CLINICAL CASE SEMINAR

Dynamics of Ovarian Function in an Adult Woman with McCune-Albright Syndrome*

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McCune-Albright syndrome is a sporadic disease characterized by polyostotic fibrous dysplasia, café-au-lait lesions, and a variety of endocrine disorders (1, 2). The molecular basis of this syndrome has recently been elucidated. Missense point mutations in the GNAS1 gene located on the long arm of chromosome 20 and encoding for the α subunit of Gs, (the G protein that stimulates cAMP) of transmembrane glycoprotein receptors have been identified (3, 4). Mutations at codon 201 substituting Arg with either Cys or His give rise to abnormal Gsα proteins that reduce the intrinsic guanosine triphosphatase activity, thereby constitutively activating the Gs protein. The mutation is found in variable abundance in different endocrine and nonendocrine tissues, consistent with the mosaic distribution of abnormal cells generated by a somatic cell mutation early in embryogenesis. Severe disease may be associated with an earlier mutational event leading to more widespread distribution of mutated cells (5).

The most commonly encountered endocrine dysfunction in McCune-Albright syndrome is gonadal hyperfunction. Precocious puberty represents the usual initial manifestation of McCune-Albright syndrome in girls. Ovarian cysts may be found on pelvic ultrasound (6–8). Other endocrine abnormalities include hyperfunction of the thyroid and adrenal cortex, as well as excessive GH secretion. The majority of patients have abnormally elevated sex steroids with low or undetectable gonadotropin levels (5). Whereas pregnancies have been described later in life (9, 10), polymenorrhea and amenorrhea due to continued gonadotropin-independent estrogen production have also been reported (11). However, clinical information regarding ovarian dysfunction in McCune-Albright patients during adolescent and adult life is scant.

Case Report

A 22-yr-old patient previously diagnosed as McCune-Albright attended our outpatient clinic for fertility counseling. She exhibited the classical clinical triad of polyostotic fibrous dysplasia along with large café-au-lait spots in the lumbosacral region and a history of precocious puberty and irregular menstrual bleeding.

Computed tomography scans showed fibrous dysplastic bone in the left humerus as well as in the sphenoid and maxillary sinus. The field of vision of the left eye was restricted due to facial bone involvement. Furthermore, she complained of recurrent maxillary sinusitis on the left side. At the age of 20 she underwent surgery in which dysplastic bone was removed from her maxillary and ethmoid sinus on the left side. At age 21 she fractured her left clavicle following an accident with a horse. Healing was markedly delayed. Several typical café-au-lait spots were located in the lumbosacral region, having a triangular shape, predominantly located at the left side and extending from L4 until S3, as well as in the neck and at the flexor surface of the lower left leg.

Menarche occurred at age 5 along with left-sided breast enlargement and development of pubic hair. At that time she exhibited low serum FSH and LH levels, whereas estradiol (E2) was in the normal adult range. Bone age and height were normal at the onset of menstruation. Symptoms did not progress during 5 yr of treatment with cyproterone acetate (12). Sexual maturation started after cessation of cyproterone acetate at 10 yr of age and was completed at 15 yr of age. Thereafter, several combined steroid contraceptive pills were prescribed for irregular menstrual bleeding without success. As far as she could remember, her menstrual cycle had been irregular (bleeding interval, 1–2 weeks) throughout life. During several periods without hormonal contraception she had unprotected intercourse with different male partners without conceiving a pregnancy. Before consultation she also suffered from intermittent pelvic pain predominantly on the right side. On physical examination, her height was 175 cm...
and body weight 58 kg. Pubic hair and breast development, as well as the appearance of her external genitals, were according to Tanner stage V. On transvaginal pelvic ultrasound several cysts were observed only in the right ovary, together with a thickened endometrial lining of the uterus and engorged uterine veins. At the time of referral, increased serum E₂ (805 pmol/L), normal FSH (2.6 IU/L), LH (3.0 IU/L), PRL (3.6 µg/L), TSH (1.6 mU/L), androstenedione (9.4 nmol/L), and dehydroepiandrosteronsulphate (2.4 µmol/L) levels were found.

Materials and Methods

Ultrasonography

Transvaginal ultrasound was carried out on initial screening and at 2-day intervals during two months. Ovarian volume, number of follicles and cysts, features of ovulation, and endometrial thickness (anterior and posterior layers measured in the longitudinal axis) were recorded. For sonographic imaging we used a 6.5-MHz vaginal transducer (model EUB-415; Hitachi Medical Corporation, Tokyo, Japan), as described previously (13, 14).

Source of tissue and preparation of cells

In the beginning of a bleeding period (day 3) laparoscopy and dilatation and curettage were performed to collect ovarian and endometrial biopsies. Before the laparoscopy, several ovarian cysts were punctured separately using transvaginal ultrasound guidance. Ovarian biopsies were taken from both ovaries for genetic analysis using monopolar scissors. Endometrial biopsies were taken using a Pipell microcurette (Laboratoire CCD, Paris, France). Samples were taken from the anterior and posterior endometrial wall. All tissue samples as well as the aspirates from cysts were placed in in vitro fertilization (IVF) medium immediately after collection. The remaining fluid was analyzed for its hormonal content.

Light microscopy

Sections of both ovaries and endometrium obtained by biopsy were prepared in neutral buffered formalin and embedded in paraffin. Thereafter, 10-µm thin sections were cut and subsequently stained with hematoxilin and eosin (15).

Hormone assays

Blood samples were obtained by venepuncture during the initial visit and at 2-day intervals during two monitored months. They were processed within 2 h after withdrawal. Serum and aspirates from the cysts was stored at −20 C. Serum was assayed for FSH, LH, E₂, progesterone (P), testosterone, androstenedione, sex hormone-binding globulin, inhibin A, and inhibin B as described previously (16, 17). Normal serum values were obtained from previous longitudinal studies in 42 normo-ovulatory volunteers (17, 18). Follicular fluid was assayed for E₂ and P. Normal follicular fluid values were obtained from normo-ovulatory volunteers (19).

DNA analysis

DNA was extracted from blood lymphocytes, endometrium, left and right ovarian tissues, and fluid obtained from ovarian follicles and cysts using commercial kits (QIAGEN, Courtaboeuf, France). PCR was performed on extracted DNAs. With the exception of minor modifications, we have used a method described previously (20) for selective enrichment of mosaic Arg 201 mutations.

Informed consent

The local Institutional Review Board was informed of the investigations being carried out. Because only one fully informed patient was involved, a research protocol approval was not required.

Results

Light microscopy

Microscopic analysis of ovarian biopsies showed primordial, primary, and secondary follicles along with Graaffian structures most pronounced in the right ovary. Although all stages of follicular development were present, larger follicles were luteinized. Secretory as well as proliferative elements were present side by side in the endometrium (Fig. 1, A and B).

Mutation analysis

Direct DNA sequencing showed the presence of a guanine to adenine transversion leading to an Arg-His substitution at position 201 in the anterior endometrial lining and right
Inhibin A decreased to a level of 4 ng/L on cycle day 39. In the right ovary, multiple dominant follicle development was observed and again growth was arrested at a diameter around 25 mm. In the left ovary, single dominant follicle growth was noted later during the cycle with a maximum diameter of 22 mm on day 32. E2 levels were 521 pmol/L on cycle day 3 and remained fairly constant until cycle day 24. Thereafter, E2 levels fell gradually to a nadir of 69 pmol/L on cycle day 37. P levels were 4.2 nmol/L on cycle day 3 and remained fairly constant during the follicular phase. On cycle day 24 a rise in P levels could be noted up to a peak value of 44.1 nmol/L reached on cycle day 32. A sharp decline was noted between days 32 and 39 in this cycle to a level of 5.8 nmol/L. Endometrial thickness was 3.7 mm at initial screening and increased gradually to 8.4 mm. On ultrasound examination a triple line was observed throughout the cycle. During menses the endometrium remained 8.4 mm thick. These results are depicted in Fig. 2B.

**Follicular fluid**

In the right ovary five follicles measuring 22, 13, 12, 10, and 10 mm were punctured whereas in the left ovary three follicles with a diameter of 5, 5, and 4 mm were aspirated separately. E2 and P levels were compared with values obtained from similar follicles from regularly cycling women (19). Results are summarized in Fig. 3. Intrafollicular E2 and P concentrations were increased in small follicles (<10 mm) but diminished in large follicles.

**Discussion**

Our findings represent the first longitudinal assessment of ovarian dysfunction in an adult patient suffering from McCune-Albright syndrome. The anticipated phenotype is the development of multiple dominant follicles as a result of increased FSH signaling. Indeed, FSH levels are increased in mothers of dizygotic twins resulting from multiple ovulations (21). Next to the development of multiple preovulatory follicles, premature luteinization and follicle maturation arrest may also be anticipated in this patient due to increased LH receptor signal transduction. This latter phenomenon may be comparable with a premature rise in serum LH observed during initial protocols for ovarian hyperstimulation for IVF without GnRH agonist cotreatment (22).

High FSH levels occurring during the luteo-follicular transition give rise to continued growth of a limited number (cohort) of follicles (23). Subsequent development of this cohort during the follicular phase is dependent on continued stimulation by gonadotropins. FSH levels decrease during the follicular phase due to negative feedback by ovarian inhibin B and E2 synthesis. Except for the dominant follicle remaining, follicles enter atresia due to insufficient support by reduced FSH levels (24). During the late follicular phase, aromatase enzyme activity of granulosa cells from the dominant follicle is also stimulated by LH (25). Under normal conditions, a good correlation between dominant follicle diameter and follicle fluid or serum E2 levels is observed (18, 19).

Increased FSH receptor signaling induced multiple dominant follicle development in the right ovary of the current
patient. Consequently, E2 levels were increased at the beginning of the cycle. In McCune-Albright patients, cyst-like structures produce E2 \textit{in vitro} comparable with normal preovulatory follicles. In contrast, small follicles synthesize substantially more E2 compared with these cysts (26). In the current study, follicular fluid E2 levels were increased in small follicles and decreased in preovulatory follicles compared with normal control subjects. Because McCune-Albright patients respond well to treatment with aromatase inhibitors (12), it might be speculated that aromatase is over-expressed in granulosa cells of McCune-Albright patients due to constitutive FSH signaling resulting in supraphysiological intrafollicular E2 concentrations.

Follicular fluid P levels were also increased in small follicles whereas in larger preovulatory follicles P concentrations were normal. Due to continuous LH receptor activation, P is synthetized prematurely by small follicles. Increasing P production is accompanied by decremental E2 synthesis due to luteinization of granulosa cells. Consequently, growth is arrested, atresia occurs, and these follicles become cysts due to premature P exposure.

In the left ovary (without the mutation), normal single dominant follicle growth and normal intrafollicular steroid levels were found. The follicle reached a normal preovulatory diameter and subsequently showed signs of ovulation. In contrast to the luteo-follicular rise in FSH during the normal cycle, a dominant follicle emerged in our patient after a distinct rise in serum FSH during the midfollicular phase of the cycle. This rise was accompanied by a transient increase in inhibin B like in the normal cycle. While the dominant follicle is growing, E2 output increases coinciding with the rise in inhibin A (27). Following ovulation, serum P levels increased along with an increase in inhibin A, suggesting normal corpus luteum function. Subsequently, P, inhibin A, and E2 levels decrease, constituting a pattern comparable with luteolysis in the normal cycle. The overall hormonal pattern was virtually the same in both cycles monitored.

It seems that some negative feedback activity of inhibin B

![Figure 2](image-url)
FSH is functioning properly in McCune-Albright patients. The feedback mechanism of the pituitary gonadal axis for appropriate feedback. Collectively, these data suggest that concentrations are increased in small follicles in the right ovary. Note that particularly estrogen and progesterone concentrations are increased in both left and right ovaries from a patient with the McCune-Albright syndrome. LH concentrations and either E2 levels or P levels indicating cycle. There is, however, no consistent relationship between LH levels throughout the cycle. LH levels were very low throughout the cycle. LH levels were very low throughout the cycle. This implies that endometrial receptivity is disturbed and natural fertility is compromised. This may represent an additional cause of infertility, even in case normal function of at least one ovary could be restored. This condition might also render future IVF procedures unsuccessful. Some women with McCune-Albright syndrome achieve normal menses and fertility, as well as pregnancies (9–11, 32–34). They might constitute a subgroup of patients in which the extent of the Gsα-mutated cells is limited. On the contrary, other patients have persistence of autonomous gonadal function resulting in irregular cycles, metrorrhagia, and other gynecological problems (8, 11, 34). These abnormalities might be underestimated because the vast majority of papers address clinical findings in younger patients.

In conclusion, the present report provides evidence for persistent autonomous unilateral ovarian dysfunction during early adulthood in McCune-Albright syndrome not compatible with normal fertility. Increased FSH and LH signaling gives rise to development of multiple dominant follicles, premature luteinization, anovulation, and cyst formation. Single dominant follicle development and normal ovulation and subsequent corpus luteum function could be observed on the contralateral unaffected ovary. Endometrial morphology is abnormal. The gynecological implications of these findings may include cycle disturbances and untreatable infertility. Extended suppression of endogenous FSH or unilateral ovariectomy should be considered when pregnancy is desired.

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**References**


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