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Partial benefit of anastrozole in the long-term treatment of precocious puberty in McCune-Albright syndrome

Cresio Alves* and Sheila Ferreira Silva

Pediatric Endocrinology Unit, Faculty of Medicine, Hospital Universitario Professor Edgard Santos, Federal University of Bahia, Salvador, Bahía, Brazil

Abstract

We report a long-term follow-up on the use of anastrozole in the treatment of peripheral precocious puberty (PP) in McCune-Albright syndrome (MAS). A girl, age 3 years and 9 months, was diagnosed with MAS due to PP, café-au-lait spots, and polyostotic fibrous dysplasia. Serum estradiol was elevated, and gonadotropins were suppressed. Pelvic ultrasound showed an enlarged uterus and a follicle cyst (13 mm) in the left ovary. Bone scintigraphy showed osteogenic lesions on the skull, humerus, tibia, and acetabulum. Bone age was 3 years and 5 months at the chronological age of 3 years. After 36 months of treatment with anastrozole (1 mg/day), there was suppression of breast growth, normalization of growth velocity and serum estradiol, and disappearance of ovarian cysts. However, there was increase in uterine volume, advancement of bone age, and two episodes of vaginal bleeding (18th and 24th months). This report shows the partial benefit of anastrozole in the treatment of peripheral PP of girls with MAS.

Keywords: anastrazole; aromatase inhibitors; McCune-Albright syndrome; precocious puberty.

Introduction

McCune-Albright syndrome (MAS) is a rare condition with a prevalence ranging from 1:100,000 to 1:1,000,000 and predominance in girls, with a 2–6:1 ratio. It is caused by somatic activating mutations of the *GNAS* gene, which encodes the α-subunit of the G protein, which couples transmembrane receptors to andenylate cyclase, leading to excess growth hormone production in the affected tissues (1). The classic phenotype is characterized by fibrous bone dysplasia, café-au-lait pigmentation, and peripheral precocious puberty (PP) (1).

PP is the most common endocrinopathy of MAS affecting girls more often than boys. In girls, PP is caused by autonomic activation of ovarian tissue followed by the growth of follicular cysts and estrogen secretion. The typical clinical presentation is breast development and vaginal bleeding, usually without pubic hair growth (1).

The most significant therapeutic experience in the management of PP in girls with MAS is the use of aromatase inhibitors. The purpose of the present article is to present the long-term follow-up response to anastrozole after 36 months of therapy in a girl with peripheral PP caused by MAS.

Case report

A girl, age 3 years and 9 months, was diagnosed with MAS at the age of 3 years and 3 months. Clinical history showed bilateral thelarche and café-au-lait pigmentation since birth, limping after the age of 18 months, and menarche at the age of 3 years and 6 months. There was family history of PP. On physical examination, weight was 14.6 kg (25th–50th percentile), height was 99 cm (50th percentile), with limping gait, protuberance on the left frontoparietal area, four café-au-lait spots with irregular border located in the paravertebral region; pubertal development showed the breasts to be in Tanner stage 3/4 and pubic hair in Tanner stage 1. There were no signs of other endocrine hyperfunctions.

Serum prolactin, cortisol, free thyroxine, free triiodothyronine, thyrotropin, insulin-like growth factor 1 (IGF-1), IGF-binding protein, calcium, phosphorus, and alkaline phosphatase were all normal; serum estradiol was 3046 pmol/L (830 pg/mL); follicle stimulating hormone (FSH) <0.10 mIU/mL; luteinizing hormone (LH) <0.1 mIU/mL. Pelvic ultrasound showed a uterine volume of 12.3 cm^3 (normal <4.0 cm^3), endometrium thickness of 0.31 cm, right ovarian volume of 0.7 cm^3 (normal <2.0 cm^3), and left ovary with a 13-mm follicular cyst. Breast ultrasound showed breast tissue bilaterally. Bone scintigraphy showed osteogenic lesions in the skull, left humerus, tibia, and acetabulum and lesions with increased osteoblastic activity in the skull and face consistent with polyostotic fibrous dysplasia. Bone age was 3 years and 6 months at the chronological age of 3 years.

Treatment with anastrozole (1 mg, orally once daily) was started at the age of 3 years and 6 months. Menstruation did not occur in the first 17 months of treatment but returned in the 18th and 24th months and did not occur until the last evaluation after 36 months of therapy. Evaluation after the first 15 months of treatment showed cessation of mammary growth, decrease in estradiol levels from 3046 to <73 pmol/L (830 to <20 pg/mL) respectively, reduction in uterine volume from 12.3 to 6 cm^3, disappearance of ovarian cyst, stabilization of growth rate of 3.5 cm/year, and bone age of 5 years and 6 months at the age of 4 years and 9 months.

On the 27th month of treatment, despite the absence of mammary growth, with a growth rate of 6 cm/year, and low

*Corresponding author: Crésio Alves, MD, PhD, Rua Plínio Moscoso, No. 222, Apto. 601, 40157-190 Salvador-BA, Brazil
Phone: +55-71-91784055, Fax: +55-71-33931021,
E-mail: cresio.alves@uol.com.br
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serum estradiol level of 14.6 pmol/L (4.0 pg/mL), the patient showed increase in uterine volume from 6 to 11.5 cm^3 but not followed by increased ovarian volume or reappearance of ovarian cyst. This was associated with advancement of bone age of 7 years and 6 months when she was 5 years and 9 months old. GnRH stimulation test at 5 years and 9 months showed a prepubertal response: baseline LH, <1.0 IU/L (<1.0 mIU/mL); peak LH, 1.1 and 1.0 IU/L (1.0 mIU/mL); baseline FSH, 2.9 IU/L (2.9 mIU/mL); peak FSH, 32.6 IU/L (32.6 mIU/mL). There were no adverse reactions to anastrozole during the 36 months of therapy. Table 1 shows the results of the hormonal evaluation before and during anastrozole treatment.

Discussion

There is no gold standard treatment for peripheral PP in girls with MAS. In practice, aromatase inhibitors, estrogen receptor modulators, medroxiprogesterone, and in selected cases, unilateral oophorectomy or cystectomy is used.

Tamoxifen, a selective estrogen receptor modulator with weak estrogenic effect and potent anti-estrogen effect, had promising short-term results. When administered to 28 girls with PP caused by MAS, tamoxifen reduced vaginal bleeding as well as the rate of growth and bone maturation (2). However, there was a progressive increase in the uterine volume, unlike the reduction described in previous studies (2).

The experience with aromatase inhibitors for treating PP caused by MAS has yielded conflicting results, and the data related to the use of third-generation agents are still limited. The aromatase inhibitors block the conversion of androgens to estrogen by reversibly binding to the cytochrome P450 part of aromatase, thus reducing serum estrogen levels. After the appearance of the first-generation aromatase inhibitors (aminoglutethimide and testolactone), more selective and longer-acting agents were developed. The second-generation agents (fadrozole) are less toxic than the first-generation agents without increasing its effectiveness, whereas the third-generation agents (letrozole, anastrozole, and exemestane), in addition to being more potent, do not require multiple daily doses.

Although testolactone has been shown to be effective in the short-term in an initial study involving five girls, as the study progressed and further included the assessment of 12 girls, after 3 years of treatment, the drug has become less effective, with recurrence of ovarian cysts and persistent vaginal bleeding in most cases (3). Also, adherence to treatment is difficult due to the need of administration of the drug in four daily doses. A prospective study involving administration of fadrozole to 16 girls with PP caused by MAS was ineffective in blocking estrogen synthesis (4). The administration of letrozole for 1–3 years to nine girls with PP caused by MAS was effective in reducing the growth rate and bone maturation and stopping or reducing vaginal bleeding during the treatment (5). Nevertheless, it caused adverse side effects, such as increased ovarian volume and cyst formation.

The effectiveness of anastrozole is not conclusive due to its restricted use and contradictory results. A German multicenter study using 1 mg/day of anastrozole showed the effectiveness of the drug for treating PP caused by MAS (1). Roth et al. (6) corroborated these results in the treatment of one girl with MAS. Nevertheless, in a prospective multicenter study involving 28 girls and using anastrozole (1 mg/day) for 1 year, no difference was observed for vaginal bleeding compared with the pretreatment period (7). Bleeding stopped in only three patients (10.7%). There were no significant changes in serum estradiol, testosterone, and gonadotropins, and the average uterine and ovarian volumes were not affected (7). The present report shows the transient effectiveness of anastrozole during the first year of treatment. However, at the end of 2 years, occasional vaginal bleeding, increased uterine volume, and advancement of bone age reappeared despite the maintenance of prepubertal levels of serum estradiol and the exclusion of development of central PP.

As aromatase is expressed in tissues other than ovary, its inhibition can cause undesirable effects on bone, lipid

Table 1 Hormonal and pelvic ultrasonographic evaluation before and during pubertal blockade with anastrozole in a girl with McCune-Albright syndrome.

	Before starting anastrozole (CA: 3 years and 6 months)	Nine months using anastrozole (CA: 4 years and 2 months)	Fifteen months using anastrozole (CA: 4 years and 9 months)	Thirty months using anastrozole (CA: 6 years)
Hormonal evaluation				
Estradiol (reference range: <110 pmol/L)	3046	78	<73	80
LH (reference range: <1.3 IU/L)	<0.1	<0.1	<0.1	0.1
FSH (reference range: 0.11–13.0 IU/L)	<0.1	3.14	2.5	2.1
Pelvic ultrasonography				
Uterine volume, cm^3	12	4.4	6	11.5
Right ovarian volume, cm^3	0.7	0.7	0.9	1.1
Left ovarian volume, cm^3	13	0.7	0.8	1.2
Ovarian cyst	13 mm	None	None	None

CA, chronological age.

(especially in high-density lipoprotein cholesterol), and hepatic metabolism. Although aromatase inhibitors may be a matter of concern because of the potential effects, such as decreased bone mineral density, arthralgia, myalgia, and cognitive impairment in the treatment of breast cancer of postmenopausal women, there is no report of such changes in children. Despite a paucity of studies using third-generation aromatase inhibitors, they appear to be well tolerated in the short-term. Supporting the good tolerability data of anastrozole treatment (8), both the present report and other experiences with girls affected by MAS have shown no adverse effects. Because anastrozole and letrozole cross the blood-brain barrier (9–11), further studies are needed to investigate their effects on the development of the infant brain.

In the interpretation of our study and the other available studies, one must consider the variable clinical course of PP associated with MAS and apparent fluctuation in disease activity. The coincidence with the latent phase of the PP can be incorrectly attributed to the pharmacological efficacy of the drug, whereas the beginning of central puberty, which has been excluded in the present report, can hide the true benefits of the therapy. We cannot rule out intermittent non-compliance as a contributor to the advancement of bone age and uterine volume on anastrazole therapy. Other possible explanations are reports of a pattern of fluctuating breast development in these patients and the possibility that the uterus may harbor G protein receptors, which are also constitutively active in this condition, contributing to uterine growth independent of estradiol production. As short-term studies cannot truly distinguish the partial effectiveness of PP therapy vs. intermittent non-compliance or the fluctuating course of the PP in MAS, prospective, controlled and long-term studies involving a substantial number of patients are needed for a more accurate determination of the long-term benefit of anastrozole in the treatment of peripheral PP in girls with MAS.

Conflict of interest statement

Potential conflict of interest: The authors state that there is no financial or other relationship that might lead to conflict of interest.

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