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Retrospective Study of Klinefelter Syndrome in Chinese Boys

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Abstract

Background: Klinefelter syndrome (KS) is a common but under-recognised condition caused by an additional X chromosome in the phenotypic male. Clinical features are non-specific and thus many patients remain undiagnosed until adulthood. Persistent androgen deficiency in KS patients may result in cardiovascular complications and has fertility implications, thus warranting earlier detection. ***Subjects:*** Nine Chinese boys with karyotype-confirmed non-mosaic Klinefelter syndrome. ***Methods:*** Retrospective review of the clinical features at presentation, baseline hormonal investigations and the treatment response was conducted. ***Results:*** The mean age at presentation was 14.3 years old. Six patients (66.7%) were referred to us from Student Health Service. Six patients (66.7%) had height percentile more than the 50th height percentile. Only two (22.2%) had gynaecomastia. All had pubic hair bit with a testicular volume of <3 ml on each side. All had elevated gonadotropins but the degree of hypogonadism was variable. All patients reported morning erection after treatment. ***Conclusion:*** Our report is the first study reviewing KS in Chinese children. The clinico-hormonal features at presentation were similar to that in Western series, except, gynaecomastia was not as common. Early recognition of KS is important to facilitate timely treatment and family planning. Student Health Service plays an important role in screening for KS.

Key words Hypogonadism; Klinefelter syndrome

Introduction

Klinefelter syndrome (KS) is caused by an additional X chromosome in males (47XXY). The condition affects 0.1-0.2% of boys in the general population.[1] The clinical features are non-specific during childhood and even adolescence and thus many are unrecognised. Abramsky and Chappel calculated that 64% of KS patients remain undiagnosed.[2] Moreover, even if diagnosed, a Danish study quotes that less than 10% are diagnosed before puberty.[1] The clinical features classically described include small firm testes, gynaecomastia and a tall, slender habitus. Besides these clinical features, almost all patients with KS show elevated basal gonadotropins, testosterone deficiency and oligospermia.[1,3] The hypogonadism is due to failure of Sertoli cells of the testes which are the site of spermatogenesis.[4] Persistent androgen deficiency may lead to loss of libido, decreased muscle bulk and tone, osteoporosis, increased risk of thromboembolism, increased mortality rate from diabetic and cardiovascular complications.[5] Earlier detection of KS would enable earlier treatment and thus prevent undesirable consequences. It also carries fertility implications. Ferhi et al noted that successful sperm recovery was significantly higher in younger men.[6] In this study, the clinical features at presentation, the baseline hormonal findings and the treatment response in Chinese boys with Klinefelter syndrome were reviewed.

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Subjects and Methods

All Chinese boys confirmed to have non-mosaic KS by karyotype between July 2001 and July 2007 at the pediatric department of a regional hospital were identified through Clinical Management System (CMS). Boys diagnosed before puberty or prenatally during amniocentesis performed for other indications and those with a mosaic pattern of KS were excluded.

Information collected included: demographic data, source and reason for referral, age, anthropometric measurements (body height, body weight), pubertal stage at presentation, presence/absence of gynaecomastia, presence/absence of large scrotal sac at presentation, baseline luteinising hormone (LH), follicle-stimulating hormone (FSH), testosterone level, age at onset of treatment, subjective response to treatment, associated morbidities and the need for special schooling.

Body height and body weight were measured in centimeters and kilograms respectively and were subsequently plotted on growth charts for local Chinese boys. Pubertal maturation was assessed using Tanner's Staging. Testicular volume was measured using the Prader orchidometer. LH and FSH levels were measured by the sandwich electro-chemiluminescence immunoassay (Cobas LH and FSH kit respectively) and the serum testosterone was measured using competitive electro-chemiluminescence immunoassay (Cobas Testosterone kit). Response to treatment was defined as presence of morning erection and subjective increase in muscle power.

All the results were described as simple percentages, mean values or median values.

This study was approved by the local Ethics Committee.

Results

We identified 12 Chinese boys with karyotype-confirmed KS who were diagnosed between July 2001 and July 2007 at our paediatric department. Two were excluded since they were diagnosed prenatally. One more was excluded since he had a mosaic pattern of KS.

Out of the 9 boys who were included, 6 (66.7%) were referred to us by Student Health Service. One was identified incidentally during admission to hospital for another problem and in the remaining two the referring body was not mentioned. Five boys (55.6%) were referred for delayed or discordant puberty and another two (22%) were referred for small testes. Only one (11%) was referred for gynaecomastia.

The mean age at presentation was 14.3 years old (Range: 11.41-15.52 years old). The heights of 6 boys (66.7%) were equal to or above the 50th percentile for normal Chinese boys at corresponding age. Three boys (33.3%) had a body mass index (BMI) above 50% for their age. None had a BMI of <3%. Regarding the pubertal staging, all had their genital stage and pubic hair stage equal to or above stage 3 and stage 2 respectively. Despite having advanced genital and pubic hair stage, all boys had a testicular size of equal to or less than 3 ml with a relatively large scrotal sac for the testis. Gynaecomastia was found only in two boys (22.2%). The anthropometric characteristics and pubertal staging of our patients are reported in Table 1.

The mean LH level was 19.4 IU/L and the range was 12.4-34.5 IU/L (reference range for 14-17 year old boys 1.3-9.8 IU/L). The mean FSH level was 43.5 IU/L and the range was 30 - 67 IU/L (reference range for 14-17 year old boys 1.5-12.9 IU/L). The mean baseline testosterone level was 6.3 nmol/L and the range was 2.38-13.67 nmol/L (reference range for 14-17 years old boys was 5.66-35.7 IU/L), (Table 2).

Sustanon was started in all boys. Mean age at the start of treatment was 15.7 years old and the range was 12.56-17.51 years old. After Sustanon was started, subjective increased frequency of morning erection was reported in all patients, whereas subjective increase in muscle power improvement was noted in 3 boys (33.3%). After initial counselling by paediatricians, only 2 boys requested referral to clinics specialised in reproductive medicine. Regarding co-morbidities, 1 (11.1%) was subsequently diagnosed to have mood disorder. No other psychological disorders were identified. All patients studied in mainstream schools.

Discussion

The classical features of KS are tall slender habitus, gynaecomastia, sparse facial and pubic hair and small testes. The first three features may be subtle, whereas, the latter two features will only be detected by careful genital examination. Moreover, sexual development is similar to normal boys before puberty.[5] Pre-pubertal levels of FSH, LH and testosterone are also normal.[4] Therefore, early recognition of KS before puberty is uncommon, except by pre-natal diagnosis performed for other indications.

Table 1 Anthropometric characteristics and pubertal staging of Klinefelter patients

	Age at presentation (years)	Reason for referral	Height (percentile)	Weight (percentile)	BMI (percentile)	Pubic hair stage (1-5)	Genital stage (1-5)	Axillary stage (1-3)	Average Testicular volume (ml)	Gynaecomastia
1	15.23	Gyneacomastia	25-50	50-75	25-50	4	4	2	2	Present
2	15.54	Small testes	50-75	25	25-50	3	3	2	3	Absent
3	11.41	Discordant puberty	>97%	>97%	90-97	2	3-4	1	2-3	Absent
4	15.52	Small testes	25-50	25-50	50-75	3	4	2	2	Absent
5	14.39	Delayed puberty	75	25	10-25	3-4	3-4	2	1-2	Absent
6	13.07	Delayed puberty	>97	75	25	3	4	1	3	Absent
7	15.47	Delayed puberty	25	25	25-50	3	3	2	2	Absent
8	14.18	Syncope	75-90	75-90	90-97	3	4	3	2	Present
9	13.7	Premature adrenarche	50-75	25-50	25	2	3	1	3	Absent

Table 2 Anthropometric and Hormonal findings in KS patients

	Number	Mean	Median	Range	Normal range
Age (years)	9	14.3	14.39	11.41-15.52	–
Height (cm)	9	166.9	166.4	162.4-173.3	–
Weight (Kg)	9	53.8	50.8	43.8-75	–
BMI (kg/m^2)	9	19.3	18.7	16-26.4	–
LH (IU/L)	9	19.4	18.1	12.4-34.5	1.3-9.8
FSH (IU/L)	9	43.5	37.6	30-67	1.5-12.9
Testosterone (nmol/L)	9	6.3	5.48	2.38-13.67	5.66-35.7

In our study, keeping with the classical description, we confirmed that Chinese boys with KS are relatively tall with 66.7% of our patients attaining a height percentile above the 50th height percentile for Chinese boys at corresponding age. Regarding the weight of KS boys, Ratcliffe reported a tendency to central obesity in 75% of KS boys.[7] However, in our patients only 33% had a BMI above the 50th percentile of BMI of that age.

Gynaecomastia has been reported with a frequency of 50-75%[4] as compared to only 22.2% in our patients. Regarding pubic hair, Smyth et al reported that 30-60% of KS patients had decreased pubic hair. In our patients, 77.7% had a pubic hair stage 3 or above according to the Tanner Staging. All our patients had a testicular volume equal to or less than 3 ml, which is small compared to their genital stage of stage 3 to stage 5. From our observation, it was noted that in contrast to low testicular volume, the scrotal sacs were well developed and large for the testicular size. We found this feature a supporting evidence for the clinical diagnosis of KS especially if associated with pubic hair stage 3 or above.

Regarding hormonal status, decreased testosterone level has been reported in 65-80% of KS patients.[4] In adult men, hypogonadism is defined as a testosterone concentration below 12 nmol/L.[5,8] The testosterone level is noted to plateau at 12-14 years of age in patients with KS.[4] In our series 88% of the patients had hypogonadism by the above definition as compared to 61-63% reported in literature.[5,8] In addition, LH and FSH levels are classically high in most cases.[4] High FSH is due to its inverse relationship with the testicular volume as a consequence of damage of the seminiferous tubules.[5] FSH and LH levels were noted to be high in all our patients with no overlap with normal value. Patients with mosaic pattern of KS, similar to the case that has been excluded in this study, do not have obvious clinical symptoms. Moreover, testicular size is normal with no

endocrine abnormalities in most cases. Our patient also did not require any Sustanon therapy since his testosterone level was normal. However, he suffered from mediastinal teratoma which is known to be associated with KS. In the literature, over 40 cases of KS with extragonadal midline germ-cell tumours (mediastinal non-seminomatous germ-cell tumours) have been reported.[8] The typical age of presentation is between 15-30 years of age.[4] Carcinoma of the breast is also reported to occur with a lifetime incidence of 3.7% in KS patients, which is 20 times more common than in the general population.[4, 9] All KS patients with breast cancer had underlying gynaecomastia.[4] None of our patients has been diagnosed to have breast cancer and this may be due to the small number of patients, the lower incidence of gynaecomastia and also the relatively younger age of our patients. The same reason may account for the fact that our patients did not have any cardiovascular morbidities or diabetes mellitus.

Other co-morbidities which have been associated with KS include learning disabilities and psychiatric problems.[4] In our series, however, none required special schooling and only one was diagnosed to have mood disorder. Most of the learning disabilities reported can be improved with proper accommodation and timely interventions at school which in turn may prevent secondary behavioral and emotional problems.[9]

Once KS has been diagnosed and the testosterone level is low, replacement therapy should be started. Early onset of treatment would prevent the sequelae of androgen deficiency including osteoporosis, hypofibrinolysis (which results in increased thromboembolic risk), obesity and diabetes.[5] Other benefits include increased libido and masculinity. After initiation of Sustanon replacement, all of our patients reported increased morning erections. One third of our patients also felt they had more muscle power and felt more masculine. Owing to retrospective nature of our study, we did not ask our patients to chart a diary of morning erection before and after Sustanon injection. Similarly, we did not objectively measure the muscle power before and after treatment. Although testosterone therapy can improve the patient's quality of life and prevent serious health consequences, it has no effect on fertility.[5] However, with advances in reproductive medicine, low spermatogenesis rate may not lead to infertility. Successful recovery of spermatozoa with subsequent intra-cytoplasmic sperm injection has resulted in pregnancies and live birth rates of 57 and 45% respectively.[5,10] However, successful sperm recovery seems to be inversely related to age.[6] Earlier diagnosis of KS is thus important to enable timely referral to tertiary fertility centers and earlier family planning.

Earlier diagnosis, however, may be only possible if primary care providers screen young boys for the disease and refer for further evaluation. Most of our patients were referred from the Student Health Service. The main reasons for referral were discordant/delayed puberty and small testes. None were referred to us by general practitioners. Therefore, the suspicion of KS can be made by a medical professional who conducts a thorough genital examination.

There are several drawbacks in our study. First of all, the number of patients is small. This may be due to under-recognition of the condition or later onset of testicular regression i.e. beyond teenage years. Moreover, we also have a significant number of patients awaiting karyotype confirmation. Secondly, our patients may be a biased sample comprising the more severe end of the phenotypic spectrum as they presented at a relatively younger age i.e. 11.41 to 15.52 years of age, and also with more severe testicular regression, i.e testicular volume equal to or less than 3 ml. Therefore, a multicentre study would add more information to the characteristics of KS patients in the Chinese population.

In conclusion, Chinese KS boys are relatively tall with low testicular volume. Gynaecomastia is a less common feature. Large scrotal sac for testicular volume is a supporting clinical clue especially if associated with advanced pubic hair stage. Earlier diagnosis is important to improve quality of life, academic performance, prevent subsequent androgen deficiency related consequences and fertility outcomes. Primary health care providers, the Student Health Service in particular, play an important role in suspecting and referring these patients to paediatricians for further management. Timely karyotype confirmation is equally pivotal.

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