Clinical Pediatric Endocrinology

Vol.31 / No.3
July 2022
pp 159–162

Case Report

Congenital hypogonadotropic hypogonadism complicated by neuroblastoma

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Highlights

- A boy with congenital hypogonadotropic hypogonadism developed neuroblastoma.
- A homozygous p.P147L (c.C440T) mutation in the *KISS1R* gene was detected that may have played a role in its development.

Abstract. A 3-mo-old male infant was referred to our hospital with micropenis. Since his serum LH, FSH, and testosterone levels were low (< 0.3 mIU/mL, 0.08 mIU/mL, and < 0.03 ng/mL, respectively), Kallmann syndrome/normosmic hypogonadotropic hypogonadism was suspected. In the process of searching for complications of Kallmann syndrome/normosmic hypogonadotropic hypogonadism, a right adrenal gland tumor was incidentally discovered. The patient was diagnosed with stage 1 neuroblastoma. A homozygous p.P147L (c.C440T) mutation in the *KISS1R* gene was detected as a cause of the congenital hypogonadotropic hypogonadism. KISS1-KISS1R signaling, which is essential for GnRH secretion, exhibits anti-metastatic and/or anti-tumoral roles in numerous cancers. High *KISS1* expression levels reportedly predict better survival outcomes than low *KISS1* expression levels in neuroblastoma. Therefore, decreased KISS1-KISS1R signaling may have played a role in the neuroblastoma in this patient.

Key words: congenital hypogonadotropic hypogonadism, neuroblastoma, KISS1R

Received: November 29, 2021 Accepted: March 11, 2022 Advanced Epub: March 30, 2022

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Introduction

KISS1 and *KISS1R* mutations are responsible for congenital hypogonadotropic hypogonadism (CHH) (1, 2). *KISS1* was originally reported as a metastasis-suppressor gene (3), and it was recently reported that its signaling might play a tumor-suppressing role in patients with neuroblastoma (4).

We report the case of an 8-mo-old boy with CHH due to a homozygous mutation in the *KISS1R* gene who was diagnosed with neuroblastoma. A homozygous mutation in *KISS1R* discovered in this patient may play a role in neuroblastoma biology. This is the first report of a case of CHH complicated by neuroblastoma.

Case Presentation

A 3-mo-old male infant was initially referred to our hospital with micropenis. His growth was normal. His penile length was 1.0 cm and the bilateral testes were palpable in the scrotum with volumes of 1 mL. There were no other abnormal findings, such as cryptorchidism or hypospadias. The laboratory findings are presented in **Table 1**. A chromosomal analysis revealed a 46,XY karyotype. Serum LH and testosterone levels were undetectable, and serum FSH level was low for his age (5, 6). Minipuberty occurs in the first 3–6 mo of life, and serum LH and testosterone levels peak at 2.5–3 mo of age (7, 8). The fact that serum LH and testosterone levels were undetectable at 3 mo of age in this patient suggested a gonadotropin deficiency. Thyroid function plasma IGF-1 and serum dehydroepiandrosterone sulfate levels were normal. Thus, isolated hypogonadotropic hypogonadism was suspected. At five months of age, a GnRH stimulation test was performed. The basal serum LH and FSH levels were low for his age (5, 6) but increased in response to GnRH (**Table 2**). Reference values for the GnRH stimulation test in infants could not be found. Since serum gonadotropin levels decrease to the prepubertal range by 4–6 mo of age in boys (5–8), GnRH stimulation test results at 5 mo of age may vary among individuals. Therefore, it was impossible to estimate the status of gonadotropin secretory capacity from LH and FSH responses to GnRH stimulation. Magnetic resonance imaging (MRI) revealed a normal pituitary gland and olfactory bulb. Since serum LH, FSH, and testosterone levels were low at 3 mo of age and MRI showed normal olfactory bulbs, normosmic CHH was suspected.

Renal ultrasonography performed to examine renal abnormalities associated with the normosmic CHH revealed a right adrenal gland tumor (35 × 30 × 24 mm) was incidentally discovered. Neuroblastoma was suspected because urinary vanillylmandelic acid and homovanillic acid levels were high (30.5 μg/mg·Cre and 33.1 μg/mg·Cre, respectively). No metastatic lesions were found on abdominal MRI or computed tomography scans. Moreover, 123I metaiodobenzylguanidine accumulated only in the right adrenal gland tumor and no bone marrow metastasis was detected. When the patient was 8 mo of age, the tumor was completely resected and he was diagnosed with stage 1 neuroblastoma. *MYCN* is an oncogene whose amplification is a poor prognostic factor. In this patient, *MYCN* amplification was not detected in the tumor sample.

After the administration of three doses of testosterone enanthate (25 mg), the patient's penile length increased to 3.5 cm. Analysis of the gene responsible for hypogonadotropic hypogonadism revealed a homozygous p.P147L (c.C440T) mutation in the *KISS1R* gene. No genetic analysis of his nonconsanguineous parents was performed. P147-KISS1R is a highly conserved amino acid among other mammalian KISS1R proteins. Polymorphism Phenotype v2 (PolyPhen-2, http://genetics.bwh.harvard.edu/pph2/) and Mutation Taster (http://www.mutationtaster.org/) were used for the in silico analysis. PolyPhen-2 predicted that the P147L-KISS1R mutation was probably damaging in nature, while Mutation Taster predicted that the P147L-KISS1R mutation was disease-causing. The minor allele frequency of the p.P147L (c.C440T) variant in *KISS1R*, as reported by the Tohoku Medical Megabank Organization (ToMMo), was 0.0005. Moreover, the P147L-*KISS1R* mutation reportedly causes an almost complete loss of function due to loss of ligand-binding affinity (9). Based on the 2015 American College of Medical Genetics and Genomics and the Association of Molecular Pathology (ACMG-AMP) guidelines (10), the P147L-*KISS1R* mutation was likely pathogenic.

This study was approved by the Ethics Committee of the Faculty of Medicine, Toho University (A19054). Written informed consent was obtained from the patients' mothers.

Table 1. Laboratory findings: Endocrinological data at 3 mo of age

IGF-1	44 ng/mL	DHEA-S	68 μg/dL
Free T_3	5.34 pg/mL	FSH	0.08 mIU/mL
Free T_4	1.43 ng/dL	LH	< 0.3 mIU/mL
TSH	3.55 μIU/mL	Testosterone	< 0.03 ng/mL
ACTH	23.8 pg/mL	Estradiol	< 5.0 pg/mL
Cortisol	11.0 μg/dL		

DHEA-S, dehydroepiandrosterone sulfate.

Table 2. Laboratory findings: GnRH stimulation test results at 5 mo of age

(min)	LH (mIU/mL)	FSH (mIU/mL)
0	< 0.3	1.1
30	7.5	20.0
60	5.9	22.3
90	4.1	19.3
120	2.6	16.9

doi: 10.1297/cpe.31.2021-0070

Discussion

KISS1-KISS1R signaling is involved in puberty induction by the stimulation of GnRH secretion from the hypothalamus (11). Homozygous and compound heterozygous loss-of-function mutations in *KISS1* and *KISS1R* cause CHH without dysosmia (1, 2). *KISS1* was first reported as a metastasis-suppressor gene (3). Thereafter, it was reported that kisspeptin encoded by the *KISS1* gene plays a role in suppressing cancer metastasis by binding to KISS1R, also known as the G protein–coupled receptor 54 (GRP54) (12). Decreased expressions of *KISS1* and *KISS1R* are reportedly a poor prognostic factor in various tumors (13). KISS1-KISS1R signaling exhibits anti-metastatic and/or anti-tumor effects in numerous cancers (14).

Neuroblastoma is the second most common pediatric solid tumor after brain tumors (15). Many genetic alterations, such as *MYCN* gene amplification, gain-of-function mutation in the anaplastic lymphoma kinase (*ALK*) gene, haploinsufficiency for the ataxia-telangiectasia mutated (*ATM*) gene, and loss-of-function mutation in the alpha thalassemia/mental retardation syndrome X-linked (*ATRX*) gene, are involved in the onset of neuroblastoma (16). The aryl hydrocarbon receptor (AHR) is reportedly one of the factors involved in neuroblastoma onset and/or progression.

AHR, a ligand-activated transcription factor, is a dioxin-binding protein. Exogenous chemicals, such as dioxins, bind to AHR and induce immunological disorders, reproductive system disorders, and tumorigenesis (17). In contrast, AHR activated by endogenous ligands plays important physiological roles in immunological development, reproductive system development, xenobiotic metabolism, and other activities (17). AHR is physiologically expressed in various tissues and overexpressed in many tumors. AHR suppresses tumorigenesis of some tumors and promotes tumorigenesis of others (18–20). In neuroblastoma, *AHR* expression downregulates *MYCN* expression, promotes tumor differentiation, and suppresses tumor growth (4, 21, 22). Reduced *MYCN* expression is one mechanism underlying the tumor-suppressive effect of AHR in neuroblastoma. Moreover, AHR activation upregulates *KISS1* expression, high levels of which in neuroblastoma have been shown to predict better survival outcomes (4). Thus, AHR signaling partially suppresses tumorigenesis due to accelerating *KISS1* expression in neuroblastoma. Therefore, decreased KISS1-KISS1R signaling due to a germline mutation in *KISS1R* may have played a role in neuroblastoma biology in this patient. The anti-tumorigenic effect of KISS1-KISS1R signaling is reportedly due to the suppression of matrix metalloproteinase-9 (MMP-9) and vascular endothelial growth factor (VEGF) expression (23). *MYCN* amplification was not detected in this patient. Therefore, the antitumorigenic effect of KISS1-KISS1R signaling in neuroblastoma may be independent of *MYCN* expression.

Nazir *et al.* reported that none of their in 120 patients with head and neck cancer had the *KISS 1* mutation (24). Since there have been no reports of germline mutations in *KISS1* or *KISS1R* in patients with malignant tumors, this patient with a homozygous *KISS1R* mutation might have developed neuroblastoma by chance. However, careful follow-up may be required for complications of various malignant tumors in patients with germline mutations in *KISS1* and *KISS1R*.

Conclusion

Here we reported the case of an 8-mo-old boy with CHH due to a homozygous mutation in the *KISS1R* gene who was also diagnosed with neuroblastoma. In numerous cancers, decreased KISS1-KISS1R signaling in the tumor tissues reportedly promotes tumorigenesis and metastasis. The germline mutation in *KISS1R* discovered in this patient may play a role in neuroblastoma biology.

Conflicts of interests: The authors declare no conflicts of interest.

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doi: 10.1297/cpe.31.2021-0070

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