity of cerebral circulation, that is the possibility of vessels to adapt in response to systemic modification or brain metabolic activity requiring an increase or decrease in cerebral blood flow.

We have studied cerebral vasomotor reactivity by one of the simple functional test - breath holding index (BHI).

After determination of each patients' flow velocity in MCA by TCD, before and after 30s apnea, BHI was calculated as follows:

$$\text{BHI (\%)} = (\text{MFV}_{\text{ap}} - \text{MFV}_{\text{rest}}) \times 100 / \text{MFV}_{\text{rest}} \times 30$$

BHI was calculated for each MCA separately and the average of BHI in two sides was considered as patients BHI. Evaluation of patients cerebral vasomotor reactivity showed significantly decreased BHI values in abusers, compared to healthy ones. Mean BHI for women patients -0.87 ± 0.53 , men patients -0.72 ± 0.41 , control ones -0.97 ± 0.44 .

Conclusion: Mn intoxications were reported for many years, mostly among employees of manganese mines, steelworks and battery-making factories. Cur-

rently population with increasing incidence of Mn intoxication consists of intravenous users of narcotics. Mn containing Methcathinone is one of the cheapest and accessible CNS stimulant.

Entry of Mn to brain can occur via three known pathways: through the capillary endothelial cells of the blood-brain barrier, by the choroid plexus of the blood-CSF (cerebrospinal fluid) barrier, or via the olfactory nerve from the nasal cavity directly to brain. The latter is important, as most of the reported toxicities have occurred through the inhalation exposure. In brain Mn is accumulated mainly in globi pallidi. Elimination of Mn from the body is via very slow process of diffusion [2,7].

Although the precise mechanism by which Mn induces neurotoxicity is poorly understood, several recent reports have suggested that Mn neurotoxicity may be associated with its interaction with other

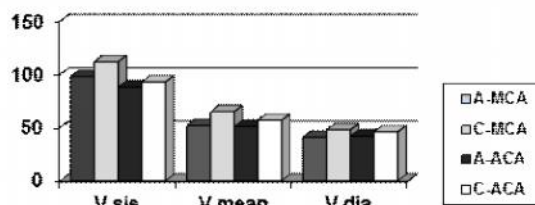


Fig. 5. Blood flow velocity (V sis, V mean, V dia) parameters in abusers (A) and control subjects (C).

essential trace elements, including iron, zinc, copper and aluminium [1, 2,6,7].

The suggestion that transition metals contribute to the neurodegeneration observed in Parkinsonian syndromes is consistent with studies of the toxicity of different Mn valence states. Mn administered as Mn^{3+} more effectively inhibits mitochondrial aconitase activity than that administered as Mn^{2+} . Cells treated with Mn^{3+} accumulate more total Mn and have a higher rate of cell death compared with cells treated with $^{2+}$. As Mn can participate in Fenton reactions, it has the potential to increase reactive oxygen species, and subsequent oxidative damage, within cells [1,2,4,6].

The onset and severity of clinical symptoms depend on the intake period as well as on individual sensitivity. The first neurological symptoms, usually gait disturbance and slurred speech may occur only some months after the beginning of ephedrone injections or years later, but generally within the first few years. There is no correlation between the duration of drug abuse and clinical severity, and in some abusers, the syndrome does not develop at all, despite ephedrone use. The most characteristic reported neurological findings were postural instability with retropulsion and falls, gait disturbance, hypomimia, limb and face dystonia, dysarthria, hypophonia, and symmetric bradykinesia. Less frequently described symptoms were limb and axial rigidity, gait freezing, postural and resting tremor, micrographia, apraxia of eyelid opening, some slowing of vertical saccades, pathological laughter, palilalia, and primitive reflexes. Few cases had oromandibular dyskinesia, blepharospasm, myoclonus, or restriction of vertical saccadic eye movements [2,6-8].

Psychiatric symptoms due to manganese intoxication may present earlier than neurological findings and remit after 3 months, depending on the dose used. Parkinson-like findings, on the other hand, present later and in most cases are permanent, even if exposure to manganese stops. The number of manganese intoxication cases due to ephedron use is increas-

ing. Most cases are reported from neurology clinics because of irreversible manganic parkinsonism that develops as a result of long-term exposure; however, psychiatric signs are observed during the prodromal phase of the disease. Such cases of psychoactive substance use may present first to psychiatric clinics, rather than to neurology clinics. These cases may present with comorbid or psychiatric impairment related to substance use. Furthermore, medical investigations and long-term follow-up among such patients are difficult to perform because motivation for treatment is low. There may be a specific ephedron user group due to the mixture being legally available outside the former USSR, and at low cost [2, 4-7].

T_1 -weighted magnetic resonance imaging (MRI) showed symmetric hyperintensity in the globus pallidus (24/75%) and substantia nigra (22/69%). Less frequently involved structures were nucleus dentatus of cerebellum (18/56%), anterior pituitary lobe (11/39%). Brain structures with increased signal intensity on T1-WI are consistent with those accumulating Mn reported by pathologists. MRI was already normal 6-8 months after the last exposure to ephedrone, but clinical signs remained unchanged.

Measurements of signal intensity in globi pallidi in regard to frontal lobes white matter allowed for objective evaluation of signal intensity and monitoring dynamics of changes in follow-up examinations [9,10].

MRI signal intensity changes reported above are not specific to Mn intoxication, thus are not sufficient for making the final diagnosis. Differential diagnosis should include hepatic encephalopathies caused by alcohol, drugs and other toxic substances abuse, viral infections and Wilson's disease. This is particularly important in multidrug dependence as it often coexists with liver damage. Moreover, intravenous route of administration may lead to infections with hepatic viruses, therefore ephedron encephalopathy might superimpose hepatic encephalopathy. Laboratory tests, particularly Mn serum and urine

levels, but also detailed medical history may contribute to establishing the final diagnosis [9-11].

Evaluation of brain haemodynamics by Transcranial Color Doppler sonography (TCCD) study revealed significantly decreased flow velocity parameters (V_{sis} , V_{mean} , V_{dias}) for the MCA and ACA in abusers compared to control subjects. There were no significant gender interactions. Beside diminished blood flow velocities, abusers show significant increase of flow resistivity. Moderate to severe vessel irregularity consistent with vasoconstriction and vasodilatation was revealed in majority of abuse patients also by the intracranial MR-angiography.

It is possible, that Ephedron, like Methamphetamine, causes acute rapid release of 5-HT serotonin, which is a potent vasoconstrictor from serotonergic synapses and leads to increased synaptic dopamine levels in several brain areas. Although its permanent neurotoxicity is still a matter of debate, there is evidence that stimulation of 5-HT_{2A} receptors in small vessels will lead to prolonged vasospasm and result in ischemia of the involved regions of the brain. The occipital cortex and globus

pallidus are the most vulnerable brain regions due to the high levels of 5-HT and 5-HT_{2A} receptors. Ischemia is, therefore, more likely to occur than hemorrhage and often involves small vessels [2,6,12].

In our opinion, Mn intoxications and ephedrone encephalopathy may become an increasing clinical problem in the future. Ephedrone addiction is an alarming new cause of toxic parkinsonism. The described cases could be just "the tip of the iceberg". In the most extreme cases, only a few months of ephedrone abuse could lead to severe and progressing disability.

Our results suggest, that MRI demonstrate systematic brain structural changes in Methcathinone abusers. Slowed cerebral blood flow velocity with increased pulsatility and impaired CRV in abusers indicate increased cerebrovascular resistance due to vasoconstriction of small cortical vessels.

Complex use of MRI and CDUS with CVR study gives valuable information about brain structural-haemodynamic changes in Methcathinone abusers. Measurements of signal intensity in globi pallidi in regard to frontal lobes white matter allow objective evaluation of signal intensity and monitoring dynamics of changes in follow-up examinations.

სამედიცინო მეცნიერებანი

თავის ტვინის სტრუქტურული ცვლილებები და ჰემოდინამიკური პარამეტრები მეთკათინონის (ეფედრონის) მომხმარებლებში

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კვლევის მიზანს წარმოადგენდა ნარკოტიკულ პრეპარატ მეთკათინონის (ეფედრონის) ქრონიკული მომხმარებლების თავის ტვინში სტრუქტურული ცვლილებებისა და ჰემოდინამიკური პარამეტრების შეფასება; ზემოაღნიშნული ფსიქოაქტიური ნარკოტიკული საშუალება მიიღება კალიუმის პერმანგანატთან პრეპარატ ეფედრონის ჟანგვის რეაქციით.

2006–2013წწ. კლინიკური მედიცინის ს/კ ინსტიტუტში შესწავლილ იქნა მეთკათინონის ქრონიკული ინტრავენული 41 მომხმარებელი (საშ. ასაკი 41წ). ყველა პაციენტს ჩაუტარდა თავის ტვინის მაგნიტურ-რეზონანსული ტომოგრაფია- მრტ (1,5T, 3T), ექსტრა-ინტრაკრანიალური სისხლძარღვის ფერადი დოპლერგრაფიული კვლევა, მრ-ანგიოგრაფია; ფსიქოლოგიური სტატუსის შეფასება, ნევროლოგის კონსულტაცია; ტრანსკრანიალური დოპლერგრაფიული ფუნქციური სინჯებით ასევე შესწავლილი იყო ინტრაკრანიალური არტერიებში ცერებროვასკულური რეაქტიულობა.

პაციენტთა უმრავლესობას აღენიშნებოდა რიგი ექსტრაპირამიდული დარღვევები, პარკინსონის დაავადების მსგავსი კლინიკური გამოვლინებით; მათ შორის ბრადიკინეზია, ატაქსია, ტრემორი, სიარულის, კოორდინაციის დარღვევა, მუსკულარული დისტონია. ფსევდობულბალური სინდრომი, ან ხასიათობრივი ცვლილებები შედარებით იშვიათ მოვლენას წარმოადგენდა. 2 შემთხვევაში აღინიშნა მწვავე იშემიური ინსულტი. ერთ შემთხვევაში 34წ. მამაკაცში, ინსულტი გამოწვეული შიგნითა საძილე არტერიის მწვავე დისსექციით, მეორე- 41წ. მამაკაცში, შუა ცერებრული არტერიის თრომბოზით.

35(85%) შემთხვევაში თავის ტვინის მრტ კვლევით თ1შეწონილ გამოსახულებებზე გამოვლინილ იქნა მანგანუმით ინტოქსიკაციისათვის დამახასიათებელი ჰიპერინტენსიურობა; მათ შორის, გამჭვირვალე ძვირფეში (30/74%), შავ ნივთიერებაში (28/68%), ნათხემის კბილისებრი ბირთვში (23/55%, წინა პიპოფიზში 16/40%). თავის ტვინის სტრუქტურული ცვლილებების გავრცელება კორულირებული იყო ნარკოტიკული საშუალების მოხმარების ხანგრძლივობასთან. მრ-ანგიოგრაფიამ შემთხვევათა 28(68%) გამოავლინა ინტრაკრანიალური არტერიების საშუალოდ ან მკვეთრად გამოხატული არათანაბარი კალიბრი, რაც ვაზოკონსტრიქციისა და ვაზოდilatაციის მონაცვლე უბნების გამოხატულებას წარმოადგენს.

ინტრაკრანიალური სისხლძარღვების დოპლერგრაფიით შემთხვევათა უმეტეს ნაწილში აღინიშნა სისხლის ნაკადის დაქვეითების ტენდენცია ვილიზიის წრის არტერიებში, უპირატესად წინა აუზის სისხლძარღვებში. ასევე აღინიშნა პულსაციის ინდექსის მატება და ცერებროვასკულური რეაქტიულობის დაქვეითება. ტკდ ცვლილებები კორულირებული იყო ნარკოტიკის მოხმარების ხანგრძლივობასთან.

დასკვნა: მრტ კვლევით ვლინდება თავის ტვინის სისტემური სტრუქტურული ცვლილებები,

დამახასიათებელი მეტაკათინონის ქრონიკული მოხმარებლებისათვის, რაც უპირატესად თვალსაჩინოა T1 შეწონილ გამოსახულებებზე. დაქვეითებული სისხლის მიმოქცევა, მომატებული პერიფერიული წინაღობის პარამეტრები და დაქვეითებული ცერებროვასკულური რეაქტიულობა შესაძლოა იყოს ეფედრონის მოხმარებლებში მცირე კალიბრის კორტიკალურ არტერიებში მკვეთრი ვაზო-კონსტრიქციის გამოვლინება.

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