Case Report

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Isolated Bilateral Midbrain Infarction in A Healthy Female Adolescent: A Case Report

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Objective: The purpose of this study was to understand the complex anatomical structure and function of the midbrain to better understand the patient's symptoms and plan effective treatment including pharmacological and rehabilitation interventions.

Design: A single case study

Methods: A 17-year-old girl presented with acute onset of drowsiness, gait disturbance, mutism, and ptosis. Physical examination revealed postural instability, rigidity of all limbs, and limitations in extraocular movement. The brain MRI revealed an isolated acute infarction in the bilateral midbrain. Considering the location of the infarction, the presenting symptoms were the result of an impairment of the dopaminergic pathway in addition to lesions in the nuclei of the oculomotor nerve. Levodopa/carbidopa was prescribed. And the intensive and comprehensive rehabilitation program was done.

Results: As a result of the study, through comprehensive intervention, which encompassed assessments such as the manual muscle test, Korean Modified Barthel Index score, and Trail-making test, significant enhancements in the patient's condition were observed. These findings provide evidence supporting the effectiveness of the intervention in promoting the patient's physical functioning and overall well-being.

Conclusions: The results of this case highlight the significance of comprehending the intricate anatomical structure and functional aspects of the midbrain, which led us to approach appropriate pharmacological and rehabilitation interventions. Through active communication among the medical team, we were able to establish a therapeutic plan, which demonstrated that effective treatment can be achieved.

Key Words: Ischemic Stroke, Midbrain, Rehabilitation, Dopamine

Introduction

The midbrain is a part of the brainstem and is responsible for movement control, arousal, and visual processing [1]. Several nerve fiber tracts and nuclei of the cranial nerves are located in different regions of the midbrain. Midbrain infarctions present with a wide range of symptoms, including motor deficits, sensory disturbances, cranial nerve dysfunction, coordination and balance problems, eye movement abnormalities, and impaired consciousness. These symptoms arise due to the involvement of various neural structures within the midbrain and can vary depending on the location and extent of the infarction. Previous studies have demonstrated that the majority of isolated midbrain infarctions are attributed to small vessel diseases, accounting for 88.8% of cases [2]. However, identifying the causative vessels of midbrain infarctions using magnetic resonance angiography (MRA) is difficult in most cases. It is therefore crucial

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to understand the anatomy of the midbrain and the correlation between clinical symptoms and the affected sites on magnetic resonance imaging (MRI). Midbrain infarctions are typically unilateral, with the anteromedial region being the most affected area [2]. The incidence of isolated midbrain infarctions has been reported to range from 0.6% [3] to 2.3% [4] of all ischemic strokes. Adolescence represents the peak period for acute ischemic stroke in children [5], with an annual incidence ranging from 0.54 to 2.4 per 100,000 [6-8]. In this report, we present a rare case of a healthy female adolescent who suffered an isolated bilateral midbrain infarction, which was successfully managed with a combination of pharmacotherapy, dopaminergic agents, and intensive rehabilitation. This case underscores the importance of prompt and accurate diagnosis, followed by a multidisciplinary approach to management that includes medication and rehabilitation.

Methods

Subjects

This study included one patient who was admitted and diagnosed with isolated midbrain infarction at Pusan National University Hospital was enrolled for the study for four weeks from January 26, 2018 to March 6, 2018. The study design was approved by the appropriate ethics review board.

On January 26, 2018, a previously healthy 17-year-old female was admitted to our hospital presenting with acute onset of drowsiness, gait disturbance, mutism, and ptosis. Physical examination revealed postural instability, rigidity of all limbs, and limitations in extraocular movement. According to the patient's parents, she had no stroke-related risk factors or family history of stroke. However, the brain MRI revealed an isolated acute infarction in the bilateral

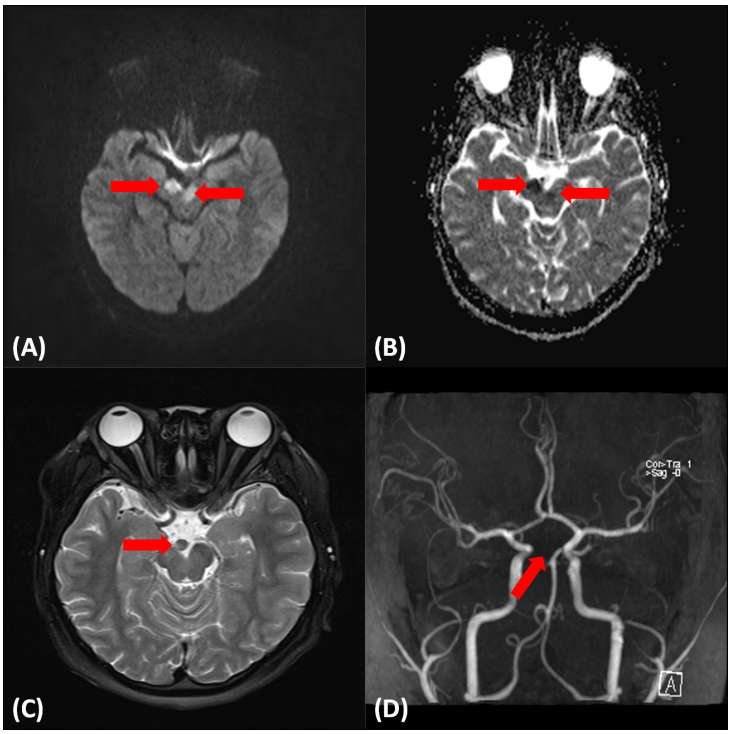

Fig. 1. Axial Image of brain MRI of bilateral midbrain infarction (A) T2WI, (B) ADC, hemorrhage in the right interpeduncular cistern (C) T2WI, MRA of circle of Willis with the right P1 segment aplasia (D) T2WI.
MRI, magnetic resonance imaging; MRA, magnetic resonance angiography; T2WI, T2-weighted image; ADC, apparent diffusion coefficient

midbrain and a hematoma in the right interpeduncular cistern. MRA of the brain revealed anomalies in the circle of Willis in which the right P1 segment showed aplasia (Fig. 1).

Examination

On the third day after symptom onset, the patient was referred to our rehabilitation clinic. She showed a slow but reproducible response to stimuli and could ambulate, requiring moderate assistance, despite having rigidity in all limbs. In the manual muscle test, which followed the Medical Research Council (MRC) Scale for Muscle Strength, both the bilateral upper and lower limbs were graded as grade 3. However, on the 7th day after onset, bradykinesia, freezing, rigidity, and upward gaze limitation especially worsened. In addition, she could obey verbal commands using nonverbal expressions, while the initiation of speech and vocalization was impossible. However, there was no definite new acute lesion on follow-up MRI.

Procedures

On February 7, 2018, on the 13th day after onset, the patient was transferred from the Department of Neuropediatrics to Rehabilitation Medicine following conservative management. Considering the location of the infarction, the presenting symptoms were judged to be the result of an impairment of the dopaminergic pathway, such as the bilateral substantia nigra and red nuclei, in addition to lesions in the nuclei of the oculomotor nerve. On the 14th day after onset, levodopa/carbidopa (125/12.5 mg twice daily) was prescribed. She recovered alertness on the second day of drug administration and her muscle strength was rechecked, showing that the bilateral lower limbs were grade 3 and the bilateral upper limbs were grade 1. The Korean Mini-Mental State Examination score was 25/30; however, the score loss resulted from impaired hand function. She was unable to perform almost all activities of daily living (ADL). Korean Modified Barthel Index (K-MBI) score was 3/100.

The intensive and comprehensive rehabilitation program comprised two daily sessions of physical therapy and one daily session of occupational therapy. Each session lasted 30 minutes and was conducted 5 days a week for approximately 4 weeks. The morning physical therapy session consisted of proprioceptive motor control training with visuospatial compensation, while the afternoon session focused on standing balance and gait training. The patient's lower limb muscle strength was relatively good, so we applied a sling and conducted assisted sit-to-stand training and stationary walking training. Additionally, to prevent joint contractures and improve muscle endurance, we also incorporated lower limb cycling exercises.

The muscle strength of the upper limbs was initially rated as grade 1, but after dopamine medication administration, we observed gradual recovery of strength. Occupational therapy involved fine motor training of both hands and activities of daily living (ADL) training and was conducted for 30 minutes in the morning. For functional activities in daily life, we performed exercises involving grasping and transferring objects, pinch training, followed by spoon and penmanship training. As part of cognitive occupational therapy, the patient was encouraged to perform continuous eye movements in all directions, especially upward, along with activities such as reading books and finding hidden pictures. These interventions aimed to enhance compliance with the training and promote cognitive improvement.

Results

Over the course of the rehabilitation training with continuous administration of levodopa/carbidopa, her symptoms dramatically improved, especially in terms of muscle strength, bradykinesia, freezing, and rigidity (Table 1). A trial-making test (TMT) was performed to evaluate executive functions. On the 24th day after onset, TMT was conducted for the first time, and the A/B of TMT was set at 271/354 s each. Set A/B of the TMT was performed at 64/79 s on the 27th day of onset and at 45/64 s on the 38th day of onset. In addition, muscle strength dramatically improved, finally reaching almost normal, although ataxic movement persisted. On the day of discharge from our clinic center and transfer to another rehabilitation center, she was able to ambulate with a walker on level ground. Although the ataxic movement still resulted in the

Table 1. A timeline of events: symptoms, diagnosis, and treatment

Timeline	Event
Day 1	Acute onset of drowsiness, gait disturbance, mutism, and ptosis. Postural instability, rigidity of all limbs, and limitations in extraocular movement.
Day 3	Slow but reproducible response to stimuli Ambulate requiring moderate assistance Rigidity in all limbs. MRC scale, both the bilateral upper and lower limbs were graded as grade 3
Day 7	Bradykinesia, freezing, rigidity, and upward gaze limitation especially worsened. Obey verbal commands using nonverbal expressions Initiation of speech and vocalization impossible.
Day 13	Transferred from the department of Neuropediatrics to Rehabilitation Medicine
Day 14	Levodopa/carbidopa (125/12.5 mg twice daily) was prescribed.
Day 15	Recovered alertness on the second day of drug administration MRC scale, both lower limbs grade 3 and both upper limbs grade 1. K-MMSE score: 25/30 K-MBI score: 3/100.
	<Prescribe the rehabilitation program> The intensive and comprehensive rehabilitation program (30 min/day, 5days/week) 1.Physical therapy (2 sessions/day) : Proprioceptive motor control training with visuospatial compensation : Standing balance and gait training. 2.Occupational therapy (1 session/day) : Fine motor training of both hands and activities of daily living (ADL) training
Day 24	TMT A/B: 271/354 s
Day 27	TMT A/B: 64/79 s
Day 38	TMT A/B: 45/64 s Muscle strength dramatically improved, almost normal Ataxic movement persisted.
Discharge day	Able to ambulate with a walker on level ground. Perform personal hygiene with assistance, such as manipulating a spoon during a meal. K-MBI score: 44/100.

limitation of some activities, her ADL levels improved. She could perform personal hygiene with assistance, such as manipulating a spoon during a meal. K-MBI score improved to 44/100.

Discussion

The midbrain, located in the proximal brainstem, is rostrally connected to the diencephalon (thalamus and hypothalamus) and caudally adjacent to the pons. This region contains numerous essential nuclei and fiber tracts that are primarily associated with motor control, as well as the auditory and visual pathways [9]. However, current neuroimaging techniques still do not discriminate well between these tracts and nuclei. Therefore, a better understanding of the midbrain's gross anatomy could provide indicators for evaluating the internal midbrain nuclei, fiber tracts, and vascular supply. This could lead to a better understanding of midbrain pathology, such as infarction, by correlating the symptoms and affected lesions.

All midbrain compartments play their respective roles, leading to distinct midbrain syndromes, such as Weber syndrome and Benedikt syndrome. These syndromes can be explained by an understanding of

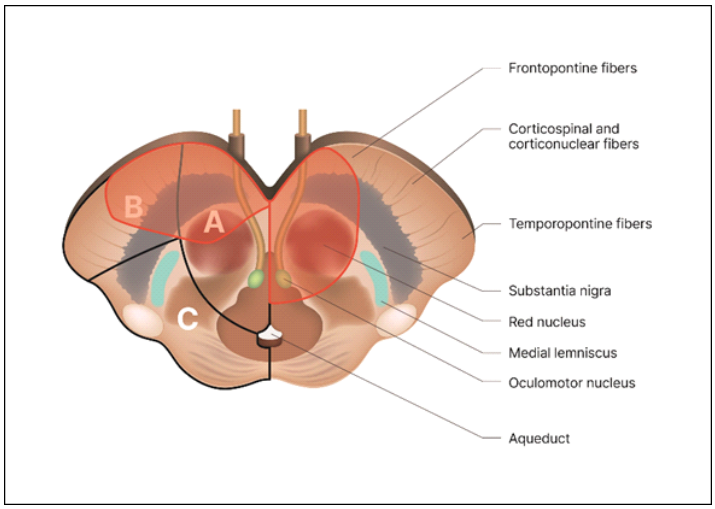

Fig. 2. Schematic imaging of midbrain with important structures and three subgroups (a) Anteromedial, (b) Anterolateral, (c) Lateral. Illustration of the region in the midbrain with affected parts highlighted in red.

their anatomical structures and functions. If certain parts of the midbrain are affected, the function of the affected parts becomes impaired, leading to related symptoms. However, considering that the nuclei, fiber tracts, and vascular supply are closely located, these distinct syndromes may overlap.

Previous studies have suggested that the midbrain can be divided into three categorized regions by horizontally distinguishing affected MRI-identified lesions (Fig. 2) [3]. The three categorized regions are anteromedial (or paramedian), anterolateral, and lateral. A previous study explained the symptoms by which each region or a combination of these regions was affected (Table 2) [3].

The MRI showed an isolated bilateral midbrain infarction, which consisted of affected and non-affected regions. The affected regions of the midbrain are highlighted in red in Figure 2. Our patient's symptoms could not be explained by a certain midbrain syndrome. Symptoms were categorized into anteromedial and right anterolateral groups, as previously described. This region contains the corticospinal tract, red nucleus, substantia nigra, and oculomotor nerves. The corticospinal tract is responsible for controlling contralateral movements of the lower face, tongue, arms, and legs [10]. The red nucleus is responsible for contralateral coordination such as ataxia, dysmetria, and dysdiadochokinesia [11]. The substantia nigra is responsible for modulating motor movement and reward functions in the midbrain dopaminergic nucleus [12]. The oculomotor cranial nerve is responsible for the visual system, such as ipsilateral eye movements, pupil constriction, and upper eyelid elevation [13]. Damage to the oculomotor nerve can lead to paralysis of the intraocular, extraocular, and levator muscles. Injury to the extraocular muscles can cause downward and lateral eye deviations, while damage to the intraocular muscles can result in mydriasis with divergent gaze. Levator muscle paralysis can lead to ptosis.

The patient's symptoms, such as bradykinesia, freezing, rigidity, and upward gaze limitation, could be explained by the affected regions of the midbrain, such as the corticospinal tract, red nucleus, substantia nigra, and oculomotor nerves (Table 2). Dopamine insufficiency could explain these symptoms, including bradykinesia, freezing, and rigidity. Levodopa, the standard treatment for Parkinson's, has previously been prescribed to treat these symptoms [14]. Over the course of rehabilitation training with the continuous administration of levodopa/carbidopa, the patient's symptoms dramatically improved, especially muscle strength, bradykinesia, freezing, and rigidity. A TMT was performed to evaluate executive functions. On the 24th day after

Table 2. Midbrain infarction region, the patient's affected region, correlated region, clinical symptoms, and treatment

Region	Affected	Correlated Region	Clinical Symptoms	Treatment
Anteromedial (Paramedian)	Both	Oculomotor nucleus	Eye movement impairment Double vision Ptosis	Comprehensive rehabilitation - Eye exercise : Tracking, Convergence exercises, Near-far focusing Prism glasses Botulinum toxin injection Surgery
		Red nucleus	Ataxia	Comprehensive rehabilitation - Strengthening - Postural control - Functional mobility - Coordination and control
		Substantia nigra	Bradykinesia Freezing Rigidity	Dopamine agonists Comprehensive rehabilitation - Strengthening - Postural control - Stretching
Anterolateral	Right	Corticospinal tracts	Weakness	Comprehensive rehabilitation - Strengthening - Range of motion exercise
		Substantia nigra	Bradykinesia Freezing Rigidity	Dopamine agonists Comprehensive rehabilitation - Strengthening - Flexibility - Balance
Lateral	Not affected	Medial lemniscus	Sensory symptoms	Comprehensive rehabilitation - Discrimination training - Proprioceptive training

onset, TMT was conducted for the first time, and the A/B of TMT was set at 271/354 s each. Set A/B of the TMT was performed at 64/79 s on the 27th day of onset and at 45/64 s on the 38th day after onset. These results indicate an improvement in executive function, considering the improvement in the time spent finishing the test.

The patient showed significant improvement in muscle strength, although ataxic movement persisted. She was able to ambulate with a walker on level ground. She could also perform personal hygiene activities with assistance, such as manipulating a spoon during a meal. The patient achieved functional recovery and was discharged safely.

In order to determine the efficacy of levodopa/carbidopa in the patient's recovery, it would be necessary to discontinue the administration of the medication, so called off-on trial. The observed improvements were genuinely associated with the dopaminergic agent or merely coincidental with the natural recovery and neuroplasticity of the brain. However, this was not feasible as the patient did not visit our outpatient clinics.

This case report presents an isolated midbrain infarction, which is a rare occurrence, particularly noteworthy as it involved a pediatric patient, further contributing to its uniqueness. The findings underscore the importance of a comprehensive understanding of the complex anatomical structure and functional aspects of the midbrain, enabling us to adopt appropriate pharmacological and rehabilitation interventions. Through robust interdisciplinary communication, we

successfully formulated a tailored therapeutic plan, demonstrating the potential for achieving effective treatment in such cases.

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