A Family with Multiple Endocrine Neoplasia Type 2A: Importance of Early Prophylactic Thyroidectomy

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Background: Medullary thyroid cancer (MTC) is a rare thyroid tumor originating from parafollicular C cells and constitutes about 5-10% of all thyroid cancers. There are 2 types including sporadic and familial MTC. In children and adolescents, MTC is usually familial and is caused by autosomal dominantly-inherited *RET* mutations. It may occur as a part of MEN 2A and MEN 2B syndromes or as isolated familial MTC. Calcitonin and carcinoembryonic antigen (CEA) can be used as tumor markers. MEN 2A is characterized by MTC (100%), pheochromocytoma (20-50%), and hyperparathyroidism (20-30%). In the presence of an individual with MEN2A, first-degree relatives and other family members must be screened for *RET* mutations, because early diagnosis and treatment are important for prognosis.

Aim: In this case report, we present a 5.6-year-old male who was identified to have heterozygous p.c634y (c.1901 G>A) mutation in the *RET* proto-oncogene when he was 2.5 years old.

Methods: A 5.6-year-old asymptomatic male was admitted because of family history of MEN 2A. His past medical history was unremarkable. Parents were not related.

Results: Physical examination revealed normal findings without any signs of goiter, thyroid nodule, or lymphadenopathy. Thyroid function was normal, serum calcitonin was <2 pg/mL, CEA was 1.65 ng/mL; parathyroid hormone, calcium and 24-hour urinary metanephrine-normetanefrine-epinephrine and norepinephrine levels were within normal limits. Thyroid ultrasonography revealed normal findings. Prophylactic total thyroidectomy was performed owing to the high-risk mutation in the *RET* proto-oncogene. Histopathological examination of the thyroid gland revealed medullary microcarcinoma focuses.

Conclusion: When a family history of MEN 2A syndrome is present, (i) clinical follow-up of asymptomatic individuals with serum levels of tumor markers is not safe; (ii) all family members should be screened with molecular analysis of the *RET* proto-oncogene; (iii) early prophylactic thyroidectomy should be performed after the assignment of risk group according to the result of molecular analysis.

Key words: Medullary thyroid cancer, *RET* proto-oncogene, MEN 2A

Familial Partial Lipodystrophy Linked to a Novel Peroxisome Proliferator-Activated Receptor -γ (PPARG) Mutation, H449L

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Introduction: Familial partial lipodystrophy (FPL) is a rare genetic disorder characterized by a selective lack of subcutaneous fat that is associated with insulin resistance and diabetes. FPL has been reported to be caused by mutations in the *PPARG* gene, which encodes a key transcription factor that regulates adipocyte differentiation and insulin sensitivity.

Methods: The objective of this study was i) to describe the phenotype associated with a novel heterozygous missense *PPARG* mutation, H449L, discovered in a Turkish family and ii) to compare the fat distribution and metabolic characteristics of subjects with the *PPARG H449L* mutation (n=4) to that of a cluster of FPL patients with various *LMNA* mutations (n=5; R482W, R582H, L306V and T528M).

Results: Compared to patients with *LMNA* mutations, fat loss was generally less prominent in subjects with *PPARG H449L* mutation. Partial fat loss was limited to the extremities whilst truncal fat mass was preserved. The PPARG H449L mutation was associated with insulin resistance, hypertriglyceridemia and non-alcoholic fatty liver disease in all affected subjects, but the severity was variable. Three of four mutation carriers were overtly diabetic or had impaired glucose tolerance. Pioglitazone therapy in these three individuals resulted in a modest improvement in their metabolic control and regular menstrual cycles in both females.

Conclusion: We suggest that relatively modest fat loss in patients with *PPARG* mutations may render the recognition of the syndrome more difficult in routine clinical practice. The *PPARG H449L* mutation is associated with insulin resistance and metabolic complications; however, the severity is variable among the affected subjects, suggesting that additional factors such as variations in other predisposing genes, gender, age, and lifestyle factors might affect the clinical features in patients with *PPARG* mutations.

Key words: Diabetes, insulin resistance, lipodystrophy, *PPARG*