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Case Report

Functional Improvement of Progressive Supranuclear Palsy-Like Syndrome with Bromocriptine: Three Cases

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Bromocriptine을 이용한 진행성 핵상마비 유사 증후군의 치료: 증례보고

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Abstract

Progressive supranuclear palsy (PSP)-like syndrome is a condition that mimics the neurological features of PSP, which is characterized by supranuclear vertical gaze palsy, cognitive decline, and postural instability. The syndrome is a reversible condition that can occur secondary to other diseases or drug regimens, while PSP is a non-reversible neurodegenerative disease. We present three patients who developed PSP-like syndrome after hydrocephalus following intraventricular hemorrhage. The patients showed symptoms of PSP and imaging findings known as the “hummingbird” sign. Bromocriptine alleviated the symptoms of the PSP-like syndrome, while levodopa had little effect. Midbrain atrophy with hydrocephalus after intraventricular hemorrhage may cause clinically and radiologically similar characteristics to PSP. Bromocriptine improved the physical function of the PSP-like syndrome, except for vertical gaze palsy. The pharmacodynamic pathway may have led to this result. Identifying the underlying medical disorder may lead to accurate diagnosis for geriatric patients with PSP-like syndrome.

Key Words

Progressive supranuclear palsy, Hydrocephalus, Bromocriptine

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Introduction

After Alzheimer’s disease, Parkinson’s disease (PD) is the second most common neurodegenerative disorder of the elderly.[1] Progressive supranuclear palsy (PSP), as the most common type of atypical parkinsonism, has a similar clinical manifestation but must be differentiated from PD. Growing interest is now associated with the differentiation of these diseases, as there is a high degree of clinical overlap, leading to misdiagnosis.[2] At the same time, many other diseases may clinically resemble PSP, manifesting as PSP-like syndrome.

PSP is characterized by supranuclear vertical gaze palsy, postural instability, frontal-subcortical cognitive

disorder, urinary urgency, and pseudobulbar syndrome.[3] Although PSP and PSP-like syndrome present with similar neurological features, PSP is a non-reversible neurodegenerative disease related to microtubule-associated protein tau dysfunction, while PSP-like syndrome is a reversible condition that mimics the neurological features of PSP, which can occur secondary to other medical conditions. These medical conditions, likely to be prevalent in geriatric patients, include diffuse subcortical cerebrovascular disease, paraneoplastic syndrome, cerebral Whipple's disease, cerebral amyloid angiopathy, and drug reactions.[2,4,5]

In the current cases, our patients presented with supranuclear gaze palsy, cognitive decline, and postural instability after hydrocephalus following intraventricular hemorrhage (IVH). Also, brain magnetic resonance imaging (MRI) findings showed significant midbrain atrophy, known as the "hummingbird" sign, a differential diagnostic marker of PSP. Here, we describe three cases of PSP-like syndrome whose symptoms improved after taking bromocriptine.

Case Reports

1) Case 1

A 49-year-old female patient was transferred to the emergency room with mental change, dysarthria, and motor weakness. Computed tomography (CT) demonstrated a subarachnoid and intraventricular hemorrhage. An external ventricular drain (EVD) insertion was performed, and a ventricular-peritoneal (VP) shunt with a pressure-adjustable valve was inserted. Eight months after the surgery, the patient was transferred to our Department of Physical Medicine and Rehabilitation.

Upon admission, she seldom responded to simple, one-step instructions and only uttered one-word phrases. She also showed rigidity of all four extremities; poor postural stability according to the Berg Balance Scale (BBS = 4); grade 3 muscle weakness according to the Medical Research Council (MRC); supranuclear vertical gaze palsy (Fig. 1A); and impaired cognitive function, with a Mini-Mental Status Examination (MMSE) score of 1.

The VP shunt functioned well, and electroencephalography showed no epileptic discharge. An MRI image demonstrated hydrocephalic features (Fig. 2A)

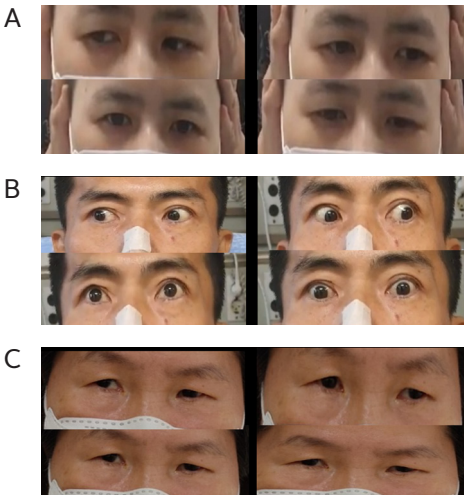

Fig. 1. Test for supranuclear vertical gaze palsy, looking right, left, up, and down. (A) Case 1, (B) Case 2, and (C) Case 3.

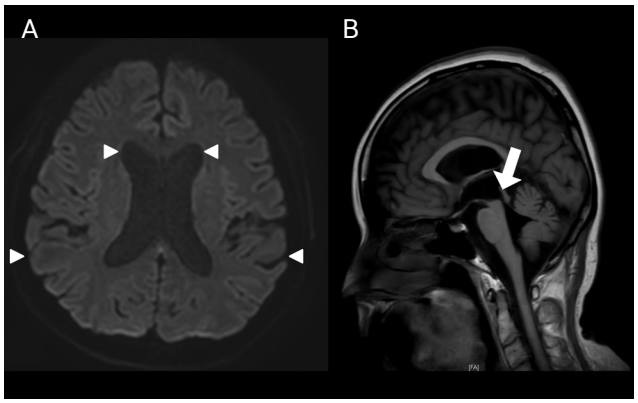

Fig. 2. (A) Transverse diffusion-weighted magnetic resonance imaging (MRI) demonstrating the hydrocephalic feature of an enlarged ventricle with Evan's ratio of 0.34. (B) Parasagittal T2-weighted MRI showing midbrain atrophy: the hummingbird sign: Case 1.

and significant midbrain atrophy with sparing of the pons "hummingbird" sign (Fig. 2B). Fluorine-18-fluorodeoxyglucose (FDG) photon emission tomography (PET) revealed diffusely decreased FDG uptake in the frontal cortical region and bilateral caudate nuclei (Fig. 3), which is a specific characteristic of PSP.[6]

Treatment with carbidopa 25 mg plus levodopa 100 mg (Perkin 125 tablets; Myung In Pharmaceuticals, Gyeonggi, Republic of Korea) was initiated nine months after the VP shunt at 187.5 mg/day, then increased gradually to 750 mg/day in three equal doses. However, despite 45 days of Perkin treatment, her symptoms did not improve.

Although the symptoms and radiological midbrain morphology of PSP were presented in this case, our first impression was PSP-like syndrome rather than PSP, considering the patient's history and the time of symptom occurrence. We stopped the Perkin regimen and initiated treatment with bromocriptine (Parlodel tablets; Novartis Korea, Seoul, Republic of Korea) at 2.5 mg/day, then gradually increased to 15 mg/day in three equal doses. The shunt valve opening pressure was not changed during the adjustment of the drug doses.

Three weeks after the initiation of bromocriptine administration, the patient demonstrated better cognitive function (MMSE score improved from 1 to 15), better postural static balance (BBS improved from 4 to 26), strengthened lower extremity muscle power (MRC grade improved from 3 to 4), and better functional independence level (modified Barthel index improved from 27 to 49). However, vertical gaze palsy showed no marked improvement.

2) Case 2

A 57-year-old male patient was admitted to the intensive care unit with mental change. CT demonstrated IVH, and an EVD insertion was performed. He was transferred to our Department of Physical Medicine and Rehabilitation five months after the onset. A follow-up CT image demonstrated hydrocephalic features, and an MRI demonstrated midbrain atrophy with the hummingbird sign (Fig. 4).

Upon admission, he presented with poor postural stability (BBS = 1), muscle weakness (MRC = grade 3), supranuclear gaze palsy (Fig. 1B), and impaired cognitive function (MMSE = 11).

Based on our first case, our first impression was PSP-like

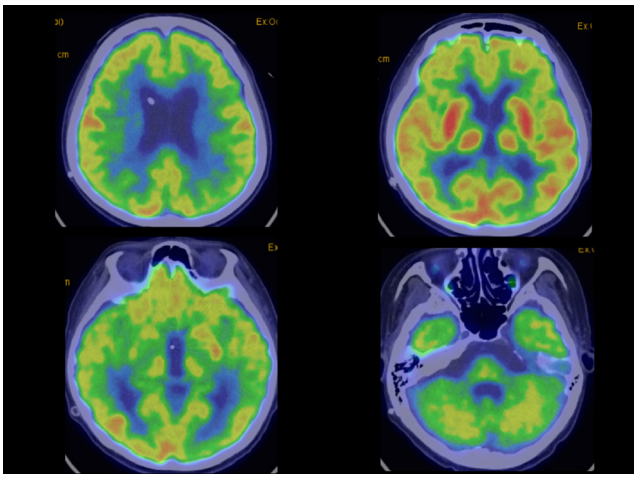

Fig. 3. Fluorine-18-fluorodeoxyglucose (FDG) photon emission tomography image demonstrating diffusely decreased FDG uptake in the frontal cortical region and the bilateral caudate nuclei: Case 1.

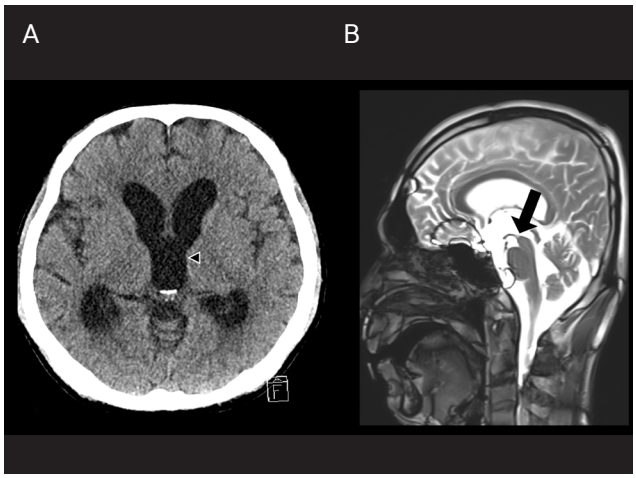

Fig. 4. (A) Brain computerized tomography demonstrating the hydrocephalic feature. (B) Parasagittal Apparent Diffusion Coefficient MRI showing midbrain atrophy: the hummingbird sign: Case 2.

syndrome, considering the patient's history. We initiated treatment with bromocriptine 2.5 mg/day. Four weeks after the initiation of bromocriptine, he demonstrated better cognitive function (MMSE score improved from 11 to 13), better postural static balance (BBS improved from 1 to 8), strengthened lower extremity motor (MRC grade improved from 3 to 4), and better functional independence level (modified Barthel index improved from 31 to 43). However, vertical gaze palsy remained unchanged.

3) Case 3

A 63-year-old female patient was admitted to the emergency room with mental change and motor weakness. CT demonstrated left thalamic intracerebral hemorrhage (ICH) with IVH; therefore, EVD insertion was performed. A follow-up CT image demonstrated hydrocephalic features; therefore, a VP shunt was inserted, and the patient was transferred to our Department of Physical Medicine and Rehabilitation.

Upon admission, she presented with poor postural stability (BBS = 9), muscle weakness (MRC = grade 2), impaired cognitive function (MMSE = 13), and vertical gaze palsy (Fig. 1 C). She also demonstrated stiffness, axial rigidity, and a tendency to fall backward, which are clinical hallmarks of PSP.

Treatment with carbidopa 25 mg plus levodopa 100 mg (Perkin 125 tablets) was initiated at 187.5 mg/day and then increased gradually to 750 mg/day in three equal doses. Despite three months of Perkin treatment, her symptoms did not improve. Based on previous cases, we stopped the Perkin regimen and initiated treatment with bromocriptine (Parlodel tablets), initially at 2.5 mg/day and then gradually increased to 5 mg/day.

Three weeks after the initiation of bromocriptine, she demonstrated better cognitive function (MMSE score improved from 13 to 20) and better postural static balance (BBS improved from 9 to 13). However, vertical gaze palsy remained unchanged.

Discussion

Midbrain morphology in hydrocephalus may share the characteristics of PSP, and it is difficult to make a differential diagnosis between PSP and PSP-like syndrome, since gait instability, cognitive decline, opthalmokinetic abnormalities, and a radiological feature known as the hummingbird sign are often present in both PSP and PSP-like syndrome.[7,8] However, PSP is a neurodegenerative disease that has an insidious onset and progresses slowly over years, whereas PSP-like syndrome, especially in the case of vascularly originated, is characterized by sudden onset and rapid progression.[2]

Our cases presented clinical manifestations and image findings of PSP after hydrocephalus following IVH. Although the image findings and clinical features could not distinguish PSP from PSP-like syndrome in these cases, our impressions were PSP-like syndrome rather than PSP, judging from the rapid progression since the onset of ICH and hydrocephalus. Furthermore, supranuclear palsy, which is the characteristic sign of PSP, usually appears three to four years after the onset of PSP. At the same time, it is presented within a few months in our cases.[9]

Recent pharmacologic therapies for PSP are symptomatic, and levodopa is used to improve bradykinesia and rigidity. However, levodopa tends to show mild to moderate efficacy, with a grade 2B recommendation.[10] Dopamine agonists can also be tried in PSP but are generally less effective than levodopa.[11] On the other hand, the pharmacologic strategy of PSP-like syndrome is not standardized and may vary depending on the etiology.

In cases 1 and 3, the patients did not respond to levodopa; therefore, we tried treatment with bromocriptine based on the results of a previous case report.[12] Although the exact neuropharmacological mechanisms are not well defined, the use of bromocriptine alleviated the symptoms of PSP-like syndrome, except for vertical gaze palsy.

In the first case, FDG-PET showed decreased uptake in the frontal cortical region and caudate nucleus, which is a characteristic of PSP, while only frontal cortical

hypometabolism is usually demonstrated in idiopathic Parkinson's disease.[6] As our patient presented with a radiological feature of midbrain atrophy, in this case, it could have affected the intermediate of the nigrostriatal dopaminergic pathway, resulting in hypometabolism in the caudate nucleus.

Bromocriptine is a dopamine agonist having both pre- and post-synaptic effects, while levodopa is a presynaptic dopamine precursor. In our cases, bromocriptine was more effective than levodopa. Pharmacological differences may have led to this result, as bromocriptine, which has a post-synaptic effect, directly stimulates the striatum. However, even with bromocriptine, the vertical gaze palsy did not improve. This is because vertical gaze palsy is related to different pathobiology rather than to the nigrostriatal dopaminergic pathway.[13] Vertical gaze palsy may be caused by a rostral midbrain lesion, including the rostral interstitial nucleus of the medial longitudinal fasciculus, the interstitial nucleus of Cajal, and several passing fibers for the vestibulo-ocular reflex.[14,15] In our cases, midbrain atrophy may have affected this area, leading to vertical gaze palsy, which is not responsive to bromocriptine. Not only in PSP-like syndrome, but also in PSP, bromocriptine is not effective to supranuclear palsy and upward gaze limitation correlates with midbrain atrophy.[16,17]

PSP-like syndrome should be suspected when a sudden appearance of PSP-related symptoms is observed after a change in medical conditions. Krzosek et al.[2] and Shetty et al.[5] reported cerebrovascular disease, paraneoplastic syndrome, cerebral amyloid angiopathy, an inadequate drug regimen, and infectious disease as medical conditions that induce PSP-like syndrome. As most of these conditions are prevalent in the elderly and given that the mean age at which PSP develops is 63 years, careful attention should be paid to geriatric patients. Identifying underlying medical disorders and history taking may lead to accurate diagnosis for elderly patients with PSP-like syndrome.

In conclusion, hydrocephalus after subarachnoid, intracerebral, and intraventricular hemorrhages causing midbrain atrophy may have clinically and radiologically similar characteristics to PSP. Additionally, in our three cases, the symptoms of PSP-like syndrome were functionally improved with bromocriptine. However, the usage period and dosage of bromocriptine were different in each case, as there was no standardized study. Future research is needed to develop an appropriate regimen considering comorbidity and efficiency.

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