Case reports

indicate any feature that can be regarded as characteristic of trisomy 9q. However, when more cases are reported a syndrome may become recognizable.

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Note added in proof
Since submitting this report two cases of trisomy 9q have been described by Turleau et al (1975). The similarity in the appearance of these patients and of ours is striking.

REFERENCES

Pseudohermaphroditism due to XY gonadal absence syndrome*

Summary. A 21-year-old phenotypic female with a 46,XY chromosome complement and gonadal absence was studied. Basal levels of plasma immunoreactive luteinizing hormone (LH), follicle stimulating hormone (FSH), testosterone, and oestradiol were measured. Pituitary sensitivity and reserve was evaluated by the exogenous administration of synthetic luteinizing hormone-releasing hormone. The episodic release of gonadotrophins was assessed by measuring plasma LH and FSH in plasma samples obtained at 20-minute intervals for a 4-hour period. Endocrine gonadal function was evaluated by a stimulation test with human chorionic gonadotrophin for 3 days. The results showed: a) persistently raised plasma levels of both LH and FSH; b) a pulsatile pattern of release of both gonadotrophins and a normal pituitary response to the synthetic hypothalamic decapetide; and c) extremely low levels of circulating testosterone and oestradiol with a lack of response to the HCG stimulus. A careful exploratory laparotomy revealed absence of uterus, Fallopian tubes, the Müllerian portion of the vagina, and gonads. No Wolffian derivatives were found. A dissociation of testosterone and the so-called Jost substance effects during early sexual development may explain the findings in this unusual abnormality. The term ‘XY gonadal absence syndrome’ including five types of variants to designate this condition is proposed.

Agonadism in phenotypically female individuals with a 46,XY chromosome complement results in an incomplete form of male pseudohermaphroditism. This clinical condition has been recently designated

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as the XY gonadal agenesis syndrome (Sarto and Opitz, 1973). Parks et al (1974) have reviewed the clinical course of the reported cases of patients with this syndrome and pointed out the importance of endocrine gonadal studies, and suggested the possibility that this syndrome represents a form of dysgenetic male pseudohermaphroditism with a scant amount of functioning testicular tissue. Very recently we have demonstrated in such an adult patient a complete lack of testicular steroidogenesis, with a concomitant increase in the circulating levels of pituitary gonadotrophins (Rios et al, 1974).

To our knowledge only 10 patients with this syndrome have been reported and endocrine functional studies have been performed in only one child and one adult. Therefore, we felt it to be of interest to report the pituitary and gonadal and one adult. Therefore, we felt it to be of interest to report the pituitary and gonadal studies performed in a 21-year-old male pseudohermaphrodit patient with gonadal absence. Because of the large variability in the internal and external genitalia in the reported cases, which suggests different pathogenic mechanisms, we think it is convenient to designate this unusual abnormality as the ‘XY gonadal absence syndrome’, including five types of variants.

**Clinical summary**

A 21-year-old phenotypic female was referred to the genetic department because of primary amenorrhea and absence of pubic and axillary hair, in spite of oestrogen-progesterone therapy for 4 years. The patient had noted slight breast development and fat deposit in the hips after treatment. She was the third child in a four-member family, all of whom were apparently normal, and was the product of an uncomplicated pregnancy and delivery. The sex of rearing and psychological orientation were female. Physical examination revealed a phenotypic female with a eunuchoid habit. Her height was 173 cm, span 173 cm, vertex-pubis 79 cm, and weight 66 kg. Neither hirsutism nor body hair was detected. Gynaecological examination showed prepupillary external genitalia, with hypoplastic labia and normal clitoris. The vagina was 2.5 cm deep and ended blindly. Uterus and adnexa could not be palpated and no masses were detected in the inguinal canals or in the labia. Buccal smears did not show chromatin X bodies, and cytogenetic studies revealed a 46,XY chromosome constitution. Pelvic pneumography showed absence of internal genitalia, and repeated urocytograms revealed lack of oestrogenic and progestational activity.

**Material and methods**

Plasma LH and FSH were measured by double-antibody radioimmunoassays (RIA) as previously described by Mendoza et al (1972). Plasma samples were assayed in duplicate. Results were expressed as nanograms (ng) of LER-907/ml. The coefficients of variation of these assays were less than 12%. LH and FSH values for normal males are 47.0±3.8 and 160.0±8 ng/ml, respectively.

Plasma testosterone and oestradiol were measured by hapten-RIA without chromatography as previously reported (Pirke, 1973; Korenman et al, 1974). The sensitivity of these assays was 50 picograms (pg)/ml. Testosterone and oestradiol values for normal males are 4.3±1.5 ng/ml and 45±10 pg/ml, respectively.

Synthetic LH-releasing hormone (LH-RH) was kindly supplied by Hoechst Farbwerke, A.G. Buccal smear for chromatin X detection and chromosome studies were carried out according to the procedure described by Moorhead et al (1960).

**Functional endocrine studies.** Pituitary gonadotrophin function was evaluated by measuring LH and FSH in plasma samples obtained through an indwelling intravenous catheter at 20-minute intervals during a 4-hour period. Pituitary reserve and responsiveness were assessed by giving an IV bolus of 100 µg synthetic LH-RH and measuring plasma LH and FSH before, and 30 and 60 minutes after injection.

Gonadal endocrine function was evaluated by measuring plasma immunoreactive testosterone and oestradiol before, during, and after administration of intramuscular HCG 5000 IU/day for 3 consecutive days. Afterwards the patient was subjected to an exploratory laparatomy.

**Results**

The basal levels of plasma LH and FSH in this patient were found to be persistently raised, as compared with values found in normal males. LH mean levels were 262.58 ng/ml (range: 150–399) while FSH mean levels were 601.53 ng/ml (range: 380–760).

A pulsatile pattern of release of both gonadotrophins (Fig. 1) similar to that found in patients with hypergonadotrophic hypogonadism of different origins (Root et al, 1972; Yen et al, 1972; Santen and Bardin, 1973; Kelch et al, 1973; Perez-Palacios et al, 1974) was observed. The plasma levels of FSH were always higher than those of LH; the ratio of FSH/LH being 2.28. A lack of coincidence of the secretory episodes of both gonadotrophins was also observed.

The IV administration of LH-RH induced a significant and even exaggerated increase in the circulating levels of LH (up to 2256.0 ng/ml). A concomitant increase on the plasma levels of FSH though to a lesser extent (up to 1340.0 ng/ml) was also observed (Fig. 1). These data clearly demonstrate an adequate pituitary responsiveness to the exogenous stimulation in spite of the already raised basal levels of plasma gonadotrophins. An identical pituitary response has been reported to
samples were after 100 identical conditions gonadal response (AG) evaluated by the increase of the LH and FSH plasma levels.

Fig. 1. Episodic fluctuations of plasma LH and FSH. Blood samples were drawn at 20-minute intervals during 4 hours. Thereafter 100 µg synthetic LH-RH was IV administered and the response evaluated by the increase of the LH and FSH plasma levels.

Fig. 2. Basal levels of plasma immunoreactive testosterone of the patient with XY gonadal absence syndrome. A lack of response (AG) after gonadal stimulation with HCG was observed. Testicular gonadal response (mean ± SD) in normal individuals (n = 15) under identical conditions is also depicted.

occur in other hypergonadotrophic patients (Kastin, Gual, and Schally, 1972; Wagner et al, 1973; Yen et al, 1973; Scaglia et al, 1974).

Plasma levels of circulating testosterone were extremely low (0.06 ng/ml) and resemble those observed in newborns, and plasma oestradiol levels were below the limit of sensitivity of the employed assay. After HCG administration, a lack of response in terms of plasma testosterone increase as compared with the response observed in normal males was found (Fig. 2). These data clearly show the absence of functional Leydig cells in this patient.

The exploratory laparotomy revealed complete absence of Müllerian and Wolffian derivatives as well as gonadal tissue.

Discussion

The non-mosaic 46,XY individual reported herein represents a form of male pseudohermaphroditism caused by absence of gonads. The patient's phenotype though of the female type lacked breast development and sexual hair growth, indicating absence of steroid sex hormone production. Further support for this concept was furnished by the finding of almost undetectable levels of plasma testosterone and oestradiol, with concomitant raised levels of plasma pituitary gonadotrophins.

Complete absence of testicular endocrine function was shown by the lack of testosterone production after HCG stimulation. As a result of this hormone synthesis impairment, the circulating levels of both LH and FSH exhibited frequent fluctuations of great amplitude suggesting periodic secretion episodes. In addition, the significant response in terms of plasma LH and FSH observed after LH-RH stimulus confirms the anatomical-functional integrity of the anterior pituitary. These data demonstrated normal function of the hypothalamic-pituitary axis in the absence of gonadal functional tissue.

The absence of Müllerian and Wolffian derivatives and gonadal tissue observed at laparotomy confirmed the results of the hormonal studies. These data demonstrated a clear dissociation of effects of the Jost substance and testosterone during early intrauterine life. Thus, lack of circulating testosterone at that time of development explains the female phenotype and external genitalia observed at birth as well as the absence of breast development, sexual hair growth, and signs of virilization at puberty. The absence of internal genitalia can be explained either by the early effect of the Müllerian inhibitory substance with later testicular re-absorption or by the absence of the gonadal anlagen.

A great variability in both the internal and external genitalia has been found in the few patients studied with this abnormality, and genetic and endocrine studies have been carried out only recently (Overzier and Linden, 1956; Schoen, King, and Baritell, 1955; Philipp, 1956; Chaptal and Pages, 1958; Harnden and Stewart, 1959; Dewhurst, Paine, and Blanch, 1963; Overzier, 1963; Emson and Buckwold, 1965; Rath, Scheibenreiter, and Thalhammer, 1968; Parks et al, 1974; Rios et al, 1974). These heterogeneous characteristics suggest that different pathogenic mechanisms during
intrauterine life may result in the clinical features of this syndrome. Therefore, we should like to propose the term ‘XY gonadal absence syndrome’ to designate this abnormality. The syndrome is defined as the absence of gonadal tissue in adulthood in individuals with an XY chromosome complement. Since gonadal agenesis or gonadal reabsorption may occur, the term absence rather than agenesis seems to be more descriptive.

This syndrome theoretically includes five different forms (Fig. 3) with a whole spectrum going from the complete absence of gonadal function during embryonic differentiation (true agonadism) to fetal gonadal function integrity (anorchia) (Kirschner, Jacobs, and Fraley, 1970; Kolodny et al, 1971), passing through the two types of incomplete agonadism and the mixed form of agonadism. We agree with Parks et al (1974) that the name ‘true agonadism’ is a misnomer if it is used for all types of gonadal absence.

The clinical and endocrine features observed in the patient reported in this paper are identical to those found in a similar case previously reported by our group (Rios et al, 1974). Both cases correspond to the incomplete type I form of gonadal absence.

No other affected member has been found in the family of most of the reported cases. However, since Overzier and Linden (1956) found this syndrome in two sibs, the pattern of inheritance, if any, remains to be ascertained.

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REFERENCES
Cervical vertebral fusion (Klippel-Feil) syndrome with consanguineous parents

Summary. We describe a female infant with the cervical vertebral fusion (Klippel–Feil) syndrome whom we recognized at birth because of her short neck, restriction of cervical movement, and low posterior hairline. X-ray examination showed anomalies of Cl, and between C2–3 and C3–4; thus, we classified her as type II, with variable cervical fusion. At 24 months she was small and manifested hearing deficiency. The mother and father were consanguineous with five common ancestors four generations ago, which resulted in a coefficient of inbreeding equivalent to a second cousin relationship. The parents and grandparents were phenotypically normal, and the parents were radiologically normal. This form of the syndrome has previously been said to be autosomal dominant. Our conclusion of determination by a single autosomal recessive gene is evidence of genetic heterogeneity.

The syndrome which results from cervical vertebral anomalies (usually fusion), attributed to Klippel and to Feil, encompasses the appearance of a short neck, painless restriction of cervical movement, and a low posterior hairline, at least as it is generally recognized. Radiological criteria define three types, based in the main on the number of vertebral fusions. The second type has been further divided according to the specific vertebrae fused.

The aetiology of this congenital malformation...