시상하부 과오종과 연관된 성조숙증을 동반한 신경섬유종증 1예

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A Case Report of Precocious Puberty in Children Associated with Hypothalamic Hamartoma in Neurofibromatosis Type 1

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Neurofibromatosis type 1 (NF1) is a common neurocutaneous syndrome that presents with multiple café-au-lait spots, skinfold freckling, dermatofibromas, neurofibromas, and Lisch nodules. Mutations of the *NF1* gene, encoding the protein neurofibromin, have been identified as the cause of this disease. NF1 can also present with precocious puberty and be associated with optic pathway tumors. Hypothalamic hamartoma as the cause of precocious puberty in patients with NF1 has been rarely described in the literature. Here, we report the findings for a patient with NF1 and precocious puberty associated with a hypothalamic hamartoma who had a newly discovered 14-bp deletion mutation in exon 5 of *NF1*. To our knowledge, this is the first time this combination is reported in the literature.

Key Words: Neurofibromatosis 1, Puberty, Precocious, Hypothalamic disease, Hamartoma

Introduction

Neurofibromatosis type 1 (NF1) is a common autosomal dominant genetic disorder with mutations in the gene neurofibromin (*NF1*) and presents with variable clinical phenotypes¹. NF1 diagnosis is based on the clinical diagnostic criteria set by the National Institutes of Health (NIH) consensus development conference in 1987². NF1 is caused by mutations in the *NF1* gene, located on chromosome 17q11.2³. It exhibits a high mutation rate, with approximately 50% of patients with NF1 carrying novel mutations⁴. Moreover, such mutations have a high rate of penetrance, near 100%⁵.

The primary clinical features of NF1 are café-au-lait spots, which progress throughout life to benign peripheral nerve sheath tumors or neurofibromas and Lisch nodules; however, other complications, such as skeletal dysplasias, learning disabilities, mental retardation, seizures, and optic gliomas are included in the clinical spectrum of the disease. Early disruption of the hypothalamic-pituitary-gonadal axis, leading to precocious puberty, is the most common endocrine disorder associated with NF1 in childhood⁶. In the general population, precocious puberty develops due to an underlying hypothalamic hamartoma in up to 10% of patients⁷. On the other hand, in NF1, precocious puberty occurs

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almost invariably in association with optic pathway tumors⁸⁾.

Herein we present a rare case of a young girl with precocious puberty with NF1 associated with a hypothalamic hamartoma, not an optic pathway tumor, and genetic analysis of the *NF1* gene revealed a novel frameshift mutation in exon 5.

Case report

A 6-year-old girl was referred to our hospital for assessment of multiple café-au-lait spots and breast budding. She was born at 40 weeks gestation by normal spontaneous vaginal delivery with average anthropometric parameters. There was no family history of neurofibromatosis or precocious puberty.

The patient's height was 110.6 cm (25–50 percentile) and

weight 19.2 kg (25–50 percentile) according to the chart of Tanner and Whitehouse. On physical examination, there were more than seven café-au-lait spots over 15 mm on the trunk and numerous axillary freckles bilaterally. Lisch nodules or oculomotor difficulties were not present. Pubic hair was at Tanner stage I and breast development at Tanner stage II. There was no abnormal finding in the neurological examination and no history of seizure. The patient thus met the criteria for a diagnosis of NF1, as described by the National Institutes of Health Consensus Development Conference Statement, 1987²⁾.

Precocious puberty was clinically diagnosed, with increased growth velocity (from 25–50 percentile to the 50–75 percentile within 6 months) and thelarche (Tanner breast stage 2). Bone age was 8 years 4 months at the chronologic age of 6 years 3 months, as per the Tanner-Whitehouse scale (Fig. 1). On the Gonadotropin-releasing Hormone (GnRH) stimulation test, the basal luteinizing hormone (LH) value was 0.07 IU/L and peak serum value was 1.5 IU/L, and showed a pre-pubertal response. The T1 weighted Brain Magnetic Resonance Imaging (MRI) showed a 13-mm sized mass in the hypothalamus, isointense to gray matter on all sequences, with no displacement on the third ventricle and no contrast enhancement, consistent with hypothalamic hamartoma (Fig. 2).

Genetic analysis of the *NF1* and *NF2* genes was conducted to test for neurofibromatosis. Informed written consent was obtained from the patient's guardians. Genetic testing for the *NF1* gene revealed a 14-bp deletion mutation in exon 5 of c.503_516del (CAGAAGACAATGTT) as a heterozygous mutant (Fig. 3). This was a frameshift deletion mutation that has not been previously reported. No mutations were observed in the genetic test for the *NF2* gene.

Fig. 1. The patient's hand posterior-anterior x-ray shows bone age of 8 years 4 months at chronological age of 6 years 3 months.

Fig. 2. Brain magnetic resonance image shows a 13-mm sized mass suggestive of hypothalamic hamartoma.

Fig. 3. Gene analysis of *NF1* showed a novel frameshift mutation in exon 5 (c.503_516delCAGAAGACAATGTT).

GnRH stimulation test values showed a pre-pubertal state; therefore, therapy for precocious puberty with a GnRH agonist (triptorelin) was not initiated. However, as she is likely to have central precocious puberty associated with the hypothalamic hamartoma, she has to be examined every 6 months for height growth, puberty progress, and hormonal status. Brain MRI is performed at yearly intervals to examine the enlargement of the hypothalamic hamartoma, and she is undergoing regular physical and neurological checkups at our outpatient clinic.

Discussion

NF1, also known as von Recklinghausen disease, is an autosomal dominant condition caused by mutations of the *NF1* gene, which is located at chromosome 17q11.2^{3,9)}. The gene is large, spanning 350 kilo-bases of genomic deoxyribonucleic acid (DNA), and contains 60 exons encoding the 2818 amino acids of the protein neurofibromin³⁾. The *NF1* mutation rate is among the highest observed in humans, with estimates ranging from about 1/7,800 to 1/23,000 gametes⁵⁾. Approximately 50% of NF1 cases result from new mutations; until now, more than 1000 gene mutations have been connected to NF1 worldwide⁵⁾. Most of the described mutations are private; several hot spots with a higher mutation rate such as exons 4b, 7, 10b, 13, 15, 20, 29, and 37 have been described¹⁰⁾. To the best of our knowledge this is the first report of a patient with NF1 caused by a 14-bp deletion mutation in exon 5.

NF1 shows multi-system and multi-organ involvement and may be associated with several endocrinological abnormalities, of which precocious puberty is well described in children^{1,6)}. Other endocrinological abnormalities reported are short stature, growth hormone deficiency, and hypogonadotropic hypogonadism¹¹⁾. Precocious puberty occurs in 3% of the population of children with NF1, which is markedly greater than its incidence

in the general population of about 0.6%^{12,13)}. Generally, it is thought that all endocrine disorders in NF1 could be related to central nervous system tumors compromising hypothalamic and pituitary function. In particular, most patients with precocious puberty associated with neurofibromatosis have optic chiasmal glioma⁶⁾. In the general population, precocious puberty is often associated with tumors of the central nervous system, including hypothalamic hamartoma.

Hypothalamic hamartoma, which is not a true neoplasm, produces precocious puberty by pulsatile release of luteinizing hormone releasing hormone (LHRH)¹⁴⁾ and is often associated with gelastic seizures, absence seizures, generalized tonic-clonic seizures, developmental delay, behavior disturbances, and dysmorphic syndromes¹⁵⁾. Hypothalamic hamartoma is not an indication for surgical resection; however, it may be indicated for patients with intractable seizures that cannot be controlled with anticonvulsants¹⁶⁾. Hypothalamic hamartoma causing precocious puberty has also been associated with oral-facial-digital syndrome type VI (Varadi syndrome)¹⁷⁾ and tuberous sclerosis¹⁸⁾, but is extremely rare in NF1. Previous studies of precocious puberty associated with hypothalamic hamartoma in NF1^{19,20)} have involved children who showed a pubertal response in the GnRH stimulation test. Our patient showed a pre-pubertal response with a similarly sized mass in the hypothalamus, but we could clinically diagnose precocious puberty due to rapid growth velocity, advanced bone age, and thelarche appearance. Although our patient's hormonal response was only pre-pubertal, as she did not have any of the known risk factors like family history or obesity, her clinical presentation of precocious puberty may have been associated with hypothalamic hamartoma.

Our patient with NF1 demonstrated evidence of precocious puberty without an optic chiasmal lesion. However, she had a hypothalamic hamartoma, which was considered to be the cause of the precocious puberty, and was presumably associa-

ted with a 14-bp deletion mutation in exon 5 of *NF1*. This combination has never been previously reported in the literature.

요약

신경섬유종증 1형은 흔히 보일 수 있는 신경피부증후군의 하나로, 담갈색 반점, 겨드랑이 주근개 모양 색소반, 피부신경섬유종 그리고 Lisch 소결절 등을 특징적으로 나타내며, Neurofibromin을 발현하는 *NF1* 유전자의 변이가 이 질환의 원인으로 알려져있다. NF1 환아에게 있어서 성조숙증을 같이 동반하는 경우가 있으며, 이런 경우 대부분 시신경 종양과 연관되어있다. 저자들은 NF1에서 시상하부 과오종과 연관된 성조숙증을 동반한 케이스를 보고하고자 하며, 이 환자의 경우 지금까지 보고되지 않았던 *NF1* exon 5의 14-bp 결실 돌연변이를 동반하고 있는 바이다.

References

- Williams VC, Lucas J, Babcock MA, Gutmann DH, Korf B, Maria BL. Neurofibromatosis type 1 revisited. *Pediatrics* 2009;123:124-33.
- Stumpf DA. National Institutes of Health consensus development conference. Neurofibromatosis. conference statement. *Arch Neurol* 1988;45: 575-8.
- Lee MJ, Stephenson DA. Recent developments in neurofibromatosis type 1. *Curr Opin Neurol* 2007;20:135-41.
- Shen MH, Harper PS, Upadhyaya M. Molecular genetics of neurofibromatosis type 1 (NF1). *J Med Genet* 1996;33: 2-17.
- Huson SM, Compston DA, Clark P, Harper PS. A genetic study of von Recklinghausen neurofibromatosis in south east Wales. I. Prevalence, fitness, mutation rate, and effect of parental transmission on severity. *J Med Genet* 1989;26:704-11.
- Cnossen MH, Stam EN, Cooman LC, Simonsz HJ, Stroink H, Oranje AP, et al. Endocrinologic disorders and optic pathway gliomas in children with neurofibromatosis type 1. *Pediatrics* 1997;100:667-70.
- Ng SM, Kumar Y, Cody D, Smith CS, Didi M. Cranial MRI scans are indicated in all girls with central precocious puberty. *Arch Dis Child* 2003;88: 414-8.
- Virdis R, Sigorini M, Laiolo A, Lorenzetti E, Street ME, Villani AR, et al. Neurofibromatosis type 1 and precocious puberty. *J Pediatr Endocrinol Metab* 2000;13: Suppl 1: 841-4.
- Rasmussen SA, Friedman JM. NF1 gene and neurofibromatosis 1. *Am J Epidemiol* 2000;151:33-40.
- Ars E, Kruyer H, Morell M, Pros E, Serra E, Ravella A, et al. Recurrent mutations in the NF1 gene are common among neurofibromatosis type 1 patients. *J Med Genet* 2003;40:e82.
- Bizzarri C, Bottaro G. Endocrine implications of neurofibromatosis 1 in childhood. *Horm Res Paediatr* 2015;83:232-41.
- Marshall WA, Tanner JM. Variations in pattern of pubertal changes in girls. *Arch Dis Child* 1969;44:291-303.
- Marshall WA, Tanner JM. Variations in the pattern of pubertal changes in boys. *Arch Dis Child* 1970;45:13-23.
- Kaplan SL, Grumbach MM. Pathogenesis of sexual precocity. In: Grumbach MM, Sizonenko PC, Aubert ML, editors. *Control of the onset of puberty*. Baltimore, MD: Williams & Wilkins, 1990;620-60.
- Minns RA, Stirling HF, Wu FC. Hypothalamic hamartoma with skeletal malformations, gelastic epilepsy and precocious puberty. *Dev Med Child Neurol* 1994; 36:173-6.
- Debeneix C, Bourgeois M, Trivin C, Sainte-Rose C, Brauner R. Hypothalamic hamartoma: comparison of clinical presentation and magnetic resonance images. *Horm Res* 2001;56:12-8.
- Stephan MJ, Brooks KL, Moore DC, Coll EJ, Goho C. Hypothalamic hamartoma in oral-facial-digital syndrome type VI (Várad syndrome). *Am J Med Genet* 1994;51:131-6.
- De Cornulier M, David A, Cohen JY. Precocious puberty revealing Bourneville tuberous sclerosis. *Arch Fr Pediatr* 1993; 50:421-3.
- Bartolini E, Stagi S, Scalini P, Bianchi A, Ciccarone A, Mascalchi M. Central precocious puberty due to hypothalamic hamartoma in neurofibromatosis type 1. *Hormones (Athens)* 2016;15: 144-6.
- Biswas KI, Kapoor A, Jain S, Ammini AC. Hypothalamic hamartoma as a cause of precocious puberty in neurofibromatosis type 1: patient report. *J Pediatr Endocrinol Metab* 2000; 13:443-4.