SPECT Findings on Neuropsychiatric Symptoms Caused by Nitrous Oxide Abuse

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Abstract

Objective To investigate the clinical, neuropsychological and changes of regional cerebral blood flow (rCBF) perfusion in patients with neuropsychiatric symptoms caused by nitrous oxide (N_2O) abuse.

Methods Sixteen patients with neuropsychiatric symptoms caused by nitrous oxide abuse were recruited. 25-30mci ^{99m}Tc-ECD was administered intravenously. the SPECT/CT images were collected with low-energy and high-resolution collimator. The region uptake statistics of different brain regions of interest between patients with N_2O abuse and normal people of the same age group from background software database were calculated automatically.

Results The clinical manifestations of the 16 patients with neuropsychiatric symptoms were mood lability, anxiety, hallucination, delusion, Agitated, Confusion, and other psychiatric symptoms. In addition, 15 patients of them also complained their memory decline. 14 patients manifested as numbness or paresthesias. 14 patients developed limb weakness, whose motor impairments were more severe in lower limbs than upper limbs. 8 patients also accompanied by urinary and defecation disturbance. Neuropsychological examination: BPRS score was 54.69±11.48, the score of HAMD was 30.00 ± 11.06, the score of HAMA was 18.06 ± 5.77, the score of MMSE was28.06 ± 2.29, and the score of MoCA was 25.06 ± 3.40. SPECT showed hypoperfusion in the frontal lobe and the temporal lobe, which consistent with the clinical findings.

Conclusion It was the first study to demonstrate obvious effect of N_2O abuse on CBF in patients with neuropsychiatric symptom. CBF perfusion imaging is helpful to detect the changes of local brain functional activity in patients with N_2O abuse.

Introduction

Global Drug Survey 2019, conducted across more than 30 countries, revealed that nitrous oxide (N_2O) was the 10th most popular substance in the studied population[1]. N_2O abuse recreationally is increasingly popular within Chinese adolescents and young adults, which leads to neurological and psychiatric complications[2]. Subacute combined degeneration and peripheral neuropathy are identified as the most common neurological manifestation[3, 4]. However, the psychiatric and cognition impairment caused by N_2O abuse have not received so much attention, and only case reports have been reported in the literature[5, 6].

Numerous studies have demonstrated significant mental health and behavioral comorbidities among patients who are inhalant abusers. They are more likely to have an episode of major depression[7], suicidality[8], and are at an increased risk for future drug abuse problems[9]. In drug addiction, functional imaging has proven to be very sensitive to detect cerebral blood flow and metabolism derangement early

in the course of this condition[10].This study focuses on single photon emission computed tomography (SPECT) study in patients with neuropsychiatric symptoms caused by N_2O abuse.

Methods

Subjects

sixteen patients that exhibited neuropsychiatric symptoms caused by N_2O abuse between February 2018 and August 2020 were enrolled. Enrollment criteria: (1) A history of N_2O inhale; (2) The patient's performance must comply with the diagnostic criteria of Inhalant-Related Disorders, as coded according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-V). (3) The Brief Psychiatric Rating Scale (BPRS) score > 35 points. Exclusion criteria: the neuropsychiatric symptoms caused by other disease or mental disorders.

This study was approved by the Ethics Committee of China-Japan Friendship Hospital. The trial number is *2018-34-K25*. Written informed consent was obtained from all the participants.

Clinical data collection

All the patients underwent a standard neurologic examination conducted by a neurologist，who registered the clinical data and analysised neuroimaging studies, and laboratory tests. Mental state examination and neuropsychological rating scale were assessed by a psychiatrist, including:（1）The Brief Psychiatric Rating Scale, (BPRS)，（2）Hamilton Depression Scale (HAMD)，（3）Hamilton Anxiety Scale (HAMA)，（4） mini-mental state examination (MMSE)，（5）Montreal cognitive assessment (MoCA).

Single photon emission computerized tomography（SPECT

SPECT scans were performed on a conventional dual-head gamma camera system (Symbia T2, Siemens Medical Solutions, Germany) equipped with low-energy-high-resolution parallel hole collimators. Brain perfusion imaging was performed for 20 min followed by intravenous injection of 25-30mci ^{99m}Tc ethylcysteinate dimer (ECD) (radiochemical purity > 95%, HTA Co. Ltd, Beijing, China) in a dimly lit and quiet room with the patient’s eyes closed. Projection images were acquired through a 20% window centered on the 140 keV peak. The scan time per view was 25s, and the matrix was 256×256. Each SPECT image was segmented into 18 regions of interest (ROI) automatically and calculated by database comparison software. The difference statistics from the average uptake value of each brain region was calculated automatically.

The statistic was calculated by means of equation:

$$statistic = \frac{(PatientValue - PopulationMean)}{PopulationStandardDeviation}$$

Statistic 1.68 indicated the increase of local CBF perfusion, while -1.68 indicated the decrease of local CBF perfusion. Statistic was normal between -1.68 to 1.68.

Statistical analysis

All continuous variables were presented as mean ± standard deviation. After SPECT image reconstruction, database comparison software was used for automatic processing and analysis. Eighteen brain regions (basal ganglia, central region, cerebellum, cingulate gyrus, frontal lobe, medial temporal lobe, occipital lobe, parietal lobe, temporal lobe) were calculated automatically. Paired sample t-test was performed on left and right brain regions. One-way ANOVA followed by least significant difference (LSD) test was used to compare the averages and variances among different brain regions. $\chi 2$ test was used to compare the changes of regional cerebral blood flow (rCBF) in different brain regions, $P < 0.05$ was considered statistically significant.

Results

Demographic and Clinical Features

There were 8 male and 8 female patients with an onset age range between 18 and 29 years old (mean age 21.56 ± 2.83 years). The duration of N_2O exposure varied from 3 to 36 months (mean 17.88 ± 11.23 months). The course of disease varied from 0.5 to 4 months (mean 1.81 ± 1.09 months). Nonmedical abuse of more than one substance was found in 4 patients. Case 1, Case 7, Case 8, and Case 10 abuse both N_2O and Cannabinoid. Eight patients were self-medicated with methylcobalamine prior to their hospital admission.

Clinical features of N_2O abuse resulting in neuropsychiatric disorders were illustrated in the Table 1, including mood lability, anxiety, hallucination, delusion, Agitated, Confusion, and other psychiatric symptoms. In addition, 15 patients of them also complained their memory decline. 14 patients manifested as numbness or paresthesias. 14 patients developed limb weakness, whose motor impairments were more severe in lower limbs than upper limbs. 8 patients also accompanied by urinary and defecation disturbance.

Table 1
Clinical features of N_2O abuse resulting in neuropsychiatric disorders

Clinical features	number of patients	%
Confusion	7	43.75
Hallucination	13	81.25
Delusion	11	68.75
Panic attacks	5	31.25
bizarre behavior	6	37.50
Manic	1	6.25
Agitated	7	43.75
anxiety	12	75.00
Mood lability	16	100.00
Suicide ideation	4	25.00
Forgetfulness	15	93.75
Numbness or paresthesias	14	87.50
Weakness	14	87.50
urinary disorder	8	50.00

The laboratory findings were shown in Table 2. Vitamin B12 levels were normal (893.00 ± 414.19 pmol/L) in the 9 self-medicated patients with methylcobalamine before admission, homocysteine levels were still high in 4 of these patients. Among the remaining 7 patients who unmedicated with methylcobalamine before admission, vitamin B12 levels (133.30 ± 64.12 pmol/L) were low in 4 patients and low-normal in the remaining 3 patients. The homocysteine levels were high in all of the unmedicated patients (62.07 ± 38.73 μmol/L). Anemia was detected in 6 patients.

Table 2
Laboratory findings of N_2O abuse resulting in neuropsychiatric disorders

	Unmedicated with methylcobalamine before admission (N = 7)		Self-medicated with methylcobalamine before admission (N = 9)	
	Mean ± SEM	Range	Mean ± SEM	Range
Vitamin B12 (133–675 pmol/L)	133.30 ± 64.12	76.00-237.00	893.00 ± 414.19	221.00-1476
Homocysteine (≤ 15μmol/L)	62.07 ± 38.73	24.68-128.56	18.50 ± 13.06	8.00-47.57
Hemoglobin (115–150 g/L)	116.29 ± 22.69	87.00-158.00	131.56 ± 22.42	103.00-160.00
MCV (82–100 fL)	92.20 ± 6.33	81.70-101.80	93.49 ± 10.68	77.30-112.7

Neuropsychological Rating Scale

Data of neuropsychological rating scale were illustrated in the Table 3. BPRS score was 54.69 ± 11.48 (anxiety depression factor score was 3.88 ± 0.47; The lacking active factor score was 3.11 ± 0.82; The thinking disturbance factor score was 2.91 ± 1.23; Activity factor score was 2.06 ± 0.66; The hostility factor score was 2.98 ± 1.17), The score of self-knowledge impairment was 2.88 ± 0.96, the score of inability to work was 4.25 ± 1.13, the score of HAMD was 30.00 ± 11.06, the score of HAMA was 18.06 ± 5.77, the score of MMSE was 28.06 ± 2.29 (Two patients scored less than 27), and the score of MoCA was 25.06 ± 3.40 (Seven patients scored less than 26).

Table 3
Neuropsychological rating scale

Rating Scale		score
BPRS factors	anxiety depression factor	3.88 ± 0.47
	The lacking active factor	3.11 ± 0.82
	The thinking disturbance factor	2.91 ± 1.23
	Activity factor	2.06 ± 0.66
	The hostility factor	2.98 ± 1.17
BPRS score		54.69 ± 11.48
HAMD		30.00 ± 11.06
HAMA		18.06 ± 5.77
MMSE		28.06 ± 2.29
MoCA		25.06 ± 3.40

Spect Studies

Regional uptake statistics of 99mTC-ECD between patients and normal people of the same age group from background software database were shown in Table 4. There was no statistical significance in the t-test results of left and right uptake statistics (P 0. 05). There were no significant difference between brain regions (F = 5. 919,P < 0.01). There were significant differences in the changes of rCBF in different brain regions (P 0. 01). Although, brain MRI was normal in all patients, SPECT showed hypoperfusion in the frontal lobe (9/16, 56.25%) and the temporal lobe (12/16, 75.00%), which consistent with the clinical findings (Table 5 and Fig. 1).

Table 4

Regional uptake statistics of ^{99m}TC-ECD between patients and normal people of the same age group

ROI	Left (Mean ± SEM)	Right (Mean ± SEM)	Average (Mean ± SEM)	Pearson correlation
Basal ganglia	-1.094 ± 2.519	-1.200 ± 2.338	-1.147 ± 2.391	0.942
Central region	0.350 ± 1.116	0.694 ± 0.990	0.522 ± 1.052	0.681
Cerebellum	-0.638 ± 1.480	-0.469 ± 1.940	-0.553 ± 1.699	0.907
Cingulate and paracingulate gyri	0.59375 ± 1.885	0.543 ± 2.202	0.568 ± 2.017	0.747
Frontal lobe	-1.575 ± 1.598	-1.925 ± 1.593	-1.743 ± 1.579	0.792
Medial temporal lobe	0.237 ± 1.862	-0.018 ± 2.660	0.109 ± 2.262	0.912
Occipital lobe	-0.793 ± 1.958	-0.775 ± 1.688	-0.784 ± 1.799	0.579
Parietal lobe	0.206 ± 2.063	0.400 ± 1.559	0.303 ± 1.801	0.800
Temporal lobe	-2.05 ± 1.580	-1.662 ± 0.879	-1.856 ± 1.273	0.692

Table 5
Regional cerebral perfusion changes of N_2O abuse resulting in psychiatric disorders

ROI	numbers(%)		
	no change	increased perfusion	decreased perfusion
Basal ganglia	10 (62.50%)	1 (6..25%)	5 (31.25%)
Central region	12(75.00%)	4 (25.00%)	0 (0.00%)
Cerebellum	9 (56.25%)	2 (12.50%)	5 (31.25%)
Cingulate and paracingulate gyri	6 (37.50%)	6 (37.50%)	4 (25.00%)
Frontal lobe	7 (43.75%)	0 (0.0%)	**9(56.25%)**
Medial temporal lobe	9 (56.25%)	4 (25.00%)	3 (18.75%)
Occipital lobe	8(50.00%)	3(18.75%)	5 31.25%)
Parietal lobe	9 (56.25%)	4 (25.00%)	3 (18.75%)
Temporal lobe	4 (25.00%)	0 (0.0%)	**12 (75.00%)**

Discussion

N_2O is colloquially known as "hippy crack'" or "laughing gas". It is increasingly taken recreationally for its euphoric and relaxing effects and hallucinogenic properties. The abuse of N_2O is a significant public health concern, predominantly affecting adolescents. Although the subacute combined degeneration of the spinal cord and peripheral neuropathy caused by N_2O abuse are gradually concerned as the most common neurological damage[3, 4], the psychiatric symptoms and cognitive dysfunction caused by N_2O abuse have not received so much attention[11, 12]. Patients enrolled in this study all consumed large amounts of N_2O for a long time before the onset of neuropsychiatric symptoms. Their psychiatric symptoms included emotional symptoms (such as mania, depression, anxiety, and fear), psychotic symptoms (hallucinations, delusions), personality changes, and impulsive and aggressive behavior, in keeping with previous reports[13]. The anxiety and depression factor score was the highest in the BPRS score, which was consistent with the HAMD and HAMA scores suggesting that the patient must have symptoms of anxiety and depression. Thinking factors (including: disorder of concept, exaggeration, hallucinations, and abnormal thinking content) have high factor scores, indicating that patients with positive psychotic symptoms are prominent, and affect self-awareness and ability to work and study. The lack of vitality factor scores in the BPRS scores indicates that in addition to the positive symptoms, the negative symptoms are also more prominent. This is not reported in previous studies. The relationship between this negative symptoms and long-term prognosis and brain function needs further follow up.

Fifteen of the 16 patients and their families complained of unresponsiveness and decreased memory. Seven of them had a MoCA score less than 26, indicating that there was a decline in cognitive function

(including memory loss, inattention, executive function decline, etc.). Both of psychiatric symptoms and cognitive dysfunction result in the decline of work and life ability.

Chronic N_2O poisoning is related to the interference of vitamin B12, inactivates methionine synthase, interferes with myelin anabolic metabolism, and also results in the accumulation of homocysteine[14]. High homocysteine causes oxidative stress and mitochondrial dysfunction, leading to nerve demyelination[15]. Homocysteine activates N-methyl-D-aspartate receptors on neuronal cell membranes, induces calcium ions to flow into neurons, and mitochondrial calcium overload, eventually leading to neuronal necrosis and apoptosis[16]. Eleven of the 16 patients in this study had elevated serum homocysteine levels, and only 4 had decreased levels of vitamin B12, which may be related to the 9 patients who had self-medicated with mecobalamin before their visit to our department. This result suggests that elevated serum levels of homocysteine are more sensitive indicator than decreased serum levels of vitamin B12 for diagnose[14].

Although the brain MRI of the patients enrolled in this study showed that the brain structure was normal, rCBF changes in different brain regions were different in this study. There are local decreased or increased blood perfusion in several brain regions rather than diffuse decreased blood perfusion. The main findings were hypoperfusion in the frontal lobe and the temporal lobe, which in accordance with the clinical manifestations of mental behavior abnormalities and cognition Functional decline caused by N_2O abuse.

N_2O as an NMDAR antagonist, similar to ketamine, can reduce the signaling of excitatory glutamate neurons, change the structure and function of hippocampal synapses, cause learning and memory disorders. Short-term N_2O exposure can cause reversible vacuolation of neurons, and long-term abuse can lead to neuron death[17]. The psychiatric symptoms and cognitive decline in these patients may be dominated by this injury mechanism. Therefore, it is worth to further study the changes of neurotransmitters caused by N_2O abuse and how they affect the learning and memory function of adolescents.

In the treatment of patients with neuropsychiatric symptoms caused by N_2O abuse, in addition to supply vitamin B12 for nerve repair, we should also perform neuropsychological testing in time to strengthen interventions for mental symptoms and enhance patient compliance, which will not only improve the prognosis of patients, but also help Prevent relapse[18].

Previous studies have shown that N_2O abuse may induce manic relapse in patients with mood disorders[19]. The occurrence of psychiatric symptoms in this study is consistent with the clinical characteristics of substance-induced mental disorders, which indicate that N_2O abuse can induce mental disorders. It is need to expand the sample size to further explore the pathogenesis and disease characteristics of N_2O-induced mental disorders.

Because most of patients reported initiation of N_2O use in late adolescence or early adulthood with risks to their still developing brain[20], education about the N_2O abuse is necessary to prevent impaired brain development. Follow up and further investigate the possible effects of N_2O on brain development in young people will lead to meaningful prevention.

Conclusions

It was the first study to demonstrate obvious effect of N_2O abuse on CBF in patients with neuropsychiatric symptom. CBF perfusion imaging is helpful to detect the changes of rCBF in patients with N_2O abuse, which can indicate changes in local brain functional activity early.

Declarations

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Conflict of Interest / Competing interests

The authors declare that they have no competing interests.

Ethics approval

This study was approved by the Medical Ethics Committee of China-Japan Friendship Hospital. The trial number is: *2018-34-K25*.

Consent to participate

Written informed consent was obtained from all the participants or his/her parents/legal representatives (for participant under 18 years old).

Consent for publication

All the participants or his/her parents/legal representatives (for participant under 18 years old) gave their consents for information about the participants to be published.

Availability of data and material

The data sets generated and analyzed during this study are available with the approval of the corresponding authors.

Authors' contributions

FL and CT have full access to all the data in the study and takes responsibilities for the integrity of the data and the accuracy of the data analysis. Study concept and design: LW, FL and CT. Acquisition of data: LW, QW, MD and XD. Neuropsychological rating: CT, RW and ZL. Magnetic Resonance Imaging: WH. SPECT/CT imaging: LY and YZ. Analysis and interpretation of data: LW, QW, and FL. Drafting of the manuscript: LW and FL. Critical revision of the manuscript for important intellectual content: All authors. Obtained funding: LW. Supervised the study: FL, CT and LW. All authors read and approved the final manuscript.

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Figures

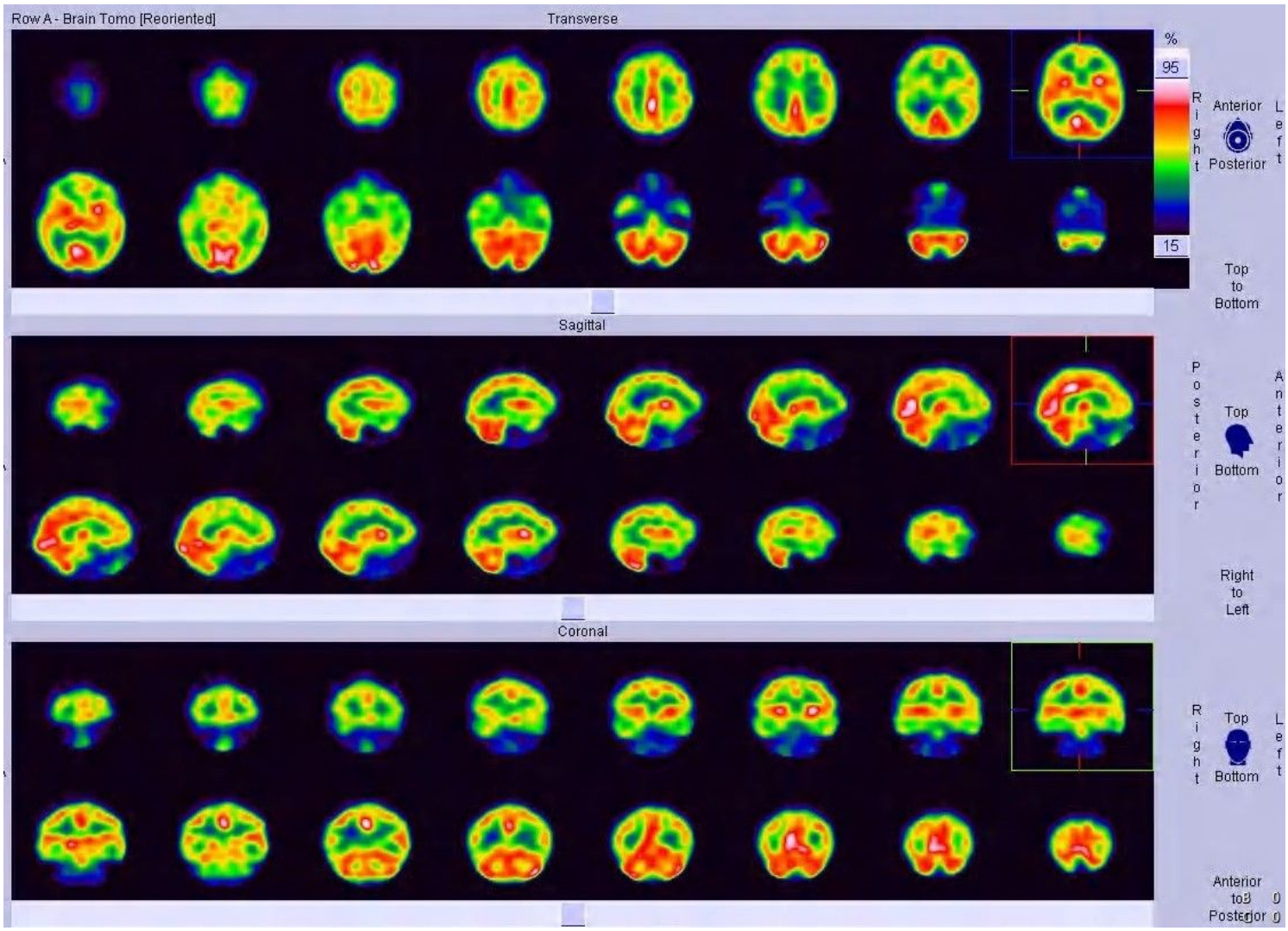

Figure 1

SPECT images of Case 2, a 19-year-old man. The Tc-99m-ECD SPECT images of Case 2 shows hypoperfusion in the diffuse cerebral cortex, especially in the frontal and temporal cortex.

Supplementary Files

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