The genetics of human reproduction

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Introduction

The attainment of full fertility in any organism requires the proper development and functioning of the reproductive system and survival of the foetus to term. Factors which operate to interfere with any of these processes will disturb the normal pattern and lead to partial or complete infertility.

The reproductive disorders of man are many and varied, but it is the contribution made by genetic anomalies which will be considered in this review. Mutations are known which affect gonadal development and sexual differentiation as well as those which act to disturb gametogenesis. Chromosomal abnormalities too can disturb genetic processes; they also contribute significantly to human foetal wastage.

Several previous reviews on various aspects of the subject have been written and to these, the reader is also referred. A review of the genetic causes of sterility in the mouse, a much more widely investigated species, has been given by Searle.

1. Gonadal failure and impaired gametogenesis

1.1 The effect of the sex chromosomes

Considering that the X and Y chromosomes play a key role in sex determination and differentiation, it is hardly surprising that mutations at the gene loci involved, or sex chromosome imbalance, will produce serious consequences for the development of the reproductive system. Hermaphroditism, sex reversal and infertility are all well-documented features.

In human cytogenetics, the discovery that sex chromosome aneuploidies like 45, X and 47, XXY, could be associated with infertility syndromes, led to the initiation of chromosome surveys among selected groups of individuals experiencing reproductive problems. In one of the earliest studies, Jacobs et al. examined the karyotypes of 32 women who had never menstruated spontaneously. Sex chromosome abnormalities were found in half of them: these included six with an XO genotype, five with sex chromosome mosaicism, three with a morphologically abnormal X chromosome, and two with an XY sex chromosome complement. This high level of sex chromosome abnormalities compared with a frequency of only 1.8 per 1000 among newborn females. The association of a male (XY) genotype with a female phenotype characterizes the two conditions of sex reversal, 'testicular feminization' and 'pure gonadal dysgenesis'. The defect in XY females heterozygous for the X-linked Tfm (testicular feminization) gene is well known, this mutation acting at the most fundamental level to disturb sex differentiation. In pure gonadal dysgenesis, gonadal failure is the primary defect and streak gonads are usually found. In the XO female with Turner's syndrome and the XXY male with Klinefelter's syndrome, gonadal failure appears to relate to germ cell atresia. Recent insights into the role of the sex chromosomes in gamete survival in the mouse have been gained. It would appear that shortly after birth in that species, a second X chromosome blocks male and facilitates female germ cell development. Oocytes at this time are known, both in man and the mouse, to have two active X chromosomes, and germ cell loss in XO females may therefore relate to deficiency of X gene products. In XO human females, germ cell loss occurs principally around the time of birth, the adult ovary being represented generally by a streak gonad. Nevertheless, limited fertility is achieved by some Turner individuals who retain oocytes over a much reduced reproductive span. Germ cell loss in XY females with pure gonadal dysgenesis may also relate to deficiency of X-linked products.

The presence of two X chromosomes in germ cells of the mouse appears to be compatible with initiation of development in the male direction but is not compatible with spermatogenesis. The XX component in XX/XY chimerae appears to degenerate just before birth, while in XX, Sxr (sex reversed) males, degeneration sets in around the time of birth. On the other hand, spermatogenesis does take place in XO, Sxr males, some germ cells surviving to form spermatids and even a few abnormal spermatozoa.

In keeping with these findings, spermatogenesis in much reduced numbers have been recorded in the testes of pre-pubertal XXY boys, but by puberty, little sign of spermatogenic activity remains. Gonadal failure resembling that seen in adult XXY men is also seen in XX...
In XX males, the story is complex and the aetiology mixed but current research is showing that at least in some cases, the paternally-derived X chromosome may harbour a testis-determining fragment of Y chromosome transferred to the X by accidental crossing-over or X-Y interchange. The identification of Y-specific sequences in the DNA of a number of XX males investigated using Y-specific probes supports this. Whether the Y chromosome functions in spermatogenesis is not clear. In the mouse, it has been argued that the Y chromosome may only serve a role in ensuring normal spermatogenic development to a late stage by providing a pairing partner for the X. (It will be shown later that normal XY pairing must be maintained for meiosis to go to completion). In man, factors which influence spermatogenesis may be situated on the long arm of the Y chromosome close to the intensely fluorescing heterochromatin.

1.2 X- and Y-autosome translocation

From studies on human female X-autosome translocations, there is evidence that the structural integrity of a critical region of the X chromosome long arm is necessary for normal ovarian function in heterozygotes. Sarto et al., first drew attention to this by pointing out that all females hitherto reported who were heterozygous for a reciprocal X-autosome translocation with a breakpoint in this region had primary or secondary amenorrhoea. Summitt et al. reviewed the literature and found that 9 of 18 females reported to be carriers of X long arm autosome translocations exhibited either streak ovaries (7 cases), ovarian hypoplasia (1 case) or underdeveloped ovaries (1 case). The X chromosome breakpoints of the 13 translocations were all located within the region Xq13-Xq26. The critical region therefore lies in the middle of the long arm and represent about two-thirds of its length. A few exceptions to this general rule have, however, been presented. These authors have described women heterozygous for a balanced X-autosome translocation with a breakpoint in the critical region but who, nevertheless, were fertile. The question as to precisely how such a chromosome exchange could affect the development and functioning of the ovary remains still to be answered. A 'position effect' explanation has been offered by Summitt et al., while Madan et al. have suggested a mechanism of variable penetrance similar to that which allows some XO women (and XO mice) to retain oocytes into adult life and thus to conceive. Burgoyne and Baker believe that meiotic pairing failure in female X-autosome translocation heterozygotes and also in XO females, could account for the oocyte atresia by selectively removing oocytes from the germ line. Reproductive lifespan is known to be curtailed in some female X-autosome translocation stocks of the mouse, as well as in XO mice, owing to a smaller pool sizes of oocytes. Observations by Speed on foetal XO oocytes in mice show a tendency on the part of the single X chromosome for self pairing or nonhomologous pairing with an autosome at pachytene in up to 50% of cells. These, Speed suggests, could be oocytes which will survive, having saturated their pairing requirement. Observations made on three XO human foetuses, however, showed most oocytes blocked at the preleptotene stage (Speed, in press), germ cell failure at least in these cases occurring before pairing had even begun.

For male carriers of an X-autosome reciprocal translocation, the consequences for spermatogenesis are severe. Meiotic development is invariably arrested at the pachytene stage, both in man and the mouse, and carriers are rendered severely oligospermic or azoospermic. For male carriers of reciprocal Y-autosome translocations the consequences are similar if perhaps slightly less severe. Spermatogenesis in a few of these cases seems to be able to proceed to the late stages both in man and the mouse, and in one human case of Y; 10 reciprocal rearrangement spermatozoa were produced in numbers which were within normal limits for the human male, pregnancy being achieved on four separate occasions. Ascertainment in this case was by birth of a child with congenital malformations.

A hypothesis to explain the sterility of male X-autosome translocation heterozygotes of Drosophila, the mouse, and man, has been put forward by Lifschytz and Lindsley. They argue that asynchrony of control of X-chromosomal and autosomal gene activity is necessary for normal spermatogenesis. The spermatogenic disturbance in X-autosome carriers, they suggest, is brought about by autosomal interference with the precocious inactivation of X-linked genes. The sterility of Y-autosome translocation heterozygotes might be explicable on the same model since the Y chromosome too is known to be inactivated early in the primary spermatocyte stage both in the mouse and in man. The effects on spermatogenesis in such cases, appear, as far as one can tell from the limited number of reports so far, to be less severe than when rearrangement takes place between an autosome and the X.

1.3 Autosome-autosome translocation

Lyon and Meredith were the first to show that certain purely autosomal translocations of the mouse cause sterility in male heterozygotes because of spermatogenic impairment. The occurrence of such translocations in man has also been noted. A mechanism by which purely autosomal rearrangements might bring about spermatogenic disturbance has been put forward by Forejt. He and his co-workers showed that in a number of male-sterile autosomal translocations of the mouse, a high frequency of centromeric contacts between the translocation configuration and the XY bivalent were formed at pachytene and particularly when chain configurations were present in the translocation. Such contacts were not seen to any great extent among the pachytene cells of male-sterile translocation carriers showing a preponderance of ring quadrivalents. Similar contacts were reported by Chandlee in sterile male mice doubly heterozygous for two partially overlapping inversions. Forejt suggested that non-random associations might produce interference with the precocious X-chromosome inactivation in the primary spermatocyte which, on the Lifschytz/Lindsley hypothesis, would be required for normal spermatogenesis. Whether oocyte numbers are lower than normal in human females who carry autosomal translocations which sterilize the male is not known but, in the mouse, evidence of reduced ovarian volume indicating an effect of the translocation on oogenesis has