KLINEFELTER'S SYNDROME

(A Case Report with Review of Literature)

by

SHERNAZ P. BILIMORIA*

The original syndrome of micro-orchidism, azoospermia and gynaecomastia described by Klinefelter in 1942 (Benirschke 1968) has had many additional features to explain the cause and cytological appearances. These include the presence of the Barr body and variants like mental retardation and eunuchoid body proportions (Porter 1968). Porter has called attention to the fact that it can be a much more common condition than is suspected and might often be missed (Porter 1968). The case in question had several interesting features and is therefore reported.

Historical Aspects:

Though this syndrome was first recognised in 1942 on a purely clinical basis, an exact delineation of it from the other examples of chromosomal aberrations was done in the late fifties, when somatic cells from these patients were shown by Bradbury *et al* (1956) and others, to be sex-chromatin positive (Bradbury *et al*, 1956; Court Brown 1961). Later, in 1959, Jacobs and Strong discovered an abnormal karyotype of 47-chromosomes, there being an XXY sex-chromatin constitution. Since then Karyotypes of XXXY (triple-X), XXXXY (tetra-X) and XXYY (Double-Y) have been reported as well (Knudson 1965). The Years 1957 and 1958 were years spent in the development of techniques which would allow the study of human chromosomes to be undertaken on a routine basis in human disease (Court Brown 1961). A contribution (Barr and Moore 1955) which may be of great importance in practice is Moore and Barr's description of a method of sexing depending on scrapings of the oral mucosa which provides a film of cells similar to those so familiar to the exfoliative cytologist in vaginal smears, done on a series of 140 subjects (81 males, 59 females). The sex was diagnosed correctly in 100 p.c of cases.

*Intern in Medicine, B. Y. L. Nair Charitable Hospital and T. N. Medical College, A. Nair Road, Bombay-8.

Received for publication on 24-7-72.

CASE REPORT

M.Y., a 20 year old unmarried muslim male first presented at this hospital on 5-7-1971 in status asthmaticus. He was actually a known case of bronchial asthma, suffering from the condition for the past 4 years and treated elsewhere. Carotid denervation was done in 1971 at Nair Hospital, Bombay. He was admitted a number of times to this hospital after that in the same state. During one of these visits, further interrogation revealed that the patient has been operated elsewhere early in 1971 for undescended testes. Two successive attempts having failed one testis was left in its original inguinal canal position. Three months after his first appearance at this hospital, he was found to have developed gynaecomastia which led to investigations from the point of view of chromosomal aneuploidy.

On examination he was a young man of normosthenic build and of average intelligence. He had characteristic male distribution of hair, though growth on the chest was scanty. The hair line on his head was rather low. There was bilateral gynaecomastia but no evidence of eunuchoidism, as the secondary sex characteristics were fairly well developed, including the tone of his voice. The span and stature measurements were equal as also the upper and the lower segment measurements. On examination of the external genitalia, it was found that the left side of the scrotum was smaller than its right counterpart and no testis could be felt in it. The right testis was found to be at the entrance of the scrotum at the level of the superficial inguinal ring, but palpation revealed it to be small in size with absence of testicular sensation. The penis was normal and a scar was noticed in the left inguino-scrotal region. The patient gave a positive history of ejaculation and erection which went in favour of his being designated a male phenotype. Cardiovascular and respiratory systems were normal. Neurological examination showed that the patient was quite cooperative; higher psychological functions and speech were normal. Fundi showed no abnormality and no psychiatric manifestations were present.

Investigations

1. Excision-Biopsy of the gynaecomastia lesion done on 16-11-1971 showed significant breast tissue with ductal, glandular and fibrofatty tissue.

2. Semen-analysis done on 21-2-1972 showed evidence of azoospermia.

3. Barr-Bertram staining of buccal smear done on 12-1-1972 employing the Feulgan technique, showed a fairly large number of cells with nuclear membrane thickening (? +ve) and a fairly large number of cells showing rather marked chromatin stippling.

4. Testicular biopsy done on 24-1-1972 showed atrophy of testicular tissue and absence of spermatogenesis.

5. Urinary 17-ketosteroid output estimated on 23-1-1972 on a sample of 24 hour urine collected under refrigeration was found to be 6.6 mgm (Normal for males 4-15 mg).

6. Urinary pituitary gonadotrophins done on the same sample of 24 hour urine was positive at 50 mouse-units (Normal +ve at 5 —10 m.u.).

7. Blood smear study done on 22-2-1972 showed occasional drumstiik like bodies, but there seemed to be a fairly frequent observation of chromatin protruberances either with short peduncles or sessile. These were often more than one per cell. This seemed to point to some chromosomal aberration.

The diagnosis was based on the presence of gynaecomastia, the small undescended testes, the biopsy picture which showed seminiferous tubules showing lack of spermatogenesis, and high pituitary urinary gonadotrophins. While the mouth scrape was not unequivocally positive, the doubtful thickening of nuclear membrane and chromatin stippling threw additional weight as will be discussed later.

Discussion

Familial incidence does occur; Reifenstein reported 9 of 10 male members in 2 generations of one family, with transmission by the female. The condition has also been verified in identical twins Lisser *et al,* 1962). As in the Down Syndrome, the mean age of the mothers of these patient is greater than normal (Knudson 1965).

The patient usually approaches the clinician for primary sterility. Gynaecomastia, eunchoidism and cryptorchidism are other important presenting complaints (Benirschke 1968 and Stewart John, 1959). There is no way of determining clinically whether a boy has Klinefelter's syndrome before puberty, unless all children have a Barr body count done at birth (Porter 1968). However, the syndrome is now being recognised before puberty, by a discrepancy between chromosomal and gonadal sex, in addition

to the histological findings of the true Klinfelter's syndrome.

This patient presented with gynaecomastia and small, undescended testes (cryptorchidism). Further investigations revealed that the testes were atrophic, spermatogenesis was absent and the urinary excretion of pituitary gonadotrophins was much above normal for his age and sex. The patient had neither mental retardation nor eunuchoid characteristics. Moreover, his secondary sex characteristics were normally developed for his age.

Frequently there is evidence of poor androgenic stimulation or response; patients may shave infrequently; hair may be sparse and its distribution feminine. This was not the case in this patient. These patients are usually sterile though by no means always impotent. This would be difficult to judge in this patient as he is unmarried. There is however, one documented instance of a chromatin positive man with XXY Klinefelter's syndrome who has fathered children but he may have been an undetected Klinefelter Mosaic (Porter 1968). Libido may be normal in the young patient with Klinefelter's syndrome, but it tends to diminish early and may progress to impotency. Lack of libido and gynaecomastia may lead to psychologic disturbances. It is of practical importance to be aware of such disturbances, because they may be severely aggravated by giving the patient testosterone, (Porter 1968). The astonishing thing about Klinefelter's syndrome is the marked variation in signs and symptoms. Thus, at one end of the scale one sees a few patients who appear entirely normal. At the other end of the scale, one sees institutionalised patients who are severely retarded with eunuchoid body proportions and gynaecomastia.

The pathological features are characteristic in the postpubertal testes. These are:

1. Small testes, averaging about 1 cm in diameter.
2. Excess fibrous tissue.
3. A lining epithelium of the seminiferous tubules consisting only of Sertoli cells.
4. Tubules devoid of epithelium and converted into a structureless hyaline mass.
5. Distortion of the architectural pattern by fibrosis and aggregation of Leydig cells in the spaces between the shrunken tubules (Porter 1968).

The testicular biopsy of this patient exhibited most of these features, especially the Leydig cell aggregations and Sertoli cell lining, but did not have the hyalinisation of the tubules.

The mouth scrape did not show clear cut, well-defined Barr Bertram bodies of significant percentage as in classical Klinefelter cytology. However, the doubtful thickening of a fairly large percentage of cells and the fairly large number of cells showing some form of chromatin stippling leads one to believe that there could be some chromosomal abnormality leading to a Klinefelter-like condition, as also did the pecularities of the blood smear.

In these patients, the gonadotrophic hormone is excreted in markedly increased quantities. According to a review of 20 cases studied by Heller and Nelson (1945), all of the urinary extracts produced vaginal canalization and a 300 to 400 per cent increase in uterine weight over that of control rats. Such canalization and uterine weight increase were encountered in only 1/4th of the assays of extracts derived from normal men.

Leutinization of follicles and formation of discrete corpora leutea were noted in the ovaries of experimental rats receiving urine extracts from these patients. This together with the finding of thick, non-translucent, non-ballooned uteri in the same animals suggested that both F.S.H. and I.C.S.H. (Leutinising hormone) were being excreted in the urine (Heller and Nelson, 1945). This was confirmed by Balze *et al* (1952) who studied 5 cases using the ultra-filter extraction method for urinary pituitary gonadotrophin assay.

The urinary 17-Ketosteroid output in these patients may be depressed. This can be attributed to less than normal amounts of circulating androgens (Balze *et al*, 1952; Heller and Nelson, 1945). Among the many steroids that comprise the complex of 17-ketosteroids, two existed in greater amounts than the others, namely, androsterone (which is active androgenically) and 3—α—OH—aetiocholanone (which is inactive androgenically). The normal 17-ketosteroid values encountered in 2 cases out of 20 studied by Heller and Nelson were attributed to the preponderent excretion of biologically inactive steroids, as aetiocholanone.

The excretion of oestrogens may vary from normal to low, but is never increased in amount.

The Klinefelter's syndrome is primarily a testicular hypogonadism which apparently starts at puberty and involves all elements of the testes. Klinefelter *et al.*, regarded the degenerative lesion of the seminiferous tubules as primary and the gynaecomastia as due to secondary hormonal disturbances (Mosbech *et al.*, 1956). Heller and Nelson and Balze, and Mosbech *et al*, 1956 reported additional cases of Klinefelter's syndrome and agreed that the disease should be regarded as primarily affecting the testes and suggested that abnormal proliferation of fibroblasts in the tubular wall led to complete hyalinization and atrophy of the germinal epithelium. According to Balze and others, F.S.H. is an essential factor in the development and maintenence of the seminiferous tubules at puberty. They postulate that in cases of Klinefelter's syndrome the seminiferous tubules receive adequate gonadotrophic stimulation (F.S.H.) at the onset of puberty, but because of the absence of local androgenic stimulation due to the failure in the normal development of Leydig cells, the germinal epithelium experience the pathologic changes already described.

Another theory has been proposed to explain the control of F.S.H. and I.C.S.H. secretion (Alwin-Paulsen 1968). In this theory Heller *et al* have suggested that gonadotrophins are normally utilized by the metabolic processes of the testes.

With primary testicular damage less F.S.H. is utilized and, therefore, appears in the urine.

Summary

A case of Klinefelter's syndrome is being reported in a young man aged 20 years. Clinical features of the condition have been discussed.

Acknowledgement

Grateful thanks are due to Dr. N. C. Amin who while heading the unit permitted me to study this case and report it. The author thanks Dr. E. J. DeSouza, Head of the Department of Anatomy for the help he has given me regarding the patient's chromosomal sex detection and to Dr. (Mrs.) S. M. Shahani regarding the hormonal assays. I am also grateful to the Dean, Dr. C. K.

Deshpande, for giving me permission to use hospital records and have the case published and to Miss A. B. Chawan and Mr. S. N. Miranda for technical help.

References

1. Alwin Paulsen, C.: Textbook of Endocrinology, 4th Edition, Philadelphia, London, Toronto—1968; W. B. Saunders Company pp. 405-451.
2. Balze, F. A., Arrillaga, F. C., Irazu, J. and Mancini, R. E.: J. Clin. Endocrinol, and Metabolism, **12:** 1426, 1952.
3. Barr, M. L. and Moore, K. L.: Lancet, **2:** 57, 1955.
4. Benirschke, K.: Progress in Infertility, Behrman and Kistner, 1st Ed., London, 1968. J. and A. Churchill Ltd. 831-832.
5. Bradbury, J. T., Bunge, R. G. and Boccabella, R. A.: J. Clin. Endocrinol. and Metabolism, **16:** 689, 1956.
6. Court-Brown, W. M.: Sex Chromosome Aberrations—II; Clinical aspects of Genetics—Jones—Proceedings of a conference held in London, 17-18th March, 1961. Pitman medical publishing company, 1st edition, 75-76.
7. Heller, C. G. and Nelson, W. O.: J. Clin. Endocrinol. **5:** 1-33, 1945.
8. Knudson, A. G., Jr.: Genetics and Disease 1st Edition. McGraw Hill inc., California, 1965, 77-79.
9. Lisser, H. and Roberto, F.: Atlas of Clinical Endocrinology; 2nd Edition., Saint Lois, 1962. C. V. Mosby and Company.
10. Mosbech, J., Povl, R. and Svend, J.: Lancet, **1:** 962, 1956.
11. Porter, I. H.: Heredity and Disease, 1st Edition, New York, 1968. McGraw Hill Inc., 37-39.
12. Stewart-John, S. S.: Lancet, **1:** 1176, 1959.

See Figs. on Art Paper VII