Hyperparathyroidism Associated with Parkinsonism

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A 70-year-old woman with hyperparathyroidism associated with parkinsonism is reported. Her primary initial symptom was parkinsonism, but it was levodopa-resistant. Chemical and hormonal findings revealed that she had hyperparathyroidism. The symptoms were relieved after the surgical removal of a parathyroid adenoma. Although this type of case has been reported only rarely, it suggests that hypercalcemia might be an aggravating factor in levodopa-resistant parkinsonism.

(Internal Medicine 31: 904–907, 1992)

Key words: hypercalcemia, parathyroid hormone, parathyroidectomy, parkinson's disease, levodopa-resistant

Introduction

Neuropsychiatric signs and symptoms have been found in patients with parathyroid gland disorders (1, 2). However, extrapyramidal motor manifestations in hyperparathyroidism (3–5) have not been reported in the literature as often as in hypoparathyroidism (6–10). Hayabara et al reported a case of Parkinson's disease associated with hypercalcemia, followed by relief of the symptoms after surgery for parathyroid adenoma (5).

Here we report a female case of hyperparathyroidism associated with parkinsonism, in which the initial predominant symptoms were parkinsonian features. The effect of parathyroidectomy on levodopa-resistant parkinsonism is described and discussed.

Case Report

A 70-year-old Japanese woman was referred to our clinic with a history of parkinsonism for 3 years and anorexia for 1 year. Before that time she had been well, and there was no family history of neurological disorders. The patient's initial symptoms included tremor in her right hand, difficulty in writing, poorly articulated speech, and difficulty in walking because of a slow gait, with frequent loss of balance. Rigidity was not so marked initially. The diagnosis of Parkinson's disease was made and levodopa (800 mg/day), bromocriptine (15 mg/day), and trihexyphenidyl hydrochloride (4 mg/day) were ad-

ministered; slight response to medication was noted. Over the next three years her symptoms progressed slowly. In January 1988, benserazide hydrochloride was added to the regimen and the dosage was slowly increased. However, her symptoms progressed and were accompanied by anorexia and body weight loss.

On November 29, 1988, she was sent to our hospital. On physical examination, no prominent abnormality was revealed except for dry skin and an erosive lesion in her right hip. Her blood pressure was 120/85 mmHg and pulse rate was 84/min and regular. On neurological examination, the patient appeared to have parkinsonism. Her mental state was at the stage of predementia. Her cranial nerves were intact except for a disturbance in the smooth pursuit with saccadic eye movement. Her face appeared masklike, and her speech was slow, soft, monotonous, and often indistinct. No focal weakness was noted; deep tendon reflexes were hyperactive and symmetric. Rigidity was present in all extremities. There was a mild bilateral resting tremor. Babinski reflexes were negative bilaterally. Sensory examination showed slightly decreased vibratory sensation. Examination of the cerebellar function revealed hypometria. The patient had a simian posture and there were bilaterally decreased associated movements. She could not stand without support and walked with the thorax bent slightly forward and with a wide base. Each step was short, and her feet were hardly lifted off the floor. Bladder and perspiration functions were slightly disturbed. She some-

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Received for publication February 26, 1991; Accepted for publication March 16, 1992

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times showed orthostatic hypotension.

Hematological findings gave normal results, except for a slightly increased white blood cell count ($9,500/\text{mm}^3$). The blood chemistry showed no abnormalities except for low serum albumin (3.6 g/dl) and cholinesterase ($0.57\Delta\text{pH}$) and high alkaline-phosphatase (242 mU/ml) and calcium (11.6 mg/dl). Tests for tumor markers such as AFP, CEA, and CA 19-9 were negative. Endocrinological examination showed the following results: serum T3 0.73 ng/ml , T4 $8.8\text{ }\mu\text{g/dl}$, TSH $0.50\text{ }\mu\text{U/ml}$, TBG $24.4\text{ }\mu\text{g/ml}$, PTH-C 0.64 ng/ml , PTH-mid 0.66 ng/ml , intact-PTH 233 pg/ml , high sensitive-PTH 1730 pg/ml , and calcitonin 25 pg/ml .

A plain X-ray film of the lumbar spine revealed generalized demineralization of the bones and localized destructive lesions (Fig. 1). Computerized tomography (CT) showed a slight cerebellar atrophy with visible cerebellar sulci, somewhat enlarged supracerebellar cistern, smaller than usual brain stem, and somewhat decreased density of both thalamic regions, but no calcification was observed (Fig. 2). ^{201}Tl - $^{99\text{m}}\text{Tc}$ parathyroid subtraction scintigraphy gave a negative study. High resolution, real time ultrasonography of the abdomen re-

Fig. 1. Plain lateral view of X-ray examination of the lumbar spine reveals generalized demineralization of bones and localized destructive lesions.

Fig. 2. Pre-operative CT scan of the head showing slight brain atrophy, slight cerebellar atrophy with visible cerebellar sulci, a somewhat enlarged supracerebellar cistern, a smaller brain stem than usual and somewhat decreased density of both thalamic regions, but no calcifications were observed.

Fig. 3. Parathyroid adenoma in which hypertrophied chief cells and some multiple nuclei accompanied by scanty stroma and irregular distribution of fibrous tissues are seen. ($\times 200$)

vealed no prominent abnormalities except for a gallstone.

Based on this data, she was clinically diagnosed as primary hyperparathyroidism. She was referred to the department of surgery for parathyroidectomy. On March 2, 1989, 395 mg of parathyroid adenoma was removed together with the subtotal thyroidectomy, because three cysts in the right lobe of the thyroid gland were found

during the operation (Fig. 3). The serum calcium level declined rapidly during the immediate post-operative period, and it was necessary to administer calcium lactate thereafter until the serum calcium level returned to normal without the substitution.

Although she was on the medication when the post-operative assessment of her neurological status was made, she regained her vitality to some extent and some of her strength. Her parkinsonian symptoms also improved gradually, but the improvement, especially in rigidity and gait disturbance, was unsatisfactory. Therefore, the dose of levodopa was increased to 500 mg/day with benserazide hydrochloride 125 mg/day, resulting in discernible responsiveness. She was able to stand and walk without support only for a while (Fig. 4). The intellectual examination performed post-operatively revealed no significant change.

Discussion

Although a considerable number of publications concerning the neuropsychiatric manifestations in hyperparathyroidism and other hypercalcemic conditions have appeared (1, 2, 11–14), the paucity of case reports describing hyperparathyroidism associated with parkin-

Fig. 4. The clinical course before and after parathyroidectomy. The serum calcium level declined rapidly during the immediate post-operative period, which required administration of calcium lactate for weeks until the serum calcium level returned to normal level without substitution.

sonism (3–5) suggests that this combination is rare. To the contrary, extrapyramidal motor manifestations in hypoparathyroidism are not uncommon (6–10).

Extrapyramidal movement disorders are present in patients with basal ganglia calcification which can be related to hypoparathyroidism (6–8) or rarely, to hyperparathyroidism (4, 15). However, calcification of the basal ganglia was not detected in the present patient. Patten et al reported two cases with hyperparathyroidism who showed a lack of arm swing (moved en bloc, with a slow, stiff gait), and an abnormal posture of their arms and hands; these signs are similar to those associated with basal ganglia dysfunction of parkinsonism but there was no description of calcification of the basal ganglia (3). The present case suggests that hyperparathyroidism may result in parkinsonism without basal ganglia calcification.

It is unlikely that the present patient had symptomatic parkinsonism caused by hyperparathyroidism, because her parkinsonism did not disappear completely after the surgery. Hypometria and wide-based gait in the neurological examination suggested cerebellar dysfunction, and CT scan revealed a somewhat atrophic cerebellum and somewhat decreased density of both thalamic regions. These findings suggest that she may have had olivopontocerebellar atrophy (OPCA) and the possibility of thalamic degeneration. However, her symptoms, including hypometria and wide-based gait, gradually improved in response to the increased dosage of levodopa combined with benserazide hydrochloride after the surgery. Moreover, she had no family history of neurological disorders. Thus, it is likely that she had Parkinson's disease with predominant parkinsonism aggravated by hyperparathyroidism. However, it was difficult to completely rule out the possible complication of OPCA and/or thalamic degeneration.

Although the precise mechanism which caused parkinsonism in our patient is somewhat unclear, hypercalcemia or a parathormone neurotoxicity independent calcium toxic effect (16, 17) may have contributed to the symptoms. It seems likely that there may be some kind of transitory functional influence of calcium or parathormone on the dopamine turnover or post-synaptic dopamine receptor site (18, 19), since her parkinsonian features improved after parathyroidectomy.

Knuth and Kisner reported a 58-year-old man with hypercalcemia, progressive dementia, and basal ganglia calcification without parkinsonism (15). In their patient, a parathyroid adenoma was disclosed at autopsy (15). The present case also showed predementia and this symptom was not markedly improved even after parathyroidectomy. This indicates that hyperparathyroidism may be associated with persistent changes in the mental state without visible intracerebral calcification. However, the mechanism underlying the development of dementia remains obscure.

In spite of the administration of a sufficient levodopa dosage, the patient did not respond well, and was aggravated greatly. Correction of her hypercalcemia by parathyroidectomy improved her clinical symptoms to some extent. Whether or not earlier diagnosis and therapy for hyperparathyroidism could have prevented the deterioration is difficult to prove. Patients showing parkinsonism unresponsive to levodopa treatment should be differentiated from hyperparathyroidism.

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