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A CASE OF HYPOGONADOTROPIC HYPOGONADISM WITH INFANTILE GENITALIA IN A 16YEAR OLD NIGERIAN MALE

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ABSTRACT

Background: Hypogonadotropic hypogonadism or secondary hypogonadism is a clinical syndrome that results from gonadal failure due to abnormal pituitary gonadotropin levels. It usually results from absent or inadequate hypothalamic GnRH secretion or failure of pituitary gonadotropin secretion. It may be congenital or acquired. The congenital form has a Normosmic and a Hyposmic/Anosmic variant.

Objective: To highlight an uncommon case of hypogonadotropic hypogonadism in a young Nigerian male.

Case: A 16 year old male Nigerian Senior Secondary School student presented to the endocrinology clinic with complaints of infantile male external genitalia. This was initially noticed by the grandfather who observed that the penis has notincreased in size since birth. However, patient became aware of the symptom at the age of 10 years. He developed axillary and pubic hair at 14 years. The hair was scanty and the frequency of shaving reduced. He also had right sided undescended testis. Nonetheless, there was no associated history of a reduction in the perception of smell, impaired vision, headaches, or hearing loss. No family history of similar illness was reported but patient had a positive family history of diabetes mellitus. Anthropometric measurements showed; height of 164cm, weight of 64kg, body mass index (BMI) of 23.8kg/m^2, arm span of 168cm, waist circumference of 94cm; crown to pubis length of 75cm , pubis to heel length of 89cm and crown-pubis/pubic-heel ratio of 0.84.

Investigations: Hormone profile showed reduced levels of follicle stimulating hormone (FSH), leutinizing hormone (LH), testosterone and estrogen levels {FSH-0.4 IU/L (1-14IU/L), LH-0.1IU/L (0.7-7.4 IU/L), estrogen-0.1 pg/L(4-94pg/L), testosterone-1 ng/ml (1.8-9.1ng/ml)} but a normal Prolactin level of 16.0ng/ml (1.8-17.0 ng/ml). Brain Magnetic Rosonance Imaging (MRI) revealed normal brain with age appropriate features and no pituitary mass. Scrotal ultrasound scan (USS) showed Right undescended testis with reduced testicular size(<2cm) and altered echogenicity and echotexture. Abdominopelvic ultrasound scan reported normal findings.

The patient had right orchidopexy with favourable outcome. He was placed on IM testosterone 125mg 3 weekly, tablet calcium /VitD3 (600mg/400iu) once daily and regular follow-up visits where treatment would be monitored by a 3-6 monthly testosterone assay, regular assessment of anthropometry and evaluation of secondary sexual characteristics

Conclusion: Hypogonadotropic hypogonadism is a rare disorder. Congenital causes may present with infantile external genitalia, and treatment is by hormone replacement therapy; which is usually lifelong.

Key words: Hypogonadotropic hypogonadism, undescended testes, infantile genitalia

INTRODUCTION: Hypogonadotropic hypogonadism or Secondary hypogonadism is a clinical syndrome that results from gonadal failure due to low pituitary gonadotropin levels. It usually results from absent or inadequate hypothalamic GnRH secretion or failure of pituitary gonadotropin secretion[1]. It may be congenital or acquired[2].

The acquired form of the disease usually occurs after sexual maturation and is not related to genetic defects. Hyperprolactinemia is the commonest cause. The prolactin inhibits GnRH thereby inhibiting release of FSH, LH and sex steroids. Other causes may include: Drugs (sex steroids and GnRH analogues), infiltrative or infectious pituitary lesions, encephalic trauma, pituitary/brain irradiation, systemic diseases (sarcoidosis, hemochromatosis, histiocytosis X), exhausting exercise, abusive alcohol and illicit drug use. The Congenital form has 2 main types: Anosmic hypogonadotropic hypogonadism (Kallmann syndrome) and Idiopathic hypogonadotropic hypogonadism (Congenital normosmic isolated form). It has an incidence of 1-10:100,000 live births[3], and an estimated prevalence of 1/10,000 to 1/86000[4]. Male to female ratio is 4:1 to 5:1, with 2/3 of cases arising from Kallmann syndrome[3].

CASE REPORT: A 16 year old male, senior secondary school student who presented with complaints of infantile male external genitalia.

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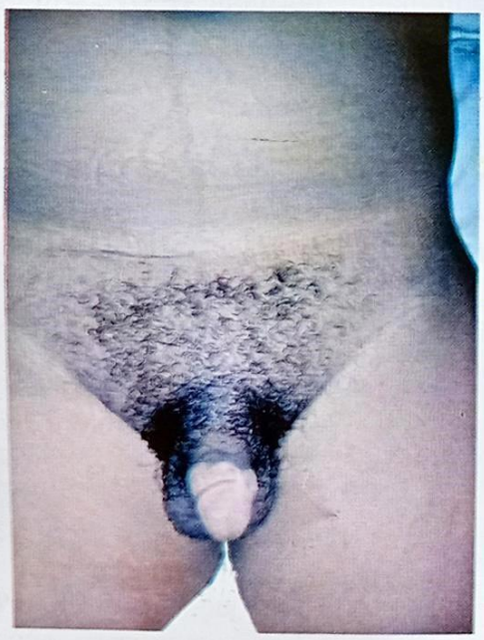
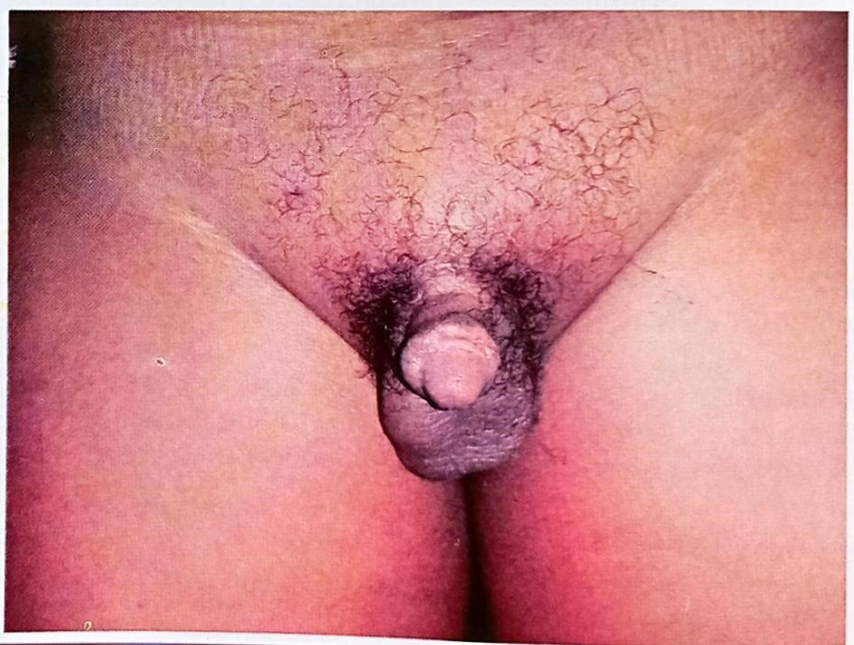
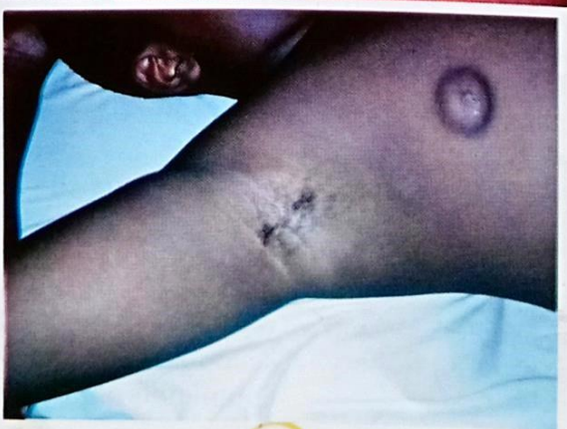
The grandfather observed that the penis and scrotum had not increased in size since birth. Patient had developed scanty axillary and pubic hair at age 14 (2 years prior to presentation) with reduced frequency of shaving of the pubic hair (shaved once a year). The patient also reported the absence of facial hair but admitted having a high pitched voice. He complained of inability to feel the right testis in the scrotal sac. No associated hyposmia, impaired visionor hearing loss was reported. There was no history of birth trauma, preceeding head traumaor family history of a similar illness. No hoarseness of the voice, cold intolerance, leg swelling, vomiting, skin hyperpigmentation, neck swelling or excessive short stature was also reported by the patient.

Physical examination revealed a young man with a pulse rate of 72 beats per min(bpm), blood pressure of 100/60mm/Hg and respiratory rate of 18cpm. He hadhigh pitched voice, scanty axillary and pubic hair, absent facial hair and central fat deposition.
Anthropometric measurements revealed the following: Height - 164cm, weight - 64kg, BMI - 23.8 kg/m^2, arm span -168cm,arm span height difference - 4cm, waist circumference -94cm, crown to pubis length -75cm and a pubic to heel length of 89cm. Crown-pubis/pubic-heel ratio was 0.84.
Urogenital examination revealed a penile length of about 2cm with sparse pubic hair distribution. The scrotum was small in size and only the left testis was palpable within the scrotal sac. The left testicle was soft in consistency and had a volume of $2cm^3$ (using Prader orchidometer) The patients was in Tanner stage 1.







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Investigations: Hormonal profile showed reduced FSH of 0.4 IU/L (1-14IU/L), reduced LH of 0.1IU/L (0.7-7.4 IU/L), reduced Estrogen of 0.1 pg/L (4-94pg/L), reduced Testosterone of 1 ng/ml (1.8-9.1ng/ml) and a normal Prolactin level of 16.0ng/ml (1.8-17.0 ng/ml).
Brain MRI showed normal brain with age appropriate features and no pituitary mass.
Scrotal USS showed right undescended testis with reduced testicular size and altered echogenicity. It also showed reduced left testicular size (<2cm^3) with altered echotexture.
Abdominopelvic ultrasound scan was normal and the Packed Cell Volume (PCV) was 30%.

Patient had right orchidopexy with a satisfactory outcome. He was subsequently placed on IM Testosterone 250mg 3 weekly, tablet Cal/D3 (600mg/400IU) once daily, and a 3 weekly follow-up visit.

DISCUSSION:

The index patient who presented to our endocrinology clinic with pre-pubertal external genitalia,normosmia and normal brain MRI was most likely a case of Idiopathic hypogonadotropic hypogonadism. Deficient hypothalamic GnRH underlies the markedly abnormal gonadotropin secretion patterns in most patients with Kallmann syndrome or Idiopathic hypogonadotropic hypogonadism. The result is hypogonadism, and absent, incomplete, or partial pubertal maturation as seen in our index patient. Some of the genes involved in the pathogenesis have been identified. However, the genes involved remain unidentified in over 50% of patients.[5] Mutations in KAL-1 gene[4], FGFR-1[6,7], FGF-8[7], CHD7, DAX1[8], PC1, KISS1R (GPR54)[9], TAC3, TACR3, NSMF[10],CCDC141, WDR11, FGF17,IL17RD, DUSP6,SPRY4, FLRT3, AXL, SOX10, SEMA3A,HS6ST11,[11,12,13,14,15,16] and in the critical components of the prokineticin pathway[17,18] have been linked to congenital secondary hypogonadism. There was no family history of the disease in the index patient, thus, this may be a sporadic case which is a common pattern of presentation.[19]
History of absent or incomplete puberty (males may present with microphallus and cryptorchidism), decreased libido, erectile dysfunction, decreased muscle strength, diminished aggressiveness and drive in men and amenorrhea (usually primary) and dyspareunia in women usually occur.[20] Such patients may have anosmia or hyposmia; features of congenital heart disease (Fatigue, dyspnea, cyanosis, palpitations, and syncope); neurological manifestations (colour blindness, hearing deficit, epilepsy, or paraplegia),[20] symptoms of primary adrenocortical insufficiency; and are also at risk of osteoporosis.
Examination may reveal eunuchoidal skeletal proportions; crown- pubis to pubis- heel ratio less than 1:1 in adults and arm span greater than height by more than 3cm with normal height for age.[21] There may be absence of facial hair and decreased body hair. Adult onset may report decreased shaving frequency, and may have lack of temporal hair recession, (male-type baldness). Males could have high pitched voice, and gynecomastia may be seen in rare cases.[21] There could be lack of breast development in females. Muscle mass is decreased, muscle strength is diminished and fat is distributed over the hip and chest especially in men.
Axillary and pubic hair may be scanty. Patient may have pre-pubertal testes (<4ml), and lack scrotal pigmentation.

At adult onset, testicular volumes are either normal or mildly decreased (10-15ml). Cryptorchidism is present in a minority of cases.[21] Males may have small penis (<8cm long in adults) and prostate size may be reduced. In women, vaginal mucosa may have a deep red colour due to lack of squamous epithelial differentiation.

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Low serum (Total and free) testosterone(usually <100ng/dl),LH and FSH are as a result of decreased gonadotropin production.[22] Serum prolactin is normal in congenital secondary hypogonadism and is used to exclude hyperprolactinemic conditions like infiltrative hypothalamic disorders (sarcoidosis & histiocytosis X) and prolactin secreting pituitary tumours.[23]

Brain MRI is important to exclude hypothalamic and pituitary lesions (75% of patients with Kallmann syndrome have abnormal olfactory findings on MRI) .[24] Transthoracic echocardiogram is equally important inorder to rule out congenital heart disease which is present in a small subset of patients. Utrasound examination of the kidneys will exclude unilateral renal agenesis as seen in some patients with Kallmann syndrome. Bone densitometry by dual-energy radiographic absorptiometry (DXA) may detect the presence of osteopenia and osteoporosis, and is equally helpful in monitoring the response of the skeleton to gonadal steroid replacement therapy.[25]

Medical options include androgen replacement therapy which could restore libido, erectile function and patient's well-being. It can also promote the development of secondary sex characteristics and may improve muscle strength.[26] Androgen can be given as an IM injection, transdermal patches and as intranasal sprays. Estrogen replacement in females promotes the development of sexual characteristics including breast development and menstrual function. It is also helpful in the prevention of osteoporosis. Progestins such as Medroxy progesterone is administered to female patients on estrogen therapy. It induces secretary changes in the endometrium which will eventually lead to withdrawal bleeding.[27] Gonadotropins (HCG) successfully restores fertility in most patients with congenital hypogonadotropic hypogonadism.[27]

CONCLUSION

This case report demonstrates a 16 year old male who presented with short penis, small testes, low serum levels of testosterone, LH and FSH. In view of these features, a diagnosis of congenital hypogonadotropic hypogonadism was made.

The patient was subsequently treated with IM injection of 125mg testosterone 3 weekly with the target of achieving normal secondary sexual characteristics and an improved quality of life

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