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【 CASE REPORT 】

Cognitive Impairment Caused by Isolated Adrenocorticotropic Hormone Deficiency Mimicking Dementia with Lewy Bodies

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Abstract:
A 73-year-old man who presented with nonspecific general symptoms and cognitive impairment was initially diagnosed with mild cognitive impairment due to dementia with Lewy bodies (DLB) based on a reduced blood flow in the parietal and occipital lobes on single-photon emission computed tomography (SPECT) imaging. However, the patient later presented with hyponatremia and hypoglycemia, leading to impaired consciousness, and was diagnosed with isolated adrenocorticotropic hormone deficiency (IAD). Hydrocortisone treatment improved the blood test scores and general symptoms, including cognitive impairment. IAD may show a DLB-like presentation on cerebral blood flow SPECT; therefore, caution is required for the correct diagnosis of IAD.

Key words: cognitive impairment, isolated adrenocorticotropic hormone deficiency, adrenal insufficiency, treatable dementia, dementia with Lewy bodies

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Introduction

Adrenal insufficiency (AI) is a known cause of treatable dementias. Isolated adrenocorticotropic hormone (ACTH) deficiency (IAD) is a rare endocrine disorder characterized by insufficient production of ACTH by the pituitary gland in the absence of other pituitary hormone deficiencies.

We herein report a case of IAD that was initially difficult to diagnose because the patient presented with various physical symptoms and cerebral blood flow single-photon emission computed tomography (SPECT) showing dementia with Lewy body (DLB)-like findings. The diagnosis of IAD was later made after a disturbance of consciousness accompanied by hyponatremia and hypoglycemia. Her cognitive function markedly improved with the administration of corticosteroids.

Case Report

A 73-year-old man who received oral levothyroxine for hypothyroidism developed elbow pain and complained of fatigue. Initially, his blood pressure was maintained with antihypertensive medication. However, when his systolic blood pressure dropped to approximately 80 mmHg, antihypertensive medication was discontinued. Subsequently, his systolic blood pressure remained at approximately 100 mmHg. The patient also had decreased appetite and anemia and underwent trunk computed tomography (CT) and endoscopy at a nearby general hospital; however, no significant findings were observed. Although head CT showed no brain atrophy, the Mini-Mental State Examination (MMSE) score was 25/30. After discharge from the hospital, the patient lost 8 kg in 2 months and tended to be bedridden and withdrawn. He was referred to our hospital because of dementia.

The patient was 162 cm tall, weighed 46.2 kg, and had a body mass index of 17.6 kg/m^2. His vital signs included

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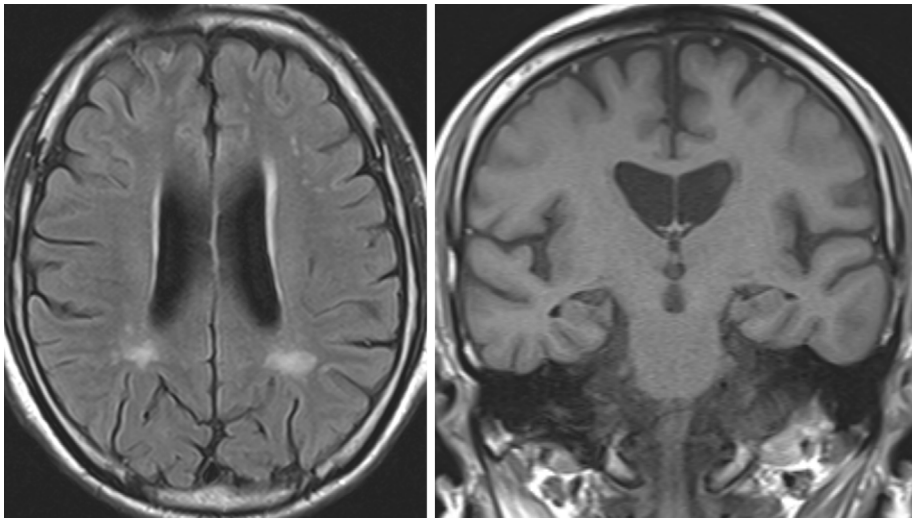

Figure 1. Head MRI showing no noticeable signal abnormalities or brain atrophy, except for some ischemic changes. The Z-score analyzed using the voxel-based specific regional analysis system for Alzheimer's disease (VSRAD) software program was 0.99.

blood pressure of 98/59 mmHg, pulse rate of 65 beats per minute, and body temperature of 36.5 °C.

The patient underwent a comprehensive neuropsychological evaluation, scoring 22 points on the MMSE (3/5 points for time orientation, 4/5 points for spatial orientation, 3/3 points for registration, 2/5 points for calculation, 2/3 points for delayed recall, 2/2 points for naming, 0/1 point for repetition, 3/3 points for verbal commands, 1/1 point for written commands, 1/1 point for writing, and 1/1 point for copying), 18 points on the Alzheimer's Disease Scale for the Japanese Cognitive Subscale (ADAS-J cog.) and 10/18 on the Frontal Assessment Battery (FAB) (2/3 points for similarities, 1/3 points for lexical fluency, 0/3 points for motor programming, 3/3 points for inhibitory control, 1/3 points for sensitivity to interference, and 3/3 points for environmental autonomy). These scores indicate moderate cognitive impairment, particularly in orientation, attention, and executive function. The Clinical Dementia Rating is 0.5. His neuropsychological profile, assessed using the Neuropsychiatric inventory, indicated deficits in depression, anxiety, and motivation. Individual muscle strength and tone were normal, although each movement was time consuming.

Initial blood tests revealed no significant findings, other than mild normocytic anemia and liver damage. Blood glucose, sodium, potassium, calcium, and vitamin B levels were within normal limits. Thyroid-stimulating hormone (TSH) levels under oral levothyroxine were normal, whereas those of free thyroxine were slightly decreased to 0.76 ng/dL (reference value: 0.90-1.70 ng/dL). Head magnetic resonance imaging (MRI) showed no noticeable signal abnormalities or brain atrophy, except for some ischemic changes (Fig. 1). Cerebral blood flow SPECT showed hypoperfusion in the parietal and occipital lobes, which was considered significant according to the easy Z-score imaging system analysis (Fig. 2). Despite the absence of brain atrophy on MRI and no significant decline in MMSE scores on short-term memory tasks, SPECT findings were consistent with those of DLB. However, the patient did not present with any parkinsonian symptoms, rapid eye movement sleep behavior disorder (RBD), or hallucinations. Therefore, the patient was diagnosed with mild cognitive impairment (MCI) of unknown cause, and donepezil was prescribed with the expectation that it would improve motivation.

After donepezil treatment, the motivation, appetite, and physical performance gradually improved. However, blood test results remained largely unchanged.

Two months later, the patient experienced pain in the left shoulder. As he experienced appetite loss and became increasingly unresponsive to treatment, he was admitted to our hospital.

Subsequently, the patient's consciousness deteriorated [Glasgow Coma Scale (GCS): E4V2M4]. Blood tests at this point showed marked hyponatremia (115.1 mmol/L), hypochloremia (82.7 mmol/L), and hypoglycemia (23 mg/dL); however, the TSH and free thyroxine levels under oral levothyroxine were in the normal range.

We considered hyponatremia and hypoglycemia to be the main causes of impaired consciousness. After correcting these issues, the patient's level of consciousness improved (GCS score: E4V5M6).

Because arthralgia, easy fatigue, hypotension, appetite loss, weight loss, liver dysfunction, and normocytic anemia were attributed to AI, hydrocortisone was administered intravenously. Pretreatment cortisol levels were significantly reduced to 0.39 μg/dL (reference range: 7.07-19.6 μg/dL). All symptoms improved with no recurrence of hypoglycemia, hyponatremia, liver dysfunction, or normocytic anemia. Contrast-enhanced CT of the abdomen revealed no adrenal gland abnormalities. Corticotropin-releasing hormone and thyrotropin-releasing hormone loading tests showed no response to ACTH and cortisol and a low response to TSH. Thus, we considered this patient to have central hypothy-

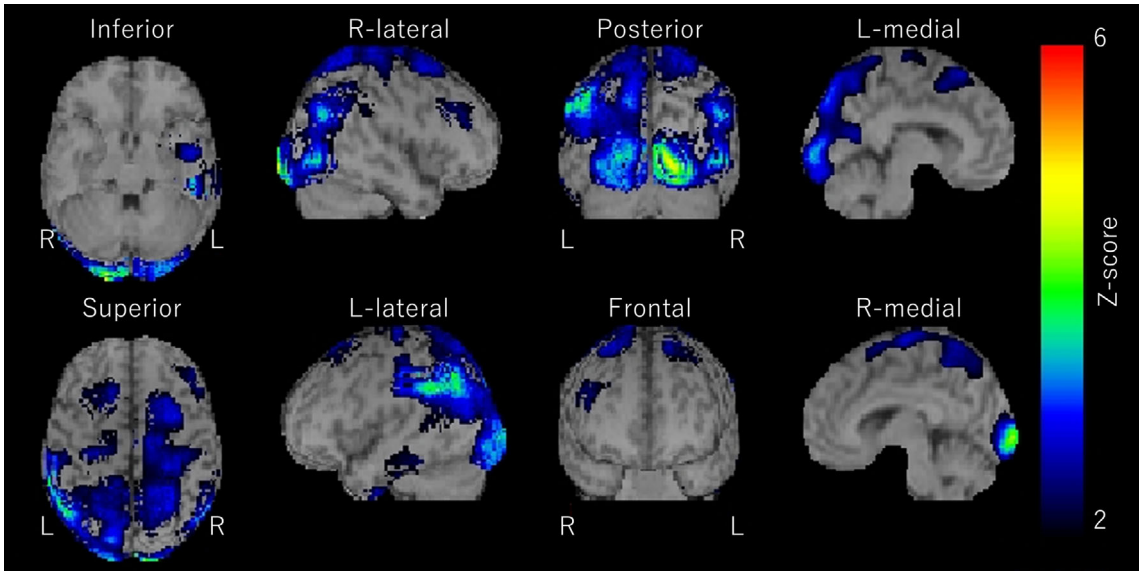

Figure 2. **Findings on brain single-photon emission computed tomography (SPECT) with ^{99m}TC-ethyl cysteinate dimer using the easy Z-score imaging system analysis. The color scale for the Z score is shown on the right side of the figure. Images are presented in color when the Z-score is >2. Hypoperfusion is visible in the parietal and occipital lobes. L: left, R: right**

roidism but with residual TSH secretory capacity. Accordingly, the diagnosis of IAD was confirmed.

Consequently, donepezil was discontinued and oral hydrocortisone (15 mg/d) was continued. Immediately after discharge, a neuropsychological assessment revealed a score of 25 on the MMSE, 12 on the ADAS, and 13 on the FAB. A follow-up neuropsychological assessment at 18 months post-discharge showed that MMSE, ADAS, and FAB scores were maintained at 25, 11, and 14, respectively. In addition, the patient did not present with any Parkinsonian symptoms, RBD, hallucinations, or cognitive fluctuations.

Discussion

In IAD, ACTH secretion is reduced, resulting in secondary AI. IAD is thought to be caused by autoimmune damage to the ACTH-producing cells of the pituitary gland. The symptoms in our case improved with corticosteroid administration, resulting in a favorable prognosis. Furthermore, as in this case, the most common complication of IAD is thyroid disease (1, 2).

Because of the nonspecific clinical symptoms of AI, the correct diagnosis may be delayed. The most common misdiagnoses are gastrointestinal or psychiatric disorders; thus, reaching an accurate diagnosis can take more than five years (2). The typical symptoms of IAD include decreased appetite, weight loss, and lethargy, as in this case. Arthralgia, hypotension, liver dysfunction, normocytic anemia, hyponatremia, and hypoglycemia are also often observed in IAD (2-4).

IAD impairs the cognitive function. However, unlike the thyroid function measured in routine clinical practice, evaluating isolated ACTH levels in the differential diagnosis of dementia of unknown etiology in the absence of signs and symptoms of endocrine dysfunction can be difficult. In the present case, only a few laboratory findings were suggestive of AI during initial treatment. Furthermore, temporary stimulation of motivation following donepezil administration made the diagnosis even more difficult. However, an episode of impaired consciousness due to hyponatremia and hypoglycemia during the clinical course provides clues for the diagnosis of IAD.

An overview of the entire course of this case suggests that the adrenal and thyroid functions of the patient were impaired from the outset. In general, when adrenal insufficiency is combined with hypothyroidism, symptoms of adrenal insufficiency become apparent when thyroid hormones are supplemented (5). Therefore, corticosteroids should first be administered when both conditions occur. However, in practice, thyroid hormones (levothyroxine) are usually administered first because, as in this case, only the thyroid function is initially assessed.

We believe that in this case, the symptoms of adrenal insufficiency were aggravated by the early introduction of levothyroxine, which caused chronic adrenal hormone deficiency.

The main feature of the present case was the DLB-like findings on cerebral blood flow SPECT. In general, DLB is often associated with hypometabolism and hypoperfusion in the occipital region as well as cholinergic neurotransmission disorders. Cholinergic neurons in the basal forebrain may be the brain regions affected earlier in DLB (6). Therefore, the observed hypoperfusion may in part be related to cholinergic dysfunction in the basal forebrain (6). All areas of the forebrain, excluding the basal ganglia, are projected from the locus coeruleus (LC) (7). The LC is a nucleus composed of

cell bodies of noradrenergic neurons that release norepinephrine (7). Noradrenergic neurons in LCs may also be targeted by glucocorticoids (8). Therefore, reduced cortisol levels may lead to reduced stimulation of the LC, resulting in a reduced basal forebrain function. We suspected that this was the reason for the DLB-like findings on the cerebral blood flow SPECT.

Accordingly, the cognitive function improved significantly after the introduction of hydrocortisone and discontinuation of donepezil. As no SPECT images were taken after hydrocortisone induction, improvement in the cognitive function with improvement in psychiatric symptoms cannot be ruled out. However, the lack of cognitive decline over the course of 18 months suggested that the MCI presented by the patient was not due to degenerative diseases, such as Alzheimer's disease or DLB.

Conclusions

This case suggests that even if SPECT findings show a DLB-like presentation, careful distinction is required if brain atrophy and short-term memory loss with any parkinsonian symptoms, RBD, hallucinations, or cognitive fluctuations are not evident. Careful attention to various nonspecific syndromes may also raise suspicion of IAD.

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

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