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Ovarian Failure in a Chromosomally Competent Adolescent Female: A Case Report

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Primary ovarian failure in adolescence is uncommon. This report depicts such a case in a 17 1/2-year-old girl whose investigation revealed elevations in the follicle-stimulating hormone and luteinizing hormone levels in association with a low estrogen level. The blood leukocyte chromosome analysis with Giemsa banding revealed a 46,XX chromosomal complement. Pelvic ultrasound disclosed a rudimentary uterus and a small left ovary. Hormonal replacement has resulted in advancement of secondary sexual characteristics and monthly withdrawal bleeding. (Henry Ford Hosp Med J 1988;36:195-7)

This case report serves as a springboard for review and discussion of ovarian failure at time of adolescence. In particular, the discussion will center on the following etiologic factors: monosomy for the X chromosome (45,X) complement, the presence and significance of the Y chromosome, and normal chromosomal complement as seen in our patient. Primary ovarian failure is characterized by an elevation of the gonadotropic hormones in association with a low estrogen level and delayed menarche.

Case Report

A previously healthy 17 1/2-year-old girl was seen in the Henry Ford Hospital emergency room and treated for a urinary tract infection. A routine medical history revealed that she had never menstruated. The patient denied ever having been sexually active, and her urine was negative for chorionic gonadotropin hormone. The patient was referred to the Adolescent Medicine Clinic where on further questioning she denied the use of any medications including oral contraceptives. The patient has lived with her maternal grandmother (her legal guardian) since birth. Little is known of the natural mother's current whereabouts as she has had only brief contact with her daughter twice since her birth. The mother was 26 years old at the time of the patient's birth. The grandmother knew nothing about the mother's prenatal care and was unaware of any background information on the patient's father. An investigation of the maternal family pedigree did not reveal any members with similar delay of menarche. In fact, all females in the pedigree had one or more children.

The physical examination revealed a normal-appearing high school girl who was mildly obese. Her vital signs were normal. She was 167 cm (66.8 in) tall (75th percentile) and weighed 80.3 kg (176.7 lb) (93rd percentile). Her blood pressure was 118/78 mm Hg. The examination revealed no thyromegaly, hirsuitism, or breast development, but sparse axillary hair was present. Fine hair growth on the mons pubis was consistent with Tanner stage II (1,2). The external genitalia were consistent with that of a normal female. The vaginal orifice was patent. A pelvic examination, performed with a Huffman speculum, revealed a small but adequate vaginal vault. The cervix was quite small. The bimanual examination revealed no adnexal masses but failed to demonstrate the uterus with certainty. Rectal examination was normal but also failed to demonstrate the uterus.

Laboratory investigation revealed total thyroxine of 131 nmol/L (10.2 µg/dL), thyrotropin-stimulating hormone (TSH) of 4.3 mU/L, and dehydroepiandrosterone sulfate of 5.2 µmol/L (1,900 ng/mL). A repeat urinalysis was negative for chorionic gonadotropin hormone. The estrogen level was prepubertal at 50 pmol/L (12.8 pg/mL) compared with the follicle-stimulating hormone (FSH) at 220 IU/L and luteinizing hormone (LH) at 120 IU/L. Ferning could not be demonstrated with cervical mucous specimens. The serum cortisol, urinalysis, calcium, and complete blood count were normal. An ultrasound of the pelvis (Fig 1) revealed a small rudimentary "sausage-shaped" uterus which measured approximately 3.7 cm in length. A small left "ovary" was identified (Fig 2), but the right ovary could not be seen. The blood leukocyte chromosome analysis with Giemsa banding revealed a 46,XX chromosomal complement. The patient was started on a medroxyprogesterone acetate challenge, 10 mg/day for ten days; there was no evidence of withdrawal bleeding one week following discontinuation of this therapy. The diagnosis of primary gonadal failure was made, and referral to the Endocrinology Clinic resulted in hormonal replacement therapy: conjugated estrogens, 1.25 mg daily, starting the first of the month through day 21, and medroxyprogesterone acetate, 10 mg daily, added the 15th day of the month through day 21. Withdrawal of therapy on day 22 has resulted in cyclic menstrual bleeding.
Results of follow-up studies six months later were as follows: FSH 54.6 IU/L, LH 19.2 IU/L, and estradiol 206 pmol/L (56 pg/mL). Repeat ultrasound of the pelvis (Fig 3) revealed a significant response to hormonal stimulation. The uterine configuration was more adult-like, measuring 5.3 cm in length X 2.3 cm anteroposterior diameter X 2.8 cm transverse diameter. The ovaries remained small. There was a significant increase in the size of the breasts with associated widening of the areola consistent with Tanner stage III (1,2).

Discussion

In females with primary ovarian failure, the defect lies in the ovary. Failure of appropriate feedback inhibition results in enhancement of gonadotropin-releasing hormone which in turn stimulates the pituitary to increase secretion of FSH and LH. Because of the ovary's inability to respond to these hormones, there is failure of the feedback inhibition loop which in turn causes dramatic elevations in the gonadotropin hormones.

Ovarian abnormalities in young females who appear otherwise normal often go unrecognized. The condition most often manifests itself at puberty when the lack of or delay in secondary sexual characteristics/ menarche becomes conspicuous.

Adolescent females born in the United States generally achieve menarche between ages 9 and 16. In fact, over the past century the age of pubertal onset has progressively decreased to the point that 50% of girls reach puberty while still in elementary school (3). Failure to achieve menarche by age 16 is consistent with the diagnosis of primary amenorrhea.

The Turner syndrome constitutes the most common cause of primary amenorrhea due to error in gonadal differentiation. In those affected individuals, a spectrum of karyotypes ranging from 45,XO, 45,X/46,XX to 45,X/46,XY has been reported (4). These females exemplify chromosomally incompetent ovarian failure and are a heterogeneous group of patients with differing etiologies which result in ovarian failure. Chromosomally incompetent ovarian failure distinguishes this group of affected females from those with 46,XX or 46,XY complement, which is termed chromosomally competent ovarian failure. Gonadal dysgenesis is a term applied to females with either chromosomally incompetent or chromosomally competent ovarian failure. It specifically refers to a deficiency in the number of oocytes, often resulting in streak gonads (4,5).

The classic Turner syndrome occurs in approximately 1 in 2,700 live newborn females. It is characterized by a 45,XO complement, short stature ≤ 150 cm (60 in), and sexual infantilism. Affected females have infantile-appearing vagina, uterus, and fallopian tubes. The ovaries, however, are comprised of fibrous streaks of connective tissue. The streak gonads typical of this disorder lack primordial follicles and hence ovulation and production of estrogen are hopelessly impaired. Other features associated with the classic Turner syndrome include a short, webbed neck, low nuchal hairline, low-set ears, shield chest with widely spaced nipples, cubitus valgus, and a malformation or hypoplasia of the nails. Familial aggregates of this disorder are rare.

Females with phenotypic chromosomally incompetent or chromosomally competent ovarian failure, in whom the presence of a Y chromosome or marker has been demonstrated, have an increased risk factor. The risk for the development of neoplasia in dysgenetic gonads containing Y material is high. Some studies suggest that as many as 30% of patients with dysgenetic gonads containing Y material will develop gonadoblastomas (6). Gonadoblastomas are tumors of dysgenetic gonads com-
posed of germ cells and sex cord cells in a distinctive histologic
pattern. Often the neoplasia arises in the first or second decade.
The malignant potential of the germ cells in the epithelial nest of
gonadoblastomas makes it imperative to remove these gonads
from all Y chromosome-bearing hermaphrodites or phenotypic
females with abnormal or dysgenetic internal genitalia.

Our patient falls into the classification of chromosomally
competent ovarian failure. Individuals in this group exhibit go-
nadal failure, but unlike those with the Turner syndrome the sta-
ture is normal and there are no outward stigmata of the disorder.
Persons with a normal chromosomal component are taller be-
cause the epiphyses stay open in the absence of ovarian steroids
(7). Familial aggregates are not uncommon in 46,XX gonadal
failure, and parental consanguinity has been reported. Somatic
anomalies are usually not present in females, but concurrent
neurosensory deafness has been reported in multiple siblings of
four typical families and one atypical family. Prevailing theo-
ries, based on such reports of multiple affected siblings with as-
associated neurosensory defects and consanguinity, incriminate
an autosomal recessive gene (8). However, the case of two
monozygotic twins, discordant for ovarian failure, suggests an
environmental rather than genetic etiology. Environmental fac-
tors could be operative in utero or during infancy (9). Thus,
chromosomally competent ovarian failure may have diverse
etiologies. Under some circumstances, depending on ovarian
histology, the disorder could result from autoimmune ovarian
deletion (10), infectious infiltrative diseases of the ovary (11),
and the gonadotropin-resistant ovary syndrome (12).

Our patient, although responsive to exogenous hormonal
replacement, is unwilling to undergo laparoscopy and gonadal
karyotyping. The absence of this information has blocked
our efforts to determine the chromosome complement of ovar-
ian tissue. In the absence of a Y chromosome, the presence of
streak gonads may be expected. The initial echogram, suggest-
ing the presence of a left "ovary," raises some doubt about the
condition.

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