Case Report

Fabry Disease Superimposed on Overt Autoimmune Hypothyroidism

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Abstract. Fabry disease (FD) is an X-linked recessive disorder caused by lysosomal α -galactosidase A deficiency. FD is characterized by the systemic accumulation of globotriaosylceramide with involvement of the heart, kidney, brain and gastrointestinal system. Recently, nonautoimmune thyroid dysfunction was recognized as an additional clinical feature of FD. In the present study, we describe a patient suffering from FD superimposed on overt autoimmune hypothyroidism. The patient was an 11-yr-old boy who presented with goiter and stunted growth, and was diagnosed with primary hypothyroidism due to autoimmune thyroiditis. During levothyroxine replacement therapy, the patient complained of burning pain in his feet and was diagnosed as suffering from FD based on low blood α -galactosidase A activity. In conclusion, we have described the first FD patient preceded by overt autoimmune hypothyroidism.

Key words: Fabry disease, α -galactosidase A, globotriaosylceramide, autoimmune thyroiditis, hypothyroidism

Introduction

Fabry disease (FD) is an X-linked recessive disorder caused by lysosomal α -galactosidase A deficiency and is characterized by the systemic accumulation of globotriaosylceramide (1). FD is recognized as a multiorgan disease with involvement of the heart, kidney, brain and gastrointestinal system (2). Recently, endocrine dysfunctions including subclinical hypothyroidism

add to the clinical picture of FD (3–6).

In the present study, we report an FD patient who first presented with overt autoimmune hypothyroidism.

Case Report

The patient is a boy born to a healthy Japanese father and a white American mother. The mother was diagnosed with autoimmune hypothyroidism at 30 yr of age and was started on thyroid hormone replacement therapy. No detailed maternal family history was available. The patient has one sibling, a healthy younger brother. The patient was a product of an uncomplicated 42-wk gestation and delivery. His birth weight was 3,230 g and his birth length

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Table 1 Clinical course of the patient

	Chronological age					Normal range
	11 yr 6 mo	12 yr 4 mo	13 yr 1 mo	13 yr 11 mo	14 yr 6 mo	
Height (cm)	146.2	152.2	158.0	165.7	171.2	
Height SD	+0.1	+0.1	+0.1	+0.5	+0.9	
Weight (kg)	45.8	46.7	47.8	50.7	54.0	
BMI (kg/m ²)	21.4	20.1	19.1	18.5	18.4	
Tanner stage	1	2	2	3	4	
Free T3 (pg/ml)	2.2	3.8	4.0	3.6	3.2	2.3–4.3
Free T4 (ng/dl)	0.6	1.6	1.9	1.3	1.2	0.9–1.7
TSH (μ U/ml)	115	0.7	0.5	3.0	7.8	0.5–5.0
Thyroid test	1,600×	—	—	—	—	<100×
Microsome test	100×	—	—	—	—	<100×
l-T4 (μ g/d)	-	100	100	100	100	

BMI, body mass index; l-T4, levothyroxine.

was 52 cm. He had been doing well until 10 yr of age, but his growth curve indicated stunted growth since then. At 11 yr and 6 mo of age, he was noted as having goiter and was referred to us. The clinical course of the patient is summarized in Table 1. His thyroid gland was diffusely enlarged. He had normal prepubertal male external genitalia. His skeletal age was 10 yr and 11 mo. Laboratory findings indicated low serum free T3 and T4 and high serum TSH (Table 1). Thyroid and microsome tests gave positive results (Table 1). Based on these findings, the patient was diagnosed as suffering from primary hypothyroidism due to autoimmune thyroiditis and was started on levothyroxine (l-T4) replacement therapy at a dose of 100 μ g/d, to which he responded well, as shown by an increasing height velocity and a decreasing body mass index (Table 1).

At 12 yr and 4 mo of age, the patient complained of burning pain in his feet during exercise. Thyroid function had been normalized by the replacement therapy (Table 1). Physical and radiological examinations revealed no abnormalities in his feet. He had no skin lesions such as angiokeratomas. He recurrently experienced burning pain in his feet since then. At 14 yr and 4 mo of age, he complained of burning

pain in his feet when taking a hot bath. Based on these findings, it was suspected that he might suffer from FD, and his α -galactosidase A activity was determined in a blood sample spotted on filter paper (7); he had very low activity (3.9 units, normal range >17.0 units) and thus was diagnosed as having FD. At 14 yr and 6 mo of age, a thyroid function test revealed an elevated serum TSH level (Table 1). Thus the l-T4 dose was increased to 150 μ g/d. The patient and parents decided to start supplemental enzyme treatment with recombinant α -galactosidase A at another university hospital, to which we referred him.

Complete blood counts, urinalyses and serum creatinine and urea nitrogen levels were normal during the follow-up period at our hospital.

Discussion

The recombinant α -galactosidase A replacement therapy for FD has been demonstrated to be effective in prevention or alleviation of the progression of tissue damage (8–11). Since the replacement therapy is now available in Japan (12), it has become crucial for a better outcome to make the diagnosis as early as possible. In our patient, the burning pain in

his feet was the only clue for the diagnosis, and it took us two years to diagnose him as suffering from FD. The delay in diagnosis was caused, at least in part, by the lack of easy access to the α -galactosidase A assay. Therefore, we assume that easier access to the assay should make early diagnosis feasible. We did not have an opportunity to measure the α -galactosidase A activity in his apparently normal younger brother. Measurement of the activity should have helped us to determine whether he suffers from FD or not.

Since the first report by Tojo *et al.* describing a 48-yr-old male FD patient with primary hypothyroidism and marked globotriaosylceramide accumulation in the thyroid gland (3), primary thyroid dysfunction has been well recognized as one of manifestations in FD patients older than 30 yr of age, which is characterized by only mildly elevated serum TSH levels and normal serum free T4 levels, that is, subclinical hypothyroidism (4–6). In FD patients, the thyroid gland is not enlarged, and thyroid autoantibodies are negative (3–6). Ultrasonography of the thyroid glands has been reported to show no abnormalities (4) or to reveal high incidence of a mild hypoechoic pattern (5, 6). Of note, thyroid dysfunction recovers after long-term enzyme replacement therapy (6). Therefore, thyroid dysfunction in FD patients is very likely to be caused by accumulation of globotriaosylceramide in the gland, not by antithyroid autoimmunity.

Although we did not have an opportunity to perform ultrasonic examination of the thyroid gland, we diagnosed our patient as suffering from primary hypothyroidism due to autoimmune thyroiditis because of the following findings: 1) he had a positive family history of autoimmune hypothyroidism, 2) he developed overt hypothyroidism as young as 11 yr of age, 3) he had diffusely enlarged goiter and 4) he had clearly positive antithyroid autoantibodies. To our knowledge, this is the first FD patient with overt autoimmune hypothyroidism. Treatment with l-T4 successfully normalized his thyroid

function, but his serum TSH level rose again in 3 yr. The elevation may be attributable to the increase in his body size and/or to the globotriaosylceramide accumulation in the thyroid gland caused by the coexistent FD. In any case, careful monitoring of thyroid function is mandatory in our patient.

In conclusion, we described the first patient suffering from FD superimposed on overt autoimmune hypothyroidism.

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