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CASE REPORT

Precocious puberty: a case of the McCune Albright syndrome

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ABSTRACT

Objective: *To present a case of McCune Albright Syndrome and to discuss the management of precocious puberty in this patient.*

Findings: *The diagnosis was made at the age of 4 years with patient having repeated attacks of long bone fractures and precocious thelarche and menarche in the presence of cafe au lait macules over the nape of the neck, back and inner aspect of left thigh. Although there was thelarche and menarche, there was neither growth spurt nor pubic and axillary hair (no adrenarche). There was feature of poly-ostotic type of fibrous dysplasia in X Rays of skull, both hands and lower limb bones. Although there was sclerotic changes at the base of the skull, she has no hearing nor visual loss. There was no feature of other endocrine hyperfunction. With Tamoxifen treatment, breast changes could be attenuated and further breast development could be arrested. However she had heavy bout of bleeding after 22 months of treatment. On discontinuation of medication, there was rebound enlargement of breast.*

Discussions: *This syndrome is not GnRH driven and is a consequence of G protein abnormality as a somatic post-zygotic mutation resulting in autonomous steroidogenesis in the absence of trophic hormone stimulation from pituitary gland. The role and rationale of use of GnRH analogue, tamoxifen and norethisterone in management of precocious puberty in McCune Albright syndrome and further management plan were discussed is advised. The joint care of Gynaecologist, Orthopaedic Surgeon and Paediatrician is advised.*

Key words : Precocious Puberty, McCune Albright Syndrome, GnRH analogue, Tamoxifen, Norethisterone

INTRODUCTION

Normal female pubertal changes is characterized by accelerated growth occurring at 11-12 years[1], breast development (thelarche) at the median age of 9.8 years, adrenarche or puberche at the median age of 10.5 years, and menarche at the median age of 12.8 years[2]. Premature or early pubertal development; i.e. physical signs of puberty in girls prior to 8 years old has been considered to be premature[3]. Precocity may be due to early activation of the hypothalamic-pituitary-gonadal axis (True Precocious Puberty or GnRH-Dependent Precocious Puberty or Central Precocious Puberty-CPP) or may be due to extra pituitary secretion of human chorionic gonadotropin

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(HCG) or sex steroid secretion independent of hypothalamicpituitary-gonadal stimulation. (Precocious Pseudo-puberty or GnRH-Independent Precocious Puberty or Peripheral Precocious Puberty PPP) GnRH-Dependent Precocious Puberty or CPP with idiopathic cause is reported to be found in 74% of precocity in girls, CPP with CNS problem in 7%, ovarian tumors in 1 1% and McCuneAlbright syndrome in 5%[4]. Although McCune Albright Syndrome is rare one, it needs prompt and proper treatment and continuous monitoring for attainment of full reproductive function and health in her life.

Case summary

ZYDNH, a six year old girl (date of birth in June 1997) was referred from Medical Unit 1 of Yangon Children's Hospital to Gynaecological Outpatient Department (Unit 1) of Central Women's Hospital on 6th June 2003 with heavy bout of bleeding per vagina for 6 days. She is a known case of McCune-Albright syndrome diagnosed at 4 years of age. She has history of repeated fractures; oblique fracture at the middle part of right femur in April 2001 (figure 1), fracture left tibia in December 2002 (figure 2), fracture in the lower third of right tibia in January 2003 and fracture in left tibia in April 2003 (figure 3). X ray of both hands (Figure 4) showed medullary expansion especially in meta-carpel with small lytic areas and X ray skull bone (Figure 5) showed sclerotic changes at the base. Radiologist impression was polyostotic type fibrous dysplasia. But there is no visual or hearing defect resulting from optic and auditory nerve compression at the base of the skull bone. Cafe-au lait patches over nape of the neck, back, left thigh (Figure 6), were present. At that time, breast development was Tanner Stage 3. She started to menstruate (menarche) in August 2001, about 2 months after breast development (thelarche). Height was 94 cm; that is on 3rd percentile for her age and weight was 13.4 Kg; that is on 5th percentile for her age according to the National Center for Health Statistics, USA (NCHS) Growth Standards[5] which are the most popular international standards (WHO 1993). Ultrasound scan of pelvis showed normal uterus with small ovarian cyst of about 2 cm on the left side. Tamoxifen 5 mg once a day was started in August 2001. After about 22 months of treatment, although established breast enlargement could be attenuated and further development could be arrested, she had heavy bout of bleeding per vagina for 6 days in May 2003. Her mother stopped medication and breast rapidly increased in size with pain and so, she was referred to Central Women's Hospital in June 2003.

On physical examination, Figure (7) shows her physical growth with height (105 cm) and weight (15 Kg) on 3rd percentile for her age according to NCHS Standard. Figure (8) shows the breast development on Tanner Stage 4 and figure (9) shows partially oestrogenized external genitalia. Table 1 shows the hormonal profile of patient with reference value for 2-8 years old girl[6]. Basal plasma level of FSH and LH were within normal range and GnRH stimulation test could not be performed. Thyroid Function Test was within normal limit. Ultrasound scan showed uterus size of 5.3 cm x 3 cm x 2.6 cm with thin endometrial midline echo with small cyst in right ovary. Norethisterone 2.5 mg twice a day was started on 27-6-2003. On her follow up visit on 10th January 2003, there was no more bleeding per vagina and no further development of breast with attenuation of already established stage. (Figure 10) There was also physical growth with height 114 cm (30th Percentile) and weight 20 Kg (40th Percentile) (Figure 11)

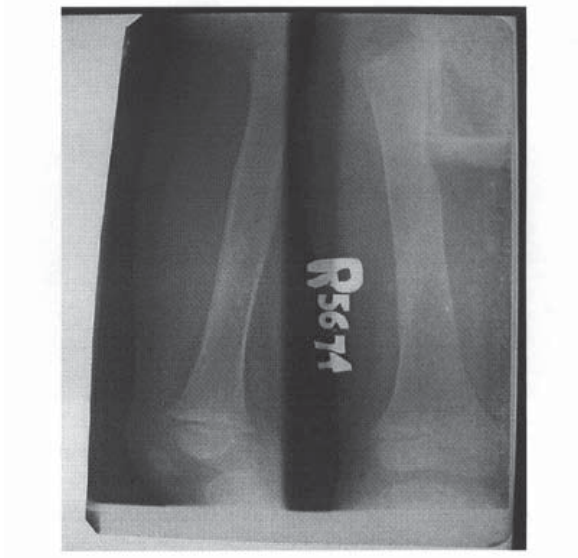

Figure 1. X ray of right femur: Oblique fracture in middle third with slight diaphyseal widening with ground glass appearance

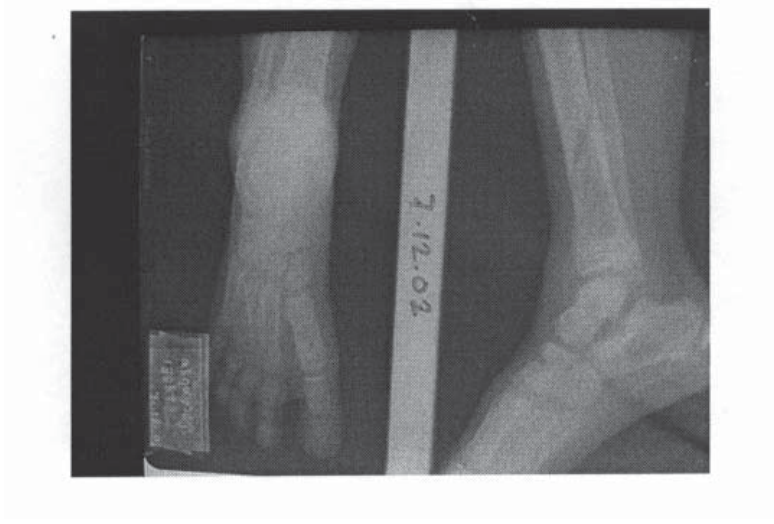

Figure 2. X ray of left leg and foot: Fracture left tibia with thinning of the cortex and loss of normal bone density in tarsal bones in December 2002

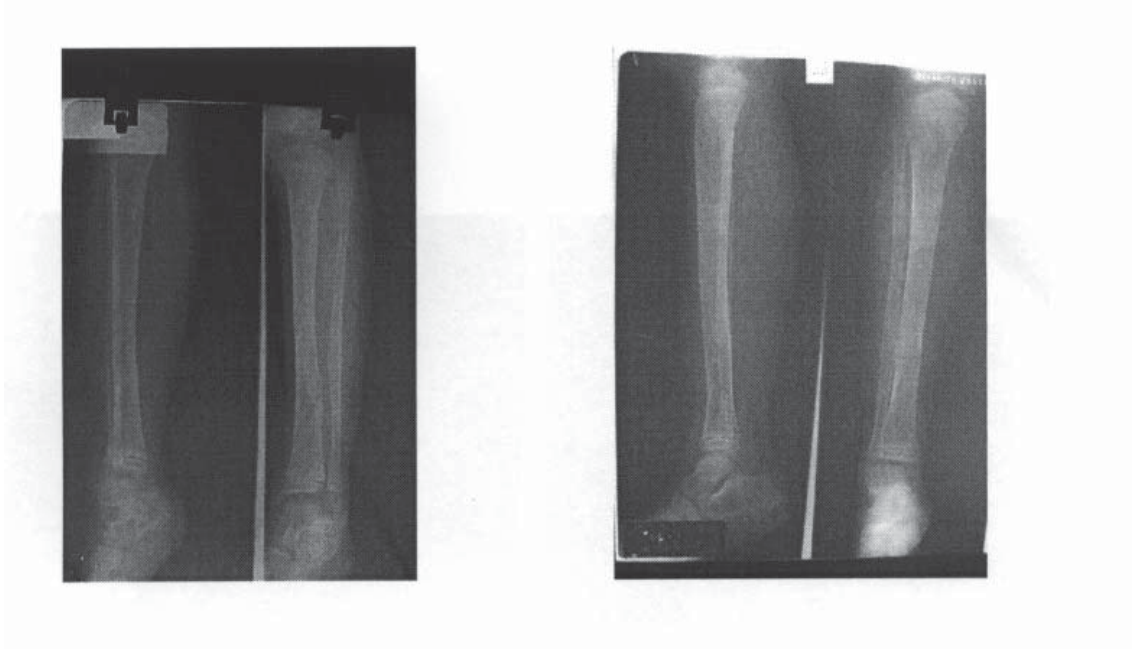

Figure 3. Fracture in the lower third of right tibia in January 2003 and fracture in left tibia in April 2003 with reduced bone density and localized lytic areas

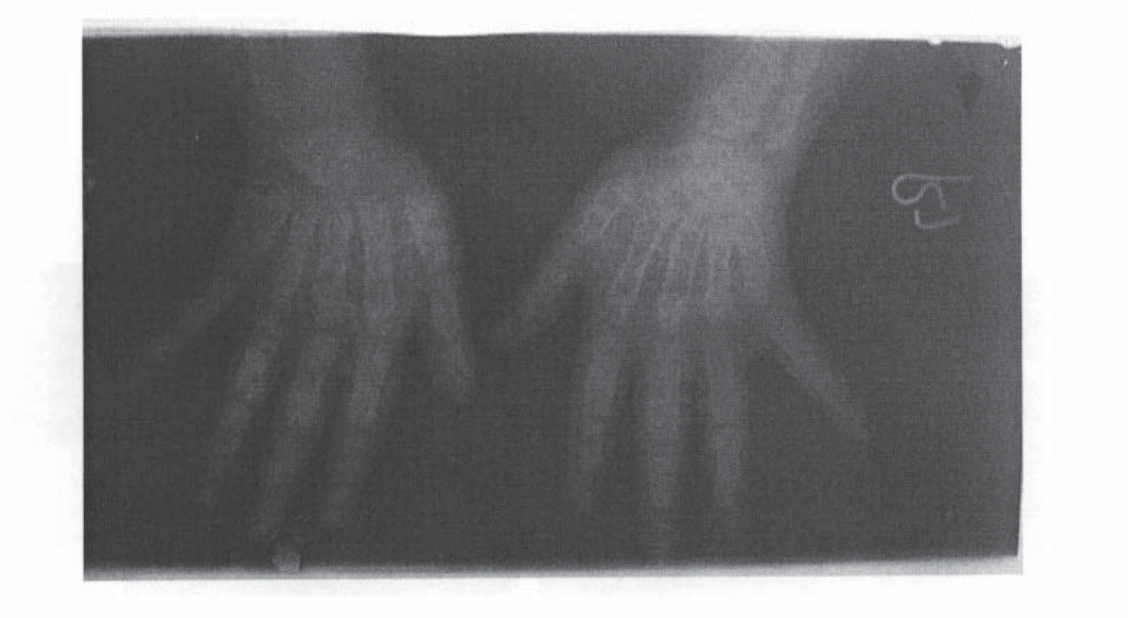

Figure 4. X ray both hands (August 2001): Medullary expansion especially in metacarpals and proximal phalanges with few small lytic areas

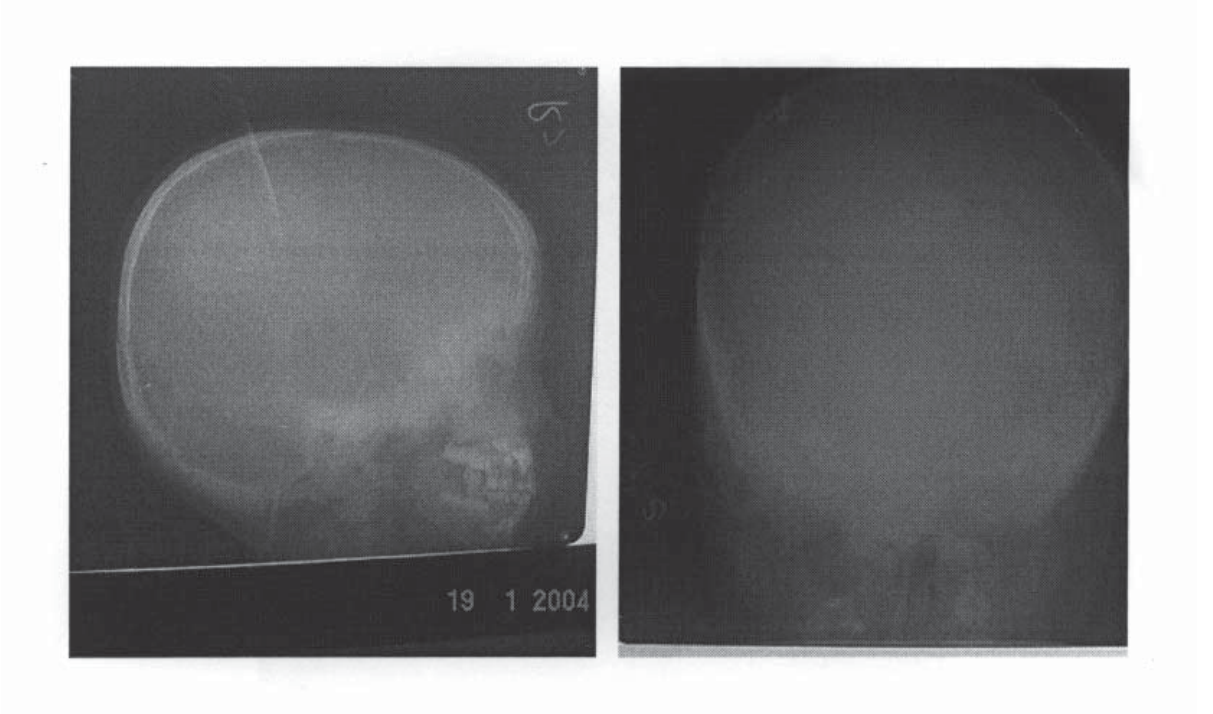

Figure 5. X ray skull: Sclerotic changes at the base of skull bone

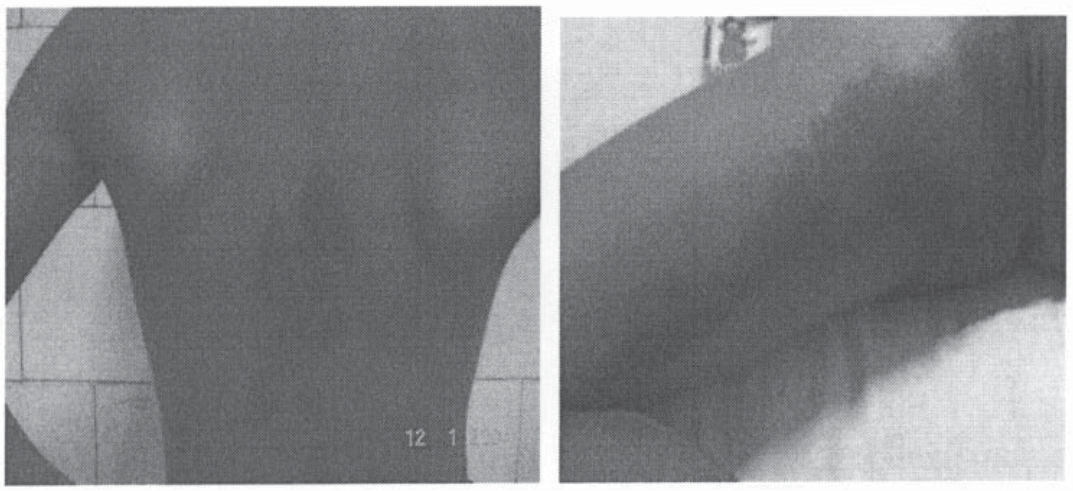

Figure 6. Café-au lait patches over the back, and left thigh

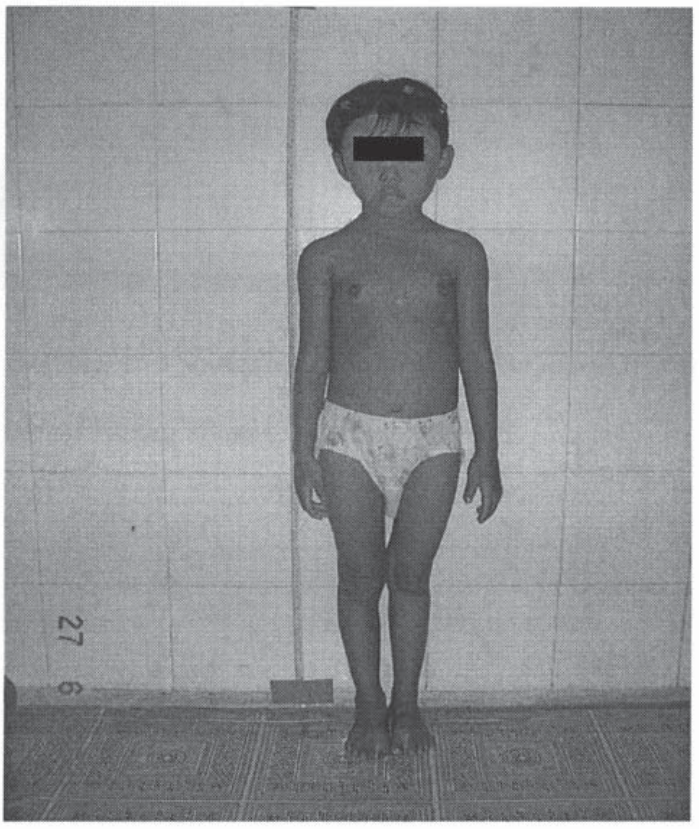

Figure 7. Finding on 1st consultation with gynaecologist at her age of 6 years:
Height = 105 cm (3rd Percentile NCHS Standards),
Weight = 15 kg (3rd Percentile NCHS Standards)
NCHS = The National Centre for Health Statistics, USA

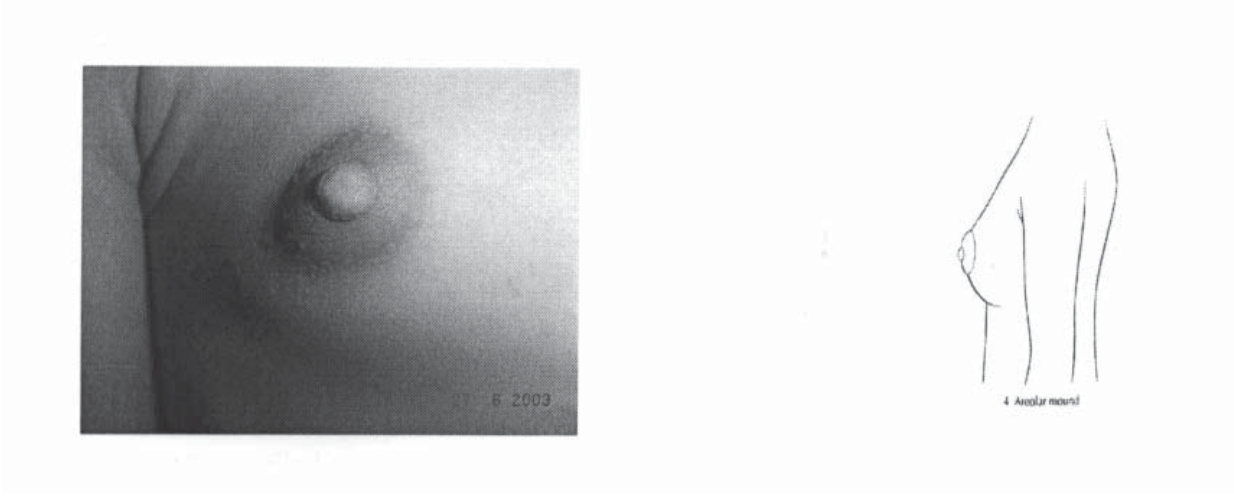

Figure 8. Finding on 1st consultation with OG at her age of 6 years: Breast Tanner Stage 4 with areola mound

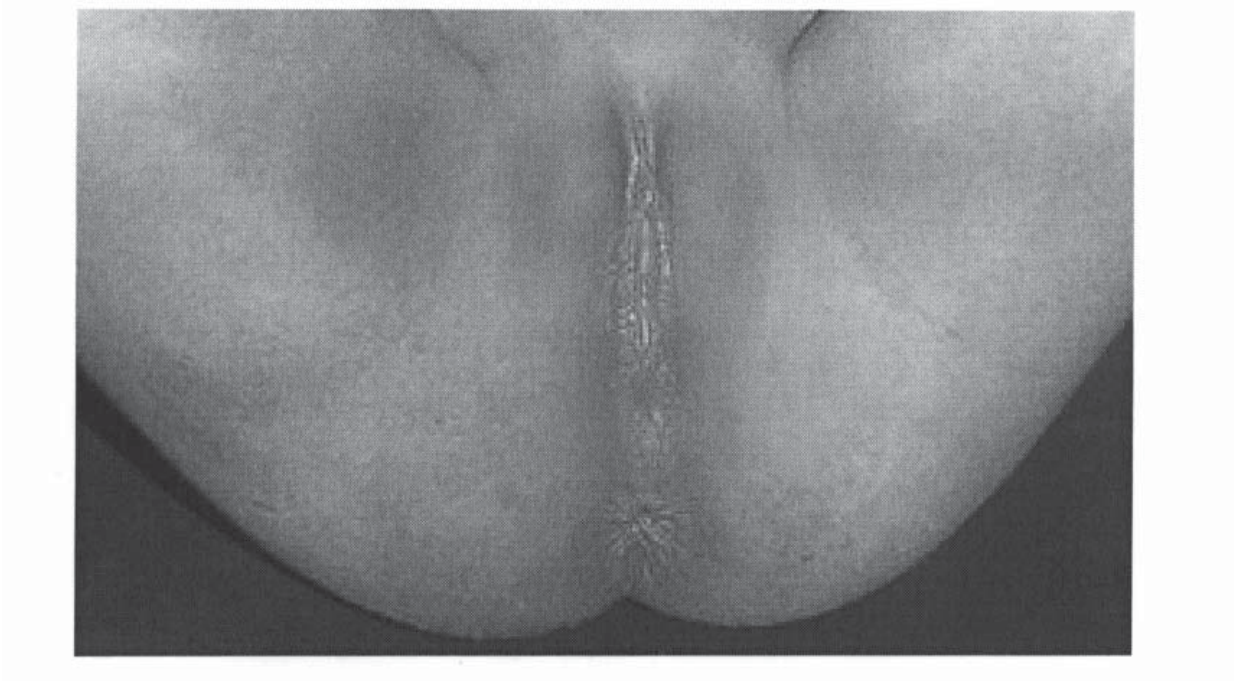

Figure 9. Finding on 1st consultation with gynaecologist at her age of 6 years: Partially oestrogenized external genitalia

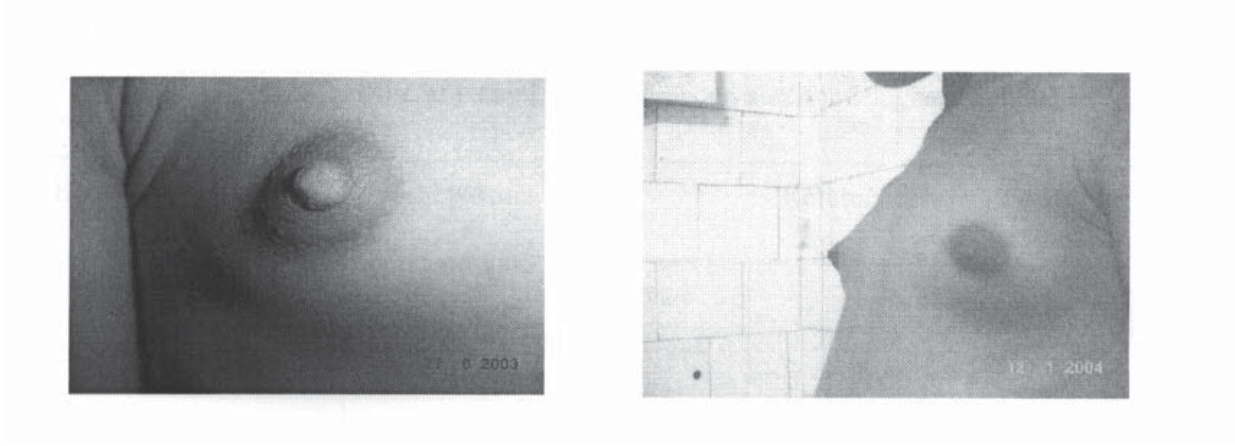

Figure 10. Finding in follow up visit, 6 months after Nor-ethisterone treatment
Arrest of further development and attenuation of established stage.

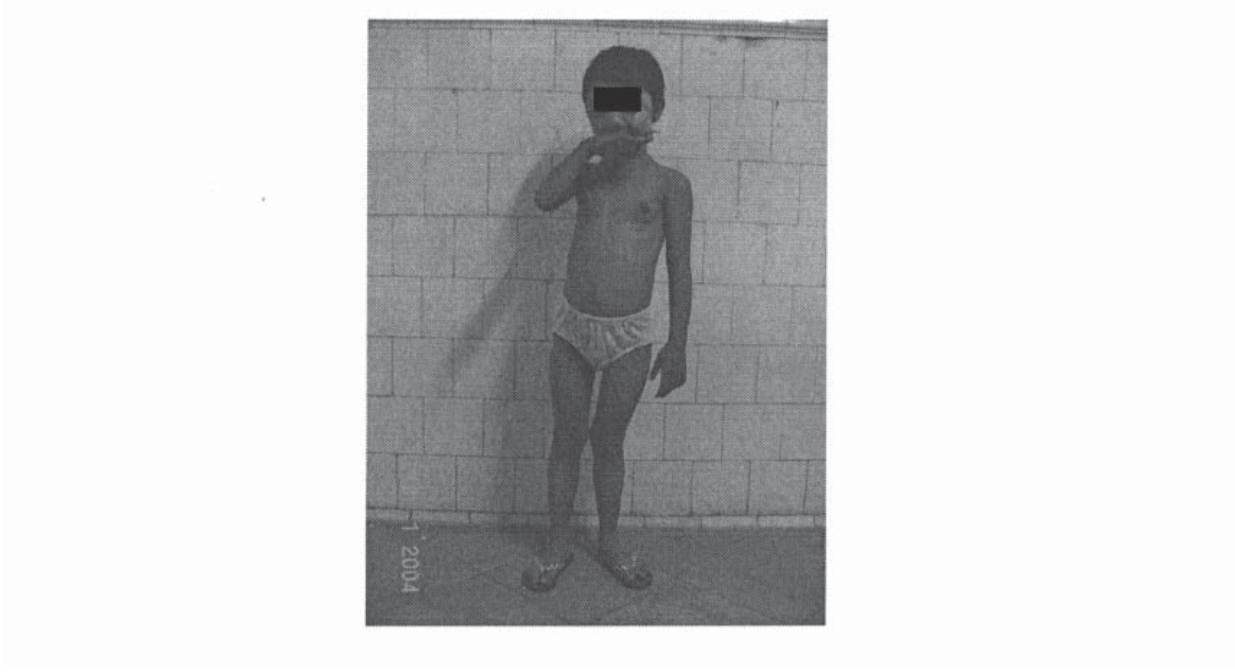

Figure 11. Finding in follow up visit, 6 months after Nor-ethisterone treatment
Height 114 cm (30th Percentile), Weight 20 kg (40th Percentile)

Table I Hormone profile of patient with reference values for 2 to 8 years old girl

Hormone	Basal plasma concentration of patient**	References*		
		Mean	Range	
FSH	0.48 miu/ml	2.3 miu/ml	<s	6.1 miu/ml
LH	2.16 miu/ml	3.3 miu/ml	<s	16.4 miu/ml
Thyroid Function Test				
T4	117 nmol/l		62 nmol/l	148 nmol/l
T3	2.7 nmol /l		0.8 nmol/l	2.5 nmol/l
TSH	0.4 mu /L			

*adapted from Bertrand, Rappaport & Sinonenko (1993)[6]

** GnRH stimulation test: not done.

<s: below the sensitivity of assay

DISCUSSION

The classical triads of the McCune Albright Syndrome are poly-ostotic fibrous dysplasia, cutaneous hyper-pigmentation and endocrine hyper-function[7, 8]. In poly-ostotic fibrous dysplasia, cancellous bone is replaced with immature woven bone and fibrous tissue and it occurs in multiple sites, especially in long bones, ribs and skull. Asymmetry of the lesions is a typical feature. Pathological fractures, and bony deformities and nerve compression can occur as complications of poly-ostotic fibrous dysplasia. Typically sclerosis at the base of skull in the region of the cavernous sinus causes optic and auditory nerve compression with hearing or visual loss. In this patient, although there was sclerosis at the base of skull, she did not have hearing or visual impairment. Regarding cutaneous hyper-pigmentation, asymmetrical large melanotic macules with irregular margins which often stop at the midline are typical for the McCune Albright Syndrome. Irregular margin is in contradistinction to the smooth margin of the cafe au lait macules of neurofibromatosis. In this patient, the cafe au lait macules are present over the nape of the neck, back and over the left thigh. Regarding endocrine hyperfunction, precocious puberty is typical feature. It may often be dissonant but may appear consonant resembling normal puberty. In this patient, thelarche appeared first, followed by menarche. But there was neither growthspurt nor pubic and axillary hair (no adrenarche). Endocrine hyperfunction can also occur in other endocrine glands, producing hyperthyroidism, Cushing's syndrome and Gigantism or Acromegaly. In this patient there was no feature of this endocrine hyperfunction.

The first description of McCune Albright syndrome in the literature was of a 9 year old girl with precocious puberty, fragile bones and dermal pigmentation, by

Weill in Berlin in 1922[9]. Fourteen years later in New York, a paediatrician named Donovan McCune described another 9 year old girl with precocious puberty, excessive skin pigmentation and hyperthyroidism[10]. The following year, Fuller Albright, a Harvard endocrinologist, became the first to delineate the Syndrome when he published a series of five cases in the NEJM[11]. Di George summed up the Syndrome in the Journal of Paediatrics in 1975[12]. Most investigators, including Albright himself, had argued that the Syndrome was the result of hyper-secretion of hypothalamic hormones. Di George cited several contemporaneous studies that provided evidence for autonomous endocrine hyperfunction, specifically hyperthyroidism with suppressed TSH and precocious puberty with suppressed FSH, LH.

McCune Albright syndrome been shown to be the result of G-protein abnormalities[13]. The mutation is at the site which codes for the intrinsic GTPase activity, responsible for mediating the inactivation of the alpha subunit with the result of constitutive activation of cAMP driven pathways in the absence of hormone stimulation. Family studies have shown the inheritance to be sporadic and it is due to a post- zygotic mutation[14]. The timing of mutation during embryogenesis determines the severity of each case. Mutation on early stage has widespread tissue involvement and mutation on later stage can have mild cases. There may only be a single adenoma.

Regarding the management of precocious puberty, GnRH analogue therapy is not indicated or not effective. Because precocious puberty in McCune Albright syndrome is not GnRH driven and it is a consequence of a somatic mutation resulting in autonomous steroidogenesis. However, patients with PPP should mature their hypothalamic-pipuitary-gonadal axis and develop true sexual precocity, and then supplementary GnRH agonist therapy is helpful[15, 16]. Regarding tamoxifen therapy, it is both an oestrogen antagonist and an oestrogen agonist. Although it has antagonist effect on breast tissue to suppress the thelarche, its agonist effect on endometium will accelerate the menarche. Many reports of endometrial hyperplasia, endometrial polyps, rapid and symptomatic growth of endometriosis and endometrial cancer were present with tamoxifen therapy. In this patient, although tamoxifen can control the breast development, heavy bout of bleeding occurred after 22 months of treatment. On withdrawal of tamoxifen, there was rebound enlargement of breast.

Activating missense mutations encoding substitutions of Arg^{201} or Gln^{227} in the G_sa gene (the so-called *gsp* oncogene) [17, 18] are known to be be involved the pathogenesis of different human endocrine diseases, such as sporadic endocrine tumors, in particular GH secreting pituitary adenomas and autonomous thyroid adenomas, and the McCune-Albright syndrome (MAS). MAS is a sporadic disorder characterized by polyostotic fibrous dysplasia, cafe-au-lait skin hyperpigmentation, and autonomous hyperfunction of several endocrine glands, such as gonads, pituitary, thyroid, and adrenal cortex, i.e. glands sensitive to trophic agents acting through the cAMP-dependent pathway[19, 20]. Mutations of the $G_s\alpha$ gene have been detected in all affected subjects, and Arg^{201} is the only location reported in MAS to date. Mutant Gsα is expressed in the affected endocrine organs as well as in tissues not classically involved in MAS; the highest proportion of mutant alleles is found in regions of abnormal proliferation. This mosaic distribution is consistent with the hypothesis that this syndrome is due to a somatic mutation in the Gsa gene occurring as an early postzygotic event.

The human $G_s\alpha$ gene maps on chromosome 20q13, and there is increasing evidence that this locus is under complex imprinting control with multiple maternally, paternally, and. biallelically alternatively spliced transcripts encoding multiple products[21-25]. Recent reports demonstrated that in thyroid, gonad, and pituitary, $G_S\alpha$ transcription mainly derives from the maternal allele[26—29]. Moreover, it has been demonstrated that in most *gsp*-positive GH-secreting pituitary tumors the mutation occurs on the maternal allele[26], most likely indicating that the same mutations on the paternal allele are clinically silent.

In contrast to acromegaly, which seems to appear only in patients with a mutation on the maternal allele, bone and skin were invariably affected in all patients with MAS. It is worth pointing out that despite the fact that four of the five bone specimens analyzed developed in the setting of a maternally derived *gsp*, all of the patients included in this study presented with both bone and skin lesions, thus excluding a specific maternal origin of the mutation in osteodysplasia. This observation suggests the absence of $G_s\alpha$ imprinting in such tissues and is consistent with the evidence of osteodystrophy in subjects affected with pseudopseudohypoparathyroidism, a disease associated with loss of function mutations of the $G_s\alpha$ gene on the paternal allele.

In this patient, Norethisterone 2.5 mg twice a day was given continuously to use its progestational effect on endometrium and on the breast tissue. Bleeding was controlled and breast development could be arrested and breast engorgement became attenuated. Treatment is generally to continue until it is appropriate to resume puberty. The definition of appropriate time is individualized for each patient. It is necessary to consider the height potentials, emotional

maturity and chronological age.

Therefore, 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 [30, 31]. 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 [32-34] polymenorrhea and amenorrhea due to continued gonadotropin-independent estrogen production have also been reported[30, 35]. However, clinical information regarding ovarian dysfunction in McCune-Albright patients during adolescent and adult life is scant.

Happle 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 [36]. However, the lack of fully convincing familial cases is consistent with the mosaic mutation hypothesis.

For the Fibrous Dysplasia, careful monitoring of vision and hearing is necessary. Pathological fractures are difficult to manage. Bisphosphonates may help with osteopenia and repeated fractures. In this patient, Calcivita was prescribed by orthopaedic surgeon. Careful monitoring is necessary to detect hyperthyroidism early, and antithyroid drugs can be given if she develops. She should be under joint care of Gynaecologist, Orthopaedic Surgeon and Paediatrician.

It is important to recognize this rare disease (McCune Albright Syndrome) affecting pre-adolescent child early. Early recognition, prompt and proper treatment is necessary in order to prevent physical, mental, emotional and sexual dysfunction and abuse. Evidences for treatment guidelines are scarce. Proper treatment, follow up and monitoring will highlight the benefits of individualized care in this case as is often seen in rare disorders not amenable to complete cure.

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