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# Cognitive dysfunctions caused by excessive exposure to manganese compounds. Cognitive disturbances in intravenous users of ephedrone (methcathinone) with manganese compounds

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**Summary**

Intravenous injection of self-produced ephedrone (metcathinone) using potassium permanganate as an oxidant can lead to severe, fixed encephalopathy. This risk applies mainly to young individuals experimenting with "home-made" drugs and results in an irreversible aggravation of overall functioning. Besides multiple neurological symptoms and movement disorders, affected individuals also experience cognitive dysfunction. No systematic research has been conducted in this field. Single case reports and small group descriptions show that assessment with screening tools such as the Mini-Mental State Examination (MMSE) is ineffective. Neuropsychological assessment conducted with other tests indicates significant dysarthric speech disorders, psychomotor function impairment, attentional disorders of varying intensity as well as dysfunctions of verbal and visual working memory processes. Some studies of this group of subjects also indicate working memory and executive function disorders. These dysfunctions seem to be permanent and do not recede following manganese use discontinuation and an improvement of the neuroradiological picture in MRI assessment. A standard test battery should be developed enabling the assessment of both cognitive and neurological dysfunctions that otherwise render some tests impossible to administer.

**Key words:** manganese encephalopathy, ephedrone, cognitive functions

## Introduction

The aim of the present work is to present the current state of knowledge in field of cognitive dysfunctions in manganese encephalopathy diagnosed in intravenous

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users of ephedrone with manganese compounds. The first mention of manganese encephalopathy appeared more than two decades ago in Russian medical publications [1]. The studies therein discussed were mostly conducted on patients from ex-USRR states, namely from Russia [2–5], Estonia [6–11], Georgia [12], Ukraine [12–15], and Latvia [16, 17]. Moreover, there also exist publications presenting research performed on emigrants from the aforementioned states [18–20] as well as on the neighbouring populations of Turkey [21–25] and Poland [26–30].

As access to Russian publications is limited, information about both the affected population as well as the associated treatment is equally scarce. The advanced stage of manganese encephalopathy with which patients begin seeking medical attention represents yet another challenge, both in terms of diagnosis as well as treatment. Therefore, the investigated population consists of individuals with neurological disorders and changes typical of manganese encephalopathy referred to as manganese-induced parkinsonism (MIP). Similar symptoms had been established in workers, such as welders, smelters and miners, exposed to manganese compounds in the workplace [31]. In the aforementioned case, manganese compounds enter the organism mainly through nasal mucosa and olfactory nerves with the first symptoms of encephalopathy usually appearing only after chronic long-term exposure counted in decades. In contrast, intravenous ephedrone (metcathinone) users, consisting mostly of adolescents and young adults experimenting with self-made psychoactive substances, develop encephalopathy symptoms much sooner. Ephedrone is extracted from drugs containing pseudoephedrine. In the case of Poland, the products mainly used for ephedrone extraction are known under the brand names of Sudafed and Acatar. Ephedrone is obtained in an acid environment by oxidising pseudoephedrine with high amounts of potassium permanganate [32]. Besides ephedrone, however, the obtained solution also contains high concentrations of manganese. Administered intravenously, manganese penetrates to the central nervous system and deposits in the globus pallidus and other subcortical structures. Manganese neurotoxicity manifests itself in serious manganese encephalopathy symptoms consisting mainly of body posture and speech disorders which usually appear after 5–9 months of exposure and precede other symptoms [10, 26]. Early asthenic symptoms could, possibly, be detected earlier with the help of neuropsychological methods. Drug addicts, however, tend to ignore the early pathological symptoms and are highly tolerant to their intensity, usually trusting that the experienced dysfunctions are transient in character [26]. Therefore, patients reporting for medical assistance often exhibit advanced symptoms of encephalopathy. As manganese is metabolised at a slow rate, symptom intensity most probably depends on the aggregate amount of injected doses. Encephalopathy symptoms are predominantly neurological in character and manifest through changes in body posture associated with balance disorders and reverse incidence. Most patients have difficulties with backtracking as well as with standing up from a squatting position without any support. The so-called “cock gait” is very characteristic of manganese encephalopathy and consists of a dystonic contraction of foot and calf muscles. Speech disorders are also very common with symptoms ranging from voice tone disorders and palilalia to, in the most severe cases, a complete inability to communicate verbally. The etiology

of speech disorders is complex and dysarthric in nature. Symptoms may also consist of forced laughter and extrapyramidal syndrome e.g. psychomotor retardation, bradykinesia, muscle rigidity, hypomimia, micrographia, impeded performance of precise movements. As opposed to Parkinson's disease, rest tremor is rare in manganese encephalopathy [10, 12, 14, 16]. Diagnosis is facilitated by establishing that the patient intravenously uses ephedrone and potassium permanganate solution and is further confirmed with an MRI picture showing hyperintensive changes in the globus pallidus, shell and thalamus nuclei in the T1 sequence [16, 17,26–29, 31]. The differential diagnosis of Parkinson's disease stresses insensitivity or minimum sensitivity to anti-Parkinson drugs, including L-DOPA [31].

## Cognitive function investigation

Most clinical descriptions of manganese encephalopathy in users of ephedrone and manganese compounds focused on such areas as neurological deficits and distinct dysarthric speech disorders, neuroradiological changes, manganese concentrations in the blood, the course of the disease, and the response to treatment. The presence of dysarthric speech disorders, making patients' communication with their environment difficult, was mentioned in that works. However, dysarthria was described in terms of neurological disorders without precise examination. Neuropsychological assessment was either ignored or treated marginally as supplement to neurological evaluation. The reason of such omission stems partly from the fact that most of the available studies represent casuistry publications or research conducted on small samples. The only study that focused solely on cognitive functions was performed by Koksal et al. [25] and consisted of a controlled investigation (9 patients and a healthy control group) with a two-year follow-up. The results showed no differences between the examined groups in the scope of language, visuospatial and constructive functions. However, the experimental group of patients with encephalopathy scored significantly worse than the control group in tests measuring verbal and nonverbal memory (both recall and recognition). Skills associated with frontal lobe function (executive functions) were also significantly impaired in the experimental group when compared to the control group. Most importantly, in the two-year follow-up assessment of the experimental group no improvement in cognitive functions was found despite minor improvement in motor functions. Only one other study has been found that includes a control group [15].

There are also published articles that make reference to neuropsychological assessment however without any further specification of, for example, the names of tests used. One such article represents a case study of a 32 year-old Polish patient and includes only the results of neuropsychological assessment (cognitive dysfunctions in verbal and nonverbal memory, visuospatial coordination and psychomotor speed) without providing – as in other works [22] – the methods used to obtain these results [28].

The problem of cognitive dysfunction in manganese encephalopathy seems to be significantly associated with worse psychosocial functioning. Although the majority of patients are hard drug users with earlier neuropsychological dysfunctions and worse psychosocial outcome, manganese-induced poisoning seems to worsen their movement

and cognitive skills significantly more in comparison with earlier problems. The following short description presents the case from own clinical practice.

Thirty-five-years-old Mr. A.B. started using drugs (heroine) in high school. Before that time he was a good student. He gave up learning for the reason of drug abuse. As the result of his parents intervention, A.B. underwent 2-year-long therapy in an inpatient centre, where he passed the final high school exams. He began to participate in methadone substitution treatment programme, occasionally drinking alcohol. A.B. lived actively undertaking temporary jobs and pursuing his hobby in which he won the national championship four times. He was a sociable person. Two years before neuropsychological investigation he started using intravenously ephedrone extracted from drugs containing pseudoephedrine with potassium permanganate, up to 10 injections daily. After one year and a half he became affected by movement disorders: muscle spasticity, the "cock gait", he had to use crutches. After a month from movement disorder onset, he started to have dysahrtric speech disorders: slurred and unintelligible speech making verbal contact with his environment difficult, palilalia. In the time of investigation, the patient reported that he was terrified by worsening of his condition and his quality of life. He spent most of time in front of TV set. A.B. lost his social relations, because he could not even maintain the phone contact for the reason of speech disorders. He lives with his parents, requiring their help in some everyday activities (shaving, fastening the buttons). Neuropsychological investigation showed severe dysarhtric speech disorders assessed with Frenchay Dysarthria Asssessment and the presence of (less severe compared to leading deficits) disorders in working memory (with the predominance of cognitive flexibility disturbances) as well as in verbal and visual learning. These dysfunctions were assessed with the use of more exact neuropsychological tests (WCST, Trial Making Test, Digit Repetition, Rey Verbal Auditory Learning Test, Benton Visual Working Memory Test). Clinical investigation showed writing disorders (micrographia). The results of screening test for dementia (Mini Mental State Examination – MMSE) ranged in standard norms. Neuroimaging assessment showed changes in basal ganglia, globus pallidus, penduculuscerebri anterior with greater intensity on the left side. Demyelination lesions were found in white matter of the right frontal lobe and right lateral ventricle. Minor cortical atrophy was found.

## Assessment with MMSE

A number of studies referred to MMSE as a screening tool for the assessment of global cognitive functioning [14, 17, 22, 25]. In the Ukrainian study, no severe (dementia type) cognitive dysfunctions were found also in memory functions. The MMSE score achieved in this study amounted to 29 points (standard norm) [14]. The Latvian research found that only one patient out of a group of 17 patients that were assessed with MMSE obtained a score indicative of moderate dementia (18 points) while the results of other tested patients did not deviate from the norm [17]. In a case study conducted by other authors, a patient showing no typical changes in the MRI picture obtained a score of 28 in MMSE [22]. In light of the above cited studies, MMSE seems to be

an ineffective tool for encephalopathy screening in intravenous users of ephedrone with manganese compounds.

## Other neuropsychological tests

Individuals with "ephedrone encephalopathy" exhibit changes in areas associated with the prefrontal cortex. Most importantly, this does not correspond to the typical changes in the neurological picture in other brain structures e.g. the globus pallidus and subcortical structures. Such results have been partly explained in the Latvian study of ten patients in whom diffusion tensor imaging (DTI) showed significant white matter changes in two brain structures associated with executive control of motor functions i.e. the premotor cortex of the right hemisphere and the dorsolateral prefrontal cortex [17].

The work of Selikhova et al.[14] provides more detailed information on the cognitive functions of patients with manganese encephalopathy as a supplement to neuroradiological and radiological assessment. The study investigated 13 patients with typical severe neurological and cognitive dysfunctions as well as with typical changes in the neuroradiological picture. The former dysfunctions (including speech and neuromotor disorders) significantly hindered or rendered impossible the correct assessment of all the neuropsychological tests. In addition to the MMSE scale – which did not fall below the norms – the Frontal Assessment Battery (FAB) was used to assess executive functions. The battery consists of six subtests: similarities, lexical fluency, motor sequences, conflicting instructions, prehension behaviour, and a "go-no-go" test. These subtests assess skills related to conceptualization, mental flexibility, programming, sensitivity to interference, inhibitory control, and environmental autonomy. The FAB investigation established minor executive function deficits, particularly in the scope of cognitive flexibility, programming, sensitivity to interference, and in the area of inhibitory control. However, the score of the Beck Depression Inventory indicated a mild intensity of depressive symptoms that could have affected the obtained test results.

A more detailed neuropsychological investigation can be found in the case study of a 28 years-old Ukrainian immigrant living in Italy who had been diagnosed with symptoms characteristic for manganese-induced parkinsonism [19]. Unfortunately, the work makes little reference to the names of most of the neuropsychological methods used, with the exception of tools assessing some parameters of executive functions and attention i.e. Trial Making Test B, the Symbol Digit Test, and a Wisconsin Card Sorting Test version modified for the needs of the research. The aforementioned study found mild deficits of the discussed processes, including cognitive flexibility measured by the number of perseverative errors in the WCST. The results related to verbal and visual episodic memory, language functions (other than the diagnosed dysarthric disorders) and visuospatial functions did not deviate from the norm.

A slightly different result profile was found in the case study of seven patients aged 19-31 from Turkey [24]. The study found mild executive function disorders combined with attention disorders (including sustained attention). In comparison to other research quoted above, the Turkish patients exhibited minor verbal and visual memory deficits.

Yildrim et al. [22] studied a 29 years-old male taking ephedrone with potassium premanganate for a period of four and half years in considerably lower doses than those described in most of the presented cases (2–3 doses every 2–3 weeks). The results of neuropsychological tests indicated minor verbal and nonverbal memory deficits. The type of verbal memory disorders observed is characteristic of frontal lobe dysfunction as it includes spontaneous learning disorders in individuals capable of correctly recalling material from memory.

Despite the fact that many studies cited above indicate that executive dysfunction is frequent, there are also some findings that do not confirm this assumption. In the work of Djamshidian et al. [15] individuals with manganese encephalopathy were compared to patients addicted to opiates in substitution treatment and a control group of healthy volunteers. The research focused on investigating different decision-making processes from both the behavioural as well as from the "reflection-impulsivity" perspective. The results show that decision-making processes were aggravated in both groups of addicted individuals as compared to the healthy controls. However, the subjects with manganese encephalopathy obtained better results than the opiate addicts in the assessment of working memory. On this basis, the authors concluded that in both groups there is a possibility of damage to connections between the orbitofrontal cortex, anterior cingulate cortex and the subcortical structures, while in patients using intravenous ephedrone with permanganate damage to the dorsolateral prefrontal cortex may not occur. This conclusion should be interpreted with caution because the selected memory test was of a different nature than in the previously cited works: it was carried out using the technique of recognition of images depicting emotion (by using emotionally negative, positive and neutral stimuli). The other interesting finding of this study is that cognitive dysfunctions in individuals with manganese encephalopathy proved to be less significant than the cognitive dysfunctions found in the opiate user group in stabilized substitution treatment. Although patients with opiate addictions differed from healthy controls in three out of four investigated parameters, patients with manganese encephalopathy differed from healthy subjects in only one domain.

## Dynamics of cognitive functions

Cognitive functions are taken into account in the assessment of the course of manganese encephalopathy – in the case of manganese substance use cessation and/or treatment. Neuropsychological assessment for this purpose was conducted in the studies of Levin [2], Ismailova et al. [3], and Koksal et al. [25]. Ismailova et al. diagnosed the investigated patients with neurodynamic dysfunction and impairment of cognitive regulation processes reflected in bradyphrenia, attentional disorders, modal-nonspecific memory disorders, increased fatigue, and cognitive flexibility disorders. The authors concluded that Mexidol treatment alleviated the neurological disorders as well as improved cognitive functions [3]. Levin found similar improvements albeit only in some of the patients [2]. According to Koksal et al. [25], an abstinence of two years from manganese substances can improve motor but not cognitive dysfunctions.

## Conclusions

The studies investigating the neuropsychological effects of long-term manganese exposure in the professional context refer to different stages of encephalopathy and allow for the comparison of groups with different symptom intensity, different levels and durations of exposure, before and after exposure cessation, as well as before and after treatment attempts (chelation, symptomatic treatment). However, the situation is more complicated in the case of intravenous ephedrone users. Reports are focused on single cases or on, at best, small and heterogeneous groups. Patients in the early stages of the disease when the adverse effects could be reversed are practically never investigated. Furthermore, most drug users are not able to discontinue manganese compound use despite the awareness that such behaviour triggers encephalopathy symptoms. Therefore, standards of neuropsychological assessment should be developed to help to detect changes in cognitive functioning at the earlier stages of manganese-induced poisoning.

Zoni et al. proposed certain standards of neuropsychological investigation, including the global assessment of patients with manganese-induced encephalopathy (of varying etiology) [33]. They suggested the investigation of intellectual functions with the WAIS-R battery or the Raven Standard Matrices Test and the assessment of psychomotor speed with the finger tapping or reaction time test. For the purpose of cognitive function evaluation, the authors proposed the Rey Auditory Verbal Test for the assessment of verbal memory and the Benton Visual Retention Test for the assessment of visual memory. Furthermore, they also indicated the Trial Making Test and symbol and repeating digits tests to assess working memory and executive functions. However, although all the aforementioned methods may be used in the early stages of manganese-induced poisoning, the assessment of individuals with severe ephedrone encephalopathy (Parkinsonism and severe speech disorders) with such tools would not be easy [14, 18]. Notably, the WAIS-R test, despite being a tool for precise clinical assessment, may prove to be too difficult for patients with severe dysarthric disorders [18]. It seems that the selection of neuropsychological tests should be adapted to patient's estimated investigation time. If it is short but there is a chance for one's cognitive monitoring, it is worth to use tests that can be repeated frequently. The examples are Trail Making Test or Colour Trial Test CTT that assess psychomotor speed and executive functions, Benton Visual Retention Test (there are different versions) and WAIS-R Digit Repetition to assess verbal memory. In the circumstances of more detailed neuropsychological examination, the Wisconsin Card Sorting Test WCST for the assessment of flexibility of cognitive processes and executive functions, and Rey Verbal Auditory Learning Test or California Verbal Learning Scale assessing verbal learning, can be applied. It is worth to assess precisely dysarthric speech disorders with the use of adequate scale (e.g. Frenchay Dysarthria Assessment) and to assess micrographia. Neuropsychological examination should be accompanied by patient's mood assessment.

The assessment of cognitive functioning seems to be necessary to improve the knowledge of the effects of manganese-induced poisoning. Neuropsychological di-

agnosis provides information that – combined with other specialized methods such as neuroimaging, psychiatric, neurological and toxicological assessment – allows for the acquisition of highly objective data at various stages of the disease. Neuropsychological assessment should not be limited to screening with tools such as MMSE [14, 17, 22, 25]. Cognitive function assessment may serve as an indicator sensitive to the dynamics of manganese neurotoxicity, particularly in subclinical, less severe cases while being less adequate at later stages of the disease when the cognitive dysfunctions seem to be persistent [25]. The assessment of the cognitive dysfunction profile should lead to adequate therapeutic and rehabilitation interventions.

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