

Management of Infertility in a Patient Presenting with Ovarian Dysfunction and McCune-Albright Syndrome

JOOP S. E. LAVEN, SERGE LUMBROSO, CHARLES SULTAN, AND BART C. J. M. FAUSER

Division of Reproductive Medicine, Department of Obstetrics and Gynecology (J.S.E.L, B.C.J.M.F.), Erasmus Medical Center, 3015 GD Rotterdam, The Netherlands; Department of Hormonology (S.L.), University Hospital Montpellier, 34295 Montpellier, France; and Department of Hormonology and Unit of Pediatric Endocrinology and Gynecology, Department of Pediatrics (C.S.), University Hospital Montpellier, 34295 Montpellier, France

Persistent autonomous ovarian dysfunction in McCune-Albright syndrome (MAS) patients is associated with the development of multiple dominant follicles, premature luteinization, cyst formation, and anovulatory infertility. Due to the mosaic distribution of the mutation, ovaries may be unequally affected. In the current patient, the least affected ovary became quiescent upon GnRH agonist-induced gonadotropin suppression. Normoovulatory cycles were restored after subsequent removal of the affected right ovary, and a pregnancy

was established within 3 months. A healthy unaffected girl was born at term after an uneventful pregnancy. The placental tissue was normal, and the mutation was not detected in the placenta, umbilical cord structures, or umbilical cord blood. GnRH analog administration may help to identify those MAS patients who might benefit from unilateral ovariectomy. Because a healthy baby was born, evidence is provided suggesting that MAS is not passed on to the children from the parents. (*J Clin Endocrinol Metab* 89: 1076–1078, 2004)

POLYOSTOTIC FIBROUS DYSPLASIA, café au lait spots, sexual precocity, and hyperfunction of multiple endocrine glands constitute the key features of McCune-Albright syndrome (MAS). The syndrome is due to a somatic mutation in the *GNAS1* gene (1, 2). Missense point mutations at codon 201 substituting Arg with either Cys or His give rise to abnormal G_{α} proteins that reduce the intrinsic guanosine triphosphatase activity, thereby constitutively activating the G_s protein (3–5). The extent and nature of the abnormality are highly variable, depending on the specific tissues involved due to the mosaic distribution of the *GNAS1* mutation (3).

The most commonly encountered endocrine dysfunction in MAS is gonadal hyperfunction. Precocious puberty represents the usual initial manifestation of MAS in girls. Ovarian cysts may be found upon pelvic ultrasound (6, 7). 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. Although pregnancies have been described later in life (8–10), polymenorrhea and amenorrhea due to continued gonadotropin-independent estrogen production have also been reported (6, 11). However, clinical information regarding ovarian dysfunction in McCune-Albright patients during adolescent and adult life is scant.

In a recent paper, we provided evidence for persistent autonomous unilateral ovarian dysfunction in an adult woman suffering from MAS. Because MAS patients show a typical unilateral involvement of symmetrical tissues, the mutation is usually only present or more abundant in either

one of the ovaries. Increased FSH and LH signaling gave rise to the development of multiple dominant follicles, premature luteinization, anovulation, and cyst formation in the affected ovary. As a result of the sex steroid-rich endocrine environment, gonadal function in the unaffected contralateral ovary is usually also disturbed. Endometrial function may be also disrupted presumably due to elevated progesterone levels throughout the cycle, implying that embryo implantation might be severely compromised, representing an additional factor in infertility (11). Hence, removal of the affected ovary might restore a normal endocrine environment, and subsequently normal ovarian function might be restored in the remaining gonad, rendering these patients fertile.

Case Report

A 22-yr-old patient previously diagnosed as having MAS 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. DNA analysis revealed a mutation (201 Arg to His) present in the right ovary only, as well as in the endometrium (11). As previously described, increased FSH and LH signaling gave rise to the development of multiple dominant follicles, premature luteinization, anovulation, and cyst formation in the affected ovary. The function in the contralateral unaffected ovary was also disturbed due to continuously elevated sex steroid levels (11).

In an attempt to suppress the function of the unaffected ovary, a GnRH agonist (Zoladex, AstraZeneca, Zoetermeer, The Netherlands) known to induce suppression of pituitary gonadotropin release was administered for 1 month. This investigation was performed to test the hypothesis that the unaffected ovary would be rendered quiescent due to the lack of tropic support, whereas the affected ovary would continue to function autonomously. Weekly transvaginal ultrasound showed a progressive disappearance of ovarian cysts in the left ovary during GnRH agonist administration, indicating that this ovary is normally responsive to FSH and LH. In contrast, the affected ovary on the right side did not respond and continued to function abnormally.

These results as well as the experimental nature of the proposed unilateral ovariectomy were discussed extensively in our team and with

Abbreviation: MAS, McCune-Albright syndrome.

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the patient. Moreover, the local Institutional Review Board was informed before the investigations had been carried out. Because only one fully informed patient was involved, a research protocol approval was not required. Subsequently, unilateral ovariectomy was performed through laparoscopy under general anesthesia. Upon laparoscopy, an enlarged (5 × 5 × 8-cm) cystic ovary was easily removed. Care was taken to leave the fallopian tube on the right side intact. The left ovary had a normal appearance, as had the remaining internal genital organs. Sections of the left ovary were prepared as previously described (11). Upon microscopic examination, primordial, primary, and secondary follicles along with Graafian structures were found. Although all stages of follicular development were present, larger follicles were luteinized without exception. The mutation was readily detectable throughout the removed ovary. Again, both canonical and mutant sequences present were indicative of the mosaic nature of the disease.

The patient recovered rapidly after the operation, and a regular menstrual cycle (28–30 d) was immediately restored. During the third cycle, she spontaneously conceived after a previous 4-yr period of infertility. After an uneventful pregnancy, at 40 wk a healthy daughter weighing 3800 g was delivered vaginally. The placenta appeared normal (650 g), and the baby displayed no external stigmata of MAS. The placental tissue was normal on microscopic examination. No evidence of the GNAS1 mutation was found in the placenta, umbilical cord, or cord blood (Fig. 1). The daughter is now 1½ yr old, and her development remains normal.

Discussion

The current findings suggest that it may be useful to apply an *in vivo* test using a GnRH agonist to investigate whether the least or nonaffected ovary in MAS patients is normally responsive to diminished stimulation by gonadotropins.

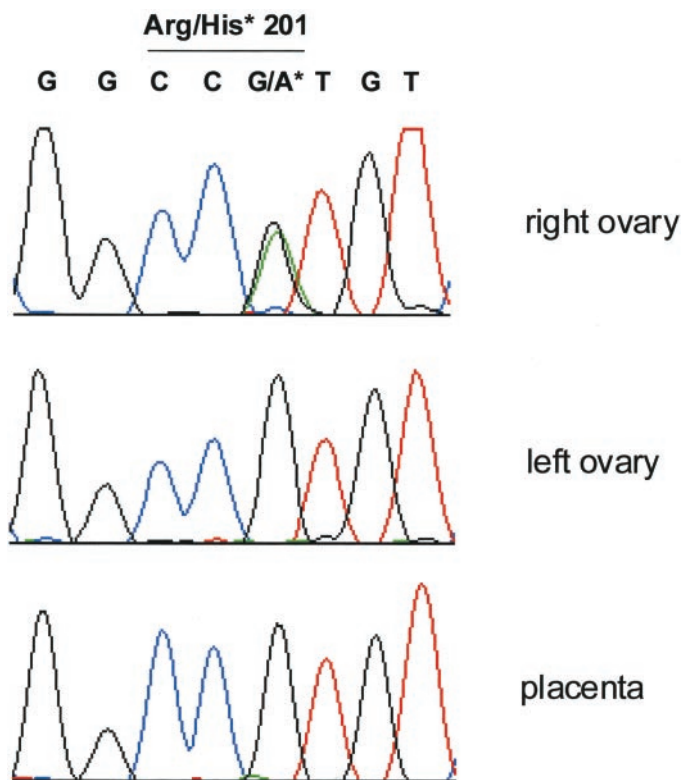


FIG. 1. Direct DNA sequencing showed the presence of a guanine to adenine transversion (G/A*) leading to an Arg-His substitution at position 201 in the right ovary. Both canonical and mutant sequences were present, the latter with a weaker intensity (green) indicating a mosaicism of normal and abnormal cells. The mutation was not detectable in the left ovary or in the placental tissue.

Moreover, the current case history provides evidence to support the concept that in adult MAS patients with persistent unilateral autonomous ovarian activity, ovarian and endometrial function can be restored through removal of the affected ovary. Finally, because an unaffected healthy daughter was born, this report provides further evidence that MAS is caused by an autosomal dominant lethal gene that is compatible with viability of the conceptus only when it occurs in the mosaic state. Hence, MAS results from a somatic mutation and therefore may not be inherited through an affected parent.

Our patient showed a typical unilateral involvement of tissue because the mutation was only found in the right polycystic ovary. This might be due to either a reduced number or an absence of mutated cells present in the left ovary not being detected by DNA analysis (11). Nevertheless, this difference in expression of the mutation seems to be compatible with normal monofollicular growth in the left ovary. However, this potentially normal ovary was still dysfunctional as a result of the abnormal sex steroid-rich endocrine environment induced by its affected counterpart. Removal of the right ovary might restore normal function of the remaining left ovary and should be considered. Testing whether this is a feasible approach may be done using an *in vivo* GnRH agonist test. If the unaffected ovary becomes quiescent under GnRH analog administration, it may be justified to remove the affected ovary. The abnormal endocrine environment, which may also affect both oocyte and endometrial function and, consequently, the outcome of *in vitro* fertilization, cannot be otherwise corrected. Hence, ovariectomy may constitute the only treatment option in symptomatic adult MAS women (11).

It has been postulated that the presence of mutated cells in the endometrium might also compromise endometrial receptivity and natural fertility (11). Surprisingly, this seems not to be the case because the patient conceived readily after ovariectomy. Because the mutated endometrial cells were only found in the anterior lining of the uterus, the remaining endometrium was apparently functionally normal. Moreover, nidation and placentation, as observed by ultrasound scans during early pregnancy, took place in the posterior nonaffected endometrial lining.

Happle (3) made the intriguing suggestion that this disorder is caused by an autosomal dominant lethal gene that is compatible with viability of the conceptus only when it occurs in the mosaic state, having arisen by somatic mutation. MAS has been reported to occur in one set of monozygotic twin girls of whom only one showed major signs of MAS whereas the other showed only mild radiological signs of the disease (12). However, the lack of fully convincing familial cases is consistent with the mosaic mutation hypothesis. In the present case, the daughter displayed no signs of MAS. Because the mutation analysis was also negative, she is unlikely to be affected. This provides further evidence for the Happle hypothesis, hereby excluding any possibility of transmission from the parents.

In conclusion, the present report shows that normal ovarian and reproductive function in MAS patients can be restored through unilateral ovariectomy, provided the unaffected ovary is successfully suppressed upon GnRH agonist

administration. Furthermore, evidence is provided that MAS might not be passed on to children by their parents.

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Address all correspondence and requests for reprints to: Joop S. E. Laven, M.D., Ph.D., Division of Reproductive Medicine, Department of Obstetrics and Gynecology, Erasmus Medical Center, Dr. Molewaterplein 40, 3015 GD Rotterdam, The Netherlands. E-mail: j.laven@erasmusmc.nl.

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