The Possible Link between GABAergic Dysfunction and Cognitive Decline in a Patient with Idiopathic Hypoparathyroidism

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Abstract

Idiopathic hypoparathyroidism (IHP) is accompanied by cognitive impairment. We report the case of a 70-year-old IHP patient with cognitive disturbance. Brain computed tomography showed bilateral calcification in basal ganglia, thalamus, and cerebellum. Neuropsychological assessment revealed low scores for intelligence, memory, and perseverative errors. Brain positron emission tomography showed a significant reduction in [18F]-Fludeoxyglucose (FDG) uptake in bilateral frontal, left temporal and parietal cortices, along with a marked reduction in [11C]-flumazenil binding in left frontal, temporal, parietal, and bilateral cerebellum. These findings suggest cognitive impairment in IHP may be ascribed to GABAergic dysfunction, thus leading to, or coexisting with, cerebral hypometabolism.

Key words: idiopathic hypoparathyroidism (IHP), FDG PET, flumazenil PET, GABA receptor, cognitive impairment


Introduction

Idiopathic hypoparathyroidism (IHP) is a relatively rare endocrine deficiency disease characterized by deficiency of the parathyroid hormone and hypocalcemia. The clinical features of this disease are tetany, muscle cramps, paresthesia, convulsions, and seizures. In addition, various degrees of neuropsychiatric disorders, including cognitive impairment, have been reported in IHP (1, 2), which makes the pathophysiology of IHP a possible cause of dementia. However, despite this understanding, the mechanism of cognitive dysfunction seen in IHP patients remains unexplored. Here, we report a case of IHP with cognitive impairment, where a global reduction in GABAergic function-related [11C]-flumazenil binding concomitant with cerebral glucose hypometabolism was found in the brain of a living patient using positron emission tomography (PET).

Case Report

Patient

A 70-year-old Japanese woman was referred to hospital in relation to a complaint of stiffness in the upper extremities. Her past medical history was as follows. In her youth she had performed normally in exercise and school work, and she had been in good health until she was approximately 40 years old. She reported involuntary muscle contractions of the face, and such episodes occurred suddenly as she was beginning to talk and lasted for a short period. When she was approximately 56 years of age, a blood test revealed a remarkable increase in the level of creatine kinase. At age 65, she suffered from bilateral cataracts, and at 70 years of
age (approximately) she noticed stiffness in her hand muscles. Her medical history showed that she had received no treatment that included surgery or irradiation of the thyroid, and there was no family history of thyroid-related disease. In addition, she was a rare consumer of alcohol, and took no medication or antipsychotic drugs such as benzodiazepines.

On physical examination, she had no stature abnormalities, including shortness of stature or brachydactyly. On neurological examination (at age 70) she exhibited a bilateral positional tremor of the upper limbs. Trousseau’s sign and the bilateral Chvostek’s sign were positive. Muscle tonus was normal with no atrophy. However, no abnormalities were found in muscle strength, coordination, the sensory system, and autonomic function.

Laboratory studies showed a low serum calcium level (6.2 mg/dL) and a high serum phosphate level (6.4 mg/dL). The levels of serum lactate dehydrogenase (LDH; 415 U/L) and creatine phosphokinase (CPK; 799 U/L) were increased. A blood gas analysis, urinalysis, blood counts, and other routine laboratory tests were normal. On endocrinological examination, the serum intact-parathyroid hormone level was found to be as low as 5.8 pg/mL, but the serum 1,25(OH)2 vitamin D3 level was normal. Furthermore, a thyroid func-

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**Figure 1.** (a) Brain computed tomography (CT) scan in a patient with IHP. A CT scan revealed calcification in the bilateral basal ganglia, thalamus, and dentate nucleus. (b) FLAIR images of MRI show mild periventricular hyperintensity.
Magnetic resonance imaging (MRI) showed mild periven-tricular hyperintensity (Fig. 1b). Magnetic resonance imaging (MRI) showed mild periven-tricular hyperintensity (Fig. 1b).

Based on the patient’s clinical and laboratory findings, she was finally diagnosed with IHP at age 70. The Ellsworth-HHoward test could have been undertaken to assess the function of the parathyroid hormone (PTH) receptor, but it was not performed. In accordance with the development of the PTH assay, the Ellsworth-HHoward test is not considered necessary in the diagnosis of IHP when the measured serum intact-PTH levels are low (2).

Neuropsychological assessment revealed deterioration in intellectual ability (total IQ, 75; verbal, 81; and performance, 74 on the Wechsler Adult Intelligence Scale III) and low scores on the Wechsler Memory Scale-Revised test (verbal memory, 72; visual memory, 71; general memory, 70; attention/concentration, 77; and delayed recall, 89). She performed relatively well in a number of categories, and completed the Wisconsin Card Sorting Test with a total score of 3 (a value of 3 or more for subjects aged >65 years old is considered normal) (3). However, the number of perseverative errors in relation to the Nelson type score was 14 (the cut-off for the perseverative score is 4/5) (4). Her Self-rating Depression Scale result was within the normal range.

This study was approved by the appropriate ethics committee, and was therefore performed in accordance with the ethical standards of the 1964 Declaration of Helsinki. The patient provided written informed consent to participate in this study.

PET imaging

After fasting overnight for at least 12 hours, [¹⁸F]-Fludeoxyglucose (FDG) PET was performed using a high-resolution brain PET scanner (SHR12000, Hamamatsu Photonics, Hamamatsu, Japan) to investigate glucose metabolism in the left frontal, temporal, and parietal lobes was observed.

PET imaging

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Figure 3. $[^{11}C]$-flumazenil PET findings. (a) Superimposed PET/MRI images of $[^{11}C]$-flumazenil binding in a patient and an age-matched normal control. The color bar denotes the level of $[^{11}C]$-flumazenil binding potential. (b) A three-dimensional stereotaxic surface projection (3D-SSP) map of brain $[^{11}C]$-flumazenil binding. In the patient, marked reductions in $[^{11}C]$-flumazenil binding are shown predominantly in the left frontal, temporal, and parietal lobes and the bilateral posterior lobe of the cerebellum with right side dominance. In contrast, there is no significant reduction in $[^{11}C]$-flumazenil binding in an age-matched normal subject.

Discussion

This study revealed significant reductions in $[^{11}C]$-flumazenil binding globally in the brain, including within the cerebellum, and in $[^{18}F]$-FDG uptake in the cerebral cortex in an IHP patient. The patient was found to have a cognitive impairment, as determined by low scores for intelligence, memory, and in executive function tests. It has been reported that the incidence of cognitive impairment in IHP patients is 8-25% (2, 10, 11), but imaging studies of higher brain dysfunction in IHP have been very sparse. As shown in this case report, global GABAergic dysfunction along with cerebral hypometabolism, is suggestive of one possible cause of cognitive impairment in an IHP patient.

Several studies claim that intracranial calcification is responsible for a deterioration in intelligence (12-15). Because calcification is commonly seen in IHP patients (2), it may be easier to assume that intracranial calcification is the cause for cognitive decline. However, the regions with calcification in our patient included the basal ganglia, thalamus, and cerebellum, and not the cerebral cortical areas. One possible explanation of the calcification theory might be that extensive calcification can affect the cognitively important
frontostriatal circuit in a top-down fashion, and disruption of the neural circuit within the fronto-temporoparietal-cortex via the cerebellum would lead to the cerebellar cognitive affective syndromes, such as executive dysfunction and memory impairment (16, 17). The patterns of these neuropsychological deficits were consistent with the findings in our patient. Some reports have contradicted this theory however, because dementia symptoms seen in IHP patients are ameliorated with treatment using 1α-hydroxycholecalciferol, while the intracranial calcification remains constant (11, 18). In addition, the patient in this study manifested a left-side dominance of hypometabolism, despite the fact that there was no laterality of calcification or brain atrophy. Thus, it is unlikely that the calcification itself would be a direct culprit for cognitive deterioration or reduced \(^{18}F\)-FDG uptake in IHP patients.

In this study, a \(^{11}C\)-flumazenil PET scan showed a significant reduction in binding in the brain, including within the cerebellum. \(^{11}C\)-flumazenil is an antagonistic radioligand that binds to the central benzodiazepine receptor sites of the GABA-A complex, and is used to investigate the in vivo GABAergic system residing in the interneurons of the cerebral cortex, which indicates that \(^{11}C\)-flumazenil can be considered a radiotracer for neuronal cell density. The reduced density of cerebellar neurons, as revealed by the remarkably low \(^{11}C\)-flumazenil uptake, is possibly due to calcification developing over a long time, and the frontotemporal glucose hypometabolism in our patient suggests that disruption of the neural network in the cerebral cortex-basal ganglia-cerebellum occurring over a long period of time might be responsible for the development of cognitive deterioration. With no vascular insult present in the MRI, this type of deterioration features frontotemporal dysfunction, unlike amnesia-centered dementia such as that seen in Alzheimer’s disease or vascular dementia. This is rather similar to the calcification theory (15, 16), but our study emphasizes that GABAergic dysfunction, together with supratentorial brain hypometabolism, may be more important than calcification deposition. Reduced \(^{11}C\)-flumazenil, and normal FDG accumulations in the cerebellum with normal cerebellar symptoms were seen in this patient. This suggests that an alteration of cerebellar GABA-A receptors might precede cerebellar dysfunction, because various neurological manifestations, including cerebellar ataxia, have been reported in patients with IHP (2, 19). Another possibility is that glucose metabolism in the cerebellum might be augmented in a compensatory manner. However, this issue needs further study.

In conclusion, in the present study, a functional brain imaging study in an IHP patient with cognitive impairment revealed decreased glucose metabolism in the frontal, temporal, and parietal cortices. It is considered that our case report, which includes reference to GABAergic imaging, can provide additional information about its possible etiology in the cognitive decline associated with IHP, suggesting that extensive GABAergic dysfunction in the cerebellum might be pathophysiologically important in the disease. Thus, a depiction of GABAergic dysfunction in the living brain, as shown in this study, may be helpful in unravelling the underlying pathology relating to cognitive impairment in IHP. To confirm this, a large-scale analysis of IHP patients with and without cognitive impairment is considered necessary.

Author’s disclosure of potential Conflicts of Interest (COI).

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