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【 CASE REPORT 】

Radiation-induced Brain Calcification Leads to L-dopa-resistant Parkinsonism and Cerebellar Ataxia

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Abstract:
We experienced a young patient who presented with progressive parkinsonism and cerebellar ataxia. Brain magnetic resonance imaging revealed progressive brain calcification, expanding from the bilateral basal ganglia to the central pons, caused by a delayed reaction to the radiation therapy that she had received to treat craniopharyngioma 14 years earlier. Heterogeneous clinical symptoms due to radiation-induced brain calcification have been described, but parkinsonism has never been reported. While dopamine transporter-single photon emission computed tomography revealed only slight damage to the dopaminergic striatal pathway, the extension of calcification to the periventricular white matter was likely responsible for her parkinsonism.

Key words: radiation-induced brain calcification, idiopathic basal ganglia calcification, mineralizing microangiopathy, parkinsonism, cerebellar ataxia

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Introduction

Parkinsonism caused by a dysfunctional nigrostriatal pathway has been observed in patients with basal ganglia mineralization, which is often associated with abnormal calcium metabolism caused by infectious diseases, endocrine disorders, and genetic mutations (1). Radiation therapy also causes basal ganglia mineralization as a delayed reaction, especially in children; however, parkinsonism has never been reported.

We herein report a woman who exhibited levodopa-unresponsive parkinsonism and cerebellar ataxia accompanied by brain calcification that had developed over more than a decade after radiation therapy.

Case Report

The present patient had undergone surgery due to craniopharyngioma at seven years old (Fig. 1A1). Local fractionated radiation therapy with a total dose of 54 Gy was conducted around the sella turcica, including the bilateral thalamus, putamen, and upper brain stem. However, recurrence required re-operation at eight years old (Fig. 1B1), leaving mild cognitive decline and panhypopituitarism as sequelae. At 11 years old, brain magnetic resonance imaging (MRI) showed a high-intensity spot at the left thalamus (Fig. 1C2), which gradually expanded to the bilateral thalamus, putamen, and red nucleus over the next 3 years, although she showed no neurological deficit.

At 20 years old, she experienced difficulty talking, swallowing, and walking stably, so she was brought to our hospital. Her eye movement was saccadic, her speech was slurred, and she also had right-side dominant rigidity and bradykinesia that was dominant in her upper limbs. She showed no pyramidal signs, including Babinski sign, spasticity, and hyperreflexia. She walked unsteadily because of limb and truncal ataxia. Blood tests, including calcium, iron, hormones regulating calcium levels, lactic acid, and pyruvate, as well as markers for collagen diseases and infection markers like human immunodeficiency virus, were all within normal ranges. Brain computed tomography (CT) showed symmetrical high-density lesions at the thalamus, pallidum, caudate, midbrain, and periventricular white matter (Fig. 2A1-3), suggesting depositions of calcification. These lesions were shown to be high-intensity deposits on T1- and

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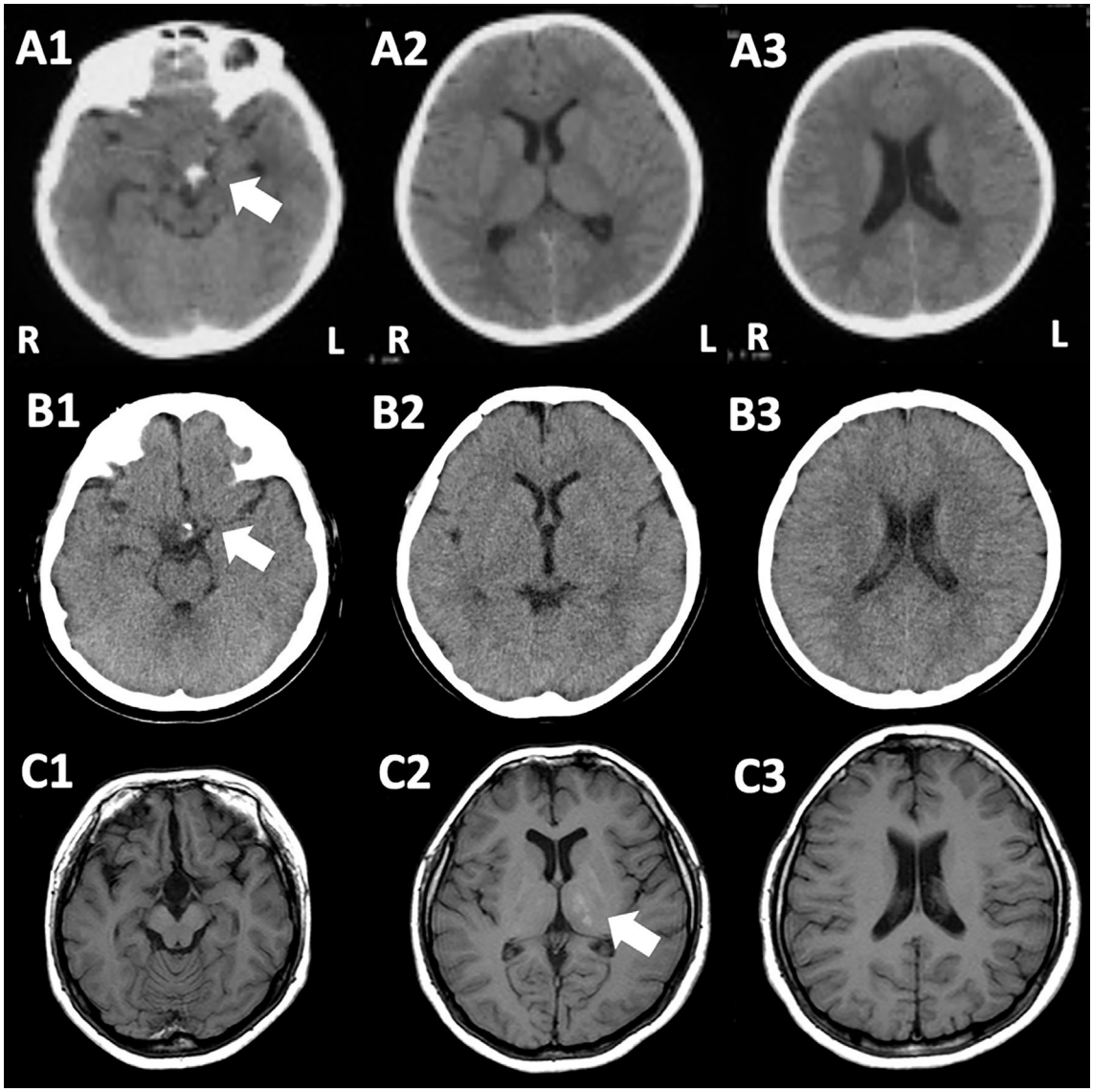

Figure 1. **Brain CT and MRI in childhood. A: The brain CT scan at the age of 7 reveals a high-density area at Sella turcica (A1 white arrow). No abnormal lesions were observed in the thalamus, pallidum, caudate (A2), or periventricular white matter (A3). B: The brain CT scan at the age of 8. Her craniopharyngioma recurs at Sella turcica (B1 white arrow), whereas other regions show no abnormality (B2, B3). C: The T1-weighted brain MRI at the age of 11 shows a high signal intensity in the left thalamus (C2 white arrow). The midbrain (C1) and periventricular white matter (C3) are unremarkable.**

T2-weighted imaging of brain MRI (Fig. 2B1-6). ^{123}I-iodoamphetamine (IMP)-single-photon-emission CT (SPECT) demonstrated a decreased blood flow in the entire cerebellum in addition to the bilateral basal ganglia (Fig. 3A), indicating crossed cerebellar diaschisis (CCD) of the corticopontocerebellar pathway. Dopamine transporter-SPECT (DaT-SPECT) showed a slight decrease in the binding of right-side dominant striatum [specific binding ratio (SBR): right 7.46, left 6.94] (Fig. 3B). Meta-iodobenzylguanidine (MIBG) myocardial scintigraphy showed a normal uptake (Fig. 3C). Taken together, these results suggested that her parkinsonism was due to mineralization of the bilateral subcortical lesions.

Genetic tests for genetic mutations responsible for neurodegeneration with brain iron accumulation or idiopathic basal ganglia calcification (IBGC), including *PANK 2*, *PLA2G6*, *FTL*, *C19orf12*, *WDR45*, *COASY*, *REPS1*, *CRAT*, *FA2H*, *ATP13A2*, *CP*, *DCAF17*, *SCP2*, *GTPBP2*, *TBCE,* and *MECP2*, were all negative. Both rapid intravenous infusion of 100 mg levodopa and oral administration of 600 mg/day levodopa/carbidopa for 3 months failed to improve her parkinsonism and ataxia.

Discussion

Basal ganglia calcification can occur secondary to several conditions (2). Most patients remain asymptomatic, but some develop either movement disorder or psychiatric disor-

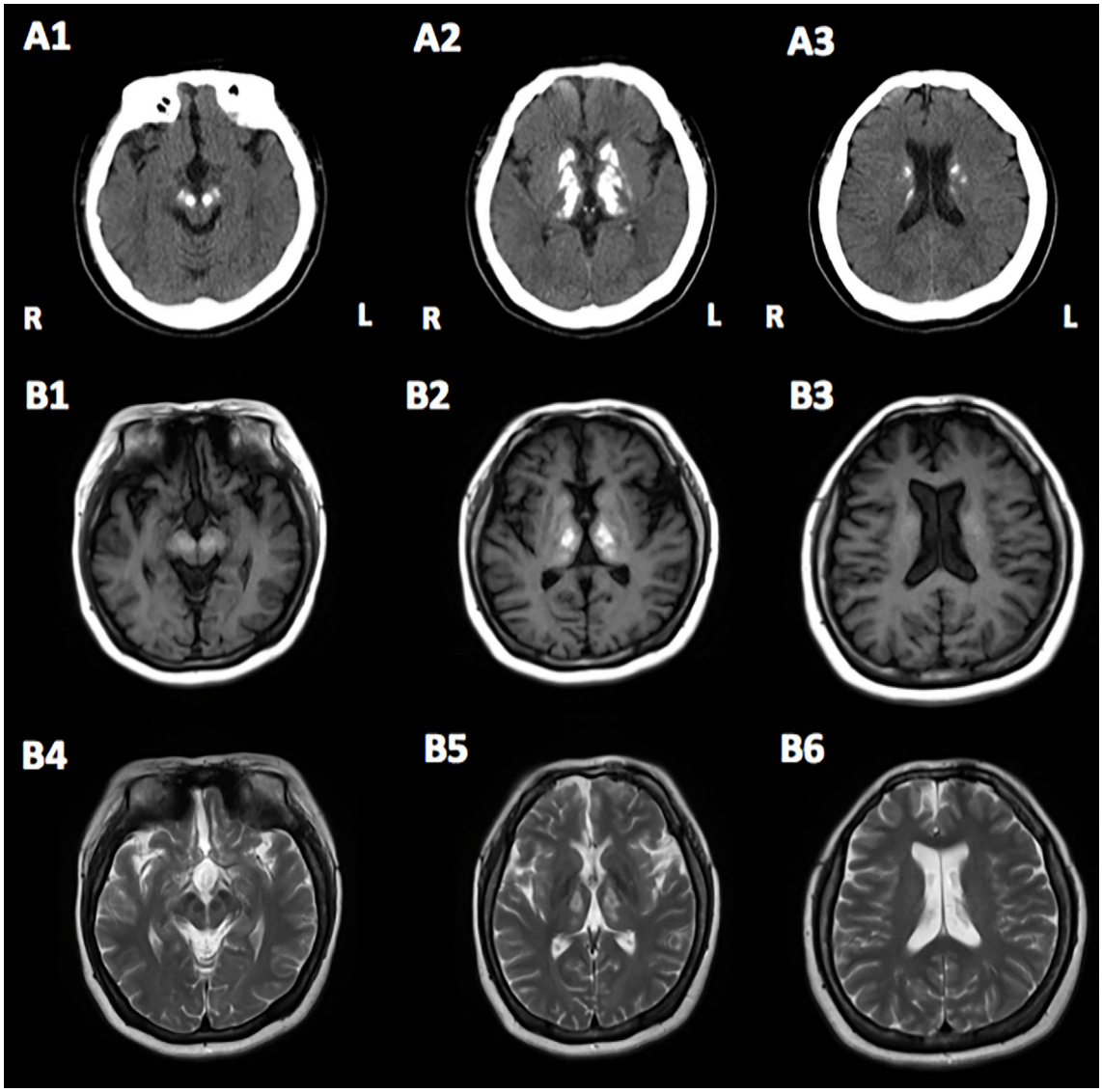

Figure 2. Findings of brain CT and MRI. A: The brain CT scan reveals high density areas at bilateral midbrain (A1), thalamus, pallidum, caudate (A2), and periventricular white matter (A3). B: T1 (B1-3) and T2 (B4-6) weighted MRI showed high intensity deposits at bilateral midbrain, thalamus and periventricular white matter.

der, depending on the affected lesions (3). Pathologically, vesicles filled with calcium deposits were observed in neurons from IBGC patients, suggesting that calcification outside neurons may affect intracellular calcium homeostasis, a disturbance of which has long been considered as a main underlying pathomechanism of Parkinson's disease (PD) (4). Indeed, a pathological hallmark of PD, which is characterized by alpha synuclein containing Lewy bodies/neurites, is also observed in IBGC patients (5). Although radiation-induced calcification has a different pathogenesis from IBGC, these results suggest that the striatal dopaminergic pathway is vulnerable to calcium deposition.

In contrast to acute or early delayed radiation reactions, late delayed reaction is often irreversible and progressive (6) and is accompanied by damage to small vessels and changes in the blood-brain barrier (BBB) permeability, which results in microangiopathy, also known as "mineralizing microangiopathy" (6), depending on the amount and duration of radiation exposure, and subsequently leads to brain parenchyma calcification (2). Importantly, proteins that are dysfunctional in patients with IBGC play a role in the BBB permeability (1, 7), indicating the importance of BBB in brain calcifications. Although brain calcification has been a common side-effect of radiation therapy and has often been associated with parkinsonism, parkinsonism specifically due to radiation-induced brain calcification has never been reported. Patients with IBGC who presented with parkinsonism showed a significant reduction in DAT binding (8), suggesting that basal ganglia calcification itself can damage the nigrostriatal dopaminergic pathway, although DaT-SPECT in our patient demonstrated an almost normal uptake (Fig. 3B), suggesting an unimpaired presynaptic function in the nigrostriatal dopaminergic pathway. Instead, the poor response to levodopa therapy suggests the possibility of post-synaptic

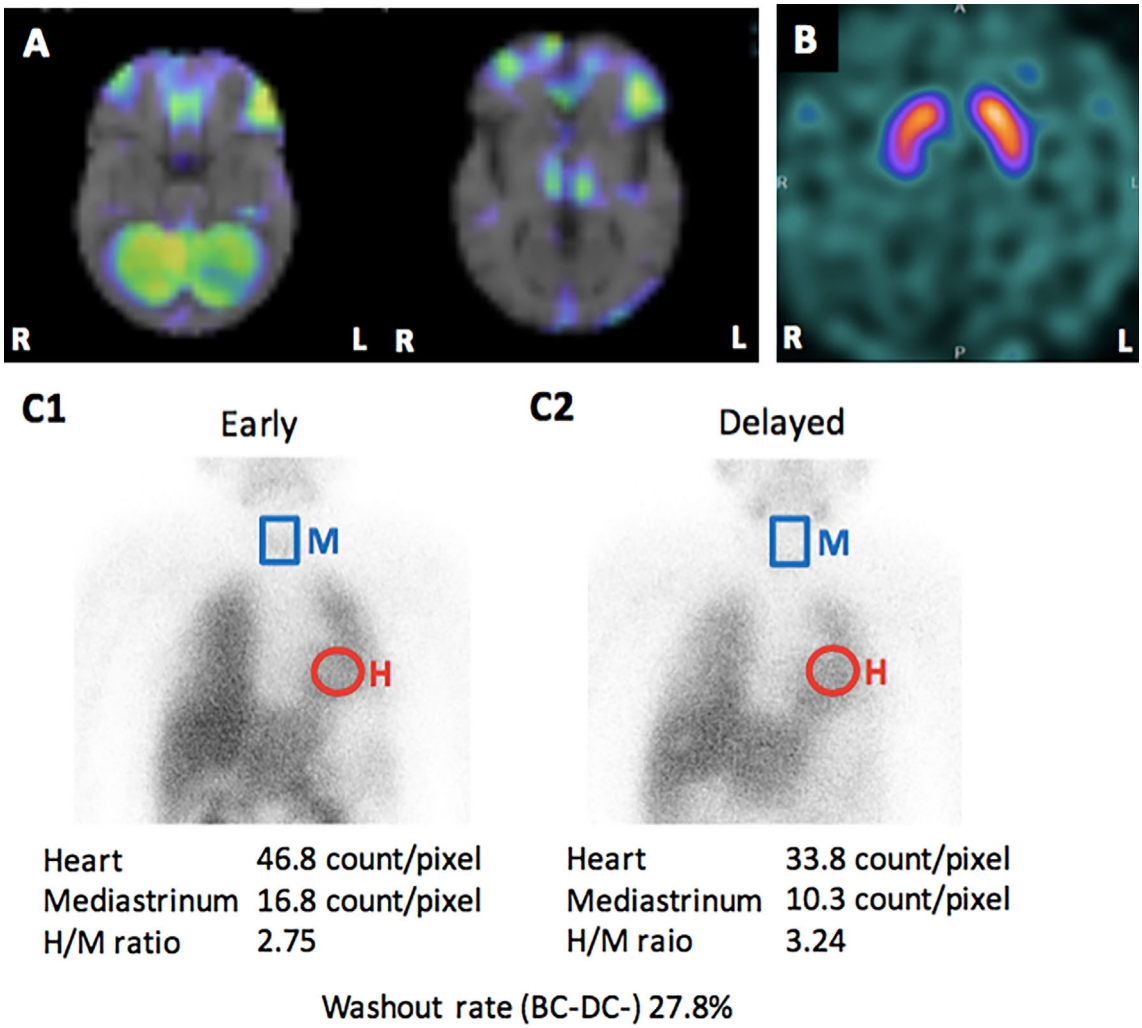

Figure 3. **Findings of nuclear medicine studies. A: ^{123}I-IMP-SPECT demonstrates decreased blood flow in entire cerebellum, in addition to bilateral basal ganglia. B: DAT-SPECT shows a slightly decreased binding of bilateral striata SBR (right 7.46, left 6.94). C: MIBG myocardial scintigraphy shows normal uptake. The H/M ratio in the early phase (E1) was 2.75 (normal range >2.2) and in the delayed phase (E2) was 3.24 (normal range >2.2). H: heart, M: mediastinum**

dysfunction in the striatum, which might have caused parkinsonism in this patient. Mineralizing microangiopathy due to brain calcification, a pathological mechanism underlying the late delayed reaction, mainly damages small vessels, which are also affected by vascular parkinsonism, showing that the target arteries are similar in size (9). Although mineralizing microangiopathy is caused by vascular endothelial injury or increased BBB permeability induced by radiation, vascular parkinsonism is caused by ischemia or atherosclerosis, neither of which existed as cardiovascular risk factors in the present patient. Both disorders are clinically characterized by lower parkinsonism, but atypical features, including upper parkinsonism, have also been reported (10, 11). Therefore, both disorders can be distinguished by not only clinical features but also clinical histories. The parkinsonism in our patient was not apparent when the calcification stayed within the basal ganglia (Fig. 1C1-3), only first presenting when it extended into the periventricular white matter (Fig. 2A1-3, Fig. 2B1-6), suggesting that this lesion was majorly responsible for her parkinsonism. However, because radiation therapy itself can lead to parkinsonism without accompanying basal ganglia calcification, making it difficult to pinpoint the origin of her symptoms.

Our case additionally showed gradually progressive limb and truncal ataxia. Although the cerebellum was free from calcification, bilateral cerebellar blood perfusion was markedly decreased (Fig. 3A), which was probably caused by CCD, as reported previously in patients with IBGC (12).

At present, no therapeutic options are available, but restoration of the BBB permeability and correcting calcium dyshomeostasis are potential targets for future treatment. Although radiation exposure has been minimized to avoid radiation-induced adverse events, the current case suggests that further restriction may be required to prevent calcification from extending to the periventricular areas.

Written informed consent was obtained from the patient for

her participation and the publication of this case report.

The authors state that they have no Conflict of Interest (COI).

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