*Endocrine Journal* 2012, **59** (2), 111-117

**ORIGINAL**

# Combined treatment with bicalutamide and anastrozole in a young boy with peripheral precocious puberty due to McCune-Albright Syndrome

Daniele Tessaris, Patrizia Matarazzo, Alessandro Mussa, Gerdi Tuli, Francesca Verna, Ludovica Fiore and Roberto Lala

*Department of Pediatric Endocrinology and Diabetology, University of Torino, Regina Margherita Children's Hospital, Italy*

**Abstract.** McCune-Albright Syndrome (MAS) is a congenital endocrine disorder due to mosaic tissutal hyper-function. We describe a boy with a molecularly confirmed MAS, clinically evident with congenital café-au-lait spots, bone fibrous dysplasia, hyperthyroidism, and renal phosphate wasting syndrome. At 4.6 years of age he disclosed a rapid progression of peripheral puberty, so we decided to treat him with bicalutamide 25 mg/day and anastrozole 1 mg/day. Combined third generation aromatase inhibitors - competitive androgen receptor blockers were employed in familial male precocious puberty (FMPP). Combined treatment was performed for 49 months from the age of 4.6 to 6.7 years. The patient underwent clinical, laboratory, and instrumental evaluation twice a year from the first admission to the current age. This treatment caused a rapid normalization of growth velocity, subsequent reduction of penile androgenization, and stabilization of testicular volume. The therapy was well tolerated for all its duration and neither side effects, nor secondary hypothalamic activation were noted. This report provides further evidence of effectiveness and safety of combined third generation aromatase inhibitors - competitive androgen receptor blockers in male precocious peripheral puberty, firstly employed in male MAS, and contributes to expand the spectrum of disorders in which their employment may reveal promising.

*Key words*: Bicalutamide, Anastrozole, Peripheral precocious puberty, McCune-Albright, GSα protein

**MCCUNE ALBRIGHT SYNDROME** (MAS, OMIM # 174800) is a rare congenital sporadic disorder with an estimated prevalence ranging from 1 in 1,000,000 to 1 in 100,000 [1]. MAS is caused by a post-zygotic somatic activating mutation of the GNAS1 gene resulting in an increased GSα protein signaling leading to hyperfunction of glycoprotein hormone receptors, autonomous cell proliferation, and hormonal hypersecretion [2, 3]. The mosaic constitutive activation of this signal transducer is clinically evident with a scattered hyperfunction of endocrine tissues with a wide phenotypic spectrum. MAS classical phenotype includes the clinical triad of bone fibrous dysplasia (BFD), café-au-lait skin spots due to skin dysplasia, and peripheral precocious puberty (PPP). Furthermore, hyperthyroidism, hypercortisolism, hyperpituitarism, kidney phosphate wasting, cholestasis and hypertrophic heart disease can be present [3, 4]. MAS is one of the two recognized causes of male PPP of genetic origin together with familial male-limited precocious puberty (FMPP). In this latter case, hormonal hyperfunction due to luteinizing hormone (LH) receptor constitutive activation, is limited to the testes [5].

As the vast majority of MAS patients with PPP are female, clinical trials have focused primarily on girls [1] and there are only few reports on males [6]. Recent therapies have targeted the synthesis and action of both androgen and estrogen. The few available experiences have been conducted in other forms of male PPP [5, 7, 8]. In particular, Kreher *et al*. employed contemporary bicalutamide and anastrozole in FMPP, with positive results in two boys [7].

In this report, we describe the first male MAS patient with PPP treated with the highly selective, non-steroi-

Submitted Aug. 18, 2011; Accepted Oct. 20, 2011 as EJ11-0214
Released online in J-STAGE as advance publication Nov. 9, 2011

Correspondence to: Daniele Tessaris, M.D., Department of Pediatric Endocrinology and Diabetology, University of Torino, Regina Margherita Children's Hospital, Piazza Polonia 94, 10126, Torino, Italy. E-mail: tessaris@alice.it

Abbreviations: MAS, McCune-Albright Syndrome; FMPP, Familial male precocious puberty; BFD, Bone fibrous dysplasia; PPP, Peripheral precocious puberty; LH, Luteinizing hormone; SDS, Standard deviation score; FSH, Follicular-stimulating hormone; LHRH, LH- releasing hormone; PH, Pubic hair stage; G, Gonadal stage

dal competitive androgen receptor blocker bicalutamide for precocious sexual behaviors and a third-generation aromatase inhibitor anastrozole to prevent decrease of final height.

## Materials and Methods

The boy has been treated and followed-up at the Department of Pediatric Endocrinology and Diabetology of the University of Torino, Regina Margherita Children's Hospital, Torino, Italy. Parent's written informed consent to the treatment was obtained according to protocols approved by the local Ethics Committee.

The patient underwent clinical, laboratory, and instrumental evaluation twice a year from the first admission to the current age. Clinical evaluation included the auxological assessment according to Tanner standards and including height (cm, SDS), weight (kg, percentiles), height velocity (cm/year, SDS), and pubertal development evaluation including testicular volume, pubic hair stage (PH), gonadal stage (G), and the eventual presence of gynecomastia. Penile size was evaluated at rest by caliper, and testicular volume by Prader's orchidometer. Laboratory assays included the dosage of basal luteinizing-hormone (LH), follicular-stimulating hormone (FSH), testosterone, and 17β-estradiol. LH and FSH secretion was evaluated twice yearly by Time-resolved fluoroimmunoassay (Autodelfia time-resolved, Perkin Elmer, Turku, Finland) [9]. Testosterone was evaluated by radioimmunoassay (Testo-CT-2, CIS International, Saluggia, Italy) method [10] and 17β-estradiol by immunoflorescentassay (Kryptor-Estradiol 17-beta, TRACE, Brahms, Hennindorf, Germany) [11]. Before starting treatment, standard LH-releasing hormone (LHRH) test was performed by intravenous injection of synthetic LHRH and dosage of LH and FSH response at 20 and 40 minutes [12]. Hepatic enzymes (alanine aminotransferase and aspartate aminotransferase) were evaluated at each admission. Instrumental investigations included a standard left-hand radiography for bone age assessment (performed yearly by Greulich and Pyle method by the same pediatric endocrinologist), and testicular ultrasonography performed twice a year by linear 10 MHz ultrasounds transducer. Bone mineral condition was evaluated by phalangeal quantitative ultrasounds DBM Sonic Bone Profiler 1200, IGEA, Carpi, Modena, Italy.

## Results

The patient was diagnosed with MAS at the age of 1.5 years when he was referred for congenital café-au-lait spots on the back and on left arm and BFD involving the proximal femora and skull base. The diagnosis of MAS was confirmed molecularly by detection of the classical mutation R201H of GNAS1 gene, identified in DNA samples from leukocytes by PCR and enzymatic digestion of the normal allele, as previously described [13]. He was subsequently followed-up twice a year. At the age of 2.3 years he developed a renal phosphate wasting syndrome and nodular goiter with hyperthyroidism. He was submitted to surgical insertion of intramedullary bilateral femoral devices for BFD [14] and subsequently treated with intravenous pamidronate 1 mg/kg/day infusion for 3 consecutive days at 6 months intervals [15], oral alfacalcidol 0.05 mcg/kg/day, phosphate oral supplemention 600 mg/day, and metimazole 0.5 mg/kg/day.

At the age of 4.6 year, when admitted for his routinary follow-up, he showed clinical and biochemical signs of precocious puberty. Testicular volume was 10 mL bilaterally and penile length 8 cm. PH and G stages were 2 and 3, respectively (Fig. 1). Gynecomastia was not pres-

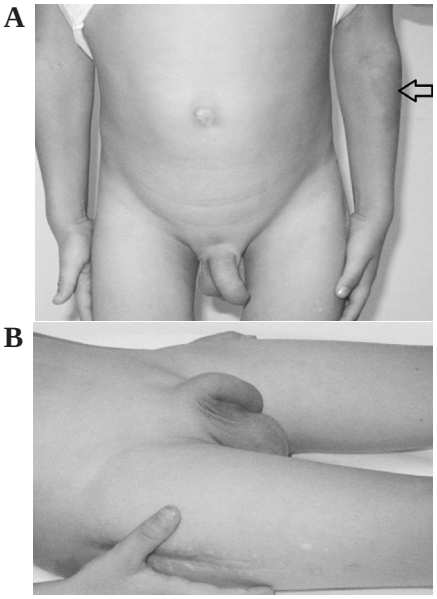


**Fig. 1** **A**: large hyperpigmented skin spot on the left arm, typical of MAS (indicated by the arrow). **B**: Testicular enlargement (8 mL volume) and penis activation (8 cm length) in the patient at the age of 4.6 years, before treatment; the scar at the right leg is a consequence of the treatment of BFD with intramedullary bilateral femoral devices.

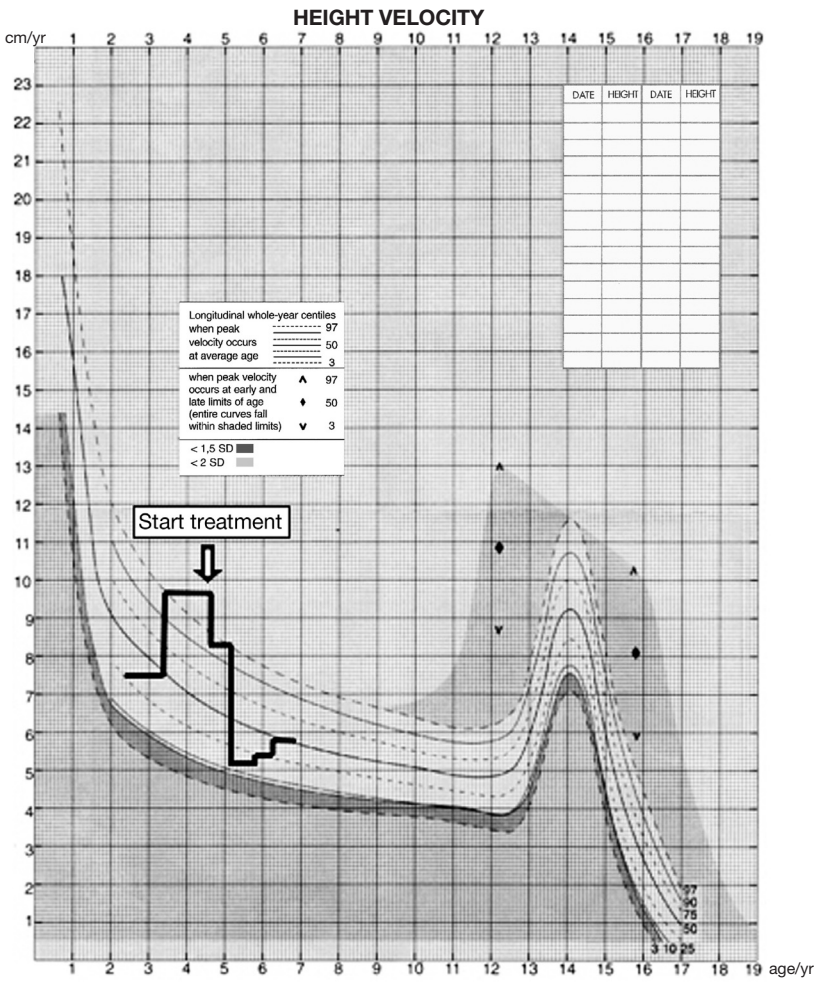


**Fig. 2** Patient's growth velocity from diagnosis through the follow-up period. Treatment start is accompanied by a prompt normalization in growth velocity.

ent. Weight was 14.5 Kg (10$^{th}$ percentile), height 106.5 cm (+0.33 SDS), and growth velocity was accelerated (9.6 cm/year +2.81 SDS). Target height was 177.0±8.0 cm (+0.35 SDS). Bone age was advanced (6 years, Greulich and Pyle method). Prominent androgen excess had become evident with adolescent attitude, restlessness behaviors, frequent erections, and masturbation, as reported by parents. Testosterone was 1.6 ng/mL (normal prepubertal values <0.3 ng/mL) and LHRH stimulation test showed no activation of the hypothalamic-hypophiseal-gonadal axis (basal LH 0.1 mU/mL, basal FSH 0.09 mU/mL, rising to 1.3 mU/mL and 1.9 mU/mL, respectively, after stimulation). 17β-estradiol was 18.0 pg/mL. Bone density was normal. Testicular ultrasound demonstrated bilaterally inhomogeneous gonadal structure with small hyperecogenic areas defined as "snowstorm appearance" [16]. Both testis were enlarged with diameters 3.1×1.3 cm at right and 3.5×1.5 cm at left. Due to the clear cut evidence of PPP we decided to treat the patient with a combined therapy based on bicalutamide 25 mg/day and anastrozole 1 mg/day.

The boy received the combined treatment for 49 months, from the age of 4.6 to 6.7 years. Over this period his growth velocity decreased from 9.6 cm/year (+2.81 SDS) to 5.8 cm/year (-0.23 SDS) at the end of the follow-up, as shown in Fig. 2. At that time he was 119.3 (+0.32 SDS), weighted 22.0 kg (50$^{th}$ percentile). Penile length decreased from 8 to 6 cm in 1 year. No signs of progression of secondary sexual characteristics or gynecomastia were evident, as possible clinical signs of hyperestrogenism. Parents reported a rapid reduction of the erection episodes and masturbatory behaviors soon after 6 months from therapy start, until complete regression, reported at 1 year. Bone age was chrono-

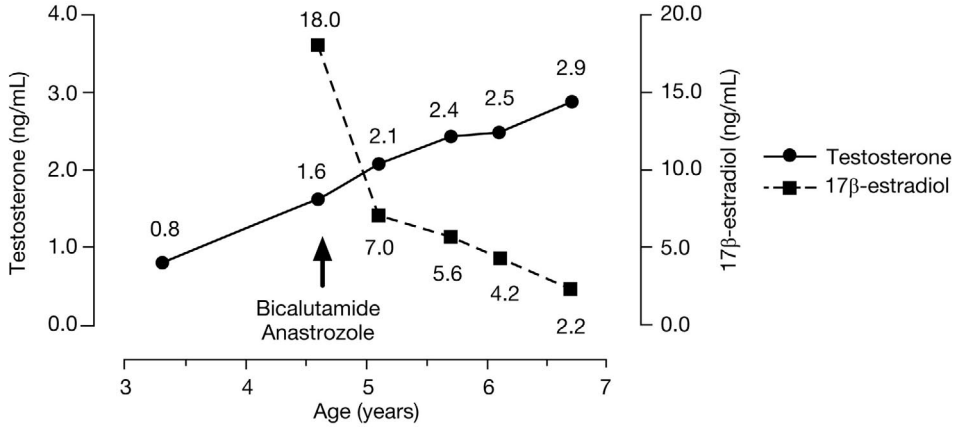


**Fig. 3** Serum testosterone and 17β-estradiol time course from the diagnosis of precocious puberty through the follow-up. The progression of testosterone levels up to values typical of middle puberty is the result of both autonomous testicular production and anastrazole inhibition of its conversion into estrogens; in fact it is contemporary accompanied by a decrease in 17β-estradiol levels.

**Table 1** Follow-up before and during combined therapy with bicalutamide 25mg/day and anastrozole 1 mg/day.

| Age | 2 years 3 months | 3 years 4 months | 4 years 6 months | 5 years 1 month | 5 years 8 months | 6 years 2 months | 6 years 8 months |
|---|---|---|---|---|---|---|---|
| Weight (Kg) | 10.0 (3rd percentile) | 12.5 (3rd-10th percentile) | 14.5 (10th percentile) | 17.6 (25th-50th percentile) | 19.0 (25th-50th percentile) | 20.5 (50th percentile) | 22.0 (50th percentile) |
| Height (cm) | 86.6 (- 0.21 SDS) | 94.5 (- 0.86 SDS) | 106.5 (+ 0.33 SDS) | 111.0 (+ 0.57 SDS) | 113.7 (+ 0.45 SDS) | 116.4 (+ 0.35 SDS) | 119.3 (+ 0.32 SDS) |
| Height velocity (cm/year) | - | 7.5 (50th percentile) | 9.6 (>97th percentile) | 8.3 (90th-97th percentile) | 5.2 (10th-25th percentile) | 5.4 (25th percentile) | 5.8 (25th-50th percentile) |
| Bone age | 2 years 6 months | - | 6 years | - | 6 years | - | 6 years 8 months |
| Testicular volume (mL) | 3-4 | 4-5 | 10 | 10 | 10 | 10 | 10 |
| Penile size (cm) | Prepuberal | 5 | 8 | 7 | 6 | 6 | 6 |
| PH | 1 | 2 | 2 | 2 | 2 | 2 | 2 |
| Androgen driven behaviors | Prepubertal | Prepubertal | Frequent erections, masturbatory behavior, agitation | Reduction | Complete regression | Absence | Absence |
| Hormonal dosages | - | | | | | | |
| LH (U/L) | | 0.07 (basal) | 0.1 (basal), 1.3 (peak*) | 0.21 | 0.22 | 0.20 | 0.11 |
| FSH (U/L) | | 0.05 (basal) | 0.09 (basal), 1.9 (peak*) | 0.20 | 0.10 | 0.20 | <0.10 |
| Testosterone (ng/mL) | | 0.8 | 1.6 | 2.1 | 2.4 | 2.5 | 2.9 |
| 17β-estradiol (pg/mL) | | | 18.0 | 7.0 | 5.6 | 4.2 | 2.2 |
| Therapy | no | no | no | yes | yes | yes | yes |

LHRH, luteinizing hormone- releasing hormone; PH, pubic hair stage. *peaking after LHRH

logical at the end of the follow-up. LH and FSH were respectively 0.10 mUI/mL and 0.11 mUI/mL. During the treatment period, testosterone progressively raised to 2.9 ng/mL paralleled to a progressive reduction in serum 17β-estradiol that was 2.2 pg/mL at the end of the follow-up (time course showed in Fig. 3). Testicular ultrasonography was unmodified with inhomogeneous structure and bilateral hyperecogenic "snowstorm" areas, signs of microlithiasis [16]. Therapy was well tolerated and the family reported no significant side effects. Compliance to the treatment was excellent. Liver enzymes were normal at all the admissions. No modification in bone density was noted.

Clinical and biochemical follow-up before and during therapy was detailed in Table 1.

## Discussion

PPP in MAS is more common in girls than in boys. Male PPP in MAS could be characterized by monolateral or bilateral testes enlargement, as shown by our patient [17]. Testicular growth is caused by Leydig cells hyperplasia [1] and hyperfunction with increased testosterone secretion leading to the premature development of secondary sexual characteristics [5].

Due to its exceptional rarity, there are few experiences concerning the treatment of PPP in MAS males. After the demonstration of the inefficacy of long-acting gonadotropin releasing-hormone agonists, alternative strategies have been experimented [18, 19]. First generation aromatase inhibitors (as testolactone) combined with antiandrogens (as spironolactone or flutamide) has been shown to control virilization signs and growth rate [20, 21]. Unfortunately, the employment of testolactone is limited by the need for frequent daily administrations. In addiction electrolyte imbalances during intercurrent gastrointestinal illness have been associated with this combination, forcing to therapy interruption [7]. Another combined approach with the antifungal ketoconazole and androgen receptor inhibitor cyproterone acetate resulted safe and effective in a 4.6 MAS boy [6]. However, the reported association between ketoconazole and hepatic injury, evidenced both in MAS and FMPP, has been considered a major limitation for the employment of this antifungal drug [5]. Moreover, ketoconazole has other frequent side effects as adrenal suppression, gynecomastia, asthenia, nausea, and diarrhea [22]. Despite short-term positive reports about the efficacy of cyproterone acetate in decreasing growth velocity and lowering testosterone levels, long-term experience has been generally unsatisfactory due to the progressive reduction of therapeutic effect after several years [23, 24].

Due to the frequent side effects of the above mentioned agents, we decided to start the combined treatment with the androgen-receptor competitive antagonist bicalutamide and the third generation aromatase inhibitor anastrozole. Bicalutamide could reduce clinical and psychological virilization due to sexual male hormone excess. Anastrozole could prevent from precocious epiphiseal closure, bone age acceleration, and exacerbation of bone fibrous dysplasia lesions caused by estrogens excess [4]. These drugs were already employed in the treatment of peripheral precocious puberty in three patients affected by FMPP [7, 8]. This is their first employment for the treatment of PPP in MAS. Bicalutamide is a member of the non steroidal anti-androgen class of drugs [25]. This molecule, with respect to other anti-androgens as cyproterone acetate, has the advantage of higher potency and selective antagonistic properties [26]. We elected the dose of 25 mg/day which seem to be the lower effective dose. Recent experiences in adults affected by prostatic cancer reported an excellent safety profile at this dose [27]. Anastrozole is a third generation aromatase inhibitor that reduces the conversion of androgens into estrogens. Anastrozole has already been employed in female PPP in MAS [28], in boys with FMPP [7], growth hormone deficiency [29], and pubertal gynecomastia [30]. In addition, this combined therapy provides a convenient once-daily dosing regimen.

The case we described shows that the combination of bicalutamide 25 mg/day and anastrozole 1 mg/day are efficacious, appropriate, and safe as therapeutic approach to male PPP in MAS. In our patient the disturbing behavior due to testosterone excess has been controlled as well as testicular volume increase and pubertal progression. The reduction of penile size indicates reduced testosterone action in spite of its increased serum concentrations. Bone age and growth velocity normalized. As far as we know, the case we reported represents the first employment of androgen-receptor antagonist and third generation aromatase inhibitors combined treatment in McCune-Albright syndrome-related peripheral precocious puberty.

Obviously, in contrast with central precocious puberty treated with long-acting gonadotropin releasing-hormone agonists, testosterone levels can not be employed to evaluate therapeutic efficacy. Actually, although testosterone level continued to rise, it had no evident metabolic effects. Testosterone's raise can result both from the persistent autonomous production by constitutionally activated Leydig cells and from anastrozole inhibition of its conversion into 17β-estradiol.

It is of note that, to minimize potential side effects, we elected a low bicalutamide dose as starting prescription (25 mg, corresponding to 1.5 mg/Kg/day at treatment start). Although we could expect to have to increase the posology, the excellent clinical response observed allowed us to maintain 25 mg through all the follow-up period (corresponding to 1. 0 mg/Kg/day at that point). Therefore, we employed approximately half of the previously reported dosages [7, 8], maintaining a comparable effectiveness. As no testicular enlargement

was noted during the treatment, the administration of gonadotropin analogs was unnecessary, differently to previous reports [7, 8]. We hypothesize the combined regimen resulted thus satisfactorily effective at central nervous system level both clinically, reducing pubertal behaviors, and biochemically, counteracting peripheral hormones chronic stimulation that can possibly trigger a secondary central precocious puberty.

Notably, the combined treatment that has been previously employed only in isolated PPP (as FMPP) was administered, in this case, in a setting of a multi-organ systemic disease, together with a complex multi-drug regimen still with no evident side effect. In particular, no raise in liver transaminases and no modification in bone density were evident.

In conclusion, our results provide further evidence, although anecdotic, of the effectiveness and safety of the combined third generation aromatase inhibitors, competitive androgen receptor blockers in male precocious peripheral puberty, contributing to expand the spectrum of disorders in which their employment may reveal promising. Longer treatment duration and follow-up until the physiological pubertal age will be necessary to confirm this preliminary data and other clinical studies are awaited.

## Declaration of Conflict of Interest

We have nothing to disclose.

## References


1. Dumitrescu CE, Collins MT (2008) McCune-Albright syndrome. *Orphanet J Rare Dis* 3:12.
2. Mamkin I, Philibert P, Anhalt H, Ten S, Sultan C (2010) Unusual phenotypical variations in a boy with McCune-Albright syndrome. *Horm Res Paediatr* 73: 215-222.
3. Shenker A, Weinstein LS, Moran A, Pescovitz OH, Charest NJ, Boney CM, Van Wyk JJ, Merino MJ, Feuillan PP, Spiegel AM (1993) Severe endocrine and nonendocrine manifestations of the McCune-Albright syndrome associated with activating mutations of stimulatory G protein GS. *J Pediatr* 123: 509-518.
4. Lala R, Matarazzo P, Andreo M, Defilippi C, de Sanctis C (2002) Impact of endocrine hyperfunction and phosphate wasting on bone in McCune-Albright syndrome. *J Pediatr Endocrinol Metab* 15 (Suppl 3): 913-920.
5. Haddad N, Eugster E (2007) An update on the treatment of precocious puberty in McCune-Albright Syndrome and testotoxicosis. *J Pediatr Endocrinol Metab* 20: 653-666.
6. Messina MF, Arrigo T, Wasniewska M, Lombardo F, Crisafulli G, Salzano G, De Luca F (2008) Combined treatment with ketoconazole and cyproterone acetate in a boy with McCune-Albright syndrome and peripheral precocious puberty. *J Endocrinol Invest* 31: 839-840.
7. Kreher NC, Pescovitz OH, Delameter P, Tiulpakov A, Hochberg Z (2006) Treatment of familial male-limited precocious puberty with bicalutamide and anastrozole. *J Pediatr* 149: 416-420.
8. Lenz AM, Shulman D, Eugster EA, Rahhal S, Fuqua JS, Pescovitz OH, Lewis KA (2010) Bicalutamide and Third-Generation Aromatase Inhibitors in Testotoxicosis. *Pediatrics* 126: e728-733.
9. Iwasawa A, Tomizawa K, Kato T, Wakabayashi K, Kato Y (1994) Time-resolved fluoroimmunoassay (TR-FIA) of gonadotropins. *Exp Clin Endocrinol* 102: 39-43.
10. Holownia P, Conway GS, Shrivastava U, Round J, Honour JW (1993) A clinical evaluation of a direct radioimmunoassay of testosterone. *Clin Chim Acta* 214: 31-43.
11. Taïeb J, Sarnel C, Benattar C, Lindenbaum A (2000) A new technique for measuring 17beta-estradiol using Kryptor (Cis Bio International): utilization to monitor ovulation stimulation. *Ann Biol Clin (Paris)* 58: 71-79 (In French).
12. Dattani MT (2001)Tests in paediatric endocrinology and normal values. In: Brook CGD, Hindmarsh P (4th ed) Clinical Pediatric Endocrinology. Blackwell Science Ltd, London: 467–490.
13. de Sanctis L, Delmastro L, Russo MC, Matarazzo P, Lala R, de Sanctis C (2006) Genetics of McCune-Albright syndrome. *J Pediatr Endocrinol Metab* 19: 577-582.
14. Ippolito E, Bray EW, Corsi A, De Maio F, Exner UG, Robey PG, Grill F, Lala R, Massobrio M, Pinggera O, Riminucci M, Snela S, Zambakidis C, Bianco P (2003) Natural history and treatment of fibrous dysplasia of bone: a multicenter clinicopathologic study promoted by the European Pediatric Orthopaedic Society. *J Pediatr Orthop B* 12: 155-177.
15. Lala R, Matarazzo P, Andreo M, Marzari D, Bellone J, Corrias A, de Sanctis C (2006) Bisphosphonate treatment of bone fibrous dysplasia in McCune-Albright syndrome. *J Pediatr Endocrinol Metab* 19: 583-593.
16. Wasniewska M, De Luca F, Bertelloni S, Matarazzo P, Weber G, Crisafulli G, Valenzise M, Lala R (2004) Testicular microlithiasis: an unreported feature of McCune-Albright syndrome in males. *J Pediatr* 145: 670-672.
17. Wasniewska M, Matarazzo P, Weber G, Russo G,

Zampolli M, Salzano G, Zirilli G, Bertelloni S; Italian Study Group for Alterations of Gs alpha Protein Function (2006) Clinical presentation of McCune-Albright syndrome in males. *J Pediatr Endocrinol Metab* 19: 619-622.

18. Low LC, Wang Q (1998) Gonadotropin independent precocious puberty. *J Pediatr Endocrinol Metab* 11: 497-507.
19. Wheeler MD (1994) Update on therapy for precocious puberty. *Compr Ther* 20: 351-355.
20. Feuillan PP (1994) McCune-Albright Syndrome *Curr Ther Endocrinol Metab* 5: 205-209.
21. Zacharin M (2005) Pediatric management of endocrine complications in McCune-Albright Syndrome. *J Pediatr Endocrinol Metab* 18: 33-41.
22. Server RG, Dalkin BL, Ahmann FR (1997) Ketoconazole- induced adrenal crisis in a patient with metastatic prostatic adenocarcinoma: case report and review of the literature. *Urology* 49: 781-785.
23. Itoh K, Nakada T, Kubota Y, Suzuki H, Ishigooka M, Izumi T (1996) Testotoxicosis proved by immunohistochemical analysis and successfully treated with cyproterone acetate. *Urol Int* 57:199-202.
24. Holland FJ (1991) Gonadotropin-independent precocious puberty. *Endocrinol Metab Clin North Am* 20: 191-210.
25. Fradet Y (2004) Bicalutamide in the treatment of prostate cancer. *Exp Rev Anticancer Ther* 4: 37-48.
26. Simard J, Singh SM, Labrie F (1997) Comparison of in vitro effects of the pure antiandrogens OH-flutamide, Casodex and nilutamide on androgen-sensitive parameters. *Urology* 49: 580-586.
27. Kolvengab GJ, Blackledge GR (1996) Worldwide activity and safety of bicalutamide: a summary review. *Urology* 47: 70-79.
28. Mieszczak J, Lowe ES, Plourde P, Eugster EA (2008) The aromatase inhibitor anastrozole is ineffective in the treatment of precocious puberty in girls with McCune-Albright syndrome. *J Clin Endocrinol Metab* 93: 2751-2754.
29. Mauras N, Welch S, Rini A, Klein KO (2002) An opel label 12-month pilot trial on the effects of the aromatase inhibitor anastrozole in growth hormone (GH)-treated GH deficient adolescent boys. *J Pediatr Endocrinol Metab* 15: 945-948.
30. Riepe FG, Baus I, Wiest S, Krone N, Sieppell WG, Partsch CJ (2004) Treatment of pubertal gynecomastia with the specific aromatase inhibitor anastrozole. *Hormone Res* 62: 113-118.