ENDOCRINE ASSESSMENT OF THE SUBFERTILE MALE IN SAUDI ARABIA

WAYNE PERRY[1]

Abstract

Twenty-three Saudi males attending an endocrine clinic because of unexplained azoospermia or severe oligospermia (< 5 million/ml) were reviewed. Surgically remedial causes such as varicocele and obstruction were excluded. Investigations included a hormonal profile (serum follicle stimulating hormone FSH, luteinising hormone LH, prolactin and testosterone) chromosomal analysis and testicular biopsy. Fifteen patients had adult seminiferous tubule failure (ASTF) of unknown aetiology, 3 mumps orchitis, 2 Klinefelters syndrome, 2 Sertoli cell only syndrome and 1 hypogonadotrophic hypogonadism.

Five patients with absent spermatogenesis on histology showed raised FSH levels. Nine patients with depressed spermatogensis histologically had normal FSH levels. This finding shows that raised FSH levels indicate extensive germinal epithelial loss and normal levels partial damage which by implication might be susceptible to gonadotrophin or other therapy. Twenty-two of the 23 patients were normally androgenised and LH testosterone values were of limited help. Mildly raised prolactin levels were seen in some patients (up to twice the upper limit of normal) but these were interpreted as stress responses and only one patient had a value > 356 IU/L on repeat testing, and his sperm count showed no response to bromocriptine therapy.

Introduction

There is some evidence to suggest that the prevalence of subfertility in this country may be higher than in the United States.[1] Only further epidemiological studies can establish this point but it is already clear that the frequency of adult seminiferous tubule failure (hypospermatogenesis and maturation arrest) of unknown aetiology is an important subset.[1,2] The aim of this paper was to analyse the causes of unexplained severe subfertility (sperm count < 5 million/ml) in which surgically remedial conditions such as varicocele and obstruction were excluded.

The value of serum FSH, LH and testosterone in the evaluation of the subfertile male was recently re-examined[3] Serum FSH appeared to rise only when germinal epithelial damage was extensive and may indicate an irreversible development. It was important to corroborate this finding for the Saudi group. LH and testosterone were considered to be of little value in patients without clinical evidence of androgen de-

[1]Department of Medicine, Colleges of Medicine & Medical Sciences, King Faisal University, Dammam, Saudi Arabia.

ficiency. The contribution of prolactin secreting tumours to male infertility is probably small[4] but would be eminently treatable and since excess prolactin is secreted in 70% of all pituitary tumours[5] it is a valuable screening test for hypogonadism from this cause. Previous reports have implicated hyperprolactinaemia as a cause of depressed spermatogenesis [6,7] and a recent report from Saudi Arabia indicated this may be a significant factor[8].

Patients and Methods

Twenty-three Saudi males aged 18–34 each with a mean of three sperm counts <5 million/ml were screened to exclude any other contributing cause to infertility such as diabetes, renal failure or drugs[9]. Patients were referred either from the urologist, primary care physician or by self-referral. The youngest patient aged 18 presented because of small genitalia and was subsequently shown to have hypogonadotrophic hypogonadism[10]. Twenty-one patients presented because of childless marriages and awareness of their low sperm count from the date of marriage varied between eight months and eight years. Only one patient presented with secondary sterility having previously had three children but no further child in the last five years. All these patients were normally androgenised.

Specific hormonal investigations in 22 patients included serum FSH, LH, prolactin and testosterone. These estimations were made with standard Amersham RIA kits (the Radiochemical Centre, Amersham, Buckinghamshire, England). Chromosomal analysis on whole blood was indicated in five patients and was performed by J.S. Pathology Services Ltd., 80–81 Harley Street, London, W1. Testicular biopsy with haematoxylin and eosin staining was performed in 15 patients. Testicular histology was reported by different observers and reviewed by the author. To avoid errors of precise interpretation as to the degree of or stage of arrest of spermatogenesis they were classified into three broad categories. Stage I showing essentially normal spermatogenesis, Stage II in which depression or arrest of spermatogenesis at various stages occurred in some or most tubules and Stage III in which most or all tubules showed a complete absence of germ cells. One patient refused biopsy and three were reluctant to undergo the procedure, in four patients it was not indicated (two Klinefelters, one hypogonadotrophic hypogonadism and one post-mumps orchitis).

Results

The diagnoses in the 23 patients are shown in Table 1. Investigations are summarised in Table 2 according to the level of serum FSH. Testosterone levels are not recorded as only one patient (23) had a frankly low level accompanied by features of hypogonadism, all other patients had levels within the normal range (3–10 ng/ml) consistent with their normal male features. Patients 1 and 4 with a clear history of mumps orchitis had histology which was indistinguishable from patient 3 with ASTF. Patient 2 had the classic "windblown" appearance of the Sertoli cell only syndrome and was reported in detail elsewhere.[1,10] Patient 5 had a similar histological appearance but sperm were present in the semen indicating that some spermatogenesis was taking place. Patients 6, 11, 13, 15 had no confirmatory histological evidence of ASTF but in the absence of any other factor this diagnosis has been made by exclusion. Neither of the patients with Klinefelters Syndrome (9, 10) had gynaecomastia, they were normally

Table 1 Diagnoses in 23 patients referred to an endocrine clinic with sperm count < 5 million/ml

15	Adult seminiferous tubule failure (1 prolactin raised)
3	Mumps orchitis
2	Klinefelters syndrome
2	Sertoli cell only syndrome
1	Hypogonadotrophic hypogonadism

Table 2

Patient	*Serum FSH (nr2–16 mIU/ml)*	*Serum LH (nr4–20 mIU/ml)*	*Sperm Count (million/ml)*	*Testicular biopsy or other remarks* Stage	
1	150.0	33.3	0	III	Post mumps orchitis
2	58.0	28.0	0	III	Sertoli cell only
3	56.0	24.0	0	III*	
4	49.0	11.8	0	III	Post mumps orchitis
5	36.4	20.6	0.5	III	Sertoli cell only
6	25.0	13.3	0	–	Probable ASTF
7	16.0	19.0	0.8	II*	
8	15.7	12	1.5	II*	
9	—	—	0	–	XXY
10	15	27	0	–	XXY
11	10.7	12	3.9	–	Probable ASTF (biopsy refused)
12	10.7		1.9	–	Post mumps orchitis
13	10.0	11.3	0.8	–	Probable ASTF
14	6.3	18.5	0	II*	
15	5.7	5.3	0.4	–	Probable ASTF
16	5.0	3.0	0	II*	
17	4.4	4.5	4.0	I*	
18	4.0	6.0	0	II*	
19	4.0	7.0	1.0	II*	
20	3.0	13.0	3.0	II*	
21	2.0	4.0	4.5	II*	Prolactin (720, 420 IU/l)
22	2.0	6.0	0	II*	
23	<1.0	<2.0	0	–	LHRH deficiency (Ref. 10)

*Adult seminiferous tubule failure (hypospermatogenesis and maturation arrest)

androgenised with pea-sized testes. Only one patient (17) had normal histology with severe oligospermia.

Figure 1 shows the clear relation between absent spermatogenesis on histology and raised FSH levels. Figure 2 shows the wide scatter of serum FSH in patients with azoospermia (none of whom had obstruction): five out of ten having normal levels. In 11 patients in which sperms were present only one had a raised FSH and applying a simple X^2 test of independence to this group the result was significant at the .05 level. This suggests that when some sperm are present in semen FSH levels will be normal and so sufficient spermatogenesis is occurring to cause normal feedback inhibition of FSH.

Prolactin levels are shown in Figure 3. Most patients had normal levels taken after the first interview. Six patients had mildly raised levels which on repeat testing one week later were almost within the upper range of normal. Patient 21 with the highest prolactin level showed a considerable fall on bromocriptine 2.5 mg b.d. but there was no change in his sperm count after two months therapy.

Discussion

This study confirms the importance of ASTF of unknown aetiology as a major factor in male subfertility in Saudi Arabia. However out of the five patients with absent spermatogenesis on histology only one had this diagnosis and suggests that the natural history of the disorder extends over some years before total failure occurs. A rise in serum FSH indicates total germinal failure (Figure 1) and this finding supports a recent comprehensive study of British subjects[3] Thus the response of FSH is a late one and most patients with severe oligospermia have normal serum FSH (Figure 2). This distinction was shown to have practical consequences for treatment. Patients with raised values have been shown not to respond to clomiphene therapy whereas oligospermic pa-

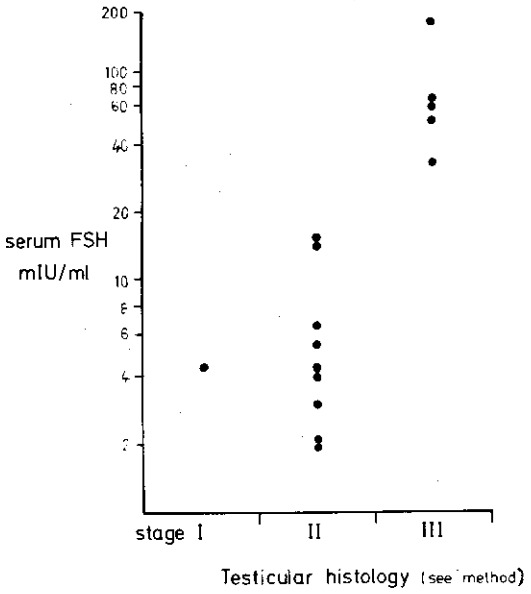

Figure 1 Note raised FSH levels when spermatogenesis is absent on histology.

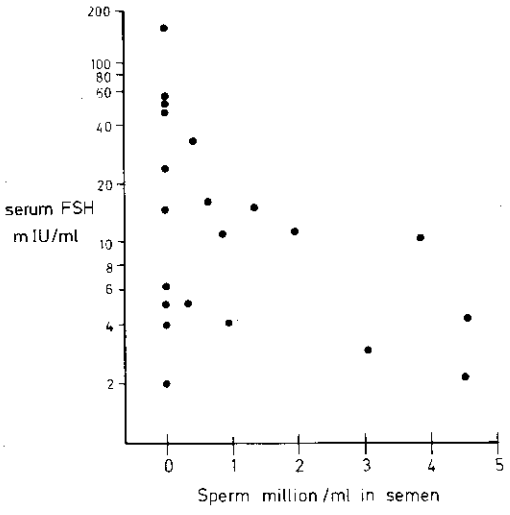

Figure 2 Note the wide scatter of FSH values in patients with azoospermia of non-obstructive cause and normal values when some sperm are present in semen.

tients with normal FSH responded well to clomiphene 25 mg daily for 6–12 months[11].

LH and testosterone levels were of little help in normally androgenised patients confirming

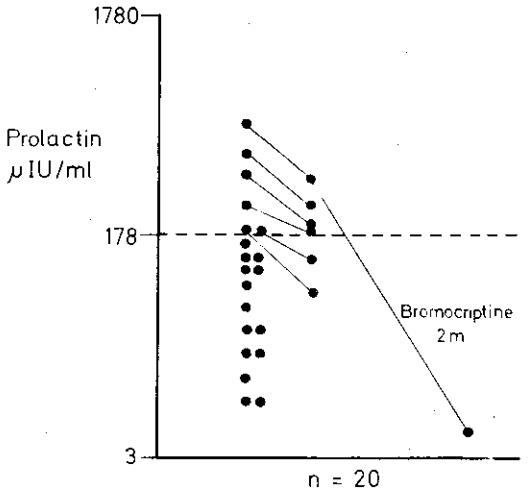

Figure 3 Mildly raised prolactin levels fell on repeat testing one week later. In the patient with highest prolactin level no sperm response was seen to bromocriptine treatment 2.5 mg b.d. for two months.

the British study.[3] However some patients do have raised LH values with testosterone in the lower range of normal with normal or raised FSH values (unpublished data). This may indicate Leydig cell dysfunction and a trial of high dosage testosterone should be considered.[12,13]

Hyperprolactinaemia does not appear to be making a significant contribution to male infertility in this country. The explanation for initially raised levels is the stress response of prolactin to the first interview and venepuncture.[14] However prolactin screening remains justified as the occasional case may be improved by bromocriptine therapy.[4]

Both patients with Klinefelters syndrome had normal buccal smears reported and it is now the author's practice to go straight to chromosomal analysis on whole blood in suspected patients with chromosome abnormalities. The aetiology of the Sertoli cell only syndrome remains an unsolved problem. Patient 2 was a pure example of this syndrome but patient 5 although having the histological appearance did have some sperm in semen. This again suggests a natural history of loss of spermatogonia over a period of years. However the possibility of a congenital defect with absent or remnant spermatogenesis similar to the example of idiopathic hypoparathyroidism remains an important possibility in this intriguing disorder.

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CARDIAC COMPLICATIONS IN HAEMODIALYSIS PATIENTS

M. SOLIMAN,[1] A. SOLIMAN,[1] M. EL-KHODARY,[1] R. BARSOUM,[1] E. EL-GHONAIMY,[1] O. EL-KHASHAB,[1] M. ABOU-ZEID,[1] and A. HASSABALLA[1]

Abstract

Cardiac complications are the leading cause of death in patients on regular dialysis treatment (RDT). These complications are felt to be accelerated by dialysis. We studied 31 patients on RDT and 15 control subjects. Clinical data and ECG were recorded, and serum levels of LDH (total, heat stable), CPK and SGOT were estimated. Hypertension and cardiovascular symptoms were found in 23 patients, pericarditis in 8 patients, ECG evidence of left ventricular hypertrophy in 23 patients and of infarction in 4 patients. Serum levels of LDH (total, heat stable) were significantly elevated (247, 180 I.U.) in RDT patients compared to controls (113, 26 I.U.) ($p<0.0.5$). In contrast CPK activity was significantly lower in RDT patients (11.9 I.U.) than in controls (21.7 I.U.) ($p < 0.05$). Meanwhile there was no change in SGOT activity.

We conclude that: (1) There is a high prevalence of cardiac complications in RDT patients; (2) Knowledge of the enzymatic changes in RDT patients may avoid false clinical interpretation of myocardial ischaemia.

Introduction

Cardiovascular complications are very common in patients receiving regular dialysis treatment (RDT). They account for more than 50 percent of deaths in patients with chronic renal failure. In fact no cardiovascular complication spares the patients with chronic renal failure[1,2] In chronic regular dialysis patients, several known risk factors for coronary heart disease are present. A history of hypertension[3] lipid abnormalities[4] and vascular calcification are commonly found[5] Other possible contributing factors include the presence of chronic severe anaemia[6], volume overload[7] resulting from A-V fistula, presence of cardiotoxic substances[8] and acetate used in the dialysate[9]. However, the relationship of these factors to the development of heart disease in patients with renal failure is not clear. Pericarditis complicating uremia in dialysis patients is frequently encountered. The reported incidence of pericarditis and/or pericardial effusion is from 6.5–50 percent and some controversy exists regarding its aetiology[10].

The diagnosis and management of cardiovascular complications in general have been discussed extensively during the last ten to twenty years. All the new diagnostic techniques are applicable to patients with chronic renal failure and include echocardiography, cardiac

[1]Nephrology and Chemical Pathology Departments, Faculty of Medicine, Cairo University.