Two XX males diagnosed in childhood

Endocrine, renal, and laboratory findings

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Laurance, B. M., Darby, C. W., and Vanderschueren-Lodeweyckx, M. (1976). *Archives of Disease in Childhood*, 51, 144. **Two XX males diagnosed in childhood: endocrine, renal, and laboratory findings.** Two prepubertal boys with bilateral cryptorchidism were identified as 46,XX after nuclear sexing studies in several tissues. Gonadal histology and chromosome studies suggested that true hermaphroditism or mosaicism were unlikely. Xg blood grouping was informative in one patient. Accepting paternity, this suggested either that both Xs were maternal, with loss, for example, of the male determining Y chromosome, or that the paternal X chromosome did not express, probably because of a deletion, the allele for the positive Xg blood group. The patients had normal thyroid stimulating hormone reserves but subnormal responses to human chorionic gonadotrophin stimulation, and may need hormonal replacement at puberty. Both had renal anomalies. We suggest that chromosome analysis is essential when cryptorchidism, hypospadias, or microgenitalia are found and that an intravenous pyelogram is desirable.

The Y chromosome is necessary for the development of fetal testes and male phenotype (Brøgger and Aagaenæs, 1965; Ferguson-Smith, 1965, 1966). There are a few previous descriptions of phenotypic males with a 46,XX karyotype and without true hermaphroditism but very few of such children, because the diagnosis is easily overlooked. Hypoplastic genitalia is the sole feature recognizable before puberty and only later reduced sexual activity, azoospermia, and occasional gynaecomastia become apparent.

Since the original clinical description of an XX male (de la Chapelle *et al.*, 1964) other case reports (Therkelsen, 1964; Brown *et al.*, 1964; Bergstrand and Lindsten, 1965; de la Chapelle *et al.*, 1965, 1971; Strauch *et al.*, 1965; Lindsten *et al.*, 1966; von Mulert, Schröter, and Wolf, 1966; de Grouchy *et al.*, 1967; Zuppinger *et al.*, 1967; Boczkowski *et al.*, 1969; Frøland, 1969; Luciani *et al.*, 1969; Mori, Mizutani, and Sonoda, 1969; Sebaoun *et al.*, 1969; Berger *et al.*, 1970; Bergman, Nowakowski, and Reitalu, 1970; George and Polani, 1970; Neuwirth and Raboch, 1970; Powers *et al.*, 1970;

Caspersson *et al.*, 1971; Sutherland, Wiener, and Bartholomew, 1972; Madan and Walker, 1974) and one review have followed (de la Chapelle, 1972). The incidence has been estimated at about 1 in 45 000 males (Polani, 1972), though a chromosome study of 3500 consecutive births in Edinburgh yielded one 46,XX patient (Ratcliffe *et al.*, 1970). The case reports have not documented renal or thyroid function or the plasma testosterone response to human chorionic gonadotrophin (HCG). The endocrine, renal, and laparotomy findings in two phenotypically male children with the 46,XX karyotype are described here.

Case reports

Case 1. This boy was referred because of bilateral undescended testes at the age of 4 years 6 months (Fig.). He had a normal-sized penis with a terminal urethra but had to sit to micturate because of severe chordae. His scrotum was poorly developed and a single, small gonad was palpable in the right inguinal canal. He was otherwise normal. A buccal smear showed 30% chromatin-positive nuclei and all were negative for Y fluorescence; the peripheral blood karyotype was that of a normal female (46,XX). At laparotomy no uterus or thickening were found but there was a rudimentary vas deferens on both sides. The bilateral intra-abdominal gonads, 1.5 cm × 0.5 cm,

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FIG.—External genitalia in Case 1.

histologically showed small embryonic seminiferous tubules widely separated by loose connective tissue in which were scanty Leydig cells. No gonial elements were present. In the adjacent tissue there were a few tubules lined by columnar epithelium probably representing Wolffian elements. Cultures of both gonads and skin produced only cells with a 46,XX karyotype. He was reinvestigated at the age of 8 years 8 months (Table).

Case 2. This boy was referred at the age of 5 years for treatment of undescended testes. He had a hypoplastic scrotum with small gonads palpable in the inguinal canals and a normal-sized penis with a terminal urethra. There were no other abnormalities. A buccal smear showed 32% chromatin-positive cells and no Y fluorescence, and the peripheral blood chromosomes were 46,XX. At laparotomy a gonad 12 mm in length, which histologically showed infantile testicular tissue, was found in each superficial inguinal pouch. The seminiferous tubules were more mature and the Leydig cells more numerous than in Case 1. No ovarian tissue or uterus were found. No gonial elements or Wolffian derivatives were present. Culture of both gonads yielded 46,XX cells only and no Y

fluorescence of the metaphase chromosomes or the interphase nuclei. Results of investigations at the age of 6 years 6 months are shown in the Table.

Discussion

These 2 patients fulfil the diagnostic criteria for XX males, since they were clinically males with bilateral histologically proved testes. True hermaphroditism is excluded. Furthermore, they lacked macroscopical or microscopical evidence of Müllerian remnants or ovarian tissue. Their leucocyte, skin, and gonadal tissue showed a consistent 46,XX pattern and no fluorescent Y body. That makes mosaicism, including XXY cells, unlikely, although it does not exclude a translocation involving only the short arm of the Y, on which is alleged to be the masculinizing (testis-determining) factor(s) (Jacobs, 1969; Angell, Gianelli, and Polani, 1970/1971; Madan and Walker, 1974).

XX males are rare and are usually undiagnosed in childhood unless there is some associated genital malformation. Out of 50 patients in whom age at diagnosis was reported only 10 were diagnosed before 15 years of age; 3 of the 10 had perineal hypospadias (de Grouchy *et al.*, 1963; Berger *et al.*, 1970; de la Chapelle *et al.*, 1971; de la Chapelle, 1972), one had a large phallus and scrotum (George and Polani, 1970), one newborn diagnosed in a survey study had normal genitalia (Ratcliffe *et al.*, 1970), but the presenting features of the remaining 5 are not recorded (de la Chapelle, 1972). Our patients were referred because of undescended testes and had no urethral abnormality. The chromatin-positive cells in their buccal smears led to chromosomal analysis. Unilateral or bilateral cryptorchidism has been reported in 8 of 44,XX males whose clinical descriptions were detailed (Brown *et al.*, 1964; George and Polani, 1970; Ratcliffe *et al.*, 1970; de la Chapelle, 1972; Sutherland *et al.*, 1972), a similar incidence to that found in Klinefelter's syndrome (Frøland, 1969).

All boys with bilateral or unilateral undescended testes should have a buccal smear studied. Laparotomy and histology of the gonads is also essential to exclude Müllerian remnants and true hermaphroditism if the palpable gonad is small for the age. In the only five laparotomies described previously no Müllerian remnants were found but in the other cases the abdomen was not explored. Histology of the testes in XX males had resembled either that of Klinefelter's syndrome (Brown *et al.*, 1964; de la Chapelle *et al.*, 1964; Strauch *et al.*, 1965; Lindsten *et al.*, 1966; de Grouchy *et al.*, 1967; George and Polani, 1970) or rarely that of germinal cell aplasia (de Grouchy *et al.*, 1963;

TABLE

Results of chromosome, endocrine, and renal investigations in two XX males

Investigation	Case 1	Case 2
Age (years)	8 6/12	6 8/12
Height (cm) (centile, male)	140 (> 90th)	117 (25th)
Weight (kg) (centile, male)	41.5 (> 97th)	21.5 (> 25th)
Bone age (years, male)	11 6/12	7
Chromosome analysis		
Cell control	30	30
Blood	46,XX	46,XX
Gonads	46,XX	46,XX
Skin	46,XX	—
Y fluorescence in interphase nuclei and metaphase chromosome	Absent	Absent
Buccal smear: % positive cells	30	32
Xg blood grouping		
Patient	Xg (a +)	Xg (a -)
Father	Xg (a -)	Xg (a +)
Mother	Xg (a +)	Xg (a -)
24-h urinary 17-oxosteroids (mg/100 ml)	4.7	2.3
11-oxygenation index	0.2	0.4
LH (IU/24 h)	69.9	159
FSH (IU/24 h)	2.1	3.4
HCG test (dose 5 × 1000 IU/day)		
Plasma testosterone (ng/100 ml)		
before test	8	6
after 3 doses	37	58
after 5 doses	85	95
TRH test (dose 0.2 mg intravenous)		
Plasma TSH (μU/ml)		
before test	<0.5	2
after 20 min	18.1	10
after 60 min	6.3	8.1
Intravenous pyelogram		
Left	Duplex pelvicalyceal system with single ureter	Normal
Right	Normal	Duplex pelvicalyceal system with duplicated ureter

LH = luteinizing hormone (upper normal limits for age 5 IU/24 h (Buckler and Clayton, 1970); FSH = follicle stimulating hormone; HCG = human chorionic gonadotrophin; TRH = thyrotrophic releasing hormone; TSH = thyroid stimulating hormone.

Lindsten *et al.*, 1966; Luciani *et al.*, 1969; Berger *et al.*, 1970) but more commonly an intermediate histological appearance has been found (de la Chapelle *et al.*, 1964, 1971; Therkelsen, 1964; Lindsten *et al.*, 1966; Boczkowski *et al.*, 1969). Scanty Leydig cells were present in only one of our patients but both had infantile seminiferous tubules separated by loose connective tissue. No Leydig cells were found in two previously reported prepubertal children (Berger *et al.*, 1970; de la Chapelle *et al.*, 1971) but they were hyperplastic in several postpubertal patients (de la Chapelle *et al.*, 1964, 1971; Therkelsen, 1964; Strauch *et al.*, 1965; Lindsten *et al.*, 1966; von Mulert *et al.*, 1966). Spermatogenesis is usually absent in adult XX males, though occasional spermatogonia were seen in one 15-year-old boy (de Grouchy *et al.*, 1967).

In the only reports of short-term stimulation with HCG there was no rise of testosterone in the urine of one adult or in the plasma of another (Sebaoun *et al.*, 1969). Our patients had a significant but subnormal increase in plasma testosterone.

This indicates reduced Leydig cell activity and may explain the inadequate secondary sex characteristics of adult XX males. Although our patients were clinically prepubertal both had raised urinary gonadotrophins and in Case 1 the bone age was advanced, for which we have no explanation.

A previous report (Lindsten *et al.*, 1966) suggested a decreased thyroid stimulating hormone (TSH) reserve in XX males but our patients had a normal TSH response to intravenous synthetic thyroid releasing hormone, providing direct evidence of normal pituitary TSH reserve.

Intravenous pyelograms were normal in 10 out of the 11 previously reported patients (de la Chapelle *et al.*, 1964, 1965, 1971; Lindsten *et al.*, 1966; von Mulert *et al.*, 1966; de Grouchy *et al.*, 1967; Berger *et al.*, 1970), the exception being a 24-year-old XX male with uraemia due to an atrophic right kidney (Powers *et al.*, 1970). Pyelograms in both our cases showed a unilateral duplex pelvicalyceal system with a single ureter in Case 1. In neither case was there a history of urinary symptoms or

infection. Duplications of the pylon are commoner in girls than in boys (James, 1972).

Several hypotheses have been postulated to explain this condition (Hungerford, Donnelly, and Nowell, 1964; Ferguson-Smith, 1966; Sanger Tippet, and Gavin, 1971; de la Chapelle *et al.*, 1971; Bartsch-Sandhoff, 1974). Mosaicism is unlikely since a large number of cells from various sites showed 46,XX cells only. The findings of fluorescence studies also make mosaicism unlikely. The same can be said for translocations of the terminal portion of the Y (Polani and Mutton, 1971), though, since Y fluorescence in the biological father was unknown this cannot be quite certain. In any event, this would be irrelevant to male determination if the masculinizing factors were elsewhere on the Y chromosome. The Xg blood group findings are informative only in Case 2 and then only on the assumption that the 'father' was indeed the biological one. If he was, translocation is one possibility. In this event it would have to have been from the Y chromosome to the X with loss of the Xg locus in the course of the exchange. The loss of this locus would give the appearance that both Xs were maternal though one was paternal and carried the father's masculinizing factors from the Y in lieu of the Xg locus. Possibly also XX males may arise from XXY zygotes if the Y becomes lost after initiating male development (Sanger *et al.*, 1971), but not necessarily so. The Xg blood groups in Case 1 were unhelpful in this respect.

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Addendum

Since this article was submitted for publication preliminary communications by Wachtel *et al.* (1975) and Bennett *et al.* (1975) support the hypothesis that the presumptive testis-determining gene(s) which resides either on the short arm or on a pericentric region of the acrocentric human Y chromosome produces an H-Y (histocompatibility—Y) antigen. The cells of certain XX human males have been shown to express this antigen, which suggests that the testis-determining gene and the H-Y locus are extremely closely linked and may indeed be identical. It is possible that the locus of the H-Y antigen normally present on the Y chromosome is transposed to an autosome in some XX males.

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Corrigendum: In the Table on p. 146 of the article 'Two XX males diagnosed in childhood' by Laurance *et al.*, *Archives*, 1976, **51**, p. 144, the Xg group of the mother of Case 2 should read 'Xg (a+)'.