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Case Series

Sex Chromosome Abnormality and Sexual Behaviour: Selective Treatment Approaches - A Case Series of 5 Klinefelter's Men

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Abstract

The study of Klinefelter's syndrome (XXY chromosome) in relation to sexual disorders is particularly relevant to forensic psychiatrists since various reports have suggested an association between these conditions [1-8]. However, the prevalence of sexual deviations or paraphilias in these men is not precisely known and may only be sporadic [2,4,9]. In 1981, Schroder., *et al.* found that men with extra sex chromosomes were more likely to have been involved in sexual crimes than other indictable offenses [10]. O'Donovan and Völmm [11] conducted a systematic review of research papers in order to establish the prevalence of sexual offending in Klinefelter men. They identified 53 papers, out of which 10 were relevant for their purposes. One of the papers, a Danish register-based cohort study, supported the notion of an increased risk of sex offending in Klinefelter men [8]. It further found that the prevalence of sexual offending was higher before diagnosis [8]. In the current paper, the authors discuss relevant aspects of sexual behaviours in a series of five men with Klinefelter's syndrome.

In light of the chromosomal and hormonal abnormalities, specific factors must also be considered prior to initiating a treatment program. The traditional approach of hormonal replacement may not always represent a reasonable alternative in presence of a sexual deviation. These considerations deserve further discussion.

Keywords: *Klinefelter's Syndrome; Sexual Disorder; Paraphilia; Management*

Introduction

In 1942, Dr. Harry F Klinefelter Jr. and his associates were the first to report on a condition characterized by gynecomastia, aspermatogenesis and increased pituitary secretion of follicle-stimulating hormone [1]. Since that time, the finding of cellular sex chromatin (Barr body) in afflicted males indicated a chromosomal abnormality as a cause of the Klinefelter syndrome [2,12,13]. At least 45 to 75% of patients with Klinefelter's syndrome are chromatin positive and at least two-thirds of the afflicted males have an XXY karyotype, and the remaining one-third have one of its variants: 48,XXXY; 48,XXYY; 49,XXXXY; or 49,XXXYY [3-5,14-17]. Mosaic patterns with chromatin

positive cells and chromatin negative cells have also been reported [2-5,18]. The majority of cases are due to meiotic nondysjunction in the early cell division of the zygote [4,5,15,18-20]. While mental retardation is not part of Klinefelter's syndrome, it has been suggested that physical and mental disabilities in Klinefelter's syndrome increase with the number of additional sex chromosomes [4,21,22].

Estimates of the incidence of sex chromatin abnormality or Klinefelter's syndrome in the general male population average about 0.2% [3,4,10,12,15,20,23-25]. Less than ten percent of diagnoses of Klinefelter's syndrome are made before puberty [26], when the syndrome usually becomes apparent [1,4,5,12,18,27]. The most consistent finding in these phenotypically male individuals relates to hypoplastic atrophic testes [1-6,10,12-15,18,20,27-30]. Frequent features include bilateral gynecomastia, paucity of facial and body hair, female pattern of pubic hair distribution, obesity and a tendency toward a female-like distribution of subcutaneous fat [1-6,10,12,14,15,18,20,27-30]. These features can be seen singularly or in combination in approximately 50% of cases [12]. The prostate gland may be smaller than usual but the penis is usually of normal size [3,5,6,12]. Libido is diminished in a significant proportion of cases [2-6,10,12,27,29]. According to some studies, a majority of individuals with Klinefelter's syndrome marry and most report normal coitus and ejaculation [6,12]. They are, however, usually sterile due to impaired spermatogenesis [6,10,12,15,27-29].

In addition to specific chromosomal findings and the presence of Barr body on chromosomal analysis, a below average excretion of androgenic hormones and alteration in gonadotrophin levels are associated with the syndrome [4,10,12,14,27,28]. Since Klinefelter., et al. first reported an increased urinary excretion of follicle-stimulating hormone (FSH), the finding has been replicated repeatedly [1,2,6,9,10,12,15,27,29]. Luteinizing hormone may be either low or high and the FSH/LH ratio is generally approximately twice that of normal men [9,6,28]. A typically low basal metabolic rate is likely due in part to a relative androgenic deficiency [6,12]. Estrogens and 17-hydroxycorticosteroids values are generally normal [6,9]. The average excretion of 17-ketosteroids varies from normal to below normal [6,9,12,14,18]. Since testicular steroids contribute no more than 1/3 of the total urinary 17-ketosteroids production, this measurement is of limited value in assessing androgenic activity [6].

Diagnosis and Staging

Cognitive and behavioural problems have been identified in individuals with Klinefelter's syndrome [31,32]. Several studies have reported that children and adolescents with the syndrome display specific impairments in language processing, including a significantly lower verbal IQ relative to performance IQ and a learning disability in reading and spelling [31-41] and specific deficits in frontal-executive functions involved in inhibitory processes [37]. Certain identified cognitive problems associated with Klinefelter's syndrome may persist into adulthood. Impairments in language, verbal processing speed, and verbal and nonverbal executive abilities have been reported in adults with the syndrome [42-45]. It has been suggested that language and executive function impairments in Klinefelter's syndrome may be due to a difficulty in encoding verbal information into working memory [45]. The frontal lobe disabilities associated with Klinefelter's syndrome may underlie psychosocial problems observed in young males [32,33,44]. A longitudinal study of males with Klinefelter's syndrome detected at birth reported psychological or social problems in many of the affected boys [41]. Social maladjustment in adolescence has been observed to range from introverted and socially withdrawn behaviour to impulsive and socially inappropriate behaviour [31,35,44,46-49].

The hypothesis of an association between Klinefelter's syndrome and psychosexual disorders is based on a limited series of case reports and case studies [3,5,12,14,18,50,51]. The prevalence of sexual paraphilias in these men is not precisely known and may only be sporadic [3,5,52]. Exhibitionism, transvestism, pedophilia and sadomasochism have been reported [3,5,6,9,12,14,29,30,50,51]. Schroder., et al. [28] looked at the frequency of XYY and XXY men among criminal offenders and found that men with extra sex chromosomes were more likely to have been involved in sexual crimes than other indictable offense. Male gender disturbances, such as a feminine identification, transsexualism and homosexual orientation have also been identified in association with the syndrome [2,3,5,9,12,14,18,29,50,53]. Immature sexuality, disturbance and paucity of heterosexual experiences, and low sexual drive are commonly found in these patients [3,5,12,14,15,18,27,51]. Some researchers have suggested that Klinefelter's syndrome is associated with solitary (non-relationship oriented) sexuality. In a study of 12 men with Klinefelter's syndrome, Kvale and Fishman [18] found that the majority used masturbation as their primary orgasmic experience. Approximately 25% of their subjects were described as "compulsive" masturbators.

Review of Cases

A diagnosis of Klinefelter's syndrome was established in five cases of individuals presenting to a university-affiliated psychiatric hospital, using Barr body analysis and chromosomal analysis. All subjects submitted to a full medical, neurological and neuropsychological examination, in addition to routine blood investigations including sexual hormones. Behavioural correlates and sexual functioning were examined in more detail. All patients signed informed consent approved by the hospital ethics committee permitting description of their conditions without revealing their names. The following clinical summaries illustrate some relevant findings and outcome.

Case #1

Mr. A was a 20 years-old single male admitted to the psychiatric hospital following a sexual assault on a 6 years-old girl. He was the product of a normal pregnancy but premature birth and spent one month after birth in an incubator. He suffered from asthma and bronchitis since his early childhood. He was a shy, reserved young man who showed poor socialization skills throughout his teenage years. Since age 4, he experienced epileptic seizures although he had been free of seizures for several years prior to his hospitalization. He complained about headaches and an EEG showed generalized potentially epileptiform disturbances. A neurological examination was normal but the physical examination revealed gynecomastia with striae on the breasts and abdomen, hypogonadism and small penis, obesity and tall stature. Personality testing revealed anxiety, self-consciousness and insecurity. On the WAIS-R, he obtained a full-scale IQ of 76 with performance IQ at 83 and verbal IQ at 73. His chromosomal pattern was 47, XXY with no mosaicism. His sex hormone profile yielded a low testosterone plasma level at 8.1 nmol/L (normal: 10 - 30) and increased LH at 44 IU/L (normal: 6 - 30). The diagnoses were those of sexual disorder, paraphilia in the form of bisexual pedophilia and organic brain syndrome on the basis of the abnormal EEG. He was treated with antipsychotic medication and showed a reduction of his sexual drive and pedophilic fantasies.

Case #2

Mr. B was a 32 years-old separated male who presented to the emergency department, complaining of depression and suicidal ideation. He was unemployed and his wife had just left him after seven years of marriage. He occasionally lost his temper against his wife for no apparent reason and she was frightened. He became increasingly depressed and withdrawn, lost his appetite and 30 pounds of weight, and his sleep was disturbed. His mood fluctuated unpredictably. He had made two previous suicide attempts. This was his first hospitalization.

A review of his personal history indicated that his childhood was happy, although he usually kept to himself, enjoying reading and meditating. He reported more ease associating with females than males, and from an early age assumed a feminine role. He idealized his mother who died when he was 16 years of age. He took over her role in the house and his hobbies consisted of cooking, crocheting and reading. He reported his father to be an alcoholic. Mr. B held several jobs, either as a chef (which he liked best) or a security guard. He had delayed puberty at 22 years of age. He never dated prior to marrying at the age of 25 after 3 months courtship. Concerning sexual dysfunctions, he experienced only delayed orgasm. After 4 years of a childless marriage, investigations confirmed his sterility and this led him to doubt his manhood. His temper outbursts became manifest at that time.

Mental status examination upon admission to the hospital was consistent with depression. He showed psychomotor retardation, social withdrawal, flat affect and depressed mood, and he described active suicidal ruminations. Personality testing suggested chronic anxiety, a moderately high level of depression and self-concern, gender identity problems with strong female interest patterns and low levels of sex drive and aggression. On the WAIS-R, he obtained a full-scale IQ of 89, verbal IQ of 83 and performance IQ of 98. While the neurological examination, EEG and tomogram of the brain were negative, the physical examination yielded interesting findings. He was tall and moderately obese with a female distribution of body fat. He demonstrated feminine mannerisms and his voice was high pitched. The upper to lower segment ratio of the body was decreased with an increased ratio of arm span to height. He presented a female-type of escutcheon, underdeveloped atrophic testes, small penis and gynecomastia. A buccal smear was positive for sex chromatin and karyotyping confirmed XXY chromosomal pattern. His sex hormone profile indicated low levels of testosterone and increased LH and FSH. Mr. B was treated with testosterone enanthate 300 mg I.M. every 3 weeks and showed a spectacular improvement of his depression.

Case #3

Mr. C was referred by a legal agency after he was caught exposing himself to young female pedestrians. At age 27, he was working as a clerk and was still residing with his parents. He first exposed his genitals to strangers at age 10 and was first charged with indecent exposure at age 16. A diagnosis of Klinefelter's syndrome was established then and he was placed on testosterone during his teen years. He was of normal intelligence with verbal IQ of 102, performance IQ of 113 and full-scale IQ of 108 on the WAIS-R. Personality testing indicated long-standing personality adjustment problems and chronic anxiety. An EEG revealed mild intermittent bitemporal disturbance of cerebral activity but neuropsychological testing failed to demonstrate any evidence of cerebral dysfunction. He was extremely shy and reserved and lacked efficient social skills. As a result of severe third degree burns accidentally inflicted to two-thirds of his back at a young age, he had spent several weeks in hospital and was left with prominent scarring. He said he did not want to develop intimate relationships with women, due to fear of having to expose his scars and experiencing rejection. His sexual outlet was therefore limited to masturbatory activity, and he was sexually aroused by the fantasy of seducing a woman only by exposing his genitals. He disliked the rest of his body. He was tall at 6'4" and relatively slim. He had a mild degree of gynecomastia and a protruding jaw. Genitals were small. The clinical neurological examination was fully normal. At the time of the referral, he had not been on hormonal replacement for at least 10 years but his plasma testosterone level was found to be in the upper limit of the normal range at 29.2 nanomoles per litre (normal: 10 - 30). FSH and LH were both elevated.

Because of his chronic exhibitionism, a behavioural treatment was initiated but did not bring about significant control over his deviant impulse. He was placed on cyproterone acetate (a medication used to decrease testosterone) and improvement was dramatic, with the disappearance of deviant sexual fantasies. He further benefited from a sexual education and social skills program and started to date age-appropriate sexual partners.

Case #4

Mr. D presented to a psychiatric hospital at 57 years of age because of anxiety and depression. This single, man with intellectual disability had never lived independently and had limited functioning ability. He was born into a middle class working family, the third of four siblings. He was a sickly child. He had rickets and wore braces in his early years. He was a slow learner and finished a grade 8 education at 15 years old. In his early twenties, he developed pulmonary tuberculosis and required a left thoracoplasty and the removal of nine ribs at age 25.

Mr. D was 38 years old when his father died of stroke. He lived with his mother over the next 12 years until she died of myocardial infarct. He subsequently resided with his sister and worked as a part-time volunteer worker in a hospital. He had no past psychiatric history except for a 3-year history of anxiety and depression.

A number of anomalies were identified on physical examination. He had a marfanoid build, with a height of 180 cm and arm span of 180 cm, spidery fingers, protruding chin and hallux valgus. He also had unilateral slow beat tremor of his right hand, and chest deformity due to thoracoplasty and kyphosis beginning at T4 level. A loud pleural rub could be heard at the left pulmonary base posteriorally and he was slightly cyanotic. In fact, chest x-ray showed pulmonary fibrosis, and he had impaired gas exchanges. His ankle jerk reflexes were diminished on the right side, vibration sense was impaired and an electromyogram revealed an unexplained peripheral motor neuropathy. EKG was borderline with non-diagnostic T wave changes. Serum electrophoresis showed a slight reduction of the alpha globulins. Endoscopy revealed the presence of hiatus hernia with erosive oesophagitis and gastritis. An EEG was normal, tomogram of the pituitary sella was normal while the CT brain scan demonstrated an incidental finding: an area 8 mm in length in the right jugular foramen representing an extension of the mastoid bone.

Personality testing was consistent with high levels of anxiety, interpersonal isolation and self-consciousness. His full-scale IQ was 54, performance IQ 59 and verbal IQ 58 on the WAIS. Chromosomal analysis displayed a 46 XYq pattern.

He was treated with a first-generation antidepressant and responded well. Follow-up was arranged with a pneumologist.

Case #5

Mr. E was a 32 years-old single male referred to a forensic service after he pleaded guilty to charges of indecent assault and theft over $200. On mental status examination he presented with mild anxiety and depressive symptoms. He talked about his sexual inadequacies with embarrassment, reporting fantasies of homicide mainly in the form of lust murder and sadism involving females between the ages of 15 and 30. His sexual experiences included kissing, petting and mutual masturbation but he never had sexual intercourse. Since age 17 he was engaged in voyeuristic activities on a nightly basis. His self-reported sexual drive was high with self-reported masturbatory activity up to several times a day. Adequate social skills required to develop a romantic relationship were lacking. His sexual outlets remained primarily voyeurism and masturbation although he also described frequent fantasies of sexual intercourse using physical force and threats.

Mr. E was the product of a normal pregnancy but with prolonged delivery resulting in minimal brain damage. He was delayed in his developmental milestones and growth and suffered from primary enuresis up to the age of 29. At the age of 4 he had febrile convulsions, and an EEG at the age of 12 revealed an active epileptogenic focus from the left frontotemporal region. He was treated with phenobarbital and phenytoin. His last seizures occurred around the age of 16. He completed grade 7 at the age of 16 and attended a training program for adults in the cleaning trade. He has since worked as a maintenance man.

His parents separated when he was 8. His father was an alcoholic who physically abused his mother and verbally abused the children. Mr. E. experimented with alcohol at the age of 29 and rapidly became a heavy drinker. He lived with his mother up to the age of 30 and then moved in with his brother.

Physical examination showed obesity with mild gynecomastia, female distribution of body hair and fat, and small testes. The WAIS-R yielded a verbal IQ of 92, a performance IQ of 90 and a full-scale IQ of 85. All other investigations including EEG were normal but chromosomal studies revealed an abnormal male karyotype with extra X and Y chromosomes. Diagnoses of Klinefelter's syndrome and sexual disorder, paraphilia in the form of sadism were made.

He has been receiving psychiatric follow-up over several years and many types of intervention were proposed by several physicians who were involved in his care. These included supportive psychotherapy and covert sensitization. He attended social skills groups and AA meetings. He was placed on Antabuse and neuroleptics, mainly chlorpromazine and thioridazine. Carbamazepine was also tried. Mr. E continued his drinking habit which was possibly a factor in his dyscontrolled behaviour. He persistently had sexual fantasies of rape, sadism and aggression. He continued to be involved in voyeurism. His basic personality was immature and manipulative. He showed poor compliance to a variety of treatment procedures and he made several suicidal gestures and self-mutilation. Cyproterone acetate was found to effectively alleviate his deviant impulses but difficulties arose due to poor medication compliance and development of depressive symptoms. He eventually improved on long-acting fluphenazine decanoate but close monitoring was maintained to ensure that his condition remained under control.

#	Genetic Analysis	Testost. mol/L (10 - 30)	LH IU/L (6 - 30)	FSH IU/L (5 - 25)	Prolactin µg/L (0 - 15)	Progest. nmol/L (< 3.0)	Estradiol mol/L (< 150)
1	47, X	8.1	44	n.a.	10.4	1.0	n.a.
2	47, XXY	9.3	38	34l	27.4	n.a.	228
3	47, XXY	29.2	45	36	3	1	165
4	46, XYq	n.a.	n.a.	n.a.	9	n.a.	n.a.
5	48, XXYY mosaic	2.6	27	21	17	1.5	74

Table 1: *Genetic findings and baseline sex hormones profile.*

Discussion and Conclusion

Life histories and clinical review of these five cases appear to have, indeed, little in common except for the sex chromosome abnormalities. Nielsen [50] commented on the difficulty of fitting most of these psychiatrically ill individuals within the usual diagnostic categories and suggested giving them a primary diagnosis of Klinefelter's syndrome along with a description of their most prevailing symptoms.

In this case series, three men presented with a sexual paraphilia or deviation. While the conservative treatment approach of Klinefelter's syndrome advocates the use of hormonal (testosterone) replacement, it is also known that testosterone influences sexual drive and behaviour in man, and increased levels of testosterone have been associated with increased sexual drive and aggression [7,54]. Yet, low levels of testosterone have also been found to be present in cases of sexually aggressive behaviour [55]. In two of the cases which presented with a sexual paraphilia (Cases #3 and 5), baseline testosterone levels were in the upper limits of the normal range and it therefore seemed unreasonable to give them testosterone supplements. In these cases, treatment was directed toward the specific sexual pathology and, perhaps paradoxically, involved the use of an antiandrogen medication (cyproterone acetate) to decrease sexual drive and deviant sexual interest patterns. For reasons of fluctuating compliance and untoward side effects, the treatment was more complicated in relation to one subject (Case #5) who eventually responded satisfactorily to a long-acting antipsychotic medication.

Prior to the introduction of cyproterone acetate on the Canadian market, another case (Case #1) received a neuroleptic medication (chlorpromazine) for the same purpose. Therapeutic benefits were evident in three cases. On the other hand, it was also demonstrated that other cases benefited from testosterone replacement.

The authors therefore recommend that a comprehensive assessment and a careful consideration of a variety of clinical factors must be completed prior to the initiation of appropriate treatment program in individuals presenting with Klinefelter's syndrome. In addition, clinicians should consider more than simply the karyotype and hormone levels. In the cases presented, a common theme was that of impaired social skills. Treatment should include social skills education and couple's therapy for men who are able to establish relationships in which the partner (male or female) is willing to participate in treatment.

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