

Chromosome and Sex-Chromatin Studies of Patients with Hypospadias*

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Various forms of chromosomal aberration have been described in patients with hypospadias associated with various other genital malformations, however cases of the condition without such malformations have not yet been investigated for the possibility of chromosomal anomalies. This communication presents the results of chromosome studies of patients with pure hypospadias.¹

Materials and Methods

Fifteen patients were included in the study, 13 of whom had corporal and two perineal hypospadias. One of the latter also had bifid scrotum, and the other, who had a vagina, had exploratory laparotomy performed, which revealed internal male genital organs. Four of the patients with corporal hypospadias had unilateral undescended testes.

Conventional methods were used for determining sex-chromatin with buccal smears, and Moorhead's method² with slight modifications was used for chromosome studies.

In every patient at least 20 metaphase plates were counted and analysed.

Results

In no case did either the sex-chromatin or the chromosome studies reveal any abnormalities.

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Discussion

Although hypospadias may be due to a malformation of the penis primordia of unknown etiology in most cases, it appears likely that endocrine abnormalities also play a role.³ The condition, which is one of the more common malformations,¹ is frequently accompanied by various forms of intersexuality. These can be divided into: balanitic or corporal (40-50 per cent), penile (25-30 per cent) and peno-scrotal, perineal or pseudo-vaginal (10-15 per cent). In a recent study involving 10,000 consecutive live-born babies at Hacettepe Children's Hospital and Maternity Home, hypospadias was encountered with a frequency of 0,3 per cent;⁴ and was found to be the second most common of the genito-urinary anomalies, the first being undescended testes. Of this 0,3 per cent, 24 (80 per cent) were glandular, five (16,7 per cent) were penile and one (3,3 per cent) was peno-scrotal. Two of the patients with glandular hypospadias also had pestalovalgus, and a second had hemangioma; one of those with penile hypospadias also had bifid scrotum, while another had a second degree cardiac murmur.

In another similar study involving 5,964 births, hypospadias was again found to be the second most common genito urinary anomaly⁵.

The incidence of hypospadias has varied in different studies between 1/1800 and 1/160³. Campbell, investigating 10,700 autopsies, reported an incidence of 1/583³ while another author found 3,26/1000 cases of the condition.⁶

Sorensen reported that 75 per cent of cases are sporadic, while the remaining 25 per cent show recessive inheritance.⁶ However, other cases have been reported showing holandric inheritance pattern. Lugard, Lesser, Campbell, and Moore showed hypospadias in 6, 3,3, and 6 generations respectively,⁶ they also showed that defect is sometimes inherited as a dominant trait. Some researchers found concordance in monozygotic twins. Lamy saw it in three pairs, while in another three he reported that there was discordance. He also saw discordance in four pairs of dizygotic twins. This indicates that inheritance pattern of hypospadias is not clear. While reports of discordance in monozygotic twins indicates the possible role of external factors, concordance in other monozygotic, as well as dizygotic twins, suggests some simultaneous external intrauterine insult.

At present, hypospadias is considered by most authorities to be a form of intersexuality rather than a result of a temporary pause in development. To support this, hypogonadism, absence of the prostate and ambiguity of the penis are not infrequently encountered at the same time.

Likewise, in most cases at least chordee is observed, and in others, though less frequently, bifid scrotum and undescended testes, sometimes bilaterally.¹

Associated malformations are found in 25 per cent of cases, the most common being cryptorchism.⁷ Others include congenital hydrocele, hypoplastic penis and persistent fetal vagina. The most common urinary anomaly is unilateral agenesis of the kidney; spina bifida is frequently seen. Hypospadias is also encountered in the following entities:

- 1- Reifenstein's Syndrome⁸
- 2- Smith-Lemli-Opitz Syndrome⁹
- 3- Hypospadias-hypertelorism syndrome (Grieg's syndrome)¹⁰
- 4- Ullrich-Feichtiger syndrome¹⁰
- 5- Cleft lip/palate, popliteal pterygium, digital and genital anomaly syndrome¹⁰
- 6- Cebocephaly¹⁰
- 7- Unilateral hypertrophy (Curtius syndrome, Steiner's syndrome)¹⁰
- 8- Ellis-van Creveld syndrome¹⁰
- 9- Congenital adrenal hyperplasia¹¹

Chromosomal aberrations have been found in some cases of hypospadias. For example, partial deletion of the upper arms of chromosome number 4 has been reported.¹² Similarly, in one family with muscular dystrophy and hypospadias a Y chromosome was found to be extremely small, although this could be a normal variation.¹³ In another patient a translocation between the Y chromosome and a member of the G group was suggested.

A more interesting finding is that many known chromosomal entities show hypospadias among other symptoms. It is not uncommon, for instance in XYY, XY/XO cases and in Klinefelter's syndrome and its variants.¹⁴⁻¹⁶ Siebner and Schlöch reported four cell lines (XO/XY/XYY/XX) in a phenotypically male patient who had hypospadias and bilateral cryptorchism, and Finley et al. found four different cell lines in a patient with ambiguous genitalia.¹⁷⁻¹⁸

In a study involving 16,000 newborn males, Halbrecht, encountered eight cases of hypospadias, one of which was chromatin positive. This patient was phenotypically male and both testes were down in the scrotum.¹⁹

Juberg et al. studied 21 cases of hypospadias by sex-chromatin and chromosomal analysis, but found no abnormalities.²⁰

Our investigations show that patients with hypospadias, but without associated malformations, are phenotypically male as their external appearance indicates. However, since no tissue culture using gonadal cells could be made, the possibility of mosaicism in such patients, although small, could not be eliminated.

Summary

Fifteen cases of hypospadias were studied by sex-chromatin and chromosome analysis. No abnormalities could be detected. Other entities associated with hypospadias are reviewed.

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