Primary Amenorrhea in an 18-year-old Japanese Female with Sensorineural Hearing Loss and Anosmia: a New Syndrome?

YOSHIKI YAMAGATA, RYO MAEKAWA, HIROMI ASADA, ISAO TAMURA, KEN TANIGUCHI, TOSHIKI TAKETANI, ICHIRO MIWA, AKI MATSUOKA, HIROSHI TAMURA AND NORIHIRO SUGINO

Department of Obstetrics and Gynecology, Yamaguchi University Graduate School of Medicine, Minamikogushi 1-1-1, Ube 755-8505, Japan

Abstract. This report documents a case with primary amenorrhea associated with sensorineural hearing loss and anosmia. The patient presented at 18 years of age with minimal sexual development and no prior menses. Her mother also presented late onset menarche, hearing loss and anosmia, and her father was also affected with hearing loss. A chromosome analysis of the patient showed 46, XX. Basal FSH and LH levels were in normal range, but the serum estradiol level was low. A serum estradiol elevation and follicular development were recognized after the injection of human menopausal gonadotropin. Genomic DNA sequencing of *FSHB*, *FSHR*, *KAL1*, *FGFR1*, *PROK2* and *PROKR2* did not show any mutation. Audiometry showed severe bilateral sensorineural hearing loss and smell testing confirmed a severely impaired olfactory function. These findings probably suggested a case of delayed puberty associated with sensorineural hearing loss and anosmia.

Key words: Primary amenorrhea, Olfaction disorders, Deafness

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PRIMARY amenorrheal cases with a normal female karyotype include several differential diseases. The basal history and physical examination can lead to an initial presumptive diagnosis, and endocrine evaluation, diagnostic imaging, and genetic examination etc. usually dictate the final diagnosis. In this report, however, we describe a fully inexplicable case of primary amenorrhea associated with sensorineural hearing loss and anosmia despite these close investigations.

Case Report

An 18 years old Japanese female visited our clinic with a primary complaint of primary amenorrhea. A pubertal evaluation revealed poor breast development

(Tanner stage II), lack of pubic hair development (Tanner stage I) and normal female genitalia. She was otherwise healthy and had an unremarkable past medical history with no indications of either neurologic disability or mental retardation. Her mother experienced menarche at 17 years of age and irregular menstruation. She also had a history of congenital deafness and anosmia. In addition, her father also had congenital deafness. Her elder brother was healthy and had no medical history. Her height was 158 cm, weight 43 kg, and a chromosome analysis showed a normal female karyotype 46, XX.

Her endocrine evaluation is showed in Table 1. She had normal basal gonadotropin concentrations, and gonadotropins were hyper-responsive after the injection of LH-RH as shown in Table 2. Pelvic Magnetic resonance imaging (MRI) and transvaginal ultrasound confirmed the presence of ovarian tissue containing small follicles (<9 mm in diameter). Based on the gonadotropin test, estradiol elevation and follicular development was observed after the injection of human menopausal gonadotropin. After informed consent

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Correspondence to: Yoshiaki Yamagata, M.D., Ph.D., Department of Obstetrics and Gynecology, Yamaguchi University Graduate School of Medicine, Minamikogushi 1-1-1, Ube 755-8505, Japan

Table 1. Endocrine findings

	Patient's value	Normal value
Estradiol (pg/ml)	25.2~41.6	
Progesterone (ng/ml)	0.1	
Testosterone (ng/ml)	0.24	0.1~0.7
Prolactin (ng/ml)	6.04	1.2~29.9
Cortisol (mg/dl)	6.3	5.0~20.0
17 α -OHP (ng/ml)	0.3	<0.6
ACTH (pg/ml)	11.2	7.8~55.7
DHEA-S (ng/ml)	1400	850~2990
TSH (mIU/ml)	0.86	0.35~4.94
Free T4 (ng/ml)	0.9	0.7~1.5

17 α -OHP: 17 α -hydroxyprogesterone, DHEA-S: dehydroepiandrosterone sulphate

Table 2. LH-RH test

(min)	FSH (mIU/ml)	LH (mIU/ml)
0	7.8	6.4
30	15.5	56.1
60	17.0	52.5

Blood sampling was performed after 100 mg of LH-RH was injected intravenously.

from the patient and ethical approval from Yamaguchi University Graduate School of Medicine were obtained, she was further examined by genomic DNA sequencing of *FSHB* (follicle stimulating hormone β -subunit), *FSHR* (follicle stimulating hormone receptor), *KAL1* (anosmin-1), *FGFR1* (fibroblast growth factor receptor 1), *PROK2* (prokineticin-2) and *PROKR2* (prokineticin receptor-2) genes. These sequence analyses revealed no mutation to be present.

She had normal external auditory meati and normal tympanic membranes. An audiogram showed severe bilateral sensorineural hearing loss (Fig. 1). Olfactory acuity was evaluated by a Toyota-Takagi test, and the olfactory function was found to be severely impaired (Fig. 2). MRI of the hypothalamic-pituitary region did not demonstrate any disorders, whereas the olfactory tract and bulb seemed to be atrophic.

Discussion

Hypogonadotropic hypogonadism associated with congenital anosmia is defined as Kallmann syndrome, which is caused by a neuronal migration arrest involving both the olfactory and the GnRH-producing neu-

Fig. 1. Audiogram. The patient demonstrated bilateral sensorineural hearing loss. **Fig. 2.** Olfactograms by Toyota-Takagi test. A, β -phenyl ethyl alcohol (odor of rose); B, cyclotene (odor of burning); C, isovaleric acid (odor of sweat); D, γ -undecalactone (odor of fruits); E, scatole (odor of vegetable chips). Opened circles ($\circ$) indicate the detection thresholds, and crosses ($\times$) represent the recognition thresholds. Olfactory function is severely impaired.

rons [1]. In addition, several cases of Kallmann syndrome have been reported to occur in association with congenital deafness [2, 3]. However, the present case is different from typical Kallmann syndrome because of the fact that her hormonal status expresses normal gonadotropism and no mutation exists in the genes that are responsible for Kallmann syndrome. In

this case, both a small follicular development and a low level of estradiol secretion were observed under a normal FSH release from the pituitary. In addition, an extraneous large amount of gonadotropin could stimulate the ovulatory follicular development. Her ovaries showed the normal early stage of follicular development by ultrasound, however, these immature follicles could not reach preovulatory size even when gonadotropin stimulation was supposed to be adequate. Despite the fact that her basal gonadotropin levels were within the normal range, her hormonal status might have been hypothalamic hypogonadism rather than normal gonadotropism. Another possibility underlying the patient's condition is that her ovaries had a somewhat deficient gonadotropin sensitivity after the achievement of middle sized immature follicular stage. It is widely recognized that follicular growth is gonadotropin dependent in both the early and later stages of follicular development, and follicles in their final phase are more dependent on gonadotropin stimulation. However, estradiol secretion, even at a low level, can induce natural follicular growth and ovulation in the future because estrogen and FSH stimulation increase FSH receptor expression of the follicle, and this alteration leads higher responsibility for normal range of gonadotropin stimulation. In any clinical condition, she may be in a delayed puberty status and natural me-

narche onset can therefore be expected.

In this case, both her parents have deafness and the mother is affected with anosmia and delayed menarche. These features might imply inherited defects, however, various modes of inheritance are possible, e.g., autosomal dominant, recessive, X-linked, or just coincidental occurrence. In this context, not all features in this patient can be necessarily attributed to one condition but they might occur simultaneously with two or more different conditions.

It is important to evaluate the ovarian function in cases with menstrual disorder associated with deafness and/or anosmia. The patient has been receiving hormone replacement therapy to develop sexual maturity and maintain bone mass. In the case of continuous amenorrhea, gonadotropin treatment might be necessary if, in the future, the patient's goal is to become pregnant. In addition, appropriate genetic counseling should be also given.

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