NUCLEAR SEX IN FAMILIAL GONADAL DYSGENESIS

By

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The unexpected finding of chromatin-negative or "male" cell nuclei in the majority of cases of Turner's syndrome and of chromatin-positive or "female" nuclei in most cases of Klinefelter's syndrome has again focussed attention on the factors responsible for the normal embryological development of the gonads, though it has not clarified them, or the mechanism of the dysgenesis of the gonads in the two syndromes.

Perhaps the most puzzling fact is that both chromatin patterns are found in patients with almost identical clinical pictures. This has been confirmed in most of the recent studies of the nuclear sex in both Turner's syndrome (Armstrong, 1955, Barr, 1955, Grumbach et al., 1955, Nelson, 1956, Polani et al., 1956, Riis et al., 1956 b) and Klinefelter's syndrome (Bunge & Bradbury, 1956, Grumbach et al., 1957, Nelson, 1956, Plunkett & Barr, 1956, Riis et al., 1956 a, b, Solval et al., 1956). In one of the largest collections of cases (Nelson, 1956), divergence between nuclear sex and sexual phenotype was found in 87 of 103 patients with gonadal dysgenesis (a better term than Turner's syndrome, since only some of the patients have all the symptoms described by Turner (1938)), and in 49 of 62 patients with Klinefelter's syndrome, also termed seminiferous tubule dysgenesis (Grumbach et al., 1957). While no clinical or histological differences have been described between chromatin-positive and chromatin-negative patients with gonadal dysgenesis except that the concomitant malformations of Turner's syndrome are less frequent in the chromatin-positive cases. Nelson distinguishes between "true" and "false" Klinefelter syndromes on the basis of histological differences in testicular biopsies: disagreement between nuclear sex and sexual phenotype should exist in the "true" cases only.

Familial occurrence of gonadal dysgenesis has been described (Granrud, 1952, Lundström, 1956, Overzier & Linden, 1956) as well as of Klinefelter's
syndrome (Nelson, 1956), but the sex chromatin pattern was only reported in one instance. A combination of gonadal dysgenesis and various forms of muscular dystrophy has been described by different investigators (Bassoe, 1956 a, b, Grumbach et al., 1957, Nadler et al., 1950, Wyss, 1956). The cases of Bassøe were two siblings, one of whom had gonadal dysgenesis of Turner's type and the other severe testicular insufficiency similar to that of Klinefelter's syndrome. Five more members of the family had the same type of muscular dystrophy. The sex chromatin pattern of these two patients is reported here with a brief discussion of the findings.

CASE HISTORIES

Detailed histories of the two cases have been published elsewhere (Bassoe, 1956 a, b), before determinations of nuclear sex were carried out. Only the most important points therefore will be mentioned here.

Case 1. A woman aged 22. Her muscular development had been retarded since birth. At the age of five she was operated upon for bilateral cataract. Menstruation had never occurred. Neurological examination led to the diagnosis of congenital muscular dystrophy. An explorative laparotomy revealed the typical picture of gonadal agenesis: a small uterus and long slender tubes were found. Instead of ovaries, sickle-shaped streaks of white thickened epithelium could be seen on both sides. The external genitalia were essentially of normal feminine type. Cytological examination of oral smears showed a definite chromatin-positive pattern in the cell nuclei.

Case 2. A man aged 26. His muscular development too had been retarded since birth, and he had been operated upon for bilateral cataract as a child. The neurological diagnosis was congenital muscular dystrophy. He had no gynaecomastia. Excretion of gonadotrophins in the urine was within normal limits in three determinations. His testes were infantile in size and soft. Biopsy revealed a thick fibrous capsule and scanty tubules with a few Sertoli cells and filled with hyaline masses. Large numbers of Leydig cells in groups were seen interstitially. Cytological examination of oral and urethral smears showed chromatin-negative cell nuclei.

Family: A third sibling was quite normal, but among the relatives five more cases of a similar type of muscular dystrophy were found (Fig. 1). There were no other cases of gonadal dysgenesis known in the family.

DISCUSSION

Out of three siblings two, one of each sex, had the same type of congenital muscular dystrophy in combination with severe hypogonadism. In both cases agreement was found between genetic and genital sex. To our knowledge, cases of gonadal dysgenesis and seminiferous tubule dysgenesis have not been found within the same family before. Although the two syndromes to some extent resemble mirror-images of each other, there might well be some fundamental differences with regard to their aetiology. We shall therefore
briefly discuss the possible significance of this occurrence, but not attempt a comprehensive review of all the problems connected with gonadal dysgenesis. Several such reviews have appeared recently (Danon & Sachs, 1957, Grumbach et al., 1957, Nelson, 1956, Witschi et al., 1957).

Animal experiments, especially those of Burns, Jost, Moore, Price, Wells, and others, have shed much light upon the development of the foetal gonads, as well as on the role of the foetal endocrine glands in the sexual development of the foetus. Jost's experiments (1953), in which early removal of the foetal gonads results in complete feminization regardless of the genetic sex of the foetus, and later removal of the testis anlage brings about a more or less pronounced degree of feminization, would seem to explain the cases of gonadal agenesis with feminine phenotype, regardless of genetic sex, as a complete inhibition of the gonadal anlage. An incomplete inhibition could explain the cases of Klinefelter's syndrome with masculine chromatin pattern. On the other hand, the experiments do not seem to be able to explain the Klinefelter cases with chromatin-positive cell nuclei.

**Fig. 1.**

Pedigree. Upright white squares and circles indicate normal men and women; slanted white squares indicate unknown sex. Black squares and circles indicate men with Klinefelter's syndrome and women with ovarian agenesis, both with cataract and muscular dystrophy. Black squares and circles with 1/4 white area indicate men and women with muscular dystrophy, but without endocrine disorder. Black circle with 1/2 white indicates woman with muscular dystrophy and epicanthus. Black double circles indicate stillbirths.
Theoretically, inhibition of the gonadal development of a given subject could be due to delayed or faulty fertilization or implantation, to disturbances originating from the mother, most likely of a hormonal nature, or to genetic causes. An "overripeness of the ova" as seen in frogs by Witschi (1956) has never been observed in the human subject. If this was due to tubal occlusion on the same side as the ovulating ovary, so that the ovum could be fertilized in the opposite tube only, then it should manifest itself more frequently. Endocrine disturbances in the mother would seem more likely as a cause: e. g. hyperoestrinism in the mother might inhibit the pituitary gland in a female foetus and thereby indirectly affect the foetal gonad. In a male foetus the gonad might be inhibited both directly and indirectly. Although hormones from the mother, of endogenous or exogenous origin, are known to be able to influence the foetus, it is unlikely that such profound changes as are seen in the two syndromes are produced by hormones from the mother.

Most authors (i. a., Danon & Sachs, 1957, Grumbach et al., 1957, and Stewart et al., 1957) consider genetic causes as the most likely. As an explanation of the "true" Klinefelter syndrome Danon & Sachs (1957) suggest that an abnormally strong masculinizing autosome may occasionally outweigh the sex chromosome combination XX. However, the supposition of such an autosome produced by mutation can hardly explain the occurrence of severe hypogonadism in two siblings of different sex. Of course this does not prevent the assumption from being valid in isolated cases of the "true" variety of the Klinefelter syndrome.

Stewart et al. (1957) from preliminary studies consider both chromatin-positive and -negative cases of Klinefelter's syndrome as genetic disturbances; the chromatin-positive cases are inherited through the father and the chromatin-negative through the mother. They believe that the inhibition of the gonads in Turner's and Klinefelter's syndromes and the concomitant malformations (i. a., muscular dystrophy) are genetically determined and that the genes involved are located in the same chromosome. «Defects could be produced by deletion of loci in consequence of inversion cross-over; some such defects would be inherited in the manner of an autosomal dominant» (Stewart, 1957).

In cases such as described here in which gonadal dysgenesis occurs in siblings of different sexual phenotype, determination of nuclear sex could give four different results: 1) a combination of a chromatin-negative Turner syndrome and a "false", viz. chromatin-negative, Klinefelter syndrome as an expression of a common masculine pattern of sex chromatin (and sex chromosomes or sex-influencing autosomes?); 2) a combination of a chromatin-positive Turner syndrome and a "true", viz. chromatin-positive, Klinefelter syndrome as an expression of a common feminine pattern of sex chromatin (and sex chromosomes?); 3) a combination of a chromatin-negative Turner syndrome and a "true", viz. chromatin-positive, Klinefelter syndrome as an occurrence of
double discrepancy between sexual phenotype and nuclear sex; and finally 4) a combination of a chromatin-positive Turner syndrome and a »false«, viz. chromatin-negative, Klinefelter syndrome as an expression of familial gonadal dysgenesis without reversal of phenotype.

The second of our cases is not quite typical of Klinefelter's syndrome, since both gynaecomastia and increased excretion of gonadotrophins in the urine are lacking. In spite of this reservation our cases would seem to belong to the fourth combination. A genetically determined defect would seem the most likely explanation of the inhibition of the gonadal development in these cases, but it is not necessarily located to the sex chromosomes as one would assume if there had been any discrepancy between the phenotype and the nuclear sex in one or both cases. It remains to be seen whether the great interest in these syndromes will reveal familial cases of any of the other three theoretical combinations.

Siebenmann (1957) described seven cases of dystrophia myotonica combined with testicular tubule fibrosis. All these cases had chromatin-negative cell nuclei, and the testicular lesions were microscopically different from the chromatin-positive Klinefelter cases. This would seem to indicate that the hypogonadism associated with muscular dystrophy is of a different nature to that of the Klinefelter syndrome. However, in their large series of 32 cases of seminiferous tubule dysgenesis Grumbach et al. (1957) found nine cases with female chromatin pattern, and one of these had myotonia dystrophica. Unfortunately, the sex chromatin pattern is not reported in the four cases of Klinefelter's syndrome and dystrophia myotonica described by Wyss (1956).

The combination of congenital muscular dystrophy and severe hypogonadism of two different types found in our cases would seem to support the hypothesis that gonadal dysgenesis is genetically determined. More such cases are needed, however, before any further conclusions are justified.

SUMMARY

Two siblings with congenital muscular dystrophy and severe gonadal dysgenesis were examined with regard to nuclear sex. One of them, a woman, had gonadal dysgenesis of Turner's type, and the other, a man, had seminiferous tubule dysgenesis (Klinefelter's syndrome). In the first case chromatin-positive and in the second chromatin-negative cell nuclei were found. The genetic sex was thus in agreement with the sexual phenotype in both cases. The muscular disorder was found in five cases among the relatives, but no other case of gonadal dysgenesis is known.

The significance of the findings are discussed in relation to the various theories on the aetiology of gonadal dysgenesis. It is concluded that the com-
Combination of different types of gonadal dysgenesis and hereditary muscular dystrophy among siblings supports the view that gonadal dysgenesis is genetically determined.

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