Concomitant Sympathetic and Parasympathetic Dysfunction after Acute Ischemic Stroke

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Abstract

Purpose: Autonomic dysfunction is an underrecognized complication of acute ischemic stroke. The cortical regulation of sympathetic activation is predominantly lateralized to the right hemisphere and parasympathetic activation to the left hemisphere. However, prior evidence is lacking regarding ischemic lesions in unilateral hemisphere that concomitantly cause sympathetic and parasympathetic dysfunction.

Case report: We present the case of a 73-year-old woman with acute ischemic stroke in the left middle cerebral artery territory, whose neurological symptoms improved significantly after thrombolysis and endovascular thrombectomy. She presented residual scattered small infarctions involving the left insula and lateral parietal cortex. However, she experienced obvious autonomic symptoms that included orthostatic hypotension, which is indicative of sympathetic dysfunction, and micturition difficulty with exaggerated reflex tachycardia, indicative of parasympathetic dysfunction. The sympathetic and parasympathetic functions sequentially resolved on days 10 and 20 after stroke onset, respectively.

Conclusion: The case revealed insight into the phenomenon and recovery course of concurrent sympathetic and parasympathetic dysfunction associated with ischemic lesions in the left hemisphere.

Keywords: acute ischemic stroke, unilateral hemisphere, autonomic dysfunction, insula, parietal lobe.

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INTRODUCTION

The insula and parietal lobe are important components of the autonomic network of the brain and play key roles in autonomic regulation[(1)]. Since the two regions are supplied by the middle cerebral artery (MCA), they are often affected by ischemic stroke and may contribute to disturbances of the autonomic system. Patients with insular infarction tend to have elevated plasma catecholamines and a variety of cardiovascular complications, such as new-onset atrial fibrillation, decreased heart rate variation, and impaired baroreflex sensitivity[(2)]. The impact of insular

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lesions on the sympathetic system may be caused by reduced modulation of the hypothalamus and enhancement of sympathetic outflow[3]. Furthermore, high stroke severity has been shown to be associated with autonomic dysregulation shifting toward sympathetic dominance[4].

The central regulation of the autonomic system is characterized by cortical lateralization[5]. The control of sympathetic activation is predominantly lateralized to the right hemisphere, and that of parasympathetic activation is localized to the left hemisphere[6]. However, a prior study showed that infarctions involving the right insular cortex may result in pathological sympathetic activation of the cardiovascular system[7]; while left insular infarction may shift the cardiovascular balance towards increased basal sympathetic tone and reduced heart rate variability[8].

In addition to the different autonomic roles of the insula on different sides, different parts of the insula, such as anterior, posterior, dorsal, and ventral portions, play different roles. A meta-analysis revealed that the dorsal anterior insula is bilaterally associated with parasympathetic regulation[9]. However, evidence is lacking about unilateral cerebral lesions that concomitantly cause sympathetic and parasympathetic dysfunction, and little is known about the recovery course of stroke-induced autonomic dysfunction. Here, we present a case of multiple small acute infarctions in the left MCA territory that involved the left insula and lateral parietal cortex, in a patient who experienced sympathetic and parasympathetic dysfunctions that sequentially recovered during the subacute phase of stroke.

Case

A 73-year-old woman without prior medical disease presented to the emergency department with sudden onset slurred speech followed by an inability to talk and right limb weakness for 90 min. Her initial blood pressure (BP) was 210/83 mmHg and heart rate (HR) was 90 beats per minute (bpm). The initial National Institutes of Health Stroke Scale (NIHSS) score was 11. A neurological evaluation revealed clear consciousness, right central type facial palsy, mild dysarthria, weakness with increased deep tendon reflex of the right limbs, positive Babinski sign on the right side, numbness on the right side, and minimal anomic aphasia.

Emergency non-contrast brain computed tomography (CT) showed that she did not have an intracranial hemorrhage. Subsequent CT angiography and perfusion study revealed hypoperfusion in the left MCA territory and segmental stenosis of the left MCA (Fig 1). She received tissue plasminogen activator (t-PA) treatment at 130 min after onset, and her NIHSS score improved to 4 during t-PA infusion.

However, right limb weakness and aphasia recurred one hour after thrombolysis, and her NIHSS score increased to 17, accompanied by relatively low BP, at 145-128 mmHg, and HR, of 85-86 bpm. Hydration was administered, but her symptoms fluctuated; thus, low-dose norepinephrine was infused to maintain systolic BP between 160 and 180 mmHg. Endovascular thrombectomy was performed four hours after admission, and complete recanalization was achieved (thrombolysis in cerebral infarction (TICI) score 3), then her NIHSS score reduced to 5. Tirofiban was administered for 24 h to treat intracranial artery stenosis, followed by aspirin and clopidogrel. While transient discontinuation of norepinephrine on day two, her BP suddenly dropped to 85/49 mmHg with heart rate 61 bpm, showing no reflex tachycardia in response to the hypotension. Therefore, norepinephrine was maintained for five days, with a gradual shift to midodrine. After excluding other hypotension etiologies, such as infection, hypovolemia, and heart disease, sympathetic dysfunction was suspected.

Brain magnetic resonance imaging (MRI) on day six showed multiple acute small infarctions in the left MCA territory, including the insula and lateral parietal cortex, and a tiny infarct in the right occipital lobe (Fig. 1). Regarding suspected autonomic dysfunction, the postural BP and HR measurements on day nine confirmed orthostatic hypotension (systolic BP reduction 23 mmHg from supine to standing) with exaggerated tachycardia (HR increment 25 bpm), indicating sympathetic dysfunction for orthostatic hypotension and probable parasympathetic dysfunction due to exaggerated reflex tachycardia (Table 1). In addition, the Foley catheter failed to be removed due to a lack of voiding effort but preserved bladder sensation, which was compatible with parasympathetic dysfunction.

The autonomic examination on day 10 showed a normal sympathetic skin response and reduced R-R interval variability, suggesting the recovery of sympathetic function with the persistence of parasympathetic

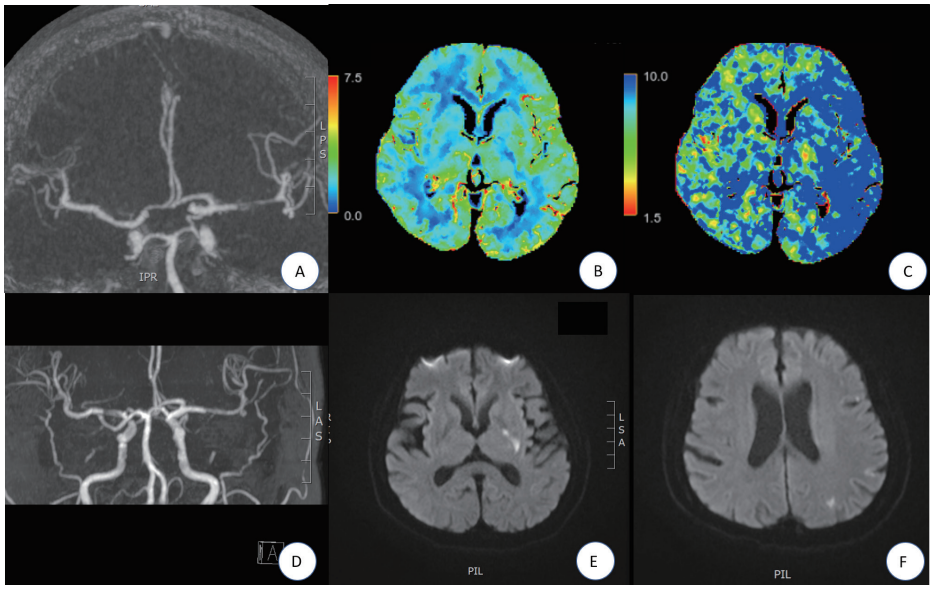

Figure 1. Brain CT and MRI findings of the patient

(A) CT angiography showed segmental stenosis of the left MCA. (B-C) CT perfusion image showed hypoperfusion of the left MCA territory without infarct core. (D) The MR angiography showed residual stenosis of the left MCA. (E-F) DWI of MRI showed infarct lesions at left insular cortex, putamen (E) and left parietal cortex (F).

dysfunction. Postural BP and HR measurements on the same day showed no orthostatic hypotension, but reflex tachycardia remained (HR increment 21 bpm) (Table 1), consistent with the findings of the autonomic examinations. The reflex tachycardia decreased (HR increment 12 bpm) on day 20, and her Foley catheter was also successfully removed on that day, indicating normalization of parasympathetic function.

Autonomic function was further evaluated using the COMPASS 31 score (Table 2)[10]. The COMPASS 31 score was 30 on day one and improved to 17 on day 20, with the greatest improvement in the domain of orthostatic intolerance.

Table 1. The serial blood pressure and heart rate related to postural changes of this patient

Day	Supine	Sitting 1 min	Sitting 5 min	Standing 1 min	Standing 5 min
Day 9	147/76 (77)	141/77 (83)	131/77 (97)	143/77 (102)	124/78 (102)
Day 10	127/77 (91)	130/77 (101)	117/74 (96)	125/82 (112)	125/82 (112)
Day 20	137/77 (84)	137/78 (88)	129/77 (91)	137/80 (96)	135/76 (96)
Day 24	129/79 (79)	160/75 (82)	159/80 (84)	152/78 (87)	149/79 (89)

Data were shown as blood pressure (heart rate)

Day: post-stroke day

Table 2. The COMPASS 31 score of this patient

	Orthostatic intolerance	Secretomotor function	Gastrointestinal function	Bladder function	Pupillomotor function	Total score
Day 1	7	3	9	3	8	30
Day 24	0	1	10	1	5	17

DISCUSSION

The patient presented with autonomic dysfunction that included orthostatic hypotension, exaggerated reflex tachycardia, and bladder dysfunction. The symptoms suggested concomitant sympathetic and parasympathetic dysfunction in the acute stage, after infarction in the left MCA territory. Her sympathetic function recovered first, followed by an improvement of parasympathetic function in the subacute stage of the stroke.

During orthostatic changes in a normal subject, the sympathetic and parasympathetic systems cooperate to regulate blood pressure and heart rate to avoid a drop in blood pressure. The heart rate increase elicited by upright posture was initiated by parasympathetic withdrawal and subsequently sustained by sympathetic stimulation via the β1 adrenergic effect[11,12]. The adrenergic efferent not only increases heart rate, but also enhances cardiac output and induces peripheral vasoconstriction of arterioles and venules to maintain the blood pressure[13]. The reflex tachycardia in this patient was not compatible with postural tachycardia syndrome, which is defined as a heart rate increment of > 30 bpm from supine to standing, usually without hypotension[14]. Postural tachycardia can be caused by low parasympathetic activity or exaggerated sympathetic efferent[14]. For this patient, the sympathetic function was inadequate, according to the orthostatic hypotension. Thus, the tachycardia was probably caused by compensatory reflex tachycardia with low parasympathetic activity.

The patient also presented micturition difficulties with a preserved bladder sensation. The discrepancy between motor and sensory functions of the bladder excluded the possibility of a pelvic nerve lesion[15]. The bladder voiding reflex stimulates the parasympathetic outflow to the bladder and urethral smooth muscle, causing contraction of the detrusor muscles via inhibition of sympathetic outflow and relaxation of the urethra via inhibition of pudendal outflow[16]. The micturition difficulty in the early stage of stroke in this case indicated parasympathetic dysfunction. This later improved simultaneously with the disappearance of the exaggerated reflex tachycardia, both indicating the improvement of parasympathetic function.

In this patient, we identified concomitant impairment of sympathetic and parasympathetic functions after acute cerebral infarction. Autonomic dysfunction occurring with mild stroke suggests that autonomic dysfunction is related to lesion location instead of stroke severity[3]. In this patient, the ischemic lesions contributing to the autonomic symptoms included the left insula and left lateral parietal cortex. The parasympathetic dysfunction after left insular infarction was in accordance with the findings of prior studies, which showed that the left insula is important for parasympathetic control. Damaging of the dorsal insular cortex on either side caused parasympathetic dysfunction[17], and stimulation of the left insula elicited more frequent bradycardia response[18]. In addition, a human brain functional mapping study showed that stimulation of the left insula elicited different heart rate responses according to stimulation sites. Specifically, stimulation of the left anterior insula induced bradycardia, while stimulation of the left posterior insula elicited tachycardia[19]. Although the minimal infarct at the left anterior insula contributed to parasympathetic dysfunction, the presence of other lesions that were negative on MRI at the left posterior insula was possible due to the large hypoperfusion area in the left MCA territory before endovascular treatment. The left lateral parietal cortex is another region controlling central autonomic tone[1] and has been associated with sympathetic function[9]. Therefore, the sympathetic dysfunction in this patient might be attributed to the left parietal lesion.

In conclusion, this patient demonstrated concomitant sympathetic and parasympathetic dysfunction after acute ischemic stroke involving the left MCA territory. The patient gradually regained sympathetic function, followed by a recovery in parasympathetic function. These findings revealed that the left insula and left lateral parietal cortex might play a role in the regulation of sympathetic and parasympathetic functions.

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