



Neurofibromatosis Type 1 and Autoimmune Hyperthyroidism in a 10.5 Years-Old Girl

Onbuçuk Yaşındaki Bir Kız Çocuğunda Nörofibromatoziz Tip 1 ve Otoimmün Hipertiroidizm Birlikteliği

Hüseyin Demirbilek¹, Serhan Küpeli², Mehmet Nuri Özbek¹, Semra Saygı³ Aysen Türedi Yıldırım⁴

Diyarbakir Children State Hospital, Division of ¹Pediatric Endocrinology, ²Pediatric Oncology, ³Pediatric Neurology, ⁴Pediatric Hematology, DİYARBAKIR

Cukurova Medical Journal 2013; 38 (4):805-808.

ABSTRACT

Neurofibromatosis type 1 (NF1) is an autosomal dominant inherited multisystem disease associated with several endocrine disorders. Association of NF1 and hyperthyroidism is extremely rare. All previously reported cases were in adult age group. Herein, we present autoimmune thyrotoxicosis associated to NF1 in a pediatric patient presenting with goiter and symptoms of thyrotoxicosis.

Key Words: Neurofibromatosis type 1, autoimmune hyperthyroidism, Graves' disease

ÖZET

Nörofibromatoziz tip 1 (NF1) endokrin bozuklukların eşlik ettiği otozomal dominant geçişli multisistem bir hastalıktır. Nörofibromatoziz tip 1 ve hipertiroidizm birlikteliği nadir görülen bir durumdur. Bugüne kadar yayınlanmış olgular genellikle erişkin yaş grubundandır. Bu yazıda guatr ve tirotoksikoz bulguları ile başvuran çocuk yaş grubu bir olguda otoimmün tirotoksikoz ve NF1 birlikteliği sunulmuştur.

Anahtar Kelimeler: Nörofibromatoziz tip 1, otoimmüne hipertiroidizm, Graves' hastalığı

INTRODUCTION

Neurofibromatosis type 1 (NF1) is an autosomal dominant inherited multisystem disorder. Diagnosis of NF1 is based on the presence of at least 2 of 7 clinical criteria described by National Institutes of Health^{1,2}. Genetic analysis of mutation in NF1 gene is generally needed for confirmation and diagnosis of cases with indefinite clinical findings. It is wellknown that there is no phenotype-genotype correlation. Widely clinical expression and various kinds of disease association lead some difficulties in management of NF1 cases. Although NF1 and hyperthyroidism association has been reported in a few adult patients, there is no reported pediatric case^{3,4,5}. Herein, to our knowledge, we report the

first case of NF1 associated with autoimmune hyperthyroidism in pediatric age group.

Case Report

A 10.5 year-old girl was admitted to our clinic with the complaints of palpitation, weight loss and swelling in the neck. Her family and previous medical history was not remarkable. In physical examination her height was 145.6 cm (50th-75th percentile), weight was 32.8 kg (25th percentile). She had tachycardia (heart rate was 139 beats/minute) and hypertension (The systolic and diastolic blood pressure was 130mmHg and 90 mmHg respectively). Thyroid gland was enlarged (grade 3 goiter) without any palpable nodule.

Exophthalmus, axillary freckling and multiple café au-lait spots were other findings (Figure 1). Laboratory examination revealed that free T₃ and free T₄ levels were elevated (Free T₃ level was 11.2 pg/ml; N: 2,56-5,01 and free T₄ level was 7.34 ng/dl; N: 0.98-1.63 respectively) with undetectable thyroid stimulating hormone (TSH level was <0.005 mIU/ml; N: 0.5-4.3). The thyroid peroxidase (anti-TPO ab) and antithyroglobulin (Anti-TG ab) antibodies were elevated (Anti-TPO ab: >1000 IU/L; N: 0-30 and Anti-TG ab: 3451 mIU/ml; N: 0-60 respectively). Thyroid ultrasonography showed enlarged thyroid gland with a heterogenous paranchyme. Thyroid Tc^{99m} pertechnetate scan revealed diffuse enlargement of thyroid gland with increased homogenous

uptake pattern. Cranial magnetic resonance imagination (MRI) were normal. Lisch nodule was not detected in ophtalmologic examination. She was diagnosed as NF1 with autoimmune hyperthyroidism. After one month of treatment with methimazole (0.5 mg/kg/day) and propranolol (1 mg/kg/day), her blood pressure and heart rate were recovered together with the normalization of thyroid function. Propranolol was stopped after complete achievement of euthyroid state. However, during follow up reduction of methimazole dose resulted in relapse of thyrotoxicosis. Now remission is provided with a maintenance dose of methimazole (0.3 mg/kg/day) at the 22nd month of the diagnosis.



Figure 1. Exophthalmus (A), cafe au-lait spots and goiter (B&C), cafe au-lait spot and axillary freckling (D) in patient.

DISCUSSION

NF1 is an autosomal dominant inherited disorder caused by mutation in NF1 gene which is a tumor suppressor gene, encoding neurofibromin⁶. Increased risk of developing a variety of benign and malignant tumors in NF1 patients is wellknown. Common endocrine manifestations of NF1 are pheochromocytoma, precocious puberty, growth hormone excess or pituitary hormone deficiency caused by hypothalamo-pituitary region

gliomas. Autoimmune diseases have been reported rarely in association with NF1 patients. Multiple sclerosis, systemic lupus erythematosus, membranous glomerulonephritis, IgA nephropathy, mixed connective tissue disease, juvenile arthritis, autoimmune hemolytic anemia, bullous pemphigoid, and Graves disease have been reported in association with NF1 patients previously^{7,8,9}.

Association of hyperthyroidism was shown in limited numbers of adult patients. Firstly Hasebe et al³ reported hyperthyroidism and pheochromocytoma in an adult patient. Sakane et al⁴ reported NF1 associated with hyperthyroidism in a 35 year old patient who presented with hypertension and tachycardia. In 2004 Bolko et al⁵ reported Graves' disease and hyperprolactinemia in a patient with Noonan syndrome neurofibromatosis type 1. In 2008, Nanda reported the first pediatric patient who has association of NF1 and autoimmune thyroiditis¹⁰. This patient was euthyroid. However, we could not find any report of NF1 and autoimmune hyperthyroidism association in pediatric age group. Since association of hyperthyroidism and NF1 is extremely rare, pathogenetic mechanism causing hyperthyroidism is not wellknown. Present case diagnosed NF1 with two clinical criteria (cafe au-lait spots on skin and axillary freckling). In combination of ultrasonographic features, presence of anti-TPO and anti-TG antibodies resembled autoimmune hyperthyroidism. Although we can not measure TSH receptor antibody, prolonged requirement for antithyroid therapy, enlarged thyroid gland and presence of exophthalmus suggested diagnosis of Graves' disease rather than hashitoxicosis. It is not clear that if relation of NF1 and Graves' disease is a coincidence or an association. On the other hand, it is known that NF1 gene encoding neurofibromin is a tumour suppressor gene and genetic mutation in this gene causes several types of cancer. Similarly, it may be an obligatory speculation that mutation in NF1 gene may keep out inhibitor mechanism of immune system and causes immune dysregulation resulting in autoimmune thyrotoxicosis. Hyperthyroidism has been reported in patients with McCune Albright Syndrome (MAS)¹¹. Coincidence of skin lesions and hyperthyroidism in our patient was suggestive for the diagnosis of MAS, however, based on absence of other features of MAS and autoimmune

nature of hyperthyroidism the diagnosis of MAS was excluded.

Herein, we describe the first case of pediatric NF1 case associated with autoimmune hyperthyroidism. Hyperthyroidism, must be kept in mind for pediatric NF1 patients who present with complaints of hypertension and tachycardia.

REFERENCES

1. National Institutes of Health. Consensus Development Conference Statement: Neurofibromatosis. Arch Neurol Chicago. 1988; 45: 575–8.
2. DeBella K, Szudek J, Friedman JM Use of the National Institutes of Health criteria for diagnosis of neurofibromatosis 1 in children. Pediatrics. 2000; 105: 608–14.
3. Hasebe N, Aizawa H, Fujiwara M, et al. A case of von Recklinghausen's disease with pheochromocytoma and hyperthyroidism. J Jpn Soc Int Med. 1984; 73: 440.
4. Sakane N, Shirakata S, Jin MB, Torii T, Yoshida T. von Recklinghausen's disease with hyperthyroidism. Intern Med. 1997; 36: 938.
5. Bolko P, Wasko R, Waligórska J, Narozna J, Sowióski J. Graves' disease and hyperprolactinemia in a patient with Noonan syndrome neurofibromatosis type 1. Ann Endocrinol (Paris). 2004; 65: 121-4.
6. Kevin P. Boyd, Bruce R. Korf, Amy Theos. Neurofibromatosis type 1. J Am Acad Dermatol. 2009; 61: 1–16.
7. Johnson MR, Ferner RE, Bobrow M, Hughes RA. Detailed analysis of the oligodendrocyte myelin glycoprotein gene in four patients with neurofibromatosis 1 and primary progressive multiple sclerosis. J Neurol Neurosurg Psychiatry 2000; 68: 643–6.
8. Corominas H, Guardiola JM, Matas L, Vázquez G. Neurofibromatosis and systemic lupus erythematosus. A matter of coincidence? Clin Rheumatol. 2003; 22:496–7.
9. Yesudian PD, Wilson NJE, Parslew R. Bullous pemphigoid and neurofibromatosis – a chance

- association requiring special vigilance. Clin Exp Dermatol. 2000; 25: 658–9.
10. Nanda A. Autoimmune diseases associated with neurofibromatosis type 1. Pediatr Dermatol. 2008;25: 392-3.
11. Tessaris D, Corrias A, Matarazzo P, De Sanctis L, Wasniewska M, Messina MF, Vigone MC, Lala R. Thyroid abnormalities in children and adolescents with McCune-Albright syndrome. Horm Res Paediatr. 2012; 78:151-7.

Yazışma Adresi / Address for Correspondence:

Dr. Hüseyin Demirbilek
Diyarbakir Children State Hospital
Division of Pediatric Endocrinology
21000 DIYARBAKIR
e-mail: dr_huseyin@hotmail.com

geliş tarihi/received :18.04.2013
kabul tarihi/accepted:25.05.2013