Hypogonadotropic hypogonadism in a female with the Johnson-McMillin syndrome

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A case of hypogonadotropic hypogonadism associated with the Johnson-McMillin syndrome is presented. This is a rare, autosomal dominant disorder, characterized by variable degrees of alopecia and anosmia, conductive hearing loss, and increased dental caries. Until now hypogonadotropic hypogonadism has only been observed in affected men. Ovulation can be induced with gonadotropins and conception can be obtained, but because prenatal diagnosis is not as yet possible, oocyte donation should be offered as an alternative for procreation.

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The Johnson-McMillin syndrome (JMS) is a rare, autosomal dominant disorder, characterized by variable degrees of alopecia and anosmia, conductive hearing loss, hypogonadotropic hypogonadism, and increased dental caries.1 Other reported manifestations include congenital heart defects, mental retardation, facial nerve palsy, and cleft palate. Until now hypogonadotropic hypogonadism has only been observed in affected men. We report the first female patient with hypogonadotropic hypogonadism and other features of the JMS.

Case report

A 28-year-old woman consulted because of primary amenorrhea. She had a history of failure to thrive in childhood and psychomotor retardation. She was wearing a hearing aid on the left side because of hearing loss caused by an abnormal ossicular chain in the middle ear. She also experienced anosmia, which was confirmed by a standardized smell test. Physical examination revealed short stature (158 cm) with relatively small head circumference (53 cm). Sparse hair was present on the skull. Other craniofacial features included bilateral microtia, ptosis of the left eyelid, right facial nerve palsy, and dental caries (Figure). The neck was short and broad with restricted rotation. The lower limbs were hypotrophic with genua valga. Breast development was staged as Tanner II. The external genitalia were normal, except for scanty pubic hair. Internal genitalia were intact but atrophic. The family history was unremarkable.

Serum levels of follicle-stimulating hormone (FSH), luteinizing hormone (LH), and estradiol were extremely low (FSH, 0.4 mU/mL; LH, 0.7 mU/mL; and estradiol 17 pg/mL). Thyroid and adrenal function were normal. A bone densitometry revealed a moderate osteopenia (T-score: −3.8 SD below the average peak bone mass; bone mineral density: 0.626 g/cm²). The karyotype was normal female (46, XX). Additional investigations revealed a heart defect with abnormal venous return, atrial septal defect, and persistent left superior vena cava. On

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ophthalmologic evaluation, a small coloboma in the right fundus was found. Magnetic resonance imaging (MRI) of the brain showed absent olfactory nerves.

Initially, she was treated with a sequential combination of oral estradiol (2 mg) and norethisteroneacetate (1 mg) for the last 10 days of the cycle. With this treatment, regular menstruation, breast development, and a significant improvement of the bone density was observed.

At the age of 31, she and her partner requested a fertility treatment. The husband was a healthy 46-year-old man. Sperm analysis revealed a moderate oligoastenoteratozoospermia. Initially, ovulation was successfully induced with pulsatile gonadotropin-releasing hormone (GnRH), but this treatment had to be stopped because of logistic problems. Follicular ripening and ovulation subsequently was induced with human gonadotropins for 8 cycles but no pregnancy occurred, neither with timed coitus (2 cycles) nor with intrauterine insemination (6 cycles). The couple decided to continue the treatment with in vitro fertilization. A pregnancy was obtained after transfer of 1 good quality embryo in the second trial but this ended in a miscarriage. Shortly after this trial, she was referred to the department of human genetics for diagnostic advice, despite that genetic evaluation in the past, when she was a child, did not result in a specific diagnosis. Because of the association of anosmia and hypogonadotropic hypogonadism, a genetic investigation for Kallmann syndrome (KS) was performed. Fluorescence in situ hybridization (FISH) analysis with gene-specific probes for KAL1 on Xp22 and FGFR1 on 8p11.2 revealed normal results. However, the clinical findings were suggestive for the diagnosis of JMS. After counselling on the hereditary aspects and the impossibility to diagnose the disease prenatally, the couple opted for oocyte donation. She recently underwent a first and successful oocyte donation. A hitherto uneventful pregnancy resulted from the transfer of a single embryo.

**Comment**

The JMS is a rare neuroectodermal syndrome, inherited as an autosomal dominant trait with variable expressivity. The exact molecular defect is not yet known. A mutation in a single gene involved in the formation of neuroectodermal derivatives of the cephalic neural crest may cause some of the developmental abnormalities that comprise this syndrome (cephalic neurocristopathy). The hypogonadotropic hypogonadism could be explained by a defect in the formation of the pituitary/hypothalamic axis from the diencephalon and Rathke’s pouch and presumably, not unlike the situation in KS, by a deficiency of GnRH generating neurons. The association of anosmia and hypogonadotropic hypogonadism is reminiscent of KS. However, the other abnormalities present in our patient are not features of KS and this diagnosis was not supported by FISH analysis.

Although for the induction of pubertal changes, estrogen treatment is usually started with a low dose that is gradually increased, this patient was treated from the start with a full substitutive dose because of her age (28 years) and the presence of osteopenia.

In conclusion, this is the first report of the occurrence of hypogonadotropic hypogonadism in female patients with the JMS. This condition should be included in the differential diagnosis of hypogonadotropic hypogonadism in association with other abnormalities such as anosmia, even in female patients. A correct diagnosis is the cornerstone for proper genetic counselling and reproductive management.

**References**