Original Research Paper

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Evaluation of Gonadal Hormones in Adult Saudi Men with Homozygous Sickle Cell Disease

Medicine

KEYWORDS: Evaluation, Gonadal Hormones, Adult, Homozygous Sickle Cell

Mohammed Al-Matar	Medical Students, King Faisal university, Saudi Arabia
Hani Alkhalaf	Medical Students, King Faisal university, Saudi Arabia
Mosa'ad seif	College of medicine, King Faisal university, Saudi Arabia
Adel Nasser Al Bargi	College of medicine, King Faisal university, Saudi Arabia
Sayed Ibrahim Ali	College of medicine, King Faisal university, Saudi Arabia
Abdulrahman Ahmad Al Naim	College of medicine, King Faisal university, Saudi Arabia
Abdullah Khalid Al Maqhawi	College of medicine, King Faisal university, Saudi Arabia

ABSTRACT

BACKGROUND: There is conflicting evidence in the literature on the etiology of hypogonadism in patients with sickle cell disease (SCD). **Aim:** Therefore, the present study aimed to assess the effect of SCD on the gonadal function in these patients and determine whether hypogonadism is primary or secondary action. Methods: The serum levels of gonadotropin-releasing hormone (GnRH), Follicle-stimulating hormone (FSH), luteinizing hormone (LH), testosterone (T), dehydrotestosterone (DHT) and prolactin (PRL) were estimated in 50 sickle cell disease men and 50 age matched control subjects.

Results: our results showed significantly lower mean values of GnRH, T and DHT and higher mean values of FSH, LH and PLN in SCD patients than in control subjects.

Conclusion: The present results suggest that the sickle cell gene abnormality has an adverse effect on endocrine functions of the testis.The secretion of GnRH is inhibited by high levels of PCL

INTRODUCTION

Sickle cell disease (SCD) is caused by a single point mutation in the human β-globin gene that results in the formation of abnormal hemoglobin (HbS) [1]

Testosterone is a hormone which is responsible for many of the physical characteristics specific to adult males. It plays a key role in reproduction and the maintenance of bone and muscle strength. The regulation of testosterone production in men is tightly controlled to maintain normal levels in blood. The hypothalamus and the pituitary glands are important in controlling the amount of testosterone produced by the testes. In response to gonadotrophin-releasing hormone from the hypothalamus, the pituitary gland produces luteinising hormone (LH) and follicle-stimulating hormone (FSH) which travel in the bloodstream to the gonads and stimulates the production and release of testosterone [2].

As blood levels of testosterone increase, this feeds back to suppress the production of gonadotrophin-releasing hormone from the hypothalamus which, in turn, suppresses production of luteinising hormone by the pituitary gland. Levels of testosterone begin to fall as a result, so negative feedback decreases and the hypothalamus resumes secretion of gonadotrophin-releasing hormone [3]

Hypogonadism is the condition more prevalent in males in which the production of sex hormones and germ cells are inadequate resulting in the delay of growth and sexual development [4]**.** The two main classifications of hypogonadism are primary hypogonadism and secondary hypogonadism. Primary or hypergonadotropic hypogonadism is characterized by sex organ failure, resulting from testicular or ovarian disease which has been suspected as an important cause of gonadal failure and infertility. Secondary or hypogonadotropic hypogonadism refers to a communication failure between the neuroendocrine system and the gonads, even though the sex organs themselves may be intact **[5][6]**

Hypogonadism is one of the most prevalent endocrinopathies in subjects with sickle cell disease (SCD). Various biochemical studies have demonstrated low levels of testosterone and dihydrotestosterone and variable levels of follicle-stimulating hormone and luteinizing hormone in SCD patients. Dada and Nduka **[7]** and Taddesse et al, [8] found that the levels of the testosterone (T), follicle-stimulating hormone (FSH) and luteinizing hormone (LH) were significantly lower in homozygous sickle cell disease (HbSS) compared to the control group. **In 1987, Osegbe and Akinyanju [9] indicated that a significantly lower mean serum testosterone, a higher mean FSH and prolactin in SCD subjects than in normal controls**

Hyperprolactinemia is a common cause of infertility in males and females. It is generally believed that the mechanism of the prolactin (PRL)-induced sexual dysfunctions is a decrease in testosterone secretion in men [10][11]. In 1994 , Parshad et al **,** [12] showed that prolactin (PRL) levels were within the normal range in the homozygous sickled hemoglobin (HbSS) patients, but other studies, found that hyperprolactinaemia occurred in most SCD patients [13]**.**

Aim: The prevalence of hemoglobinopathies in the eastern region of Saudi Arabia is increased and the mechanism of its effect on hypogonadism is unclear, the present study aimed to determine whether these impaired functions are due to an intrinsic (primary) defect of the testis or secondary to failure of the hypothalamic/pituitary gland, the serum gonadotrophins [e.g. follicule-stimulating hormone (FSH), luteinizing hormone (LH)], prolactin (PRL)] testosterone (T), dehydrotestosterone (DHT) were assayed in both SCD patients and control subjects

The prevalence rate of sickle cell disease is increased among Saudis in the eastern region of Saudi Arabia with limited studies about its effect on testicular function of these patients.

MATERIALS AND METHODS

Materials

The fluorescence assay kits were purchased from VIDAS, BioMérieux, SA, 69280 Marcy-l'Etoile/France for estimation of testosterone (T), dihydrotestosterone (DHT), gonadotropin-releasing hormone (GnRH), follicle-stimulating hormone (FSH), luteinizing hormone (LH) and prolactin (PLN) by using VIDAS Fluorescent instrument (BioMérieux, SA, 69280 Marcy-l'Etoile/France)

Subjects

They are from Al-Ahsaa City, Saudi Arabia comprised of 50 male patients with homozygous sickle cell disease that they were selected from the Hematology Clinic at King Fahd Hospital whose ages ranged from 16-29 years (20.8 ± 4.3) were studied. All the patients were in a clinically steady state their hemoglobin (Hb) types were determined electrophoresis at pH 8.4. Fifty age matched volunteers were randomly selected from those attending other clinics or accompanying patients and free from any blood diseases (as proved by revision of their records).

All subjects did not have any medicine for at least a month before taking the blood sample. The study was performed in the steady state, i.e., free of acute clinical illness. Written informed consent was obtained from all participants enrolled in the study.

Exclusion criteria include

No history or evidence of cardiovascular, hepatic, renal, or gastrointestinal disease or the presence of chronic infectious illnesses (including HIV infection), or inflammation and no blood transfusion within 3 months of study.

Ethical Considerations were fulfilled and study protocol was approved from authorities at King Faisal University in collaboration with the King Fahd Hospital, Saudi Arabia

Anthropometry

Weight was measured using an electronic scale (Seca 770, Hamburg, Germany). Subjects were weighed barefooted and with minimal clothes. Standing body height was measured with the use of Harpenden stadiometer with the shoulder in relaxed position and arms hanging freely and without shoes to the nearest 0.5 cm. Measurements were taken by single technician to overcome inter-rater error. Scales were re-calibrated after each measurement. BMI was calculated as weight in kilograms divided by height in meters squared. **[14].**

Blood sampling

5 ml Blood samples were freshly withdrawn from both normal and sickle cell disease patients in the morning after overnight fasting in a dry, clean test tube under study inpatient King Fahd hospital. These blood samples were immediately transferred from the King Fahd Hospital and Medical Center at King Faisal University to our laboratory at the College of Medicine, King Faisal University in an icebox. After blood clotting, the blood samples were centrifuged at 5000 rpm for 10 minutes and the clear sera were separated and stored at -20°C until assayed

Methods

Serum GnRH, T, DHT, FSH, LH and PRL were measured by Fluorescent assay kits, according to the manufacturer's instruction (VIDAS, BioMérieux, SA, France)

Statistical Analysis

Data were analyzed with the SPSS 16.0.7 (SPSS, Chicago, IL, USA) for Microsoft Windows XP (Redmond, WA, USA) statistical software package. Group comparison was performed by using a one-way analysis of variance (ANOVA. Values are expressed as mean ± standard deviation, and $p < 0.05$ was considered statistically significant.

RESULTS

Table 1, demonstrates the base-line data including anthropometric measurements and the characteristics of both SCD patients and their controls. A total of 100 male subjects (normal = 50, and sickle cell disease (SCD) = 50) with age ranged from 25-36 years. The mean age of SCD subjects is 34.9 ± 6.23 years and their control subjects aged 33.5 ± 6.65 years. Age distribution showed no significant difference between the two groups, SCD patients were resided in the rural region. Body weight, body mass index (BMI) and hemoglobin levels were disproportionately higher among control subjects compared to SCD patients.

Table 2 demonstrates the levels of testosterone (T), dehydrotestosterone (DHT), follicle-stimulating hormone (FSH), Luteinizing hormone (LH), gonadotropin-releasing hormone (Gn-RH), and prolactin (PLC). Mean concentrations of T, DHT and Gn-RH were significantly reduced, whereas the mean values of FSH, LH and PLC were significantly increased among SCD patients compared to their age and gender matched control subjects

DISCUSSION

Hemoglobinopathies are associated with fertility disturbance in both males and females. The diagnosis of hypogonadism in men was established by their physical findings and serum testosterone levels.

Measurement of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) and testosterone in patients with hypogonadism distinguishes primary hypogonadism from secondary hypogonadism.

In primary hypogonadism (gonadal failure with hypergonadotropic), testosterone level is reduced with increasing of FSH and LH. In secondary hypogonadism [(gonadal insufficiency) due to pituitary or hypothalamic dysfunction (hypogonadotropic)], the serum testosterone, FSH and LH levels are low **[9].**

Primary hypogonadism is chiefly distinguishable from secondary hypogonadism in that subnormal serum sex hormones and gamete production levels occur in conjunction with high or normal serum follicle-stimulating hormone (FSH) and luteinizing hormone (LH) levels. In secondary hypogonadism, the serum FSH and LH levels are low or normal [1] [2] [3] .

The association between sickle cell anemia and sexual maturation has long been recognized but is not well understood [15]. The lower testosterone levels in male patients under study with homozygous sickle-cell (SS) disease may be attributed to either abnormalities of the hypothalamic and/or pituitary dysfunction (secondary testicular failure) or primary testicular failure.

The data of Abbasi et al, [16] suggested that the hypogonadism in sickle cell anemia patients may be a primary testicular problem with high gonadotropin levels and a normal gonadotropin-response upon GnRH stimulation. In contrast, the results obtained by Dada & Nduka **[7]** and Agbaraji et al, **[17]** showed that FSH, LH and T, were significantly reduced in SCD patients and suggested that gonadal dysfunction in SCD was of pituitary origin (secondary hypogonadism).

Thus, our results conflict with the views of Dada & Nduka **[7]** and Agbaraji et al, [17] that the testicular failure was entirely the result of pituitary failure but agree with those of Abassi et al., **[16]** and Parshad et al, **[12]** that hypogonadism is more consistent with primary testicular.

The basic mechanism through which SCD produces lesions such as splenic infarcts, necrosis of femoral head and papillary necrosis, is vasoocclusion of small blood vessels by sickled RBCs, infarction and tissue hypoxia associated with chronic anemia **[18].** Thus, the second mechanism of the gonadal dysfunction in SCD patients may be resulted from vasoocclusion of either hypothalamic-pituitary blood vessels which would result in low serum gonadotrophins (FSH, LH, PRL), and consequently low testosterone and DHT (secondary hypogonadism) or vasoocclusion of the testicular vessels resulting in

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target organ failure with low testosterone and high gonadotrophins (primary hypogonadism). It is also conceivable that vasoocclusion may affect both systems producing a complex of pituitary-testicular failure .

Our results show the decreasing levels of testosterone and DHT with increasing levels of FSH & LH in our SCD patients. This suggests that pituitary function was intact but that the testes were unable to respond to stimulation in these patients. Thus, the hypogonadism of our patients may be attributed vasoocclusion of the testicular vessels resulting in target organ failure with low testosterone and high gonadotrophins (primary hypogonadism). This means that these men have primary testicular failure or destruction of pituitary hormone receptors on the testis. Our finding is confirmed by the study of Maomi et al**,** [19] which reported that the frequent episodes of intravascular sickling, vasoocclusion, and infarction, as well as tissue hypoxia associated with chronic anemia, are responsible for the testicular failure in SCD. In addition, Friedman et al,[20] and Maomi et al, [19] also found a decreased testicular size in males with sickle cell disease Hyperprolactinaemia was found in many infertile men.**[21] .**

The reduction of gonadotropin-releasing hormone (GnRH) secretion in our SCD patients may be attributed to the increased production of pituitary hormones, e.g. FSH, LH and PRL. Elevated prolactin may inhibit the secretion of hypothalamic gonadotropin-releasing hormone (GnRH) neurons. Prolactin may act directly on GnRH neurons to suppress GnRH secretion, or the effects may be indirect, mediated through other afferent pathways, perhaps via other neurons influencing GnRH release. **[22] [23] [24].**

Conclusion: These observations suggested that androgenesis is defective in SCD patients. The tendency of higher gonadotrophins, e.g. FSH, LH, PRL, associated with lower testosterone & DHT in SCD patients suggested that the hypothalamic/pituitary function in these patients is intact and that the primary testicular failure lies in the testis. The decrease of GnRH is inhibited by high secretion of PCL

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