CLINICAL, CYTOGENETIC, HORMONAL AND ULTRASOUND STUDY OF PHENOTYPIC FEMALES

by

A. JYOTHY
M. D. SADHNANI
C. KUSUM KUMARI
and
G. S. ISAAC

SUMMARY

Clinical, cytogenetic, hormonal and ultrasound investigations were carried out in 5 phenotypic females. The chromosome analysis indicated a normal male karyotype in all the cases. FSH and LH levels were very high. An attempt has been made to correlate these observations which are useful in the management of these cases.

Introduction

Pure gonadal dysgenesis is a condition wherein individuals appear as phenotypic females and have streak gonads similar to those observed in Turner's syndrome but without somatic anomalies. The Karyotype in such cases may be normal: female-46 XX and male-46 XY (Espiner *et al*, 1979). In male psudohermaphroditism, individuals with male genetic constitution testes, differentiate partially or completely as phenotypic females. Testicular feminization is an extraordinary form of pseudohermaphroditism and has been recognised as a distinct entity characterised by female phenotype and XY Karyotypes. These males have female external genitalia, absent uterus, and intra-abdominal tests (Hauser 1963).

From: Institute of Genetics, Hospital for Genetic Diseases, Begumpet, Hyderabad-500 016.
Accepted for publication on 2-6-86.

In the present paper we report the clinical, cytogenetic and hormonal profiles of 5 phenotypic females representing the above conditions.

Material and Methods

Cases with primary amenorrhea referred from various hospitals formed the material for the study. The subjects were thoroughly examined and detailed history of the patient and her family were recorded. Chromosome preparations were made according to a modified method of Moorhead *et al* (1960) and stained according to Seabright. X and Y chromatin analysis was done in all patients. Atleast 30 well spread metaphases were analysed visually and 2 were Karyotyped after microphotography.

Ultrasonic scanning was done for all the patients to determine the uterine size by using Gray scale compound contact scanner (Sonograph EPTM (unirad)

GZD Model 849) with 3.5 mHZ transducer. Most of the cases were followed with diagnostic laparosopy and confirmed the ultrasonographic findings.

Hormones like FSH, LH were assayed according to radio-immuno assay techniques.

Case Reports

Case 1

An 18 year old girl, tall and thin built had primary amenorrhea. She was 2nd born of 3 children of normal non-consanguineous parents. On physical examination, her height was 168 cm and weight 65 kgs. Breast development was slightly seen but the pubic and axillary hair was totally absent. There was no palpable mass present in the abdomen and inguinal region. Ultrasonic scanning report revealed absence of uterus.

Case 2

A 16 year 9 months old girl had primary amenorrhea and no weight gain. She was the youngest of 4 daughters in the family. Family history disclosed that the other 3 sisters died with a fever complaint. The parents are non-consanguineous. On physical examination her height was 162 cm and weight 39.2 kgs. Breasts were not developed. Secondary sex characters were completely absent. Ultrasonic scan showed absence of uterus.

Case 3

A 25 year old female with primary amenorrhea was 4th among the 12 children born to non-consanguineous parents. On physical examination she was found to have average physique. Her height was 154.5 cm and weight 56.3 kg. Her voice was very hoarse and she had an increased carrying angle. Secondary sex characters were completely absent. She was under hormonal therapy for a period of 4 years. During that period she had a sort of menstrual flow for 4 days. Ultrasonic scanning showed uterus with a length of 3.5 cm., breadth 2 cm. and AP 2 cm. Laparotomy revealed small, retroverted uterus. Right ovary appeared like a small wedge shaped streak with a fibrous tissue and left ovary was absent.

Case 4

An 18 year old girl was brought with a history of not attaining menarche. She was 158.5 cm tall and thin built weighing 36.1 kgs. She was the fifth born of eight children of normal parents of consanguineous marriage. Consanguinity was also present in the paternal grand parents.

External genitalia were normal and female type. She was born with congenital absence of vagina and presence of intraabdominal testes. Uterus was absent. Testes were removed by operation.

Case 5

A 4 year old girl with bilateral inguinal swellings visible on straining was 1st born of a non-consanguineous marriage. But the family history showed that inguinal hernia was prevalent on the mother's side. Hence the condition appears familial. On physical examination her height was 97 cm. and weight 14.5 kgs. Her milestones of development were normal. External genitalia were normal. Heart/lungs were clear. Past history showed that she had no pain in the abdomen. Her bilateral inguinal swellings were operated at the age of 3½ years.

Results and Discussion

The cytogenetic and hormonal findings of the subjects studied are given in Table I. The clinical features observed in these cases fully satisfied those described for tessticular feminization and pure gonadal dysgenesis. Intelligence was normal and psychological development with regard to behaviour was that of a female which is similar to the reports of Masica *et al* (1969) and Money *et al* (1968).

Chromosome analyses indicated a normal male Karyotype in all the 5 cases. The buccal smears were negative for X-chromatin and positive for Y-chromatin.

TABLE I

Cytogenetic and Hormonal Findings in 5 Subjects Investigated

Case No.	Cytogenetic analysis			Hormonal Assay	
	Karyo-type	X-chromatin	Y-Chromatin	FSH uIU/ml	LH uIU/ml
Case 1	46, XY	Negative	Positive	120*	84*
Case 2	46, XY	Negative	Positive	100*	92*
Case 3	46, XY	Negative	Positive	115*	90*
Case 4	46, XY	Negative	Positive	—	—
Case 5	46, XY	Negative	Positive	—	—

* elevated.

Normal values: FSH (Mid cycle 15-30 uIU/ml)

LH (Mid-cycles 15-45 uIU/ml)

These results were completely in agreement with the observations made by Jacobs *et al* (1959), Puck *et al* (1960) and Chu *et al* (1960).

All the 5 cases included in this study belonged to the category of testicular feminization except for case 3 which exhibited pure gonadal dysgenesis. Follicle stimulating hormone (FSH) and leutinizing hormone (LH) were assayed as they were much useful in the management of cases with primary gonadal failure. Portuondo *et al* (1984) reported elevated levels of serum FSH and LH in dysgenetic gonads devoid of germ cells. Similar observation of streak gonads and elevated FSH and LH was noted in case 3. Elevated levels of these hormones were also found in other 2 cases which could be due to non-functional gonads (Testes?). These assays could not be done in two cases as they did not report for follow-up studies.

The normal course of sexual development in humans is feminine and the Y-chromosome intervenes with it and directs the undifferentiated gonads to organise into testes. The testes thus organised synthesise and secrete a hormone testosterone which initiates further development of male sex. But in the present situation the sexual development did not take up male line, although a normal male Karyotype was observed, but it was diverted in a female line; and it is difficult to conclude where the defect was. According to Wachtel (1979) secondary sexual development is under the influence of an X-linked gene present on Tfm locus. Mutation occured at this locus would divert to feminine development although the chromosomal constitution is that of a male (46, XY). Thus the cause of primary amenorrhea in such cases (XY females) is not due to the chromosome constitution as such but perhaps may be due to a gene mutation which may influence sexual development. However, further studies may provide the stage at which the mutated gene will interfere with the consequential hormonal changes that take place to initiate feminine development, although chromosome constitution is perfectly of normal male type.

References

1. Chu, E. H. Y., Grumback, M. M. and Morishima, A.: J. Clin. Endocrinol Metab. **20**: 1608, 1960.

2. Espiner, E. A., Veale, A. M., Sands, V. E. and Fitzerald, P. H.: N. Eng. J. Med. 283: 6, 1970.
3. Hauser, G. A.: Testicular feminization in intersexuality, edited by C. Overzier. 255: Academic, London, 1963.
4. Jacobs, P. A., Baike, A. G., Court-Brown, W. M., Foerest, H., Roy, J. R., Stewart, J. S. S. and Lennox, B.: Lancet. 2: 591, 1959.
5. Mascia, D. N., Money, J., Ehrhardt, A. A. and Lewis, V. G.: John Hopkins Med. J. 124: 34, 1969.
6. Money, J., Ehrhardt, A. A. and Masica. D. N.: John Hopkins Med. J. 123: 105, 1968.
7. Moorhead, P. H., Nowell, P. C., Mellman, W. J., Battips, D. M. and Hungerford, D. A.: Expl. Cell Res. 20: 613, 1960.
8. Protuondo, J. A., Araceli, B., Juan, C., Melchor Jaine, G., Tanago and Neyro: Obstet. Gynec. 64: 757, 1984.
9. Puck, T. J., Robinson, A. and Tijo, J. H.: Proc. Soc. Exp. Biol. Med. 103: 192, 1960.
10. Wachtel, S. S.: H-Y antigen and sexual development in vallet HL. Porter IH (ed.) Genetic mechanism of sexual development, New York, p. 271, 1979.