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Hypogonadism in Patients with Sickle Cell Disease: Central or Peripheral?

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Abstract

There is conflicting evidence in the literature on the etiology of hypogonadism in patients with sickle cell disease (SCD). A cross-sectional study was done to determine whether hypogonadism in male patients with SCD is due to primary testicular failure or secondary pituitary/hypothalamic dysfunction and assess the association between hypogonadism and serum ferritin levels. Hormonal assessment for serum concentrations of testosterone, follicle stimulating hormone (FSH) and luteinizing hormone (LH) was done for 34 men with SCD and their charts were reviewed for relevant clinical variables. Eight men (24%) were classified hypogonadal based on their serum testosterone levels. These men have significantly lower LH ($p = 0.001$) and FSH ($p = 0.01$) levels than normogonadal men, indicating a central etiology. There was no significant difference between hypogonadal and normogonadal men with respect to ferritin levels ($p = 0.71$). Our study indicates a central etiology of hypogonadism in patients with SCD. In this small study ferritin level was not significantly related to hypogonadism.

Keywords

Ferritin; Hemoglobinopathy; Hypogonadism; Testosterone

Introduction

SCD is a hereditary hemoglobinopathy characterized by abnormal hemoglobin production, hemolytic anemia and intermittent occlusion of small vessels leading to acute and chronic tissue ischemia, chronic organ damage and organ dysfunction. A $\beta^{6\text{val}}$ to $\beta^{6\text{glu}}$ single point mutation in the β -globin gene results in the formation of sickle cell hemoglobin. When an individual has one mutant and one normal allele, the consequences are very mild. SCD develops when both alleles are mutant. However, SCD variants can occur in compound heterozygous individuals where a β -S mutation is inherited from one parent and a different β -gene mutation, such as that of thalassemia or hemoglobin C, is inherited from the other parent. In fact, the sickle cell-hemoglobin C disease and the sickle β -thalassemia syndromes are the most common compound heterozygous conditions [1].

SCD is the most prevalent genetic hematologic disorder in the USA where 2 million people carry the sickle cell gene (heterozygous state) and about 72,000 have SCD (homozygous state). The disease is common in African Americans with 1 out of 500 African American newborns having SCD [1]. Very few studies have addressed hypogonadism in the SCD population and there is no consensus on the underlying etiology leading to hypogonadism. Two studies have shown lower mean testosterone with elevated follicle stimulating hormone (FSH) and an exaggerated increase in luteinizing hormone (LH) and FSH after gonadotropin-releasing hormone (GnRH) injection in men with SCD compared to controls, suggesting primary testicular failure as the etiology [2, 3]. On the other hand, three studies have shown lower mean testosterone and inappropriately normal or low LH and FSH levels, suggesting hypothalamic-pituitary dysfunction [4–6]. Male hypogonadism can lead to significant morbidity including impotence, infertility, osteoporosis and metabolic syndrome. Detection and treatment of hypogonadism in men with SCD is expected to result in considerable improvements in quality of life.

Materials and Methods

Male patients with SCD between the ages of 18 and 50 seen at the Benign Hematology Clinic at the Detroit Medical Center were eligible for the study if they were not on testosterone therapy and had had no acute illness within the 7 days prior to the date of interview. The study protocol was approved by Wayne State University/Detroit Medical Center Human Investigation Committee.

Eligible participants were recruited between September 21 and December 21, 2010. A total of 19 patients consented to participate in the study. Blood samples were drawn between 9 and 11 a.m. and sent to the laboratory for hormonal assay.

A pilot study of 15 adult male SCD patients aged 18–38 years was previously performed at the same site and their data are included in the analysis to give a total of 34 men with SCD in the final analysis. Hormonal measurements were performed by the Pathology Department of Wayne State University School of Medicine/Detroit Medical Center. Total testosterone was measured by an ELISA, and FSH and LH by a two-site sandwich immunoassay chemiluminescence method (Centaur XP, Siemens). The intraassay and interassay variations of all hormone measurements were below 5%. Other clinical and laboratory data, including BMI, hemoglobin, total bilirubin, ferritin and creatinine levels, were collected from the Electronic Medical Records.

Participants were classified as hypogonadal (serum testosterone $\leq$ 250 ng/dl) or normogonadal (serum testosterone $>$ 250 ng/dl). The normal range for FSH and LH serum concentrations were 1.5–12.4 and 2–14 mIU/ml, respectively. Hypogonadal men with high FSH and LH were classified as having primary/peripheral hypogonadism, whereas those with inappropriately normal or low FSH and LH were considered to have secondary or central hypogonadism. Kruskal-Wallis tests were used to assess the statistical significance of differences between the groups with Stata 11.1.

Results

Almost all participants in our study have homozygous SCD-SS genotype except 2 with SCD-SC and one with SCD-S β^+ thalassemia. Eight out of 34 patients (24%) had serum testosterone levels below 250 ng/dl and were classified hypogonadal. Hypogonadal men were somewhat older and heavier than normogonadal men (table 1). FSH and LH levels were either low or inappropriately normal in all the 8 patients with low testosterone, which

indicates central hypogonadism (fig. 1, 2). Differences in ferritin levels were not statistically significant (fig. 3).

Discussion

The prevalence of hypogonadism in this group of patients with SCD (24%) is in agreement with what was reported by Osegbe and Akinyanju [2] and by Friedman et al. [7]. The studies of SCD patients by Osegbe and Akinyanju [2] and Abbasi et al. [3] showed that the cause of hypogonadism was due to primary testicular failure. On the other hand, el-Hazmi et al. [4], Modebe and Ezech [5] and Dada and Nduka [6] reported that the underlying cause for hypogonadism in their study patients was secondary to hypothalamic/pituitary dysfunction. Our study showed that all patients with hypogonadism have either low or inappropriately normal FSH and LH levels, suggesting a central etiology.

Although small, our study did not show statistically significant differences in ferritin levels between hypogonadal and normogonadal men. Organ damage, particularly pituitary dysfunction, from ferritin deposition is described as a possible etiology for hypogonadism in patients with hematologic disorders that are associated with hemolysis and subsequent iron overload [8]. Serum ferritin level can be used as a surrogate marker for iron overload, although assessing the state of iron overload in patients with SCD constitutes a diagnostic challenge because of the unreliability of serum ferritin levels which are elevated in inflammatory states [9]. Further investigation with a larger sample size and pituitary imaging is required to establish a direct cause and effect relationship.

Of interest, animal and human studies have shown a high prevalence of hypogonadism in the setting of chronic opioid use [10]. Although a significant proportion of patients with SCD are likely to be on chronic opioid treatment for pain control, data on opioid use was not collected in our study. This could be an interesting area for future research as studies have shown opioids to result in proliferation of vascular endothelial cells which might worsen other complications of SCD, particularly retinopathy [11].

Conclusion

The study has several limitations including a small sample size, its retrospective and cross-sectional design and lack of dynamic testing to assess the pituitary gonadotroph reserve. Despite these limitations, the study indicates that hypogonadism in most patients with SCD is likely to be of central origin. A well-controlled study with a larger sample size is required to investigate the exact etiology of hypogonadism in patients with SCD. The effects of iron overload and opioid use on endocrine function needs to be further studied as well. Identifying and treating hypogonadism in SCD is also expected to improve quality of life and prevent morbidity from potential sequelae of testosterone deficiency, including metabolic syndrome.

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Fig. 1. Distribution of LH levels in SCD men with normo- and hypogonadism. Median and interquartile range for serum LH are 5.6 (4.1, 7.6) and 1.6 (0.9, 3.7) mIU/ml, respectively (p = 0.001).

Fig. 2. Distribution of FSH levels in SCD men with normo- and hypogonadism. Median and interquartile range for serum FSH are 55.5 (3.8, 7.8) and 2.9 (0.8, 4.1) mIU/ml, respectively ($p = 0.01$).

Fig. 3. Distribution of ferritin levels in SCD men with normo- and hypogonadism. Median and interquartile range for serum ferritin are 332 (111, 608) and 119 (91, 823) ng/dl, respectively ($p = 0.71$).

Table 1

Characteristics of the study population (median and interquartile range)

	Testosterone levels	
	>250 ng/dl (n = 26)	250 ng/dl (n = 8)
Age, years	27.5 (20, 36)	34.5 (28, 37)
BMI	22 (21, 24)	28 (23, 32)
Testosterone, ng/dl	441.5 (414, 579)	100.2 (33.2, 178)
Hemoglobin, g/dl	9 (7.8, 10.2)	8.9 (7.8, 9.9)
Total bilirubin, mg/dl	2.3 (1.8, 4.2)	3.5 (2, 3.9)
Creatinine, mg/dl	0.8 (0.7, 1.2)	0.7 (0.7, 0.8)