Psychiatry Research: Neuroimaging 231 (2015) 160–167

Contents lists available at ScienceDirect

Psychiatry Research: Neuroimaging

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

Longitudinal changes in the dopamine transporter and cognition in suicide attempters with charcoal burning

Kai-Chun Yang [a], Shyh-Jen Wang [b], Wen-Chi Hsieh [c,d], Jiing-Feng Lirng [e], Chen-Chang Yang [f], Jou-Fang Deng [f], Chun-Lung Lin [g], Yuan-Hwa Chou [c,h,*]

[a] Psychiatry Section, Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden
[b] Department of Nuclear Medicine, Taipei Veterans General Hospital & National Yang Ming University, Taipei, Taiwan
[c] Department of Psychiatry, Taipei Veterans General Hospital & National Yang Ming University, Taipei, Taiwan
[d] Department of Industrial and Systems Engineering, Chung Yuan Christian University, Taoyuan, Taiwan
[e] Department of Radiology, Taipei Veterans General Hospital & National Yang Ming University, Taipei, Taiwan
[f] Department of Toxicology, Taipei Veterans General Hospital & National Yang Ming University, Taipei, Taiwan
[g] Department of Psychiatry, Taoyuan Armed Forces General Hospital, Taoyuan, Taiwan
[h] Institute of Neuroscience, National Yang-Ming University, Taipei, Taiwan

ARTICLE INFO

Article history:
Received 4 July 2013
Received in revised form
24 August 2014
Accepted 3 December 2014
Available online 12 December 2014

Keywords:
Carbon monoxide poisoning
[^{99m}Tc] TRODAT-1
Wisconsin card sorting test
Executive function

ABSTRACT

Suicide with charcoal burning, which results in carbon monoxide (CO) poisoning, is common in Asia. This study was designed to elucidate associations between changes in the dopamine transporter (DAT) and cognitive function in patients following CO poisoning during a follow-up period of 6 months. Participants comprised 31 healthy controls (HCs) and 21 CO poisoning patients. Each subject underwent single photon emission computed tomography with [^{99m}Tc] TRODAT-1 to measure DAT availability and completed a cognitive battery assessing attention, memory, and executive function. For CO poisoning patients, a second DAT measurement and repeated cognitive evaluations were performed 6 months later. At baseline, DAT availability over bilateral striatum in CO poisoning subjects was significantly lower than in HCs. After 6 months, there was no significant change of DAT availability in CO poisoning patients. CO poisoning patients also had worse cognitive performance in all domains compared with HCs at baseline. After 6 months, most cognitive functions were significantly improved, except for the Wisconsin Card Sorting Test (WCST), a measure of executive function. Interestingly, changes in the WCST were significantly correlated with changes in DAT availability during the 6-month follow-up period. The persistence of reduced DAT availability and its association with impaired performance on the WCST indicate a crucial role of DAT in the recovery of executive function following CO poisoning.

1. Introduction

Carbon monoxide (CO) poisoning is a major cause of poisoning deaths in the United States (Ernst and Zibrak, 1998; Weaver, 2009). It is also a leading cause of suicide deaths in Taiwan, Hong Kong, and other Asian countries where suicide by charcoal burning has increased rapidly (Pan et al., 2010; Tsai et al., 2011). The clinical symptoms of CO poisoning are non-specific and varied, including cognitive dysfunctions, personality changes, urine and fecal incontinence, gait disturbances, parkinsonism and other movement problems, depression, anxiety and mutism (Ernst and Zibrak, 1998; Hurley et al., 2001; Kesler et al., 2001; Hay et al., 2002; Parkinson et al., 2002; Porter et al., 2002; Weaver et al., 2002; Pulsipher et al., 2006; Kondziella et al., 2009; Weaver, 2009; Chang et al., 2010; Ku et al., 2010; Yang et al., 2011). The cognitive impairment caused by CO poisoning involves multiple domains, such as attention, visual and verbal memory, executive function, calculation, and visuospatial function (Hurley et al., 2001; Kesler et al., 2001; Hay et al., 2002; Parkinson et al., 2002; Porter et al., 2002; Weaver et al., 2002; Pulsipher et al., 2006; Kondziella et al., 2009; Chang et al., 2010, 2011). Cognitive impairment is one of the most serious sequelae of CO poisoning because it may prevent the full recovery of pre-morbid functions in CO poisoning patients (Hurley et al., 2001; Weaver et al., 2002).

Most previous studies have shown impaired cognitive functions following CO poisoning (Kesler et al., 2001; Parkinson et al., 2002; Porter et al., 2002; Weaver et al., 2002; Pulsipher et al., 2006). Notably, in order to minimize the between-subject variation, Porter et al. demonstrated that CO poisoning patients showed significantly improved test scores at 6-month follow-up (Porter et al., 2002), whereas two other studies showed no significant improvement of cognitive impairment in CO-poisoning patients

* Correspondence to: Department of Psychiatry, Taipei Veterans General Hospital, No. 201, Sec 2, Shih-Pai Road, 112, Peitou, Taipei, Taiwan
Tel.: +886 2 28711290; fax: +886 2 28768403.
E-mail address: c520608@ms64.hinet.net (Y.-H. Chou).

http://dx.doi.org/10.1016/j.pscychresns.2014.12.002
0925-4927/

after a 2-month follow-up (Hay et al., 2002) or a 10-month follow-up (Chang et al., 2010). The discrepancies between these studies warrant further clarification.

In healthy subjects the dopamine transporter (DAT) plays a crucial role in controlling dopamine release (Backman et al., 2006; Cropley et al., 2006), which has been reported to be associated with cognitive functions including attention, set-shifting, working memory, cognitive flexibility, episodic memory, logic memory, and executive functions (Mozley et al., 2001; Backman et al., 2006; Cropley et al., 2006; Chou et al., 2007; Hsieh et al., 2010). [^{99m}Tc] TRODAT-1 is a single photon emission computed tomography (SPECT) radiotracer, which can be readily labeled with Tc-99m for imaging DAT binding in the human brain (Acton et al., 1999; Kushner et al., 1999). This tracer has previously been used to study the role of DAT in neuropsychiatric diseases and to explore the relationship between the DAT and cognitive functions (Mozley et al., 2001; Chou et al., 2007; Hsieh et al., 2010; Chang et al., 2011).

We recently found that CO-poisoning patients have significantly lower DAT availability that, if combined with the clinical symptom of loss of consciousness, may predict delayed neuropsychological deficits (Yang et al., 2011). This result may suggest that the DAT plays a role in the pathophysiology of cognitive impairment in CO-poisoning patients. Therefore, we designed the present study to further explore the pathophysiology of cognitive function and elucidate the association between changes in DAT availability and cognitive functions in CO-poisoning patients over 6 months of follow-up.

2. Methods

This project was approved by the Human Ethical Committee at the Taipei Veterans General Hospital and each participant provided written informed consent before the experiment was initiated.

2.1. Protocol design

Patients who attempted suicide by charcoal burning were prospectively recruited from 1 May 2007 to 31 March 2009. They were diagnosed with CO poisoning if their initial carboxyhemoglobin (COHb) level was more than 10% or if obvious exposure to carbon monoxide and CO-poisoning-related symptoms were confirmed (Weaver et al., 2002; Yang et al., 2011). Patients were excluded from the study if they were younger than 20 years, older than 65 years due to the significant effect of age on DAT availability (Mozley et al., 1999), pregnant, moribund, substance abusers, or receiving medications that have a direct pharmacological effect on DAT availability, such as bupropion (Booij and Kemp, 2008). Each subject received a diagnostic interview with collection of demographic data, clinical assessments and a psychological battery for cognitive function assessment. A SPECT study was scheduled for the first 3 days after each subject was admitted to our hospital, if the subject could tolerate the scanning procedure. Magnetic resonance image (MRI) was scheduled for the first week. The SPECT imaging, clinical assessments and cognitive function assessment were repeated after 6 months.

Healthy controls (HCs) were recruited from 1 September 2006 to 31 December 2010 by local advertisements. Each subject was interviewed by a trained psychiatrist using the Mini-International Neuropsychiatric Interview (M.I.N.I.) (Sheehan et al., 1998) to exclude the possibility of major physical illnesses, psychiatric disorders, or a history of substance abuse.

2.2. Clinical assessments

Psychiatric diagnoses were formulated by a trained psychiatrist based on the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM IV; American Psychiatric Association, 1994). Several clinical factors such as the serum COHb levels, sessions of hyperbaric oxygen therapy (HBOT), and loss of consciousness were determined. At the time of the SPECT measurements, Mini-Mental State Examination (MMSE), Hamilton Rating Scale for Depression (HAM-D), Hamilton Rating Scale for Anxiety (HAM-A), Simpson-Angus Scale (SAS), and Clinical Global Impressions Scale-Severity (CGI-S) assessments were administered at day 3 after admission and repeated 6 months later.

2.3. Cognitive assessments

A psychological battery that evaluated attention, verbal memory, visual memory, and executive functions was administered at week 1 after admission and repeated 6 months later by psychologist as described previously (Chou et al., 2012). Attention was measured by a Go/No-Go task of attentional performance. Memory was assessed by subtests of the Wechsler Memory Scale-III (WMS-III), namely the Word Lists Test for verbal memory functions and the Face Test for visual memory functions. We administered two executive function tests, the Wisconsin Card Sorting Test (WCST) and the Color Trails Test (CTT), a culturally fair analog of the Trail Making Test (Shan et al., 2008).

2.4. Radiochemistry preparation

Preparation of [^{99m}Tc] TRODAT-1 ([2-[[2-[[[3-(4-chlorophenyl)-8-methyl-8-azabicyclo[3,2,1]oct-2-yl]methyl](2-mercaptoethyl)amino]ethyl]amino]ethanethiolato (3-)-N2,N2′,S2,S2′]oxo-[1R-(exo-exo)]-(99m)Tc-technetium) was carried out as previously described (Kung, 2001), with minor modifications (Chou et al., 2007). In brief, it was prepared from a lyophilized kit by adding 1.110 MBq freshly eluted Tc-99-pertechnetate to a 5-ml saline preparation. The [^{99m}Tc] TRODAT-1 was obtained in a neutral solution (pH = 7.0–7.5) with more than 90% radiochemical purity over 6 h as determined by high performance liquid chromatography (HPLC). The shelf life of the lyophilized kit is more than 2 months when stored at room temperature.

2.5. SPECT measurements

Our SPECT procedures with [^{99m}Tc] TRODAT-1 for DAT imaging have been described previously (Chou et al., 2007; Yang et al., 2011). All subjects consumed a low-protein diet for 24 h before the [^{99m}Tc] TRODAT-1 injection and SPECT measurement. Each subject received a single bolus injection of 740 MBq (20 mCi) of radiotracer and SPECT images were acquired between 240 and 280 min after the injection using a two-head gamma camera system (E-Cam Variable Angle; Siemens Medical Systems Inc.), equipped with a low-energy fan-beam collimator. The image matrix size was 128×128 and the pixel size was 3.9 mm. Full width at half-maximum (FWHM) was 7.3 mm, and each slice thickness was 3.894 mm. Images were reconstructed using back-projection with a Metz filter. Attenuation correction was performed with the first order of Chang's method.

2.6. MRI acquisition

Each subject underwent T1-weighted MRI to exclude the possibility of intracranial brain lesions and as anatomical guidance for further SPECT image analyses. MR images were obtained using a 1.5 T GE scanner Excite-II system (repetition time/echo time = 8.54 ms/1.836; field of view = $260 \times 260 \times 1.5$; matrix = $256 \times 256 \times 124$; number of excitations = 1; inversion time = 400 ms; flip angle = 15; bandwidth = 15.63).

2.7. Definition of the regions of interest (ROIs)

ROIs were drawn directly on the SPECT composite images guided by an MR brain image over the striatum and the cerebellum as described previously (Yang et al., 2011). The striatum was drawn to include three consecutive transverse slices containing the highest levels of radioactivity, and the right and left sides of the striatum were assessed separately. The cerebellum was chosen as the reference region and drawn on each of two adjacent slices where the cerebellum could be clearly identified on the SPECT images. The procedures for delineating the ROIs were the same but applied independently for the baseline and follow-up measurements. All imaging analyses were performed by the PVIEW tool of the PMOD version 3.0 software (PMOD Group, Zurich, Switzerland), implemented on a personal computer.

2.8. Calculation of the specific uptake ratio (SUR) of DAT

Our procedures for calculating the SUR have been described previously (Chou et al., 2007; Yang et al., 2011), and their validity has been established in kinetic analysis studies (Acton et al., 1999; Kushner et al., 1999). Briefly, the SPECT system measured the total counts in a ROI (C_{ROI}). On the assumption of negligible specific binding in the cerebellum, this region was used as a reference for the representation of free and non-specific binding (C_n) in the brain. Thus, the specific binding of [^{99m}Tc] TRODAT-1 ($C_b(t)$) in the striatum was calculated by subtracting the mean count per pixel in the cerebellum (C_n) from those in the ROIs (C_{ROI}). The equation was defined as follows:

$$C_b(t) = C_{ROI}(t) - C_n(t) \quad (1)$$

Since composite images for the striatum and the cerebellum were integrated from 240 to 280 min after the [^{99m}Tc] TRODAT-1 injection, which included the equilibrium peak, the equation for calculating the SUR was defined as follows:

$$\mathrm{SUR} = \frac{\int_{280}^{240} C_b(t)}{\int_{280}^{240} C_n(t)} \quad (2)$$