Full Length Article

Neurotoxicity of carbon monoxide targets caudate-mediated dopaminergic system

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A R T I C L E   I N F O

A B S T R A C T

The clinical features of parkinsonism in carbon monoxide (CO) intoxication have been associated with striatal-related neuronal networks. As parkinsonian and neuropsychiatric features are both related to presynaptic dopaminergic integrity, the aim of this study was to explore the clinical significance of ^{99mTc}TRODAT-1 in grading neurobehavioral scores and parkinsonian severity in CO intoxication.

We enrolled 64 patients with CO intoxication, including 29 with parkinsonism (parkinsonism[+] group) and 35 without (parkinsonism[−] group). All of the patients received ^{99mTc}TRODAT-1 neuroimaging evaluations, comprehensive neurobehavioral tests and assessments of the severity of parkinsonism using Unified Parkinson's Disease Rating Scale (UPDRS)-part III motor score. Univariate and multivariate regression analyses were used to test the predictive factors and scores for a diagnosis of parkinsonism and its severity.

The parkinsonism(+) group had significantly lower cognitive scores and higher neuropsychiatric total scores compared with the parkinsonism(−) group, both of which were independently related to the severity of parkinsonism. ^{99mTc}TRODAT-1 regional caudate signals were correlated with tremors at rest, action or postural tremors of the hands, bradykinesia and hypokinesia, and visuospatial, verbal fluency, abstract thinking and digit backwards scores. Scores of the neurobehavioral tests and UPDRS items were highly correlated ($p < 0.01$).

Our results validated the initial hypothesis in that neurobehavioral deficits and parkinsonian symptoms were highly related. This association was independent of demographic factors and initial carboxyhemoglobin level. Within the presynaptic dopaminergic circuit, the clinical role of the caudate in mediating the clinical symptoms in CO intoxication may outweigh the putamen.

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1. Introduction

Suicide by inhalation of barbecue charcoal gas is common in Asia (Chang et al., 2014). Those who survive may experience carbon monoxide (CO) intoxication and present with a broad neurobehavioral spectrum (Chang et al., 2012). Evidence suggests that specific pathological mechanisms may mediate individualized immune responses after toxic exposure to CO (Chang et al., 2010a; Lapresle and Fardeau, 1967; Penney et al., 1991; Plum et al., 1962; Prockop and Chichkova, 2007; Wagner et al., 1989). The cognitive profiles of patients with CO intoxication (Chang et al., 2009) are highly variable, and depend on the integrity of networks involving

the temporal-parietal cortex and prefrontal-temporal white matter bundles (Chen et al., 2015).

Injuries in the pallidum, caudate nucleus, mid-brain and pallidoreticular tract (Auer and Benveniste, 1996) have been associated with the severity of parkinsonism in CO intoxication. Recently, a CO-related parkinsonian neuronal network has been constructed (Chang et al., 2016), collectively consisting of the medial and lateral frontal area, caudate nucleus, dorsomedial prefrontal areas and temporal-parietal gray matter. Using glucose PET and metabolic covariance network analysis, these regions present a spatially-scattered but functionally coherent severity-specific network for the motor features of parkinsonism. The glucose metabolic activity of these cortical hubs has also shown signal collinearity with striatal 99mTc-[2-[[2-[[[3-(4-chlorophen-yl)-8-methyl-8-azabicyclo [3,2,1] oct-2-yl] methyl] (2-mercap-toethyl) amino] ethyl] amino]-ethanethiolato(3-)-N2,N2,S2, S2] oxo-[1R-(exo-exo)] ([99mTc]TRODAT-1).

Direct comparisons between the topography of parkinsonian (Chang et al., 2016) and cognitive (Chen et al., 2015) networks shared anatomical similarities, of which the frontal-striatal regions are most significant. [99mTc]TRODAT-1 binds selectively to presynaptic dopamine transporters in the caudate and putamen neurons (Wilson et al., 1996). In addition to the association with the severity of parkinsonism in Parkinson's disease (PD) (Huang et al., 2003, 2004), [99mTc]TRODAT-1 signals have been reported to be associated with neuropsychiatric symptoms in bipolar disorder, attention deficit and hyperactivity disorder, post-traumatic stress disorder and schizophrenia (Chang et al., 2010; Felicio et al., 2010; Hsieh et al., 2010). This study will explore whether TRODAT can be used to predict the severity of neural damage associated with the symptoms of CO intoxication.

A simple neuroimaging biomarker that can accurately predict clinical features is of clinical relevance. Focusing on the dopamine transporter binding properties of [99mTc]TRODAT-1 in the striatum (Choi, 1983; Ginsburg and Romano, 1976; Hopkins et al., 2006), we investigated the relationships between neuropsychological and parkinsonian domains in 64 patients with CO intoxication. We also explored the diagnostic ability of [99mTc]TRODAT-1 with regards to neurobehavioral and parkinsonian symptoms.

2. Material and methods

2.1. Design and patient enrolment

This study was approved by the Institutional Review Board of Chang Gung Memorial Hospital and complied with the ethical standards established in the Declaration of Helsinki. The experiments were undertaken with the written, informed consent of each subject and their caregiver (where appropriate).

The neurology clinic at Kaohsiung Chang Gung Memorial Hospital initiated this study in 2011. The clinical diagnosis of CO intoxication was made based on a history of a charcoal-burning suicide attempt and an elevated carboxyhemoglobin level (>10%) (Chang et al., 2012). The exclusion criteria included a pre-existing intracranial disorder, an agitated mood or an impaired arousal state that prevented accurate assessment of neuropsychiatric status (Chen et al., 2013).

2.2. Clinical diagnosis of parkinsonism and severity assessment

The clinical diagnosis of CO-related parkinsonism was made based on the judgment of symmetric rigidity, bradykinesia, gait disturbances and postural instability by a movement specialist who was blinded to the clinical diagnosis (Chang et al., 2016). The patients were divided into two groups: Parkinsonism (+) group (n = 29) or parkinsonism(−) group (n = 35) (Table 1). The Hohn and Yahr stage were included to reflect the overall motor severity and the severities of parkinsonian features were further evaluated using the Unified Parkinson's Disease Rating Scale (UPDRS)-part III motor score. We included two different rating scales to reflect

Table 1
Demographic data between patients with or without clinical diagnosis of Parkinsonism.

	With Parkinsonism (n = 29)			Without Parkinsonism (n = 35)			P values
	mean	±	SD	mean	±	SD	
Female gender (%)	19 (54.3%)			18 (62.1%)			0.530
Age	36.31	±	9.19	39.23	±	9.46	0.218
Education (Years)	11.24	±	3.27	11.20	±	3.51	0.962
Carboxyhemoglobin (%) (mean, range)	22.4, 15–46			24.5, 14–53		\	0.78
Conscious disturbance period (day)	1.45	±	0.8	1.54	±	0.5	0.75
Intervals from intoxication (months)	20.6	±	3.4	20.3	±	4.1	0.83
Mini-mental state examination score	19.28	±	8.54	25.94	±	4.89	0.001
NPI total scores	23.55	±	16.59	13.63	±	13.94	0.012
Hohn_and_Yahr_stage	2.66	±	1.56	0.51	±	0.92	<0.001
UPDRS (Summation of Item 18–31)	22.48	±	10.72	2.63	±	3.54	<0.001
Speech (Item 18)	1.62	±	1.12	0.29	±	0.57	<0.001
Facial Expression (Item 19)	1.62	±	1.01	0.20	±	0.41	<0.001
Tremor at rest (Item 20)	0.28	±	0.65	0.06	±	0.24	0.094
Action or Postural Tremor of hands (Item 21)	0.55	±	0.74	0.31	±	0.63	0.170
Rigidity (Item 22)	1.38	±	1.27	0.11	±	0.32	<0.001
Finger Taps (Item 23)	1.90	±	0.98	0.17	±	0.45	<0.001
Hand Movements (Item 24)	1.93	±	1.16	0.11	±	0.40	<0.001
Rapid Alternating Movements of Hands (Item 25)	1.66	±	1.26	0.09	±	0.28	<0.001
Leg Agility (Item 26)	2.21	±	1.32	0.23	±	0.49	<0.001
Arising from Chair (Item 27)	1.45	±	1.45	0.14	±	0.36	<0.001
Posture (Item 28)	1.66	±	1.32	0.17	±	0.45	<0.001
Gait (Item 29)	2.21	±	1.40	0.29	±	0.57	<0.001
Postural Stability (Item 30)	2.14	±	1.38	0.29	±	0.57	<0.001
Bradykinesia and hypokinesia (Item 31)	1.90	±	1.21	0.17	±	0.45	<0.001

Data represents mean ± standard deviation. UPDRS = Unified Parkinson's Disease Rating Scale; NPI = neuropsychiatric inventory. Clinical diagnosis of Carbon monoxide-related Parkinsonism was based on the judgment of symmetric rigidity, bradykinesia, gait disturbances and postural instability by a movement specialist without clinical reference of any data.