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【 CASE REPORT 】

Reversible Non-parkinsonian Bradykinesia with Impaired Frontal Lobe Function as the Predominant Manifestation of Adrenal Insufficiency

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Abstract:
A 69-year-old Japanese man with a history of suprasellar surgery and irradiation developed bradykinesia and mild fatigue without muscle weakness, myalgia, pyramidal or extrapyramidal signs, parkinsonian symptoms, or ataxia. An endocrinological work-up revealed anterior hypopituitarism associated with secondary adrenal insufficiency. Higher brain function tests indicated an impaired frontal lobe function. The patient's bradykinesia, fatigue, and frontal lobe dysfunction improved within 2 weeks after the initiation of corticosteroid replacement therapy. To our knowledge, this is the first reported case of adrenal insufficiency manifesting as non-parkinsonian bradykinesia. Physicians should consider reversible non-parkinsonian bradykinesia associated with frontal lobe dysfunction as an unusual manifestation of adrenal insufficiency.

Key words: adrenal insufficiency, bradykinesia, frontal lobe dysfunction, hydrocortisone, hypopituitarism, non-parkinsonian

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Introduction

Glucocorticoids are a class of corticosteroids secreted from the adrenal cortex that act on most organs and tissues by binding to corticosteroid receptors (mineralocorticoid receptors and glucocorticoid receptors) (1).

Adrenal insufficiency (AI) is a clinical syndrome that is primarily characterized by glucocorticoid deficiency (2). AI can cause various general symptoms, such as fatigue generalized weakness, anorexia, weight loss, hypotension, hypoglycemia, and hyponatremia. However, the nonspecific symptoms of AI are sometimes insidious and vague, and the diagnosis of AI is challenging.

The brain is a major target organ for glucocorticoids, and corticosteroid receptors are widely expressed throughout the brain, including the hippocampus, hypothalamus, cerebellum, and cerebral cortex. Glucocorticoids play an important role in maintaining many brain functions. Although the effects of glucocorticoid deficiency on the brain are not fully understood, there are reports of AI patients who presented with neuropsychiatric symptoms (3, 4) or neurological manifestations, such as cognitive impairment (5), auditory and visual impairment (6, 7), and parkinsonism (8).

We here report the rare case of a patient with AI that manifested as non-parkinsonian bradykinesia associated with an impaired frontal lobe function, both of which improved rapidly after the initiation of corticosteroid replacement therapy.

Case Report

A 69-year-old Japanese man with a 1-year duration of non-parkinsonian bradykinesia was admitted to our hospital

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Table 1. Evaluation of Movement and Higher Brain Function.

A. Movement function: serial changes in the sit-to-stand and walking time, before and after corticosteroid replacement therapy for adrenal insufficiency

	before	3 days	1 week	10 days	2 weeks	3 months
Sit-to-stand and walking time (s)	68	64	63	57	53	53

The patient moved from sitting on a chair to a standing position, walked straight for 35 meters, turned and returned to the chair, and sat down again. The time for this sequence of actions was measured.

B. Cognitive function: serial changes in the MMSE and HDS-R scores, before and after corticosteroid replacement therapy for adrenal insufficiency

	before	1 week	2 weeks
MMSE	30	30	30
HDS-R	29	30	30

The maximum scores of the Mini-Mental State Examination (MMSE) and revised version of Hasegawa's Dementia Scale (HDS-R) are 30 and 30, respectively (10 ,11).

C. Frontal lobe function: serial changes in the FAB score, before and after corticosteroid replacement therapy for adrenal insufficiency

Items	before	1 week	2 weeks
Conceptualization	2	2	3
Mental flexibility	1	2	3
Motor programming	2	3	3
Sensitivity to interference	3	3	3
Inhibitory control	3	3	3
Environmental autonomy	3	3	3
Total score	14	16	18

The frontal assessment battery at bedside (FAB) consists of six items, the scores for each item range from 0 to 3 points, and the maximum total score is 18 (12).

in March 2017. With the except of paternal type 2 diabetes mellitus, the patient's family history was unremarkable. The patient had never smoked cigarettes and did not have a drinking habit. The patient was diagnosed with type 2 diabetes mellitus diagnosed at 47 years of age, which had been treated with antidiabetic medication. He also had a history of brain surgery and external radiotherapy for suprasellar craniopharyngioma at 52 years of age. In the spring of 2016, he developed non-parkinsonian bradykinesia and mild fatigue. Blood tests showed low levels of free thyroxine (FT_4) (0.48 ng/dL) and free triiodothyronine (FT_3) (2.22 pg/mL) and relatively low thyroid-stimulating hormone (TSH) (1.74 μIU/mL). The patient began thyroid hormone replacement therapy with oral levothyroxine (75 μg/day). However, his bradykinesia gradually worsened during thyroid hormone replacement therapy. He was referred to us for further neurological and endocrinological evaluation in March 2017. Because he had a history of surgery and radiotherapy for a suprasellar tumor, we suspected hypopituitarism and associated central hypothyroidism and AI. The oral levothyroxine was discontinued before admission because hormone replacement therapy with thyroid hormone alone can exaggerate AI symptoms when hypothyroidism and AI coexist (9).

On physical examination at admission, the patient was alert and his height, weight, temperature, blood pressure, and pulse rate were 164 cm, 67 kg (body mass index, 24.9 kg/m^2), 36.4°C, 109/60 mmHg, and 71 per minute, respectively. Although he had not noticed appetite loss, he had experienced a gradual 10-kg body weight loss over the past year. He did not have a headache, disturbed sleep, depressed mood, feelings of sadness or emptiness, or loss of interest or pleasure. There was no skin pigmentation, struma, gynecomastia or galactopoiesis, chest rales, heart murmur, abdominal tenderness, or peripheral edema. Fundoscopy revealed no evidence of diabetic retinopathy. He had mild bilateral auditory impairment and defluxion of his body hair, including his underarm and pubic hair. No eye movement abnormality, visual impairment, dysphagia, bulbar paralysis, limb paralysis, spinal or cerebellar ataxia, pyramidal or extrapyramidal tract symptoms, involuntary movements, masked face, tremors, postural instability, joint or muscle contractures, or bladder or rectal disturbance were found. He had no pain, atrophy, weakness, spasticity, stiffness, rigidity, or other tonus abnormalities in the muscles of the trunk or extremities, and he scored 5 out of 5 on a manual muscle testing. He had right and left forearm strengths of 24 kg and 21 kg, respectively, which were age-appropriate.

His movements, including gait and speech, were smooth but slow. Specifically, the patient took longer to start and carry out intended movements. To quantify the slowness of his movements, a movement function test was performed and it took him 68 seconds to perform a series of actions (Table 1A).

He obtained almost full scores on a Mini-Mental State

Table 2. Blood Chemistry on Admission (March 2017).

Hematology		
Red blood cells	465×10^4 /μL	(435-555)
Hemoglobin	13.7 g/dL	(13.7-16.8)
Hematocrit	39.7 %	(40.7-50.1)
White blood cells	5,700 /μL	(3,300-8,600)
Platelets	19.1×10^4 /μL	(15.8-34.8)
Blood chemistry		
Total protein	7.5 g/dL	(6.6-8.1)
Albumin	4.5 g/dL	(4.1-5.1)
Aspartate aminotransferase	23 IU/L	(13-30)
Alanine aminotransferase	13 IU/L	(10-42)
Urea nitrogen	14.6 mg/dL	(8.0-18.4)
Creatinine	0.59 mg/dL	(0.65-1.07)
Sodium	141 mmol/L	(138-145)
Potassium	3.9 mmol/L	(3.6-4.8)
Chloride	104 mmol/L	(101-108)
Creatine kinase	87 IU/L	(59-248)
Myoglobin	40.7 ng/mL	(0-59.9)
Aldolase	3.1 U/L	(2.7-7.5)
C-reactive protein	0.08 mg/dL	(0-0.14)
Anti-nuclear antibody	Negative	
Anti-Jo-1 antibody	Negative	
GAD autoantibody	<5.0 U/mL	(<5.0)
Fasting plasma glucose	102 mg/dL	(70-109)
C-peptide	2.1 ng/dL	(0.8-2.5)
Glycated hemoglobin	6.4 %	(4.6-6.2)
Plasma osmolality	287 mOsm/L	(275-290)
Plasma arginine vasopressin	1.1 pg/mL	
Growth hormone	0.03 ng/mL	(0-2.47)
Prolactin	21.2 ng/mL	(3.6-12.8)
Thyroid-stimulating hormone	0.56 μIU/mL	(0.50-5.00)
Adrenocorticotropic hormone	31.0 pg/mL	(7.2-63.3)
Luteinizing hormone	<0.1 mIU/mL	(0.8-5.7)
Follicle-stimulating hormone	0.6 mIU/mL	(2.0-8.3)
Free triiodothyronine	2.11 pg/mL	(2.30-4.00)
Free thyroxine	0.45 ng/dL	(0.90-1.70)
Insulin-like growth factor 1	12 ng/mL	(65-209)
Free testosterone	0.2 pg/mL	(5.3-11.5)
Cortisol	2.1 μg/dL	(4.5-21.1)
Dehydroepiandrosterone sulfate	145 ng/mL	(240- 2,440)
Aldosterone	6.2 ng/dL	(3.0-15.9)
Plasma renin activity	0.2 ng/mL/h	(0.2-2.3)

The reference range for each parameter is shown in parentheses.

Blood samples were taken in the morning in a fasting state with the patient in the supine position. The tests were conducted 7 days after discontinuing the oral levothyroxine (75 μg/day).

GAD: glutamic acid decarboxylase

Examination (MMSE) (10) and the revised version of Hasegawa's Dementia Scale (HDS-R) (11) (Table 1B). However, the results of a frontal lobe function test, the frontal assessment battery at bedside (FAB) (12), suggested a slightly impaired frontal lobe function (Table 1C).

The laboratory findings showed relatively low basal levels of adrenocorticotropic hormone (ACTH), TSH, growth hormone (GH), luteinizing hormone (LH), and follicle-stimulating hormone (FSH) in the presence of low serum FT_4, cortisol, insulin-like growth factor 1, and free testosterone (Table 2). The patient's serum prolactin level was slightly elevated. His type 2 diabetes mellitus was well controlled with no hypoglycemic attacks under treatment with oral hypoglycemic agents (glimepiride, 0.5 mg/day and metformin, 1,500 mg/day) and subcutaneous insulin injection (insulin aspart, 20 units/day).

A rapid ACTH stimulation test (Table 3A) showed sufficient aldosterone secretion, but the cortisol response was in-

Table 3. Endocrinological Investigation.

A. Rapid adrenocorticotropic hormone stimulation test in March 2017 (day 2 of admission)

	Time (min)		
	0	30	60
Cortisol (μg/dL)	1.4	7.4	9.2
Aldosterone (ng/dL)	6.0	18.0	18.9

Blood samples were taken 0 (just before), 30 and 60 min after synthetic adrenocorticotropic hormone 1-24 (cosyntropin hydroxide 0.25 mg) was administered intravenously in the morning (9 AM). Plasma endogenous adrenocorticotropic hormone levels and plasma renin activity before cosyntropin administration were 30.7 pg/mL and 0.3 ng/mL/h, respectively.

B. CRH/GRF/TRH/LHRH stimulation test in March 2017 (day 6 of admission)

	Time (min)					
	0	15	30	60	90	120
Adrenocorticotropic hormone (pg/mL)	22.3	112.2	99.2	64.4	57.4	66.4
Cortisol (μg/dL)	3.9	9.9	11.2	11.3	10.0	10.9
Thyroid-stimulating hormone (μIU/mL)	0.23	0.77	1.17	1.46	1.59	1.54
Growth hormone (ng/mL)	0.03	0.23	0.48	1.03	1.20	0.59
Prolactin (ng/mL)	17.1	38.0	38.5	38.3	34.8	32.2
Luteinizing hormone (mIU/mL)	<0.1	0.1	0.1	0.2	0.2	0.2
Follicle-stimulating hormone (mIU/mL)	0.6	0.8	0.9	1.2	1.5	1.4

The following were administered intravenously in the morning (9 AM): human corticotropin-releasing hormone (CRH; 100 μg), growth hormone-releasing factor (GRF; 100 μg), thyrotropin-releasing hormone (TRH; 500 μg), and luteinizing hormone-releasing hormone (LHRH; 100 μg). The test was conducted 12 days after discontinuing the oral levothyroxine replacement (75 μg/day). The patient had low serum levels of free thyroxine (0.42 ng/dL) and free triiodothyronine (1.64 pg/mL).

C. GHRP-2 stimulation test in March 2017 (day 8 of admission).

	Time (min)				
	0	15	30	45	60
Growth hormone (ng/mL)	0.04	0.30	0.31	0.19	0.09
Adrenocorticotropic hormone (pg/mL)	26.4	107.9	85.2	60.5	48.0
Cortisol (μg/dL)	2.3	6.9	9.2	7.7	5.7

Growth hormone-releasing peptide (GHRP)-2 (100 μg) was administered intravenously in the morning (9 AM).

complete. The mean value of three measurements of 24-h urinary free cortisol excretion on three consecutive days (29.4 μg/day, reference range: 26.0-187.0 μg/day) was low-normal. A combined anterior pituitary stimulation test (Table 3B) showed decreased responses of GH, FSH, LH, and TSH. An apparently adequate ACTH response was observed, but the cortisol response was insufficient. The growth hormone-releasing peptide-2 stimulation test (Table 3C) showed decreased GH release and an apparently adequate release of ACTH; however, the cortisol response was insufficient.

Computed tomography showed no abnormalities in the thyroid gland, lungs, liver, pancreas, kidneys, or adrenal glands. Iodine-123-metaiodobenzylguanidine myocardial scintigraphy showed normal uptake, with early and delayed phase heart-to-mediastinum ratios of 2.98 and 3.65, respectively. MRI showed no brain or spine abnormalities, including the cerebrum, hippocampus, basal ganglia, cerebellum, and brainstem, and the cervical, thoracic, lumbar, and sacral spinal cord, with the except of a thin hypophyseal stalk and a deformed pituitary gland with no recurrent tumor (Figure A-G). Magnetic resonance angiography of the brain detected no arterial abnormalities.

These findings indicated a diagnosis of anterior hypopituitarism associated with the previous brain surgery for a suprasellar tumor. The patient was deemed to have a disturbed hypophyseal stalk, with impaired pituitary somatotrophs, thyrotrophs, and gonadotrophs, and relatively intact corticotrophs and lactotrophs.

Corticosteroid replacement therapy was initiated with oral hydrocortisone (10 mg/day) for secondary AI on day 10 of admission. His non-parkinsonian bradykinesia and fatigue improved within 2 weeks (Table 1A), as did his FAB score, indicating improvement in the frontal lobe dysfunction (Table 1C).

On day 24 of admission, the oral levothyroxine (75 μg/day) replacement therapy for his central hypothyroidism was resumed, and the oral hydrocortisone dose was increased to

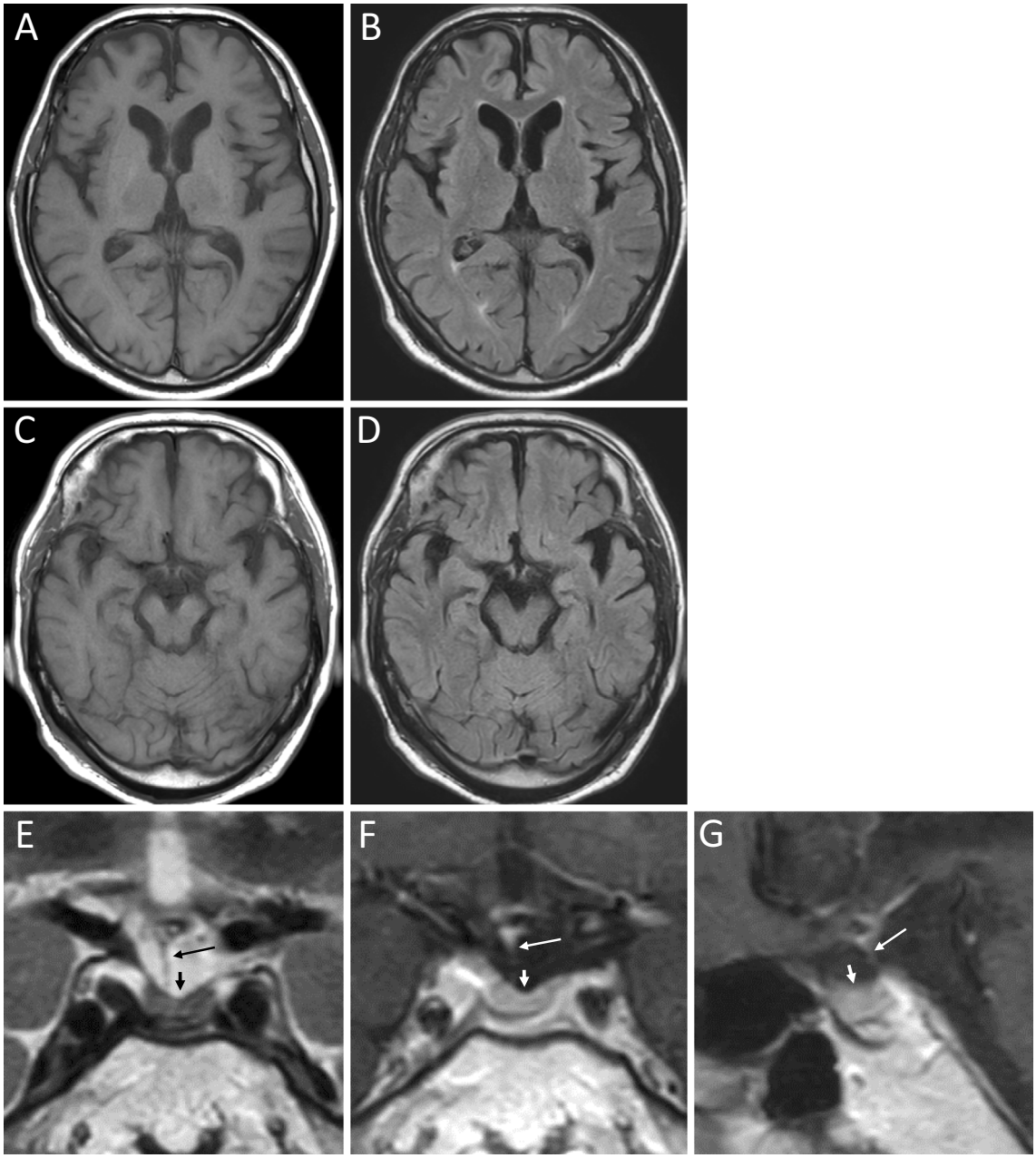

Figure. **Brain magnetic resonance imaging (March 2017). (A-D) Plain transverse T1-weighted (A, C) and fluid-attenuated inversion recovery (B, D) images show no abnormalities in the cerebrum, hippocampus, basal ganglia, cerebellum, hypothalamus, or brainstem. (E-G) T2-weighted imaging (coronal plane) (E) and gadolinium-enhanced T1-weighted imaging (F, coronal plane; G, sagittal plane) showed a thin hypophyseal stalk (arrow) on the right side of the midline and a deformed pituitary gland (short arrow). No recurrent tumor was found.**

12.5 mg/day. The patient was discharged on day 28 of admission.

Since discharge, his clinical course has been uneventful, with no movement abnormality (Table 1A) on replacement therapy with oral hydrocortisone (12.5 mg/day) and levothyroxine (75 μg/day) for his AI and hypothyroidism secondary to anterior hypopituitarism.

Discussion

A patient who had undergone surgery and radiotherapy for a suprasellar tumor 16 years previously developed bradykinesia and mild fatigue without muscle weakness, myalgia, joint contracture, pyramidal or extrapyramidal tract signs, parkinsonian symptoms, or ataxia. A higher brain function test, the FAB, indicated slight impairment of the frontal lobe function (Table 1C). Brain MRI detected no abnormalities with the exception of a stable postsurgical suprasellar state, with no recurrent tumor (Figure). A detailed endocrinological examination revealed anterior hypopituitarism with multiple pituitary hormone deficits, associated with GH deficiency, central hypothyroidism, and AI (Ta-

ble 3). Brain surgery and radiotherapy for a suprasellar tumor can cause late-onset dysfunction of the pituitary gland and other parts of the brain, including the frontal lobe (13, 14). GH deficiency, hypothyroidism, and AI may each cause fatigue and slow movement (2, 15, 16). Our patient had experienced worsening bradykinesia and fatigue on thyroid hormone replacement therapy; however, his symptoms improved and FAB scores normalized within 2 weeks after the initiation of corticosteroid replacement therapy (Table 1A and C). These findings suggest that our patient had reversible non-parkinsonian bradykinesia and an impaired frontal lobe function, both of which were caused mainly by AI secondary to hypopituitarism associated with the previous brain surgery and irradiation for a suprasellar tumor. To our knowledge, this is the first reported case of AI manifesting as non-parkinsonian bradykinesia.

The mechanisms underlying the reversible non-parkinsonian bradykinesia accompanied by an impaired frontal lobe function in our AI patient remain unclear. The major components of the central nervous system hierarchy essential for producing normal movements include the frontal lobe (planning, sequencing, and executing movements), spinal cord (carrying efferent motor and afferent sensory information), basal ganglia (modulating movement forces), and cerebellum (correcting movement errors) (17). Impairment of the basal ganglia can cause bradykinesia, which is usually associated with extrapyramidal tract disorders, such as parkinsonism (18). As the frontal cortex plans and executes precise movements, coordinating different body parts to carry them out (17), bradykinesia may occur without extrapyramidal tract symptoms if the frontal lobe function is impaired (19). Studies have implied a connection between glucocorticoids and specific areas of brain perturbation, including the hippocampus and frontal lobe region (20, 21). Our patient did not present with extrapyramidal tract disorders; his bradykinesia was associated with frontal lobe dysfunction including altered motor programming, and both his bradykinesia and frontal lobe dysfunction improved rapidly after the initiation of glucocorticoid replacement therapy (Table 1A and C). These findings suggest that the non-parkinsonian bradykinesia in our patient was caused by reversible frontal lobe dysfunction due to glucocorticoid deficiency.

The clinical characteristics of AI in our patient included pronounced non-parkinsonian bradykinesia associated with impaired frontal lobe function, while the typical general symptoms of AI, such as weakness, anorexia, low blood pressure, hypoglycemia, and electrolyte disturbance, were less obvious. In a similar case, AI manifested only as marked neuropsychological manifestations without the typical general symptoms of AI (4). The reasons for the divergence between marked neurological and less marked general symptoms of AI in our patient are uncertain. However, the clinical presentation of AI varies from case to case depending on many factors, including age, the degree or duration of glucocorticoid deficiency, the severity of the impairment of the affected organs, and the acuteness with which adrenal function is lost (7, 22). Our patient developed AI symptoms 16 years after suprasellar surgery and radiotherapy. Endocrinological tests indicated central AD (Table 3A-C), while urinary levels of free cortisol implied that his glucocorticoid deficiency was mild. In addition, the presence of type 2 diabetes mellitus associated with obesity may mask or reduce the AI symptoms of hypoglycemia and appetite loss (23). Brain irradiation has the potential to cause dysfunction of glucocorticoid actions in the brain through the altered expression of the corticosteroid receptor (24); thus, the previous brain radiotherapy might have reduced the damage threshold of glucocorticoid deficiency in the brain of our patient. These findings suggest that a gradual-onset mild chronic glucocorticoid deficiency, coexisting type 2 diabetes mellitus, and a frontal lobe that was easily affected by glucocorticoid deficiency resulted in less marked general symptoms compared with the frontal lobe symptoms and probably accentuated the non-parkinsonian bradykinesia as the predominant manifestation of AI in our patient.

The pathophysiology of hypopituitarism after brain surgery and radiotherapy for a suprasellar tumor may include hypothalamus or pituitary damage, and alteration of the hypophyseal stalk and portal vessels (9). Our patient had low basal GH, gonadotropins, and TSH levels, relatively low ACTH levels, and slightly high basal prolactin levels. The administration of exogenous GRF, LHRH, TRH, and CRH produced incomplete secretion of pituitary GH, gonadotropins, and TSH and apparently adequate release of prolactin and ACTH, while the cortisol release was insufficient (Table 3B). The patient showed poor GH release, but adequate ACTH release with insufficient cortisol release in response to the administration of GHRP-2 (Table 3C), which is a secretagogue of both pituitary GH and ACTH (25). Brain MRI showed a thin pituitary stalk and deformed pituitary gland (Figure E-G). Therefore, the patient probably had impaired pituitary somatotrophs, gonadotrophs, and thyrotrophs, and relatively intact lactotrophs and corticotrophs, and had an altered hypothalamus or hypophyseal portal system that reduced the secretion or delivery of hypothalamic hormones, including CRH, TSH, and prolactin-inhibiting factor, to the anterior pituitary.

Only a few studies have investigated the cognitive function, including the memory, attention, concentration, and executive function, of AI patients in comparison to controls using different objective measures (5, 26-28). Regarding the frontal lobe function (29), studies using the Stroop Color Word Test (SCWT) (26) or the Brief Test of Adult Cognition by Telephone (27) found no impaired performance (including executive function, reasoning, attention, and speed of processing) in patients with primary AI (Addison's disease) who received corticosteroid replacement therapy, while the SCWT performed after the short-term discontinuation of corticosteroid replacement detected impaired attention (28). A recent study has shown that patients with Addison's disease - even on corticosteroid replacement therapy - exhibit

impaired executive functions, as assessed by the Verbal Fluency Test and the Trail Making Test (5). In the present case, the patient with non-parkinsonian bradykinesia was suspected of having frontal lobe dysfunction, and we performed the FAB before starting corticosteroid replacement. There are few reports on objective evaluation of the frontal lobe function of patients with untreated AI. In our patient, the slightly low FAB scores normalized and his fatigue and non-parkinsonian bradykinesia improved after the initiation of corticosteroid replacement therapy (Table 1C). These findings imply that the serial changes in the FAB scores reflected at least a partial resolution of his frontal lobe dysfunction, which had been caused by glucocorticoid deficiency.

Unlike hypercortisolemia-induced brain impairments, such as the brain atrophy associated with cognitive impairment (30, 31), few studies have focused on the imaging features of the brain affected by hypocortisolemia. A previously reported patient with Addison's disease who showed psychiatric symptoms as the only manifestation of AI, showed no morphological abnormalities on brain MRI (4). A case of isolated ACTH deficiency manifesting predominantly as parkinsonism showed no morphological abnormality in the brain, with the exception of an empty sella, on MRI (8). Similarly, MRI of our patient detected no morphological abnormality in the brain, with the exception of a stable post-surgical suprasellar state (Figure A-G). In comparison, a study using brain blood oxygenation level-dependent functional MRI implied an association between brain functional changes, such as brain plasticity and functional control reorganization, and glucocorticoid deficiency in patients with chronic renal failure undergoing hemodialysis (32). Thus, in the future, structural and functional imaging investigations, such as functional MRI, may be useful for detecting brain alterations in similar cases, when patients present with AI manifesting with neurological symptoms.

In conclusion, we herein described the case of a patient who exhibited non-parkinsonian bradykinesia associated with frontal lobe dysfunction as the predominant manifestation of AI. His bradykinesia and frontal lobe dysfunction improved rapidly after the initiation of corticosteroid replacement therapy. Physicians should be aware that reversible non-parkinsonian bradykinesia associated with an impaired frontal lobe function is an unusual manifestation of AI.

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

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