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Sex Chromosome Aberrations in Childhood

II. 45,X and 45,X-mosaics

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Systematic screening tests were performed to observe the most frequent clinical manifestations of sex chromosome aberrations. Cytogenetic examinations revealed such aberrations in 23 children of a female phenotype. 45,X anomaly was detected in thirteen, 45,X/46,XX_{qi} in two, 45,X/46,XX in seven cases, and 45,X/46,XY in one case.

All examined patients were stunted in growth. Short stature and lack of puberty were present in all the cases. Other anomalies such as webbed neck, low posterior hairline, chest and bone deformities, congenital heart and kidney malformations, further mental retardation — though frequently present — are not necessarily associated with the syndrome.

Sex chromosome aberrations associated with the female phenotype have been known for long. MORGAGNI [31], for instance, recognized in 1761 a correlation between short stature, ovarian aplasia and congenital renal malformations. In 1930 ULLRICH [44] suggested that all somatic disorders accompanying nanism constituted a single syndrome, but it was TURNER [43] who summarized the various symptoms of the syndrome which bears his name. Accumulation of information led to differentiations and the coining of new terms. WILLKINS and FLEISCHMANN [46] used the term ovarian agenesis, while DEL CASTILLO [10] the rudimentary ovary syndrome. GRUMBACH [19] demonstrated that gonadal aplasia was associated with negative sex chromatin, while RANNIE and ERSKINE [39] were the first to introduce the concept of pure gonadal dysgenesis. Eventually, in 1959, it was separately shown by FORD [15] and FRACCARO [17] that one X chromosome was missing in the majority of these cases, so they recognized the aetiological background of the disease. According to SINGH and CARR [42], the ovarian structure is still normal if the sex chromosome pattern of a 3-month-old foetus is XO or XX. Later, however, the gonads and germ cells undergo degeneration if the chromosome complement is 45,X. Relying on this observation the clinical manifestation of the anomaly has been called ovarian dysfunction.

The syndromes based on ovarian dysfunction have been systematized by POLANI [38]. The presence of sterile

gonads and consequent amenorrhoea, further the absence of secondary sex characters are the features typical of these syndromes which may be divided in three main types.

(1) Turner's syndrome: short stature (body height seldom exceeding 152 cm); webbing of the neck; in most cases also other somatic anomalies.

(2) Ovarian dysgenesis: Turner's syndrome without a pterygium.

(3) Pure gonadal dysgenesis. This category comprises all cases not fitting into the first or the second type.

Types *(1)* and *(2)* are pathogenetically identical inasmuch as practically all patients of these categories are of short stature and the constitution of their sex chromosomes is numerically or structurally anomalous. The body height of individuals in group *(3)* is usually normal; most of them have a normal sex chromosomal complement (46,XX); yet, while the number of sex chromosomes is normal, their quality is different in some cases (46,XY). Diagnosis in such instances is not possible without laparotomy and histological examination.

XO is the most frequent chromosomal aberration in patients with ovarian dysgenesis. The incidence of mosaicism with structurally normal X chromosomes amounts to 1 : 6, and with the Y chromosome, to 1 : 20. A structural anomaly with or without mosaicism exists in 25% of the cases. It usually consists in an isochromosome of the longer arm of the X chromosome [38].

Screening tests of newborn babies showed the frequency of X monosomy to be 0.03% [2, 29, 30, 37, 41]. Frequency at the time of fertilization is certainly much higher [9]; it was for instance shown by RUZICSKA and CZEIZEL [40] that 95% of the zygotes with X monosomy had died in utero.

Examining from another angle the incidence of X monosomy or that of mosaicism accompanied by the absence or a structural anomaly of the X chromosome it was found that girls of short stature [47], women with primary amenorrhoea [23], and mentally retarded female patients [7, 18, 20] show these disorders considerably more frequently.

No data are available concerning the frequency of 45,X mosaicism. FORD [16] and JOB [24] concluded that the frequency of postnatal mosaicism presumably exceeded the incidence of 45,X, a result of the fact that the technique employed for neonatal screening tests or the examination of sex chromatin alone are not suitable for the detection of mosaicism [38]. Only in 3 cases among the 17 patients with Turner's syndrome of BARTA [4] and in 2 cases of 11 such patients in the material of FALK [11] was a mosaicism diagnosed. FERRIER [14] suggests that 30% of the patients with Turner's syndrome are mosaics.

There are many papers dealing with the anomalies at issue [3, 4, 5, 12, 13, 16, 25, 27, 28, 32, etc.], and the increase in the number of observed cases as well as the increasing reliability of observations have resulted in the description of numerous types of

the syndrome. The present study concerns 23 cytogenetically verified cases of 45,X and 45,X mosaicism.

Material

To detect sex chromosome anomalies, we have performed cytogenetic examinations of the patients of our institute and of the outpatients of the endocrinologic clinic. The principles of selection and the method of chromosomal examination (including the elusive criteria of mosaicism) have been described elsewhere [33, 35].

Results and Discussion

Among the 23 children with female phenotype and abnormal chromosomal constitution we found 13 cases of 45,X; 7 cases of 45,X/46,XX; 2 cases of mosaicism with structural anomaly: 46,XX/46,XX_{qi}; and one case of 45,X/46,XY.

Data regarding sex chromatin and chromosomal examinations are shown in Table I, the history and the indications of cytogenetic examination in

Table I
Sex chromatin and chromosomal constitution

No.	Name	Sex chromatin		Number of mitoses examined	<45	45	46	No. of karyotyped cells	Karyotype
		Barr bodies	Drum-stick						
1	M. S.	neg.	0/500	16	1	15	0	10	45,X
2	S. S.	neg.	0/500	25	3	22	0	14	45,X
3	V. V.	neg.	0/500	17	0	17	0	11	45,X
4	M. K.	neg.	0/500	28	2	26	0	15	45,X
5	M. K.	neg.	0/500	18	1	17	0	10	45,X
6	A. R.	neg.	0/500	40	3	37	0	10	45,X
7	E. T.	neg.	0/500	19	1	18	0	12	45,X
8	K. G.	neg.	0/500	12	0	12	0	8	45,X
9	K. B.	neg.	0/500	24	3	21	0	14	45,X
10	I. N.	neg.	0/500	18	0	18	0	10	45,X
11	I. B.	neg.	0/500	24	1	23	0	10	45,X
12	M. N.	neg.	0/500	24	2	22	0	10	45,X
13	E. C.	neg.	0/500	22	3	19	0	12	45,X
14	M. V.	neg.	0/500	52	2	32	18	16	45,X/46,XX/46,XXqi
15	H. B.	23/200	10/500	33	1	25	7	22	45,X/46,XXqi
16	A. M.	x	x	15	0	7	8	15	45,X/46,XX
17	J. B.	neg.	2/500	57	4	12	41	40	45,X/46,XX
18	A. M.	neg.	0/500	58	6	14	38	15	45,X/46,XX
19	M. S.	x	9/500	140	5	26	109	42	45,X/46,XX
20	R. M.	16/200	6/500	123	6	19	98	42	45,X/46,XX
21	J. T.	neg.	0/500	41	1	21	19	18	45,X/46,XX
22	K. R.	neg.	0/500	50	3	41	6	28	45,X/46,XX
23	M. D.	neg.	0/500	36	6	9	21	33	45,X/46,XY

TABLE II

History and indications for cytogenetic examination

No.	Age of		Which pregnancy? Birth weight (g)	History	Family history	Indication for cytogenetic examination
	father	mother				
1	23	21	1. 2500			Oedema of extremities at birth Heart anomaly
2	24	24	2. 2500	Oedema of extremities at birth	Father: 46,XY Mother: 46,XX Healthy sibling: 46,XY	Pterygium Hypertrophy of clitoris
3	?	21	1. 2000		Mother: low stature Sibling: familial hyperkeratosis	Pterygium
4	?	?	?			Pterygium
5	27	28	2. 3400		Both parents alcoholic. Three siblings alive. One child stillborn	Pterygium Congenital heart defect
6	?	21	1. 2500		Mother: 45,X/46,XX/47,XXX Low, obese	Pterygium Absence of puberty
7	38	24	1. 3500	Coarctation of aorta, persistent ductus Botalli operated	Father alcoholic Mother: psychopath	Pterygium, epicantus Congenital cardiopathy Delayed dentition
8	41	39	1. ?		Healthy sibling	Absence of puberty Hypertrophic clitoris
9	39	35	3. 3000		Diabetic mother Two healthy siblings	Absence of puberty Irregular ears
10	39	27	2. 2500	Pyloric stenosis	Familially delayed puberty Healthy sibling	Absence of puberty
11	27	26	1. 3150		Father: hypacusis Mother: hyperthyroidism Sibling: healthy	Pterygium

TABLE II (cont.)

No.	Age of		Which pregnancy? Birth weight (g)	History	Family history	Indication of cytogenetic examination
	father	mother				
12	21	20	1. 3200	Oedema of extremities at birth	Mother: low stature	Low stature Absence of puberty Skeletal anomaly
13	31	27	2. 2300		Stillbirth after first pregnancy	Absence of puberty Obesity
14	54	42	2. 3250		Healthy sibling	Absence of puberty
15	33	29	4. 3600	Oedema of extremities at birth Naevi	Two of 9 siblings mentally retarded. 3 siblings of mother retarded	Hypertelorism Mental retardation
16	27	20	1. 2200			Dystrophy Irregular ears
17	?	?	?			Mental retardation, Down's syndrome?
18	37	25	3. 3200		Healthy siblings	Pterygium Irregular ears
19	31	29	2. 3600		Healthy sibling	Pterygium
20	21	19	1. 2250		Father alcoholic	Pterygium Mental retardation
21	38	24	2. 3200		Absence of dentin in 3 maternal generations	Absence of puberty Familial dentin defects
22	42	39	3. 3500		Healthy siblings	Absence of puberty
23	23	23	1. 2400	Intestinal malrotation, operated		Delayed puberty

Table II, clinical manifestations in Table III.

The phenotype brought about by the XO anomaly may change from patient to patient. Short stature is the only common feature of these patients irrespective of age. The delay of growth is well represented by the ratio

TABLE III

Clinical symptoms

No.	Age, years	Height, cm	Quotient of actual height and height corresponding to chronological age	Somatic signs				Organ	
				Pterygium	Deep hairline	Lateral mammillae	Shield chest	Heart	Kidney
1	0.7			—	—	+	+	Ventricular septal def.	
2	4	96	0.79	+	+	+	+		
3	6	116	0.94	+	+	+	+		
4	10	119	0.68	+	+	+	+		Right side agenesis
5	11	114	0.53	+	+	+	+	Coarctation of aorta	
6	13	106	0.34	+	+	+	+		Ren arcuatus
7	14	134	0.70	+	+	+	+	Coarctation of aorta, patent ductus	
8	14	147	0.88	—	+	+	+		
9	15	134	0.65	+	+	+	+		
10	15	140	0.67	—	+	+	+		
11	16	139	0.65	+	+	+	+		
12	18	134	0.54	+	+	+	+		Double and polycystic on the right side
13	19	147	0.65	—	—	—	—		
14	17	141	0.61	—	+	+	+		
15	11	119	0.53	—	±	+	+	Coarctation of aorta	

and somatic data

anomalies			Gynaecological examination	Mental condition
Skeleton	Short 5th metacarpus	Diverse		
		Died at 8 months		
Knock knee. Dislocation of heep	+	Clinodactily. Cutis laxa. Irregular ears	Hypertrophic clitoris	Normal
Cubitus valgus Knock knee	+	Retarded dentition		Retarded
Dislocation of heep	+	Absence of enamel	Impalpable uterus	Retarded
Short fingers	+	Gothic palatae		Retarded
Cubitus valgus Knock knee	+	Deformity of auricles	Impalpable uterus	Retarded
	+	Retarded dentition	Undeveloped uterus and labia maiora	Normal
			Impalpable uterus, hypertrophic clitoris	Normal
	+	Absence of enamel Irregular ears	Undeveloped uterus and external genitals	Normal
Dislocation of heep	+		Undeveloped uterus and external genitals	Normal
Cubitus valgus		Gothic palata		Normal
Dislocation of heep, cubitus valgus	+	Absence of enamel	Undeveloped uterus and external genitals	Normal
Cubitus valgus Short fingers		Obesity	Undeveloped uterus	Retarded
			Undeveloped internal and external genitals	Normal
		Hypertelorism Pigmented naevi		Retarded

TABLE III

No.	Age, years	Height, cm	Quotient of actual height and height corresponding to chronological age	Somatic sings				Organ	
				Pterygium	Deep hairline	Lateral mammillae	Shield chest	Heart	Kidney
16	1.5	71	0.50	—	+	—	—		Right side polycystic kidney
17	4	85	0.50	+	+	—	+		
18	5	100	0.73	±	+	+	+	Coarctation of aorta	Right side aberrant artery
19	8	120	0.87	+	+	—	—		
20	9	101	0.40	+	+	—	+		Right side aberrant artery
21	14	150	0.98	±	+	+	+		
22	17	135	0.58	—	+	—	+		
23	15	136	0.67	—	+	+	+	Coarctation of aorta	

of the individual's actual height to the normal body height at the given age. Our results in this respect were in agreement with those of LEMLI and SMITH [28] in that the mean quotient was 0.66 in cases of 45,X, and 0.61 in those of 45,X mosaics, against 0.92 in the normal population.

Somatic characteristics. The frequency of a low posterior hairline (Fig. 1), and of a shield chest with laterally placed mammillae (Fig. 2) was approximately equal in the examined material. The pterygium necessitated a cosmetic operation in two cases (Fig. 3). One patient exhibited extensive pigmented naevi (Fig. 4).

An irregular position or deformity of the auricles are no typical concomitants of the syndrome. However, the position of the ears is a significant diagnostic clue, sometimes the only symptom of some chromosomal aberration. It was exactly a displacement of the ears — in combination with other minor signs — which has made us to suspect two of our patients of some genetic anomaly.

Patient No. 16, A. M., with a birth weight of 2500 g. The infant had a poor appetite, lagged in development, she had fever and 4—5 loose mucous stools daily. At admission the height was 71 cm, the height quotient 0.50; weight, 7500 g. The

(cont.)

anomalies			Gynaecological examination	Mental condition
Skeleton	Short 5th metacarpus	Diverse		
	+	Irregular ears		Normal
		Clinodactily		Retarded
Delayed bone age				Retarded
				Normal
Knock knee	+		Infantile uterus	Retarded
	+	Familial absence of enamel	Impalpable uterus	Normal
			Impalpable uterus	Normal
Cubitus valgus			Uncertain uterus infantile, external genitals	Normal

baby was restless. The internal organs and nervous system were normal. There were a convergent squint; deeply seated jutting ears; low posterior hairline; transverse line in left palm (Fig. 5). Intravenous urography, performed on account of massive pyuria, pointed to the possibility of a polycystic right kidney. X-rays revealed a shortness of the fifth metacarpal bone. Karyotype, 45,X/46,XX.

Anomalies of the internal organs

1. Kidney. Among the 13 patients with 45,X, one had a polycystic double kidney on the right side, another had renal agenesis likewise on the right side and one had a horseshoe kidney. Of the 10 mosaics, two patients had an aberrant right renal artery and one patient was suspected of having a polycystic kidney on the right side.

2. Heart. Congenital cardiac malformations are not invariably present in the 45,X syndrome; they are frequenty concomitant. Among the 17 cases of BARTA [4] there was one such combination, among the 11 cases of FALK [11] there were four, and among the 25 patients of LEMLI and SMITH [28] thirteen. While any form of cardiac anomaly may accompany the syndrome, coarctation of the aorta is regarded by VERNANT [45] as the

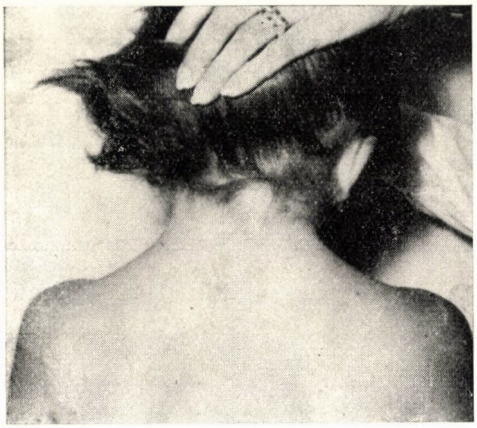

FIG. 1. Patient No. 3. Karyotype 45,X. Low posterior hairline

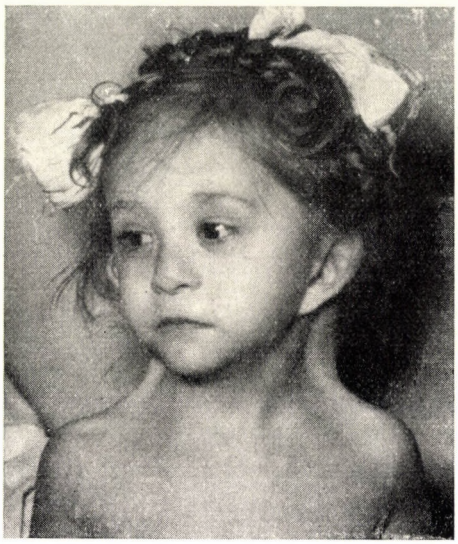

FIG. 3. Patient No. 3. Karyotype 45,X. Large pterygium colli

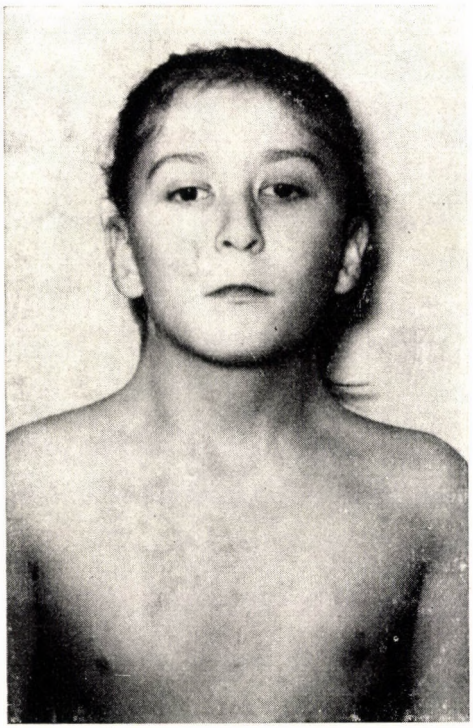

FIG. 2. Patient No. 7. Karyotype 45,X. Laterally seated mammillae

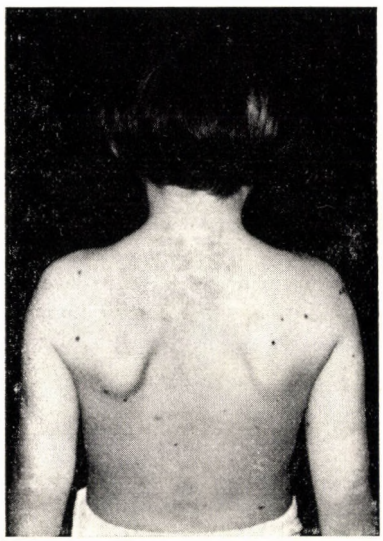

FIG. 4. Patient No. 15. Karyotype 45,X/46,XX_{qi}. Pigmented naevi all over the body

most frequent one. Among the 100 patients with congenital heart defect of DAHL [8], 18 had chromosomal aberrations, four with the karyotype 45,X. It seems therefore justified to assume that the frequency of 45,X is

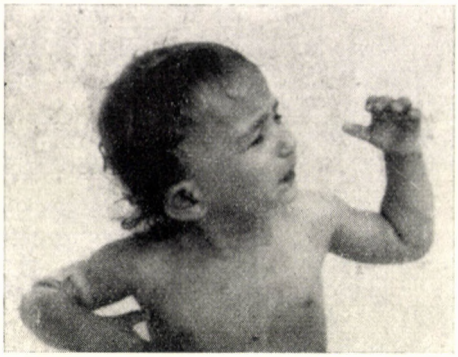

FIG. 5. Patient No. 16. Karyotype 45,X/46,XX. Irregularly placed jutting ears; transverse line on left palm

much higher among patients with a congenital malformation of the heart than among the general population.

In our material there were 5 cases of coarctation of the aorta, of which 3 were mosaics and one case of ventricular septal defect.

3. Skeleton. Conspicuous shortness of the fifth metacarpal bone and of the phalanges of the corresponding finger, described by ARCHIBALD [1], is a characteristic symptom of the syndrome. The sign if it occurs in the family has no diagnostic value but should raise the suspicion of a chromosomal aberration if the deformity is not familial. BOCZKOWSKI [6] regards it as an important diagnostic sign. We made X-rays of the metacarpal bones in 12 cases and found them abnormally short in all of them.

Patient No. 6, A. R. was subjected to cytogenetic examination at the age of 13 on account of delayed growth and puberty. The patient's mother was of short stature and mentally retarded, with short extremities and a chondrodystrophic exterior. Her karyotype was 45,X/46,XX/47,XXX. Physical examination revealed slight microcephaly, webbing of the neck, low posterior hairline, deformity of the auricles (Figs 6, 7, 8). There was no sign of puberty and the child appeared to be retarded both physically and mentally. The pyelogram revealed a horseshoe kidney with satisfactory renal function. The patient was sex chromatin negative with a karyotype 45,X in all examined mitoses. In view of the maternal karyotype the hereditary nature of the 45,X monosomy was clear in this case.

Other skeletal anomalies are also frequent. There were in our material 6 cases of knock knee and cubitus valgus, 2 cases of the dislocation of the hip and 2 cases with both of these anomalies.

4. Other disorders. Practically every congenital anomaly has occurred in

FIG. 6. Patient No. 6, age 13, with karyotype 45,X, and her healthy contemporary

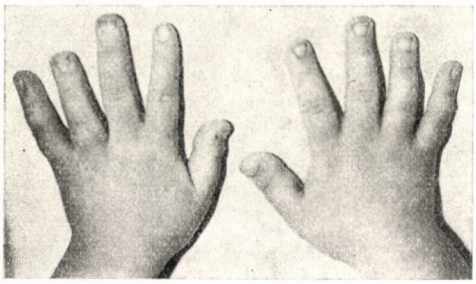

FIG. 7. Patient No. 6. Short 4th and 5th fingers on left hand

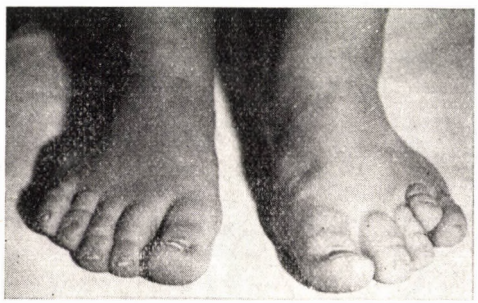

FIG. 8. Patient No. 6. Short 4th toe on left foot

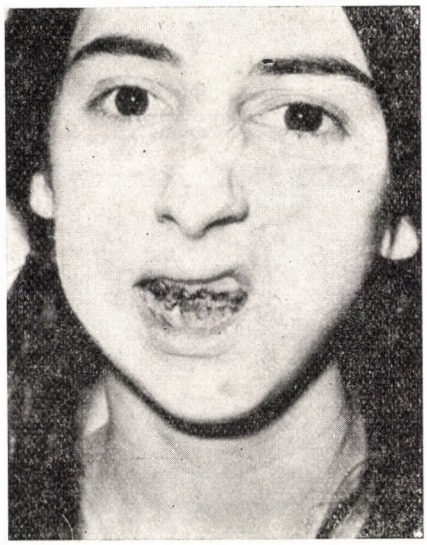

FIG. 9. Patient No. 21. Karyotype 45,X/46,XX. Dentin defects

connection with the 45,X condition Dentition anomalies are comparatively frequent. Our material included 3 cases of disturbed dentin development and 2 cases of retarded dentition.

Patient No. 21, J. T. was the second child of healthy parents, her sibling was likewise healthy. The patient was examined on account of irregular dentition. She had a birdlike face, irregular teeth with a marked dentin deficiency (Fig. 9). There was no trace of puberty, the hairline was deep, the patient had a shield chest with laterally situated mammillae. Rectal palpation revealed the presence of an infantile uterus. Mentally the child was normal. Dentin deficiency was found to be a family trait.

5. Disturbances of sexual development were observed in all examined patients of suitable age. There was no cycle and the secondary sex characters on the external genitals, pubic hair, breasts were missing.

6. Mental condition. Chromosomal aberrations are comparatively frequent among mentally deficient subjects. In the present material nine patients were mentally retarded (45,X in five, and 45,X mosaic in four cases).

It can be seen from Table II that certain phenomena (birth weight below 2500 g in 9 cases, neonatal oedema of the extremities in 4 cases) were more, others (e.g. pyloric stenosis in one case) less frequent. Age of the parents and other available familial data had no diagnostic value.

Cytogenetic examinations

Sex chromatin was negative in all children with the karyotype 45,X. Among the 10 mosaics, sex chromatin

was positive in three cases, uncertain in one case; in one case the examination was omitted for technical reasons. It has been stressed earlier [26, 33] that the examination of sex chromatin reveals only numerical irregularities but is not suitable for the detection of structural anomalies of the sex chromosome or the existence of mosaicism [38]. Reliable diagnosis must be based on knowledge of the karyotype.

A typical 45,X karyotype is presented in Fig. 10. We had two cases of X-isochromosome (Fig. 11) and one case with the chromosomal pattern of 45,X/46,XY (Fig. 12).

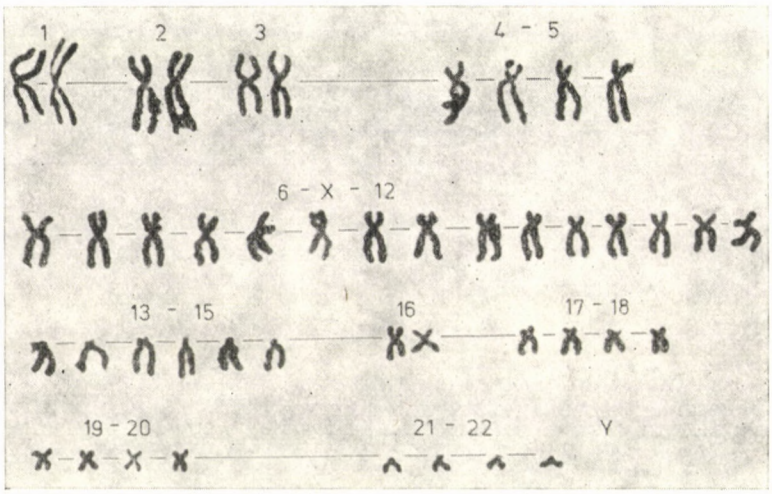

FIG. 10. Patient No. 12. Typical 45,X karyotype

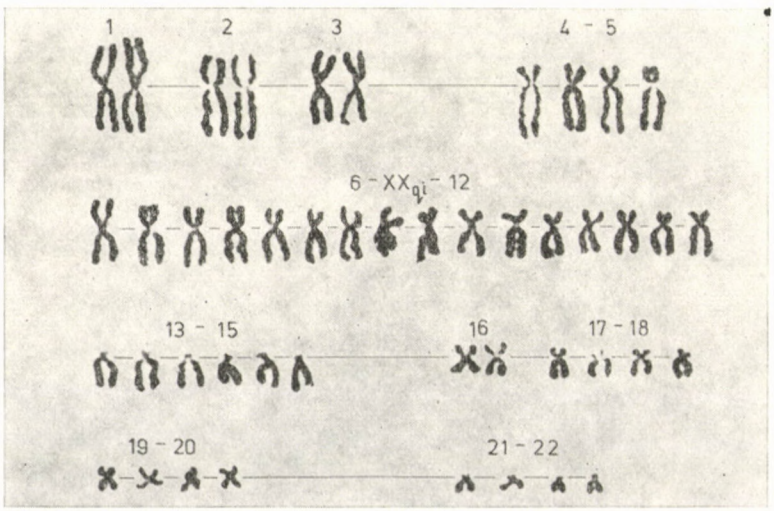

FIG. 11. Patient No. 14. Karyotype with isochromosomy. 45,X/46,XX/46,XX_{qi}

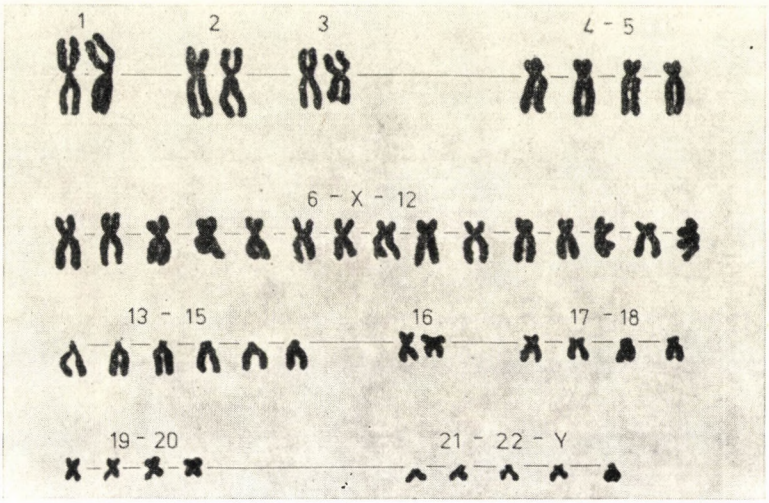

FIG. 12. Patient No. 23. Karyotype 45,X/46,XY

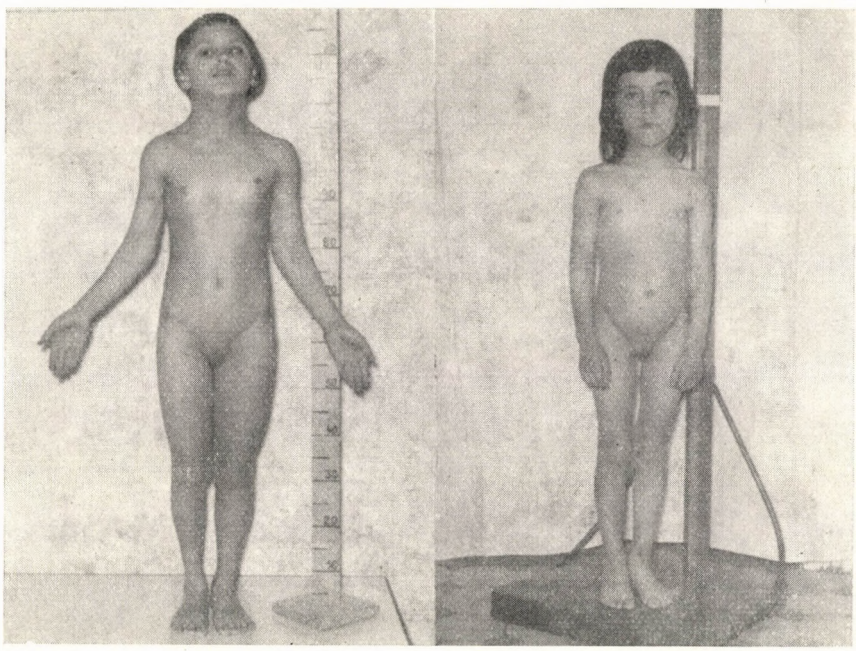

FIG. 13. Two children of the same age. Left: patient No. 4, karyotype 45,X. Right: patient No. 19, karyotype 45,X/46,XX

Dermatoglyphics

Comparison of the dermatoglyphic pattern of 45,X patients with those of normal individuals showed that X-monosomy increases the pattern intensity and the total ridge count [21, 22, 36]. The mean total ridge count was in our 45,X cases 183.17, and in the 45,X-mosaics, 158.22. These values were considerably higher than the average of 121.79 found in the normal population in Budapest [34].

Conclusions

The advance of cytogenetics has greatly facilitated the detection of mosaicism. This condition is certainly more frequent than would appear from the literature [14, 16, 25]. However, we cannot accept the view that, in cases of mosaicism, there is a linear correlation between the number of anomalous cells and the clinical picture. It may, of course, occur that the clinical manifestations are less pronounced in cases of mosaicism [25], but literary data [4, 11, 17] and our experience do not support this concept.

Among the 24 patients of the present series there were 10 cases of mosaicism. A still higher percentage was previously observed among patients with Klinefelter's syndrome [26]. All of the ten mosaics exhibited one or more typical symptoms of the syndrome 45,X (stunted growth in particular). The clinical picture in itself furnishes no clue for a differential diagnosis between X monosomy and mosaicism (Fig. 13).

Which are then the signs pointing to aberrations of the sex chromosome in the female phenotype?

At any age, backwardness in growth, webbing of the neck, low posterior hairline, deformity of the auricles shield chest, short fifth metacarpus, irregular dermatoglyphic configuration.

At birth, oedema of the extremities of unknown origin and possibly also simultaneous heart and kidney anomalies, especially in subjects with a low birth weight.

Between 10 and 12 years of age, short stature, delayed puberty, possible mental deficiency separately or in combination with the other symptoms.

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