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Turner's Syndrome With XO/XX Mosaicism: A Case Presentation

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TURNER'S SYNDROME WITH XO/XX MOSAICISM

A Case Presentation*

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DR. MELLINGER:

This morning's patient presents an unusual example of one of that growing number of conditions known to be associated with an abnormality of number, form, or function of chromosomes. She is a high school student who was referred to our clinic last August with complaints of obesity and failure to menstruate. She had been overweight all her life. Adopted and knowing nothing about her ancestry, she could not indicate whether her body habitus was consistent with other family members. In addition to resistent obesity, there had been no menses and there was no evidence of secondary sex character development, although when first examined the patient was three months past her 16th birthday. She had no other complaints but did admit to easy bruisability.

On examination, this patient of 16 years was found to be 55½" tall and to weigh 144½ lbs. She was symmetrically obese, with a flushed face and a moderate cervicodorsal hump. There were pink striae across her abdomen and hips. Her blood pressure was 130/90. The axillary and public hair were less abundant than expected for her age, and there was a mild growth of downy facial hair. There was no evidence of significant secondary sex character development, but there were no other physical abnormalities such as edema or acne. The cervix or uterus could not be palpated by rectal or vaginal examination.

After routine laboratory studies proved to be normal, special endocrine studies were obtained. These included urinary 17-ketogenic steroid excretion of 11.8 mg. for 24 hours (normal range, 10 to 22 mg/24 hours) confirmed by urinary free hydrocortisone level of 144 micrograms per 24 hours. The latter test in our laboratory has a normal value up to 250 micrograms per 24 hours. On two occasions, gonadotropin excretion exceeded 64 mouse uterine units. Since normal 16-year-old subjects excrete pituitary gonadotropin in the range of 8 to 32 units, the titer was clearly elevated for this patient. In contrast, a vaginal smear demonstrated significant deficiency of estrogen.

*Abridged transcript of regular Tuesday Morning Medical Clinic proceedings. Edited by W. S. Haubrich, M.D., clinic committee chairman.

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The epithelium consisted almost entirely of the basal cell layer with no evidence of the maturing and cornification that result from estrogen secretion.

In summary, the laboratory data demonstrate normal adrenal steroid levels, estrogen deficiency and increased gonadotropin secretion. Because we suspected a congenital anomaly of gonadal development, the buccal epithelium was examined for sex chromatin bodies. In our Cytology Laboratory, the normal number of cells with paranuclear clumps in female individuals exceeds 20 per cent, while male individuals have less than 5 per cent sex chromatin positive buccal mucosal cells. In the patient, 10 per cent of the cells were positive.

Now, I want to go over just a little bit of history with the patient. First of all, how old are you?

Patient: Sixteen.

Dr. Mellinger: Have you always been overweight?

Patient: Yes, even when I was a little child.

Dr. Mellinger: Have you ever been able to reduce your weight?

Patient: Well, I am now.

Dr. Mellinger: Very good! Have you ever tried before?

Patient: No.

Dr. Mellinger: Have you always been the shortest one in your class at school?

Patient: Yes, mostly.

Dr. Mellinger: Are you still growing?

Patient: I am not sure.

Dr. Mellinger: Have you ever failed a grade in school?

Patient: Once.

Dr. Mellinger: You failed one year. What grades do you receive now?

Patient: C's and D's.

Dr. Mellinger: Now before you came to see us, had you ever had any kind of medical treatment to accelerate your growth and maturing?

Patient: No.

Dr. Mellinger: You are now taking some estrogenic tablets to advance your maturity?

Patient: Yes.

Dr. Mellinger: How long did you take the pills before you had a period?

Patient: I took them for 20 days, had an injection, and then had my first menstrual period.

Dr. Mellinger: Does the medicine bother you in any way?

Patient: No, I feel very well.

Dr. Mellinger: From this interview we know that the patient has a uterus. She menstruated in response to the first course of hormonal therapy. We can also deduce that she is mentally adequate, at least of average intelligence. Many individuals who have a chromosome abnormality have an intellectual handicap.

In summary, this 16-year-old, short, obese girl presented primary amenorrhea as her chief clinical problem. She had normal adrenal function, despite the history of easy bruisability and the presence of pink striae across her hips and abdomen. There was laboratory evidence of estrogen deficiency with a normal pituitary gonadotropin response, excluding hypopituitarism as the cause of her amenorrhea. Suspecting congenital disease, we sought to determine the presence or absence of normal chromosomes by the simple technique of buccal smear. However, the buccal smear of 10 per cent

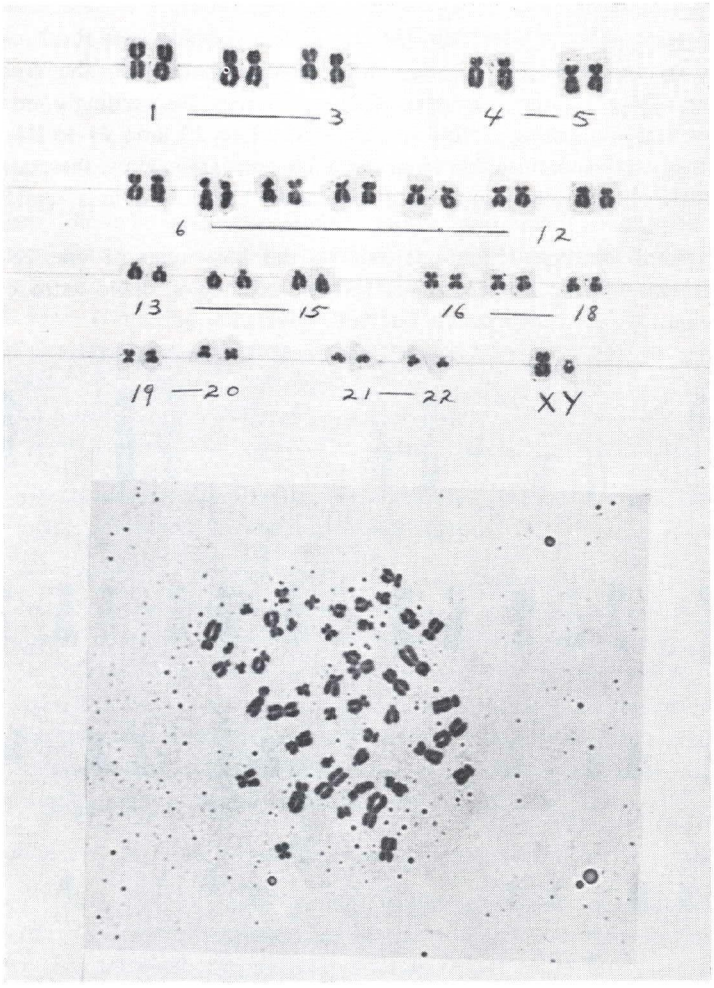

Figure 1

Karyotype of a normal male subject prepared from a metaphase leucocyte. The paired chromosomes (22 autosomes plus XY) are shown with the spread from which they were derived.

chromatin positive cells was characteristic of neither sex, making karyotype analysis the necessary next step. In our hospital, the karyotype is determined by Dr. LoGrippo and Mr. Peakman through an analysis of leukocyte chromosomes. The leukocytes of a heparinized blood specimen are incubated with phytate, and mitosis is arrested in metaphase by the addition of colchicine. In hypotonic solution the cells will swell, and when squashed by the thumb under a cover slip, the metaphase chromosomes will spread, hopefully not overlying one another so that the numbers can be counted and analyzed. Dr. Pierre Caron instituted this study in our hospital two years ago, and the first illustration (Figure 1) demonstrating the normal male karyotype was prepared by him. The numbering system in the illustration is that adopted by the Denver conference on genetic disease.[1] The first three chromosome pairs are similar; they are the largest and the centromere is centrally placed. In the next two pairs, 4 and 5, the centromere is somewhat more eccentric and the chromosome is smaller. The largest group of pairs are numbered 6 to 12 and are not distinguishable from the X chromoosme. group of pairs are numbered 6 to 12 and are not distinguishable from the X chromosome. if the total number is 16, there are two X chromosomes. Succeedingly smaller groups of similar pairs are numbered 13 to 15, 16 to 18, 19 to 20, and 21 to 22, the last of which are not usually distinguishable from the Y chromosome. Thus, there are 5 of these small acrocentric chromosomes in a male karyotype, but only 4 in a female.

The second illustration (Figure 2) shows the karyotype of one cell from the patient. There are only 45 chromosomes with no Y, and a single extra chromosome

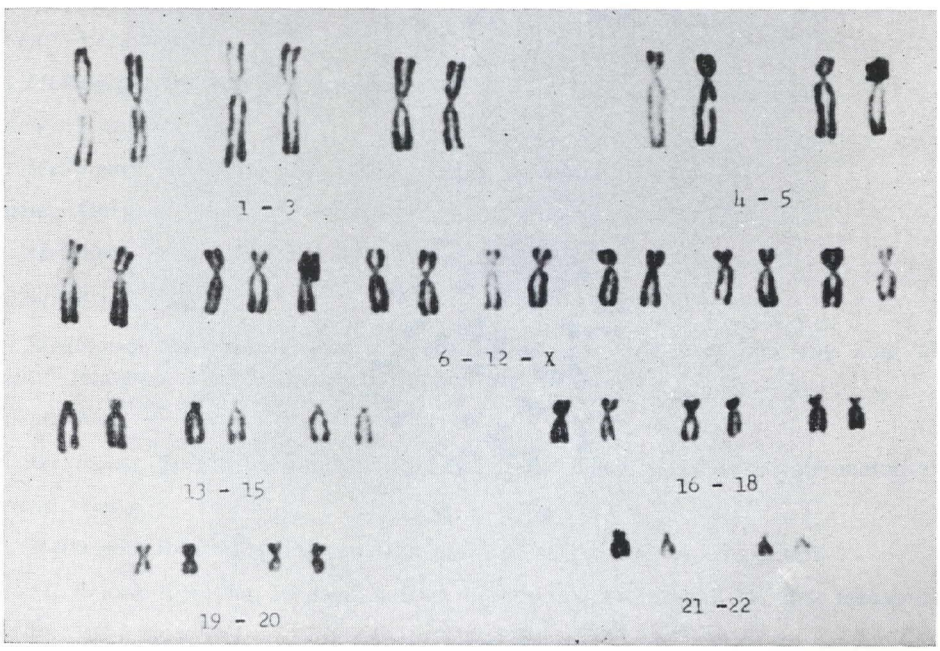

Figure 2

Karyotype from the abnormal (XO) cell line of the patient. There are 22 pairs plus one X chromosome.

in the 6 to 12 group. This karyotype may be characterized as XO. These cells, however, could not account for the 10 per cent sex chromatin positive cells in the buccal smear because the chromatin body in the buccal epithelium is observed only in the presence of two X chromosomes. The paradox was resolved by multiple leukocyte preparations which revealed that only 30 of the 50 cells analyzed were XO with 45 chromosomes, and that 15 were XX with 46 chromosomes, a normal female karyotype. Thus one-third of the cells were XO, two-thirds were XX, indicating a chromosome mosaic or two cell lines of 45 and 46 chromosomes, respectively. The fact that only 10 per cent of the buccal cells contained the sex chromatin body suggested that there were two cell lines with only part of the cells carrying XX chromosomes. This XO/XX karyotype was found in 7 of 57 analyses reported by Lindsten[2] in his fine monograph on Turner's syndrome, and the present case is considered another example of mosaicism in this disorder. Instead of the more common simple X chromosome deficiency, two cell lines coexist, with one X chromosome deficient in one cell line. The finding has no known clinical significance; the patient requires estrogen replacement under any circumstance, but it is a considerable intellectual satisfaction to be able to define this interesting problem. I will be pleased to hear any questions that you wish to raise.
From the audience: What is her prognosis?

Dr. Mellinger: She will become sexually mature, and this I think has considerable physical benefit quite aside from the fact that she will menstruate regularly. She will remain infertile, and grow very little. The stature is limited by the mesenchymal defect, not by any known endocrine deficiency. She will menstruate only so long as she takes estrogens, of course. It is of interest that there are apparently none of the other physical stigmata of Turner's syndrome such as a cardiovascular defect, high palate, edema, skeletal abnormality, or the pterygium anomaly with webbed neck, low-set ears and low posterior hairline. Her significant features are short stature and immaturity.

From the audience: If this condition can be diagnosed in early life is there an effective therapy that offers improved growth and development?

Dr. Mellinger: There is no reliable way to alter the stature. By buccal smear examination the condition can be detected at birth, and such a test is recommended especially in the presence of congenital anomalies, such as webbed neck peculiar ears, or most significantly in infants, pedal edema. With our pediatric group, we have diagnosed many such cases, but we usually do not recommend therapy. In the event of marked immaturity, the judicious administration of anabolic steroids is considered. The place of growth hormone administration is not settled, but probably will prove of little value. Sex hormone replacement is begun at the time of adolescence.

From the audience: Is there endocrine significance to the colored striae?

Dr. Mellinger: No. I think many young people who gain too much weight have pink striae. They are more characteristic in the young obese than in older subjects. I don't believe they have other clinical significance.

From the audience: Is the search for nuclear "drumsticks" of value in evaluting such patients?

Dr. Mellinger: Yes, it is helpful. It is a more arduous procedure than the buccal smear and has essentially the same significance. Dr. John Rebuck will make this study if you wish for confirmation, but the buccal smears are quite reliable. The drumstick probably also represents sex chromatin, being positive in females and negative in males, although there are many fewer drumsticks in leukocytes than there are sex chromatin bodies in the buccal mucosa.

From the audience: How do these chromosome abnormalities occur?

Dr. Mellinger: The accepted etiology for the more common types of the congenital anomaly we have presented is nondisjunction, or unequal division of the chromosomes in the formation of the germ cells. In the case of XO Turner's syndrome, nondisjunction is thought to occur in the father, permitting sperm without a sex chromosome to unite with an oocyte. The resulting zygote bearing a single X chromosome develops the clinical features of Turner's syndrome. Chromosome deficiency of the germ cells cannot account for mosiacism, however; the presence of two distinct cell lines must result from unuequal distribution of chromosomes in the cell division of the zygote itself. The early cell divisions are probably normal, but a later nondisjunctional mitosis presumably initiates two abnormal cell lines, one with 45 chromosomes (XO) and one with 47 chromosomes (XXX). The latter either may not survive or may characterize a different tissue and not be revealed in the leucocyte analysis that reveals the deficient XO cells as well as the original XX line.

REFERENCES

1. Book, J. A., Lejeune, J., and Levan, A.: A proposed standard system of nomenclature of human mitotic chromosomes, Lancet 1:1063, 1960.

2. Lindsten, Jan: The nature and origin of X chromosome aberrations in Turner's syndrome, Almqvist & Wilssells, Uppsala, Sweden, 1963.