

Short communication

Frontal-lobe syndrome and psychosis after damage to the brainstem dopaminergic nuclei

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Abstract

A patient developed frontal-lobe syndrome and psychotic symptoms after infarction in the pontomesencephalic junction. Stereotaxic lesion localization on magnetic resonance imaging and statistical analyses of regional cerebral blood flow (rCBF) disclosed an involvement of the rostral brainstem dopaminergic nuclei and hypoperfusion in the frontal-subcortical circuit components. We suggest that the patient's cognitive and behavioral disturbances were associated with disruption of ascending dopaminergic projections to the frontal-subcortical circuits.

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1. Introduction

Dopaminergic neurons in the rostral brainstem innervate the frontal cortices, limbic structures, ventral striatum, and thalamus, forming the mesocorticolimbic dopaminergic system (MDS) [1–3]. Animal studies have provided evidence of involvement of the MDS in cognition, motivation, and the sleep–wake cycle. Although abnormalities of the MDS have been implicated in psychoses, schizophrenia, and cognitive and behavioral symptoms in Parkinson's disease and dementia with Lewy bodies [3,4], human evidence of circumscribed damage to the rostral brainstem dopaminergic nuclei or their projections to the telencephalon is scarce [5].

We performed stereotaxic lesion localization on magnetic resonance imaging (MRI) and statistical analyses of regional cerebral blood flow (rCBF) in a patient who developed frontal-lobe syndrome and psychotic symptoms after infarction in the pontomesencephalic junction. The results suggest that the patient's symptoms are ascribable to disruption of the ascending dopaminergic projections to the frontal-subcortical circuit components.

2. Report of a case

A month before referred to our hospital, a 74-year-old woman suddenly developed visual and auditory hallucinations, visual illusions, and nocturnal roaming. The patient had no metabolic problems or medication history that may have affected her behavior and cognitive function. She complained of “floods pouring out from the bureau drawer,” that “the door looks distorted,” and “I hear an old popular song about a sad love affair playing all day”. She roamed around in her house in the middle of the night and served cups of coffee to guests who were not there. The visual hallucinosis and nocturnal

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Table 1
Results of neuropsychological tests

Neuropsychological tests [full score]	1 month after the onset	2 months	4 months
Mini mental state examination	21*	27	30
WAIS-R VIQ/PIQ/FIQ		107/91/99	
WMS-R verbal/visual/ general memory index / attention/delayed recall		89/112/98/ 91/94	
Category fluency (/min)	7*	10*	10*
Raven's colored progressive matrices		28	
Trail making test A/B (sec)		195*/ gave up*	
Color-form sorting initial/ altered sorting		Achieved/ failed*	
Porteus maze (years)		9*	
Tower of Toronto 3 discs		Gave up*	
Wisconsin card sorting test categories/perseveration		4/31	

Asterisks indicate defective performance scores.

WAIS: Wechsler Adult Intelligence Scale-Revised; WMS-R: Wechsler Memory Scale-Revised.

restlessness disappeared after a few days, but she lost spontaneity and occasionally complained that she was useless.

On her first visit to our hospital, one month after the onset of her symptoms, the patient showed evidence of apathy, psychomotor retardation, and mild depression. Neurological examination revealed hypophonia and postural instability. There was no evidence of other parkinsonian signs, such as rigidity and resting tremor, pyramidal signs, or cranial nerve abnormalities. Her vision and hearing were normal, and she scored 21 on the Mini Mental State Examination (MMSE). One month later, she was admitted to our hospital for further investigation.

On admission, the patient still had auditory hallucinations and visual illusions, but her spontaneity and cooperation were considerably improved, and the hypophonia and postural instability had completely resolved. She achieved 27 on the MMSE and performed poorly on tests of executive function, including color-form sorting, Porteus Maze, Trail Making Test, and Tower of Toronto (Table 1). She had no

impairment of memory, language, or visuospatial abilities. Her residual symptoms subsided spontaneously without any specific treatment, and she achieved a full score on the MMSE 4 months after the onset of her symptoms.

3. Neuroimaging

MRIs revealed an infarct in the left upper pons and a small previous infarct, which was already known about, with a diameter of 0.5 mm in the dorsocaudal part of the left external globus pallidus (Fig. 1A and B). A stereotaxic lesion analysis was performed on 3D-SPGR images (256×256 matrices, 220 mm field of view, 1.0 mm thick). Sections reconstructed parallel to the plane through the mamillary body and posterior commissure were superimposed over the corresponding atlases at the levels of the middle and lowermost margin of the inferior colliculus [6]. The lesions involved the parabrachial pigmented nucleus (PBPG) and the medial substantia nigra pars compacta (SNc) (Fig. 1C and D). The corticospinal tract and cranial nerves and their nuclei seemed to have been spared.

Regional CBF was assessed using *N*-isopropyl-*p*-[¹²³I] iodoamphetamine (IMP)-single photon emission computerized tomography (SPECT) at 1 month and 4 months after the onset. The SPECT data were collected in 64×64 matrices, and were reconstructed in sections parallel to the anterior commissure–posterior commissure plane with 8 mm thickness. The count of each voxel was normalized to the average voxel count of the whole brain. *Z*-score maps were produced with the easy *Z*-score Imaging System (Daiichi Radioisotope Laboratory, Tokyo, Japan), in which SPM99 (The Wellcome Department of Neurology, London, UK) implements anatomical standardization and smoothing algorithms [7]. Based on the rCBF images of 20 healthy subjects (mean age 65.6 years, SD=10.6), normative mean and standard deviation (SD) images were constructed. Then each of the patient's voxel values was converted to a *Z*-score ($Z = [\text{individual value} - \text{normative mean}] / \text{normative SD}$). A *Z*-map showing voxels exceeding the threshold of *Z*-score > 1.7 (one-tailed $p < 0.05$) was demonstrated on the standardized anatomical space. At the first session, the regions with decreased rCBF included the dorsolateral and medial

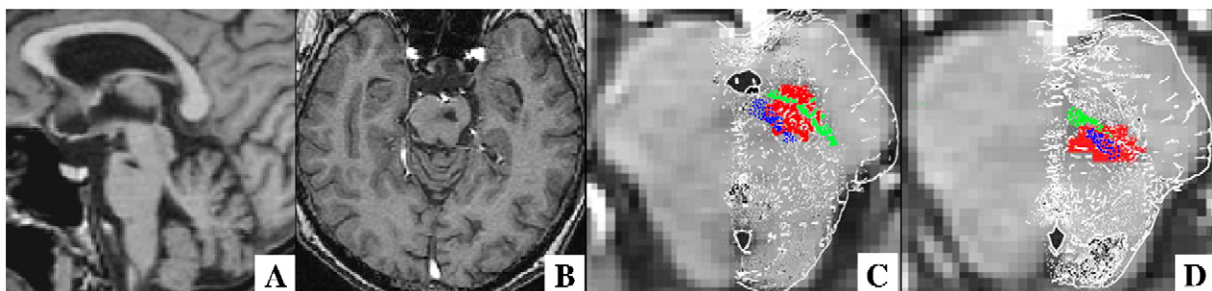


Fig. 1. MRIs showing an upper pontine infarct (A and B). Sections reconstructed parallel to the plane through the mamillary body and posterior commissure were indicated with the corresponding atlases at the levels of the middle (C) and lowermost margin (D) of the superimposed inferior colliculus. The colored areas indicate the lesion (red), the substantia nigra pars compacta (green), and the parabrachial pigmented nucleus (blue).

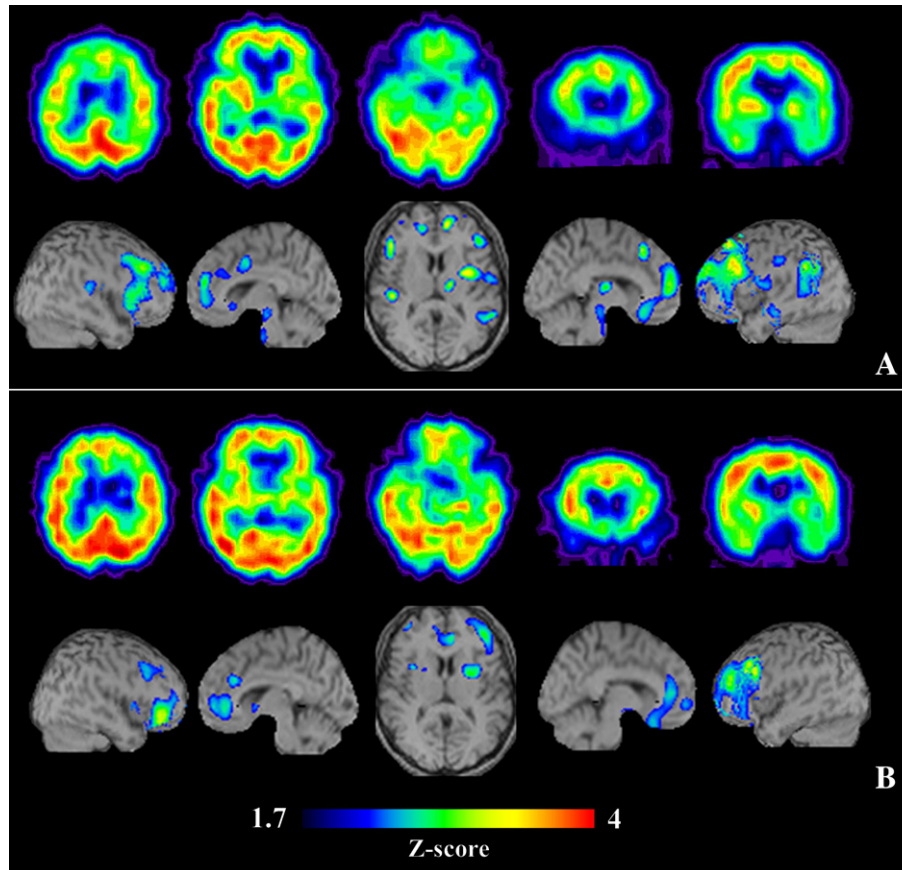


Fig. 2. rCBF images and Z-maps of the first (A) and second (B) SPECT sessions. The colored areas indicate regions with decreased rCBF of Z-score > 1.7 (one-tailed $p < 0.05$). The regions with decreased rCBF include the dorsolateral and medial prefrontal cortices, the anterior cingulate cortex bilaterally, and the left medial thalamus and temporo-parietal junction at the first session (A). Hypoperfusion was substantially improved 2 months later, when the symptoms had resolved (B).

prefrontal cortices, anterior cingulate cortex bilaterally, and the left medial thalamus and temporo-parietal junction (Fig. 2A). The second examination, which was performed after the patient's symptoms subsided, showed improvement of rCBF in these structures (Fig. 2B).

4. Discussion

The patient described here developed apathy and executive dysfunction after a rostral brainstem infarct. These symptoms are similar to those of frontal-lobe damage and are often observed in diseases involving subcortical structures, e.g., striatal and thalamic vascular diseases, progressive supranuclear palsy, and Huntington's disease [8]. These types of frontal-lobe-like syndromes associated with subcortical lesions arise from disruption of the frontal-subcortical circuits. The dorsolateral prefrontal cortex (DLPFC), orbitofrontal cortex (OFC), and anterior cingulate/medial prefrontal cortex (ACC/MPFC) form parallel closed circuits with the striatum, pallidum, substantia nigra, and thalamic nuclei. Different types of cognitive and behavioral syndromes emerge subsequent to disruption of each circuit: (i) a dorsolateral prefrontal syndrome with impaired "executive" cognitive function, (ii) an orbitofrontal syndrome with personality changes charac-

terized by disinhibition and irritability, and (iii) an anterior cingulate/medial prefrontal syndrome with marked reduction of spontaneity. Since these circuits share common subcortical components, diseases affecting the subcortical structures result in mixed symptoms of more than one distinct circuit [9,10]. As with these cases, our patient, who suffered from rostral brainstem infarction, developed "mixed-type" frontal-lobe syndrome. Corresponding to the clinical features, such as apathy and executive dysfunction, rCBF reduction was found in both ACC/MPFC and DLPFC on SPECT.

Our patient developed psychotic symptoms, i.e. hallucinations and delusions, and disturbance of the sleep-wake cycle as well as a frontal-lobe syndrome. Hallucinations associated with rostral brainstem lesions was first described in the early 20th century and is known as "peduncular hallucinosis" [11]. Disruption of the ascending modulatory neurotransmitter system has been proposed as a putative pathomechanism. The lesion in our patient involved the PBPG and medial SNc in the upper pons, which are the caudal extension of the dopaminergic nuclei of the ventral midbrain [6]. These structures project to the prefrontal cortices, limbic structures, ventral striatum, and thalamus, forming the MDS [1–3]. Besides the rostral brainstem, hallucinations and delusions are observed in damage to the ventral striatum and paramedian thalamus

[12,13]. This constellation of anatomical locations suggests that disruption of the MDS is a crucial factor in the emergence of hallucinosis. Although serotonergic and cholinergic dysfunction reportedly contributes to the emergence of hallucinations, the serotonergic and cholinergic nuclei, e.g., the suprallemniscal nucleus, median raphe nucleus, and pedunculopontine and dorsolateral tegmental nuclei, were not involved in our patient.

We found rCBF reduction also in the left temporo-parietal cortex at the first SPECT session. The projections arising from the rostral brainstem dopaminergic nuclei dominate in the frontal cortices but also terminate in the posterior cortical regions [6,14]. Hypoperfusion in the temporo-parietal cortex is explicable as a remote effect of the brainstem lesion. Hypoperfusion in this region was circumscribed and transient in contrast to wide-spread frontal hypoperfusion. These SPECT findings are consistent with the patient's symptoms, i.e. predominant frontal-lobe symptoms and lack of parietal symptoms such as alexia, agraphia, and constructive deficit.

Clinical observations and the results of neuroimaging analyses suggest that our patient's frontal-lobe-like and psychotic symptoms are ascribable to damage to the rostral brainstem dopaminergic nuclei and its projections to the frontal-subcortical circuit components. Our findings provide human evidence of a significant role of the rostral brainstem dopaminergic neurons in cognition and behavior and a functional relationship between the MDS and frontal-subcortical circuits. However, there is a possibility to underestimate an involvement of the other regions other than the frontal cortices because our SPECT analyses were based on relative rCBF decrements not on absolute ones. In addition, direct association between the observed symptoms and SPECT findings is not clarified in this case report. To confirm our findings, it is necessary to analyze the relationship between neuroimaging findings and behavioral characteristics in a greater number of the patients with the rostral brainstem damage. Despite some limitations, we believe that the present results have important implications for understanding the pathomechanisms of psychoses, schizophrenia, and cognitive and behavioral problems in Parkinson's disease and dementia with Lewy bodies.

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