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.

Reports of agonadism are scarce (Overzier and Linden, 1956; Philipp, 1956; Chaptal et al, 1958; Dewhurst et al, 1963; Emson and Buckwaltd, 1965; Sarto and Opiotz, 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 Wolfian 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

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Table

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<thead>
<tr>
<th>Time (min.)</th>
<th>LH</th>
<th>FSH</th>
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<tbody>
<tr>
<td>0</td>
<td>2650</td>
<td>967</td>
</tr>
<tr>
<td>15</td>
<td>4250</td>
<td>1275</td>
</tr>
<tr>
<td>30</td>
<td>5000</td>
<td>1312</td>
</tr>
<tr>
<td>60</td>
<td>5000</td>
<td>1312</td>
</tr>
<tr>
<td>120</td>
<td>4875</td>
<td>1020</td>
</tr>
<tr>
<td>180</td>
<td>5000</td>
<td>976</td>
</tr>
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Normal response to LH-RH†

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<tr>
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<th>Basal</th>
<th>Max (M ± SE)</th>
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<tbody>
<tr>
<td>LH</td>
<td>127 ± 15</td>
<td>758 ± 170 (M ± SE)</td>
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<tr>
<td>FSH</td>
<td>212 ± 21</td>
<td>315 ± 20</td>
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* Values are expressed in ng/ml of LER-907 (National Pituitary Agency, NIHMD, USA).
† Taken from Zárate et al (1973).

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 in all cases of LH and FSH is probably a reflection of an increased pituitary gonadotrophin reserve. This interpretation is consistent with the finding of an increased pituitary gonadotrophin content in gonadal dysgenesis patients, as reported by Silen and Yen (1973).

REFERENCES

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 A1,Leb 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% A1 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-[14C]-N-acetylgalactosamine and GDP-[14C]-fucose. A normal A1 control plasma gave 29% incorporation when tested under the same conditions with UDP-[14C]-N-acetylgalactosamine. The 2'-fucosyltransferase activity fell within the range expected for an A1, 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 transferrases are concerned, like a normal A1 person.

A1,Leb blood group specific substance

The hybrid A1,Leb blood group specific substance is a glycosphingolipid present in the plasma of a person who has inherited the A1, Le, H, and Se genes (Swanson et al, 1971; Tilley et al, 1975). The A1,Leb substance coats red cells in the same way as ordinary Le and Leb substances.

Red cells coated with A1,Leb are agglutinated by an antibody anti-A1,Leb which does not agglutinate cells coated with either A1 or Leb alone (Seaman, Chalmers, and Franks, 1968; Crookston, Tilley, and Crookston, 1970; Gundolf, 1973).

In twin or bone-marrow transplantation chimaeras, A1,Leb 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-A1,Leb 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, A1,Leb. 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 A1,Leb 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.