Journal of the Neurological Sciences 353 (2015) 102–106

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

Chronic manganism: A long-term follow-up study with a new dopamine terminal biomarker of ^{18}F-FP-(+)-DTBZ (^{18}F-AV-133) brain PET scan

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ARTICLE INFO

Article history:
Received 12 January 2015
Received in revised form 8 April 2015
Accepted 9 April 2015
Available online 17 April 2015

Keywords:
^{18}F-FP-(+)-DTBZ
^{18}F-AV-133
IPD
Manganese
Positron emission tomography
Type 2 vesicle monoamine transporter

ABSTRACT

Recent experimental studies revealed that dopamine neuron dysfunction in chronic manganism may be due to a reduced capacity of dopamine release in the striatum. The findings imposed further difficulty in the differential diagnosis between manganism and IPD. We conducted a long-term clinical follow-up study of 4 manganism patients, applying a new tracer ^{18}F-9-fluoropropyl-(+)-dihydrotetrabenazine (^{18}F-AV-133) with positron emission tomography (PET). Twenty age-matched subjects including 4 manganism patients, 8 idiopathic Parkinson's disease (IPD) patients, and 8 healthy controls were enrolled for comparison. Volumes of interest of the bilateral putamen, caudate nuclei and occipital cortex as the reference region were delineated from individual magnetic resonance images. The clinical features of the manganism patients still progressed, with increased scores on the Unified Parkinson Disease Rating Scale. The ^{18}F-AV-133 uptake in the IPD patients decreased at the bilateral striatum, compared with the healthy controls. In the manganism patients, there was no decreased uptake of radioactivity involving the bilateral striatum, except Patient 4, who had a stroke with decreased uptake in the right posterior putamen. The ^{18}F-AV-133 PET finding reveals that nigrostriatum neurons are not degenerated in chronic manganism and can provide a useful neuroimage biomarker in the differential diagnosis.

1. Introduction

Chronic excessive exposure to manganese (Mn) fumes or dust may induce the neurological abnormality of manganism, with symptoms very similar to idiopathic Parkinson's disease (IPD) [1,2]. Typical symptoms of manganism patients are different from those of patients with IPD [3,4], but some atypical symptoms of manganism patients create a diagnostic challenge [5–7]. In addition, several epidemiological studies have revealed that the inhalation of Mn fumes among welders may accelerate the onset of IPD or even induce IPD [8–10]. These findings have enlarged the gray zone between diagnoses of manganism and IPD.

Neuroimaging studies such as brain magnetic resonance images (MRI) and brain positron emission tomography (PET) scans may provide clinical tools to differentiate manganism from IPD. In brain MRI studies, high signal intensities can be found in T1-weighted images in the early stage of manganese exposure and then disappear 3 months to 1 year after cessation of exposure [11]. Brain PET with [18F]-6-fluoro-dopa or dopamine transporter binding (DAT) with either TRODAT-1 or [123I]-beta-CIT showed a normal or nearly normal uptake in manganism patients [3,12,13]. However, in recent studies, a decrease in dopamine uptake in the putamen and caudate areas, similar to IPD, may develop after exposure to manganese fumes among welders or in psychostimulant drug (ephedrone) abusers [6,9,10]. Lately ^{18}F-9-fluoropropyl-(+)-dihydrotetrabenazine (^{18}F-AV-133), a novel PET tracer, has been developed for imaging the type 2 vesicle monoamine transporter (VMAT2) in dopaminergic neuron degeneration and can provide better resolution, especially for IPD patients [14,15].

We previously reported 6 patients with chronic Mn intoxication at a ferromanganese alloy factory in Taiwan in 1985 [2]. In the current study, we investigated brain ^{18}F-dihydrotetrabenazine (^{18}F-DTBZ) PET (^{18}F-AV-133 PET) using a long-term follow-up study design. To our knowledge, no such long-term comparative study has been

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http://dx.doi.org/10.1016/j.jns.2015.04.018
0022-510X/

conducted among manganism patients, and this is the first to investigate manganism patients using VMAT2 PET.

2. Materials and methods

Four out of the original 6 patients participated in the follow-up study; 1 of the 6 patients was unavailable and another expired in 1990 [2,16]. All patients developed Parkinsonian features in a smelting department of a ferromanganese alloy factory in Taiwan. The patients were investigated using the Unified Parkinson Disease Rating Scale (UPDRS) and the clinical features were charted using video-recording. Brain ^{18}F-AV-133 PET studies were conducted with these 4 manganism patients (age: 67.8 ± 5.3 years). Eight IPD patients (age: 66.3 ± 2.9 years) served as abnormal controls and 8 age-matched volunteers (age: 65.5 ± 3.6 years) were also included as healthy controls (HCs) for the brain ^{18}F-AV-133 PET scan. The modified Hoehn and Yahr stages (mH &Y) scores for IPD were in the range of 1 to 3, and the symptomatic durations of illness were between 1 and 21 years. The study protocol was approved by the Institutional Review Board of Chang Gung Memorial Hospital and the Governmental Department of Health, with written informed consent obtained prior to all procedures for each participant. Neurologic examinations were performed for all subjects including assessment of duration of illness and mH &Y stages.

2.1. Data acquisition

^{18}F-FP-(+)-DTBZ was prepared and synthesized at the cyclotron facility of Chang Gung Memorial Hospital as described previously [17]. All subjects were studied in a Biograph mCT PET/CT System (Siemens Medical Solutions, Malvern, PA, USA) with a 3-dimensional (3D) acquisition mode. All subjects underwent MRI for screening of other diseases, obtaining structural information and delineating volumes of interest (VOIs), and for performing spatial normalization with PET images. Subjects were then imaged on a 3T Siemens Magnetom TIM Trio scanner (Siemens Medical Solutions, Malvern, PA, USA).

After injection of 380.1 ± 11.8 MBq of ^{18}F-FP-(+)-DTBZ, a single 10-min PET scan was acquired 90 min post-injection in 3D mode [18]. PET images were then reconstructed using the 3-D OSEM algorithm (4 iterations, 24 subsets; Gaussian filter: 2 mm; zoom: 3) with CT-based attenuation correction, and also scatter and random corrections as provided by the manufacturer. The reconstructed images were measured with a matrix size of 400 × 400 × 148 and a voxel size of 0.68 × 0.68 × 1.5 mm^3.

2.2. Image analysis

All image data were processed and analyzed using PMOD image analysis software (version 3.3, PMOD Technologies Ltd., Zurich, Switzerland). Each PET image was co-registered to the corresponding MRI, and the individual MRI was spatially normalized to the Montreal Neurological Institute (MNI) MRI template [19]. The spatial normalization parameters were then applied to the corresponding PET image to obtain the normalized PET image in the MNI domain. VOIs of bilateral caudate nuclei, anterior/posterior putamen, nucleus accumbens, substantia nigra, raphe, amygdala, hippocampus, thalamus, hypothalamus, locus coeruleus, brain stem and occipital cortex were defined on the MRI template. The occipital cortex was included as the reference region to calculate the standard uptake value ratio (SUVR). In the IPD group, the contralateral VOIs were defined as the striatum opposite the predominantly affected limbs, and were evaluated separately from the ipsilateral VOIs. VOIs in the HCs and Mn intoxication patients were defined as the left and right sides for future analysis.

2.3. Statistical analysis

Regional SUVRs computed from ^{18}F-FP-(+)-DTBZ images were statistically compared among HCs, IPD patients, and Mn intoxication patients using nonparametric Kruskal–Wallis tests with Dunn's multiple comparison post hoc test in GraphPad Prism (version 5.0, GraphPad software, San Diego, CA). A p value of 0.05 was selected as the threshold of statistical significance in each test.

3. Results

The ages of the patients that underwent ^{18}F-AV-133 PET ranged from 62 to 73 years, and the ages of manganism onset ranged from 36 to 48 years, with duration of exposure from 5 to 13 years. The main clinical manifestations included micrographia, masked face/dystonic smile, hypophonia/stuttering speech, dystonic foot, wide-based gait, difficulty in turning, difficulty in walking backwards, postural instability, and rigidity. Tremor was not prominent and presented in 2 patients only (Patient 1 in the hands while walking, and patients 1 and 4 in the tongue while stretching their tongues out) (Table 1).

Table 1
The demographic data of 4 patients with manganism.

Patients	1	2[a]	3	4[b]
Age (years)	69	62	73	64
Age of onset (years)	45	36	48	39
Duration of exposure (years)	13	7	13	5
Micrographia	+++	+	+	+
Masked face/dystonic smile	++	+	+	++
Hypophonia or stuttering speech	++	++	+	++
Tremor	+ (hand and tongue)	−	−	+ (tongue)
Dystonic foot	++	−	+	+++
Gait en bloc	+++	NA	++	+++
Wide base gait	+	NA	++	+
Difficulty in turning	+++	NA	++	+++
Difficulty in walking backwards	+++	Cannot walk	++	+++
Postural instability	++	Cannot stand	++	+
Rigidity	+++	++	+	++
Clinical asymmetry of the Parkinsonian features	+(R > L)	−	−	+(L > R)
Spasticity	−	+++ (left)	−	−
UPDRS	64 (in 2004) 72 (in 2013)	19 (in 2004) 17 (in 2013)	33 (in 2004) 40 (in 2013)	62 (in 2004) 71 (in 2013)

−: absent; +: present in a mild degree; ++: present in a moderate degree; +++: present in a severe degree; R: right; L: left; UPDRS: Unified Parkinson's Disease Rating Scale; NA: not available.

[a] Patient 2 had recurrent strokes in 1987 and 2006, resulting in left hemiplegia, some UPDRS scores could not be measured on the left side.

[b] The patient had a silent stroke in the right temporal and posterior putamen.

Table 2
Demographic data and mH & Y scores of Mn intoxication patients, healthy controls (HC) and IPD patients.

Subjects	HC	Mn intoxication	IPD
Number	8	4	8
Age (Y)	65.5 ± 3.6	67.8 ± 5.3	66.3 ± 2.9
Gender (M/F)	2/6	4/0	7/1
mH &Y stage	–	2.7 ± 0.4	2.6 ± 1.7

mH &Y stage: modified Hoehn & Yahr stage; M: male; F: female Mn: manganese.
Y: years; IPD: idiopathic Parkinson's disease; HC: healthy control.

Bradykinesia was noted in 3 patients, and not in Patient 2. Patient 2 had 2 episodes of stroke in 1987 and 2006 that resulted in complete left hemiplegia and a wheel-chair bound aftermath. Clinical asymmetry of the Parkinsonian features was observed in patients 1 and 4. The UPDRS scores ranged from 64, 19, 33, and 62 in 2004 to 72, 17, 46 and 71 in 2013, respectively. Because Patient 2 had left hemiplegia, the score of UPDRS was only measured in the right limbs. The ages of the 4 manganism patients and 8 age and mH &Y stage-matched IPD patients and 8 age-matched volunteer HCs were 67.8 ± 5.3 years, 66.3 ± 2.9 years and 65.5 ± 3.6 years, respectively (Table 2). The scores of mH &Y were 2.7 ± 0.4 in manganism and 2.6 ± 1.7 in IPD. Fig. 1 shows the average SUVR image of the normal controls, manganism patients and IPD patients. In the manganism patients, the SUVR ratio was very similar to that of the HCs. In the IPD patients, the SUVR was clearly decreased compared with the HC and manganism groups. Fig. 2 shows the striatal regional SUVR of the HC, Mn intoxication and IPD patients. The uptakes of the manganism patients were all within normal limits in the caudate, anterior putamen and posterior putamen, except one (Patient 4 had a silent cerebral infarction in the right temporal and posterior putaminal areas). However, in the IPD group, the decrease in regional SUVR was statistically significant compared with the HC group ($p < 0.01$ in the contralateral anterior putamen and bilateral posterior putamen, and <0.05 in the contralateral caudate and ipsilateral anterior putamen). In addition to the caudate, anterior and posterior putamen, the contralateral putamen had a statistically significant decreased SUVR in the IPD as compared with the HC group ($p < 0.05$). In the manganism patients, the SUVR showed no statistically significant changes compared with the HCs (Table 3). Also, there was a relatively symmetrical distribution of monoaminergic radioactivity in the bilateral striatum in the manganism patients, except Patient 4.

4. Discussion

We followed-up the clinical manifestations of the patients for 26 years and confirmed further progression in 4 patients with chronic Mn intoxication after cessation of exposure. Measurements had previously revealed rapid progression in the initial 5–10 years and a plateau during the following 10 years, and then more progression in the last 8–10 years [16,20,21]. The mechanism was unclear, but the aging effect due to oxidative stress or free radicals could not be ruled out [22]. The most striking fact is that the manganism patients survived 26 years after presentation, which is quite unusual for IPD patients.

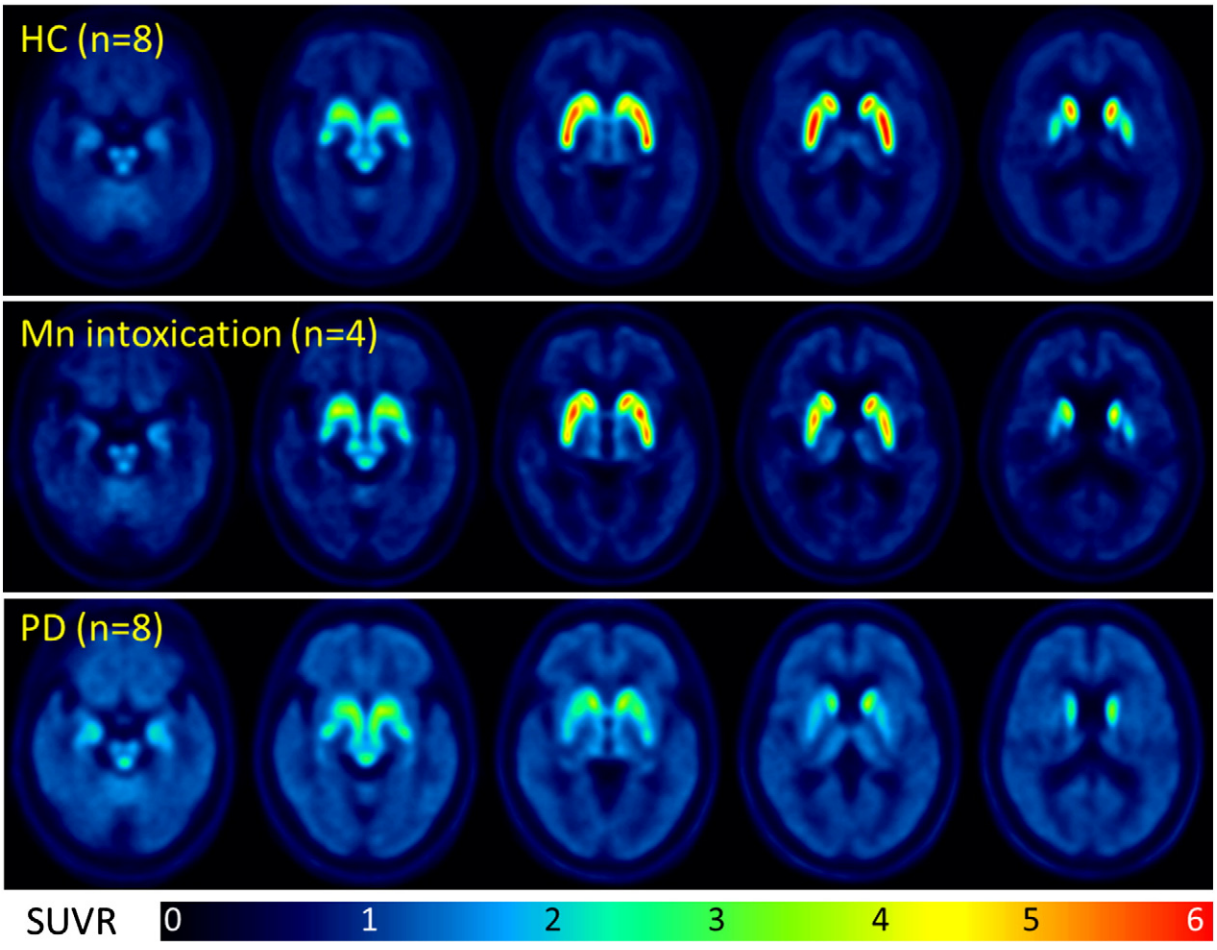

Fig. 1. The SUVR ratio in the manganism patients was very similar to that of the healthy controls. In the PD patients, the SUVR was clearly decreased compared with the HC and manganism groups.

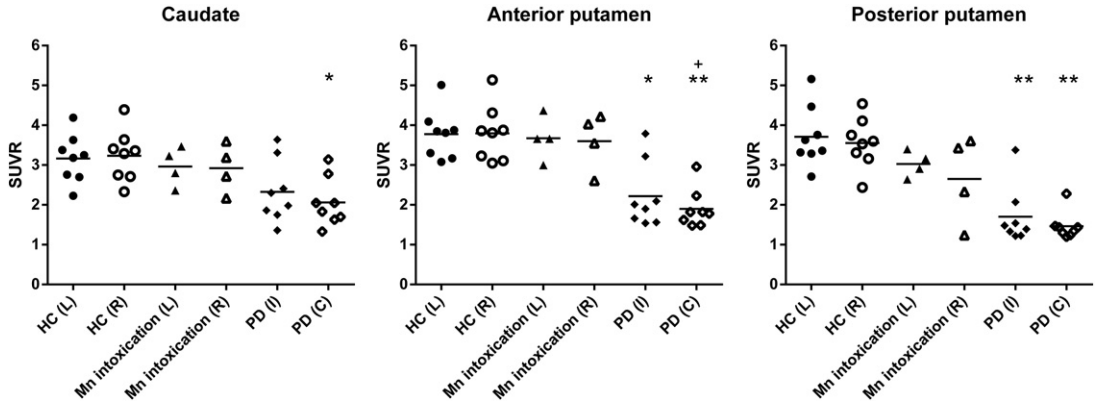

Fig. 2. In the striatal regional SUVR, the uptakes of AV-133 in manganism patients were all within normal limits in the caudate, anterior putamen and posterior putamen, except in 1 patient (Patient 4 had a cerebral infarction in the right temporal and posterior putaminal areas). However, in the IPD group, the regional SUVR had a statistically significant decrease compared with the normal HC group ($p < 0.01$ in the contralateral anterior putamen and bilateral posterior putamen and $p < 0.05$ in the contralateral caudate and ipsilateral anterior putamen).

Molecular imaging is a useful tool for the diagnosis of IPD, because IPD patients exhibit a decrease in pre-synaptic dopamine neuron terminal markers in the striatum. Previous PET studies or dopamine transporter (DAT) with either beta-CIT or TRODAT-1 has shown a normal nigrostriatal dopaminergic pathway [12,13]. Several studies by Kim et al. [5,11] and Criswell et al. [23] found a decreased uptake in the striatum in DAT/SPECT or FDOPA PET, and elevated Mn concentrations among welding workers or patients with end-stage liver disease. The reason may be that the early IPD patients worked in Mn-contaminated environments or had end-stage liver disease. Some may argue that the decrease in DAT measured by SPECT may not represent the DAT loss in the striatum, but an interference in DAT binding by a progressive accumulation of Mn in the synaptic cleft [24]. In addition, some neuroimaging studies in non-human primates revealed that dopamine neuron dysfunction in chronic Mn intoxication may not have resulted from dopamine neuron degeneration [23] but a reduced capacity of dopamine release in the striatum [24,25]. Our previous post-synaptic D2-raclopride PET study showed a slightly decreased uptake of raclopride in the caudate and putaminal areas, indicating a minimal loss of D2 function [13]. Therefore, whether postsynaptic pathway lesions could be a true pathology in manganism patients or not is still uncertain. Experimental studies with monkeys actually demonstrated that the globus pallidus was the main pathological hallmark in Mn intoxication [22]. The complexity among the several mechanisms in manganism patients can be better explored by the new dopamine terminal biomarkers such as the striatal VMAT2, because VMAT2 is an intracellular protein, rather than a membrane protein as in other DAT scans such as TRODAT-1 or beta-CIT.

Table 3
All regional SUVR in HC, Mn intoxication and IPD patients.

	HC (n = 8)	Mn intoxication (n = 4)	IPD (n = 8)
Caudate			
Caudate (L/I)	3.17 ± 0.61	2.97 ± 0.49	2.33 ± 0.78
Caudate (R/C)	3.24 ± 0.64	2.92 ± 0.61	2.06 ± 0.61*
Anterior putamen			
Anterior putamen (L/I)	3.77 ± 0.62	3.67 ± 0.56	2.22 ± 0.83*
Anterior putamen (R/C)	3.80 ± 0.70	3.60 ± 0.72+	1.90 ± 0.49**
Posterior putamen			
Posterior putamen (L/I)	3.71 ± 0.77	3.03 ± 0.33	1.71 ± 0.73**
Posterior putamen (R/C)	3.56 ± 0.63	2.65 ± 1.10	1.47 ± 0.34**
Substantia nigra			
Substantia nigra (L/I)	2.08 ± 0.40	2.08 ± 0.28	1.77 ± 0.23
Substantia nigra (R/C)	1.99 ± 0.31	2.06 ± 0.30+	1.65 ± 0.17*
Nucleus accumbens			
Nucleus accumbens (L/I)	2.37 ± 0.76	2.93 ± 0.57	2.12 ± 0.58
Nucleus accumbens (R/C)	2.18 ± 0.85	2.63 ± 0.76	1.94 ± 0.71
Hippocampus			
Hippocampus (L/I)	1.24 ± 0.09	1.11 ± 0.05	1.26 ± 0.12
Hippocampus (R/C)	1.21 ± 0.08	0.98 ± 0.26+	1.25 ± 0.11
Amygdala			
Amygdala (L/I)	1.44 ± 0.15	1.58 ± 0.21	1.57 ± 0.20
Amygdala (R/C)	1.40 ± 0.14	1.45 ± 0.25	1.56 ± 0.22
Thalamus			
Thalamus (L/I)	1.18 ± 0.12	1.13 ± 0.14	1.10 ± 0.17
Thalamus (R/C)	1.15 ± 0.12	1.05 ± 0.10	1.12 ± 0.13
Raphe	2.01 ± 0.26	2.25 ± 0.24	2.29 ± 0.32
Hypothalamus	2.29 ± 0.28	2.30 ± 0.36	2.42 ± 0.26
Locus coeruleus	1.94 ± 0.11	2.09 ± 0.19	2.28 ± 0.18*
Brain stem	1.71 ± 0.13	1.75 ± 0.16	1.74 ± 0.11

L: left; R: right; I: ipsilateral side for PD; C: contralateral side for PD.
* $p < 0.05$ significantly different from HC.
** $p < 0.01$ significantly different from HC.
\+ $p < 0.05$ significantly different from Mn intoxication.

Chronic Mn intoxication may induce Parkinsonian features similar to IPD patients, yet with a slight difference including prominent lower body Parkinsonism, foot dystonia, dystonic smile, less resting tremor, and less effect with L-dopa treatment [3]. However, in recent epidemiological studies, Mn exposure may have accelerated the onset of Parkinsonism or even induced IPD in welders [8–10,26]. In addition, Mn-induced Parkinsonism was also found in psychostimulant drug abusers in eastern European countries and Russia [6,27,28] and in patients with chronic liver disease [29] not related to occupational exposure. Recent reports have made the differential diagnosis between manganism and IPD more complicated and challenging for clinicians.

PET radioligands that target VMAT2 have been proposed to be better biomarkers for quantification of dopamine/serotonin presynaptic neurons [14,15]. In animal studies, VMAT2 density was linearly correlated to the integrity of substantial nigra dopamine neurons [17]. The results of human studies using ^{11}C-DTBZ and PET showed a good effect on the objective quantification of nigrostriatal integrity [14]. A novel radiotracer from derivatives of DTBZ labeled with ^{18}F was also developed recently [15,30]. In this study, we found normal uptake of SUVR in the caudate, anterior putamen and posterior putamen in manganism patients compared with HCs. In contrast to the IPD group, the SUVR was decreased in the corpus striatum (caudate and putamen), indicating that the new imaging ligand with PET can clearly differentiate manganism and IPD. In manganism patients, the normal uptakes of VMAT2 in the caudate and putamen areas clearly demonstrated that the nigrostriatum neurons were not degenerated. In Patient 4, the significant decrease in SUVR in the posterior putamen and right hippocampus was possibly related to a silent infarction. The present study showed that SUVR in the posterior putamen was decreased in manganism patients compared to HCs, although the difference was not statistically significant. The reason may be partly related to the infarction in Patient 4. With this new image ligand and PET scan, we further confirmed that typical manganism patients can be differentiated from IPD.

5. Conclusion

The subjects in this study were confirmed manganism patients due to Mn exposure, as determined by their history and follow-up studies. We also discussed these patients compared to welders or end-stage liver disease patients showing similar findings to IPD patients.

Our finding further indicates that the new neuroimaging tracer ^{18}F-AV-133 with PET can show that nigrostriatum neurons are not degenerated in chronic manganism patients and may provide a useful biomarker in the differential diagnosis between manganism and IPD. Brain AV-133 PET can provide better imaging due to the longer half-life of ^{18}F, and can have a broader clinical application than ^{6}F-dopa PET and DAT scans such as TRODAT-1. This long-term follow-up study of manganism patients for a period of 26 years also reveals a slow clinical progression.

Conflict of interest

The authors declare that there is no conflict of interest.

Acknowlegments

We would like to thank Yu-Chen Hsieh for her technical assistance. We also thank Avid Radiopharmaceuticals, Inc. (Philadelphia, PA, USA) for providing the precursor for the preparation of 18 F-AV-133. This study was carried out with financial support from NSC 100-2314-B-182A-092-MY3, NSC 86-2314-B182A-048, and NSC 100-2314-B-182-003, CMRPG3C0611, CMRPG3C0612, and CMRPG390793.

References

[1] Cotzias GC, Horiuchi K, Fuenzalids S, Mena I. Chronic manganese poisoning: clearance of tissue manganese concentrations with persistence of the neurological picture. Neurology 1968;18:376–82.
[2] Huang CC, Chu NS, Lu CS, Wang JD, Tsai JL, Tseng CL, et al. Chronic manganese intoxication. Arch Neurol 1989;46:1104–6.
[3] Calne DB, Chu NS, Huang CC, Lu CS, Olanow W. Manganism and idiopathic Parkinsonism: similarities and differences. Neurology 1994;44:1583–6.
[4] Jankovic J. Searching for a relationship between manganese and welding and Parkinson's disease. Neurology 2005;64:2021–8.
[5] Kim Y, Kim JM, Kim JW, Yoo CI, Lee CR, Lee JH, et al. Dopamine transporter density is decreased in Parkinsonian patients with a history of manganese exposure: what does it mean? Mov Disord 2002;17:568–75.
[6] de Bie RM, Gladstone RM, Strafella AP, Ko JH, Lang AE. Manganese-induced Parkinsonism associated with methcathinone (ephedrone) abuse. Arch Neurol 2007;64:886–9.
[7] Kessler KR, Wunderlich G, Hefter H, Seitz RJ. Secondary progressive chronic manganism associated with markedly decreased striatal D2 receptor density. Mov Disord 2003;18:217–28.
[8] Racette BA, Tabbal SD, Jennings D, Good L, Perlmutter JS, Evanoff B. Prevalence of parkinsonism and relationship to exposure in a large sample of Alabama welders. Neurology 2005;64:230–5.
[9] Racette BA, McGee-Minnich L, Moerlein SM, Mink JW, Videen TO, Perlmutter JS. Welding-related Parkinsonism: clinical features, treatment, and pathophysiology. Neurology 2001;56:8–13.
[10] Racette BA, Antenor JA, McGee-Minnich L, Moerlein SM, Videen TO, Kotagal V, et al. [18F] FDOPA PET and clinical features in Parkinsonism due to manganism. Mov Disord 2005;20:492–6.
[11] Kim Y. Neuroimaging in manganism. NeuroToxicology 2006;27:369–72.
[12] Ech Wolters, Huang CC, Clark C, Peppard RF, Okada J, Chu NS, et al. Positron emission tomography in manganese intoxication. Ann Neurol 1989;26:647–51.
[13] Shinotoh H, Snow BJ, Chu NS, Huang CC, Lee C, Lu CS, et al. Presynaptic and postsynaptic striatal dopaminergic function in patients with manganese intoxication: a positron emission tomography study. Neurology 1997;48:1053–6.
[14] Felicio AC, Shih MC, Godeiro-Junior C, Andrade LA, Bressan RA, Ferraz HB. Molecular imaging studies in Parkinson disease: reducing diagnostic uncertainty. Neurologist 2009;15:6–16.
[15] Hsiao IT, Weng YH, Hsieh CJ, Lin WY, Wey SP, Kung MP, et al. Correlation of Parkinson disease severity and ^{18}F-DTBZ positron emission tomography. JAMA Neurol 2014;71:758–66.
[16] Huang CC, Lu CS, Chu NS, Hochberg F, Lilienfeld D, Olanow W, et al. Progression after chronic manganese exposure. Neurology 1993;43:1479–83.
[17] Tsao HH, Lin KJ, Juang JH, Skovronsky DM, Yen TC, Wey SP, et al. Binding characteristics of 9-fluoropropyl-(+)-dihydrotetrabenzazine (AV-133) to the vesicular monoamine transporter type 2 in rats. Nucl Med Biol 2010;37:413–9.
[18] Lin KJ, Lin WY, Hsieh CJ, Weng YH, Wey SP, Lu CS, et al. Optimal scanning time window for 18F-FP-(+)-DTBZ (18F-AV-133) summed uptake measurements. Nucl Med Biol 2011;38:1149–55.
[19] Mazziotta JC, Toga AW, Evans A, Fox P, Lancaster J. A probabilistic atlas of the human brain: theory and rationale for its development. The International Consortium for Brain Mapping (ICBM). Neuroimage 1995;2:89–101.
[20] Huang CC, Chu NS, Lu CS, Chen RS, Calne DB. Long-term progression in chronic manganism: ten years follow-up. Neurology 1998;50:698–700.
[21] Huang CC, Chu NS, Lu CS, Chen RS, Schulzer M, Calne DB. The natural history of neurological manganism over 18 years. Parkinsonism Relat Disord 2007;13:143–5.
[22] Olanow CW, Good PF, Shinotoh H, Hewitt KA, Vingerhoets F, Snow BJ, et al. Manganese intoxication in the rhesus monkey: a clinical, imaging, pathologic, and biochemical study. Neurology 1996;46:492–8.
[23] Criswell SR, Perlmutter JS, Crippin JS, Videen TO, Moerlein SM, Flores HP, et al. Reduced uptake of FDOPA PET in end-stage liver disease with elevated manganese levels. Arch Neurol 2012;69:394–7.
[24] Guilarte TR. Manganese and Parkinson's disease: a critical review and new findings. Environ Health Perspect 2010;118:1071–80.
[25] Guilarte TR, Burton NC, McGlothan JL, Verina T, Zhou Y, Alexander M, et al. Impairment of nigrostriatal dopamine neurotransmission by manganese is mediated by pre-synaptic mechanism(s): implications to manganese-induced parkinsonism. J Neurochem 2008;107:1236–47.
[26] Sadek AH, Schulz PE. Welding-related Parkinsonism: clinical features, treatment, and pathophysiology. Neurology 2001;57:1738–9.
[27] Sanotsky Y, Lesyk R, Fedoryshyn L, Komnatska I, Matviyenko Y, Fahn S. Manganic encephalopathy due to “ephedrone” abuse. Mov Disord 2007;22:1337–43.
[28] Stepens A, Logina I, Liguts V, Aldins P, Eksteina I, Platkājis A, et al. A Parkinsonian syndrome in methcathinone users and the role of manganese. N Engl J Med 2008;358:1009–17.
[29] Krieger D, Krieger S, Jansen O, Gass P, Theilmann L, Lichtnecker H. Manganese and chronic hepatic encephalopathy. Lancet 1995;346:270–4.
[30] Lin SC, Lin KJ, Hsiao IT, Hsieh CJ, Lin WY, Lu CS, et al. In vivo detection of monoaminergic degeneration in early Parkinson disease by (18)F-9-fluoropropyl-(+)-dihydrotetrabenazine PET. J Nucl Med 2014;55:73–9.