A Case of Multiple Endocrine Neoplasia Type 2B early Diagnosis by RET Proto-oncogene Analysis and Prophylactic Total Thyroidectomy

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Multiple endocrine neoplasia type 2B (MEN 2B) is a rare autosomal-dominant hereditary syndrome which includes medullary thyroid carcinoma (MTC), pheochoromocytoma, multiple ganglioneuromas, gastrointestinal disorders and marfanoid face. MTC is the main cause of death in patients that have not received early and prophylactic treatment. Clinically useful direct DNA tests have recently been available to identify gene carriers before any clinical or biochemical abnormalities are present. Prophylactic total thyroidectomy is recommended to affected children at an early stage of the disease to prevent the development of metastases of MTC. We report a case of MEN 2B patient who was diagnosed by RET proto-oncogene analysis and performed prophylactic total thyroidectomy.

Key Words : Multiple endocrine neoplasia, Medullary thyroid carcinoma, RET proto-oncogene, Prophylactic thyroidectomy

Introduction

Multiple endocrine neoplasia 2B (MEN 2B) is a rare autosomal-dominant hereditary syndrome including medullary thyroid carcinoma (MTC), pheochoromocytoma, multiple ganglioneuromas, gastrointestinal disorders and marfanoid face. Among the several disease entities, MTC is present in almost of MEN 2B cases, and often appears in the 1st decade of life[1].

MTC is the main cause of death in patients who do not receive early and prophylactic treatment. They are usually symptom-free at an early age.

Molecular analysis of the RET gene has changed the history of this syndrome, as it allows the identification of MEN 2B mutations in asymptomatic patients and makes it possible to perform a prophylactic thyroidectomy in children. Prophylactic thyroidectomy plays a very important role for improving survival rate of MEN 2B patients[2-4].

We report, together with a literature review, a case of MEN 2B patient whose mother also had been diagnosed with MEN 2B and who was performed total thyroidectomy due to MTC. He was diagnosed by RET proto-oncogene analysis and performed prophylactic total thyroidectomy.

Case Report

A 13-month-old boy visited Severance hospital, Seoul, Korea to perform further evaluation and proper management for MEN 2B. His mother was performed total thyroidectomy 5 years ago and modified neck node dissection was also performed 2 weeks ago due to recurred MTC. The patient and his mother was performed RET proto-oncogene mutation analysis showing that they had a missense mutation at 918th codon in exon 16 and these results confirmed that their diagnosis was MEN 2B. His mother had a tongue biopsy and

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mucosal neuroma was confirmed by EMA and S-100 positive.

When the patient was admitted, his blood pressure was 102/65 mmHg (75-90 percentile), pulse rate 130 beats/min, respiratory rate 27 times/min, and body temperature was 36.7℃. His height was 74 cm (25-75 percentile), and weight 9.3 kg (50-75 percentile). He had no nausea, vomiting and diarrhea or constipation. He was not ill-looking. No throat injection nor tonsillar hypertrophy was shown. He had no palpable cervical lymphadenopathy nor palpable neck masses. His lung sound was clear and he had regular heart beat without murmur. He had no hepato-splenomegaly. He had thick lumpy lips but no definite mucosal neuroma could be identified (Fig. 1) but he had bilateral small protruding mass inside his mouth which resembled mucosal neuromas (Fig. 2). His mother had a marfanoid face but he lacked this characteristic.

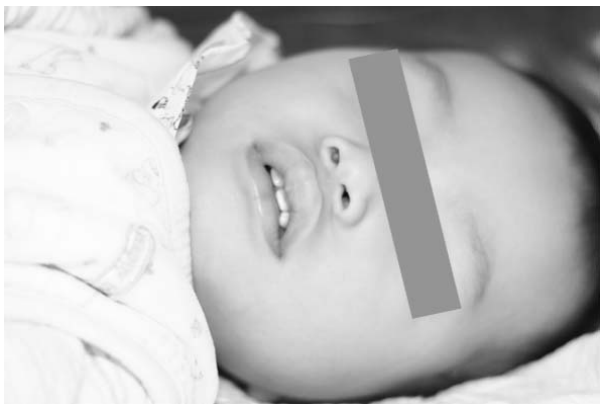

Fig. 1. Thick lumpy lips.

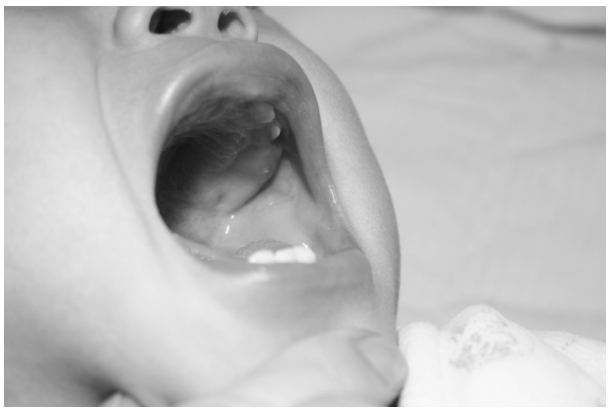

Fig. 2. Small protruding mass on his inside lip. It seems like mucosal neuroma.

The complete blood count test showed that the white blood cell count was 12,040/μL (neutrophil 22.3%), hemoglobin 12.4 g/dL and platelet 502,000/μL. Results of liver function test showed alkaline phosphatase 223 IU/L, AST 70 IU/L, ALT 63 IU/L, total bilirubin 0.1 mg/dL. His calcium and phosphate levels were 10.7 mg/dL and 5.5 mg/dL, respectively. And serum PTH level (normal range : 10-65 pg/mL) was 9.12 pg/mL. The results of Hepatitis B viral markers showed that HBsAg was negative, anti-HBc negative, and anti-HBs positive. Thyroid function test results showed that T_3 (normal range : 80-200 ng/dL) was 149.36 ng/dL, free T_4 (normal range : 0.73-1.95 ng/dL) 1.28 ng/dL, TSH (normal range : 0.4-3.1 IU/mL) 1.45 IU/mL, thyroglobulin 33.96 ng/mL, thyroglobulin Ab (normal range : 0-60 U/mL) 7.09 U/mL and microsome Ab (normal range : 0-60 U/mL) 18.05 U/mL. These were all within normal range. His calcitonin level (normal range : 0-10 pg/mL) was elevated to 153.87 pg/mL (Table 1). Basal calcitonin level, 5 minutes and 10 minutes after calcium infusion (2 mg/kg) calcitonin level were 84.10 pg/mL 76.44 pg/mL and 55.65 pg/mL respectively without significant increasing. Basal calcitonin level was elevated, but stimulated calcitonin levels were within the normal range (Table 2).

Plasma epinephrine (normal range : 0.0-0.3 ng/mL) was 0.036 ng/mL, and norepinephrine (normal range :

Table 1. The Patient's Endocrinologic Laboratory Data

	Before thyroidectomy	After thyroidectomy
Serum calcium (mg/dL)	10.7	8.7
Serum phosphate (mg/dL)	5.5	6.8
PTH (pg/mL)	9.12	2.16
Calcitonin (pg/mL)	153.87	
T_3 (ng/dL)	149.36	152.18
free T_4 (ng/dL)	1.28	1.48
TSH (IU/mL)	1.45	3.97
Thyroglobulin (ng/mL)	33.96	
Thyroglobulin Ab (U/mL)	7.09	
Microsome Ab (U/mL)	18.05	
Plasma epinephrine (ng/mL)	0.036	
Plasma norepinephrine (ng/mL)	0.199	
Urine epinephrine (g/day)	1.0	
Urine norepinephrine (g/day)	1.5	
Urine metanephrine (g/day)	0.084	
Urine vanillymandelic acid (g/day)	0.14	

0.0-0.8 ng/mL) was 0.199 ng/mL showing normal range. Urine epinephrine (normal range : 0-20 g/day) and norepinephrine (normal range : 15.0-80.0 g/day) were 1.0 g/day and 1.5 g/day. Urine metanephrine (normal range : 0.0-1.3 mg/day) and vanillylmandelic acid (normal range : 0.0-8.0 mg/day) were 0.084 mg/day and 0.14 mg/day suggesting no pheochromocytoma (Table 1).

There were no abnormalities of the thyroid and parathyroid evident in the CT (Fig. 3), but there were several hypoechoic nodules in thyroid gland evident in the US (Fig. 4). There were no lesions evident on the thyroid scan (Fig. 5).

Table 2. The Results of Serum Calcitonin Level after Calcium Infusion

	0 min	5 min	10 min
Calcitonin (pg/mL)	84.10	76.44	55.65

Normal range of serum calcitonin : 0-10 pg/mL

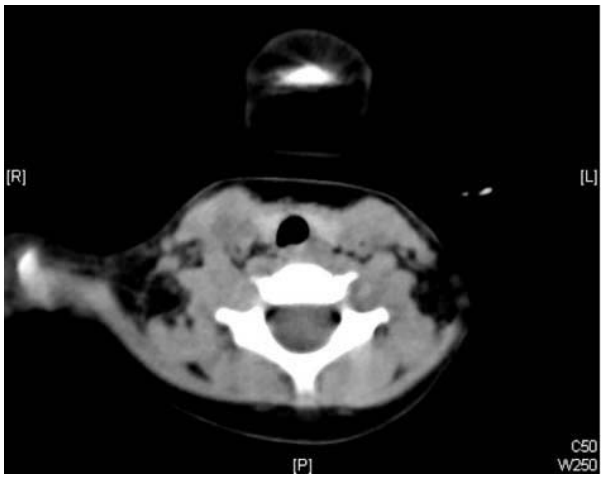

Fig. 3. There was no abnormality in thyroid and parathyroid in CT neck.

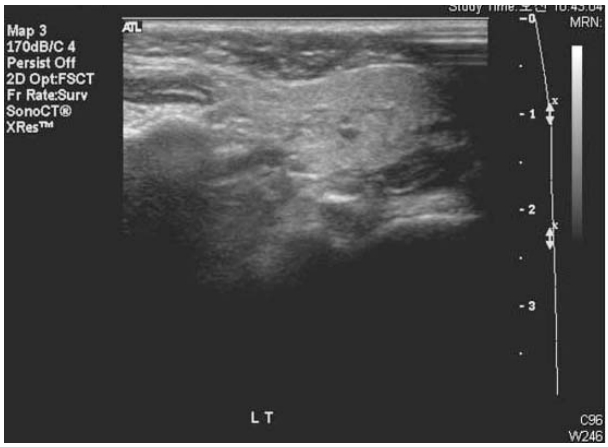

Fig. 4. Hypoechoic several nodules in thyroid gland at US.

Treatment and progress

On the 8th day of admission, the patient had prophylactic total thyroidectomy with cervical lymph node dissection. Central cervical lymph nodes were dissected but lateral lymph nodes were not dissected because there were no evidence of metastasis to central lymph node. Pathologic results showed that his thyroid gland was normal (Fig. 6) and there was no C-cell hyperplasia which is usually found in MEN 2B. After total thyroidectomy, we found the patient's PTH level to be low which was 2.16 pg/mL. Serum calcium and phosphate level were 8.7 mg/dL and 6.8 mg/dL, respectively. Serum calcium was decreased. We performed

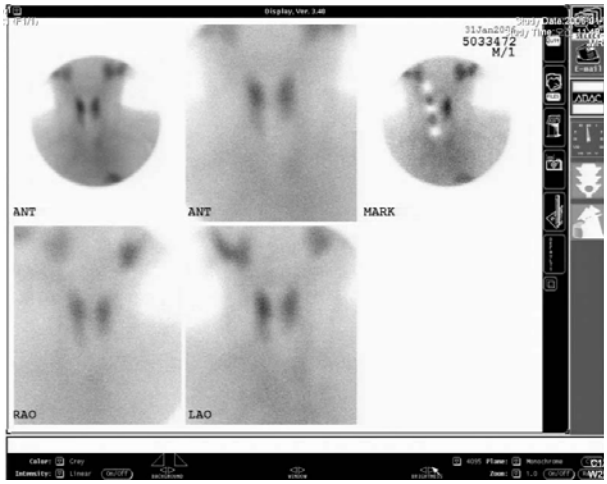

Fig. 5. There was no lesion on thyroid scan.

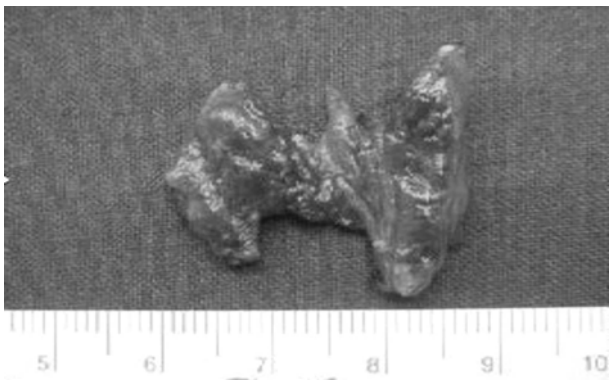

Fig. 6. Thyroid glands is normal. Pathology shows that there is no C-cell hyperplasia in his thyroid glands.

thyroid function test and the patient's T_3 was 152.18 ng/dL, free T_4 1.48 ng/dL and TSH 3.97 IU/mL (Table 1).

Because of the low calcium level, oral calcium (elemental calcium 520 mg/day), and vitamine D (0.5 g/day) was prescribed. Due to the possibility of hypothyroidism after thyroidectomy, levothyroxine (0.05 mg/day) was prescribed. The paitent was discharged without any surgical complications and the patient visits to the out-patient clinic for regular follow up sessions.

Discussion

MEN is a syndrome with possible neoplastic involvement of two or more endocrine glands which originate embryonically from neural crest cells[6]. There are three types of MEN. In type 1 (MEN 1), patients have combinations of tumors of the pituitary, parathyroid and pancreas. In type 2 (MEN 2), there are two sub-types which are called type 2A (MEN 2A) and type 2B (MEN 2B). Type 2A has an association of adrenal pheochoromocytoma, medullary thyroid carcinoma (MTC) and parathyroid disease, whereas as type 2B involves pheochromocytoma, medullary thyroid carcinoma and mucosal neuroma on the lips, tongue and cheeks, distinctive facial appearance and Marfanoid habitus[6].

MEN 2B is a rare autosomal-dominant hereditary syndrome and MTC is present in 100% of MEN 2B cases and often appears in the 1st decade of life. MTC is the main cause of death in patients not receiving early prophylactic treatment. Surgical treatment is the only therapy that has been proved effective in cases with localized tumor[1, 7].

The diagnosis of MTC had depended on the demonstration of elevated plasma calcitonin levels either at the baseline or after intravenous administration of calcium or pentagastrin. Unfortunately, many patients identified in this way showed an advanced stage of the disease. In 1993, germline missense mutations in the RET proto-oncogene (chromosome 10q11.2) that is associated with a point mutation in the methionine residue in exon 16 (codon 918) in the intracellular tyrosine kinase receptor domain of RET were found in the patients with MEN 2B[4, 8]. Clinically useful direct DNA tests are now available to identify gene carriers before any clinical or biochemical abnormality is present. Affected children are successfully offered prophylactic total thyroidectomy at an early age of the disease to prevent the development of metastases of MTC and this genetic screening by blood test is the most cost-effective and least invasive procedure[5, 9].

Age at performing presymptomatic thyroidectomy in MEN 2 depends on the specific DNA mutation in the RET proto-oncogene (Table 3). Codon 883, 918, 922 mutation have a high risk of local and distant metastasis. If the child has a mutation on these codon, prophylactic total thyroidectomy is usually advised during the first year[10, 13].

The prognosis in patients with MEN 2B depends on early diagnosis and surgical treatment. When MTC shows clinical manifestation, it can be too late for curative therapy. Recently Torre et al.[1] reported cases of MEN 2B with the aiming of underlining the importance of early diagnosis and treatment. The patient who died had MTC with lymph node metastasis at 13 years old, but had already shown signs and symptoms of MEN 2B at 5 years, but other two patients who had early diagnosis by RET mutation analysis and prophylactic total thyroidectomy were healthy for several years and had no recurrence. We could express concern

Table 3. Prophylactic Thyroid Management according to RET Genotype[13]

Risk level	Risk	RET genotype (mutation in codon)	Recommended age for surgical intervention	
			Thyroidectomy before age (years)	Central lymph node dissection before age (years)
3	Highest	883, 918, 922	0.5	0.5
2	High	634, 630	5	(≥10)
		609, 611, 618, 620	5	(≥20)
1	Least High	768, 790, 791, 804, 891	5 or 10	(≥20)

regarding the risk of complications of surgery in young children. For example, there is permanent hypoparathyroidism that is most troublesome and should be avoided[4].

Because MTC can metastasize to the lung, liver and bone, post-operative management and surveillance is also important. Peczkowska et al.[8] reported that measurements of serum calcitonin and CEA are the cornerstone of postoperative assessment for residual disease and should be done shortly after surgery and 2 or 3 months later.

After total thyroidectomy, all patients should receive lifelong replacement therapy with levothyroxine and the dose of levothyroxine should be adjusted by periodic serum thyrotropin (TSH) determinations. We prescribed levothyroxine 0.05 mg/day to the patient.

A patient who has been diagnosed as MEN 2B might also have pheochromocytoma, so we checked our patient's blood pressure and serum catecholamines (epinephrine, norepinephrine), and urinary excretion of catecholamines (epinephrine, norepinephrine) and their metabolites (vanillylmandelic acid, metanephrines). In this case, the levels were all within normal range. So, we can conclude that the patient did not have pheochromocytoma. Unfortunately, Peczkowska et al.[8] reported that patients with MEN 2A and MEN 2B have an expected 50% lifetime risk of developing pheochromocytoma, therefore we should follow-up on the patient's blood-pressure, serum catecholamines, urine catecholamines and metabolites.

Parker et al.[12] reported that MEN 2B patients may have prominent corneal nerves, thickened eyelids, mild ptosis and eversion of the upper eyelids, but the patient did not have any ophthalmologic problem.

We report a case of MEN 2B who was diagnosed early by RET proto-oncogene analysis. Because the patient had a prophylactic thyroidectomy with neck lymph node dissection at early an age, a good prognosis of the disease is expected.

Abstract

다발성 내분비 신생물 제2B형(Multiple endocrine neoplasia type 2B) 은 상염색체 우성으로 유전되는 희귀질환으로, 갑상선 수질암, 크롬친화세포종, 다발성 신경절신경종, 위장관 장애, 마르팡형 얼굴등을 가지는 것을 특징으로 한다. 이중 갑상선 수질암이 조기 진단 및 치료를 받지 못한 환자에게 있어 사망률에 가장 중요한 역할을 한다. 현재 임상적으로 증상이 나타나기 이전에 DNA test를 통한 진단이 이루어지고 있어, 가족력이 있는 환아에게 있어 조기진단 및 조기 치료가 가능한 현실이다. 갑상선 수질암의 재발로 두차례 수술 후에 다발성 내분비 신생물 제2B형으로 진단받은 환자의 아이가 DNA test를 통하여 조기 진단 받은 후 예방적 갑상선 전절제술을 시행한 1례를 경험하였기에 문헌 고찰과 함께 보고하고자 한다.

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