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TESTICULAR REGRESSION SYNDROME: OCCURRENCE IN THREE SIBLINGS

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Three young siblings with micropenis, small atrophic testes and urethral opening at the tip of the penis are described. No other congenital anomalies were noted. The three siblings were given 200 mg IM monthly long acting testosterone for 3 months to increase the length of the penis and all of them responded well. These data support the clinical diagnosis of embryonic testicular regression syndrome. Bahrain Med Bull 1996;18(2):

Normal sex differentiation of the XY mammalian foetus is mediated by the foetal testis, which sequentially determines Mullerian duct regression, Wolffian duct stabilization, closure of the urogenital sinus and urethral groove and growth of the phallus**1.**

In human, testicular hormone insufficiency in the male foetus during the second half of pregnancy leads to micropenis without structural abnormalities of the genital tract[2,3], whereas 46XY patients with total gonadal aplasia are usually phenotypic females[4]. Therefore male and female phenotypes are part of the spectrum of this order. Thus at one end there is a group with female external and internal genitalia where the insult to the testes occurred before 8 weeks of gestation (46 XY gonadal dysgenesis), and at the other end and when the insult to the testes occur after the 14th week of gestation resulting in anorchia where the internal and external genitalia are normal, but no gonadal tissue. In between these two ends, a variable degree of ambiguity of the external and internal genitalia may happen (dysgenetic male pseudo hermaphrodite).

Bergada and associates were the first to report four cases with this association in 1962[5].

We report three siblings with male phenotype, 46XY karyotype and atrophic testes and describe their response to treatment with testosterone.

THE CASES

Three siblings were referred to our Paediatric Endocrinology

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Clinic, Qatif Central Hospital, Saudi Arabia, because of short stature. They were the sons of unrelated 35 years old mother and 50 years old father. There was no history of sexual abnormalities in either family.

The three siblings aged 9, 10 and 16 years. The height and weight of the first child was in the 25th percentile, the second between the 5th and 10th percentile and the third in the 10th percentile. The stretched penile lengths of the patients were 2 cms, 2.5 cm, and 4 cm respectively. In all, the scrotal sacs were rudimentary and the testes very small and atrophic. The urethral openings were at the tip of the penis. The remainder of the examination was within normal limits.

Table 1. Results of investigations on the three siblings

Testosterone base line (N=0-10 ug/dl)	Testosterone post B-UCG	LH (N=1-9 mlU/L)	FSH (N=1-5 mlU/L)	Cortisol (N=5-12 ug/dl)	Chromosomes	Age of patients
<0.2nmole/1	<0.2nmole/1	1.6miu/l	0.84miu/l	14ug/dl	46XY	DH-9
<0.2nmole/1	<0.2nmole/1	1.2miu/l	0.59miu/l	13ug/dl	46XY	R-10
<0.26nmole/1	<0.29nmole/1	2miu/1	1miu/1	11ug/dl	46XY	M-16

Table 1 shows the laboratory investigations on the three siblings. The testosterone levels of all the patients were very low (< 0.2 Nome/L). After stimulation with B human chorionic gonadotropin (2000 units/m2/day for 3 days) there was no increase in the testosterone level indicating testicular failure. The cortisol level, growth hormone dynamic studies, insulin hypoglycaemic tests were also normal. The LH and FSH were at the prepubertal level.

Chromosome analysis showed a normal male karyo type 46,XY in each patient.

All 3 siblings were given long acting testosterone 200 mg IM monthly for 3 months to increase the length of the penis. All of the patients responded very well to treatment as shown by comparing the initial penile length in Figure 1 with the post-treatment length in Figure 2.

DISCUSSION

Various terms have been used to describe the spectrum of genital anomalies resulting from cessation of testicular function during the middle phase of male sex differentiation from 8-14 weeks of gestation. The term vanishing testes syndrome was used in 1957 to describe a heterogeneous group of male pseudo hermaphrodites where the testes vanished due to obscure reasons at some time during the process of male sex differentiation. These patients have 46,XY karyotype. At one end of the spectrum is the group of patients with female external and internal genitalia in whom the deficiency of embryogenic testicular function presumably occurred before 8 weeks of gestation. This condition is called 46,XY gonadal dysgenesis[6]. Lack of testicular function between 8-10 weeks of gestation leads to ambiguous genitalia and variable development of the internal genitalia. This form of male pseudohermaphroditism has been referred to as XY gonadal agencies[7-9].

Loss of testicular function after the critical phase of male differentiation (12-14 weeks of gestation) results in anorchia, a syndrome characterised by the finding of normal male differentiation both internally and externally but no gonadal tissue. This syndrome can occur sporadically or may be familial[10-12], as described by Bergada and colleagues, the first to report four cases with this association in 1962[5]. In 1980, Josso and Briard[13] reported two siblings with variable degrees of sexual ambiguity; one was a phenotypic male with micropenis, while the other was a phenotypic female with slight fusion of the genital folds. In 1991, Smith et al1[4] reported 77 cases of testicular regression syndrome characterised by rudimentary epididymis and spermatic cord with absence of testicular tissue.

The clinical and laboratory data on our patients are consistent with a diagnosis of familial anorchia. The patients are 46, XY males who have complete fusion of the labio-scrotal folds, micropenis with normal urethral opening and atrophic testes which do not respond to B-HCG stimulation test. No further tests such as genitogram or testicular biopsy could be done, because the parents denied permission for further investigation. Despite non responsive tests to B-HCG

stimulation, neither MRI or CT scan or laparotomy has been entertained because the testes were felt in the scrotum.

CONCLUSION

Our patients fit with the diagnosis of testicular regression syndrome as described by Bergada and colleagues and other authors. In view of the complete fusion of the labio-scrotal folds, we believe that the insult to the testes in these siblings must have occurred after the 12th week of gestation. The diagnosis of anorchia in this family indicates a genetic component in its aetiology, but sheds no light on the pathogenesis of embryonic testicular degeneration.

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