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Case series

Inducing Puberty in Nigerian Children: A Case series

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Abstract

Background: Delayed puberty is defined clinically by the absence or incomplete development of secondary sexual characteristics bounded by an age at which 95 percent of children of that sex and culture have initiated sexual maturation. Delayed puberty usually results from inadequate gonadal steroid secretion most often caused by a variety of hypothalamic, pituitary, and gonadal disorders. It manifests with the absence of virilization and testicular enlargement (<4 mL) by 14 years in males and as primary amenorrhea and the absence of breast development by 13 years in females. **Methodology:** A retrospective review of Nigerian children with indications for pubertal induction. **Case series:** We present the cases of five Nigerian children who had induction of pubertal development. All the patients successfully achieved puberty following the use of Ethinyl-estradiol and Levonorgestrel as evidenced by the successful appearance of secondary sexual characteristics. The males and two of the females are on follow up while one female was lost to follow up after reaching Tanners stage III of breast development and having achieved menarche.

Keywords: *Ethinyl- estradiol, Inducing Puberty, Levonorgestrel, Testosterone.*

Introduction

Puberty is the period during which we attain adult secondary sexual characteristics and reproductive capability. Its onset depends upon the reactivation of pulsatile gonadotropin-releasing hormone (GnRH) secretion from its relative quiescence during childhood, on the background of an intact potential of pituitary-gonadal function.

Delayed puberty is defined clinically by the absence or incomplete development of secondary sexual characteristics bounded by an age at which 95 percent of children of that sex and culture have initiated sexual maturation.[1,2] Delayed puberty usually results from inadequate gonadal steroid secretion most often caused by a variety of hypothalamic, pituitary, and gonadal disorders.[2,3] It manifests with the absence of virilization and testicular enlargement (<4 mL) by 14 years in males and as primary amenorrhea and the absence of breast development by 13 years in females.[4,5,6] There is a broad spectrum of pubertal timing that varies among different populations, separated in time and space. Delayed puberty usually represents an extreme of normal, a developmental pattern referred to as constitutional delay of growth and puberty (CDGP), but organic defects of the hypothalamic-pituitary-gonadal axis predisposing to hypogonadism may always be initially distinguishable from it. Constitutional delay of growth and puberty (CDGP) and organic, or congenital hypogonadotropic hypogonadism are both significantly more common in boys than in girls, moreover, around 1/3 of adults with organic hypogonadotropic hypogonadism had evidence of partial puberty at presentation and confusingly, some 5-10% of these subsequently may exhibit recovery of endogenous gonadotrophin secretion including men with Kallman syndrome.

This study intended to highlight our current practice in diagnosis and management of delayed puberty especially where one is faced with difficulty and threat to life.

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Materials and Method

This is a retrospective review of Nigerian children with indications for pubertal induction. Case notes of all the patients who had puberty-induced between January 2011 and December 2014 were reviewed. Information extracted from their case notes includes biodata, Pregnancy, labour, delivery, and neonatal history. The patient's growth and developmental milestones, family and social history as well as history of chronic illnesses were obtained. Sexual maturity rating (SMR), and findings on induction and growth parameters were also obtained.

Results

Five children from Zaria (3) and Calabar (2), Nigeria had induction of puberty. There are 2 males and 3 females whose ages range from 9-24 years. All the patients are from families of lower- and middle-income social class. Two of the cases aged 16 and 24 years respectively had delayed puberty due to Turner syndrome. One patient, a female aged 19 years had Kallman syndrome. Multiple Pituitary Hormone Deficiencies (MPHD) were diagnosed in a 16-year-old boy. A Child (9-year-old) with Marfan syndrome had puberty induced for growth reduction. The diagnosis of the primary conditions was based on the clinical criteria [7-10] and laboratory features as depicted in Tables 1 and 3. The characteristics of the patients are shown in Tables 1 and 2 below.

Table 1: Characteristics of five Nigerian Children who had induction of puberty

Age in yrs	sex	Weight in kg	Height in cm	BMI	SMR	Clinical features	Diagnosis
16	M	29	137	15.7	I	Short stature, high - pitched voice, normal intelligence	Multiple Pituitary Hormonal deficiencies (MPHD)
9	M	22.5	148.5	10.2	I	Tall stature since birth, growth velocity of >12cms/yr, marfanoid facies, short trunk, long limbs	Marfan syndrome
16	F	34.5	138	18.1	I	Short stature since birth, absent breast, no menarche, no webbing of the neck or other features of Turner syndrome	Turner syndrome
24	F	42	143	20.5	I	Short stature, absent breast development, no menarche	Turner syndrome
19	F	64	168		I	Absent breast development, no menarche, tall stature, anosmia	Kallman syndrome

Table 2: Radiological Features

Cases no/Diagnosis	CT-scan	X-ray	Ultrasound
1. Multiple pituitary hormonal deficiencies		Delayed bone age, normal thyroid gland, normal pituitary gland	
2. Marfan syndrome		Arachnodactyiy , scoliosis, normal bone age.	Cryptorchidism
3. Turner syndrome		Delayed bone age and infantile uterus	Infantile size uterus
4. Turner syndrome		Bone age 12 -13yrs	Infantile size uterus and ovaries not visualised
5. Kallmann syndrome		Bone age 12 -13yrs	Infantile size uterus, ovaries not visualised, double fused left kidney, right kidney missing with no calyceal system

Table 3: Hormonal profiles of the patients who had pubertal induction

Variable	Case 1	Case 2	Case 3	Case 4	Case 5
T3(0.8 -2)ng/ml	1.8	-	1.8	0.98	0.88
T4(38 -98)ng/ml	2.1	-	95	59	46
TSH(0.4 - 5.2)iu/ml	1.9	-	1.5	2.2	3.2
LH(0.5 - 10.5)miu/ml	<0.5	8	15	15.4	4.6
FSH(2 -12) miu/ml	3.1	2	92	70	62
Estradiol(18 - 595)pg/ml	-	-	<9	13.5	28.4
Testosterone(3 - 10)ng/ml	1.3	2.6	-	-	-
Fasting growth hormone(5.4ug/l)	0.15	-	-	-	-

Females were started on oral ethinylestradiol and later on, Levonorgestrel while the males had testosterone injections due to the non-availability of transdermal estrogen, testosterone patches, and serious psychosocial issues. All started puberty successfully reaching an acceptable near-final height of 5th centile for those with short stature and growth deceleration in the child with Marfan syndrome. The males and two of the females are on follow up while one female was lost to follow up after reaching tanner stage 3 for breast development and having achieved menarche.

Discussion

The diagnosis of Marfan,[7] Kallmann [8] and Turner syndromes [9] as well as multiple pituitary hormonal deficiencies [10] in these patients were based on the accepted clinical criteria [7,8,9] and suggestive laboratory evidence. Hormonal stimulation tests, chromosomal, and genetic studies would have confirmed the diagnoses,[7,8,9] however these tests are not readily available and are beyond the reach of the caregivers.

The aims of pubertal induction include the attainment of

secondary sexual characteristics including induction of menses, generation of the pubertal growth spurt, acquisition of bone mineral mass, and uterine development sufficient for assisted reproductive interventions. Puberty can be initiated by the use of pulsatile GnRH, gonadotropins, and sex steroids. Sex steroids will induce the development of the secondary sex characteristics alone, while combined administration of gonadotropins and GnRH may induce gonadal development including fertility. Oral ethinyl estradiol and later on Levonorgestrel were used for the females while the males had testosterone injections due to the non-availability of transdermal estrogen, and testosterone patches which were shown to be superior in both primary and secondary outcomes during puberty induction. [10] Sex steroids were used to induce puberty in all the subjects as the last resort to avert calamity as well as improve the quality of life of these patients.[11,12] In children with MPHD, replacement should also be directed at other hormonal deficiencies.[10] Our patient with MPHD was on levothyroxine before pubertal induction therapy

In children with Marfan syndrome, hormonal therapy[13] has been used to induce puberty and reduce the patient's ultimate height if hormonal treatment is commenced before puberty. In a retrospective study in 31 untreated (17 boys) and 43 treated patients (21 boys) with Marfan syndrome, a statistically significant effect of therapy on final height was observed only in boys using a pharmacologic dosage and there were no clinically important short-term side effects [13]The rate of height increment in our patient also reduced significantly compared to the height velocity before the pubertal induction.

Kallman syndrome is the most common form of gonadotropin deficiency with a frequency of 4 in 100,000 people. A diagnosis of KS is often difficult to make due to genetic heterogeneities and the broad spectrum of phenotypic presentations and patients are commonly diagnosed in late adolescence or early adulthood.[8]

Adolescent females with ovarian failure require estrogen therapy for induction of puberty and other important physiologic effects. Currently, healthcare providers have varying practices without evidence-based standards; Shah et al [9] investigated the potential differential effects of treatment with oral conjugated equine estrogen, oral 17β estradiol, or transdermal 17β estradiol on biochemical profiles and feminization in girls with ovarian failure and found both effective in inducing puberty. However, a better effect was noticed with the transdermal patch in terms of growth. The decision to use the oral oestrogens in our patients was based on the serious psychological stress and threat to life as one of the patients was attempting suicide.

Conclusion

Despite the unavailability of standard therapy for inducing puberty in our setting, it is still possible to overcome some treatment and diagnostic challenges in children requiring induction of puberty. However, Psychological counseling is ongoing for the patients and families in trying to cope with feelings of denial, anger, blame, depression, or guilt and re-education concerning daily activities Conservative treatment of other skeletal problems involves mostly physiotherapy and other orthotic support. Other medical conditions were been co-managed with the relevant specialist.

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