Ovarian dysfunction by activating mutation of GS alpha: McCune-Albright syndrome as a model

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Abstract

The McCune-Albright syndrome is characterized by cafe-au-lait spots, precocious puberty, and fibrous dysplasia. It is due to mutations in the gene encoding the GS protein α subunit coupling 7-transmembrane-domain receptors to adenylate cyclase, leading to constitutive adenylate cyclase activation and cAMP overproduction. Endocrinologists and gynecologists are confronted with new issues when these children reach adulthood. Gonadal function and fertility are often abnormal in women in whom puberty was precocious, owing to the persistence of a variable degree of ovarian autonomy that hinders adequate follicular development and ovulation.

Keywords: McCune-Albright syndrome; Precocious puberty; Gsp mutation
2. Pathophysiology

2.1. Mutations in the GSα gene

More than 15 years ago, mutations of the gene encoding the 7-transmembrane-domain receptor-coupled G protein α subunit called GNAS (Guanine Nucleotide Binding α-subunit gene), leading to constitutive adenylyl cyclase activation and to increased cellular cAMP production, were identified in the organs targeted by the syndrome (skin, ovary, testicle, bone, pituitary, thyroid and adrenal glands) and also in liver and heart [7,8]. These are somatic point mutations in exon 8 of the GSα gene (gsp mutations), replacing the arginine at position 201 of the protein sequence (by cysteine or histidine) and the glutamine at position 227 (by arginine or leucine). A new mutation (R201G) was more recently described [9]. The mutations are post-zygotic – occurring early during embryonic development – and therefore have a mosaic distribution [2,4].

2.2. Locus GNAS is under complex imprinting control

Locus GNAS maps on human chromosome 20q13. This region has been recently shown to be under complex imprinting control. In fact, by using alternative promoters and first exons splicing into common site in exon 2, GNAS locus gives rise not only to the GSα gene, but at least to three other genes products, the extra large αs-like protein (XLαs), the neuroendocrine secretory protein 55 (NESP55) and a non-translated transcript deriving from exon 1A. A fourth antisense transcript is believed to play a role in regulating NESP55 expression. The XLαs, antisense and 1A transcripts are expressed only in paternal allele (the promotor is methylated on the maternal allele), whereas NESP55 is expressed specifically from maternal allele (its promotor is methylated on the paternal allele) [10,11].

In some endocrine normal tissues (thyroid, pituitary, ovarian granulosa cells), only the maternal allele is transcribed, whereas in others (adrenal and lymphocytes), both alleles are transcribed [12]. In ten patients with McCune-Albright syndrome, gsp mutations were found on maternal allele in six patients [13]. In the two patients with acromegaly, gsp mutations were on the maternal allele. In the patients with toxic thyroid adenoma, gsp mutation was either on the maternal or paternal allele. In the five patients with precocious puberty, four had mutations on the paternal allele. In one patient with adrenal tumor, mutation was demonstrated on the paternal allele. These data confirm the importance of GSα imprinting in the pituitary gland and point out the high degree of tissue specificity of this phenomenon. However, they need to be confirmed in larger series.

3. Gonadal involvement

3.1. Consequences of precocious puberty and importance of rigorous treatment

Between 35 and 50% of affected girls have precocious puberty, which is the most frequent sign. Precocious puberty is far rarer in boys (15%) [14–19]. Untreated girls have a diminished final height: height velocity is initially increased, leading to early, rapid linear growth but this is rapidly followed by an early fusion of growth plates. Cystic exacerbations lead to fluctuating estradiol hypersecretion. Bone age is almost always advanced in girls with precocious puberty. GnRH agonist therapy is ineffective, given the autonomous, peripheral nature of the estrogens hypersecretion [14,15,20]. In contrast, aromatase inhibitors are remarkably effective on signs of hyperestrogenemia and, in the longer term, on bone maturation and final height [21,22]. However, due to sub-optimal compliance, there remains some concerns with final height which, we hope, might be improved with the use of new generation drugs, either anti-estrogen or aromatase inhibitors. Tamoxifen yielded promising results [23] and preliminary data show that third-generation aromatase inhibitors, such as letrozole [24], are also very interesting, being clearly more effective than second-generation ones [25]. Results with anastrozole were more disappointing [26].

In general, despite the feedback control exerted by autonomous steroid hormones secretion by the gonads, central puberty driven by hypothalamic activity occurs spontaneously at about 11 years of age in girls and 13–14 years in boys [16,27–29]. Only one of our female patients kept persistent gonadotropin suppression due to very severe continuous estradiol hypersecretion by ovarian cysts, long after the normal age of puberty, suggesting possible absence of central puberty in this patient, as previously reported [29]. Thus, final height of this patient was –3 SD.

3.2. Gonadal disorders during adulthood

Ovarian autonomy leading to precocious puberty can be associated with gonadal disorders in adulthood. Also, there may be some concerns with fertility in some of these patients. In fact, there have been very few reports dealing with the course of autonomic ovarian function during adulthood.

We were able to conduct extensive endocrine investigations in six patients with precocious puberty who we followed into adulthood, between the ages of 21 and 30 years. The adult height of these patients was 151 cm (−1 SD) on average, and −3 SD in one case. The final height of such patients is determined not only by the precocious onset of puberty but also by the severity and sites of bone dysplasia. Puberty occurred between the first months of life and seven years of age in these six patients. It was always revealed by metrorrhagia and/or breast development. Five of the six patients were treated with medroxyprogesterone acetate after the diagnosis of precocious puberty, with little effect. Two patients underwent surgery for ovarian cysts at ages 11 years and 19 years, after cyst rupture accompanied by abdominal pain. However, as much as possible, a very conservative approach has to be preferred in case of ovarian cysts due to the very high risk of castration, in particular when both ovaries are involved [30].

In adulthood, gonadal function can follow three patterns depending on the degree of gonadal hypersecretion and its intermittent/continuous nature. One of our patients had regular menstrual cycles, and her gonadal and gonadotropic function was normal. Her ovaries were of normal size and she was able to conceive naturally. In contrast, four patients had irregular...
cycles, three and five years after the onset of central puberty, after a period of regular menstruation. The menstrual cycles of the last patient are totally erratic, and correspond more to metrorrhagia (desquamation of the hyperplastic endometrium). Ovarian autonomy has been studied in details in four patients: it was variable in three cases, leading to irregular menstruation and cyst formation. Spontaneous plasma estradiol concentrations in these anovulatory patients varied unpredictably between 54 and 186 pg/ml. Androgen levels were normal in all four patients. Serum concentrations of inhibit A and inhibit B were normal in the four patients studied. Three of the four patients had a normal gonadotropin response to GnRH test, illustrating the absence of total suppression of the gonadotropic axis by the autonomous ovarian secretion. In the last patient (the most severely affected), serum gonadotropin levels remained low and did not respond to GnRH administration (this patient had the most precocious puberty, and apparently did not undergo normal “central” puberty). The ovaries were large in three of the four patients, with a largest mean diameter of between 37 and 80 mm. The ovaries were asymmetrical and, in some cases, contained several unilateral or bilateral cysts larger than 30 mm. The ovaries of one patient were of normal size and morphology. The patient whose ovarian autonomy is the most severe had endometrial hyperplasia and developed uterine myomata at age 21 years. GnRH agonist therapy was tried in three patients. Gonadotropin and estradiol secretion were initially stimulated in two patients, and their plasma FSH and LH concentrations fell sharply thereafter; the plasma estradiol concentration in two patients, and their plasma FSH and LH concentrations fell from 145 to 19 pg/ml and from 107 to 20 pg/ml. Escape occurred in one patient after the third week of treatment, with a re-increase in plasma estradiol concentrations. The size of the ovaries also decreased, from a mean maximal diameter of 55 ± 18 mm to 48 ± 17 mm, but the interpretation of this variation is difficult as such variation may be observed spontaneously in the patients. In the most severely affected patient, GnRH agonist administration did not modify FSH or LH levels. The estradiol concentration remained high, and cannot be modified. The size of the ovaries also did not change.

Thus, a variable degree of ovarian autonomy persists in women with the McCune-Albright syndrome who have a history of precocious puberty. In some cases, gonadotropic function seems to override ovarian autonomy, allowing near-normal regulation of the menstrual cycle and unassisted conception. In other cases, the persistent partial ovarian autonomy leads to irregular menstruation, anovulation and cyst formation. Gonadotropic function sometimes interferes with this ovarian autonomy. In the third pattern of gonadal function (which, hopefully, seems to be very rare), the gonadotropic axis remains inhibited by permanent and severe ovarian autonomy. Intermittent progestin treatment is required to prevent endometrium hyperplasia and the long-term risk of endometrial neoplasia. Very few extensive gonadal and gonadotropic investigations have been reported in adults with the McCune-Albright syndrome [21,22,28,29,31]. Outcome was very similar to that of our patients.

### 3.3. Pregnancy

Anovulation is frequently related to persistent gonadotropic suppression in some patients. Cases of natural conception have been reported, and probably involved women with minor ovarian autonomy [3,16,32–35]; this was the case in one of our patients.

In one of our patients who had no spontaneous ovulation because of gonadotropic inhibition (albeit partial) due to ovarian autonomy, and in whom several ovulation induction procedures failed to induce pregnancy, it was decided to excise the largest ovary. This led to ovulation and conception in the following three months. Genetic testing of her healthy unaffected daughter born at term did not find gsp germinal mutation. This is not unexpected as GSS gene is considered as an autosomal dominant lethal gene that is compatible with viability of conceptus only when it occurs in the mosaic state. Therefore, McCune-Albright syndrome results from a somatic mutation and may not be inherited from affected patients [36]. A similar case was published in 2004 [37]. A right ovariectomy was proposed to a 22-yr-old young woman after GnRH agonist administration showing cyst regression only in the left ovary. A gsp mutation was confirmed in the left ovary, whereas the right ovary was normal. Thus, GnRH analog administration may help to identify those patients who might benefit from unilateral ovariectomy. It must be pointed out that our patient, after her successful pregnancy, kept a lower degree of ovarian autonomy but had episodes of estradiol hypersecretion. Nevertheless, a second spontaneous pregnancy occurred two years after ovariectomy. The case of another woman in whom restoration of ovulation was also observed after unilateral right ovariectomy has recently been reported [38].

Fibrous dysplasia rarely progressed at adult age, even during pregnancy, although an aggravation of bone disorders in a pregnant woman was reported in 1988 [33]. We observed no aggravation of bone problems in the four patients of our series who became pregnant; this included a woman with visual disorders due to severe dysplasia of the skull base encasing the optic nerves. No aggravation was observed in a similar case reported elsewhere [35].

### 4. Conclusion

The McCune-Albright syndrome, characterized during childhood by a combination of cafe-au-lait skin spots, precocious puberty and fibrous dysplasia, raises new issues in adulthood. While no new dysplastic lesions occur after puberty and pre-existing lesions stabilize, their consequences (pain, fractures, vertebral collapse, etc.) can be disabling. Gonad function and fertility are often disturbed in adult women with a history of precocious puberty, owing to the persistence of a variable degree of ovarian autonomy, which prevents adequate follicular development and ovulation. Progestin therapy is important to avoid endometrial hypertrophy, together with the risk of leiomyomata and, potentially, of endometrial neoplasia.
Conflicts of interest

None.

References