

## Review Article

# The mechanisms of limb hemiplegia after ipsilateral brain hemisphere stroke

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**Abstract:** Post-stroke limb hemiplegia has an important impact on the quality of life of patients. Strokes above the tentorium cerebelli often lead to contralateral limb hemiplegia. However, in clinical practice, some cases of limb hemiplegia after ipsilateral brain hemisphere stroke also occur from time to time. The discrepancy of clinical symptoms and neuroimaging performance complicates diagnosis and differential diagnosis. In this paper, different aspects of ipsilateral motion path in adults, neurodevelopmental malformation, cortical motor function remodeling in stroke recovery, and double crossing of the corticospinal tract fibers were reviewed to explain the mechanisms of limb hemiplegia after ipsilateral brain hemisphere lesions.

**Keywords:** Corticospinal tract, neural remodeling, hypoplasia, hemiplegia

## Introduction

Cases of limb hemiplegia after ipsilateral brain hemisphere stroke can be encountered by chance in clinical practice (**Table 1**) [1-17]. Limb movement is mainly mediated by the corticospinal tract (CST). About 75-90% of the corticospinal tract (CST) originating from the central anterior gyrus, premotor area, and parietal lobe crosses to the contralateral side at the intersection of the medulla oblongata, forming a lateral CST [18, 19]. Only approximately 10% of the fiber bundles do not cross but form the anterior CST which terminates in the ipsilateral anterior horn [6]. Some anterior CST fibers do not cross, and some authors believe that they dominate the movement of the ipsilateral limb only during human embryonic development and that the ipsilateral CST function is inhibited by the corpus callosum after 10 years of age [20]. Therefore, a stroke in the cerebellum tentorium usually leads to hemiparesis opposite to the side of the infarct lesion. However, in real practice, we often encounter limb hemiplegia following ipsilateral brain hemisphere stroke, which is difficult to explain due to the mismatch between the brain lesions and clinical manifestations.

## Ipsilateral motion path in adults

Patients with refractory epilepsy underwent intracranial implantation of subdural electrode arrays and/or depth electrodes for monitoring changes in intracranial potential parameters without taking epilepsy drugs [21]. It was found that the cortical motor potentials of these patients were significantly associated with their ipsilateral limb activities, suggesting that some limb movements may be controlled by the ipsilateral cerebral cortex. The ipsilateral cerebral hemispheres may dominate the movement of the limbs through non-intersecting fiber bundles or through the corpus callosum pathway [22].

Alurkar reported a case in which the main symptoms were a recurrent right upper limb weakness and paresthesia within 3 months. Magnetic resonance imaging (MRI) showed that the acute cerebral infarction lesion was located in the right coronary region. Carotid angiography showed severe stenosis of the right internal carotid artery, and the blood flow velocity was significantly slowed down. The vascular condition was consistent with the infarction lesion

## Limb hemiplegia after ipsilateral brain hemisphere stroke

**Table 1.** Reported cases of limb hemiplegia after ipsilateral brain hemisphere stroke

Author-date	Gender-age	Dominant hemisphere	Stroke type	Lesion of infract	Stroke history	Confirmatory imaging
Fisher [1], 1992	F, 75	NA	IS	L, internal capsule, putamen and caudate nucleus	R, internal capsule and caudate nucleus, IS	Neuropathology
Hosokawa [2], 1996	M, 60	L	ICH	R, internal capsule and thalamus	No	CT, MRI, MEP, SEP
Terakawa [3], 2000	M, 62	L	ICH	L, internal capsule and basal ganglia	No	CT, MRI, fMRI, TMS, SEP
Ago [4], 2003	M, 59	L	IS	L, corona radiata	R, putamen, ICH	MRI, fMRI
Song [5], 2005	F, 62	L	IS	L, corona radiata	R, corona radiata and thalamus, ICH	MRI, fMRI
	M, 41	L	IS	L, corona radiata	R, corona radiata, IS	MRI, fMRI
	M, 74	L	IS	R, thalamus	L, corona radiata, IS	MRI, SPECT
Yamamoto [6], 2007	M, 76	L	IS	R, corona radiata	L, corona radiata, IS	MRI, SPECT
	M, 64	L	IS	R, corona radiata and globus pallidus	L, paraventricular Region, IS	MRI, SPECT
	M, 55	NA	IS	L, corona radiata and thalamus	No	MRI, DTI
Ng [7], 2011	M, 55	NA	IS	L, corona radiata and thalamus	No	MRI, DTI
Kang [8], 2012	M, 35	NA	IS	R, right middle and inferior frontal gyrus, supramarginal gyrus, insular gyrus, internal capsule, head of caudate nucleus, putamen, and globus pallidus	No	MRI, TMS, SEP
Alurkar [9], 2012	M, 55	L	IS	R, corona radiata	No	MRI, DTI
Kwon [10], 2013	M, 55	L	IS	R, pons	L, basal ganglia, frontal lobe, parietal lobe, temporal lobe, IS	MRI, DTI
Saada [11], 2014	M, 57	L	IS	L, occipital, frontal and parietal lobes	R, basal ganglia, IS	MRI
	F, 57	L	IS	R, frontal lobe	R, internal capsule, IS	MRI
Yamada [12], 2015	M, 55	NA	ICH	L, putaminal	No	CT, MRI, DTI
Kobayashi [13], 2015	M, 79	NA	IS	L, internal capsule	R, pons, IS	MRI, TMS, MEP
Xu [14], 2016	M, 58	L	IS	L, frontal lobe	R, pons, IS	MRI, CTA
Hebant [15], 2016	M, 74	R	IS	L, internal capsule	R, internal capsule	MRI
	M, 68	NA	IS	R, internal capsule	No	MRI
Inatomi [16], 2017	M, 68	NA	IS	R, pons	L, corona radiata, IS	MRI
	M, 73	NA	IS	L, corona radiata	R, globus pallidum	MRI, fMRI, TMS
	M, 59	NA	IS	L, pons	L, thalamus, IS R, thalamus, ICH	MRI, fMRI, TMS
	M, 60	NA	IS	L, precentral gyrus, superior parietal lobule	R, putamen, ICH	MRI, TMS
	M, 72	NA	IS	R, corona radiata	L, medulla, IS L, pons, IS	MRI
	F, 65	NA	IS	L, corona radiata and putamen	R, corona radiata, IS	MRI
	F, 72	NA	IS	R, corona radiata	R, medulla, IS	MRI, TMS
	F, 71	NA	IS	L, cingulate gyrus, corpus callosum	R, corona radiata, IS	MRI, fMR, TMS
	F, 78	NA	IS	R, pons	L, internal capsula to occipital lobe, IS	MRI, fMRI
	F, 68	NA	IS	L, internal capsula	R, internal capsula, IS	MRI, fMRI
Patra [17], 2018	M, 80	NA	IS	R, corona radiata and putamen	L, corona radiata and internal capsula, IS	MRI, fMRI, TMS
	M, 73	NA	IS	R, corona radiata, sup.frontal gyrus	No	MRI, fMRI
	M, 70	NA	IS	L, cingulate gyrus, precentral gyrus	L, putamen and internal capsula, IS	MRI, fMRI
	M, 79	NA	IS	R, corona radiata	L, corona radiata	MRI, fMRI, TMS
	F, 44	R	IS	R, fronto-temporal cortex	No	CT, CTA, MRI, DTI, DSA

CTA, computed tomogram angiogram; DSA, digital subtraction angiography; DTI, diffusion tensor imaging; F, female; fMRI, functional magnetic resonance imaging; ICH, intracerebral hemorrhage; IS, ischemic stroke; L, left; M, male; MEP, motor evoked potential; NA, not available; R, right; SEP, sensory evoked potential; TMS, transcranial magnetic stimulation.

[9]. In order to further clarify the pathogenesis, diffusion tensor tractography (DTT) imaging revealed that the bilateral pyramidal tracts of the patient did not cross, which reasonably explained the ipsilateral limb weakness. A similar situation was mentioned in the report of Patra [17]. Jerry recently reported a non-crossing CST in a microsurgical resection of vestibular schwannomas in a patient with structurally normal cerebral hemisphere [23]. These cases show that there is a complete non-crossing of the CST in some adults, and the hemisphere stroke in this type of patients affects only the ipsilateral limb.

In addition to primary motor area, human motor cortex also includes premotor cortex, and the supplementary motor area [24]. The nerve fiber bundles from the central anterior gyrus, the premotor area, and the parietal lobe pass through the radial crown and the inner capsule to the reticular nucleus of the brainstem, and the reticular spinal cord bundle subsequently descends [6]. Some of the fiber bundles do not cross and are used to control the ipsilateral side. Therefore, damage to a certain part of the cerebral cortex or of a fiber bundle can cause ipsilateral limb weakness. The supplementary motor area (SMA) is located in the superior frontal gyrus on the inner side of the cerebral hemisphere [25]. It is considered to be involved in the complex movement control of the human body [26, 27]. Using fMRI to observe the activation of brain areas when the human hand performs different actions [28], it was found that while performing complex exercises, the bilateral SMA was also activated (except for the activation of the primary motor area of the contralateral cerebral hemisphere), indicating that the region can participate in bilateral upper limb movement. In addition, Saada [11] mentioned that the secondary motor zone in the precentral insular cortex can also participate in some bilateral limb movements. Inatomi [16] reported the case of a patient with a cerebral infarction lesion located in the left cingulate gyrus and corpus callosum, which did not injure the CST. However, this type of lesion may damage the SMA, resulting in hemiplegia of the ipsilateral limb.

### Neurodevelopmental malformation

Brainstem dysplasia is often accompanied by congenital non-crossing CST, horizontal gaze palsy with progressive scoliosis (HGPPS) [12],

posterior fossa deformities such as Dandy-Walker malformation, Joubert syndrome, Möbius syndrome (which may be associated with defects during neurodevelopment), cellular abnormal proliferation, abnormal guiding mechanisms, and other, yet undiscovered molecular mechanisms [29-31]. The motor brain of these people usually supports the limb movement of the ipsilateral cerebral motor cortex. Therefore, their limb paralysis caused by stroke occurs on the same side of the lesion, but it is often necessary to perform head MRI and DTT to confirm the diagnosis.

HGPPS is a rare autosomal recessive hereditary disease, and its pathogenesis is mainly related to a mutation in the gene *ROBO3* [32]. The protein translated by this gene plays an important role in cell migration and axonal midline crossing during brainstem development [33]. Therefore, when the *ROBO3* gene is mutated, it can cause brainstem hypoplasia, resulting in non-crossing or partially-crossed nerve fiber bundles of the brainstem, which can cause many nerve fibers to mutate, leading to HGPPS. Ng reported a 55-year-old Indian man with left limb weakness [7]. The patient had horizontal gaze and scoliosis since he was born. The brain MRI showed left putamen and corona radiata infarction and indicated HGPPS imaging features such as split pons, butterfly medulla, and small brain stem. DTT indicated that there was no crossover in the patient's CST. Gene sequencing analysis revealed that a G>T mutation occurred in exon 17 of the coding region of the *ROBO3* gene, resulting in a change of the original sequence from GAG to TAG. That study was the first to provide adequate clinical evidence of ipsilateral limb paralysis after cerebral hemisphere infarction in HGPPS patients. However, some patients carrying a heterozygous mutation of the *ROBO3* gene do not present related malformations [34], and, hence, the relationship between the *ROBO3* genotype and phenotype needs further investigation. Studies of patients with posterior fossa deformity showed that the obvious shape characteristics are accompanied by brainstem hypoplasia and a non-crossing pyramidal tract [35, 36]. However, no reports of strokes in these cases were retrieved.

Recently, uncrossed corticospinal tracts in a patient with ichthyosis and hemiparesis were reported. The ipsilateral hemiparesis after

stroke may be caused by the *FLG* gene mutations which is associated with ichthyosis [37].

### **Cortical motor function remodeling in stroke recovery**

Paralysis after stroke has a significant impact on the survivor's quality of life [38]. Rehabilitation training for hemiplegia after stroke is an important treatment for reducing disability. The activation of the cerebral cortex during the training is very important for the recovery of motor function [39, 40]. The mechanism includes increasing the stimulation of the surrounding infarct area [41], increasing the dependence on the SMA and the premotor area [42], and remodeling the cortical motor function [43]. The recruitment of homologous regions in the contralesional hemisphere and the reorganization in perilesional tissue are significant parts of the remodeling [44]. A remodeling of the cortical motor function may cause the limb to become dominated by the ipsilateral cortical motor area, and patients with recurrent stroke may thus have symptoms of ipsilateral limb paralysis.

Nelles found that patients with stroke had a significant increase in regional cerebral blood flow in the bilateral sensorimotor cortex when passively moving the hemiplegic elbow [42]. Simultaneously, the bilateral parietal cortex, contralateral sensorimotor cortex, ipsilateral prefrontal cortex, SMA, and cingulate cortex were significantly activated. Therefore, the idea of remodeling the cortical function of the motor and sensory system during stroke rehabilitation was proposed, but the location and mechanism of remodeling could not be determined. Song studied 2 cases of left limb paralysis after left hemisphere stroke in patients with a history of right cerebral hemisphere stroke without sequelae [5]. Functional magnetic resonance imaging (fMRI) further suggested that their left hand movement activated the bilateral sensorimotor cortex (SM) and the right motor cortex on the right side. We believe that the motor nerves in the healthy hemisphere were remodeled during the recovery period after stroke and that the ipsilateral limb movement pathway after remodeling was independent of the pre-stroke CST. Kim [45] conducted an fMRI study of 10 post-stroke patients and found that the recovery of the motor function in the subacute phase relied mostly on the primary sensorimo-

tor cortex of the healthy brain. However, the activation signal in the chronic phase is mostly located in the sensory motor cortex of the injured hemisphere. A recent study also found an evidence implicated that ipsilateral secondary motor area plays a limited compensatory role for the paretic hand after stroke [46]. In summary, SM in bilateral cerebral hemispheres is involved in post-stroke remodeling processes.

A study proved that interhemispheric integration is decreased after stroke [47]. The DTI imaging showed that fractional anisotropy in the ipsilesional CST is increased during rehabilitation treatment of stroke patients [48]. Some scholar [16] believes that the crossed CST is preferentially injured in the first stroke, the non-crossing CST in the healthy hemisphere becomes active after stroke, and a recurrent stroke is more likely to damage these bundles. This may be related to the reduction of interhemispheric inhibition [49]. In addition, animal experiments have shown that the CST that crosses the contralateral cervical spinal cord from the healthy hemisphere after stroke can undergo germination, crossing the midline once again and reaching the ipsilateral cervical spinal cord, thus promoting the recovery of limb motor function [50]. However, it has been reported in the literature that the recovery of limb movement function under the influence of the ipsilateral motor pathway is poor and that mirror movement disorder is likely to occur [51]. Therefore, although the ipsilateral movement pathway plays an important role in the rehabilitation process, its suppression is necessary in order to achieve a better rehabilitation outcome.

### **Double crossing of CST**

A double-crossing case of CST in a patient with split brain syndrome on the right side was reported [52]. The 49-year-old man of that case had a left hemiplegia from birth. fMRI showed activation areas in both cerebral hemispheres while the patient was moving his left upper limb. Moreover, the activated area of the left cerebral hemisphere was approximately the same as the activation corresponding to the right upper limb. The bilateral upper limb motor-evoked potential was detected upon stimulation of the left cerebral cortex. It was suggested that the left hemiplegic limb movement was

dominated by the ipsilateral cerebral hemisphere. DTT showed that the CST from the undamaged cerebral hemisphere was divided into three groups of fiber bundles: the first group presented double crossed fiber bundles, the second group of fiber bundles did not cross but descended along the ipsilateral brainstem, and the third group intersected at the right of the medulla plane. Although this may have occurred due to the patient's right cerebral hemisphere malformation, the first two groups of fiber bundles may explain why the left limb of the patient was dominated by the ipsilateral cerebral hemisphere. Similarly, in another case of a patient with malformations [53], the right brain innervating the bilateral limbs was found to be undamaged, but DTT showed that the fiber bundle from the motor cortex of the right cerebral hemisphere did not cross before reaching the ipsilateral spinal cord. This suggested that not all ipsilateral motor innervation systems in patients with split-brain malformations are due to the double crossing of CST fibers. In addition, the mechanism of congenital mirror movements may also involve the ipsilateral CST [54]. Until now, there has been no study of stroke events in this type of patient; therefore, it is not possible to confirm whether the deformity is one of the mechanisms of ipsilateral hemiplegia after stroke.

### Conclusion

Limb hemiplegia after ipsilateral brain hemisphere stroke is rare. There are many mechanisms for its occurrence, including damage in non-crossing motor pathways, brainstem dysplasia, and cortical motor function remodeling in stroke recovery. In clinical practice, these events should be carefully identified by DTT, fMRI, and transcranial magnetic stimulation for timely diagnosis and treatment. Due to the small number of sample cases and limited research methods, there is still a lack of understanding of the specific mechanisms of post-stroke motor pathways remodeling and rehabilitation. In-depth study of its pathogenesis will help guide the recovery of this type of post-stroke patients in the future.

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### Disclosure of conflict of interest

None.

### Abbreviations

CTA, computed tomogram angiogram; CST, corticospinal tract; DSA, digital subtraction angiography; DTI, diffusion tensor imaging; DTT, diffusion tensor tractography; F, female; fMRI, functional magnetic resonance imaging; HGPPS, horizontal gaze palsy with progressive scoliosis; ICH, intracerebral hemorrhage; IS, ischemic stroke; L, left; M, male; MEP, motor evoked potential; NA, not available; R, right; SEP, sensory evoked potential; SM, sensorimotor cortex; SMA, supplementary motor area; TMS, transcranial magnetic stimulation.

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