Am J Transl Res 2025;17(1):493-498
www.ajtr.org /ISSN:1943-8141/AJTR0159199

Case Report

Hemichorea-hemiballismus induced by intravenous thrombolytic therapy for acute ischemic stroke: a case report and literature review

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Received July 15, 2024; Accepted December 26, 2024; Epub January 15, 2025; Published January 30, 2025

Abstract: Hemichorea-hemiballismus (HCHB) is a rare hyperkinetic movement disorder characterized by unilateral, involuntary, and irregular movements. Although HCHB is the most common poststroke movement disorder, its occurrence as a complication of intravenous thrombolysis is extremely uncommon. While previous studies have demonstrated that intravascular interventions and intravenous thrombolysis can effectively alleviate HCHB symptoms in stroke patients, the pathophysiologic mechanisms underlying HCHB induced by reperfusion therapy remain poorly understood. Herein, we report a case of HCHB induced by intravenous thrombolysis in an acute ischemic stroke patient and explore its possible pathophysiologic underpinnings. Through detailed clinical observations, comprehensive neuroimaging analyses, and an extensive literature review, we investigated the relationship between reperfusion therapy and HCHB onset. Our findings suggest that HCHB induced by reperfusion therapy may be associated with increased metabolic activity in the basal ganglia or reperfusion injury following the restoration of cerebral blood flow. This study provides novel insight into this rare complication, raises clinician awareness, and lays the foundation for future research into HCHB's mechanisms and treatment.

Keywords: Hemichorea-hemiballismus, acute ischemic stroke, intravenous thrombolysis, reperfusion therapy, basal ganglia

Introduction

Poststroke movement disorders present a diverse range of manifestations and are broadly categorized into two types: hyperkinetic disorders, which are characterized by increased in involuntary movements, and hypokinetic disorders, which are characterized by a paucity of movement or slowed actions [1]. Hemichorea-hemiballismus (HCHB) is the most prevalent movement disorder following stroke and typically presents as rapid, irregular, and involuntary choreiform movements of the limbs, which may occur unilaterally or bilaterally, and it is often accompanied by facial dyskinesias such as grimacing or pouting [2]. Previous research has indicated that interventions aimed at improving cerebral blood flow, such as intravascular treatments and intravenous thrombolysis, can effectively mitigate these involuntary symptoms [3-5]. However, the occurrence of HCHB as a complication of intravenous thrombolytic therapy is exceedingly rare, with only a handful of cases reported in the literature. This study presents a case of HCHB following intravenous thrombolysis for acute ischemic stroke (AIS) in a patient who was treated at our institution, aiming to provide novel insight into this poorly understood phenomenon.

Case report

An 80-year-old male presented to our hospital with sudden-onset of frequent vomiting and unilateral limb weakness on the right side that had begun two hours prior. The vomitus was non-coffee-colored and voluminous, and this condition was accompanied by reduced movement in the right limbs. Initially, the patient was alert and communicative, but his consciousness deteriorated over time.

https://doi.org/10.62347/ODOK7620

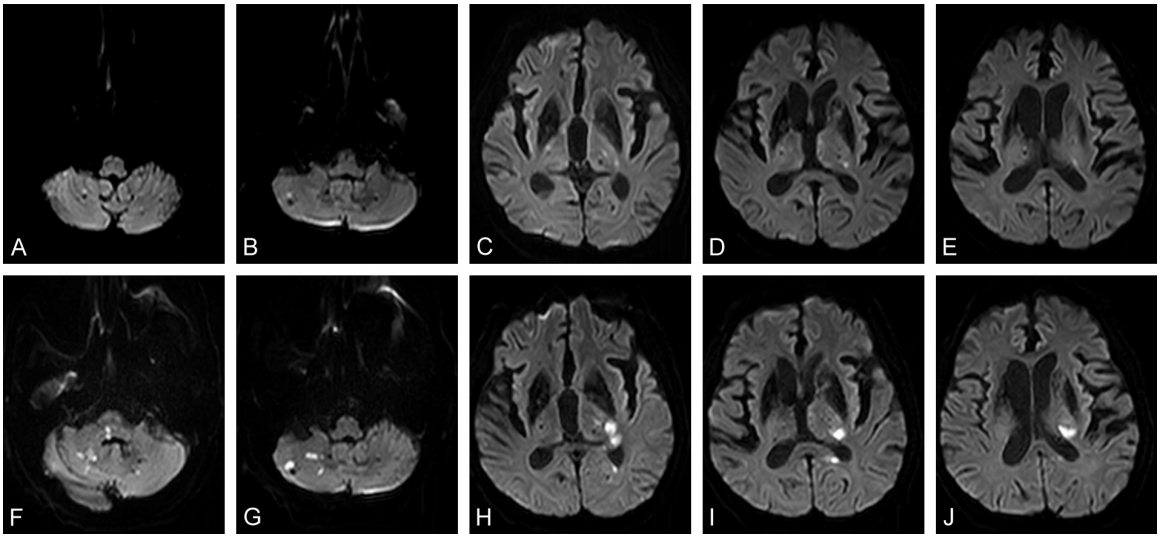

Figure 1. Diffusion weighted imaging of the patient's brain. A-E: Images taken two hours post-thrombolysis showing multiple acute cerebral infarcts in the bilateral basal ganglia, left occipital lobe, and cerebellum. F-J: Follow-up Diffusion Weighted Imaging (DWI) conducted two days after thrombolysis, illustrating persistent infarcts in the bilateral basal ganglia, left occipital lobe, and cerebellum. Compared to earlier images, there was a marked reduction or disappearance of the diffusion restriction signal at the right thalamic infarct site. New high-signal lesions appeared in the left occipital lobe, basal ganglia, and cerebellum.

Upon emergency admission, a cranial CT scan revealed no high-density lesions, suggesting AIS (**Figure 1**). There were no contraindications for thrombolysis, and the patient was administered intravenous alteplase (56.7 mg, 0.9 mg/kg). Approximately 35 minutes after thrombolysis initiation and approximately 35 mg of alteplase, the patient developed sudden, involuntary, and irregular choreiform movements in the left limbs, characterized by internal rotation of the arm and flexion of the wrist, elbow, and knee joints, as well as twisting movements of the dorsum of the foot (Supplementary Video 1). Facial grimacing, forehead wrinkling, and pouting were noted, along with severe gingival bleeding, leading to the cessation of thrombolysis. The patient's medical history included impaired glucose tolerance for three years, with no remarkable personal or family history.

Neurological examination: The patient was somnolent with dysarthria. The pupils were equal, round, and sluggishly reactive to light. Neck stiffness was absent. Muscle tone was decreased bilaterally, with no response to pain stimulation in the right limbs; however, left limbs were responsive. All tendon reflexes were absent, and bilateral pathological signs were positive. The National Institutes of Health Stroke Scale (NIHSS) score was 18, and the Glasgow Coma Scale score was 8. Other neurological examinations were noncooperative.

Laboratory and diagnostic findings: The fasting blood glucose level was 9.49 mmol/L, the glycosylated hemoglobin level was 6.9%, the D-dimer level was 1.24 mg/L, and the fibrinogen level was 4.59 g/L. Paroxysmal atrial fibrillation was observed by telemetry. Electroencephalography revealed diffuse slow waves. Brain MRI performed two hours post-thrombolysis revealed multiple acute infarcts in the left periventricular area, bilateral thalami, and both cerebellar hemispheres. A follow-up MRI two days later revealed multiple cerebral infarcts in the bilateral basal ganglia, left occipital lobe, and cerebellum; the diffusion restriction signal of the right thalamic lesion was significantly reduced or resolved.

Hospital course and follow-up: Involuntary movements in the left limbs spontaneously resolved by the second day of hospitalization. Symptomatic treatment consisted of fluphenazine (2 mg, twice daily) and clonazepam (1 mg, once daily). By the time of discharge on day nine, the patient still exhibited involuntary dorsiflexion movements of the left foot. Muscle tone was slightly reduced on both sides, but all the limbs could be lifted off the bed surface;

Table 1. Summary of case reports on HCHB induced by intravenous thrombolysis for acute ischemic stroke

Characteristic	Murakami et al., 2015 [16]	Uemura et al., 2023 [18]	Present Case
Age (years)/Sex	72/Female	86/Female	80/Male
Neuroimaging Findings	Right temporoparietal lobe infarction; MRA: not available	Left temporo-occipital infarction; MRA: recanalization of left MCA	Bilateral periventricular, thalamic, and cerebellar infarction; Decreased DWI signal in right thalamic region at 48 h
IV rtPA regimen	Administered within 3 hours of onset	0.6 mg/kg; administered at 2 hours post-onset	0.9 mg/kg; administered at 2 hours post-onset
Involuntary movement	Left hemichorea-hemiballismus	Right hemichorea	Left hemichorea-hemiballismus
Time to HCHB Onset†	Within 24 hours	5 days	During rtPA infusion
Treatment and outcome	No specific treatment; spontaneous resolution by day 9	Haloperidol (5 mg/day); complete resolution within 24 h	Fluphenazine (4 mg/day) and Clonazepam (1 mg/day); partial improvement at 3-month follow-up

†Time from rtPA administration to HCHB onset. Abbreviations: MRA, magnetic resonance angiography; MCA, middle cerebral artery; DWI, diffusion-weighted imaging; IV rtPA, intravenous recombinant tissue plasminogen activator; HCHB, hemichorea-hemiballismus.

moreover, the NIHSS score improved to 8. During a three-month follow-up visit, occasional involuntary flexion movements of the left ankle and wrist were observed. Clonazepam was discontinued, and fluphenazine was continued to manage the movement disorder.

Literature review

To gain a comprehensive understanding of the clinical characteristics and pathophysiologic mechanisms of HCHB following intravenous thrombolytic therapy, we conducted a systematic literature review on PubMed, Web of Science, Embase, and China National Knowledge Infrastructure (CNKI) databases. The search strategy included the following terms: "Hemichorea-Hemiballismus" combined with "Intravenous Thrombolytic", "Recombinant Tissue Plasminogen Activator", or "reperfusion therapy". Additionally, we manually searched the reference lists and related articles of the retrieved literature to identify any additional relevant studies.

After removing duplicate records, two independent researchers performed an initial screening based on titles and abstracts, and discrepancies were resolved through discussion. The primary investigator subsequently reviewed the full texts and further selected studies that met the following inclusion criteria: (1) case reports or case series describing HCHB as a complication of intravenous thrombolytic therapy and (2) studies providing detailed clinical information and neuroimaging findings. The exclusion criteria were as follows: (1) studies focusing on HCHB caused by factors other than intravenous thrombolysis; (2) studies lacking sufficient clinical or neuroimaging data; and (3) review articles, commentaries, or editorials. Ultimately, we identified two case reports of HCHB induced by intravenous thrombolytic therapy, which are summarized in **Table 1**.

Discussion

HCHB is a rare hyperkinetic movement disorder with diverse etiologies and is most commonly associated with cerebrovascular diseases, neurodegenerative disorders, metabolic syndromes, and autoimmune diseases [6]. AIS is the most prevalent cause of HCHB, accounting for approximately 50-60% of all cases [7]. HCHB may manifest as an initial or solitary clinical symptom of stroke, typically occurring immediately during an acute cerebrovascular event, although it can also be delayed or evolve as a poststroke sequela [8].

Recent studies have suggested that poststroke movement disorders are not merely the result of localized anatomical damage but are more likely associated with dysfunction in neural networks that regulate motor control (**Figure 2**) [9]. Such disorders can arise when any part of the motor circuitry, including the cerebral cortex (primary motor area, premotor and supplementary motor areas), subcortical structures (basal ganglia, thalamus, internal capsule, and diencephalon), or cerebellum, is involved [2].

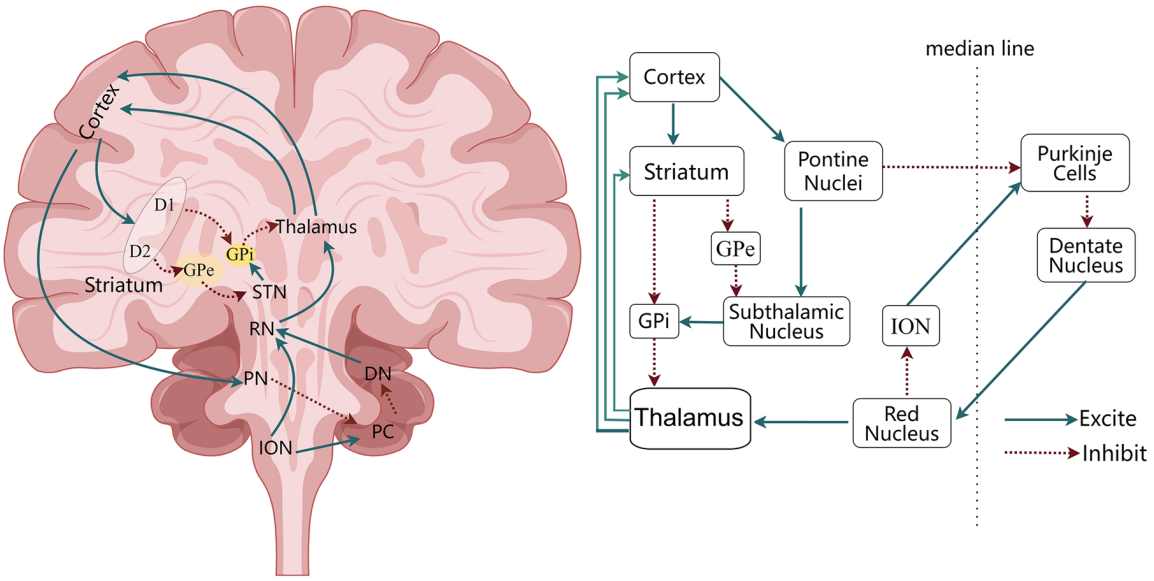

Figure 2. Schematic representation of the basal ganglia and cerebellar neural circuits involved in motor control. This diagram illustrates the direct and indirect pathways of motor control within the basal ganglia. The direct pathway, which facilitates movement, involves the following circuit: cortex-striatum-medial globus pallidus-ventrolateral nucleus of the thalamus-cortex. In contrast, the indirect pathway, which inhibits movement, involves the following circuit: cortex-striatum-lateral globus pallidus-subthalamic nucleus-medial globus pallidus-ventrolateral nucleus of the thalamus-cortex. Additionally, the cerebellum influences cortical motor areas by two main pathways: the dentate nucleus-thalamic pathway and the pontine nuclei-cerebellum-Purkinje cell pathway. The Guillain-Mollaret triangle, which consists of the contralateral dentate nucleus, red nucleus, and inferior olivary nucleus, also plays a role in motor regulation. Abbreviations: D1, Dopamine receptor 1; D2, Dopamine receptor 2; GPi, Internal globus pallidus; GPe, External globus pallidus; STN, Subthalamic nucleus; RN, Red nucleus; DN, Dentate nucleus; ION, Inferior olivary nucleus; PN, Pontine nuclei; PC, Purkinje cells. This diagram was created using FigDraw software.

It is widely accepted that poststroke HCHB is most closely associated with disruptions in the direct and indirect pathways of the cortico-striato-pallido-thalamic circuit [10]. In this circuit, neurons with varying functions antagonize and regulate each other to maintain a delicate functional equilibrium [10]. Ischemic damage to the basal ganglia can lead to regional hypoperfusion or disruption of crucial neural connections and fiber tracts, causing circuit dysfunction. This ischemic impact inhibits the gamma-aminobutyric acid (GABA)ergic pathway from the striatum to the external segment of the globus pallidus, subsequently reducing the inhibitory effect of globus pallidus externus neurons on the thalamic nuclei and the internal segment of the globus pallidus. The resulting thalamic disinhibition releases excessive motor excitatory impulses, leading to contralateral hemichorean movements [11-14].

Although the precise mechanisms underlying HCHB induced by reperfusion therapy remain unclear, previous research has begun to elucidate them. Sugita et al. utilized magnetic resonance angiography and ^{18}F-fluorodeoxyglucose positron emission tomography to study two patients who developed HCHB following bypass surgery from the superficial temporal artery to the middle cerebral artery. Their findings revealed significantly enhanced glucose metabolism in the striatum during involuntary movement episodes, alongside notable dilation of the lenticulostriate arteries. As symptoms subsided, striatal metabolic activity returned to normal levels. These observations suggest that reperfusion therapy may induce secondary metabolic hyperactivity in the striatum, triggering HCHB [15].

Similarly, Murakami et al. reported a case of HCHB following intravenous thrombolytic treatment for AIS in the frontotemporal lobe, where single-photon emission computed tomography imaging revealed increased blood flow in the contralateral basal ganglia. The authors hypothesized that localized hyperperfusion post-thrombolysis could be a critical factor in the development of HCHB [16].

In the present case, the patient exhibited sudden choreiform movements in the left limbs during intravenous thrombolysis, which gradually resolved over several hours. Imaging studies revealed a reduction in diffusion restriction signals at the original right thalamic infarct site post-thrombolysis (**Figure 1**). Given that the majority of involuntary movements occur contralateral to the stroke site [2], it is plausible that HCHB in this patient was closely linked to changes in cerebral hemodynamics following thrombolysis.

Specifically, the restoration of blood perfusion to the right thalamic infarct likely improved the blood supply to the ipsilateral basal ganglia, potentially increasing metabolic activity within this region. This increase may activate inhibitory projections from the striatum to the medial globus pallidus, indirectly strengthening excitatory transmission from the thalamus to the cerebral cortex and ultimately precipitating contralateral involuntary movements. Moreover, prolonged ischemia might lead to the accumulation of excitotoxic substances and reactive oxygen species as well as calcium overload, which can trigger reperfusion injury and disrupt the function of basal ganglia circuits, culminating in the manifestation of hemichorea [17].

In conclusion, HCHB induced by reperfusion therapy is an exceedingly rare complication. Its underlying mechanisms may be associated with enhanced metabolic activity in the basal ganglia or reperfusion injury following the restoration of blood flow. This case report should increase awareness among clinicians about it and provides novel insight into its mechanisms. Further research, including larger case series and prospective studies, is warranted to elucidate the risk factors, clinical course, and long-term outcomes of HCHB following reperfusion therapy.

Acknowledgements

This work was supported by the Natural Science Foundation of Xiamen, China (Grant No. 3502Z20227270).

Disclosure of conflict of interest

None.

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Supplementary Video 1. Video of the onset of lateralized chorea in a patient after thrombolysis.