A CASE OF GONADAL DYSGENESIS OR THE ULLRICH-TURNER SYNDROME WITH ANDROGENIC MANIFESTATIONS

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This syndrome is thought to have been originally described by Ullrich (1930) and Turner (1938), but Meyer (1925) and Baer (1927) have given earlier descriptions of cases of 'ovarian agenesis' presenting with androgenic manifestations.

Grumbach, van Wyk and Wilkins (1955), in a thorough review of the subject, have proved the value of sex typing of nuclei in 22 cases, and by basing the same arguments as Russell, Levin and France (1955) on Jost's experimental work have suggested a partial explanation for the aetiology of this syndrome.

This report is of a child dying at 7 months, who had the cardinal features of the Ullrich-Turner syndrome associated with androgenic manifestations.

Case Report

Marion G. was the third child of healthy unrelated parents and was delivered normally at term after an uneventful pregnancy and labour. The mother had not received antenatal hormone therapy nor had she been exposed to x rays. The family history contributed nothing. The infant weighed 7 lb. 2 oz. at birth and despite obvious abnormality of the external genitals was considered to be female. The child was artificially fed but made poor general progress and was admitted to hospital on July 23, 1955, for investigations at the age of 7 months.

The infant was wasted (weight 11 lb. 4 oz.) and pale, being just under the average length for her age (25.5 in. against 26.6 in.). There was considerable coryza and some degree of inspiratory laryngeal stridor. The skull was brachycephalic (maximum circumference 16½ in.), the anterior fontanelle was widely open and the ears were prominent.

The following features of the Ullrich-Turner syndrome were present, some of which are illustrated in Figs. 1-3: Skin webbing of the posterior neck (Fig. 1), the skin being lax and thick; epicanthus, small mandible and high arched palate; broad chest ('shield chest') with hypoplastic nipples (Fig. 2); coarctation of aorta (loud

praecordial systolic murmur, raised systolic blood pressure in arms (right 120 mm. Hg, left 125 mm. Hg) and absent femoral pulses); cubitus valgus and tapering fingers, the proximal and middle phalanges being swollen; pitting oedema of the dorsa of the feet.

A phallus (? enlarged clitoris) was present, 3 cm. long and covered with lax rugose skin (Fig. 3), apart from which the external genitalia were normal.

Sixteen days after admission the child developed fulminating bronchopneumonia and severe diarrhoea. There was no response to treatment and death occurred within 48 hours.

Laboratory investigations gave the following results: (1) 17-Ketosteroids in 24-hour specimen of urine, 2.2 mg. (normally less than 1 mg. at this age); (2) bone age 1 year approximately, i.e., slightly in advance of chronological age; (3) sex typing by the leucocyte method (Dr. W. M. Davidson), male, and by skin biopsy (Dr. J. B. Gibson) male.

Necropsy

A necropsy was performed on August 12, 1955, and the relevant findings are as follows:

There was marked left ventricular hypertrophy and the thicknesses of the right and left ventricular walls were 3 mm. and 11 mm. respectively. A 4-mm. segment of the aorta just distal to the opening of the ductus arteriosus (which was closed) was stenosed, the diameter of the lumen being reduced to 2 mm.

Small scattered areas of collapse were seen in the lungs.

The immature vagina, cervix, uterus and tubes were normally developed. At the ovarian sites were two flat, oval, yellowish structures (4 × 2 mm.).

Histology

In many areas of the lungs the alveoli were filled with a chronic inflammatory exudate.

The cortices of the adrenals were clearly defined and the bands of collapsed reticulin at the site of the X zone were evident (Fig. 4). The cortical lipid content was not raised and there were no hyperplastic nodules. Broster-Vines, Ponceau-fuchsin stains gave negative results.

FIG. 1.—Webbing of the neck.

FIG. 2.—The epicanthus, prominent ears, 'shield chest' and hypoplastic nipples.

FIG. 3.—The phallus.

FIG. 4.—Section of adrenal rest, showing typical adrenal cortical arrangement of cells. ($\times 100$.)

FIG. 5.—Section of uterine wall, showing endometrical infoldings. ($\times 100$.)

The pancreas, thyroid, pituitary and thymus glands presented normal histological features. There was no evidence of Crooke's 'hyaline change' of the basophilic cells of the pars anterior of the pituitary (eosin-pyrrhol blue stain).

The pre-tibial skin showed no evidence of myxoedematous change.

The centres and lines of ossification of the femoral, rib and vertebral bones had a regular pattern.

The phallus consisted of vascular fibrous tissue covered by normal skin. The labia majora consisted of fibrous tissue with normal overlying skin and no testicular elements were seen.

The appearances of the cervix, uterus and Fallopian tube were normal for this age and in the uterus small endometrial infoldings (Fig. 5) and an inactive stroma were easily distinguished. The structure at the ovarian sites consisted of well-differentiated adrenal cortical tissue (see Fig. 4), but the lipid content of the cells was not raised and Broster-Vines, Ponceau-fuchsin stains were negative.

A section through one of the broad ligaments revealed a structure consisting of dense connective tissue resembling primary mesenchyme (or ovarian stroma). Scattered through this stroma were nests of large cells with ill-defined cell boundaries and with large round or oval vesicular nuclei containing two or three prominent nucleoli. Fine clumps of chromatin were scattered evenly throughout the nuclei. Nearer the surface were cords of large round cells with hyperchromatic nuclei and these cords lay parallel to the surface. No Leydig cells or vestiges of the mesonephros were present in this structure.

Discussion

This infant presented many of the features of this curious syndrome which suffers from a confusion of eponymous titles. The following alternative names have been suggested: Ovarian agenesis (Turner, 1938); status Bonnevie-Ullrich (symmetrical form) (Rossi, 1945; Oberman, 1955); pterygium (Skjelbred, 1953), or webbing syndrome of Ullrich-Turner (Russell *et al.*, 1955); gonadal dysgenesis (Grumbach *et al.*, 1955); Allbright's syndrome (Potter, 1952).

Rossi and Caflisch (1951), in a review of 68 cases, have listed 30 possible congenital abnormalities which may occur in this syndrome and in the present case 10 of these were found.

Sexing of the skin and polymorphonuclear leucocytes according to the method devised by Moore, Graham and Barr (1953) is now a recognized investigation in these cases (Polani, Hunter and Lennox, 1954).

The relatively frequent occurrence of coarctation of the aorta in this syndrome has been noted by some workers who have pointed out that this anomaly occurs with much greater frequency in males (8 : 1, Lewis, 1933; 5 : 1, Gould, 1953). The finding, by this method, that a high proportion of

these patients are 'chromatin-negative', i.e., males, is therefore of great interest and in fact 20 of 22 cases investigated by Grumbach *et al.* were chromatin-negative and two patients in the chromatin-negative group had coarctation of the aorta. The present case is a further example of this association.

In their recent review of this syndrome Grumbach *et al.* have drawn attention to the experimental work of Jost (1947) on rabbits. Jost, performing intra-uterine operations, removed the foetal gonads at different phases in sex differentiation, beginning at a stage when the testis could be identified histologically, but the genital tract was still undifferentiated. In the female castrated foetus he showed that the Müllerian derivatives (female genital system) differentiated in a normal fashion apart from a slight reduction in size. In the male castrated foetus, on the other hand, the Wolffian derivatives (male genital system) failed to develop and instead a complete and normal female genital system developed in its place. Unilateral castration of the male foetuses caused the Müllerian derivatives on the castrated side to develop in place of the Wolffian system. It would seem, therefore, that the all-important factor in sex differentiation of the genital tract is the presence of some locally acting tissue 'organizer' secreted by the male gonad. Jost has further shown that castration of the male rabbit foetuses at successively later stages allows increasing degrees of differentiation of the Wolffian derivatives but arrests their further development. Beyond a certain stage, however, castration of the male foetus will fail to prevent normal development of the Wolffian system. Grumbach *et al.* regard these patients with gonadal dysgenesis as the human counterparts of the castrated rabbit foetuses and suggest that some deleterious agent of unknown nature affects the embryos. In the case of the human male this would have to occur before the 28 mm. embryo stage (eighth week) in order to prevent differentiation of the male genital system. The associated malformations in this syndrome could also be determined at this stage (Grumbach *et al.*).

It would be attractive to align the present case with its androgenic manifestations with one reported by Grumbach *et al.* in which there was phallic enlargement and to suggest, as do these authors, that these cases correspond to the male rabbit foetuses of Jost which have been castrated at an intermediate stage.

Meyer (1925), Baer (1927), Pich (1937), del Castillo, de la Balze and Argonz (1947), Russell and Swyer (1952), Gordan, Overstreet, Traut and

Winch (1955), Grumbach *et al.* (1955), Greenblatt, Carmona and Higdon (1956) have all recorded cases of this syndrome with androgenic manifestations. In five of these cases there has been a histological examination of a 'genital ridge', found in the broad ligament at laparotomy, and this has shown in each case the presence of nests of Leydig (hilar) cells scattered through a connective tissue stroma closely resembling that of the ovary. With the exception of Greenblatt *et al.*, the authors correlated the presence of these cells with the androgenic manifestations, but admitting at the same time that they are found in cases without any evidence of masculinization. Greenblatt *et al.* were unable to allow the possibility of this correlation in their case because the androgenic manifestations occurred in association with low urinary 17-ketosteroids.

The histological appearance of the structure in the broad ligament of this case, and the absence of any specific features which would enable one to identify it as a primitive testis or ovary, suggest that it represents undifferentiated gonadal tissue (Gillman, 1948). However, no Leydig cells could be found in this 'genital ridge' and it seems preferable, therefore, to relate the phallic enlargement, bone age maturity (usually retarded in this syndrome) and the slightly elevated 24-hour urinary 17-ketosteroids to adrenal hyperplasia.

It is of interest here to note that '... in the male animal castration is followed by adrenal cortical hypertrophy' (Soffer, 1951). There was, however, no morphological evidence of adrenal hyperplasia in the present case, apart from the presence of heterotopic adrenal tissue, but correlation of the structural changes in the adrenal cortex with its biological activity is difficult and histochemical stains for 17-ketosteroids are not specific (Pearse, 1953).

In Baer's case, a 23-year-old 'female' with a male habitus and sexual infantilism came to laparotomy and was found to have bilateral adrenal rests at the usual ovarian sites, no ovaries being present. Baer also attributed the androgenic manifestations to the ectopic adrenal tissue. In the human embryo at the 12 mm. stage the genital ridge and suprarenal ridge lie in continuity, therefore it is easily understood that heterotopic adrenal

cortical tissue can appear in relation to the usual gonadal sites, as seems to have happened in the case reported here and in Baer's case (Hamilton, Boyd and Mossman, 1952).

Summary

A case of 'gonadal dysgenesis' in a male ('chromatin-negative'), aged 7 months, is described.

Recent theories concerning the aetiology of this syndrome are outlined and the possible cause of the androgenic manifestations in this case is discussed.

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