Comparative cytogenetical and morphological studies in ovarian dysgenesis

MAGDOLNA GAÁL, J. LÁSZLÓ, AND P. BÖSZE

From the Department of Pathology, Institute for Medicine in Relation to Physical Education and Sports, Budapest, and the Cytogenetic Laboratory of the Department of Gynaecology and Obstetrics, Postgraduate Medical School, Budapest, Hungary

SYNOPSIS In 14 cases of the Turner syndrome and pure gonadal dysgenesis streak gonads were studied histologically. In cases where the 46,XX line was unimpaired the blood vessels of the gonad showed severe degeneration in at least 30 to 50%. These streak gonads usually contained some of the characteristic ovarian elements as well as the vascular lesions. In gonosomal monosomy, on the other hand, a similar intensive vascular degeneration could not be found and the gonad consisted of indeterminate connective tissue. These observations are strong indications of a close correlation between karyotype and the histology of the streak gonad, which may supply further information on the manner and timing of the development of the streak gonad.

Since the early descriptions of Morgagni (1967), Ullrich (1930), and Turner (1938), the Turner syndrome has been understood as a failure of female sexual differentiation which is associated with primary amenorrhoea, short stature, sexual infantilism, a webbed neck, and other somatic anomalies such as certain defects of the skeletal system (shield chest, cubitus valgus, and genu valgum etc) and of the cardiovascular system and genito-urinary tract. Instead of the normal ovaries there are connective tissue bands (gonadal streaks) in the same situation accompanied by hypoplasia of the uterus, vagina, and Fallopian tubes.

Ford, Jones, Polani, de Almeida, and Briggs showed in 1959 that the syndrome was characterized by a 45,X karyotype, but it was proved that the disease can also occur with gonosomal mosaicism or with structural anomalies of the second X chromosome, sometimes even in the presence of a Y chromosome.

Moreover Swyer (1955) and later Polani (1970) distinguished a group of pure gonadal dysgenesis in women with primary gonadal failure whose height is over 152 cm and are without either webbed neck or any other somatic abnormalities. In pure gonadal dysgenesis primary ovarian malfunction may be associated with a normal 46,XX or XY chromosome pattern or with certain mosaic forms and structural aberrations.

Histologically the gonadal streak consists of fibrous connective tissue with a whorl-like pattern that resembles ovarian stroma and is covered with germinal epithelium consisting of cuboidal or flattened columnar cells. A distinct tunica albuginea cannot be found beneath the germinal epithelium. The scanty cortical connective tissue is lacking in germ cells and primordial or Graafian follicles. Under the narrow peripheral stroma there is the medulla of loose connective tissue and the hilum containing a large number of blood vessels and nerves among the groups of hilus cells and remnants of fetal elements, ie, ducts of the rete ovarii and parovarian ducts.

Singh and Carr (1966) studied the ovaries of 45,X fetuses between the ages of 5 weeks and 4 months. It was proved that until the fourth month of gestation the histological picture of these ovaries corresponds in every detail—even in the number of germ cells—to the gonads of normal 46,XX fetuses. However, the number of germ cells and follicles decreases gradually in the second half of gestation to a point when the whole organ consists of stromal connective tissue without any follicles.

Nevertheless, in the gonads of some patients with sex monosomy Carr, Hagger, and Hart (1968) could demonstrate degenerated germ cells and atretic follicles. This observation was the basis for the authors to explain the rarely occurring menstruation. As regards the development of the syndrome

of ovarian dysgenesis, this evidence may refute such arguments that imply an uncompleted migration of germ cells in the genital ridge. Although it is bipotential the gland is much more likely to proceed in its differentiation as an ovary despite the chromosomal aberration. In the absence of the second X chromosome, however, it cannot develop beyond a certain stage of maturity, when regression sets in. Thus the chief defect in this disease is a regressive atrophy, ie, a secondary degeneration of the ovaries.

Márquez-Monter, Armendares, Buentello, and Villegas (1972), on the basis of the morphological and cytogenetical relationship of ovarian dysgenesis, described the presence of special ovarian elements associated with an inactive X chromosome in every instance, either as a mosaic form or as a gonosome with structural aberration. Primary follicles have never been found in 45,X cases.

Since the vascular condition of an organ provides sound information on its developmental and functional stage, we studied the relationship between chromosomal pattern and gonadal vascular morphology in streak gonads removed at laparotomy.

Materials, Methods, and Results

Laparotomy was performed on 14 of our patients whose clinical and cytogenetical examination was indicative of streak gonad. The patients were aged between 17 and 22 years. The specimen of streak gonad was fixed in formol. The slides were stained with haematoxylin and eosin, Mallory, Masson's trichrome, or Weigert's resorcin-fuchsin. Histologically particular attention was paid to the condition of the small arteries and capillaries passing the ovarian stroma and between the medulla and the scanty cortex.

Chromosome analysis was performed with a peripheral lymphocyte culture prepared as described by Moorhead, Nowell, Mellman, Battips, and Hungerford (1960) and modified by Hungerford (1965). Thirty metaphases were analysed in each case. For identifying structural aberrations we employed Giemsa banding, a fluorescent technique, and autoradiography. Barr bodies were counted in oral mucosal smears stained with thionine.

We classified the cases into two groups on the basis of the condition of the blood vessels as observed histologically.

Category I comprised six of our patients. All of these patients were characterized by severe vascular alterations in the streak gonad. The walls of the small and medium-sized arteries were thick and hyalinized. The capillaries between the dense stroma and the medulla were similarly affected in some cases even within the stroma of the ovary. In

addition to a partial hyaline degeneration of the vascular wall, marked intimal proliferation was observed in the medium-sized vessels. The lumina of the capillaries with the thick, hyalinized walls were narrow and some of them were wholly obliterated. Some of the small arteries contained hyaline thrombi. The connective tissue of these gonadal streaks was easily identifiable by the characteristic ovarian stroma with a few degenerated primordial follicles. In the hilum there were groups of Leydig cells and some remnants of the mesonephric ducts (figs 1, 2, and 3).

The karyotype was 46,XX in two of the cases and 45,X/46,XX with 30 to 50% of a normal cell line in a further two cases. In two cases structural aberrations of the second X chromosome were found. Thus, the first two cases corresponded to pure gonadal dysgenesis with a streak gonad and sexual infantilism. The four other cases were classified as the Turner syndrome (table I).

In the group II we placed eight other cases. In these the vessels of the streak gonad were found

Fig 1 Degenerated arterioles in a streak gonad. Note the thickened wall and the narrow lumen of the vessels.

Fig 2 Hyalinization of the vessels.

intact, but the streak contained very few, if any, ovarian components. The connective tissue in the streak showed only slight similarity to ovarian stroma. This type of streak gonad was associated with pure 45,X or 46,XY karyotypes, in some of the cases with 45,X/46,XX mosaicism with a low percentage of structurally disordered second X chromosome. In all but one of these cases the clinical signs could be classified as the Turner syndrome. The exceptional case was an XY type of pure gonadal dysgenesis (table II).

Fig 3 Hyalin degeneration of the wall of a medium-sized artery.

Discussion

The streak gonads were studied histologically in 14 cases of the Turner syndrome and pure gonadal dysgenesis respectively. A correlation was found between the pathohistological pattern of the blood vessels of the streaks and the karyotype of the patients.

No.	Patient, Age, Diagnosis	Height (cm)	Karyotype	Webbing of the Neck	Ovarian Elements in Streak Gonad	Degree of Vascular Lesion
1	SZ.T. 20 Turner syndrome	142.5	46,XX	+	++	+++
2	K.K. 18 Pure gonadal dysgenesis	158	46,XX	-	+++	+++
3	P.J. 18 Turner syndrome	138.3	45,X/46,XX 30%	-	+	+++
4	J.A. 18 Turner syndrome	144.8	45,X/46,XX 50%	-	++	+++
5	SCH.A. 20 Turner syndrome	152.4	46,XX/46,XXq- 50%	-	+	+++
6	SZ.M. 22 Turner syndrome	145	46,XX/46,X,i(Xq) 50%	-	Leydig cells ++	+++

Table I Cases of streak gonad with vascular lesion

No.	Patient, Age, Diagnosis	Height (cm)	Karyotype	Webbing of the Neck	Ovarian Elements in Streak Gonad	Degree of Vascular Lesion
1	K.E. 17 Turner syndrome	145-7	45,X	—	—	—
2	B.E. 18 Turner syndrome	144-8	45,X	—	—	—
3	A.A. 17 Turner syndrome	145-5	45,X/46,XXp— 25%	—	—	—
4	K.I. 20 Turner syndrome	142	45,X/46,XXp— 15%	—	—	—
5	K.I. 21 Turner syndrome	144	45,X/46,XX 10%	—	—	—
6	B.M. 15 Turner syndrome	127-2	45,X/46,XX 10%	—	—	—
7	R.E. 22 Turner syndrome	151-5	45,X/46,XY 50%	—	—	—
8	K.E.20 Pure gonadal dysgenesis	160	46,XY	—	—	—

Table II Cases of streak gonad without vascular lesion

The blood vessels in the streak gonad showed severe degeneration in those cases that had a karyotype of 46,XX or contained at least 30 to 50% of unimpaired XX line in mosaic form in addition to a 45,X cell line.

On the other hand, the capillaries and small arteries were free from these vascular changes when the streak gonad was associated with 45,X or 46,XY karyotypes and in such cases of mosaicism where the percentage of the unimpaired XX cell line was very low or the short arm of the second X chromosome was structurally affected.

This particular association between karyotype and morphological pattern is very suggestive of the possibility that in pure gonadal dysgenesis and in the mosaic forms of the Turner syndrome, where the unimpaired XX line was present to a high degree, the ovary begins to develop normally. This progression is, however, gradually taken over by regression and a degeneration of germ cells and blood vessels if the second X chromosome was partially lacking or its genetic activity was impaired. The damage to the gonads in these cases appears to have occurred at a later stage of fetal life, perhaps postnatally, but certainly not during embryonic life.

The normal progress of gonadal development had already ceased at the embryonic level in cases having a 45,X karyotype or a structural aberration of the second X chromosome, most likely because the primitive germ cells had been destroyed early in gestation. Therefore in this type of streak gonad regressive vascular changes could not be demonstrated.

As we know, one X chromosome is necessary for ovarian formation and the formation and migration of germ cells; the second heterochromatic X acts as a regulator of ovarian development and the rate of germ cell atresia. Therefore in cases of sex monosomy or structural aberration of the short arm

of the second X chromosome, the ovarian development comes to an early standstill or fails completely. Nevertheless in a 46,XX chromosome pattern or in mosaicism, with a high percentage of unimpaired XX line, the gene(s) responsible for ovarian development situated on the short arm of the second X chromosome must be assumed to have been active for some time in embryonic or fetal life. However, in mutation of the gene or genom this effect became insufficient for developing a normal, functionally active ovary, and regressive vascular changes took place causing atrophy and cicatrization of the organ leading to the formation of a streak gonad.

References

- Carr, D. H., Haggard, R. A., and Hart, A. G. (1968). Germ cells in the ovaries of XO female infants. *Amer. J. clin. Path.*, **49**, 521-526.
- Ford, C. E., Jones, K. W., Polani, P. E., de Almeida, J. C., and Briggs, J. H. (1959). A sex-chromosome anomaly in a case of gonadal dysgenesis (Turner's syndrome). *Lancet*, **1**, 711-713.
- Hungerford, D. A. (1965). Leukocytes cultured from small inocula of whole blood and the preparation of metaphase chromosomes by treatment with hypotonic KCl. *Stain Technol.*, **40**, 333-338.
- Márquez-Monter, H., Armendares, S., Buentello, L., and Villegas, J. (1972). Histopathologic study with cytogenetic correlation in 20 cases of gonadal dysgenesis. *Amer. J. clin. Path.*, **57**, 449-456.
- Moorhead, P. S., Nowell, P. C., Mellman, W. J., Battips, D. M., and Hungerford, D. A. (1960). Chromosome preparation of leukocytes cultured from human peripheral blood. *Exp. cell Res.*, **20**, 613-616.
- Morgagni, G. B. (1767). *De Sedibus et Causis Morborum*, Lib. III, XLVI, Sermo est de veneris impedimentis, et sterilitate in utroque sexu. *Epistola anatomica medica*, vol. 3, p. 381. Typographia Academica, Louvain.
- Polani, P. E. (1970). Chromosome phenotypes—sex chromosomes. In *Congenital Malformations*, edited by F. C. Fraser and V. A. McKusick, pp. 233-250. Excerpta Medica, Amsterdam and New York.
- Singh, R. P., and Carr, D. H. (1966). The anatomy and histology of XO human embryos and fetuses. *Anat. Rec.*, **155**, 369-384.
- Swyer, G. I. M. (1955). Male pseudohermaphroditism: a hitherto undescribed form. *Brit. med. J.*, **2**, 709-712.
- Turner, H. H. (1938). A syndrome of infantilism, congenital webbed neck and cubitus valgus. *Endocrinology*, **23**, 566-574.
- Ullrich, O. (1930). Über typische Kombinationsbilder multipler Abartungen. *Z. Kinderheilk.*, **49**, 271-276.