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Characteristic of neuropsychological deficits in patients diagnosed with manganese encephalopathy due to ephedrone use – case series analysis

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Summary

Aim. The study presents neuropsychological characteristic of 16 individuals with manganese-induced parkinsonism due to intravenous ephedrone use.

Method. Overall cognitive function screening as well as full examination of various cognitive domains (verbal learning, visual memory, working memory, executive functions, construction and visuospatial functions) with the use of elastic neuropsychological test battery were performed. Dyshartric speech disorders were also precisely evaluated. Additionally, all individuals filled in *the Beck Depression Inventory* (BDI), which is used to assess mood.

Results. All patients had evident dysarthric speech disorders accompanied with palilalia and writing disorders (micrographia) in the majority of investigated individuals. Neuropsychological screening diagnosis showed no overall cognitive deficits at the level of dementia. Mild decrease in verbal learning and visual memory processes was found; as well as ideomotor but no construction praxis disorders. Results of working memory and executive function assessment indicated decrease in cognitive flexibility and logical conceptualization abilities, as well as set-shifting disorders. Patients varied significantly in their severity of executive dysfunction. Duration of ephedrone use was found nonsignificant for patients' cognition. The mean BDI score indicated moderate depression. Higher level of depressive symptoms was associated with poorer overall cognitive screening, decrease of visual and verbal learning as well as phonemic verbal fluency.

Key words: manganese encephalopathy, ephedrone, cognitive functions, mood, neuropsychological diagnosis

Introduction

Manganese encephalopathy [1] manifests with neurological symptoms occurring due to exposure to neurotoxic influence of manganese on the central nervous system (CNS).The disease occurs not only in individuals exposed to higher manganese con-

centrations in environmental circumstances (e.g., in residents of areas of industrial manganese use or industrial workers). Manganese encephalopathy symptoms has been found also in intravenous ephedrone users, accessing it in a process of home-made drug production. The first mention of such individuals appeared over 20 years ago in Russian studies on patients from ex-USRR states and the neighboring countries [2, 3]. Although this problem seems rare it still might be relevant in a population of drug users all over the world.

Individuals self-inject ephedrone for the euphoric effect. The substance is extracted from drugs containing pseudoephedrine, usually from cheap and commonly available medications with no need of prescription (e.g., popular nose drops). Ephedrone is obtained in an acid environment by oxidizing pseudoephedrine with potassium permanganate [4]. The obtained solution also contains high concentrations of manganese. Administered intravenously, manganese penetrates to the CNS and deposits in the globus pallidus and other subcortical structures. Manganese neurotoxicity manifests itself in serious manganese encephalopathy symptoms, e.g., body posture and speech disorders which usually appear after 5–9 months of exposure [5, 6].

Cognitive dysfunctions in users of ephedrone with manganese compounds has been reported [7]. However, most of them were single case studies focused on neurological deficits, changes in the brain and the response to symptomatic treatment (e.g., with mexidol [8] or chelation [9]). Although dysarthric speech disorders were found in these patients in every particular study, they were only mentioned generally, in terms of neurological disorders – detailed characteristics of patients' cognitive functioning were ignored. However, in systematic database search with the use of PubMed, two works focused solely on cognitive functions were found. One of these studies showed no cognitive improvement after 2-year follow-up despite better results in patients' motor functions [10]. The second study concerned detailed dysarthric speech disorder assessment [11]. Most of the studies on manganese encephalopathy cited in this article did not address emotional functioning, including depressive mood. Whereas, more detailed information could expand knowledge of cognitive and emotional functioning of individuals with ephedrone encephalopathy. This could help in creating diagnostic and therapeutic standards (e.g., neuropsychological therapy, psychotherapy) for these patients. Consistent standards would allow for better observation of changes in cognitive functions and patients' mood during treatment.

The present work is the first multiple case study of a group of intravenous ephedrone users with manganese encephalopathy in Poland. It aimed to characterize neuropsychological and emotional status of these patients, as well as to find associations between their depressiveness and the level of cognitive functioning. Moreover, the present article aimed to show the clinical picture of manganese

encephalopathy in light of diagnostic methods that (in majority) were popular and widely used among clinical psychologists and neuropsychologists working in the public healthcare. Their use allowed for overall as well specific cognitive function assessment, in spite of problems in statistical correctness of presented results in terms of Polish normalization.

Material

The study group consisted of 16 patients with manganese encephalopathy – 12 men and 4 women who self-injected ephedrone with the frequency up to 20 injections daily. Patients varied in terms of age (+35 years; 27–52 years), but not education (+12 years of formal education) and duration of ephedrone use (+2 years). All of them had a history of previous drug use, 14 patients used to take heroine (3 of them were undergoing methadone substitution program) and 2 individuals – amphetamine. All investigated patients, besides three patients taking methadone, declared current abstinence, including cessation of ephedrone with manganese compounds intake during at least six months. Seven individuals at the time of investigation were living in drug addiction care centers, the rest of investigated individuals stayed under family care.

All investigated patients were admitted to outpatient hospital clinic. Before the neuropsychological assessment they were examined by a psychiatrist and neurologist who confirmed severe symptoms of manganese-induced parkinsonism according to the standards for the diagnosis of the disease [5] and its differentiation from Parkinson's disease [1]. The majority of patients had visible body posture and movement (steppage gait) disorders as well as speech disorders. The majority of patients had specific disorders (gait disturbance) consisting in movement and speech initialization delay and then in difficulties to stop this reactions. Palilalia was present in 12 patients. In 10 patients handwriting was impaired –micrographia (associated with abnormally smaller handwriting). Although neither ecological measurement methods nor observation in natural environmental circumstances were applied in patients' assessment, investigated individuals' reports indicated significant worsening of their everyday functioning. They had difficulties with managing simple everyday tasks (e.g., getting dressed, eating meals). The clinical interview allowed to reveal other irreversible negative consequences of the condition as the loss of employment or ability to perform one's favorite activities (e.g., playing a musical instrument) and the need to be taken care by others (e.g., parents or care center staff). The majority of investigated subjects declared no acceptance of their present state and reported decreased quality of life.

The study was conducted as statutory research with no external funding and approved by ethical committee of the institution in which patients were investigated. All

patients gave written informed consent to participate in the study. Neuropsychological assessment was preceded by short interview, to collect psychosocial data. The assessment process was divided into three separate meetings. Because of severe speech disorders which caused difficulties in telephone contacts, all arrangements of meetings, cancellations etc., were conducted via sms. Not all individuals were able to complete the whole neuropsychological test battery. One patient was unable to perform the whole ACE-R because of mutism. The patient came from a distant therapeutic centre with a caregiver who assisted the patient in walking and providing information. This individual withdrawn participation in another stages of neuropsychological assessment due to financial problems (lack of possibility to cover expanses that would allow to re-arrive with a caregiver). Another two patients refused to perform *the Wisconsin Card Sorting Test* during the first meeting without explaining the reason. One patient did not take part in assessment with the use of *the Rey Auditory Verbal Learning Test* (in the second meeting) because of severe dysarthric speech disorders. Another individual did not show up at the third meeting – the patient sent a message saying that he would not participate in the study, without giving any reason.

Method

Neuropsychological assessment

Global cognitive function screening as well as more specific tests were used in order to assess verbal learning, visual memory, working memory, executive functions, and constructive functions. Verbal fluency, as the ability to generate words according to semantic (categorial) or phonemic (letter) criteria in one minute, was also evaluated. Verbal fluency involves complex cognitive processes as executive functions and semantic memory [12, 13]. It is also associated with verbal intelligence, language skills, psychomotor speed, and visuospatial functions [14]. Dysarthric speech disorders were also examined.

Methods of neuropsychological assessment used in this study were popular tools widely used in clinical practice in Poland and worldwide. Despite this, Polish standards for the majority of them were not published, which seems to be a main limitation of many neuropsychological assessment methods in Poland [15]. For that reason the presented results should be interpreted with caution and treated as the results of experimental methods that did not meet statistical normalization criteria. Methods of neuropsychological assessment as well as investigated cognitive domains are presented in Table 1.

Table 1. **Neuropsychological tests used in assessment of intravenous ephedrone users and assessed cognitive domains**

Neuropsychological test	Test coefficients	Assessed cognitive domain	Additional information	N
Addenbrooke's Cognitive Examination (ACE-R) Including Mini-Mental State Examination [16]	Maximum number of points possible to obtain in the global score and in subscales	Global cognitive function screening for dementia	Assessment of attention and orientation, memory, language functions, verbal fluency and visuospatial functions	15 16
Wisconsin Card Sorting Test (WCST) [17]	PE (percent of perseverative errors) NPE (percent of non-perseverative errors) %CONC (percent of conceptual level responses) CC (number of completed categories)	Executive function and working memory in changing environmental (reinforcement) circumstances	Measurement of cognitive flexibility, logical conceptualization and the effectiveness of thinking	14
Trial Making Test A [18]	Performance time (seconds)	Psychomotor speed		12
Trial Making Test B	Performance time (seconds)	Executive function	Set-shifting ability	
Wechsler Adult Intelligence Scale [19] Digit Span Block Design	Recalculated scores	Immediate verbal memory and working memory. Motor functions as well as visuospatial and constructive functions		13
Benton Visual Retention Test [20, 21]	The difference between number of correct answers and errors to the number of expected answers and errors	Visual perception and immediate visual memory		13
Rey Auditory Verbal Learning Test [22]	Assessment of learning curve in following five repetitions of list A (1A–5A) Qualitative assessment of entering list B and after 20-minute delay (7A) Errors in Recognition Task	Auditory verbal learning and memory Resistance to distraction and delay Recognition processes		12

table continued on the next page

Verbal Fluency Test [23, 24]	The number of words generated in one minute according to category (Semantic Test) or starting with a given letter (Phonemic Test)	Executive function, semantic memory	Association with verbal intelligence, language skills, psychomotor speed, and visuospatial functions	12
Dysarthria assessment: Frenchay Dysarthria Assessment [25]	5-level scale of disorder severity	Severity of dysarthric speech disorders. 8 subscales: reflexes (cough, salivation, swallowing), respiration, lips, mandible, soft palate, laryngeal, tongue, intelligibility		12

Mood assessment

All investigated patients filled in *the Beck Depression Inventory* [26] in order to subjectively assess their depressive symptoms.

Procedure

On the first meeting, clinical interview, screening with the use of the ACE-R as well as *the Wisconsin Card Sorting Test* (WCST) were performed. During the second meeting patients were investigated with *the Rey Auditory Verbal Learning Test* (RAVLT), *Benton Visual Retention Test* (BVRT), *Trial Making Test*, and two subscales of the WAIS-R test: Digit Span and Block Design). The assessment with *the Frenchay Dysarthria Assessment* and *Verbal Fluency Test* were performed on the third meeting. Patients also filled in *the Beck Depression Inventory.*

Besides the WCST all tests were administered in non-computer versions. In the WCST assessment the American computer version (4.51) [17] with the current license was used. Instruction was given in Polish language. Before starting the test, it was ensured that the investigated person correctly understood the foreign words "right" and "wrong" appearing on the computer screen.

Statistical analysis

Statistical analysis was performed with the use of STATISTICA 10. The first step of statistical analysis was to calculate the descriptive statistics of psychosocial variables (age, education, the length of ephedrone use), results of neuropsychological tests and

the BDI score. Mean values, upper and lower quartiles as well as standard deviations were obtained. Results of neuropsychological tests were calculated for the number of individuals who completed all tests (from 12 to 16 patients). The next step aimed to identify correlations between psychosocial variables, results of neuropsychological tests and the BDI score using the Spearman's *R* correlation coefficient (used due to lack of normal distribution of analyzed data). All correlations were calculated at the level of statistical significance $p < 0.05$.

Some results of studied individuals were referred to the healthy control group. Mean scores of the WCST and TMT A and B were compared to results of 13 individuals without psychiatric or neurological disorders, matched owing to the enabled access to the database of the Department of Clinical Neuropsychology, Collegium Medicum in Bydgoszcz, Nicolaus Copernicus University Collegium Medicum in Torun. Non-parametric Mann-Whitney *U* tests were used for between-group comparisons.

Results

Mean results of neuropsychological tests (excluding dysarthria assessment) and *the Beck Depression Inventory* are presented in Table 2.

Table 2. **Results of neuropsychological tests and the Beck Depression Inventory of 16 intravenous ephedrone users with manganese-induced parkinsonism**

Neuropsychological test	N	Mean	Min. value	Max. value	Lower quartile	Upper quartile	SD
ACE-R	15	89	75	100	85	93	6.04
MMSE	16	27	23	30	27	30	2.40
ACE-R Attention and orientation	16	16	13	18	17	18	1.84
ACE-R Memory	16	21	15	26	18	25	3.31
ACE-R Verbal fluency	15	10	7	14	10	11	1.79
ACE-R Language	15	24	20	26	24	26	1.74
ACE-R Visuospatial functions	15	14	12	16	14	15	1.18
WAIS-R Digit span Calculated result	13	9	4	16	6	12	3.77

table continued on the next page

WAIS-R Block design Calculated result	13	10	7	15	8	16	1.02
RAVLT 1A	12	5	2	10	4	6	1.95
RAVLT 2A	12	8	5	14	6	10.50	2.67
RAVLT 3A	12	9	3	13	8	12	2.90
RAVLT 4A	12	10	8	14	8.50	11	2.06
RAVLT 5A	12	11	8	13	10	12.50	1.65
RAVLT 1B	12	5	3	8	3.50	6	1.70
RAVLT 6A	12	8	4	11	8	10	2.10
RAVLT 7A	12	9	5	11	7.50	10.50	2.13
RAVLT Recognition errors	12	2	0	6	1	3.50	2.10
BVRT Number of correct answers	13	6	4	10	5	7	1.57
BVRT Expected number of correct answers	13	7	7	9	7	8	0.72
BVRT Number of errors	13	6	0	12	5	7	3.06
BVRT Expected number of errors	13	2	1	4	2	3	0.89
WCST % PE	14	14	6	33	8	20	8.06
WCST % NPE	14	12	5	23	8	19	5.97
WCST % CONC	14	40	9	86	12	57	28.31
WCST CC	14	5	2	6	5	6	1.21
WCST 1 cat	14	42	11	84	12	74	30.44
TMT A seconds	13	29	14	44	22	36	9.32
TMT B seconds	13	77	35	137	57	88	27.30
VFT phonemic Number of correct words	12	40	22.00	65	34.50	45.50	11.37
VFT phonemic Perseverations	12	0.75	0	3	0	1.50	1.21

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VFT phonemic Intrusions	12	0.33	0	3	0	0	0.88
VFT semantic Number of correct words	12	26.16	11	46	20	30	9.48
VFT semantic Perseverations	12	0.58	0	3	0	1	0.99
VFT semantic Intrusions	12	0.83	0	4	0	1.50	1.40
BDI	12	25.25	8	48	16	31.50	11.77

Descriptive statistics: the number of investigated patients (N), means, minimum and maximum values, lower and upper quartiles, standard deviations (SD).

ACE-R – Addenbrooke's Cognitive Examination – Revised Scale; WCST – Wisconsin Card Sorting Test; % PE – percent of perseverative errors; % NPE – percent of non-perseverative errors; % CONC – percent of conceptual level responses; CC – number of completed categories (max. 6); 1 cat – the number of trials to complete the 1st category; TMT – Trial Making Test; WAIS-R – Wechsler Adult Intelligence Scale – Revised; RAVLT– Rey Auditory Verbal Learning Test (number of words in the following repetitions of list A: 1A–7A;1B – number of words in the repetitions of list B); VFT – Verbal Fluency Test; BVRT– Benton Visual Retention Test; BDI – Beck Depression Inventory

Results of neuropsychological tests

Global cognitive function screening

The mean result of *the Addenbrooke's Cognitive Examination* (ACE-R translated by M. Roessler) was 89 points (out of 100 possible to obtain). In turn, the mean score of *the Mini-Mental State Examination* (MMSE) included in the ACE-R was, on average, 28 out of 30 possible points. The between-individuals difference in test performance was significant (ACE-R min. 75 points, max. 100 points, *SD* = 6.04; MMSE min. 23 points, max. 30 points, *SD* = 2.40). The results suggested global cognitive function decrease in some patients and no such disorders in others. Qualitative analysis of individual ACE-R subtests indicated correct orientation in time and space, verbal and working memory problems (e.g., mental subtraction). It also indicated poorer visuospatial functions.

Memory and learning processes

In the studied group, mean result of immediate verbal memory assessment using the WAIS-R Digit Span subtest was within age norms (the mean calculated result was 10), however, there were significant differences in test performance between particular subjects (min. 4, max. 16, *SD* = 3.77).

The curve of learning processes in the RAVLT was dynamic, however, studied patients were able to remember only 11 out of 15 words in fifth list repetition. In all investigated individuals minor susceptibility to distraction was noticed (after presenting of the list B the number of remembered words diminished to 8). The patients also made on average 2 errors in recognition task. Standard deviation values in following list repetitions ranged from 1.70 to 2.30.

In the assessment with *the Benton Visual Retention Test*, a method suggested by the authors of Polish normalization was used. This method consisted in the assessment of differences between the number of correct answers and errors made and the expected number correct answers and errors (a difference of 3 points indicates a decrease in cognitive functioning). As a premorbid intelligence quotient, the assumed intellectual norm was adopted, which was justified by the data from clinical interview of investigated patients. None of them was diagnosed with intellectual disability, they had, on average, 12 years of formal education. Investigated individuals generated 6 correct answers on average (4–10; *SD* = 1.57) and made 6 errors on average (0–12; *SD* = 3.06). The difference between mean number of obtained and expected correct answers and errors was 1 point, however the difference between mean number of obtained and expected errors was 4 points.

Analysis of above results indicated mild decrease of verbal and visual memory processes.

Executive function assessment

In the assessment of WCST results ($n = 14$) indicators of cognitive flexibility, logical conceptualization and effective thinking skills were taken into account. The following parameters were assessed: percent of perseverative and non-perseverative errors, percent of answers according to logical conceptualization, number of completed categories (max. 6), and trials to complete the first category. The test performance varied between particular subjects. For instance, standard deviation in the number of perseverative errors in the WCST was 8.06. Among individuals who completed the WCST were patients with serious cognitive flexibility disorders (33% of perseverative errors) and individuals with no disturbances in that cognitive domain (e.g., 6% of perseverative errors).

Similar diversity of results was found in *Trial Making Test* (TMT) performance ($n = 14$). Mean time of TMT A performance (29 seconds) indicated correct psychomotor speed while mean result of the TMT B (77 seconds) indicated slightly weakened set-shifting function. The divergence of TMT results was smaller in psychomotor speed assessment (*SD* = 9.32) than in executive function assessment (*SD* = 27.30).

Mean scores of tests measuring various aspects of working memory and executive function were referred to available but yet unpublished norms of the WCST and TMT,

accessible due to access permit to the healthy individual database of the Department of Clinical Neuropsychology, Collegium Medicum in Bydgoszcz, Nicolaus Copernicus University Collegium Medicum in Torun. Results of 13 healthy, education-matched (12 years), individuals (9 women and 4 men) were selected. Healthy individuals were significantly older than individuals in the experimental group (mean age 44 years, while the mean age of patients was 35 years), which could be associated with potentially poorer results of healthy individuals due to age factor. Comparison of WCST and TMT results with scores from healthy individuals database as well as the reference of TMT scores to the Polish version of the Halstead–Reitan battery [27], is presented in Table 3. WCST results were not compared with the known Polish adaptation [28] because it does not concern computer version of the test.

Table 3. **Differences in WCST and TMT performance between intravenous ephedrone users with manganese-induced parkinsonism (n = 14) and healthy individuals (n = 13) investigated in the Department of Clinical Neuropsychology, Collegium Medicum in Bydgoszcz, Nicolaus Copernicus University in Torun. Mean values, p levels and Mann-Whitney U test values. Comparison of TMT scores with the Polish normalization of the Halstead–Reitan battery**

Neuropsychological test	Ephedrone users	Healthy individuals	p value	Mann-Whitney U test
WCST % PE	14	9	0.03**	35.50
WCST % NPE	12	9	0.22	50
WCST % CONC	40	78	0.001**	16
WCST CC	5	6	0.27	52
WCST 1 cat	42	15	2.96	20.50
TMT A (seconds)	29 (75^{th} – 90^{th} percentile)*	24 (75^{th} – 90^{th} percentile)*	0.18	44
TMT B (seconds)	77 (25^{th} – 50^{th} percentile)*	50 (50^{th} – 75^{th} percentile)*	0.01**	25.50

WCST – Wisconsin Card Sorting Test; % PE – percent of perseverative errors; % NPE – percent of non-perseverative errors; % CONC – percent of conceptual level responses; CC – number of completed categories (max. 6); 1 cat – the number of trials to complete the 1^{st} category; TMT – Trial Making Test (seconds)

* comparison with the norms of the Polish version of the Halstead-Reitan battery

** statistically significant differences

In the WCST, manganese encephalopathy patients, in comparison with healthy controls, had significantly poorer results regarding the number of perseverative errors (significantly more in the experimental group) and the number of conceptual level re-

sponses (significantly lower in the experimental group). Patients with encephalopathy also needed more time to complete the TMT B.

Constructive function assessment

The results of visuospatial constructive function assessment with the use of the WAIS-R Block Design subtest indicated normal condition of these processes. The mean calculated score was 10 points (min.7, max. 15, *SD* = 1.02). Only two individuals scored below the age norm.

Verbal Fluency

Results of particular patients ranged between the ability to generate 22–65 words in semantic (*SD* = 11.37) and 11–46 words in phonemic (*SD* = 9.48) test in one minute. The majority of patients made neither perseveration nor intrusion errors. Patients had an ability to generate on average 40 words in semantic test (associated with following categories: animal, fruit and vegetable), which corresponded to 90th percentile (in a scale ranging from 10th to 90th percentile) according to American norms, and on average 26 words in phonemic test (words beginning with F, A or S) in one minute, which corresponded to 10th percentile. The reference of *the Verbal Fluency Test* mean results to American norms [23, 24] could suggest normal ability to generate words in one minute in the assessment of semantic but not phonemic fluency. However, this cannot be done taking into account language differences – resulting from different number of words beginning with letters F, A and S in Polish and English language. Therefore the scores of the VFT should be interpreted solely in terms of the clinical sample.

Dysarthric speech disorder assessment

The Frenchay Dysarthria Assessment (FDA) adapted by Marika Litwin, was applied in 12 patients out of the whole studied group. It indicated moderate severity of dysarthric speech disorders. The diversity of results between individuals was significantly smaller than in most of the described studies (*SD* = 1.02–3.99). The most affected area was the ability to initiate spontaneous speech. In some people, these disorders were very severe, however, not in all subjects they were accompanied by palilalia. In majority of patients shortened phonation time as well as laryngeal pitch and volume weakness were observed. Various severity of disorders (from mild to severe) were present in movements of lips (stretching, stiff 'frozen' lips in speech), tongue (in particular associated with elevation of the tongue) and mandible (excessive stiffness, mostly observed in speech). In some patients, mild or moderate problems associated with soft palate function for speech were observed; one patient had problems with

leakage of foods and drinks through the nose while eating. The majority of studied patients had mild or moderate problems in breathing control, particularly shortening of exhalation. In eight patients mild or moderate salivation problems were observed, mostly while leaning, during sleep or at the moment of weakened concentration. In five subjects various severity of choking with food or saliva was present. Three persons had mild or moderate swallowing problems. Detailed FDA assessment with data relating to micrographia and palilalia are presented in Table 4.

Table 4. **Dysarthria assessment in 12 intravenous ephedrone users with manganese-induced parkinsonism with the use of the Frenchay Dysarthria Assessment; together with data data relating to handwriting disorders (micrographia) and palilalia**

Patient	1	2	3	4	5	6	7	8	9	10	11	12
Reflexes												
cough	++++	-	-	++	-	++	-	-	-	+	-	+
swallowing	-	-	-	++	+	-	-	+	-	-	-	-
salivation	-	-	+	++	+	+	+	++	-	-	++	+
Respiration												
at rest	+	-	++	+	+	-	-	-	+	++	+	+
in speech	+	-	++	+	+	++	-	-	-	+	-	+
Lips												
at rest	-	-	+	-	+	-	-	+	-	-	+	-
spread	-	+	-	-	-	-	-	-	-	++++	-	-
closing	-	+	-	+	-	-	-	+	-	+	-	-
alternate	-	+	+	+	-	+	+	+	+	+	+	-
in speech	+	+	++	++	++	++	-	++	+	++	+	+
Mandible												
at rest	-	-	+	+	+	-	+	+	-	+	-	-
in speech	-	+	-	++	++	+	+	+	-	+	-	-
Soft palate												
foods	-	-	-	++	-	-	-	-	-	-	-	-
maintenance	-	-	-	-	+	+	-	+	-	-	-	+
in speech	-	+	+	++	++	-	-	-	-	-	-	-
Laryngeal												
phonation	-	-	+	+++	+	+	+	+	+	++	++	+
pitch	+	++	+	+	+	-	+	+	+	+	+	-
volume	+	+	+	++	+	+	-	-	-	++	+	-
in speech	+	+	+	+	+	++	+	+++	++	+	+	+

table continued on the next page

Tongue												
at rest	+	-	-	+	-	+	-	-	-	++	+	-
protrusion	-	++	-	+	++	-	-	+	-	+	+	-
elevation	++	++	+++	++	++	-	++	+	-	++	++	+
lateral	++	++	-	+	++	-	-	+++	-	-	+	+
alternate	-	-	-	-	-	-	-	++	-	-	-	+
in speech	+	+	-	+	-	+	-	+	-	+	-	+
Intelligibility												
words	-	++++	-	++	-	++	-	-	-	-	-	-
sentences	++	++++	+++	++	-	++++	-	-	-	-	-	-
spontaneous speech	+++	++++	+	+	-	++++	-	++	+	+	+	+
Handwriting disorders (micrographia)	1	0	0	0	1	1	1	1	1	0	0	1
Palilalia	1	1	1	0	1	1	0	1	1	0	0	1

Disorder severity assessment: – no disorders, + mild disorders, ++ moderate disorders, +++ severe disorders, ++++ very severe disorders.

Micrographia and palilalia 0 – absence, 1– presence

Associations between depressiveness and cognitive functioning

The mean score of the BDI, which was administrated in 12 patients, indicated the moderate level of depressive symptoms (25 points). However, there were significant differences between patients (*SD* = 11.77), which mean that some of them did not have depressive symptoms (8 points) while others assessed it at the level of moderately severe depression (48 points). Greater severity of depressive symptoms was associated with lower overall ACE-R score, worse results of the BVRT (higher number of errors and lower number of correct answers), lower number of words in fourth repetition of list A in the RAVLT, as well as lower number of words generated in one minute in the phonemic *Verbal Fluency Test*. The results are shown in Table 5.

Table 5. **Significant Spearman's R correlations between neuropsychological tests scores and the BDI score in intravenous ephedrone users with manganese-induced parkinsonism (n = 16)**

BDI &	Spearman's R
ACE-R	-0.66
BVRT Errors	0.83

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BVRT Correct answers	-0.71
VFT phonemic number of words	-0.75
RAVLT 4A	-0.85

ACE-R – Addenbrooke's Cognitive Examination; BVRT – Benton Visual Retention Test; RAVLT 4A – Rey Auditory Verbal Learning Test, fourth repetition of list A

Association between cognitive functioning and psychosocial factors

Correlations between the results of neuropsychological tests and psychosocial variables are presented in Table 6. No statistically significant associations were found between results of neuropsychological tests and duration of ephedrone use. The age of patients correlated with (1) the percentage of perseverative errors in the WCST (the older the patients were, the more errors they made), which indicates age-related decrease in cognitive flexibility, as well as with (2) lower number of completed WCST categories, which indicates decreased effectiveness of thinking in older subjects. Older age also correlated with higher percentage of conceptual level responses in the WCST and better immediate verbal memory measured using the WAIS-R Digit Span subtest.

Higher number of years of education correlated with higher number of words given in the RAVLT in 6th repetition of list A as well as with lower number of errors in the RAVLT Recognition Task. This variable also correlated with higher number of correct answers in the WCST and lower number of errors in *the Benton Visual Retention Test*.

Table 6. **Significant Spearman's R correlations between psychosocial variables and results of neuropsychological tests in intravenous ephedrone users with manganese-induced parkinsonism (n = 16)**

Psychosocial variable	Neuropsychological test	Spearman's R
Age	WCST % PE	0.53
	WCST CC	-0.67
	WCST % CONC	-0.64
	WAIS-R Digit Span	0.60
Education (number of years)	RAVLT 6A	0.64
	RAVLT Recognition Task	-0.66
	BVRT Correct Answers	0.76
	BVRT Errors	-0.64

WCST – Wisconsin Card Sorting Test; % PE – percent of perseverative errors; CC – number of completed categories; % CONC – percent of conceptual level responses; WAIS-R – Wechsler Adult Intelligence Scale-Revised; BVRT – Benton Visual Retention Test; RAVLT 6A– Rey Auditory Verbal Learning Test, 6th repetition of list A

Discussion of results

The present work concerns cognitive and emotional functioning of intravenous ephedrone users diagnosed with manganese encephalopathy. Moreover, it aimed to assess the relationship between depressiveness and cognitive functioning of investigated patients.

Global cognitive function assessment

The mean result indicating no global cognitive functioning decrease at dementia level, seemed not surprising in light of previous studies. Although none of previous authors used *the Addenbrooke's Cognitive Examination* (ACE-R), MMSE results similar to those obtained in this study were found in other works. For instance, the Ukrainian study [29] found neither global cognitive dysfunctions, nor memory dysfunctions specific for dementia. The MMSE score was 29 points. In turn, in the Lithuanian study [30], only one patient out of a group of 17 that were assessed with the MMSE obtained a score indicating moderate dementia (18 points), while the results of other tested patients did not deviate from the norm. In a case study conducted by Turkish authors, a patient showing no typical changes in the MRI picture obtained a score of 28 points in the MMSE [31]. In light of the present assessment and above cited studies, the MMSE alone seems to be an ineffective diagnostic tool. In this study, however, the use of the more extensive and complex, compared to the MMSE, screening tool – ACE-R, proved to be valuable, especially its subscales related to mental subtraction and visuospatial functions assessment.

Learning and memory processes

Results of the present study concerning mild disorders of learning and memory functions in verbal as well as in visual aspect confirm findings of Koksal et al. [32]. The authors investigated a group of 9 patients with ephedrone encephalopathy and a group of healthy controls. The results showed no differences between examined groups concerning language, visuospatial and constructive functions. However, only in the experimental group of patients with ephedrone encephalopathy, verbal and nonverbal memory disturbances – in learning, recall as well as in recognition – were found. Verbal and visual memory disorders, however, without recognition deficits, were also found in a case study of Yildrim et al. [31]. The type of verbal memory disorders were described as characteristic of frontal lobe dysfunction as it included spontaneous learning disorders in individuals capable of correctly recalling material from memory. The present study did not confirm that observation, as disorders of verbal material recognition were present in investigated patients.

Visuospatial functions

The mean result of constructive functions assessment indicated the efficiency of these processes within the norm. At the same time, visuospatial assessment in the ACE-R global cognitive screening yielded results suggesting a reduction in these functions. Referring to the study of Koksal et al. [10], who used the same methods as applied in the ACE-R (Necker cube and *Clock Drawing Task*) and obtained results within the norm, it might be suggested that patients in the present work had poorer visuospatial abilities compared to individuals investigated in the cited research. On the other hand, the obtained results show that in spite of evident difficulties in tasks requiring spatial planning and motor functions, abilities of abstract visuospatial thinking and pattern-based construction were correct in majority of patients.

Verbal fluency

None of studies cited above investigated verbal fluency, therefore it is difficult to compare the obtained results to previous data. The test performance varied between particular subjects. It might be associated with different severity of palilalia – individuals with severe disorders could have greater difficulties in articulating words.

Executive function assessment

In comparison to healthy subjects, mean results of manganese encephalopathy patients indicated greater cognitive rigidity and poorer logical conceptualization and set-shifting. However, particular patients varied in efficiency of executive function and working memory. In some patients these functions seemed to be normal, while in others they were significantly disturbed.

The results of international studies on cognitive functions in patients with ephedrone encephalopathy are not consistent. In the mentioned studies of Koksal et al. [10, 32] (including 9 and 7 patients), who used different methods compared to the present study, executive function was mildly impaired when compared to the control group. In turn, Colosimo and Guidi [33] used, as in the present study, the WCST and TMT to assess executive function in their case study. The patient had mild disorders of cognitive flexibility (measured by the percentage of perseverative errors in the WCST, as in the present study) and set-shifting evaluated by the TMT B. Disturbances in executive function in patients with ephedrone encephalopathy were also confirmed by the study of Selikhova et al. [29]. The authors investigated 13 patients and used *the Frontal Assessment Battery* (FAB) to assess executive function. They found established minor deficits in cognitive flexibility, programming, sensitivity to interference, and in the area of inhibitory control. A different perspective of working memory and executive

function decline in ephedrone encephalopathy patients was shown by Djamshidian et al. [34] who compared 15 individuals with manganese encephalopathy to 13 patients addicted to opiates and a control group of 18 healthy individuals. Their study focused on investigating different decision-making processes from both the 'behavioral' as well as from the 'reflection' impulsivity perspective. The authors showed that decision-making processes were aggravated in both groups of addicted individuals as compared to the healthy controls. However, subjects with manganese encephalopathy scored better on executive function measurement, compared to patients with opiate addiction (despite stabilized substitution treatment). These findings seem to be interesting in light of the present work which investigated patients with the long history of drug use, particularly heroin addiction. In the present study, duration of ephedrone use was generally not correlated with results concerning executive function. However, it might be hypothesized that executive dysfunction present in some individuals could result from specificity of their history of drug use. However, results should be interpreted with caution because the variable most associated with executive dysfunction, including cognitive flexibility, was age of the patients.

Dysarthric speech disorder assessment

Results of dysarthria assessment in majority were consistent, however, in some aspects different form findings of the only detailed dysarthria examination of 14 intravenous ephedrone users by Selikhova et al. [11]. In the mentioned study, results of patients with manganese-induced parkinsonism were compared to results of patients with Parkinson's disease. The assessment of dysarthria was accompanied by magnetic resonance imaging, which in patients with ephedrone encephalopathy showed hyperintensity in the striatum and globus pallidus. As symptoms most characteristic for ephedrone encephalopathy, the authors found spontaneous speech disorders and inability to regulate pitch and volume. These data are consistent with the results of the own study presented in this article; similarly as the observation that dysarthric speech disorders were still present despite discontinuation of the use of ephedrone with manganese compounds. The authors noticed in their patients a robotic – flat prosody, whispering or monotonous phonation. Similarly as in the present study, palilalia was present in most but not all patients and cases of mutism also appeared. However, Selikhova et al. [11] did not find reflex disorders – choking, salivation and swallowing, which were present in some patients presented in this article.

Associations between cognitive functioning and depressiveness

The present article emphasized the meaning of mood factor which should be taken into account while interpreting the results, as the mean BDI score indicated

moderate depressive symptoms in subjective assessment. Similar level of depression in patients with manganese encephalopathy was reported in other cited works [29]. Not only does it seem to be adequate to patient's situation (difficulties in everyday life functioning), but also it might potentially worsen the performance in neuropsychological tests. In this study, greater severity of depressive symptoms was associated with worse score in overall cognitive screening as well as a decrease in visual and (to a lesser extent) verbal memory and a decrease in phonemic verbal fluency. In the interpretation of these relationships, one can also consider the hypothesis that more depressive people were more aware of their greater difficulties in producing utterances and poorer motor skills.

Conclusions

The study presents the first in Poland neuropsychological assessment of the group of intravenous ephedrone users with manganese encephalopathy. The most relevant findings are as follows:

1. Dysarthric speech disorders – in particular spontaneous speech disorders (in some subjects limiting the ability to generate words) and volume and pitch weakness – were dominant disorders in the group of patients with manganese encephalopathy.
2. Palilalia and handwriting disorders (micrographia) were found in the majority of patients.
3. Accompanying disorders concerned a decrease in learning and memory processes (including recognition disorders), the severity of which might be assessed with decreased mood.
4. In the assessment of visuospatial constructive functions, ideomotor but not constructional praxis disorders were found.
5. In comparison with healthy controls, the patients were characterized by a decrease in cognitive flexibility, logical conceptualization and set-shifting. Executive function assessment showed mixed results, which could be additionally affected by age factor and other variables not controlled in the present study (e.g., factors associated with pre-ephedrone substance abuse history).

The present study seems to broaden clinical knowledge about the neuropsychological diagnosis of people with manganese encephalopathy. It might contribute to the creation of standards of diagnostic and therapeutic assistance targeted at patients with this rare disease.

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