GONADAL DYSGENESIS WITH
XX-ISOCHROMOSOME CONSTITUTION AND
ABNORMAL THYROID PATTERNS

By

ABSTRACT

The authors report a female patient with XXi constitution for the long arm of the X chromosome associated with thyroid abnormalities, high digital ridge count and chronic suppurative otitis media. This is followed by a discussion of the correlation between genotype and phenotype, comment on the Lyon hypothesis, the relationship of thyroid abnormalities to this condition, autoimmune disease, unbalanced sex chromosomal constitution and the association with a high total digital ridge count.

Finally a single hypothesis is proposed for the associated clinical entities that have been found and the suggestion that the classification of this particular type of gonadal dysgenesis be considered as a new syndrome, the »XX-isochromosome syndrome«.

Approximately twenty patients with XX-isochromosome (XXi) and without evidence of mosaicism have already been reported (Fraccaro et al. 1960; Jacobs et al. 1961; Hamerton et al. 1962; Forbes & Engel 1963; Lindsten et al. 1963; Lindsten 1963; Sparkes & Motulsky 1963; Williams et al. 1964, 1966; Ree 1965).

These cases show the common features of classical gonadal dysgenesis: short stature, sexual infantilism and primary amenorrhoea with streak ovaries. However, they lack the other somatic malformations common to the Turner's syn-

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drome, except for one patient reported by Hamerton et al. (1962) who had severe mental retardation, webbing of the neck and other gross somatic abnormalities. Four of the patients with X-isochromosome had Hashimoto’s thyroiditis (Williams et al. 1964; Sparkes & Motulsky 1963).

In this communication we are presenting a case study which is typical of this group of patients. Several aspects of this condition, we feel, are worthy of further comment.

CASE REPORT

This 22-year-old female of Danish origin was referred to us because of primary amenorrhoea. She denied any history of vaginal bleeding or discharge. Pubic and axillary hair development began at age 19 and was only scant in amount. Breast development was minimal and she was rather vague to when this occurred. There was no history of previous endocrine therapy.

Her past history was of interest in that she had trouble with her hearing over many years and was investigated for this in Denmark (date unavailable). She underwent mastoid surgery five years ago. Subsequent to our seeing here she developed an acute suppurative otitis media, was treated with Erythromycin following which she developed evidence of severe cholestatic jaundice, which is being fully investigated at the present time.

She is the second of six children. Both parents are living and well and are of normal height. One sister aged 16 years underwent menarche 9 months ago. This sister has a twin brother who is apparently normal. One sister aged 23 is married and has two children. Another brother aged 14 and a sister aged 5 are apparently normal. There is no family history of amenorrhoea, diabetes or goitre. Paternal and maternal age at birth were 31 and 22 years respectively.

Physical examination revealed the following findings: Height 1.54 m. Weight 51 kg. Pubis to floor: 83.8 cm. Pubis to crown: 71.1 cm. Span 161.3 cm. Blood pressure 140/90 mm Hg. Pulse 80 per minute. I. Q. normal. No webbing of the neck was noted. The thyroid gland was slightly and diffusely enlarged but no bruit was heard. Carrying angles were somewhat increased, good femoral and pretibial pulses were palpable bilaterally. There were no transverse palmar creases. The nails were normally developed and there was no abnormality of the fourth metacarpal. The chest showed no evidence of being shield shaped. Breasts and nipples were widely spaced and there was slight but definite breast development with doming of the areola and bilateral nipple development. There was little or no pigmentation of these structures. Axillary hair was sparse and pigmented. Heart and lungs showed no abnormality. Abdominal examination was negative and pubic hair was sparse. External genitalia were juvenile and appeared slightly reddened at the introitus and very hypo-oestrogenic. On rectal examination a small uterocervical body was felt in the midline. No adnexal masses were palpable, the clitoris was not enlarged.

Culdoscopy was performed by Professor R. A. H. Kinch. The genitalia were pre-pubescent with very small labia minora and majora, and a very narrow introitus. The vagina was rugose in appearance. Bimanual examination revealed an extremely small cervix and a very small uterus. Pelvic structures were easily visualized. The uterus was thin, pale and flat, and arising from each side of it were two streaks. The ovarian
ligaments simply carried on as a white and fibrous band. There was no evidence of any ovarian tissue whatsoever.

**Laboratory investigation**

Buccal smear revealed larger than normal Barr bodies in a high percentage of cells (Fig. 1). FSH was positive at 25, and negative at 35 RUU (normal 2–12 rat uterine units). Blood glucose -97 mg/100 ml.

**Thyroid studies**

\[ \text{PBI} = 8.6 \mu g/100 \text{ ml (normal 4–8 } \mu g/100 \text{ ml).} \]

\[ \text{\(^{131}\text{I}} \text{ uptake} = 33 \% \text{ at 4 hours, 56 }\% \text{ at 24 hours (normal 15–40 }\% \text{ at 24 hours). Resin sponge uptake of triiodothyronine (T}\_3\text{ uptake)} = 21.7 \% \text{ (normal = 25–35 }\% \text{). PB}\text{\(^{131}\text{I}} \text{ = } 0.666 \% \text{ of dose per litre of plasma (normal less than 0.20 }\% \text{). Conversion ratio = 85 }\% \text{ (normal less than 30 }\% \text{).} \]

After suppression with 75 \(\mu\)g triiodothyronine daily for 3 days the \(^{131}\text{I}} \text{ uptake fell to 14 }\%\text{.}

Perchlorate test – negative (no discharge of unbound inorganic iodine).

Thyroid antibodies – negative (tanned red cell technique).

**Chromosome studies**

(i) Peripheral blood culture was carried out by a modification of a standard technique (Moorhead et al. 1960); and (ii) fibroblast of skin were grown in tissue culture (Lejeune et al. 1960).

The modal number was found to be 46 in both leucocytes and tissue culture explants. There were only 15 chromosomes in the 6–12 (C) + X group. In all all metaphase plates and karyotypes examined there were 3 elements resembling chromosome number 3. This was confirmed by measuring the relative length and the arm ratio. In the tissues studied there was no evidence of mosaicism (Fig. 2).
Dermatoglyphic analysis

Dermatoglyphic analysis was performed by Dr. H. C. Soltan. The dermatoglyphics of this patient were unremarkable except for the presence of large digital patterns giving a high total ridge count (186). Both axial triradii were in the low or t position and both palmar and fifth finger creases were normal.

X-ray examination of chest, skull and limbs revealed no abnormalities.

**DISCUSSION AND COMMENTS**

This case represents a classical example of the variation which exists among patients with gonadal dysgenesis. In fact, certain characteristics are in common with Turner's syndrome and most of them, except for ovarian development, sexual infantilism and primary amenorrhoea, seem to be expressed to a minor degree (Ferguson-Smith et al. 1964). The characteristic somatic malformations of the classical Turner's syndrome are lacking, except in one case reported by Hamerton et al. (1962).
Since the discovery of the X-isochromosome, some light has been shed on the role of the X chromosome in sexual differentiation.

According to the Lyon-Beutler hypothesis (Beutler et al. 1962; Lyon 1961, 1962) inactivation of one X chromosome is a random process which occurs early in embryonic life, i.e. about the 16–18th day after fertilization (Park 1957). This inactivation results in sex chromatin body formation. Furthermore, it has been shown that it is the structurally abnormal X chromosome, if present, which always forms the Barr body. This has been shown in studies of the late replication pattern with tritiated thymidine in cases of XXi, Xx and XXr* (Muldal et al. 1963; Gianelli 1963). Additional support is derived from the correlation which exists between the size of the Barr body in cases of XXi, Xx, Xx and XX (Jacobs et al. 1961; Lindsten 1963). MacLean (1962) studying the correlation between the percentage and size of drumsticks of leucocytes in cases of sex chromosome abnormalities has found similar evidence.

The genetic end result in these patients with XXi constitution is that they are actually monosomic for the short arm and trisomic for the long arm of the X chromosome. From this it could be inferred that for the complete differentiation of the gonad (ovarian tissue) it is necessary that a double dose of some genes located on the short arm of the X chromosome be present. According to this, any abnormality giving rise to such an unbalanced situation would lead to a condition entirely similar to the Turner’s syndrome (Barr 1966). This fact has been outlined by Ferguson-Smith (1965). Furthermore, Jacobs et al. (1961) has postulated that short stature in Turner’s syndrome and XXI constitution could be a consequence of the loss of the short arm material of the X chromosome. Since there are some phenotypic differences between XX and XO, Xx or XXi, despite the inactivation of the structurally abnormal X chromosome, it could reasonably be postulated that both X chromosomes are genetically active before the 16–18th day. Thus it is quite feasible that in this early period the consequences of the genetic imbalance are imprinted on gonadal and somatic tissue leading to the characteristic phenotypes of these patients.

There is also increasing evidence that inactivation of the X chromosome may be incomplete (Russell 1963, 1964). This incompleteness might mean either that (a) some loci on the X chromosome may escape inactivation (Ferrier 1965) or (b) that the inactivation does not occur in all tissues (Lyon 1963). Considering the first possibility, there is enough information available to assume that in somatic female cells, part of the short arm of each X chromosome remains active (Ferguson-Smith 1965). Furthermore, it is already known that X chromosomes in oogonia are both isopycnotic and hence it can be

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* Key: XXi = X-isochromosome, XXr = Ring X chromosome, Xx = Deletion of the short arm of the X chromosome.
inferred that inactivation does not occur in female germ cells (Ohno & Makino 1961) suggesting that oogonia require two active X chromosomes for their normal development and maturation. Recently, however, Singh & Carr (in press) studying a series of nine aborted XO embryos ranging in age from 1 to 4 months, found primordial germ cells in the gonads of these embryos. This would suggest that two X chromosomes are not entirely necessary for the development of primordial germ cells.

Considering our particular case we would like to discuss some findings which seem to us to be beyond the realm of chance and which merit further comment. We have found (a) some abnormal thyroid function tests without any clinical expression of thyroid disease, other than a slight diffuse goitre, (b) the presence of an impairment of hearing subsequent to a chronic suppurative otitis media and (c) an increase in total ridge count in the dermatoglyphic study.

Considering the thyroid function, we found a high $^{131}$I uptake at 4 and 24 hours. This was well depressed after the administration of $T_3$. PB$^{131}$I was high with an increased conversion ratio. However, the clinical condition was that of euthyroidism. Thyroid autoantibody studies and a perchlorate test were both negative. The latter has been found positive in some stages of Hashimoto’s thyroiditis. Although we realize that a thyroid biopsy would help us to further elucidate the problem, the patient has refused such a procedure, and therefore, concomitant Hashimoto’s thyroiditis cannot be ruled out. Regarding these results as well as previous reports of thyroid abnormalities in patients with sex chromosome abnormalities (Lewitus 1962; Barr et al. 1959, 1964; Davis et al. 1963) some interesting points have been brought forth which we consider worthy of comment at this time. The finding of an elevated thyroidal $^{131}$I uptake in patients with chromatin-negative Turner’s syndrome (Lewitus 1962) is especially intriguing when compared to the low $^{131}$I uptake and deficient response to TSH of women with triple and tetra-X chromosome constitution reported by Plunkett et al. (1964). Since the discovery of the first case of the XXi constitution associated with Hashimoto’s thyroiditis (Engel & Forbes 1961), at least three other such cases have been described (Sparkes & Motulsky 1963; Grumbach & Morishima 1964). More data were accumulated with the study of thyroid autoantibodies in a group of 25 patients with gonadal dysgenesis. Of these, 13 had significant autoantibody titers. Subsequently, the study was extended to patients with mongolism and their relatives in order to establish whether other types of aneuploidy would be associated with thyroid autoantibodies, and also whether thyroid autoimmunity predisposed to aneuploidy. The results of that investigation suggests that the last possibility is more feasible (Fialkow 1966). Furthermore, in a case XXi/XO associated with ulcerative colitis and lymphocytic infiltration of the thyroid reported by Williams et al. (1966), a very attractive hypothesis has been postulated to
explain the autoimmune phenomenon. This theory is based on the "lyonization" mechanism. According to this theory, the inactivated X chromosome ("sequestered") plays no part in controlling protein synthesis. Hence, in the patient with a uniformly inactivated chromosome an immunological tolerance will develop to the proteins coded by the non "sequestered" chromosome. If by chance, all or part of the inactivated chromosome is able to code protein synthesis "de novo" that new protein would become "strange" to the organism. This phenomenon may occur in any tissue. In addition they suggest that such reactivation may account in some cases for autoimmune disease in females.

The association of a chronic suppurative otitis media and secondary impairment of hearing has been noted by other authors (Lindsten 1963; Stratton 1965). In the case reported by Williams et al. (1966) the patient also had a history of purulent otitis media associated with cholesteatoma. To account for this, the authors postulate that cases of gonadal dysgenesis are associated with malformations of the inner and middle ear which predisposes them to ear infections. Furthermore, it is well known that some cases of hyperploidy of autosomal chromosomes are associated with malformations of the external ear (shape of the ear and its implantation). This is particularly true in mongolism and the E group trisomy, suggesting that genes which control the external ear configurations are distributed on several autosomes. Thus genes controlling internal and middle ear development may be located on the missing portion of the X chromosome. In their absence middle and inner ear malformations result.

The total digital ridge count of 186 is comparable to other reports. Five patients with XX-isochromosome studied by Lindsten et al. (1963) had a mean value of 174.6 and Ree (1965) in another case found a total ridge count of 182. It is now established that XO Turner's syndrome patients tend to have an elevated total ridge count (Penrose 1963; Holt & Lindsten 1964; Uchida & Soltan, in press). In the latter two studies the mean total ridge counts for samples of 29 and 46 XO patients respectively were 166.1 and 187.5 as compared to 130.4 and 127.0 for samples of 50 and 500 control females. It appears, therefore, that our XX-isochromosome patient tends to resemble XO patients in this dermatoglyphic feature. On the other hand, our patient showed neither higher than average axial triradii nor the presence of full or partial transverse palmar creases. These two dermatoglyphic features have been shown to be quantitatively different in samples of XO patients (Penrose 1963; Uchida & Soltan, in press). Thus, our case resembles XO patients in total digital ridge count but differs from the mean values for these latter two features.

Thus, based upon the above findings, we suggest that the XX-isochromosome constitution be considered as a new syndrome exhibiting the following clinical features: 1, normal intelligence; 2, short stature; 3, streak ovaries; 4, primary amenorrhoea; 5, sexual infantilism; 6, absence of webbing of the
neck or other major somatic malformations; 7, an increase in the total digital ridge count; 8, high incidence of thyroid abnormalities, especially Hashimoto's thyroiditis. Finally, and of utmost importance, the presence of an unusually large Barr body and drumsticks. Any combination of the above clinical features with positive sex chromatin pattern and enlarged Barr body or drumsticks, should lead one to expect this specific chromosomal constitution.

ACKNOWLEDGEMENTS

The author is much indebted to the Medical Research Council of Canada for their sponsorship of his fellowship.

We also wish to thank Dr. H. C. Soltan for his assistance in the dermatoglyphic study and criticism of the manuscript, Dr. F. R. Sergovich for performing the thyroid antibody study and Professor R. A. H. Kinch for his gynaecological evaluation of the patient. We wish to express our gratitude to Miss Marlene Moore for typing the manuscript.

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Received on July 26th, 1966.