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Research Article

Testicular Ultrasound Assessment in Thalassemic Men

Abstract

Objective: To evaluate testicular volume, varicocelle, hydrocelle, microlithiasis, semen parameters and measure serum FSH, LH, and Testosterone concentrations in young male thalassemic patients.

Design: Prospective study.

Setting: Tertiary care hospital.

Patients and Method: This study investigated 62 young adults with beta thalassemia (47 major, 15 intermedia), aged 18–41 years who underwent different chelation therapies. The patients' serum ferritin levels range was from 182 to 11053 ng/mL (mean 2067 ng/mL) at the time of study.

Results: The mean size of right testis was 11.4 ml and the mean size of left testis was 11.7 ml. In 3.2% of patients the testes volume was under 4 ml. Varicocele was seen in 11.3% of patients. Microlithiasis was detected in 4.8% of patients. Hydrocele was seen in only in 1.6% of patients. Hypogonadism was seen in 22.6% of patients.

Conclusion: This study suggests that in thalassemic men, testicular volume in ultrasound has significant correlation with concentrations of serum Testosterone, LH, FSH and sperm parameters.

Introduction

Beta thalassemia is a hereditary hemoglobinopathy which is mostly seen in Mediterranean countries. The appliance of appropriate chelation therapy in combination with on time transfusion has considerably added to the life expectancy of these patients [1]. In spite of the advancement of management, iron accumulation in different organs owing to frequent transfusions and also extramedullary hematopoiesis, leads to their diminished quality of life. Endocrinopathies are one of the most prominent complications in beta thalassemia patients. In fact, pubertal failure, sexual dysfunction and infertility, due to hypogonadism could be seen in 51% to 66% of these patients [2-8].

The lack of ability of a sexually active couple to accomplish pregnancy after 1 year of unprotected sexual intercourse is defined as infertility. In 30% of cases, this is solely secondary to male factors. In an extra 20% of cases, there is a male factor infertility component [9].

In general population, the etiologies of male infertility are multiple whereas in male β-thalassemia patients, iron deposition in the endocrine organs is typically considered to be the main cause of infertility [10].

The primary role of imaging is to define an anatomical cause of infertility. A comprehensive assessment is required for the most appropriate and cost-effective therapy to be delivered [11].

For primary evaluation of the scrotum, scrotal ultrasound seems to be an excellent technique since it can frankly reveal the testis and the peritesticular structures' abnormalities, such as varicocoeles and epididymal abnormalities.

The prevalence of scrotal abnormalities in infertile men has been reported to be between 38%-65%., in which 58%-67% have not been detected clinically [12,13]. These data shows that ultrasound evaluations could be helpful in detecting the cause of infertility.

Our endeavor in this study was to evaluate the testicular volume and scrotal abnormalities in male patients with Beta-thalassemia major and intermedia and assess their relationship with other factors influencing their fertility.

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Materials and Method

We conducted a prospective study between January 2001 and January 2003 at the tertiary care hospital in Tehran, Iran. The study included 62 males with Beta-thalassemia major and intermedia, whose ages ranged between 18 and 41 years. Among the patients, 52 had been regularly transfused since early childhood and underwent different chelation therapies using subcutaneous desferrioxamine and/or oral deferasirox and/or deferriperone.

Competence and cooperation were requisites for patients' participation. Excluded participants included those who used steroids or medications causing hyperprolactinemia.

Tanner's classification of testicular development was used to evaluate patients' puberty. Stage I (prepubertal genitalia) was defined as testicular size ≤4 mL (long axis of ≤2.5 cm), and adult genitalia was defined as size ≥25 mL (≥5 cm in length). The nonappearance of secondary sexual characteristics at the age of 14 years with a testicular volume of less than 4 mL was considered as delayed puberty [14]. Testicular volume was calculated with scrotal ultrasound. Images with transverse and longitudinal views of each testis were obtained, and length, width and height measurements were made using electronic calipers. The empirical formula of Lambert, length × width × height × 0.71 was used for the calculation of testicular volume.

Blood samples were collected from patients after an overnight fasting, for assessment of their basal LH, FSH, and Testosterone.

Conventional semen analysis was carried out after an abstinence interval of 3–4 days using manual procedures and light microscopy in the central hospital laboratory according to the last World Health Organization guidelines [15]. The semen analyzer was blinded to patients' names and diagnosis [16-18].

Iron overload was assessed by direct and indirect methods. It was evaluated by measuring serum ferritin level. Also T2* MRI of heart and liver was assessed for iron overload.

Version 16.0 of SPSS for Windows was used for data entry and analysis. Numeric variables were expressed as mean ± standard deviation. Results were analyzed by ANOVA, followed by the independent t test. $P \leq 0.05$ was considered statistically significant.

The study was approved by the university's ethical Committee. Prior to initiation of the study, patient informed consent was obtained.

Results

The age range of the patients was between 18 to 41 years. Their mean age was 27.2 years. Among the patients, 75.8% were major and 24.2% were intermedia and totally 83.9% were transfusion dependent. Age, type of thalassemia and transfusion dependency did not have significant correlation with any of the other assessed determinants in our patients ($p>0.05$).

The mean volume of patients' ejaculate was 2.3 cc. The mean concentration of sperm was 61.04 million per milliliter. Totally, 61.3% of patients had acceptable sperm concentration (≥15 M/ml) but 21% had azospermia and 22.4% had oligospermia.

The range of testes volume in our patients was between 1.2 ml to 29 ml. The mean size of right testis was 11.4 ml and the mean size of left testis was 11.7 ml. Only 3.2% of patients had testicular volume less than 4 ml which is indicative of the puberty process not being started. However, those patients who had lower testicular volumes significantly had lower ejaculate volume, lower sperm concentration, lower percents of motile and progressively motile sperms and also lower percents of normal morphologic sperms ($P = 0.04$). The frequency of hypogonadism was significantly higher in patients whose testicular volume was lower ($P=0.02$). Varicocele, hydrocele and microlithiasis were seen in 11.3%, 1.6% and 4.8% of patients, respectively.

The mean level of FSH was 3.7 mIU/ml, LH was 4.6 mIU/ml, and Testosterone was 4.8 ng/dl. The frequency of hypogonadothropic hypogonadism and hypergonadotropic hypogonadism was 16.1% and 6.5%, respectively. The mean level of serum ferritin was 2067 ng/dl. In 74.2% of patients cardiac MRI was normal. In 21% of patients hepatic MRI was normal. Nevertheless, no significant correlation was found between the iron overload determinants and testicular volume.

According to iron chelators, 50% of patients were using deferoxamine, 50% of patients were using deferasirox and 21% of patients were using deferiperrone. Utterly, iron chelators did not have any impact on testicular volume.

Discussion

Patients with beta-thalassemia put up with severe anemia and are reliant on blood transfusion, which is to blame for tissue hemosiderosis in these patients. On the other hand, successful male fertility necessitates all the process of spermatogenesis, epididymal maturation, sperm storage, sperm transport and accessory gland function to be normal. However, iron deposition in beta-talassemia patients affects all organ systems [19,20]. Multiple endocrinopathies, particularly hypogonadotrophic hypogonadism which considerably impacts their fertility is a common happening in polytransfused thalassemic patients [21,22].

In our study, the triangular correlation between hormones, testes' volume and sperms was confirmed.

In the study by Soliman et al., testostrone levels were correlated significantly with all the sperm parameters [23]. This was also true in our study and patients who had lower levels of serum FSH, LH, and testosterone, had significantly lower ejaculate volume, lower sperm concentration, lower percents of motile and progressively motile sperms and also lower testicular volumes. De Sanctis et al., showed that FSH, LH and testosterone levels were significantly lower in major thalassemia patients with acquired hypogonadism [24]. This statement was also true in our study. However, they

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documented that serum ferritin level >2000 ng/ml (severe iron load) was significantly more encountered in patients with acquired hypogonadism. In our study, level of serum ferritin and severity of iron overload in heart and liver MRI did not correlate with FSH, LH, testosterone levels and sperm parameters. It has been established that harm to the gonads from iron overload is an irreparable process, even if the iron level is corrected afterwards [25]. This demonstrates the significance of prevention of iron overload by the means of on time and appropriate iron chelation therapy. Moreover it affirms the demand of intensive chelation for β-thalassemia patients with normal puberty, in order to save the remaining functional cells.

In testicular microlithiasis (TM) multiple small foci of calcification are seen inside the testicular parenchyma [21], TM is most often diagnosed as an incidental finding throughout scrotum ultrasound. Its frequency varies broadly between studies and ranges from 0.6% to 9% [26-29]. Microlithiasis etiology in testis is unknown but the process is considered to involve the degenerating cells inside the seminiferous tubules, and fibrosis [30]. It is coupled with a few conditions including germ cell tumors, Klinefelter's syndrome, cryptorchidism, pseudohermaphroditism, alveolar microlithiasis, and infertility [31]. A number of studies have also reported testicular cancer in patients with preexisting testicular microlithiasis [32-34]. The correlation between TM and infertility is still vague. Several authors have reported patients with TM and infertility concurrently [35], signifying that the bond connecting these two issues could be more than coincidental. Kessaris and Mellinger have reported that 1.3% of the infertile males they had evaluated with ultrasound were identified to have TM [36,37]. Aizenstein et al. state a rather higher occurrence of TM (2.8%) in 180 otherwise healthy, asymptomatic infertile male patients in their study [38]. On the other hand, reviewing the literature, in only one study the Incidence of testicular microlithiasis in patients with β-thalassemia major was reported 12.1 % [39]. In our study, TM was detected in 4.8% of patients and did not correlate with testicular volume, sperm parameters and hormonal levels.

Varicocele is defined as an abnormal venous dilatation of the pampiniform plexus. It is thought to cause pain and discomfort, developmental failure of testis, or infertility [40]. Varicocele's prevalence in adolescents and adult males is about 20% but in infertile males is up to 40%. The exact relation between varicocele and infertility is not evident. It is obvious that after surgical interventions for varicocele, sperm quality and fertility rate improves [41,42]. In β-thalassemia patients no report about the incidence of varicocele was seen in the literature review, though in our study, 11.3% of patients had varicocele.

It is thought in hydroceles, the liquid pressure in the tunica vaginalis can cause a warm environment or a decrease in testicular circulation affecting the spermatogenesis. Studies have reported that the incidence of hydrocele in infertile males compared with controls was considerably higher [43,44].

Fatherhood is indubitably one of the main factors which could improve the thalassemic patients' quality of life, therefore, the issue of male fertility and its affecters should be considered in mind. The evaluation of infertile male patients is crucial in order to recognize potentially treatable causes of infertility and a key component in this trail could be scrotal ultrasound.

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