

Cortical hemichorea–hemiballism

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Abstract Hemichorea–hemiballism (HCHB) was infrequently related to cortical lesions such as tumor or infarction. Although functional derangement of the basal ganglia (BG) or the thalamus (Th) was suggested, pathomechanism of HCHB secondary to cortical lesions remains uncertain. We recruited the patients with HCHB secondary to cerebrovascular diseases, excluding other causes such as hyperglycemia. All the patients were studied with brain magnetic resonance imaging/angiography (MRI/MRA) and single-photon emission computed tomography (SPECT). Those with only cortical abnormalities in neuroimaging studies were sorted out as the cases of cortical HCHB. Statistical parametric mapping (SPM) analysis of SPECT was performed to investigate the pathomechanism of cortical HCHB. Ten patients (three males and seven females) were included in our study. Six patients had acute BG lesions with SPECT abnormalities, and one had old BG lesions with abnormal SPECT. Three patients were classified as cortical HCHB with lesions only in the frontal and parietal cortices in MRI and SPECT. SPM analysis revealed additional hypoperfusion in frontal areas, leaving BG and Th free of any perfusion abnormalities. Although cortical HCHB was strictly defined by MRI and SPECT, cortical HCHB was not uncommon (30 %). Further analysis showed intertwined

networks among the frontal and parietal lobes for cortical HCHB. Cortical dysfunction is important in the pathogenesis of cortical HCHB even without significant involvement of BG and Th.

Keywords Hemichorea · Hemiballism · Single-photon emission computed tomography (SPECT) · Statistical parametric mapping (SPM)

Introduction

Cortical lesions such as tumors or infarctions may be associated with hemichorea–hemiballism (HCHB) [1–10]. It remains uncertain whether such cortical lesions independently contribute to the pathogenesis of HCHB. Although dysfunction of the basal ganglia (BG) was assumed, functional studies investigating the role of the BG in patients with cortical lesions were rarely done with conflicting results [4, 5, 11].

In the present study, we studied cortical HCHB in which no evidence of BG or thalamus (Th) involvement was found by magnetic resonance imaging (MRI) or technetium-99m hexamethylpropylene amine oxime (^{99m}Tc -HMPAO) single-photon emission computed tomography (SPECT). We then tested the contribution of various brain regions to cortical HCHB using statistical parametric mapping (SPM) analysis of SPECT.

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Subjects and methods

Subjects

Clinical data were collected retrospectively. The Institutional Review Board at Kyung Hee University Hospital

reviewed and approved this protocol and exempted this study from the need to obtain informed consent.

Patients with HCHB and visible vascular lesions were included. All patients underwent 1.5T MRI scanning with T1- and T2-weighted imaging (T1WI and T2WI), fluid-attenuated inversion recovery imaging (FLAIR), and 99m Tc-HMPAO SPECT. In some patients with acute infarction, diffusion-weighted imaging (DWI) and apparent diffusion coefficient (ADC) mapping were done. As HCHB could be associated with diabetes mellitus (DM), those with poorly controlled DM (serum glucose ≥ 150 mg/dL or HbA1c ≥ 7.0 % at the time of presentation) or abnormal high signal intensities in the BG on T1WI scans (a characteristic of hyperglycemic HCHB) were excluded. Patients with no visible lesions in neuroimaging scans and non-vascular causes such as tumor were also excluded.

The control group for SPM analyses consisted of five females (mean age: 68.4 ± 9.3 ; range 60–84). Control subjects were retrospectively and randomly selected among patients who had visited our clinic for transient headache or dizziness. These subjects had no history of neurologic illness and were normal upon neurologic examination. Routine laboratory hematologic work-ups were unremarkable. Brain MRI, magnetic resonance angiography (MRA) and SPECT showed normal findings with minimal white matter change (<1 point using Fazekas' scale) [12].

Brain MRIs were reviewed and classified into three categories: (1) acute infarction confirmed by relevant clinical history, medical records, and abnormal signal intensities on T2WI and FLAIR images and in some cases substantiated by abnormal signal intensities in DWI and ADC mapping; (2) old lesion with clinical evidence as confirmed by clinical and radiological data; (3) incidental ischemic lesions in the BG and Th without any clinical evidence such as weakness. Extra- and intra-cranial vasculature was examined using MRA. White matter changes were evaluated using Fazekas' scale [12].

99m Tc-HMPAO SPECT and image analysis

Subjects lay in a supine position with eyes closed in a secluded examination room and were injected with 1,110 MBq (30 mCi) of 99m Tc-HMPAO in an antecubital vein. Images were acquired 10 min after injection. A triple-head SPECT scanner (MultiSPECT 3; Siemens, OH, USA) with low-energy, high-resolution fan-beam collimators (FWHM = 9.7 mm) was used. Each detector head acquired 40 projections over 120° with a 128×128 matrix. Transaxial, sagittal and coronal images were reconstructed by filtered back-projection using a Butterworth filter (cut-off frequency 0.32 cycles/pixel) and employing Chang's first-order method with an attenuation coefficient of $\mu = 0.12/\text{cm}$. As acetazolamide is useful in detecting impaired

vascular reservoir, another SPECT was retaken 30 min after administration of 1,000 mg of acetazolamide in those with steno-occlusion of major cerebral vessels.

Images were analyzed using SPM99 (Institute of Neurology, University College of London, UK) [13]. All images were spatially normalized into the MNI standard template (Montreal Neurological Institute, McGill University, Montreal, Quebec, Canada) to remove inter-subject anatomical variability before image analysis [14, 15]. Spatially normalized images were smoothed by convolution using an isotropic Gaussian kernel with 16-mm full-width at half-maximum. The count of each voxel was normalized to the total count of the brain (proportional scaling in SPM) to remove the differences in global cerebral blood flow (CBF) between individuals. After spatial and count normalization, statistical comparisons between groups were performed on a voxel-by-voxel basis using *t* statistics and generating SPM (*t*) maps. Perfusion abnormality was investigated at a height threshold of $P = 0.005$ (uncorrected) and an extent threshold of 200 voxels.

Results

Ten patients were included (three males and seven females; mean age: 67.5 ± 17.7 years). Three patients had well-controlled DM and six had hypertension.

Six patients (Cases 1–6) had acute infarction in the BG or subthalamic nucleus (STN; Table 1). They were presented with HCHB at onset. One patient (Case 7) had suffered a stroke 1 year before and visited us due to hemichorea. Repeated neuroimaging and laboratory work-ups 1 week after the onset of hemichorea were unremarkable except an old infarction in the BG. Seven patients (Cases 1–7) also showed abnormal perfusion in the BG (6 with hypoperfusion and 1 with luxury perfusion). Three patients (Cases 8, 9, 10) had only cortical lesions with normal SPECT images in the BG and Th (cortical HCHB). Two patients with cortical HCHB (Cases 8 and 9) had decreased perfusion or perfusion defects in the parietal cortex (Pc), whereas the third patient (Case 10) showed frontal cerebromalacia and abnormal perfusion in the Pc only after acetazolamide injection (Figs. 1b, 2b, 3b, c). SPM analyses showed additional hypoperfusion in the frontal cortices (Fc), including the supplementary motor area and premotor area in all the patients with cortical HCHB (Figs. 1c, 2c, 3d).

Case reports of cortical HCHB

Case 8

A 70-year-old woman was admitted because of involuntary movements of the right extremities. She had been healthy

Table 1 Clinical and radiological characteristics of the patients with hemichorea–hemiballism

Case	Sex	Age	Affected side	HTN	DM	DM lab	SPECT	MRI			MRA
								Acute infarction	Old lesions w/ clinical evidence	Incidental ischemic lesions in BG/Th	
1	F	80	Rt	0	0		Dec perfusion in Lt Put/CN/Th and Tc	Lt GP	(-)	(-)	3 Unremarkable
2	F	90	Rt	1	1	sGlu = 87 mg/dL HbA1c = 5.4 %	Dec perfusion in Lt Put/CN	Lt GP	(-)	Both Put	9 Unavailable
3	M	67	Lt	1	0		Dec perfusion in both Put/CN	Rt GP	(-)	Both Th	9 Unremarkable
4	F	40	Lt	0	0		Dec perfusion in Rt Th and Fc; Luxury perfusion in Rt Put/CN	Rt Put/CN	(-)	(-)	0 Unremarkable
5	F	67	Lt	1	1	sGlu = 82 mg/dL HbA1c = 6.5 %	Dec perfusion in Rt Th, both Put/CN	Rt STN	(-)	Lt Put	13 Lt MCA stenosis
6	M	77	Lt	1	1	sGlu = 133 mg/dL HbA1c = 3.9 %	Dec perfusion in Rt Put/CN and perfusion defect in Rt Pc, Tc and Oc	Rt STN	Rt Pc, Tc and Oc	(-)	1 Basilar artery stenosis
7	M	33	Lt	1	0		Perfusion defect in Rt Put/CN, Pc and Oc	Rt Pc, Tc, Put, GP	(-)	Rt MCA occlusion	0
8	F	70	Rt	0	0		Dec perfusion in Lt Pc	Lt Pc	(-)	(-)	3 Lt cavernous ICA stenosis
9	F	76	Rt	1	0		Dec perfusion in Lt Pc	(-)	Lt Pc and Tc	(-)	9 Lt MCA occlusion
10	F	75	Rt	1	0		Perfusion defect in Lt Fc (Dec perfusion in Lt Pc after acetazolamide)	Lt Fc	(-)	(-)	6 Both ICA occlusion

HTN hypertension, DM diabetes mellitus, lab laboratory findings, SPECT single-photon emission computed tomography, MRI magnetic resonance angiography, w with, WML white matter lesion (Fazekas' scale¹²), sGlu serum glucose level, HbA1c glycated hemoglobin, F female, M male, Lt left, Rt right, Th thalamus, GP globus pallidus, Put putamen, CN caudate nucleus, STN subthalamic nucleus, Fc frontal cortex, Tc temporal cortex, Pc parietal cortex, Oc occipital cortex, MCA middle cerebral artery, ICA internal carotid artery

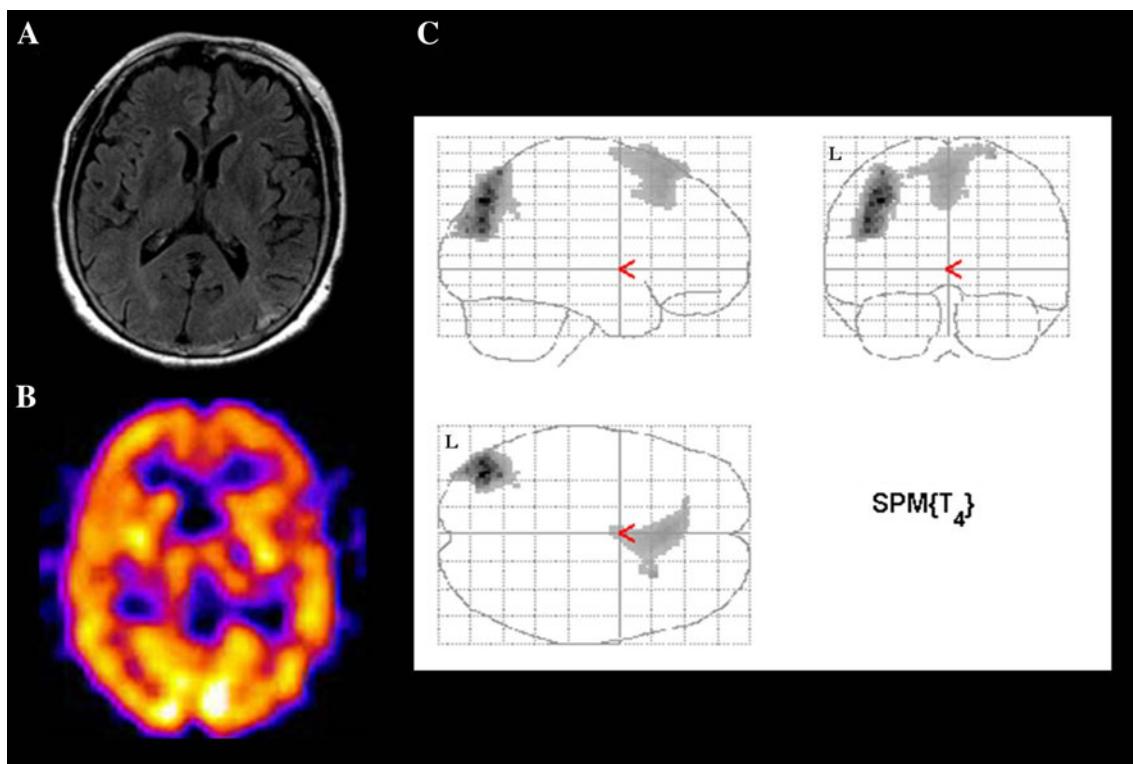


Fig. 1 Neuroimaging of Case 8. **a** Brain magnetic resonance imaging shows an infarction in the left parietal cortex. **b** 99m Tc-HMPAO single-photon emission computed tomography shows decreased perfusion in

the left parietal cortex and normal perfusion in the basal ganglia and the thalamus. **c** Statistical parametric mapping (*t*) map shows decreased perfusion in the parietal cortex and bilateral frontal cortices

without significant medical history such as DM and hypertension. The abnormal movements were continual, jerky, of large amplitude, and flinging movements of limbs, compatible with hemiballism. Neurologic examination including a cortical sensory examination was normal. Haloperidol was effective and used for 2 months. She had no further episodes of hemiballism without any medication over a follow-up of 4 years.

Case 9

A 76-year-old woman visited our clinic due to abnormal movements. She had a history of hypertension and right hemiparesis that began 2 months prior to her admission. Neurologic examination showed mild weakness in her right leg (4+/5) with normal sensation. Her involuntary movements were continuous, irregular, and of small amplitude, compatible with hemichorea. Cortical sensory examination was normal. She was free of hemichorea after treatment with clonazepam and valproic acid. She remained free of involuntary movements over 4 years of follow-up.

Case 10

A 68-year-old hypertensive woman was admitted due to recurrent episodes of involuntary movements. She had a

history weakness in her right leg after a stroke 15 years ago. Her involuntary movements began several months before admission to the clinic. The movements lasted a few minutes and occurred several times a month, sometimes up to twice a day without any identifiable provoking factors.

Carotid bruits were bilaterally audible. Neurologic examination showed mild weakness in the right leg (4+/5) with normal sensation. Cortical sensory examination was also normal. We observed one episode during admission. Her involuntary movements lasted about 2 min and were confined in right extremities. They were frequent, jerky, of large amplitude, and like flinging her limbs in the initial phase (about 45 s) and became less frequent and violent in the later phase (Video 1). She was responsive to our verbal questions during the episode. Her electroencephalography (EEG) was normal.

After discharge with aspirin, dipyridamole, clonazepam and valproic acid, she was followed for 3 months and reported only one episode of hemiballism. However, headaches and language abnormalities suddenly developed. A follow-up neurological examination showed right homonymous hemianopsia, ideational apraxia, and profound sensory aphasia. Her motor weakness did not change. A brain CT showed acute infarction in the left parieto-occipitotemporal area (Fig. 3e). She was discharged with aspirin and cilostazol. No additional episodes of hemiballism occurred over a follow-up of 5 years.

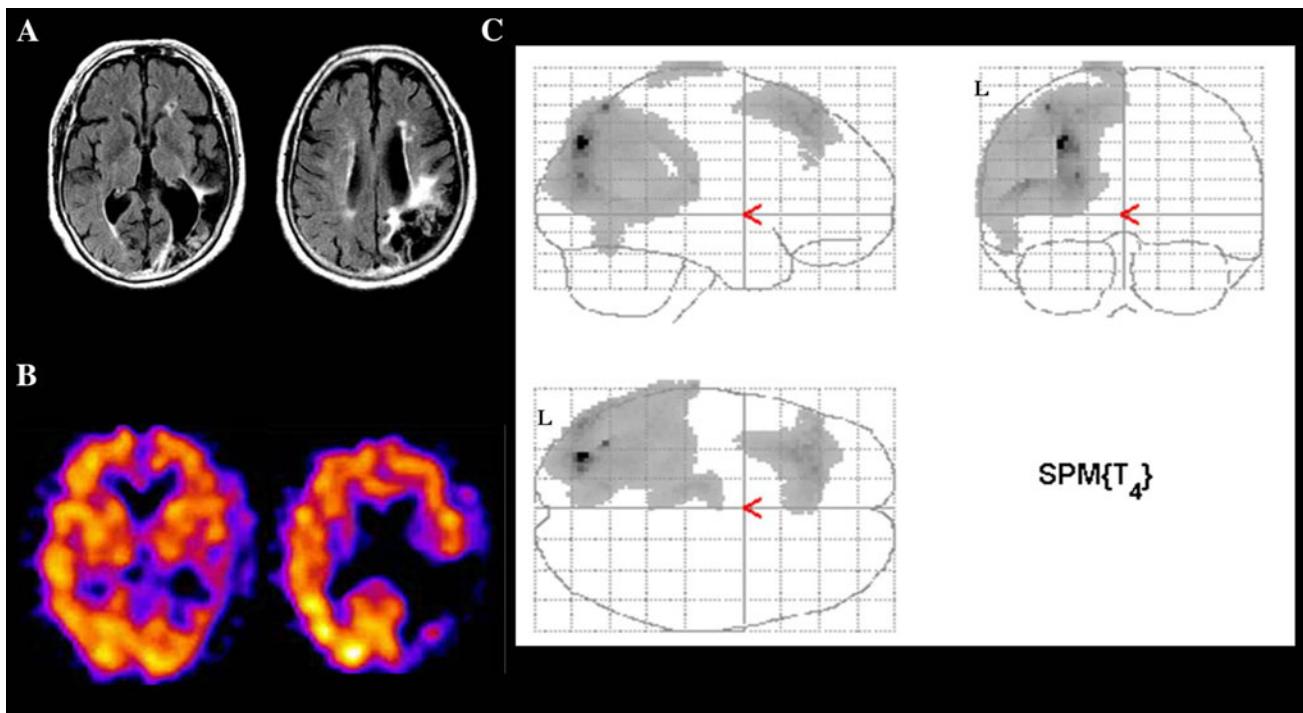


Fig. 2 Neuroimaging of Case 9. **a** Brain magnetic resonance imaging shows an infarction in the left parietotemporal cortex. **b** ^{99m}Tc -HMPAO single-photon emission computed tomography shows perfusion defect in the left parietotemporal cortex and normal perfusion

in the basal ganglia and the thalamus. **c** Statistical parametric mapping (t) map shows decreased perfusion in the frontal cortex in addition to perfusion defect in the parietotemporal cortex

Discussion

Previous case studies have reported an association between HCHB and cortical vascular lesions in 10–26 % of patients [7, 9, 10, 16]. Few functional studies have been done [4, 5]. Because patients with HCHB that is associated with cortical lesions have been loosely defined without functional studies of the BG or Th, cortical HCHB has not been identified as an independent entity [7, 9–11, 16, 17]. In the present study, only cases with normal findings in the BG and Th in both MRI and SPECT images were defined as having cortical HCHB.

Parietal lesions and hypoperfusion were characteristic of cortical HCHB in our patients (Figs. 1, 2, 3). Interestingly, in previous studies the Pc was reported to be most frequently affected in HCHB associated with cortical lesions as compared to other cortical areas [3–10, 18]. There has been only one recorded patient with sensory abnormalities contralateral to a parietal infarction, suggesting a pseudo-chorea secondary to a Pc lesion [3]. However, sensory abnormalities contralateral to Pc lesion was absent in other studies with detailed case descriptions and in our patients, which suggests an independent mechanism apart from sensory derangement [4–6, 8]. As she retained her consciousness during the episodes with normal EEG and her abnormal movement was a typical hemiballism, epilepsy or

limb shaking transient ischemic attack could be ruled out in Case 10.

In the parietofrontal network model, limb movement is closely wired between the Fc and Pc [19]. Thus, functional or structural abnormalities in either the Fc or Pc can result in abnormal wiring between the cortices. In Cases 8 and 9, in addition to the Pc lesions, perfusion abnormalities were found in the ipsilateral and bilateral Fc, including the premotor and supplementary motor areas (Figs. 1c, 2c). Although the BG might receive efferent copies from the cortices via the putamen or the subthalamic nucleus in a current hypothetic BG model for movement control, the role of the BG was indistinct in our patients with cortical HCHB [20]. Thalamic disinhibition was suggested as a pathomechanism of non-cortical HCHB, but was also inconspicuous in our study [21]. Thus, a distorted network generated by both Pc and Fc dysfunction could have resulted in HCHB in these cases.

A leading role of the Pc in the pathogenesis of HCHB was sequentially demonstrated in Case 10. In her first manifestations, she suffered recurrent episodes of hemiballism. The initial work-ups showed cerebromalacia and perfusion abnormality in the Fc. Visual and SPM analyses of baseline SPECT images failed to detect perfusion abnormalities in the Pc, but a decreased vascular reservoir was found in the Pc after an acetazolamide injection (Fig. 3c). The latent hypoperfusion in the Pc by the

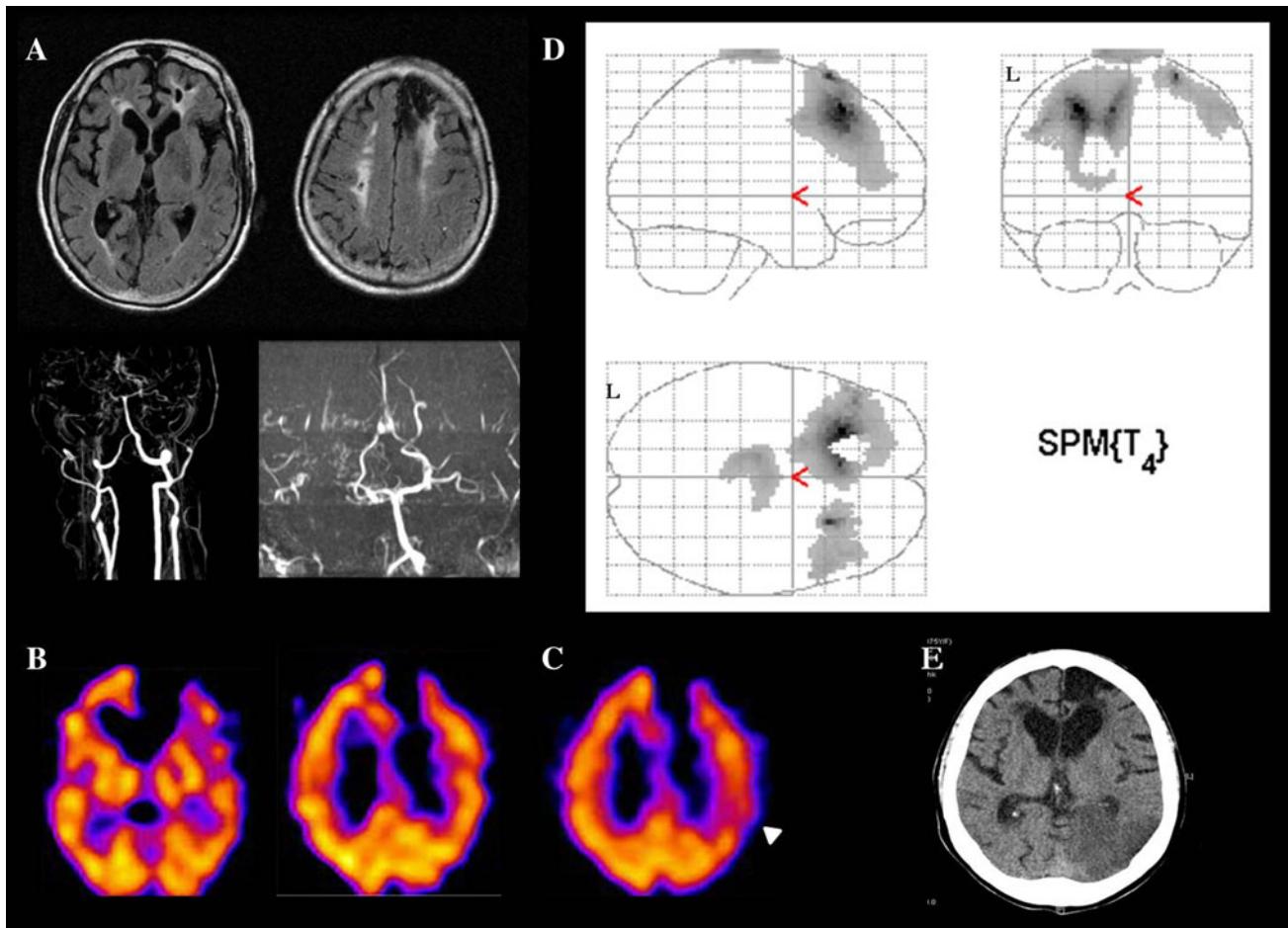


Fig. 3 Neuroimaging of Case 10. **a** Brain magnetic resonance imaging shows cerebromalacia in the left frontal cortex. Brain magnetic resonance angiography shows bilateral occlusion of internal carotid arteries. **b** 99m Tc-HMPAO single-photon emission computed tomography (SPECT) shows perfusion defect in the left frontal cortex and normal perfusion in the basal ganglia and the thalamus. **c** Brain

SPECT after acetazolamide administration shows decreased perfusion reserve in the left parietal cortex (arrowhead). **d** Statistical parametric mapping (t) map shows decreased perfusion in bilateral frontal cortices. **e** Brain computerized tomography taken after the second stroke during follow-up shows an infarction involving left parieto-occipital cortex

occlusion of the bilateral internal carotid arteries may not be severe enough to result in permanent damage of the *Pc*. Unstable perfusion would be more compatible with paroxysmal episodes of hemiballism than continuous ones. Interestingly, her hemiballism was resolved after a *Pc* infarction (Fig. 3a, c, e). The *Pc* provides sensory input to the *Fc* in the parietofrontal network model [19]. Thus, the elimination of unstable signals from the *Pc* might be beneficial to the stabilization of the deranged network.

In a classical model of movement disorders, either structural damage or functional alteration of the *BG* is frequently considered as central problem, and pathologic signals from diseased the *BG* are bound for the *Fc* to send final orders to affected body parts (Fig. 4c). In case of *Pc* lesions, pathologic cues from the *Pc* can reach the *Fc* via direct inter-cortical network for sensorimotor integration, resulting in movement disorders (Fig. 4b).

There were a few limitations in our study. First, as our study was retrospective, some studies such as DWI, ADC and acetazolamide SPECT were not done in all the patients. However, DWI and ADC map gave no additional information regarding the pathologic lesions responsible for HCHB, and acetazolamide SPECT showed latent abnormality only in one patient (Case 10). Second, other neuroimaging techniques such as positron emission tomography (PET) or functional MRI could have provided a functional map with higher resolution. Herein, we analyzed SPECT data by SPM method in addition to visual assessment, which enabled us to secure an unbiased and comprehensive view on the pathologic network.

The present study suggests that there may be an independent contribution of the cortical areas to the pathogenesis of cortical HCHB even without significant involvement of the *BG* and *Th*. Derangement of the wiring

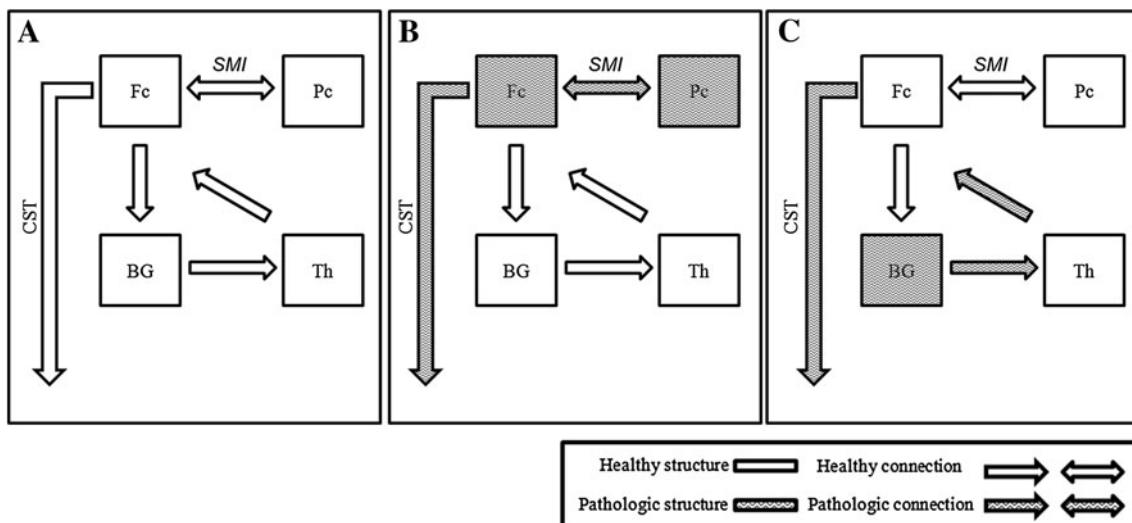


Fig. 4 Models of movement disorders. **a** Key structures for movement control. The frontal cortex (Fc) and parietal cortex (Pc) is closely wired for harmonized sensorimotor integration (SMI). The basal ganglia (BG) involves in the modulation of movement via the thalamus (Th). Final commands from the Fc are sent to body parts via corticospinal tract (CST). **b** A cortical model. Either the Fc/Pc lesions

or disharmonized SMI can result in abnormal output from the Fc, leading to movement disorders. **c** A classical BG model. The BG affected by either functional or structural disorders send altered signals to the Fc via the Th. Pathologic cues from the *healthy* Fc result in movement disorders

between the Fc and Pc may be one possible mechanism of cortical HCHB. Prospective studies with PET or functional MRI will be helpful in deciphering detailed roles of cortical structures on cortical HCHB.

Conflicts of interest The authors declare that they have no conflict of interest.

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