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TURNER'S SYNDROME IN MALES

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TURNER'S SYNDROME in its typical expression is a congenital disorder of phenotypic females. Characteristic clinical features are short stature, gonadal dysgenesis or aplasia with sexual infantilism, and various somatic anomalies including pterygium colli (webbed neck), cubitus valgus, shield-like chest, high arched palate, low-set and protruding ears, and low posterior hairline. Approximately 80 per cent of these patients are cytologically chromatin negative, with a karyotype of only 45 chromosomes including a single, unpaired X chromosome (XO).

The counterpart of this disorder in males occurs much less frequently and is not universally considered an entity. More than 50 such patients have been reported.[1,19] As a contribution to further understanding of the syndrome, we are reporting five additional male patients with Turner's syndrome, four of whom were initially examined for congenital heart disease.

CASE 1. The patient, a boy of Rumanian and Polish ancestry who has two apparently normal older siblings, has been followed by the Pediatric Cardiology Clinic for a heart murmur present from birth. He was born prematurely at eight months gestation, weighing 5 lbs. 10 oz. Although he remained smaller than average for his age throughout childhood, his physical development otherwise appeared normal, and excercise tolerance remained normal. Left lateral strabismus was surgically corrected at age six years. Cardiac catheterization at age 8½ years confirmed the diagnosis of moderately severe valvular pulmonary stenosis (RV-86/0-4 mm. Hg. PA=22/6 mm.Hg.), following which pulmonary valvulotomy under direct vision was successfully performed. Orchidopexy for right undescended testis was accomplished at age 9½ years. Subsequent cardiac study indicated that the pulmonary stenosis had been relieved. It was considered that the nature and severity of the cardiac defect was insufficient explanation for impaired preoperatively. Furthermore, at age 12 years, four years postoperatively, his growth pattern had not improved. Accordingly, he was referred to the Endocrinology Clinic for evaluation.

At age 12 years, he appeared well-proportioned, though small for his age. Height was 50 inches and weight 57 pounds, a normal height and weight for age eight years on Iowa Growth Curves. Ophthalmological examination revealed only moderately severe myopia. Definite pterygium colli was present, but there were no apparent skeletal abnormalities save for slight cubitus valgus. External genitalia appeared normal although both testes were small and firm, and there was no evidence of sexual maturation. Skull x-rays were normal. Bone age determined from wrist x-rays was interpreted as 10 years (chronological age 12 years, 3 months). Urinary gonadotropin assay was negative at 4 mouse uterine units.

Therapy with methyltestosterone, 10 mgs. daily, for 18 months resulted in improved vigor, a weight gain of 12 pounds, growth of 3-3/4 inches in height, and an advance in bone age of

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24 months. Development of secondary sex characteristics advanced moderately. Urinary gonadotropin remained negative at age 14. Although the gonadotropin assay is positive in normal boys this age, the developmental retardation of the patient could account for delayed pubertal activation of the pituitary.

CASE 2. The patient, the oldest of five siblings of Irish ancestry, was first examined in the Pediatric Cardiology Clinic at age 8½ years for evaluation of a recently discovered heart murmur. Although the initial impression was that of a small patent ductus arteriosus, cardiac catheterization was performed because of a somewhat atypical murmur. The ductus could not be catheterized and the blood oxygen determinations failed to show a clear-cut gradient, but hydrogen electrode catheter studies revealed left to right shunting at the pulmonary artery level. A small patent ductus was divided at subsequent surgery.

Although no abnormalities had been noted at birth, and early development had been considered normal, multiple anomalies were apparent at the time of his initial study here. At age 8½ years, the patient was 49½ inches tall and weighed 47½ lbs., a normal height and weight for age 6½ to 7½ years. In addition to a fairly marked pterygium colli, accompanied by low cervical hairline and lowset ears (Figure 1), there was facial asymmetry and left external strabismus. Loss of curvature of the cervical spine was the only evident skeletal

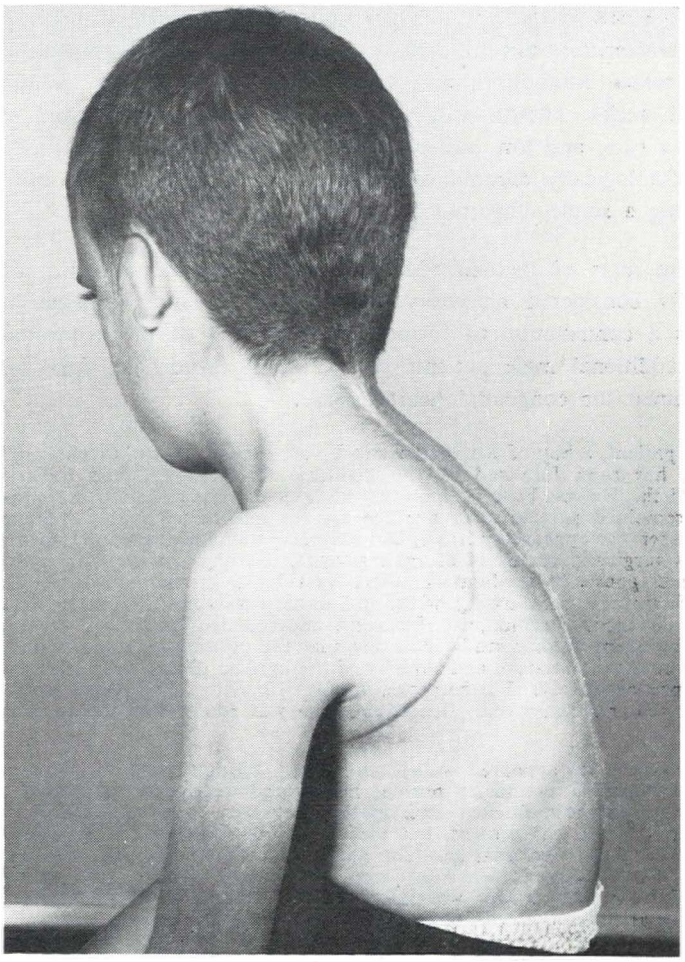

Figure 1

Case 2. Note pterygium colli, low hairline, prominent low-set ears. Surgical scar represents repair of patent ductus arteriosus.

anomaly. Both testes were present in the scrotum, and the external genitalia were clinically those of a normal prepubertal male. Wrist x-rays for bone age were interpreted as showing a skeletal age of between five and six years.

CASE 3. A boy of Mexican ancestry, aged three years 11 months, was referred for cardiac evaluation because of a heart murmur first noted several months previously. His exercise tolerance and general development were normal save for small stature not consistent with the family pattern.

The clinical findings, indicative of valvular aortic stenosis, were confirmed by right and retrograde left heart catheterization and cineangiocardiography. The only abnormal physiologic findings were elevated pulmonary artery wedge pressure and a systolic gradient across the aortic valve of 55 mm.Hg. The gradient is not of sufficient magnitude to warrant aortic valve surgery at present, and the patient has been well since his initial evaluation.

As in Case 2, webbing of the neck growth impairment not reasonably explained by his cardiac defect were observed at the time of his examination. He appeared to be of normal intelligence. In addition to the moderate pterygium colli and small stature, he was found to have low-set ears and a very high, arched palate, a somewhat low cervical hairline and decreased curvature of the cervical spine. He was 36 inches tall and weighed 31 pounds, an average height and weight for American children of age 2-1/3 years. Bone age, also compared to the normal American population, was 2.8 years (chronologic age three years 11 months). The external genitalia, including testes, were considered normal for the patient's age.

By age five, the patient has a height-weight age of 3½ years, while his two older siblings are of average height and weight for age, according to Iowa Growth curves.

CASE 4. The patient, known to have congenital heart disease since infancy, was 10 years 2 months old when he was first studied for a possible chromosomal abnormality. Physiologic studies with cineangiocardiography had revealed a complex form of tetralogy of Fallot with subpulmonary stenosis, an extremely large ventricular septal defect approaching single ventricle, and a large atrial defect with marked left to right shunting at that level. The degree of left to right shunting at the atrial level suggested mitral valve obstruction.

His only sibling was stillborn, reportedly as a result of a congenital heart lesion. A maternal half-brother is a normal adult, 6 feet, 2 inches in height. The patient was born after seven months gestation, weighing 4 pounds, 9 ounces. A heart murmur was heard at birth, but no somatic anomalies were noted. Because of cyanosis and dyspnea, present from early childhood, a Brock pulmonary vavulotomy was done at age 5½ years, with temporary improvement. However, recurrent hypoxia and dyspnea necessitated the performance of a right Blalock anastomosis at age nine years. This procedure was complicated by right chylothorax due to a chylous fistula which required surgical repair six months later. Although he is only mildy cyanotic and has remained relatively free of hypoxia, the chronic use of digitalis and diuretics has been required.

When examined at age 10 years, the patient was found to be a normally intelligent but physically underdeveloped boy who appeared with slight cyanosis. He weighed 37 pounds and was 43-1/3 inches tall, a normal height and weight for age five years. Except for myopia the eyes were normal. The teeth were irregularly spaced and the hard palate was high and creased. Definite pterygium colli and low-set ears were present. The extremities were normal. Genitalia were infantile, a small right testis being the only evident gonadal tissue. X-rays of the wrists and hands revealed a bone age of seven years.

Administration of methandrostenolone, 5 mg. daily produced marked genital growth, improved appetite and a sense of well-being. Fluid retention occurred, and the congestive heart failure became somewhat more difficult to control; but during eight months of therapy, non-edematous body weight increased 10 pounds, height increased four inches, and bone age advanced two years. (Figure 2).

Case 5. The patient, now seven years old, is of Irish ancestry and has two normal older siblings. He has been under the care of this clinic since infancy. At birth, the sex of the child was in question. No testicular tissue was palpable, and the phallus was very small covered by a long prepuce. There was a penile urethra. Sex chromatin was negative by study of leucocytes and skin biopsy. He ate poorly and grew slowly, weighing only 12 pounds when six months old. At that time, bone age by wrist x-ray was interpreted to be between three and six months. Urinary 17-ketosteroids, serum protein-bound iodine and sweat chloride were all normal. Subsequent recordings of height and bone age are indicated in Figure 3.

Figure 2

Case 4. The patient at age 11 years, after eight months of anabolic hormone therapy. The patient had Tetralogy of Fallot, markedly delayed growth and bone age, pterygium colli, low-set ears, high palate, bilateral cryptorchidism. Growth and sexual maturation resulted from administration of methandrostenolone.

At age six, a left branchial cleft cyst was removed. At that time the patient was considered as a possible example of male Turner's syndrome. The cryptochidism was unchanged. The penis had enlarged somewhat, coincident with chorionic gonadotropin therapy prescribed during his fourth year, although the retarded growth rate was unchanged. The skull was asymmetric with a large cranial vault, and moderate pterygium colli was present. The palatal arch was very high and there were striking simian palms. Cardiac examination was normal except for a soft systolic murmur at the apex considered to be functional. Cardiac fluroscopy and electrocardiogram were normal.

At age 6-9/12 years, he weighed 44 pounds (weight age of 5-4/12 years) and was 42½ inches tall (height age of 4-8/12 years). Bone age was interpreted to be 2-8/12 to three years. Buccal smear was chromatin negative and the karyotype was that of normal males. Anabolic steroid therapy was instituted.

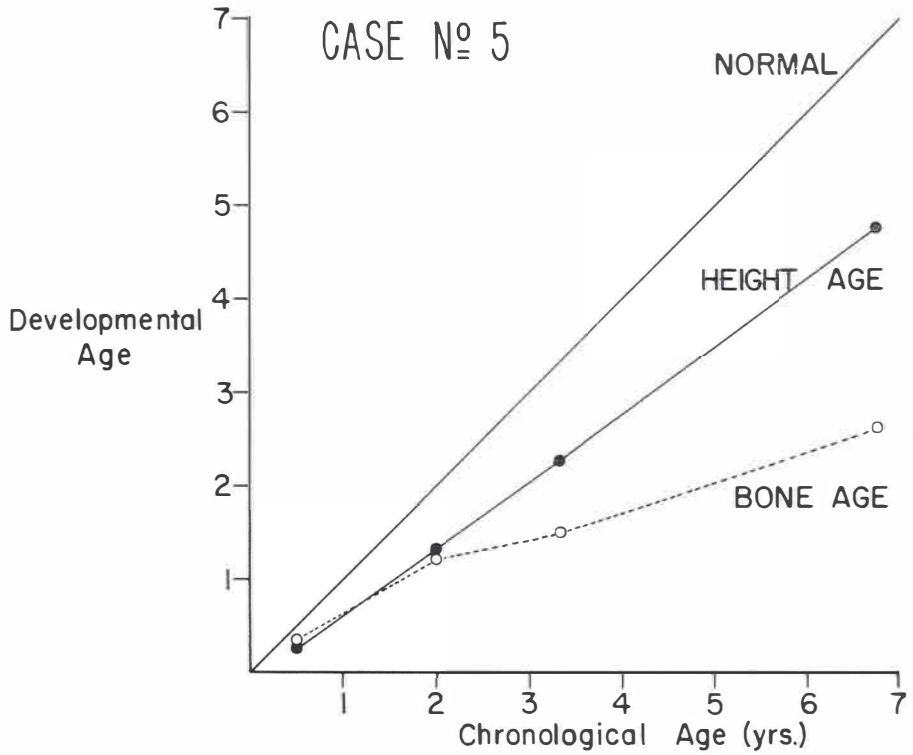

Figure 3

Case 5. Growth and bone age of the only patient who has no heart lesion. Other features are cryptorchid testes, large asymmetric skull, high palatal arch, pterygium colli, simian palms.

Chromosome Studies

Chromosome analysis from culture of peripheral leucocytes was completed for four subjects. Leucocyte preparations from Case 1 were unsatisfactory for analysis on two separate attempts. Results for the other four subjects are recorded in Table I. These chromosome analysis are identical with those found for normal male individuals. Figure 4 is a characteristic karyotype prepared from a cell of Case 4. Buccal smears of all five subjects were negative for the sex chromatin body.

Discussion

A male subject with clinical characteristics of Turner's syndrome was first reported by Weissenberg in 1928.[1] The interest generated by the demonstration that the disorder in females is associated with a chromosome abnormality has lead to an increasing number of case studies in male subjects during the past decade. In contrast to the findings in female patients, however, chromosome analyses of males have usually demonstrated a normal karyotype.[2] The diagnosis of Turner's syndrome in the male therefore must rest entirely on clinical criteria. All subjects reported have had abnormally short stature and most have had dysgenetic gonads. In addition,

CASE 2					
CHROMOSOME COUNT	<45	45	46	47	TOTAL NO. OF CELLS
COUNTED		1	21		22
ANALYZED			3		3
CASE 3					
CHROMOSOME COUNT	<45	45	46	47	TOTAL NO. OF CELLS
COUNTED	1	3	20	1	25
ANALYZED		2	11		13
CASE 4					
CHROMOSOME COUNT	<45	45	46	47	TOTAL NO. OF CELLS
COUNTED	2	1	32		35
ANALYZED	1		15		16
CASE 5					
CHROMOSOME COUNT	<45	45	46	47	TOTAL NO. OF CELLS
COUNTED		1	28		29
ANALYZED			4		4

Table I

Chromosome analyses of peripheral blood leucocytes in male patients with Turner's syndrome. Satisfactory preparations could not be obtained in Case 1. Cells were analyzed from micro-photographs. (See Fig. 4)

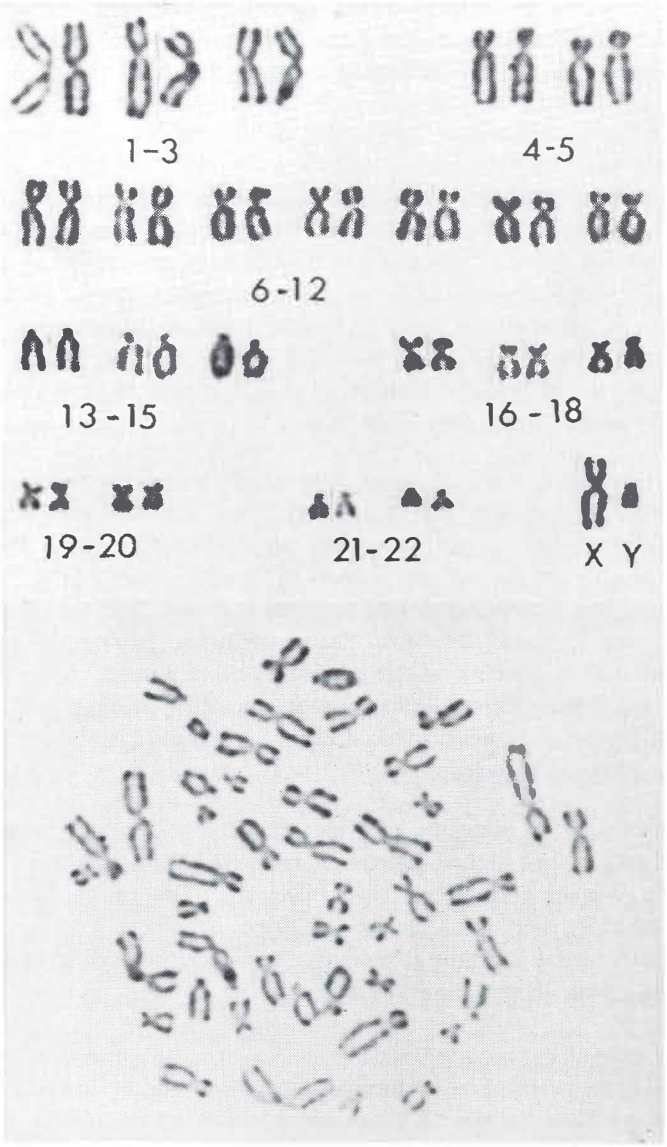

Figure 4

Case 4. Typical chromosome preparation. No abnormalities of the karyotype were found in any of the patients.

the somatic anomalies frequently observed in phenotypic females with Turner's syndrome have also characterized the male patients. The following are the most common among these: 1) the pterygium-type anomaly such as webbing of the neck, low-set ears and a low hairline; 2) eye anomalies, especially epicanthal folds, ptosis or strabismus; 3) skeletal anomalies, most commonly a high-arched palate, cubitus valgus, anomalies of the metacarpal, carpal or phalangeal bones and osteoporosis

of the spine; 4) a wide variety of congenital heart lesions; 5) anomalous renal development such as bifid ureters or horseshoe kidney; 6) mental retardation; 7) congenital lymphedema of the extremities.

Of the patients described in this report, cardiovascular anomalies were the most prominent presenting features. These included Tetralogy of Fallot, pulmonary stenosis, patent ductus arteriosus, and valvular aortic stenosis, but coarctation of the aorta was not present in this group of male patients nor in those reported by Steiker et al.[7] In the other reported male cases the evidence of congenital cardiac defects is nearly 50 per cent with an unexpected absence of coarctation. Only two instances were found, both reported by Bishop,[19] and no details documenting the diagnosis were provided. In contrast, Haddad and Wilkins[20] reported a 20 per cent incidence of cardiovascular anomalies in 55 cases of Turner's syndrome in females with coarctation of the aorta present in 14 per cent.

Each of our cases exhibited small stature and delayed bone age. Mehrizi and Drash,[21] reporting the growth rate of 533 children with acyanotic congenital heart disease, found that only 18 per cent were physically retarded in both height and weight. The severity of the cardiac defects in three of our four patients with congenital heart disease is not considered sufficient to account for significant growth impairment (Case 1, 2 and 3). Our patient with the most prominent retardation (Case 4) is the only one with cyanotic congenital heart disease. Although the severity and nature of his cardiac defect is adequate to account for marked growth impairment, the prominent associated non-cardiac anomalies strongly implicate genetic factors as well in his physical retardation.

All of the five boys presented pterygium colli, low occipital hairline and prominent, low-set ears. High-arched palate characterized three patients, two had strabismus and three were cryptorchid (two bilateral). The two boys with apparently normal pre-pubertal genitalia ("Bonnevie-Ullrich syndrome") may well manifest abnormalities of gonadal function at puberty. Testicular biopsies have not been done, and no chromosomal abnormalities were found.

With few exceptions, reported genetic studies of male patients with these clinical manifestations have revealed sex chromatin negative buccal smears, karyotypes of 46 chromosomes with a normal "XY" component and no dectectable anomaly of the autosomes.[2,14] One exception is a case reported by Oikawa and Blizzard.[9] Their male patient had a positive buccal smear and a modal chromosome number of 46. In these cells only four small acrocentric chromosomes were present along with one normal-sized X and a large chromosome interpreted to be either trisomy of #3 or a second X, larger than the first. Laguens and co-workers[17] also reported a male patient with features of Turner's syndrome and a chromatin-positive buccal smear. The karyotype revealed a modal chromosome number of 47, with a probable XXY complement, and an associated aberration of autosome #1. Although this karyotype is more characteristic of Klinefelter's syndrome, the clinical features and testicular morphology were not typical of the disorder. The "male" case reported by Bloise

et al.[11] presented the execptional findings of hermaphroditic external genitalia, short stature, low-set ears, low hairline, and a high-arched palate. The internal genitalia were represented by a single rudimentary testis but the karyotype was similar to that of "female Turner's" patients, 45 chromosomes with XO sex chromosome complement. Thus the patient may be classified as a male pseudohermaphrodite with somatic features of Turner's syndrome. Lambert and Netter[22] have studied a patient who also presented features suggesting male pseudohermaphroditism with Turner's syndrome. The patient, a dwarfed phenotypic female with retarded bone age but without other evident congenital anomalies, became virilized at puberty. Gonadotropin titers were elevated and the buccal smear was chromatin negative. Surgical exploration revealed unilateral intraabdominal testis with a contralateral rudimentary gonad characteristic of Turner's syndrome. Chromosome analysis of cultured aponeurotic tissue was interpreted to show mosaicism, some cells with 46 chromosomes and an XY complement, others with only 45, characterized as XO. Through the courtesy of Dr. Joel I. Hamburger,* a similar "transitional" case has been studied by the authors. A phenotypic female, this patient grew to be only 58 inches tall, but presented no other evidence of anomalous development except for congenital deformity of the right thumb. At adolescence, the patient experienced no menarche, but became moderately virilized. Buccal smear was chromatin negative and chromosome analysis of leukocyte cultures also revealed XY-XO mosaicism. At laparatomy, intra-abdominal testes were removed.

The characteristic idiogram of the female Turner's patients, 44 autosomes with only one X chromosome, has lead to the assumption that the clinical syndrome results from the loss of chromatin material. Other abnormal karyotypes in the female subjects have been reported, varying from only partial deletion of one X chromosome[23,24] to the presence of one normal and one abnormally large X chromosome,[25] as previously described in the male patient of Oikawa, et al.[9] In addition, chromosomal mosaicism has been reported in a significant number of cases. The nearly constant finding of some sex chromosomal abnormality in these subjects has strengthened the concept that Turner's syndrome in phenotypic females is indeed a genetically determined clinical entity. In the absence of any autosomal defect, it is reasonable to postulate that the absence of one sex chromosome accounts not only for the genital maldevelopment but also for the widespread mesenchymal abnormalities.

The absence of apparent chromosomal aberrations in most male cases detracts from the proposed unifying etiologic concept of the disorder and raises the question of what relationship exists between these male and female subjects. Despite the attractive simplicity of the concept that Turner's syndrome in the female is the result of a sex chromosome deficiency, a genetic basis for the disorder has not been established in all patients. Some female cases have been described with normal appearing chromosomes,[26] and the typical clinical features and idiogram have been associated with normally functioning ovaries.[27] As noted above, many female subjects

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have been reported with positive buccal smears, some of whom have 46 chromosomes with one normal X and one large chromosome, considered by Lindsten to be an iso-chromosome for the long arm of X.[28] Accordingly it is not possible to state that chromosome *deficiency* causes the disorder in all phenotypic females and we need not reject clinically similar males from the same classification on the basis of an apparently normal male karyotype.

An interesting hypothesis recently expressed by Lyons concerns the behavior of the X chromosome in mammals.[29] The chromosomal counterpart of Turner's syndrome (XO) occurs frequently in mice. In contrast to the Turner's patient however, XO mice are normal fertile females, therefore providing a laboratory model for the study of X chromosome behavior in mammals. From her study of the inheritance of sex-linked characters in these mice as well as in human beings, Lyons contends that one X chromosome becomes genetically inactive during early embryologic life. The absence of one X chromosome in the XO mice produces no deleterious effect on somatic development, as might be anticipated if only one of the pair is genetically active. Why then should the absence of one X chromosome produce a widespread disorder in the human fetus? Studies indicate that the time of inactiviation for one X chromosome in mice is the seventh intrauterine day whereas in the human embryo both chromosomes are active until the 16-18 day.[29] It appears that the presence of both sex chromosomes is necessary for the very early development of a fetus. In the male the Y chromosome must serve the function of the subsequently inactivated X in early life, and also help determine the development of the undifferentiated gonad into a testis. In the male patient with Turner's syndrome it can be postulated that the Y chromosome is defective to some degree. Genetically sufficient to insure development of testes, which may be functionally inadequate after fetal life, the defective Y chromosome is apparently not adequate to prevent the mesenchymal abnormalities that characterize the Turner's syndrome. Nowakowski[30] has postulated that this Y chromosome defect is in the form of a dominant mutation, which is not transmissible because it produces a sterile gonad. Similarly, Turner's syndrome accurring in females who do not show the characteristic lack of one sex chromosome may be the result of a genetic fault if one of the X chromosomes is functionally abnormal.

Turner's syndrome must be differentiated from other similar clinical conditions. For example, Mann[31] and others have emphasized resemblance of the disorder to Albright's hereditary dystrophy, sometimes called pseudohypoparathyroidism or pseudo-pseudohypoparathyroidism. This latter syndrome is also characterized by dwarfism and bony anomalies, particularly shortening of the fourth metacarpal bone. Most other aspects of Turner's syndrome are not seen in these cases and there is no known chromosomal anomaly, but the similarity of the mesenchyme defect suggests a relationship. The mode of inheritance, however, seems very different in the two syndromes; Albright's dystrophy is transmitted as either an autosomal or a sex-linked dominant character, whereas Turner's syndrome is usually considered to be the result of a chromosome abnormality.

TURNER'S SYNDROME IN MALES

Trisomy of chromosome #17[32] or #18[33], sometimes termed the group E syndrome,[34] produces multiple congenital defects some of which are similar to those of Turner's syndrome. The characteristics of this disorder are webbing of the neck, low-set malformed ears, flexion deformity of the fingers, mental retardation and anomalies of the feet, heart, eyes or eyelids, chest and kidneys. All of these patients die soon after birth and no defects of internal genitalia have been reported. The predominance of females suggests that the condition is not compatible with term development of the male fetus.[35] Other conditions associated with abnormal karyotypes (usually with extra chromatin material) may occasionally present some of the features described in Turner's syndrome[36]; however, the associated defects are generally not suggestive of the disorder under discussion.

The suggested minimum criteria for designating a phenotypic male patient as a case of Turner's syndrome include retarded growth and maturation, gonadal dysgenesis and any of the large number of somatic defects described above. Although these defects are strikingly similar in both phenotypes, the incidence and variety of serious congenital heart disease, excepting coarctation of the aorta, seems more frequent in male than female patients with the syndrome. Perhaps the presence of such anomalies serves to call attention to the condition in male subjects, as occurred in our experience, whereas the sexual anomaly is more striking in the female, especially at puberty.

Whatever the true nature of this disorder, it is almost inescapable that its source is a chromosome abnormality. The occurrence of the syndrome in male patients appears to be an uncommon manifestation of the same widespread developmental anomaly well known in females. Until the unifying etiologic explanation for these disorders is at hand, it appears wise to study and report the variations of the syndrome and to retain the eponym by which it is designated.

SUMMARY

Five male patients with the developmental anomalies characteristic of Turner's syndrome are reported. All five presented abnormally small stature and delayed bone age with pterygium colli, low occipital hairline and prominent, low-set ears. High-arched palate was present in three patients and strabismus in two. Three patients were cryptorchid while the two with apparently normal testes were prepubertal.

Four of the patients had congenital cardiac defects which were documented by appropriate physiologic studies. Review of the more than 50 cases of male Turner's syndrome described in the medical literature reveals an incidence of congenital heart disease approximating 50 per cent. A notable exception is coarctation of the aorta, the most frequent severe cardiovascular anomaly in phenotypic female Turner's patients, with only two undocumented instances reported in male Turner's cases.

Chromosome analyses were successful in four of the five patients and revealed a normal male karyotype in each. With few exceptions, similar normal chromosome

complements have been reported for all male Turner's patients studied. Since abnormal karyotypes, usually chromatin deficiency, are characteristic of the female Turner's patients, the identity of the disorder in the two sexes is open to question. However, the striking similarity of the developmental anomalies suggests a common etiology. If the disorder has genetic cause, a qualitative chromatin defect may be invoked in those patients whose chromosomes are quantitatively normal.

Whatever the etiology of the syndrome, it is important to recognize its external features in either sex, to search for serious associated cardiovascular anomalies, and to correct the gonadal insufficiency by appropriate hormone therapy.

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