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Testicular Feminization Syndrome

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HISTORY

A young girl, aged 17, presented in Gynaecology Clinic with history of Primary Amenorrhea & Maldevelopment of secondary sex characters, noticed by the patient for the last 2–3 years. At birth her mother had noticed a swelling on the right side of vulva, which gradually subsided in her infancy. She was a bright young girl, who liked sports and participated in games at the national level. One of here maternal cousin had primary amenorrhea but she was never investigated.

ON PHYSICAL EXAMINATION

She was good looking, five feet & eight inches tall girl with a stout built. Gynaecological examination and examination of secondary sex characters, revealed that she had attractive feminine features, smooth and hairless skin, good scalp hair, breast developed, but not of the size as expected with her built. Axillary and pubic hair scanty with concave upper pubic hair line. No palpable gonadal mass in either groin was felt. The clitoris was hypertrophic, labia majora normal and labia minora poorly developed and fused at the dorsal surface of the enlarged clitoris. Vagina was short and ended blindly.

The following investigations were carried out:-

Buccal Smear for Barr Bodies	Chromatin Negative
Serum FSH-50 miu/ml (normal (2-20)	High
Serum L.H.-60miu/ml (normal (4-40)	High
Serum Testosterone 54 ng/ml normal (47-49)	Normal
Serum Prolactin 2-1 ng/ml	Normal
Urinary 24 hours 17 Ketosteriods	8 mg/24 hours Normal (6-12)

Ultrasound of pelvis failed to demonstrate the presence of uterus or ovaries X-ray chest was negative. Radiologically bone age was compatible with chronological age. Intravenous urography was normal. Karyotyping was done at National Institute of Health, Islamabad. Autosomes 44, Sex chromosomes xy.

In view of the above history, physical examination and the investigations, a diagnosis of TESTICULAR FEMINIZATION SYNDROME was made. The situation was explained to the parents and they were counseled about the future of their ward, who has now been brought up as a a female and would continue to stay as a female. Their consent for carrying out any operative procedure was also obtained.

EXAMINATION UNDER ANAESTHESIA,

Diagnostic laparoscopy and laparotomy was decided. Clitoris was (4.5 cm x 1.5 cm x 1.5 cm) fused with poorly developed labia minora. Labia majora normal. The vagina was 2" long. Gonads (testes) were not palpable in either labia or Inguinal canal. At Laparoscopy uterus and Fallopian tubes were absent. An oval mass looking like gonad was noticed at pelvic brim on the left side. On the right side no gonadal mass was noted. Laparotomy was carried out by Pfannenstiel incision. Uterus and Fallopian tubes were not visualised. On the left side of the pelvic brim, an oval structure (4x3x1 cm) with white glistening surface was attached to the peritoneum, on slit incision of this mass, seminiferous tubules like tissue protruded out from tunica albuginea. Left orchidectomy was carried out.

On the right the gonad was discovered under the right rectus muscle above deep inguinal ring. Right orchidectomy was carried out. Patient had an uneventful post operative recovery. She was prescribed 0.05 mg Ethinyloestradiol twice daily to achieve better development of the breasts.

Histopathology revealed, (i) Enlarged clitoris with, well developed corpora cavernosa, with tunica ulbuginea. (ii) Atrophic but partially functional testes.

DISCUSSION

A better name for testicular feminization syndrome is androgen insensitivity syndrome and though it is a rare condition, yet a well recognized entity. Prader designated an incidence of one in 29000 males. In 1953 Morris collected 80 cases from the literature and added two of his own. The disease appears to be due to insensitivity of the sex end organs to circulating androgens. This anomaly appears to be inherited by a X-linked recessive or sex-limited autosome dominent gene. It may occur in more than one members of the family. The etiological mechanism is probably faulty androgen binding in the end organ cell cytoplasm. In a genetic male i.e XY fetus, differentiation of the testes is evident at 7 weeks gestation, under the influence of the Y-chromosomes through H-Y antigen. The developing testes produces Anti mullerian hormone which inhibits the development of the Mullerian system in an XY fetus and causes its regression, where as the production of testosterone in the now developing testes, gives rise to the development of male type external genitalia and the Wolffian system. When end organ insensitivity exists because of genetic predisposition, ambiguity of the genital organs will develop, as in this case, despite the fact that the genetic sex is XY.

Patients with this disorder are usually reared and grown as females These patients are known to be attractive females, with well developed breasts, feminine voices, good scalp hair scanty axillary and pubic hair. The patients seek medical attention only when they fail to menstruate. These individuals are phenotypic female with male karyotype. Testes in these patients are usually normal in size and lie either in the groin or abdomen, as in this case. The seminiferous tubules in these testes are small and immature, but at times they may be functional. There is absence of ovaries, uterus and tubes & vagina is partially developed, with fused labia. The clitoris may or may not be enlarged. After adequate counseling with the patients and their parents, it is best that these individuals continue to live as females. It is best to remove the testes located in the abdomen, for fear of development of cancer in these organs, for the reported incidence of cancer is about 10%, mostly malignant seminoma, if the tests continue to reside in the abdomen.

QUESTIONS

(Dr. Parvez)

Q. Why Bilateral orchidectomy was done?

A. Incidence of malignant seminoma in the Juntra peritoneal testes is reported to be as much as 10-30 depending on longevity of such residence. Bilateral orchidectomy is advisable in patients who are going to live as females for the above stated reason.

(Dr. Bashir)

Q. Why this patient who is a genetic male, was not helped to become a male?

A. This patient who has been reared and grown as a girl and who is now well adjusted in her gender role as a female will pose uncountable psychological problems if an attempt is made to allocate her to male sex. Also to provide here with functional phallus will not be possible.

(Dr. Javed)

Q. 1. What is the role of anti Mullerian hormone?
ii. Was any element of vas deference found at operation.

A. i. The anti Mullerian hormone which begins to be formed at 9th week by sertoli cells of the developing testes acting in unilateral fashion, causes the regression of the Mullerian duct system in an XY fetus.

ii. No element of vas was found at operation.

Q. Where was the right testicle situated?

A. Right testicle was extra peritoneally, situated under the right rectus muscle just above the deep inguinal ring.

DR. QAMAR ZAMAN (*Cons. Obs & Gynae.*) : The whole subject of intersex as you may have realised from these transparencies is a complex one and it is very difficult to read, very difficult to comprehend and very difficult to transmit to an audience and that is why in the earlier part of this session, I noticed a few of you sleepy. To put things in certain prospective, you should understand defination of your ownself first.

What you are? How you are? and why you are?

These are six definations into which those of us who are male and those of us who are female will fit in.

First is the chrososomal sex. Males have XY and female will have XX chromosomes and in this business of chromosomes a lot can happen e.g. deletions, dislocations, translocation and mosacism.

Next is what is one's gonadal sex, whether one has testes or ovaries.

The third is the external genitalia where really the sex is allocated by Dais - and Obstetricians at birth to most of us.

Next is the development or possession of Internal genitalia which obviously go through a certain process of development.

Next most important will be the Hormonal status that is produced by sex gonad present in the body.

Then of course is the sex of rearing and this is the part where most of the questions are really related to.

Next is the gender role as how we conduct ourselves, how we talk, how manly, one is - and how feminine one is!

Now as you would realise, that to be put in these seven categories, it requires a lot of effort to be a male and it is not so easy to have put this apparently girl looking individual into a male role.

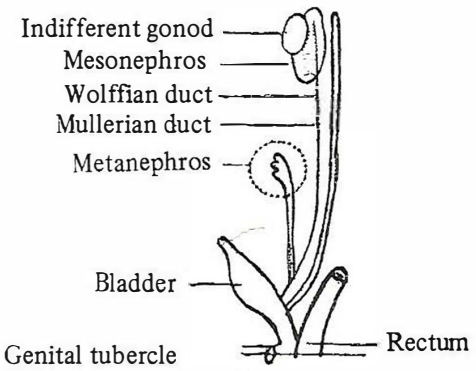
It is very important now, once to look and I would like for the rest 3-4 minutes to take you, all-where everyone began, our journey of life.

First beginning of life is of course the meeting of spermatozoon which carries either an 'X' or 'Y' chromosome and ovum which always carries the 'X' chromosomes. It will either give rise to an XX embryo an XY embryo and that will be the genetic sex. Role of the sex chromosomes is only one and that is to give direction for further growth to the primitive gonad.

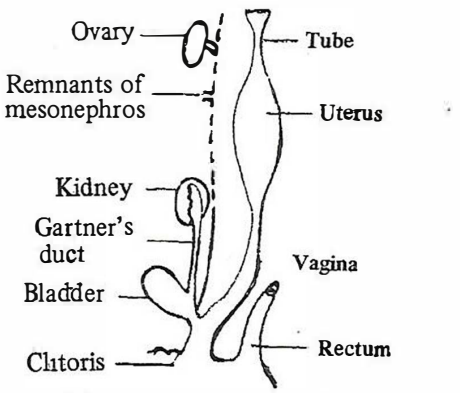
Upto about 6 weeks or so of the gestational age, the primitive gonad which is sort of referred overthere has got no sex whatsoever. It has 3 types of cells which have the potential of either growing into the testes or growing into the direction of ovaries.

Just it is about this time that the 'Y' chromosome by virtue of possessing H-Y Antigen which carries genetic message from the 'Y' chromosome goes and acts on the yet undifferentiated gonads.

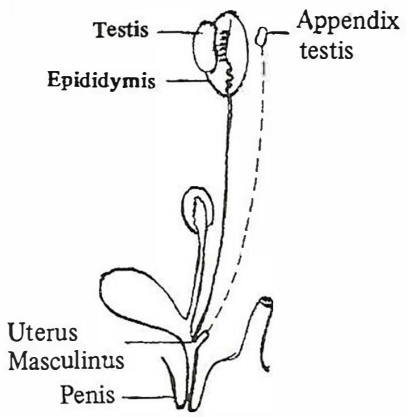
If the genetic sex is XY, by virtue of H-Y antigen that I just mentioned, undifferentiated gonads will begin to differentiate into the histological direction of a testes.



(a) Indifferent stage



(b) Female development



(c) Male development

Fig. Diagrammatic representation of genital tract development. (a) indfferent stage. (b) Female development. (c) Male development. (By couresty. of Balliere Tindall).

If the H-Y antigen is not present and these are "X", "X" or "XO", the direction would be in the direction of ovary, had it not been for 'Y' chromosome and testes, most of us, - all of us infact would be females.

For the male you require very strong message right from the very beginning and that is then, it begins to happen. So testes are first to begin to differentiate. Now once the testicular tissue comes into being, it begins to function right from there by producing, Anti Mulleian Hormone and Testosterone.

Those of us who are destined to be male, Anti Mullerian hormone will then at about 9 weeks of pregnancy go and act on Mullerian duct system and cause it s regression with the result that tubes and uterus will not be formed.

As you would see (in figure) before 9 weeks of pregnancy, there is both potential of wolffian duct system which would give rise to male genital organs and of Mullerian duct system which will give rise to the female genital organs.

In the absence of Anti Mullerian hormone and in the presence of XX chromosomes, since Anti Mullerian hormone is not present, Mullerian system would any way grow and as such Tubes and uterus will come into being.

As far as external genitalia are concerned, they are embryologically represented by a genital tubercle which in female grows into clitoris and in male, it grows further and become a penis and a genital fold and swelling which fuses and becomes scrotum in male in which testes will descend, and in female, these do not fuse and become labia majora and labia minora. Now these are, what is called End Organs of External genitalia. It is something wrong in these End organs that they do not respond to the action of testosterone (3)

At this level, the 5 alpha reductase, an enzyme which was mentioned is needed. In the presence of 5-alpha reductase, Testosterone is converted into Dihydrotestosterone in the cells of these 3 external genital organs to grow into the direction as is destined for it. Something is wrong in the cytoplasm or in the end receptor of these External genitalia, then these things do not develop and this what exactly happened in this patient. 5-alpha reductase deficient people would have bigger clitoris or penis, would have heterosexual desires,which this girl did not have, thus though we can not test for 5-alpha reductase, yet it is logical to persume that in this case it has been purely an end organ androgen insensitivity, giving rise to our XY female.

PRADER, A: Gonadendysgenesie used testicular feminisierung.

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