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ORIGINAL ARTICLE

Neurobehavioral performance of patients diagnosed with manganism and idiopathic Parkinson disease

Dag G. Ellingsen[1] · Grigoriy Shvartsman[2] · Rita Bast-Pettersen[1] · Maxim Chashchin[3,4] · Yngvar Thomassen[1] · Valery Chashchin[2,3]

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Abstract

Purpose There is a lack of knowledge about neurobehavioral performance among patients with manganism and how their performance differs from that of idiopathic Parkinson disease patients (PD). This study was initiated with the aim to describe and compare neurobehavioral performance among patients diagnosed with manganism, PD and a group of referents.

Materials and methods Neurobehavioral performance was assessed in 34 patients diagnosed with manganism, 13 with PD, and 43 healthy workers (turners/fitters) who served as the reference group. Seventeen of the manganism patients had also been tested approximately 65 months previously.

Results Manganism patients scored substantially more poorly than referents on tests for motor speed, manual dexterity and balance. They also performed more poorly than the PD patients on the postural sway test. In contrast, the PD patients had higher postural tremor intensity with narrower frequency dispersion than manganism patients. The pattern of neurobehavioral performance was more asymmetrical in PD compared to manganism patients, in particular when testing for tremor intestity, grooved pegboard and static steadiness, indicating lateralized impairment in the PD patients. The amount of bradykinesia was comparable between the patient groups. Neurobehavioral performance deteriorated slightly among 17 manganism patients followed for 65 months compared with the age-related decline among referents.

Conclusions Patients with manganism had severe bradykinesia and balance disturbances, but only slight postural tremor. In contrast, PD patients had significant postural tremor and bradykinesia, but only slight balance disturbances. Their neurobehavioral performance indicated lateralized impairment, more unilateral. Neurobehavioral performance deteriorated slightly in manganism patients during a 65-month follow-up.

Keywords Welders · Manganese · Neurobehavioral performance

Introduction

Long-term high occupational exposure to manganese (Mn) may cause a severe neurological disease known as manganism. Significant exposure occurs in many industries, e.g., Mn ore mining, alloy, steel and dry-cell battery production, and welding (Lucchini et al. 2015). The first cases of manganism were reported among Mn ore crushers in 1837 (Couper 1837). Since then, cases have been reported among exposed workers, e.g., in the production of Mn alloys, steel and batteries as well as in mining (Rodier 1955; Tanaka and Lieben 1969; Chin-Chang et al. 1989; Wang et al. 1989; Emara et al. 1971).

Manganism has been reported to start gradually, often with psychiatric symptoms and dystonia, but also with motor deficits similar to symptoms and signs observed in idiopathic Parkinson disease (PD) (Calne et al. 1994). A propensity to fall backward and less prominent tremor than in PD have also been noted (Olanow 2004). This contrasts

✉ Dag G. Ellingsen
dag.ellingsen@stami.no

[1] National Institute of Occupational Health, P.O. Box 8149 Dep, 0033 Oslo, Norway

[2] Northwest State Medical University named after I.I. Mechnikov, 191015 St. Petersburg, Russia

[3] Northwest Public Health Research Centre, St. Petersburg 191036, Russia

[4] City Centre of Occupational Health, St. Petersburg 191014, Russia

with the hallmarks of PD, in which rest tremor, bradykinesia, rigidity and postural instability are key clinical signs (Guilarte 2010).

The diagnosis of manganism has traditionally been based on neurological examinations. In contrast, numerous epidemiological studies of workers with ongoing occupational exposure to Mn have used neurobehavioral methods, although these methods have not been applied for clinical cases of manganism. Thus, the link between subtle subclinical neurobehavioral effects associated with ongoing exposure and neurobehavioral performance in severe clinical disease is lacking. It is difficult to compare neurobehavioral test results across epidemiological studies of Mn-exposed populations due to the large variety of applied tests. However, impaired performance on finger tapping, simple reaction time and digit symbol tests were reported to be associated with current Mn exposure in a meta-analysis by Meyer-Baron and coworkers (2013). Whether these tests are sensitive when used to detect patients with manganism has not been reported.

The issue whether clinical manganism is a progressive disorder when occupational Mn exposure has ceased has hardly been studied. The half-life of Mn in rat brain is approximately 2 months (Crossgrove and Cheng 2004), while the half-life was around 8 months in the head of macaque monkeys (Newland et al. 1987). Experimental studies of patients on parenteral nutrition and cynomolgus monkeys exposed to welding fumes have shown that increased magnetic resonance imaging signal intensities of Mn are reversible within approximately 5–9 months after exposure cessation (Takagi et al. 2001; Han et al. 2008).

Thus, it is reasonable to assume that the group of six Mn-intoxicated workers from a Taiwanese Mn alloy smelter followed up for 10 years after cessation of exposure had normal brain Mn concentrations. Clinical neurological examinations suggested that the disease progressed slowly, especially gait disturbances (Huang et al. 1998). To our knowledge, no patients with manganism have been followed up with neurobehavioral examinations. Few studies on the neuropathology of manganism in humans and in non-human primates are available. A consistent pattern of damage to the globus pallidus with sparing of the substantia nigra (pars compacta) in humans has been reported (Yamada et al. 1986; Perl and Olanow 2007), while morphological alterations in the globus pallidus, subthalamic nuclei and substantia nigra (pars reticularis) were observed in non-human primates (Guilarte 2010). This pattern is distinctly different from the neuropathological alterations observed in PD, in which the globus pallidus is spared and the substantia nigra (pars compacta) is severely and consistently affected (Dickson 2012). Whether these neuropathological differences also result in different patterns of neurobehavioral alterations in manganism and PD patients has not been studied.

Also, neuroimaging studies show some important differences between the two diseases. Patients with PD have decreased levels of presynaptic dopamine markers in the striatum (Felicio et al. 2009). Manganism patients most likely have normal dopamine synthesis and dopamine transporter levels (Guilarte 2010; Guilarte and Gonzales 2015). The few patients with manganism that have been examined had normal results on 6-fluorodopa PET (Wolters et al. 1989; Kim et al. 1999), in contrast to asymptomatic highly exposed welders with mean blood Mn concentration of 20.7 µg/L (normal values < 10.8 µg/L) who had reduced caudate 6-[^{18}F]fluoro-L-dopa uptake (Criswell et al. 2011). It is imaginable that these differences in dopamine metabolism may be related to the disappearance of Mn from the brain after exposure cessation.

The aim of this study was to characterize neurobehavioral performance in a group of former welders who had been diagnosed with manganism and since that time were not occupationally exposed to Mn for many years. A further aim was to compare their neurobehavioral performance with that of a group of newly diagnosed PD patients not yet on PD medication. Finally, the study also addresses the progression of manganism in patients who were examined between 5 and 6 years earlier. This study is part of a larger investigation of welders exposed to Mn in St.Petersburg, Russia (Ellingsen et al. 2014, 2015).

Materials and methods

In 2003, 27 patients diagnosed with manganism were examined with neurobehavioral tests (Ellingsen et al. 2008). These patients, who were not employed as welders at that time, were invited to participate in a re-examination at the Northwest Public Health Research Centre (NWPHRC) in St. Petersburg during 2008/2009. Two of these patients had died, four had moved out of the region and were thus not eligible for participation and four refused to participate. Consequently, 17 of the original 27 patients were re-examined. Patients with known alcohol or substance abuse were not included in the study.

All patients diagnosed with manganism are clinically followed up every third year according to standard practice in Russia. In addition to the original patients, all patients that were triennially re-examined at the NWPHRC during 2008/2009 were also invited to participate in this study. Altogether, another 17 patients were invited, and all agreed to participate. Thus, the study population comprised 34 manganism patients, of whom 4 were females. All had been welders and had not been occupationally exposed to Mn since the diagnosis was established. At the time of the study, they were retired and on disability pension. They had all received the International Classification of

Diseases (ICD) 10 diagnosis T57.2. The ICD is a diagnostic classification system, maintained by the World Health Organization, providing codes for the classification of diseases.

In Russia, the severity of manganism is classified into mild (Grade 1), moderate (Grade 2) and severe (Grade 3) (Drogichina 1968; Melnikova 1995). Grade 1 is characterized by general weakness, fatigue, reduced physical and mental ability, decreased motor activity and increased drowsiness. Objectively, light muscular hypotonia, hyperhidrosis, weakening of facial expression, lability of pulse and blood pressure, and sensory disorders can be observed. Grade 2 is characterized by additional signs of intellectual–mental disorders, extrapyramidal symptoms (bradykinesia, moderate increase in muscle tonus, coordination disorders) and hypoesthesia of the distal areas of the extremities. Grade 3 is characterized by additional features such as an akinetic-rigid syndrome with physical inactivity, hypomimia, a masklike face, hypertonic muscles, dyscoordination, finger tremor in the outstretched hands, lethargy and slowness of movements, emotional explosiveness, a "rooster" gait, retro- and propulsion and monotone speech. Main differential diagnoses include cerebrovascular disorders, idiopathic PD and other secondary parkinsonism. The diagnosis of occupational manganism must be supported by documented occupational history and sufficient exposure data. The final judgment on occupational origin of manganism is made by a qualified medical expert group. Neurological symptoms and signs recorded in their personal medical files were graded into absent (0), slight (1), moderate (2) and severe (3). The most severe symptoms and signs among the 34 manganism patients were asthenia, bradykinesia, hypesthesia and hypomimia with arithmetic mean (min–max) scores of 2.2 (1–3), 2.0 (0–3), 1.7 (0–2) and 1.7 (0–2), respectively.

A further aim was to recruit for comparison 25 patients with parkinsonism unrelated to Mn exposure. When patients recruited from three district polyclinics responsible for serving approximately 100,000 inhabitants in St. Petersburg have suspected parkinsonism, they are referred from the policlinics to the Department of Neurology at the Mechnikov University Hospital (St. Petersburg) and hospitalized for extensive medical examinations before confirmation of the diagnosis. Twenty-nine successive patients were referred from the polyclinics to the hospital, but in 4 subjects parkinsonism was not confirmed. Of the remaining 25 patients, one was excluded due to a cerebral insult, leaving 24 patients. Thirteen were diagnosed with idiopathic PD (ICD 10, G20.0), and 11 with vascular Parkinson disease (VP) (ICD 10, G21.4). The VP patients were not further considered for this study. The PD group comprised eight females. During hospitalization, and before L-dopa treatment started, they were invited to participate in this study. All agreed to participate.

Idiopathic PD is classified in Russia according to a standardized protocol based on a modified Hoehn and Yahr scale valid for the whole country (Hoehn and Yahr 1967; Goetz et al. 2004). The important motor symptoms of PD include rest tremor, akinesia, rigidity and postural instability. Usually, the disease begins with trembling, rigidity or awkwardness in one of the extremities. Slowness of speech and micrographia are other signs. Postural instability and gait disturbance may occur. A number of non-motor symptoms, including vegetative disturbances, autonomic dysfunction, cognitive/neurobehavioral disorders and sensory and sleep abnormalities are common.

As the youngest patient was 47 years old, all participants 47 years or older that served as referents in a cross-sectional study of welders conducted in St. Petersburg at the same time served as referents in the present study (Ellingsen et al. 2014). They were turners/fitters employed in one plant producing heavy machinery and two shipyards. The referents were in generally good health and had no known alcohol or drug abuse. They also had no history of occupational organic solvent exposure for more than 3 years before the study and had never been occupationally exposed to lead (Pb) or mercury (Hg). Table 1 shows the background data for all participants.

Neurobehavioral examinations

The participants underwent a structured interview emphasizing education, illnesses and other background data. Subjective symptoms were recorded using a self-administered neuropsychiatric questionnaire containing 16 questions (Lundberg et al. 1997). The examiner was not blinded with respect to which group the participants belonged to.

Tests for attention and processing speed

The digit symbol test (Lezak et al. 2012) from the Wechsler Adult Intelligence Scale (WAIS) requires the subject to recode symbols into digits. The number of symbols correctly recoded within 90 s was recorded. The test is considered to assess visuomotor/processing speed. The digit span test (Lezak et al. 2012) from the WAIS is a test for attention span and working memory. In this version, the subject was required to repeat as many digits as possible after oral presentation, either in the same order (digit forward) or in the reverse order of presentation (digit backward). The maximum number of digits repeated was recorded.

Motor tests

The finger tapping test (Lafayette Instrument Company) requires the subject to press a tapping key with the index finger as fast as possible for 10 s (Reitan and Wolfson 1985).

Table 1 Background characteristics and exposure data among patients with manganism or idiopathic Parkinson disease (PD) and referents

	Manganism ($N=34$)		PD ($N=13$)		Referents ($N=43$)		p values		
	AM[a]	Min–max	AM	Min–max	AM	Min–max	A	B	C
Age***	58.8	47–77	68.5	49–84	54.2	47–70	0.003	<0.001	<0.001
Male/female (number)	30/4	–	5/8	–	43/0	–	0.03	<0.001	0.001
Education (yrs)*	10.8	4–16	12.9	4–19	12.6	9–19	0.009	ns	0.03
Current smokers (%)[c]	38	–	8	–	37	–	ns	ns	ns
Alcohol (L/year)[de]	2.2	0–56.2	0	0–10.4	2.4	0–35.4	ns	ns	ns
sCDT (%)[b]***	0.6	<DL[e]-9.3	<DL	<DL-1.1	0.7	<DL-6.6	ns	ns	ns
Coffee (cups/day)	0.6	0–3	0.5	0–5	0.9	0–5	ns	ns	ns
Mild head injury (%)[c]	18	–	31	–	7	–	ns	0.04	ns
Welding (yrs)	23.7	7–33	–	–	–	–	–	–	–
Years since diagnosis	10.2	4–17	–	–	–	–	–	–	–
B-Mn (µg/L)**[f]	9.8	4.2–22.4	11.4	3.7–19.0	7.9	4.4–12.3	0.01	0.002	ns
U-Mn (µg/g creatinine)[b]	0.07	0.01–0.83	0.13	0.02–1.4	0.08	0.02–1.4	ns	ns	ns
B-Pb (µg/L)	27	6–59	26	6–67	28	10–70	ns	ns	ns
B-Hg (µg/L)	1.8	0.1–6.2	1.9	0.2–7.6	2.3	0.1–6.4	ns	ns	ns
U-Hg (µg/g creatinine)	0.22	0.03–1.03	0.15	0.02–0.37	0.24	0.02–0.89	ns	ns	ns

[a]Arithmetic mean

[b]Geometric mean

[c]Prevalence

[d]Median

[e]*DL* detection limit

[e]***ANOVA $p<0.001$; **ANOVA $p<0.01$; *ANOVA $p<0.05$

[f]Urine and blood samples missing for eight referents and seven patients

[A]p values calculated between manganism patients and referents

[B]p values calculated between PD patients and referents

[C]p values calculated between manganism patients and PD patients

The score was defined as the median number of presses based on three trials. The foot tapping test (Matthews and Kløve 1964) requires the subject to press a lever with the foot in standing position as quickly as possible. The mean number of presses after two trials of 10 s each was recorded. A dynamometer was used to measure grip strength (in kg) (Lafayette Psychological Instruments Model 78,010). The subject is required to hold the device in the palm of the hand and squeeze a stirrup as firmly as possible (Reitan and Wolfson 1985).

The grooved pegboard test for manual dexterity and motor speed consists of a small board containing a 5 × 5 set of slotted holes angled in different directions and 25 pegs with a ridge (Matthews and Kløve 1964). The task is to insert the pegs into the holes as quickly as possible. Time to completion (in s) was recorded. The Kløve–Matthews Static Steadiness Test is a stylus-and-hole apparatus to assess tremor and fine eye–hand coordination (Matthews and Kløve 1964; Bast-Pettersen and Ellingsen 2005). The subject is required to hold the stylus in nine successively smaller holes for 15 s each. The number and duration (in s) of contacts between the stylus and the base plate were recorded.

Computerized tests

The computerized test system CATSYS® 2000 (Danish Product Development Ltd, Snekkersten, Denmark) was used to quantify tremor, auditory reaction time and postural stability. The CATSYS Tremor Pen® (version 7.0) consists of a biaxial micro-accelerometer embedded in a low-mass stylus connected to a data logger. Tremor is recorded in a frequency band ranging from 0.9 to 15 Hz. The subject is required to hold the pen in front of the body without any support for the assessment of postural tremor. The testing time was 16.4 s, consisting of 2 s for stabilization and 14.4 s for recording of tremor intensity (TI), center frequency (CF50), dispersion of power and harmonic index (HI) (Ellingsen et al. 2008).

Postural stability was assessed with the postural sway test, consisting of a platform with sensors recording the position of the force center resulting from the subject's position. The subjects were required, while standing erect, to remain balanced during one test period with their eyes open and one during which they were blindfolded. Each period was 70 s, with total test time of 65 s. The variables measured were the

mean, transversal and sagittal sway, sway area, sway intensity and sway velocity (Ellingsen et al. 2008). In the simple reaction time test (SRT) (test time 4 min), the subject is required to press a handle with the thumb of the dominant hand in response to an auditory stimulus (beeping sound).

Collection and analysis of biological samples

Blood and urine samples were collected between 8.30 and 9.30 AM of the day when the neurobehavioral examinations were carried out as previously described (Ellingsen et al. 2013, 2014). Whole blood was analyzed for Mn, Pb and Hg (B-Mn, B-Pb, B-Hg), and urine for Mn and Hg (U-Mn, U-Hg) with an inductively coupled plasma high-resolution magnetic sector-field mass spectrometer, also as previously described. Carbohydrate-deficient transferrin in serum (sCDT) for the assessment of high alcohol consumption was measured by capillary electrophoresis with Capillarys™ (Sebia Inc., Georgia, USA) as previously described (Ellingsen et al. 2014). Concentrations below detection limit (DL) (0.4%) were given a substitute value of ½ DL. Concentrations < 1.7% were considered as normal by the laboratory.

Statistics

Continuous variables were log-transformed when the skewness of the distribution exceeded 2.0. Geometric means (GM) are presented for these variables, while arithmetic means (AM) are used otherwise. Analysis of variance (ANOVA) was used for group comparisons of continuous variables between groups. The post hoc least significant difference (LSD) test was calculated when more than two groups were compared to identify the groups that differed from each other. Student's paired *t* test was used to assess follow-up results in the same individuals. A general linear model was used to adjust for differences in age and sex between groups. To assess the magnitude of differences in performance between the referents and the manganism patients expressed as number of standard deviations (SD) poorer performance, an SD score was calculated according to the formula "$SD = (x - \bar{x})/s$", where $\bar{x}$ is the sample mean score of the referents and s the corresponding SD, while x is the neurobehavioral score of the manganism patients.

Two-tailed p values < 0.05 were considered to be of statistical significance. The statistical package SPSS®, version 25.0 (IBM Corp, Armunk, NY, USA), was used.

Results

The PD patients were older than the manganism patients and the referents (Table 1). The manganism patients had been diagnosed at an average age of 48.6 years (range 35–68) (not tabulated). Their AM stage of disease was 1.8 (range 1–3) (not tabulated). They had been welding for 23.7 years on average before diagnosis and had stopped welding approximately 10 years before the study. Four patients with manganism, and eight with PD were females. The median self-reported alcohol consumption was low in all groups. The mean B-Mn concentrations were significantly higher in the PD and manganism patients than in the referents.

Neurobehavioral test results adjusted for age and sex are presented with unadjusted means in brackets (Table 2). The patient groups performed more poorly than the referents on all tests except the digit span test, although not all differences were of statistical significance. There were few significant differences in scores for the motor tests between the patients with manganism and with PD. The manganism patients reported substantially more subjective symptoms than PD patients.

Computerized test results adjusted for age and sex showed higher TI and HI and narrower dispersion of power among PD patients when compared to manganism patients and referents (Table 3). In contrast, manganism patients performed significantly poorer on the sway test than PD patients and referents, while patients with PD had scores comparable to those of the referents. Manganism patients had the poorest SRT test scores, while PD patients had scores comparable to those of the referents after adjustment for age and sex.

Figure 1 shows all neurobehavioral tests where the differences in terms of standard deviations between the referents and the manganism patients were larger than 2. Such large differences were observed for the Finger tapping, grooved pegboard, postural sway (blindfolded) and SRT tests.

Differences in lateralized impairment in terms of differences in test scores between the hand (or foot) with the better performance and the one with the poorer performance were calculated for all tests that were administered bilaterally. No indication of lateralized impairment was found for the manganism patients (Table 4). The bilateral difference in performance was, however, statistically significantly larger for the PD patients compared to both the referents and the manganism patients for grooved pegboard, static steadiness (number and timer) and TI. None of the patient groups differed from the referents with regard to side differences in performance on the foot tapping and finger tapping tests.

Seventeen patients with manganism and 39 referents had also been examined, on average, 65.1 and 69.6 months earlier, respectively (Tables 5, 6). There were, as expected, slight age-related declines in performance among the referents for several of the neurobehavioral tests. The declines were generally somewhat larger among the manganism patients. However, statistically significantly larger declines among the manganism patients compared to the referents were only observed for the finger tapping test ($p = 0.009$), TI (dom and n-dom, $p = 0.008$ and $p = 0.007$, respectively),

Table 2 Neurobehavioral test results, adjusted for age and sex, among patients with manganism, idiopathic Parkinson disease (PD) and referents

	Manganism ($N=34$)		PD ($N=13$)		Referents ($N=43$)		p values		
	AM[a]	Min–max	AM[a]	Min–max	AM[a]	Min–max	A	B	C
Hoehn–yahr	–	–	2.8	2–4	–	–			
Finger tapping (no.)									
Dominant***	24.9 (24.9)	5–48	29.9 (22.1)	1–47	43.1 (45.5)	23–57	< 0.001	0.003	ns
Non-dominant***	22.4 (22.3)	6–41	24.5 (18.7)	6–38	38.6 (40.4)	28–54	< 0.001	< 0.001	ns
Grooved pegboard (sec)									
Dominant[b]***	97 (99)	71–196	110 (128)	65–340	74 (70)	49–106	< 0.001	< 0.001	ns
Non-dominant[b]***	103 (105)	72–249	149 (183)	72–634	83 (78)	59–123	0.002	< 0.001	0.002
Foot tapping (no.)									
Dominant***	26.7 (26.7)	5–47	31.8 (23.7)	10–40	38.6 (41.1)	25–62	< 0.001	ns	ns
Non-dominant***	25.9 (25.9)	5–48	28.9 (21.5)	9–35	36.5 (38.7)	25–55	< 0.001	0.047	ns
Static steadiness									
Dominant									
Number**	414 (409)	142–1181	314 (306)	82–688	264 (271)	39–907	0.002	ns	ns
Timer (sec)*	27 (27)	10.1–63	27 (38)	7.3–102	18 (15)	1.1–55	0.01	ns	ns
Non-dominant									
Number*	397 (389)	163–946	505 (484)	26–1331	280 (292)	70–823	0.03	0.02	ns
Timer (sec)*	31 (31)	12.6–94	47 (57)	11–135	24 (21)	1.6–69	ns	0.004	0.03
Digit span (no.)[c]									
Forwards	5.3 (5.1)	3–9	5.9 (5.8)	4–9	5.8 (6.0)	4–8	ns	ns	ns
Backwards	3.6 (3.6)	2–5	4.1 (3.9)	2–6	4.1 (4.1)	3–7	0.046	ns	ns
Digit symbol (no.)[c]***	28.1 (27.1)	9–46	28.3 (27.1)	11–45	39.8 (40.8)	19–62	< 0.001	0.008	ns
Symptoms (no.)***	12.9 (13.1)	8–16	6.6 (7.3)	1–12	3.0 (2.7)	0–9	< 0.001	< 0.001	< 0.001

Non-adjusted mean values are shown in brackets. *P* values are calculated between adjusted values

[a]Arithmetic mean

[b]Geometric mean

[c]Digit symbol and digit span are adjusted for age, sex and education; ***ANOVA $p<0.001$; **ANOVA $p<0.01$; *ANOVA $p<0.05$

[A]p values calculated between manganism patients and referents

[B]p values calculated between PD patients and referents

[C]p values calculated between manganism patients and PD patients

static steadiness test (timer, dom, $p=0.003$) and sway area ($p=0.04$). Central frequency was also altered (dom and n-dom, $p=0.02$ and $p=0.049$, respectively).

Discussion

This study compares the neurobehavioral performance of patients diagnosed with manganism or PD, and referents. Results of a follow-up of the neurobehavioral performance of former welders diagnosed with manganism are also presented. The manganism patients had been diagnosed after extensive examinations according to the standardized diagnostic protocol valid for Russia (Drogichina 1968). The selection of the PD patients was laborious, as only patients not yet on L-dopa medication were included. The diagnosis was made after extensive examinations at the Neurological Department of the Mechnikov University Hospital (St. Petersburg) according to the standardized diagnostic protocol valid for Russia (Levin and Fedorova 2012).

The manganism patients were younger than the PD patients. Studies have shown that manganism patients often receive the diagnosis before the age of 60 years (Rodier et al. 1955; Wang et al. 1989). The mean age at disease onset in this study was 48.6 years. This contrasts with the age at onset for PD, where the incidence rate increased rapidly in subjects older than 60 years of age (Wirdefeldt et al. 2011). The true incidence of VP is unknown, but 3–12% of all parkinsonism patients have been suggested to have VP (Sibon et al. 2004; Thanvi et al. 2005). Eleven out of 24 parkinsonism patients were not considered for this study because they received a diagnosis of VP.

The majority of the manganism patients were males. The majority of the PD patients were females, although PD incidence was higher among males (Wirdefeldt et al. 2011). The male and female life expectancies were around 60 and

Table 3 Results measured with the computerized CATSYS test system adjusted for age and sex among patients with manganism, idiopathic Parkinson disease (PD) and referents

	Manganism ($N=34$)		PD ($N=13$)		Referents ($N=43$)		p values		
	AM[a]	Min–max	AM	Min–max	AM	Min–max	A	B	C
Tremor									
Dominant									
TI[c] (m/s^2)[b]**	0.25 (0.24)	0.08–0.98	0.34 (0.35)	0.09–3.7	0.15 (0.15)	0.08–0.52	0.003	0.006	ns
CF50[d] (Hz)	6.6 (6.6)	3.0–10.5	6.5 (5.9)	3.6–8.3	6.3 (6.5)	2.7–10.9	ns	ns	ns
Dispersion[e] (Hz)*	2.5 (2.5)	0.4–4.9	2.3 (1.9)	0.2–4.7	2.8 (2.9)	1.2–5.1	ns	ns	ns
Harmonic Index	0.92 (0.92)	0.81–0.97	0.95 (0.96)	0.88–0.98	0.92 (0.92)	0.85–0.99	ns	ns	0.047
Non-dominant									
TI (m/s^2)[b]***	0.23 (0.23)	0.09–0.90	0.41 (0.47)	0.13–3.1	0.15 (0.14)	0.07–0.42	0.004	< 0.001	0.02
CF50 (Hz)	6.8 (6.7)	3.6–10.3	6.5 (5.9)	1.3–8.1	6.8 (7.0)	2.9–10.7	ns	ns	ns
Dispersion (Hz)*	3.0 (3.0)	0.4–5.2	2.0 (1.4)	0.2–3.9	3.1 (3.3)	1.3–5.0	ns	0.01	0.01
Harmonic Index**	0.92 (0.91)	0.82–0.98	0.96 (0.96)	0.89–0.99	0.90 (0.90)	0.80–0.96	ns	0.001	0.008
Postural sway									
Eyes open									
Mean (mm)[b]**	7.8 (7.8)	1.1–18.1	5.6 (6.7)	3.7–9.6	6.0 (5.7)	2.1–10.2	0.006	ns	0.04
Intensity (mm)[b]*	6.3 (6.3)	1.1–15.1	5.4 (5.4)	2.8–12.1	4.7 (4.7)	2.3–15.5	ns	ns	0.01
Velocity (mm/s)[b]**	14.1 (14.1)	2.3–47.6	9.1 (11.2)	5.2–22.4	10.8 (10.1)	5.4–18.8	0.01	ns	0.009
Area (mm^2)[b]**	519 (522)	12–2720	240 (396)	105–1015	330 (282)	52–1832	0.02	ns	0.01
Blindfolded									
Mean (mm)[b]***	9.9 (9.8)	3.8–28.4	6.7 (7.5)	3.5–11.6	5.8 (5.7)	3.4–9.1	< 0.001	ns	0.009
Intensity (mm)[b]***	9.4 (9.3)	1.8–30.9	4.9 (5.8)	2.8–9.7	5.9 (5.7)	3.8–9.7	< 0.001	ns	< 0.001
Velocity (mm/s)[b]***	24.0 (23.8)	5.8–98.1	13.2 (15.0)	5.8–38.9	14.4 (13.9)	7.7–30.9	< 0.001	ns	0.002
Area (mm^2)[b]***	1035 (1014)	57–7108	351 (506)	93–1186	385 (351)	99–1035	< 0.001	ns	0.001
Simple reaction time									
SRT (ms)[f,b]***	420 (418)	213–1174	293 (360)	229–1069	247 (232)	179–386	< 0.001	ns	0.008
SD[g,b]***	132 (131)	42–683	62 (84)	31–359	56 (51)	25–178	< 0.001	ns	0.001

Non-adjusted mean values are shown in brackets

[a]Arithmetic mean

[b]Geometric mean

[c]Tremor intensity

[d]Center frequency

[e]Frequency dispersion

[f]Simple reaction time

[g]Standard deviation

***ANOVA $p<0.001$; **ANOVA $p<0.01$; *ANOVA $p<0.05$

[A]p values calculated between manganism patients and referents

[B]p values calculated between PD patients and referents

[C]p values calculated between manganism patients and PD patients

75 years in Russia when the study was conducted (Grigoriev et al. 2014). Thus, many men die before they reach the age of 60 years, when the incidence of PD increases sharply. Therefore, the probability of men developing PD was lower. There are sex differences in performance of several of the tests used, e.g., in the grip strength, finger tapping, reaction time and sway tests (Despres et al. 2000; Heaton et al. 2004; Strauss et al. 2006). Thus, sex was included as covariate in the statistical analysis.

Poor finger tapping and foot tapping test scores in both patient groups compared with the referents show that they have bradykinesia in common. Bradykinesia has been reported previously in manganism and PD (Wang et al. 1989; Triumfov 1998). However, postural tremor characteristics separated the groups. Tremor intensity was higher in PD patients and the frequency dispersion was substantially more narrow. A narrow frequency dispersion and higher TI of postural tremor have been observed previously in PD

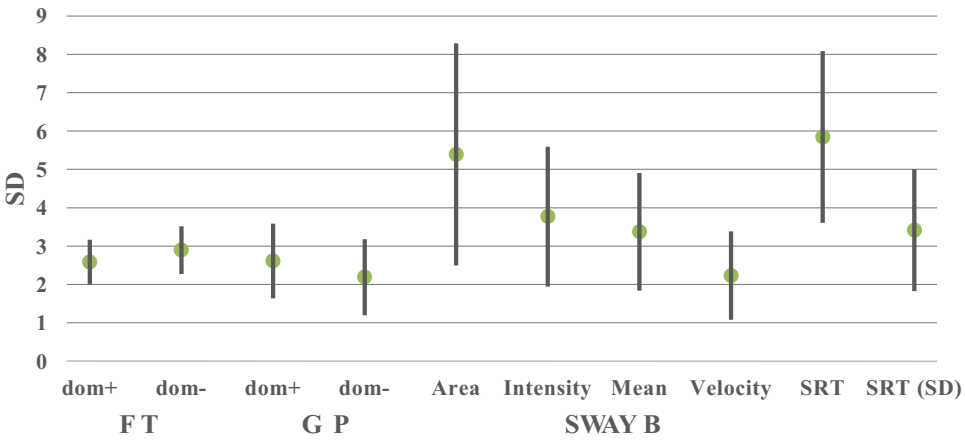

Fig. 1 Mean (and 95% CI) number of standard deviations (SD) differences in performance between manganism patients and referents for all neurobehavioral tests where manganism patients scored at least 2 SD poorer than the referents. *FT* finger tapping test, *GP* grooved pegboard test, *Sway B* postural sway test, blindfolded, *SRT* simple reaction time test

Table 4 Difference in neurobehavioral test scores between the hand (or foot) with the better result compared with the one with the poorer result (adjusted for age) among patients with manganism or idiopathic Parkinson disease (PD) and referents

	Manganism ($N=34$)		PD ($N=13$)		Referents ($N=43$)		p values		
	AM[a]	95% CI	AM	95% CI	AM	95% CI	A	B	C
Finger tapping (no.)	4.9	3.0–6.8	5.1	1.5–8.6	6.9	5.1–8.7	ns	ns	ns
Foot tapping (no.)	2.3	1.4–3.3	4.0	2.2–5.7	3.5	2.6–4.4	ns	ns	ns
Grooved pegboard (s)***	10.8	0.5–21.6	66.0	45.4–86.9	14.0	4.3–23.7	ns	<0.001	<0.001
Dynamometer (kg)	4.6	3.3–6.0	4.2	2.1–6.2	4.3	2.9–5.7	ns	ns	ns
Static steadiness									
Number*	104	57–150	246	158–334	86	42–131	ns	0.003	0.005
Timer (s)***	8.0	4.9–11.0	21.3	15.6–27.1	8.3	5.4–11.2	ns	<0.001	<0.001
Catsys 7.0 tremor									
Tremor intensity (m/s^2)***	0.10	−0.01–0.22	0.73	0.52–0.94	0.04	−0.07–0.15	ns	<0.001	<0.001
Center frequency (Hz)	1.1	0.7–1.5	0.9	0.1–1.7	1.2	0.8–1.6	ns	ns	ns
Frequency dispersion (Hz)	1.1	0.8–1.3	1.3	0.7–1.8	0.7	0.4–0.9	ns	ns	ns
Harmonic index	0.05	0.04–0.06	0.02	0.001–0.04	0.05	0.04–0.06	ns	ns	0.02

P values are calculated between adjusted values

[a]Arithmetic mean

***ANOVA $p<0.001$; **ANOVA $p<0.01$; *ANOVA $p<0.05$

[A]p values calculated between manganism patients and referents

[B]p values calculated between PD patients and referents

[C]p values calculated between manganism patients and PD patients

patients (Farkas et al. 2006). In contrast, manganism patients had tremor frequency dispersion similar to the referents but somewhat higher TI, indicating only moderately increased postural tremor.

The manganism patients scored substantially poorer than the referents and the PD patients on the postural sway test, indicating balance disturbances as one sign of manganism. The performance of the PD patients and the referents was similar. The sway test results declined substantially among the manganism patients when they were blindfolded, while blindfolding had little and similar effect on performance among the PD patients and referents. Balance dysfunction has previously been noted as one characteristic disturbance in manganism (Olanow 2004). Balance is dependent on vision, vestibular functions and proprioception, and it has been suggested that the basal ganglia is part of the circuitry involved in the integration of information for postural control (Redfern et al. 2001). Deep brain stimulation of nucleus thalamicus and internal globus pallidus in severely affected PD patients improved standing postural control (Collomb-Clerc and Welter 2015). Thus, it is of interest that globus pallidus damage and morphological alterations in the globus pallidus and subthalamic nuclei have been observed in Mn-affected humans and in non-human primates, respectively (Yamada et al. 1986; Perl and Olanow 2007; Guilarte 2010). Balance is also impaired in severely affected PD patients, but

Table 5 Neurobehavioral test results recorded at baseline and at follow-up 65.1 (64–71) months later in manganism patients and in referents followed up 69.6 (62–77) months after baseline

	Manganism ($N=17$)		$p^{\#}$	Referents ($N=39$)		$p^{\#}$
	Baseline	Follow-up		Baseline	Follow-up	
	AM[a] (Min–max)	AM (Min–max)		AM (Min–max)	AM (Min–max)	
Age (yrs)	49.9 (41–58)	55.6 (47–63)	–	47.5 (41–66)	54.3 (47–70)	–
B-Mn (µg/L)	8.7 (5.2–19.1)	10.2 (4.2–22.4)	0.02	7.1 (3.8–14.3)	8.0 (4.4–12.3)	ns
Welding (yrs)	23.1 (15–30)	23.1 (15–30)	–	–	–	–
Months of follow-up	–	65.1 (64–71)	–	–	69.6 (62–77)	–
Grooved pegboard (s)						
Dominant hand[b]	104 (63–284)	99 (71–194)	ns	67 (51–91)	71 (52–106)[2]	ns
Non-dominant hand[b]	108 (77–303)	106 (72–249)	ns	71 (55–99)	78 (59–123)	0.01
Finger Tapping (no.)						
Dominant hand	27.9 (3–55)	23.4 (5–48)	0.03	44.6 (27–63)	45.0 (23–57)	ns
Non-dominant hand	28.5 (2–53)	19.4 (6–40)	0.004	41.7 (26–53)	40.1 (28–54)	ns
Dynamometer (kg)						
Dominant hand	33.5 (11–50)	31.2 (8–56)	ns	52.8 (17–69)	49.2 (37–62)	0.05
Non-dominant hand	30.7 (7–53)	29.0 (5–51)	ns	50.2 (16–70)	46.5 (26–57)	0.04
Foot tapping (no.)						
Dominant foot	29.5 (8–46)	24.4 (5–47)	ns	41.6 (25–62)	40.7 (25–62)[1]	ns
Non-dominant foot	26.5 (6–48)	23.7 (5–48)	ns	39.5 (25–63)	38.6 (25–55)	ns
Static steadiness						
Dominant hand						
Timer (s)	20.0 (1.9–41)	32.0 (11–63)	0.004	13.7 (0.9–32)	14.6 (1.1–55)	ns
Number	334 (20–1136)	482 (161–1181)	0.02	210 (25–603)	262 (39–907)	0.03
Non-dominant hand						
Timer (s)	22.7 (5.2–75)	34.5 (13–94)	0.03	16.1 (1.0–42)	22.0 (1.6–69)	0.02
Number	299 (62–1121)	444 (171–946)	0.002	213 (28–616)	291 (70–823)	0.009
Digit span						
Forwards (no.)	5.1 (4–8)[2]	5.3 (4–9)	ns	5.6 (4–7)	6.0 (4–8)	ns
Backwards (no.)	3.3 (2–6)[2]	3.3 (2–5)	ns	3.9 (3–6)	4.2 (3–7)	ns
Digit symbol (no.)	31.9 (17–48)[3]	27.5 (9–44)	ns	43.9 (25–65)	40.6 (19–62)	ns
Number of symptoms	12.6 (9–16)	13.8 (11–16)	0.006	3.4 (1–14)	2.8 (0–9)	ns

[a]Arithmetic mean

[b]Geometric mean

[1,2,3]Number of subjects missing

[#]p values calculated between baseline and follow-up in manganism patients and referents, respectively

not in less affected patients (Goetz et al. 2004). This is also indicated in the present study, as the three PD patients, classified as Hoehn and Yahr stage 4, had poorer performance on the sway test than the other PD patients, e.g., the GM sway intensity (blindfolded) being 8.3 vs 5.2 mm ($p=0.004$).

A substantial lateralized impairment of tremor intensity was observed in the PD patients, which is compatible with previous observations (Farkas et al. 2006). The bilateral TI difference among the manganism patients was, in contrast, small and similar to that of the referents. A significantly larger difference in performance between the two hands among the PD patients was also observed for the grooved pegboard and the static steadiness test scores in contrast to tests assumed to measure bradykinesia (foot and finger tapping tests).

Unilateral hand tremor at rest is the earliest symptom of PD (Guilarte 2010). It appears from this study that patients diagnosed with manganism have symmetrical clinical manifestations with lateral differences in performance similar to the referents, as opposed to more unilateral manifestations in PD patients at these stages (mean Hoehn and Yahr 2.8) of disease.

Only one study has previously assessed the progression of manganism (Huang et al. 1998). That 10-year clinical follow-up of five patients reported a deterioration of gait, rigidity, foot tapping speed and writing (Huang et al. 1998).

Table 6 CATSYS Tremor 7.0 and postural sway test results recorded at baseline and at follow-up 65.1 (64–71) months later in manganism patients and in referents followed up 69.6 (62–77) months after baseline

	Manganism ($N=17$)		$p^{\#}$	Referents (N = 39)		p
	Baseline	Follow-up		Baseline	Follow-up	
	AM[a] (Min–max)	AM (Min–max)		AM (Min–max)	AM (Min–max)	
Tremor						
Dominant						
Intensity (m/s^2)[b]	0.15 (0.08–0.70)	0.30 (0.10–0.98)	0.001	0.13 (0.07–0.32)	0.15 (0.08–0.44)	ns
Center frequency (Hz)	7.7 (4.8–11.6)	6.4 (3.0-8.9)	0.02	7.2 (5.2–9.6)	6.4 (2.7–10.9)	0.002
Dispersion (Hz)	2.7 (1.0-4.2)	2.1 (0.4-4.0)	0.01	2.8 (0.2–4.9)	3.0 (1.4–5.1)	ns
Non-dominant						
Intensity (m/s^2)[b]	0.15 (0.08–0.33)	0.26 (0.10–0.90)	0.009	0.15 (0.08–0.45)	0.14 (0.07–0.42)	ns
Center frequency (Hz)	7.6 (4.0-12.1)	6.4 (3.6–8.1)	0.02	7.9 (5.0–12.3)	6.9 (2.9–10.7)	0.003
Dispersion (Hz)	3.2 (1.2–4.9)	2.7 (0.4–5.2)	ns	3.0 (0.7–4.6)	3.3 (1.3–4.9)	ns
Postural sway						
Eyes open						
Intensity (mm)[b]	6.0 (3.1–13.9)	7.4 (3.3–15.1)	0.04	4.1 (1.8–10.4)	4.9 (2.6–15.5)	0.03
Velocity (mm/s)[b]	12.7 (6.0-24.7)	16.4 (7.8–47.6)	ns	9.7 (5.2–23.2)	10.4 (6.0–18.8)	ns
Area (mm^2)[b]	366 (104–1183)	676 (212–2720)	0.006	225 (67-1328)	302 (87–1832)	0.03
Blindfolded						
Intensity (mm)[b]	10.5 (3.6–35.9)	12.0 (6.3–30.9)	ns	5.3 (2.7–8.3)	5.7 (3.8–9.7)	ns
Velocity (mm/s)[b]	23.5 (11.8–71.1)	30.8 (11.7–98.1)	ns	13.9 (7.3–21.3)	14.2 (7.7–30.9)	ns
Area (mm^2)[b]	1127 (274-10872)	1552 (479–7108)	ns	324 (87-1293)	365 (118–1035)	ns

[a]Arithmetic mean

[b]Geometric mean

[#]p values calculated between baseline and follow-up in manganism patients and referents, respectively

In the present study, 17 of the manganism patients had been examined on average 65.1 months previously. There was a trend toward declining performance on the finger tapping test among these patients, indicating further development of bradykinesia beyond the natural age-related decline observed among the referents that were followed up 69.6 months later. Also static steadiness test performance and TI declined more in the manganism patients than in the referents, supporting the previous study reporting slight neurological deterioration of manganism patients (Huang et al. 1998).

The manganism patients were retired in contrast to the referents. Most research regarding decline related to retirement has focused on cognitive functioning, but a recent systematic review concluded that there is a major research gap in the field of retirement on age-related cognitive decline (Meng et al. 2017). Even less is known about the impact of retirement and motor functions. There was no significant difference between groups in deterioration on the cognitive tests applied in the present study (digit symbol and digit span).

A recent meta-analysis suggested that finger tapping, simple reaction time and digit symbol test results are associated with current Mn exposure (Meyer-Baron et al. 2013). This was also observed among currently exposed welders who were studied as part of this larger investigation (Ellingsen et al. 2014). Results on these tests are severely impaired among the manganism patients. The point estimates of the difference in performance between manganism patients and referents were 18.2 for finger tapping (dom hand) and 173 ms for SRT in contrast to only 2.2 and 15 ms when the currently exposed welders were compared to the referents. However, the most severe impairment in terms of SD poorer performance among the manganism patients was observed for the postural sway test (blindfolded). In contrast, no significant difference in performance was observed between the currently exposed welders and referents (Ellingsen et al. 2014). These results point to the question of the mechanisms for causing the severe deterioration in neurobehavioral performance among the manganism patients. In a follow-up part of our investigations in St. Petersburg, we observed that three welders, who had normal neurobehavioral test scores at baseline after 21 years of welding, developed a severe bradykinetic syndrome with impaired balance control and no postural tremor at follow up around 6 years later (Ellingsen et al. 2015). Thus, our overall findings could suggest that the development of disease may be similar to what is known from PD, where symptoms and signs may occur suddenly and relatively severely.

There is substantial misclassification of PD, and only approximately 75% of clinical cases are confirmed upon autopsy (Gelb et al. 1999). There are no data on misclassification of the diagnosis of manganism, but we cannot rule out that some patients in the present study have been misclassified. Misclassification would theoretically dilute the estimates of differences between groups. The clinical signs observed among the manganism patients are similar to those observed in other manganism patients (Calne et al. 1994). However, manganism, like PD, is classified according to disease severity, which may differ between studies. Parkinson disease is diagnosed in Russia according to internationally accepted criteria, and the clinical picture of the PD patients is in accordance with what is generally observed.

The present study shows that patients diagnosed with manganism have severe bradykinesia and balance disturbances at this stage of disease. Unlike these severe disturbances, only slight postural tremor was observed. Few cognitive tests were applied, but results from a test of attention span and working memory (digit span forwards and backwards) were similar to the referents. Several differences in neurobehavioral performance between patients diagnosed with PD and patients diagnosed with manganism were observed. The main differences are the poorer postural sway performance in manganism, and more postural tremor as shown by higher TI and more narrow frequency dispersion in PD. A further noticeable difference was the asymmetrical pattern of performance in PD, which was not observed in the manganism patients. Finally, manganism patients had only slight deteriorations in neurobehavioral performance during a nearly 6 years follow-up. These results may help in diagnosing manganism and to distinguish manganism from idiopathic PD. Further, the neurobehavioral tests shown to be impaired among the manganism patients should be included in further epidemiological studies of Mn-exposed workers.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval The study was approved by the Norwegian Regional Ethical Committee for Medical Research (REK2), the Ethics Committee of the NWPHRC (St. Petersburg, Russia), and the Office of Research Protection, US Army Medical Research and Materiel Command (Fort Detrick, MD, USA). Participation was voluntary. Informed written consent was obtained from each participant.

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