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Original Article

Distinguishing non-obstructive azoospermia from obstructive azoospermia in Taiwanese patients by hormone profile and testis size

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Abstract

Background: An accurate diagnosis of the etiology of azoospermia is crucial, as sperm retrieval methods differ between patients with non-obstructive azoospermia (NOA) and obstructive azoospermia (OA). The aim of this study was to determine hormone and testes size cutoff values to identify the cause of azoospermia in Taiwanese patients.
Methods: The medical records of azoospermic patients were retrospectively collected from April 2008 to July 2016, including hormone profile, physical examination findings, and testes size. Bilateral testes biopsies or microdissection testicular sperm extraction were performed in all patients for a definite diagnosis. The diagnostic parameters used to distinguish NOA from OA were analyzed using the *t*-test and receiver operating characteristic curves.
Results: A total of 51 patients with OA and 156 with NOA were included. The mean levels of testosterone (4.5 vs. 3.4 ng/ml) and E2 (26.3 vs. 19.2 pg/ml) were significantly higher in the OA group, whereas the levels of follicular stimulating hormone (FSH) (5.6 vs. 25.4 mIU/ml) and Leutinizing hormone (LH) (3.7 vs. 11.6 mIU/ml) were lower. Receiver operating characteristic curve analysis revealed that FSH and right testis size were the best individual diagnostic predictors. Using a combination of FSH >9.2 mIU/ml and right testis size <15 ml, the positive predictive value for NOA was 99.2% and 81.8% for OA.
Conclusion: A combination of FSH >9.2 mIU/ml and right testis size <15 ml was a strong predictor of NOA in our Taiwanese patients.

Keywords: Azoospermia; FSH; Hormone; Testis

1. Introduction

Azoospermic males comprise 1% of the general population and up to 10−20% of those presenting to infertility clinics.[1] Azoospermia is defined as the absence of spermatozoa in two different ejaculated semen samples after centrifugation (1000×*g* for 15 min),[2,3] and the etiology can be classified into three principle categories: pre-testicular, testicular, and post-testicular.

An accurate diagnosis of the etiology of azoospermia is crucial and mandatory for these patients, as the treatment approach differs according to the cause of azoospermia. Male hypogonadotropic hypogonadism, the most common cause of pre-testicular azoospermia, is treated with gonadotropin replacement therapy, whereas restoration of fertility may be possible for patients with post-testicular azoospermia caused by reproductive tract obstruction after recanalization. For patients with testicular azoospermia caused by congenital (genetic abnormalities),

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acquired (testicular torsion, trauma, mumps, surgery and varicocele) or idiopathic disorders, microdissection testicular sperm extraction (TESE) has been proven to be a preferable surgical technique in terms of higher sperm retrieval rate and low complication rate compared with conventional TESE.[4−6]

In clinical practice, azoospermia can be categorized as obstructive or non-obstructive. Obstructive azoospermia (OA) is less common than non-obstructive azoospermia (NOA), and accounts for 15−20% of all men with azoospermia.[7] Testicular biopsy plays an important role in the diagnosis of OA, however hormone profiles and testicular size have also been used to predict the cause of azoospermia by using a cutoff value of 7.6 mIU/ml for follicular stimulating hormone (FSH) and a testicular long axis of 4.6 cm.[8] However compared to Caucasians, Asian males tend to have higher FSH and smaller testes,[9,10] and as a result it is essential to establish reference points for Asians.

The aim of this study was to determine the optimal cut-off values for testes size and endocrine profile for Asian males to predict the cause of azoospermia. Azoospermia related to hypogonadotropic hypogonadism is classified as being NOA and it can be identified by hormone profile, therefore these patients were not included in this study.

2. Methods

2.1. Patients

From April 2008 to July 2016, a total of 217 azoospermic patients with no history of cryptorchidism or testicular-related surgery were enrolled, including 166 with NOA and 51 with OA. Ten hypogonadotropic hypogonadism patients were excluded, and the remaining 156 patients with NOA were analyzed. Every patient underwent a detailed examination to identify the etiology of azoospermia, including a detailed history, physical examination, two consecutive semen analyses, hormone profile (FSH, Leutinizing hormone (LH), testosterone, prolactin, and estradiol), chromosome karyotyping, and Y chromosome microdeletion. Bilateral testicular size was measured by a single andrologist with the assistance of an orchidometer. To differentiate between OA and NOA, bilateral testes biopsies or microdissection TESE were performed for a definitive diagnosis. The study was performed according to the Taipei Veterans General Hospital approved Institutional Review Board protocol (IRB number: 2017-07-013CC).

2.2. Statistical analysis

The Student's *t* test was used to compare hormone profiles and testes size between the OA and NOA groups. Results were expressed as mean ± standard deviation and analyzed using SAS ver.9.0, and a *P* value less than 0.05 was considered to be statistically significant. Receiver operating characteristic (ROC) curves were used to determine the appropriate cut-off values for hormone profile and testes size to discriminate NOA from OA. Accuracy was assessed by the area under the ROC curve (AUC), and results were considered to be excellent for AUC values between 0.9 and 1, good for AUC values between 0.8 and 0.9, fair for 0.7−0.8 AUC values, poor for 0.6−0.7 AUC values, and failed for AUC values between 0.5−0.6.[11]

3. Results

The demographic data and characteristics of the patients are listed in Table 1. The mean levels of testosterone (4.5 vs. 3.4 ng/ml) and E2 (26.3 vs. 19.2 pg/ml) were significantly higher, and the levels of FSH (5.6 vs. 25.4 mIU/ml) and LH (3.7 vs. 11.6) were significantly lower in the OA group. The NOA group had a significantly smaller bilateral testes size compared to the OA group ($p < 0.0001$). There were no differences between the two groups in age or prolactin level. In order to determine the cutoff values to discriminate between the two groups, we performed ROC curve analysis.

Fig. 1 depicts the ROC curve for FSH, LH, testosterone, E2, right testis and left testis size. Overall, FSH had the best response in terms of AUC (with a 95% CI for the area being between 0.9253 and 0.9897), followed by right testis (with a 95% CI for the area being between 0.8680 and 0.9552), left testis (with a 95% CI for the area being between 0.8587 and 0.9489), LH, E2 and testosterone. A cutoff value of 9.2 mIU/ml for FSH could discriminate the etiology of azoospermia with a sensitivity of 89.7% and a specificity of 90.2%, and using a cutoff value of right testis size of 15 ml, had a sensitivity of 76.3% and a specificity 92.2% (Fig. 2). Using a combination of FSH >9.2 mIU/ml and right testis size <15 ml (Table 2), the positive predictive value for NOA was 99.2% and 81.8% for OA.

4. Discussion

The hypothalamic-pituitary-gonadal (HPG) axis is critical for the development of reproductive organs and spermatogenesis,[12,13] and three different activation periods of the HPG axis have been identified. At the 8th week of gestation, the testes of the fetus secrete testosterone and anti-Müllerian hormone to induce masculinization, Wolffian duct differentiation, and regression of the Müllerian duct to prevent the formation of a uterus and fallopian tubes.[14,15] The second period of testosterone surge starts at 1 week of age and peaks to a pubertal level at 1−3 months. The elevated testosterone

Table 1
Mean serum levels for the endocrine profile and testis size of the patients with different etiologies of azoospermia.

Diagnostic parameter	Obstructive azoospermia	Non-obstructive azoospermia	*p*
FSH (mIU/L)	5.6	25.4	<0.01
LH (mIU/L)	3.7	11.6	<0.01
Testosterone (ng/ml)	4.5	3.4	<0.01
Prolactin (mIU/L)	11.5	11.4	0.95
E2 (pg/ml)	26.3	19.2	<0.01
Right testis (mL)	9.9	17.6	<0.01
Left testis (mL)	9.8	17.4	<0.01

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