

- Riekhof, P. L., Horton, W. A., Harris, D. J., and Schimke, R. N. (1972). Monozygotic twins with the Turner syndrome. *American Journal of Obstetrics and Gynecology*, **112**, 59-61.
- Russell, A., Moschos, A., Butler, L. J., and Abraham, J. M. (1966). Gonadal dysgenesis and its unilateral variant with testis in monozygous twins: related to discordance in sex chromosomal status. *Journal of Clinical Endocrinology and Metabolism*, **26**, 1282-1291.
- Shine, I. B. and Corney, G. (1966). Turner's syndrome in monozygotic twins. *Journal of Medical Genetics*, **3**, 124-128.
- Turpin, R., Lejeune, J., Lafourcade, J., Chigot, P. L., and Salmon, Ch. (1961). Presomption de monozygotisme en dépit d'un dimorphisme sexuel: sujet neutre haplo X. *Comptes Rendus Hebdomadaires des Séances de l'Académie des Sciences*, **252**, 2945-2946.

Addendum

Since this paper was submitted for publication, another pair of monozygotic twins, discordant for phenotypic sex, was described (Karp *et al*, 1975). As in our case, the normal male had a karyotype of 46,XY, while the female's chromosome constitution was 46,XY/45,X, similar to our case. However, the phenotypic female twin had an enlarged clitoris and histology of one gonad showed some testicular structures. This girl also had fewer clinical signs of Turner's syndrome than our patient. Thus the case of Karp *et al* could have been assigned to the syndrome of mixed gonadal dysgenesis (Davidoff and Federman, 1973).

REFERENCE

- Karp, L., Bryant, J. I., Tagatz, G., Giblett, F., and Fialkow, P. J. (1975). The occurrence of gonadal dysgenesis in association with monozygotic twinning. *Journal of Medical Genetics*, **12**, 70-78.

An XX female with sexual infantilism, absent gonads, and lack of Müllerian ducts*

Summary. A patient with a 46,XX chromosome constitution showed the following main characteristics: lack of secondary sexual development, female external genitalia with absence of vagina, no gonadal structures, and complete lack of internal genitalia. This is a variant of the gonadal agenesis syndrome so far only described in association with an XY chromosome component. Endocrinology demonstrated that in the absence of gonadal feedback the pituitary responsiveness to synthetic luteinizing hormone-releasing hormone was increased.

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Reports of agonadism are scarce (Overzier and Linden, 1956; Philipp, 1956; Chaptal *et al*, 1958; Dewhurst *et al*, 1963; Emson and Buckwold, 1965; Sarto and Opitz, 1973; Levinson *et al*, 1975) and its aetiology remains ill understood at this time. Hitherto, all patients with gonadal agenesis syndrome have been found to possess an XY karyotype so that it has been suggested that the fetal testis was functional for a sufficient time to induce the Müllerian duct inhibition, but not long enough to maintain Wolffian duct development. A short activity of the fetal testis would also account for the partially virilized external genitalia which is a common finding in these patients. The syndrome has been discussed under various names as 'true agonadism', 'vanishing testicles', 'XY female with absent gonads', and 'the XY gonadal agenesis syndrome'. The purpose of the present communication is to report what is, to our knowledge, the first case of gonadal agenesis associated with a 46,XX sex chromosome constitution.

Case report

The proband, aged 17, was admitted to hospital on 9 August 1974, because of primary amenorrhoea and retardation of sexual development. The patient had been brought up as a woman since she had a feminine phenotype (Fig. 1). Height was 145 cm, lower segment 75 cm, span 147 cm; weight was 45 kg. Breasts were prepubertal and axillary hair was absent. External genitalia (Fig. 2) showed immature labia majora and

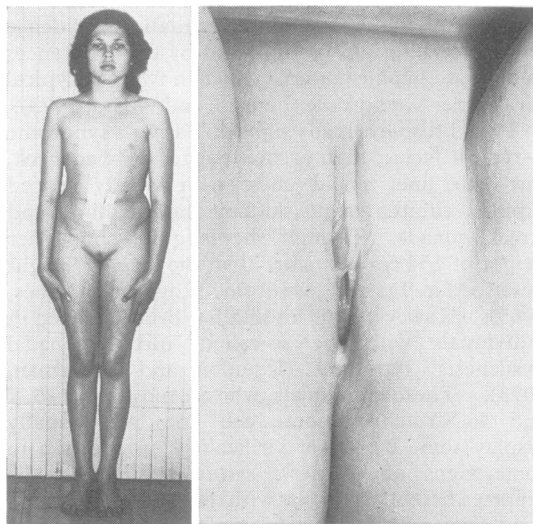


FIG. 1.

FIG. 2.

FIG. 1. General appearance of the patient.

FIG. 2. The external genitalia show the normal infantile type.

TABLE

EFFECT OF INTRAVENOUS ADMINISTRATION OF 100 μ g SYNTHETIC LH-RH (Ayerst, ICI) ON SERUM LEVELS OF LH AND FSH IN PATIENT WITH ABSENT GONADS

	Time (min.)					
	0	15	30	60	120	180
LH	2650	4250	5000	5000	4875	5000
FSH	967	1275	1312	1312	1020	976

Normal response to LH-RH†

	Basal	Max
LH	127 \pm 15	758 \pm 170 (M \pm SE)
FSH	212 \pm 21	315 \pm 20

* Values are expressed in ng/ml. of LER-907 (National Pituitary Agency, NIHMD, USA).

† Taken from Zárate *et al* (1973).

minora, a normal clitoris, and absence of the vagina; uterus and gonads could not be palpated. The patient showed no webbing of the neck, cubitus valgus, nail defects, shortness of metacarpals, or signs of congenital heart disease. The rest of the physical examination was unremarkable. At exploratory laparoscopy, no internal genitalia or gonads were found. Routine laboratory tests were all normal. She was found to excrete normal amounts of 17-ketosteroids and 17-hydroxysteroids. The urinary 24-hour output of total oestrogens was 8 μ g and the gonadotrophin activity in urine by bioassay was above 54 mouse units. Cytogenetic analysis revealed Barr bodies in a buccal smear, and the lymphocytes of the peripheral blood showed a 46,XX karyotype.

The pituitary gonadotrophin reserve was studied by the administration of synthetic luteinizing hormone-releasing hormone (LH-RH) as shown in the Table. The raised basal gonadotrophin levels in this patient were associated with a significantly greater release in response to LH-RH for both LH and FSH when compared with that seen during the follicular phase of the menstrual cycle. IVP disclosed no abnormalities of kidneys or bladder; however, a double ureter was found on the left side. Radiology of sella turcica, spine, hands, and chest were all unremarkable or negative. Bone age was consistent with the chronological age.

The family history showed that the patient was the last of her mother's 11 pregnancies which had resulted in the birth of 10 brothers. All 10 brothers matured at the usual age; they are all normal and have no anomalies. The three older brothers are married and each of them has at least one child. The mother and father were 41 and 46 years old, respectively, when the patient was born; they are apparently not related to each other and are of normal intelligence and stature. No relative is known to have had problems like of those of the patient.

Discussion

All cases of agonadism previously reported are similar in many respects. All were X chromatin negative and, where studied, had an XY constitution; all lacked breast development and showed several minor extragenital anomalies; as a rule there seem to be no consistent major abnormalities. The vagina was absent in all cases, and an enlarged clitoris and variable degrees of labioscrotal fusion were described. The internal genital anomalies are similar in all cases. True internal genital structures such as uterus, Fallopian tubes, or gonads were lacking. The unique explanation for the genital gonadal anomalies of this syndrome is a complete primary deficiency of all genital duct elements, with concomitant absence of the fetal ovary. The XX gonadal agenesis syndrome is different from the vaginal atresia syndrome in which a 46,XX sex chromosome constitution is combined with normal ovarian development and maturation of female secondary sex characteristics, and frequently with major anomalies (eg of kidneys, the cardiovascular system, the vertebral spine, etc). It is likely that the XX gonadal agenesis syndrome represents a genetic disorder; however, at the present time the mode of inheritance of this condition remains to be clarified.

The present study also shows that in the absence of gonadal feedback the pituitary responsiveness to LH-RH is significantly increased. The enhanced response for both LH and FSH is probably a reflection of an increased pituitary gonadotrophin store. This interpretation is consistent with the finding of an increased pituitary gonadotrophin content in gonadal dysgenesis patients, as reported by Siler and Yen (1973).

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REFERENCES

- Chapal, J., Jean, R., Pages, P., Campo, C., Bonnet, H., and Duntze, F. (1958). Sur un cas de dysgénésie gonadique avec manifestations androgéniques. *Archives Françaises de Pédiatrie*, **15**, 613-622.
- Dewhurst, C. J., Paine, C. G., and Blank, C. E. (1963). An XY female with absent gonads and vestigial pelvic organs. *Journal of Obstetrics and Gynaecology of the British Commonwealth*, **70**, 675-680.
- Emson, H. E. and Buckwold, A. E. (1965). Agonadism. *Canadian Medical Association Journal*, **93**, 1080-1083.

- Levinson, G., Guzmán-Toledano, R., Canales, E. S., and Zárate, A. (1975). Síndrome de agonadismo o agenesia gonadal en una paciente con pseudohermafroditismo y cariotipo 46,XY. *Revista de Investigación Clínica*, **27**, 231-237.
- Overzier, C. and Linden, H. (1956). Echter Agonadismus (Anorchismus) bei Geschwistern. *Gynaecologia*, **142**, 215-233.
- Philipp, E. (1956). Die Fehlbildungen der Keimdrüse. *Deutsche medizinische Wochenschrift*, **81**, 1298-1302.
- Sarto, E. G. and Opitz, M. J. (1973). The XY gonadal agenesis syndrome. *Journal of Medical Genetics*, **10**, 288-293.
- Siler, T. M. and Yen, S. S. C. (1973). Augmented gonadotropin response to synthetic LRF in hypogonadal state. *Journal of Clinical Endocrinology and Metabolism*, **37**, 491-494.
- Zárate, A., Canales, E. S., De la Cruz, A., Soria, J., and Schally, A. V. (1973). Pituitary response to synthetic LH-RH in Stein-Leventhal syndrome and functional amenorrhea. *Obstetrics and Gynecology*, **41**, 803-808.

Further observations on the Birmingham chimaera

Summary. The appropriate ABH-gene specified glycosyltransferases in the plasma of the Birmingham chimaera were estimated. These observations and the demonstration of A_1Le^b blood group specific glycosphingolipid in the plasma indicate that the minority population of red blood cells probably represents the true blood groups of the patient.

We recently reported (Battey *et al*, 1974) a human female chimaera with two red cell populations and an overwhelming preponderance of lymphocytes which were of the normal male karyotype 46,XY. We have further investigated this patient in the light of new knowledge.

Case report

Blood group gene products in plasma

The patient has a mixture of about 93% O and 7% A_1 red cells. We, therefore, investigated the patient's plasma for *A*- and *H*-gene specified transferases, with the undermentioned results:

α -N-acetylgalactosaminyltransferase (the primary product of the blood group A gene) activity at pH 6	28%
α -2'-fucosyltransferase (the primary product of the blood group H gene) activity at pH 7.2	11%

The percentages represent the amount of radioactivity transferred to a low molecular weight acceptor from UDP-[14 C]-N-acetylgalactosamine and GPD-[14 C]-fucose. A normal A_1 control plasma gave 29% incorporation when tested under the same conditions with UDP-[14 C]-N-acetylgalactosamine. The 2'-fucosyltransferase activity fell within the range expected for an A_1 , and was rather high for an O donor. A few O sera

do have activities as high as the figure given above; we find, however, that the average for A donors is higher than for O or B donors (M. A. Chester and W. M. Watkins, unpublished observations). It can, therefore, be claimed that the patient behaves, as far as her transferases are concerned, like a normal A_1 person.

A_1Le^b blood group specific substance

The hybrid A_1Le^b blood group specific substance is a glycosphingolipid present in the plasma of a person who has inherited the *A*₁, *Le*, *H*, and *Se* genes (Swanson *et al*, 1971; Tilley *et al*, 1975). The A_1Le^b substance coats red cells in the same way as ordinary Le^a and Le^b substances.

Red cells coated with A_1Le^b are agglutinated by an antibody anti- A_1Le^b which does not agglutinate cells coated with either A_1 or Le^b alone (Seaman, Chalmers, and Franks, 1968; Crookston, Tilley, and Crookston, 1970; Gundolf, 1973).

In twin or bone-marrow transplantation chimaeras, A_1Le^b substance coats the subject's true red cells as well as those derived from grafted bone-marrow (Crookston *et al*, 1970; Swanson *et al*, 1971; Wrobel *et al*, 1974).

The red blood cells of our patient were tested with an anti- A_1Le^b serum kindly provided, through Dr K. L. G. Goldsmith, by Dr Carolyn Giles, who had obtained it from Mrs Marie Crookston. All the red cells were agglutinated by this reagent; this showed that her O red cell population was also 'stamped' with her true genetic marker, A_1Le^b . Tests with a potent anti-A also showed that her O cells were coated with A-substance.

Discussion

Although our patient was said not to be a twin, her twin may have been aborted or assimilated. We were unable to obtain firm evidence that dispermy was responsible. If she is really a twin (and we suspect she is), the true blood groups of our patient are those represented by her minority red cell population, as indeed her true sex is that represented by her minority lymphocyte population (46,XX). Similar observations have been made by Wrobel *et al* (1974). The presence of normal amounts of *A*-gene transferase and of A_1Le^b blood group specific substance in our patient's plasma does not necessarily indicate that she is really a twin. A final opinion must await the results of similar studies in dispermic chimaeras. If she is really a dispermic chimaera, she would of course have two 'true' red cell populations.

In our patient and in other chimaeras, there is much disproportion between the relatively small numbers of red cells which constitute the minority population and the normal levels of the corresponding serum transferase. It is, therefore, highly likely that a large proportion of the ABH-blood group gene specified transferases in plasma are derived from sources other than the bone-marrow.