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Relations between Testicular Feminization and Seminiferous Tubule

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Testicular Feminization과 세정관과의 관계

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요 약

Teter와 Boczkowski(1966)는 testicular feminization syndrome을 두 그룹으로 분류했는데, 그것들 중에서 하나는 陰毛가 없고 정상적인 陰核을 갖고 있는 경우(A group)이며, 다른 한 그룹은 陰毛도 있고 陰核은 팽대된 경우이다 (B group). 그러나 본 연구의 대상자는 위의 두 그룹의 중간형을 나타낸다 (C group).

각 그룹의 차이점을 알기 위하여 우리들은 鼠蹊部에서 제거한 精巢의 미세구조를 관찰하였으며, 精巢培養과 血球培養을 시도하여 染色體를 분석하였다.

C그룹의 細精管은 Leydig세포나 Sertoli세포의 분포나 성숙도 그리고 基底膜의 두께 등에서 A나 B그룹과 상이한 점을 나타낸다.

陰毛나 陰核의 형태상의 차이는 위와 같은 차이점들로 인해 야기된 것이라고 생각된다.

INTRODUCTION

The criteria of sex determination are the differentiation of the genital gland whether it is the ovary or testis, the structure of genital organs, the degree of development of non-genital organs such as skeleton and muscle and the distribution of body hair and fat body. All these are controlled by many conditions such as the constitution of sex chromosomes and autosomes, sex chromatin and surroundings depending on the individual. Out of these the most important one is the constitution of sex chromosomes and most people are greatly affected by it.

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However, there are some cases that differentiation to the opposite direction of the sex chromosome constitution occurs when disorders in hormone receptor sites of cells happen at the important stage of sex determination during embryogenesis. Because the patient with this abnomality had shown many differences from general intersex, Schillar (1940) differentiated it from many diversites of intersex and Morris (1953) explained the clinical characteristics of this syndrome and named it "Testicular Feminization Syndrome".

This syndrome is a type of Androgen Resistance Syndromes which can be divided into four types. Complete testicular feminization syndrome, one of these four, is introduced in this paper and Teter and Boczkowski (1966) divided this syndrome into two group; One without pubic hair and with normal clitoris (A group) and the other with pubic hair and enlarged clitoris (B group).

The patient discussed in this paper is a 24-year-old female with a normal intelligence and the phenotype of normal female but who has been suffering from primary amenorrhea. Her external genitalia, voice, hair and the way of thinking were same as other normal female. But after close examination, it was found that she had immature testes at both sides of inguinal region instead of having uterus, ovary or oviduct which a female should have was found.

Differently from Teter and Boczkowski's classification, the characteristics of the patient with pubic hair and almost normal clitoris are introduced in this paper.

MATERIALS AND METHODS

To study the constitution of chromosomes and the hereditary nature of this syndrome, the patient's mother and brother's bloods as well as patient's blood were collected and cultivated for 72 hours in RPMI 1640 medium (Gibco) supplemented with 20% fetal bovine serum. Metaphase spreads of G-banded chromosomes were analyzed to find out the disorders of chromosome number and structure (Priest, 1977). And her sex chromatin was examined by doing buccal smear from both sides of her buccal mucosa (Riis and Fuchs, 1966).

The testes were removed from both sides of her inguinal canal and only part of them were cultivated in four culture flasks (Priest, 1977) and the remains were embedded in paraffin to observe micro-struture of the tissue.

RESULTS

The patient discussed in this paper is a 24-year-old female with primary amenorrhea and who has a blind ending vagina of about 5cm in length and pubic hair. In addition, She has testes at both sides of inguinal region but not uterus or ovary. Other clinical characteristics are shown on Table 1.

Teter and Boczkowski classified testicular feminization syndome into two groups A and B; A group with normal clitoris and no pubic hair and B group with pubic hair and

Table 1. Clinical characteristics of testicular feminization

Case, Age	Body type	Pubic hair	Fatty tissue distribution	Breast development		Clitoris
				General	Nipples	
Group A,						
a, 22	Feminine	Abscent	Rather feminine	Overdeveloped	Pale, juvenile	Small
b, 24	Rather boyish	Abscent	Rather eunuchoid	Underdeveloped	Juvenile	Small
c, 27	Rather feminine	Abscent	Android or neutral	Underdeveloped	Juvenile	Small
d, 18	Feminine	Abscent	Female type	Well-developed	Pale	Normal
Group B,						
e, 22	Feminine	Present	Female type	Well-developed	Normally pigmented, erectile	Moderate hypertrophy
f, 21	Feminine with some musculine features	Present	Female type	Well-developed	Well-pigmented	Hypertrophy
g, 21	Feminine	Present	Female type	Small	Well-pigmented, erectile	Hypertrophy
Group C,						
h, 24	Feminine	Present	Female type	Well-developed	Pale	Small

Group A, Group B; Reference groups Group C; Patient discussed in this paper

Group A; Hairless woman without clitoral enlargement

Group B; Patients with clitoral enlargement and pubic hair

Group C; Patient with normal clitoris and pubic hair

(Reference group; Adapted from data given in Teter and Boczkowski, 1966)

Table 2. Testicular morphology of testicular feminization

Case, Age	Seminiferous tubules			Leydig cells		Position of testes
	Size topography	Tubular content	Tubular walls	Distribution	Maturity	
Group A,						
a, 22	Small, irregular distribution	Immature Sertoli cells	Thin	Adenomatous pattern encircling tubules	Immature	Abdominal
b, 24	Small, irregular distribution	Immature Sertoli cells	Thin	Adenomatous pattern closely encircling tubules	Immature	Abdominal
c, 27	Rather small, irregular distribution	Immature Sertoli cells	Thin	Large groups closely encircling tubules	Immature	Abdominal
d, 18	Small	Well-developed Sertoli cells	Thin	Large shoals closely encircling tubules	Immature	Abdominal
Group B,						
e, 22	Quite large, regular distribution	More mature Sertoli cells	Thickened, fibrotic	Small clusters in triangular areas between tubules	Mature	Inguinal and abdominal
f, 21	Rather irregular, small	Degenerating Sertoli cells	Thickened, partially hyalinized	Small clusters between tubules	Quite mature	Inguinal and labial
g, 21	Large, regular distribution	Quite normal Sertoli cells	Thickened, fibrotic	Small clusters in triangular areas between tubules	Quite mature	Inguinal and labial
Group C,						
h, 24	Large	Normal Sertoli cells	Thickened, hyalinized	Large groups closely encircling tubules and small clusters between tubules	Mature	Inguinal

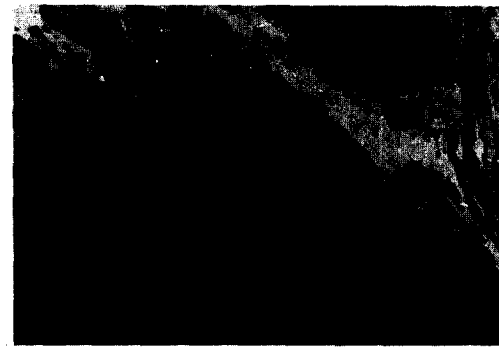

Fig. 1. Patial seminiferous tubules Hyalinized basement membranes and increased Leydig and Sertoli cells were shown in this photograph. Interestingly basement membranes were in contact with Leydig cells.

enlarged clitoris. However, the patient discussed in this paper has almost normal sized clitoris and pubic hair. Therefore, she is considered as an intermediate case of these two groups. Her other phenotypical characteristics are similar to those of group A and B.

Testes in her inguinal region were removed by two operations at an interval of four months and only part of them were cultivated and the rest were embedded in paraffin and sectioned for the purpose of observing the micro-structure of them. A and B groups showed differences in the maturation degree of Sertoli and Leydig cells, the distribution of them in seminiferous tubules and the width of tubular wall. Meanwhile, C group partially involves the characteristics of both groups A and B (Table 2, Fig. 1). In the result of buccal smear from the both sides of patient's buccal mucosa, her X chromatin was not found (Fig. 2) and from the blood culture of her mother and brother as well as her, her karyotype was proved 46, XY, her mother 46, XX and her brother 46, XY respectively with no abnormalities on G-bands (Table 3, Fig. 3).

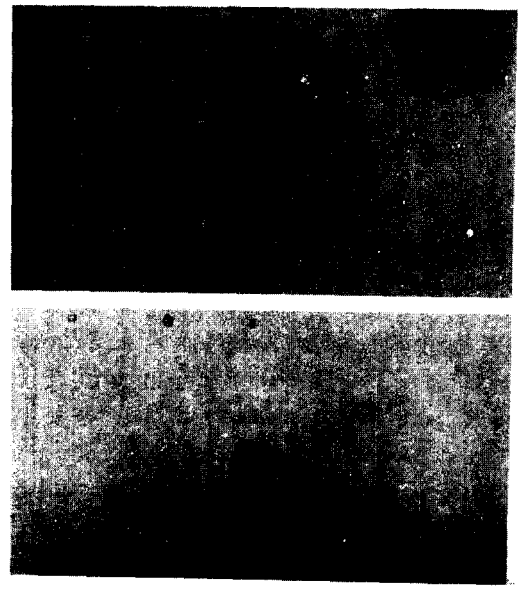

Fig. 2. Buccal smears from patient's buccal mucosa showing no sex chromatin
upper: from right buccal mucosa
lower: from left buccal mucosa

Table 3. Analysis of cells in metaphase

Case	Cells analyzed	No. of chromosomes per cell				Karyotype
		45	46	47	other	
Patient	Blood cells	1	42	·	·	46, XY
Patient's mother	Blood cells	·	38	·	·	46, XX
Patient's brother	Blood cells	1	29	·	·	46, XY

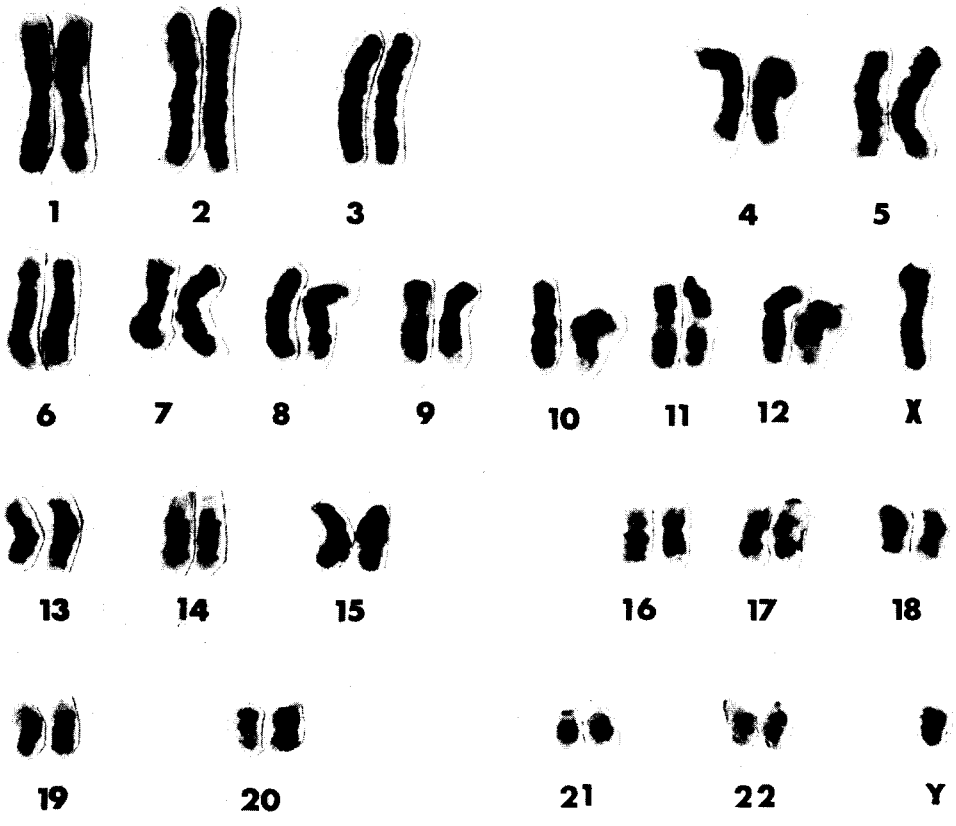

Fig. 3. Patient's karyotype showing no disorders in chromosome number and structure (from blood culture)

Two testes which were located in her inguinal region were removed by operations at an interval of four months and only part of them were cultured as mentioned above. Fibroblasts cultivated confluently in flask were subcultured and harvested to analyze the chromosome number and structure. The result obtained from testicular culture was the same as that from blood culture. That is, her karyotype was 46, XY and there were not found any abnormalities on G-band (Table 4).

The results of hormone assay are shown on Table 5.

Table 4. Analysis of metaphase chromosomes in fibroblasts obtained from testes of the patient

Cells analyzed	No. of chromosomes per cell				Karyotype
	45	46	47	other	
Cultured Fibroblasts (Right testis)	2	21	·	·	46, XY
Cultured Fibroblasts (Left testis)	·	19	·	1	46, XY

Table 5. Hormone assays

Case	17-Ketosteroids (mg/24hr)	LH (M.U.)	FSH (M.U.)	Testosterone (ng/ml)	Progesterone (ng/ml)
Group A,					
a	13.1		80		
b	13.0		20		
c	20.2		6		
d	12.3		52 & 59		
Group B,					
e	12.5		100		
f	19.5		10		
g	18.5		30		
Group C,					
h	6.54 (83/ 9/25)	70.4 (83/ 9/26)	26.2 (83/ 9/26)	9.29 (83/10/ 7)	0.15 (83/ 9/26)
	6.85 (83/10/18)	38.5 (83/ 9/30)	29.8 (83/ 9/30)	8.06 (83/10/21)	0.21 (83/ 9/30)
	6.54 (83/10/21)	36.3 (83/10/ 7)	39.4 (83/10/ 7)		0.15 (83/10/ 7)
	1.51 (84/ 2/ 7)	44.8 (83/10/21)	37.1 (83/10/21)		0.21 (83/10/21)

1st operation date; 1983/9/26
2nd operation date; 1984/2/6

DISCUSSION

There are four different types in Androgen Resistance Syndome (Stanbury *et al.*, 1978). They consist of complete testicular feminization (X-linked recessive), incomplete male pseudohermaphroditism (Type 2) (autosomal recessive) (Simpson *et al.*, 1971; Moore *et al.*, 1975) and incomplete or partial testicular feminization (mode of inheritance uncertain) (Wilson, 1975; Griffin *et al.*, 1976). Among these four types, the patient discussed in this paper has all the characteristics of complete testicular feminization and is able to be considered as an intermediate case of the two groups that Teter and Boczkowski classified. Except for pubic hair and clitoris, there are no other major differences in clinical characteristics among group A, B and C (Table 1). However, there quite a few differences in the position or composi-

tion of each group's testis (Table 2). The main difference between group A and B is the maturation degree of Sertoli and Leydig cells. In the view point of the distribution of seminiferous tubules, group C is more closely related to group B rather than group A. While Leydig cells of group B are not in contact with tubular wall, those of group C are in contact with tubular wall like those of group A. Judging from the results mentioned above, we can see that group C has partially the characteristics of both groups A and B. Therefore, it can be assumed that the factors which cause differences among groups have contributed to the morphological changes of clitoris and pubic hair.

The position of the testes also seems to be a cause of changes for the sexual differentiation and clitoris size. For example, the testis of patient involved in group B had been moved from labial region to abdomen by operation. Two years later the patient became some more feminine and the patient's clitoris became smaller (Teter and Boczkowski, 1966).

In the early development stage of fetus, the testes are found the abdominal region and at the scrotum in newborn baby. The testes of group A are located in abdomen while those of group B are descended to inguinal canal or labium major. Since the testes of this paper's patient are located in the inguinal region, she is considered to be a mid-form between group A and B.

Except for 17-KS this patient's hormone level was almost the same as the average man's(Table 5). Her 17-KS secretion was very low but the meaning of it is uncertain.

From the above results, we can see that testicular feminization syndrome do not consist of only group A and B but involve any other groups in it. That is, group C which is a case between group A and B is such an example.

Recent studies on the testicular feminization syndrome deal with problems created from binding between cultured skin cells which were originated from various region of patient's body and dihydrotestosterone(DHT) (Meyer *et al.*, 1975). DHT binding sites of genital skins such as foreskin, labium major and scrotum have about twice the number of them of non-genital skin such as arm or abdomen.

By using fibroblasts cultured from the testis of a kind of genital tissue which was removed from the patient's inguinal canal, the study on testicular feminization syndrome will be able to be developed.

SUMMARY

Teter and Boczkowski (1966) classified testicular feminization syndrome into two groups; One with no pubic hair and normal clitoris (A group) and the other with pubic hair and enlarged clitoris (B group). However, the patient discussed in this paper shows a mid-form of these two groups (C group).

To find out differences among A, B and C groups, we have observed the micro-structure of testes removed from her inguinal canal and analyzed the chromosomes obtained from

testicular and blood culture.

Her seminiferous tubules show some differences in the maturation and distribution of Leydig and Sertoli cells and in the thickening of basement membrane as compared with group A and B.

We suppose that such differences are responsible for the morphological changes of clitoris and pubic hair.

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