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ORIGINAL ARTICLE

Incidence of gynaecomastia in Klinefelter syndrome adolescents and outcome of testosterone treatment

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Abstract

The aim was to define the true incidence of gynaecomastia in adolescent boys with Klinefelter syndrome (KS) and to observe testosterone treatment effects on its duration by examination of the prospectively collected data from a specialist referral clinic for boys with KS, with comparison being made with KS boys identified by a historical newborn chromosome screening programme, together with chromosomally normal controls. Fifty-nine boys over age 13 years were referred to a specialist KS clinic; 21 developed gynaecomastia. The comparator was 14 KS boys identified at birth and 94 chromosomally normal control boys. Testosterone was routinely started at the onset of puberty if gynaecomastia, a manifestation of clinical hypogonadism, was present. Oral or transdermal testosterone was administered in the morning, in a reverse physiological rhythm, and doses were increased according to standard pubertal regimens. The incidence of gynaecomastia was not increased in both the KS cohorts compared with controls. The incidence and age of onset of gynaecomastia was 35.6%, at 12.3 (1.8) years in the KS clinic group; 36.0%, at 13.7 (0.6) years in the newborn survey group; and 34.0%, at 13.6 (0.8) years in the controls. Full resolution of the gynaecomastia occurred in the 12/14 KS clinic boys on testosterone treatment who had completed puberty and as long as adherence was maintained.

Conclusion: The incidence of gynaecomastia in KS boys (overall 35.6%) is not increased over typically developing boys. Commencing testosterone when gynaecomastia develops with physiological dose escalation and full adherence can result in the resolution of the gynaecomastia.

What is Known:
- *Gynaecomastia is a common feature in Klinefelter syndrome men.*
- *Hypogonadism occurs from mid-puberty onwards with the absence of the usual rise in testosterone levels.*

What is New:
- *The incidence of pubertal gynaecomastia in Klinefelter syndrome is not different from typically developing boys.*
- *Early and prompt starting of testosterone gel treatment and increasing the dose physiologically may help to resolve the gynaecomastia without the need for surgery.*

Keywords Adolescent gynaecomastia · Klinefelter syndrome · Hypogonadism · Testosterone treatment

Introduction

All nine young adult males in the first description by Klinefelter in 1942 had gynaecomastia [1]. He had said that although these cases were not uncommon, there were few reports found in the literature, and very little has changed nearly 80 years on. Klinefelter syndrome (KS) 47,XXY is the commonest chromosome variant in males. Newborn chromosome surveys have indicated that the incidence is one in 576–760 live male births,

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but KS is rarely diagnosed in childhood or adolescence [2–6]. Gynaecomastia is a recognised association, but the true incidence is not clear, and the literature is very sparse, mostly comprising of reports in adult males. These give the prevalence of between 44 and 75% [7, 8]. However, in adults, the gynaecomastia is much more likely to be persistent on account of the hypogonadism. No sentinel hormonal abnormalities, in particular significantly higher oestradiol/testosterone ratios, have been directly linked with those KS boys developing gynaecomastia [5, 6, 8, 9]. We know that the onset of puberty in KS is not in itself delayed [2, 5, 9]. There is however a subsequent failure of the rise in testosterone in KS boys from mid-puberty onwards, and the principal deficiency in testosterone concentrations from mid-puberty is during the daytime due to the failure of the morning rise of testosterone [2, 4, 5, 8–10]. The link between this element of the hypogonadism and the appearance and indeed the persistence of the gynaecomastia has not yet been drawn.

There are published recommendations for starting testosterone treatment on account of the biochemical and the clinical hypogonadism in KS boys, but the ideal timing of this treatment and the precise indications for starting are not absolutely clear [11–13]. There have also been reports both of non-improved and improved cognitive outcomes from testosterone supplementation [4, 14]. Biochemical hypogonadism includes a low morning testosterone concentration and raised gonadotropins. Clinical hypogonadism includes poor secondary sex characteristics and low muscle tone, lethargy, and obesity. The presence of gynaecomastia is also recognised as a feature of clinical hypogonadism [12, 13]. Whether testosterone influences the course of gynaecomastia development and progression has not been clarified. However, two of the newborn survey follow-up programmes in Edinburgh [2] and Toronto [4] had randomised testosterone treatment within their respective cohorts and had suggested that the incidence and extent of gynaecomastia were lower in the treated boys.

This paper examines the incidence and duration of gynaecomastia in a cohort of KS boys from the only specialist clinic for boys and adolescents with KS in the UK compared with those identified during a historical UK newborn chromosome screening programme, together with a control cohort from the same study in whom the details of gynaecomastia are yet unreported. As randomised controlled studies of testosterone treatment during puberty had already taken place; all the boys with significant gynaecomastia in the clinic cohort were offered testosterone replacement to observe the effect [2, 4]. The outcome and the consequences of this physiological testosterone replacement on the persistence of the gynaecomastia are reported here.

Patients and methods

At University College Hospital in London (UCLH), a specialist clinic for KS boys was set up in 2010, and more than 80 non-mosaic 47,XXY boys have been referred over a 10-year period. Reasons for referral included those who were identified antenatally and those with developmental delay, speech delay, behavioural issues, and congenital defects such as undescended testes. The age of onset and duration of gynaecomastia during intervention with testosterone were studied prospectively in the 59 boys who were 13 years and over in 2021. Clinical observations were conducted by the author. All boys were followed up until handover to an adult multidisciplinary specialist clinic for KS took place. Gynaecomastia was defined as areolar enlargement together with the presence of palpable breast tissue to differentiate this from the pseudogynaecomastia of obesity. The degree of breast growth was recorded according to the Tanner scale (B), and also measurements of breast tissue disc diameters were made with a ruler. Blood samples were not taken as the clinic was in the afternoon and testosterone concentrations are known to be low at that time of the day and be of limited diagnostic use.

In the KS clinic, testosterone treatment was commenced once spontaneous puberty had begun and when significant gynaecomastia was included as a sign of developing clinical hypogonadism [12, 13]. Either oral testosterone undecanoate (Restandol®) 40 mg [15] or 2% transdermal testosterone gel (Tostran®) 10 mg (one pump) [16] was prescribed, the choice depending on patient preference and treatment availability at the time. It was recommended that the treatment was taken or applied each morning with a view to supplementing the relative diurnal testosterone deficiency in early to mid-puberty. Physiological increases in testosterone were advised in standard increments at approximately six monthly intervals up to Restandol 120mg or Tostran 40mg according to the British Society for Paediatric Endocrinology and Diabetes clinical guidelines [17]. The boys were seen in the KS clinic at approximately six monthly intervals, and monitoring was by clinical observation.

Comparison was made with the Edinburgh newborn survey which has been reported previously [2]. Over 34,000 infants born in the city had cytogenetic screening at birth, and the 70 with sex chromosome variants were followed up in parallel with a chromosomally normal control group. Details of the extent and duration of the gynaecomastia have not been published previously. The incidence of gynaecomastia was elucidated prospectively in the 14 non-mosaic 47,XXY boys whose data and follow-up were complete for this parameter and in 94 of the chromosomally normal controls. In that study, alternate KS boys (by birth order) had been randomised to receive oral testosterone undecanoate (Restandol®) 40 mg daily at the onset of puberty [2, 9, 12]. Observations were

made by the author for the control boys and jointly with the study lead in the KS boys. Serum and salivary testosterone concentration variations have been published previously [2].

Results are reported as mean (standard deviation) and range.

A full *PubMed* search of the literature was conducted using keywords 'Klinefelter syndrome; adolescent; pubertal; gynecomastia; testosterone' for comparison, together with the author's knowledge of the newborn cytogenetic survey literature.

Ethics approval

Data from UCLH patients were collected retrospectively as observations from the clinical notes and did not require a separate ethics review according to a NHS Health Research Authority assessment. The Edinburgh newborn survey and follow-up programme were conducted in accord with the UK Medical Research Council guidelines for research in children.

Results

Using the same criteria to record the presence and resolution of gynaecomastia, the incidence in the KS boys was 35.6% in the KS clinic, 36.0% in those identified by newborn screening, and 34.0% in the newborn survey controls (Table 1). The age of onset was 12.3 (1.8) years in the KS clinic boys, 13.7 (0.6) years in the newborn survey KS boys, and 13.6 (0.8) years in the control boys. In the KS boys, gynaecomastia was usually bilateral, but it was unilateral in 19% of the controls. Obesity was marked in four KS clinic boys with gynaecomastia. Gynaecomastia most commonly appeared at Tanner puberty stages G3 and G4 in both KS and controls and in the control boys at a mean testis volume of 14.2 (3.7) ml (Table 2). Testis volume was not regarded as an appropriate parameter in the KS boys for comparison due to the recognised failure of the testes to enlarge.

Of the 21/59 KS clinic boys over the age of 13 years with gynaecomastia, two had slight areolar elevation and were under observation, and two had spontaneous resolution. One boy had already completed puberty, and no treatment was indicated. Fourteen boys received testosterone treatment and had completed puberty. Three more who had developed gynaecomastia were still under treatment at the time of this report. Twelve of the 14 treated boys had complete resolution of the gynaecomastia. Two of these who had slight recurrence of the gynaecomastia resolved with oral testosterone undecanoate at a higher dose (80mg), and they were switched to intramuscular testosterone undecanoate (Nebido ®) when they required adult testosterone replacement. The two boys who had persistent gynaecomastia both failed to comply with the testosterone regimen and in addition had severe obesity.

In the KS clinic group, the mean duration of the breast development was 1.9 (1.4) years in the 12 treated boys in whom the gynaecomastia resolved (Table 2). In the KS newborn survey group, the mean duration was 2.4 (0.7) years, these three boys also having received testosterone treatment. One untreated boy in this group required surgery. The duration was a mean of 1.0 (0.5) years in the 10 control boys in whom this parameter was specifically recorded.

Discussion

Gynaecomastia is a well-recognised feature of KS. What is particularly noteworthy is that the incidence of gynaecomastia

Table 1 Prevalence of gynaecomastia, age of onset, duration, and links to puberty parameters in the three cohorts. Mean (SD). G and B are Tanner genital and breast stages. *MTV* mean testicular volume (ml)

	Prevalence N(%)	Age onset (yr)	B stage	G stage	MTV (ml)	Duration (yr)
UCLH KS clinic	21/59 (35.6%)	12.3 (1.8)	2-4	2–4	n/a	All bilateral 1.9 yr (1.4) yr range 0.25-4.25 yr
KS Edinburgh newborn survey	5/14 (36.0%)	13.7 (0.6)	2-3	4-5	n/a	All bilateral 2.4 (0.7) yr range 1.5–3.2 yr—all 3 testosterone treated One untreated referred to surgery after 1.4 yr
XY controls Edinburgh newborn survey	32/94 (34.0%)	13.6 (0.8)	2–4	2–4 (28% at G3) (69% at G4)	14.2 (3.7) range 7–20	19% unilateral

Table 2 Age and duration (mean + SD) of onset of gynaecomastia and start of testosterone treatment and outcomes in the 14 treated to completion of puberty KS clinic boys. G, B, and PH are Tanner puberty stages. TU = *Restandol* oral testosterone undecanoate (mg). T = *Tostran* 2% transdermal testosterone gel (mg). S = *Sustanon* IM testosterone esters (mg). N = *Nebido* IM testosterone undecanoate (mg)

Pt no	Age of onset (yr) & treatment start	Age at treatment start if later (yr)	BMI SDS	G	PH	B (right)	B (left)	Gynaecomastia duration (yr)	Testosterone treatment + comments
1	13.5		−1.3	3 to 4	3 to 4	2	3	0.25	T10 changed to S125
2	13.8		−1.3	3	3	2	2		
		14.2		3	3	3 to 4	3	3.3	TU 40 to 120
3	10.1		2.2	3 to 4		2	2		S25 elsewhere
		12.5		4	4	4	4	Persisted but reduced	TU80 to 120
4	11.9		−0.8	2	2	2	2	4.25	TU40 to 120 gone 15.1 yr. Slight recurrence treated with N500
5	11.9		−0.8	2	2	2	2	2.5	TU40. N500
6	11.4		2.3	2	2	2	2	1.8	T10 to 20
7	11.2		2.6	3	3	2	3	4	TU40 to 120
8	12.4			3 to 4		2	2		
		12.9	−0.2	3 to 4		2	3	0.86	T20
9	11.6			3 to 4	3 to 4	2	2		
		14.5	−0.7	4	4	2	2	0.5	T20
10	12.9		0.2	3 to 4	2	3 to 4	3 to 4	1.6	TU40/T10 to 20
11	14.8		−1.2	4	4	2	2	0.9	TU40
12	14.6		0.4	3 to 4	2	2	2	0.45	TU40/T10 to 20
13	10.4		3.1	2 to 3		3 to 4	3 to 4	Persisted	TU40 to 120. Poor compliance. Referred for surgery BMI +3.4 SDS
14	12		−0.6	3 to 4	1	2	2	2.5	TU40
Mean	**12.3**							**1.9**	
SD	**1.8**							**1.4**	

in this group of KS boys of 35.6% is remarkably similar to the controls (34.0%), although the recorded duration is slightly longer than the controls. The Edinburgh newborn cytogenetic survey reported here 5/14 (36%) [2] and Ratcliffe *et al.* in a study of adolescent KS boys in Edinburgh identified by a previous newborn chromatin survey found a prevalence of 4/11 (36.4%) at age 16 years [18]. Stewart *et al.* in the Toronto newborn cytogenetic survey follow-up study found 7/28 (25%) by age 18 years [5], and Robinson *et al.* found a slightly higher incidence 6/14 (42.9%) by age 16–23 years [6] (Table 3). The Danish newborn survey did not report the incidence of gynaecomastia separately [3]. Using an identical observation process with careful recording, it seems possible to determine that the incidence of gynaecomastia in KS boys does not appear to be increased over that of typically developing boys, a novel conclusion based on examination of the data presented here and in agreement with findings from other population screening studies which are the most reliable sources of the true incidence.

Although this report focusses on the outcome of testosterone intervention, the KS clinic untreated gynaecomastia incidence is the largest referred patient cohort described to date and represents the findings in routine clinical practice. Few other clinic-based reports of gynaecomastia are found. Topper *et al.* in a Tel Aviv clinic referred cohort reported 3/10 (30%) 10–25 years [10] and Rogol *et al.* in a US multicentre study of testosterone gel 6/21 (28.6%) [16]. Aksglaede *et al.* in Copenhagen reported 16/34 (47%) under 15 years of age, but this greater prevalence of gynaecomastia was also reported at 49% in normally developing boys in the same city which is higher than elsewhere [8, 19, 20]. Adding the newborn studies and the referral clinic series together here identified 191 KS boys, 68 of whom (35.6%) were reported as having gynaecomastia (Table 3).

This is also the first report of a successful hormonal intervention for managing gynaecomastia in most of the adolescent boys with KS. Findings of the higher prevalence of gynaecomastia in KS adults may be as a direct result of the persistent hypogonadism, the untreated low diurnal testosterone levels in late puberty failing to resolve the gynaecomastia.

The indications for starting testosterone replacement in adolescent boys with KS have never been precisely determined.

Table 3 Comparison of percentage of identified KS boys with gynaecomastia ascertained by newborn surveys or clinic referrals and the stated mean age or range and the source from referenced publications

Mode of ascertainment		Age range or mean (SD)	Number with gynaecomastia	%
Newborn surveys				
Ratcliffe et al. [2]	Edinburgh newborn cytogenetic survey	13.7 (0.6)	5/14	36.0%
Ratcliffe et al. [18]	Edinburgh newborn sex chromatin survey	16.6 (0.9)	4/11	36.4%
Stewart et al. [5]	Toronto newborn cytogenetic survey	18–21 yr	7/28	25.0%
Robinson et al. [6]	Denver newborn cytogenetic survey	16–23 yr	6/14	42.9%
Group total & mean			**22/67**	**32.8%**
Clinic referrals				
This study	UCLH KS clinic referrals	12.3 (1.8)	21/59	35.6%
Topper et al. [10]	Tel Aviv clinic referrals	10–25 yr	3/10	30.0%
Rogol et al. [16]	US multicentre clinic referrals	14.0 (1.4)	6/21	28.6%
Aksglaede et al. [8]	Copenhagen clinic referrals	<15 yr	16/34	47.0%
Group total & mean			**46/124**	**37.1%**
Overall total & mean			**68/191**	**35.6%**

The occurrence of gynaecomastia is one potential indication of clinical hypogonadism [12, 13]. Testosterone replacement was started at the appearance of clinically significant gynaecomastia once the onset of puberty had been documented. Oral or transdermal testosterone was chosen on account of the pharmacokinetics of each preparation being able to mimic the natural pubertal diurnal rhythm. The patients were recommended to take or apply the testosterone in the morning to supplement the hypothetical relative testosterone deficiency during the daytime in mid-pubertal boys. Although no significant abnormalities in the testosterone/oestradiol ratio had been noted in single blood samples in KS boys with gynaecomastia, more extensive studies in typically developing boys had suggested that there was an imbalance in this ratio during the daytime which reversed on its resolution [5, 9, 10, 19–22].

There was complete resolution of the gynaecomastia in all the KS clinic boys who complied with the treatment throughout puberty, taking into account dosage escalation according to standard pubertal management replacement schedules, and transferring to adult testosterone replacement regimens with intramuscular testosterone esters once sexual development was complete. Escalation of the testosterone dose was helpful in two of the boys who had recurrence of the gynaecomastia in mid-puberty.

If testosterone is started when breast enlargement is first noticed, these findings suggest it should continue under close observation with physiological dose increases until its disappearance. Should it recur, resolution seems to be achieved by restarting and escalating the dose of testosterone within the physiological range according to standard treatment guidelines. Of the 59 boys in the UCLH KS clinic group observed from the start of puberty, 21 had developed gynaecomastia. One was referred post-puberty, one resolved spontaneously, and the only treatment failures (one partial) in the 14 boys observed throughout puberty were in the two boys in whom adherence was an issue, and both were severely obese. This observation lends weight to the hypothesis that persistent gynaecomastia in KS is related to the hypogonadism from mid-puberty onwards. Severe obesity in itself may be a contributory factor. Even with testosterone treatment, as in both cohorts of KS boys in this report, the duration of the gynaecomastia was longer than in the controls. By way of affirmation of this conclusion, breast development in all the control group boys resolved spontaneously and more quickly than the KS boys, the incidence and timing being similar to other reports [19, 20, 22].

Only one other study had directly hinted that there might be an effect of testosterone treatment on the gynaecomastia in KS boys. Stewart *et al*. from the Toronto newborn survey follow-up study gave intramuscular testosterone for 2 years to half of the KS boys in their cohort from age 13 years during their follow-up programme [4]. Four of their 12 untreated boys had significant gynaecomastia with one requiring surgery. Of the nine testosterone-treated boys, they suggested that the testosterone may have reduced the extent of the gynaecomastia, with only one of the treated boys having transient breast enlargement. One other, a treatment failure, was referred for surgery. In retrospect, although the numbers were small, persistent and significant gynaecomastia was mainly a feature of the untreated KS boys. In line with this, in the Edinburgh newborn survey follow-up programme, the only boy requiring surgery had not received testosterone supplementation. In a clinic-based study of six young adults with

KS, Ruvalcaba had reported that testosterone treatment could be associated with resolution of the gynaecomastia in all but one [23]. The reported absence of any effect in Rogol *et al.* could have been due to the insufficient treatment duration (6 months) or insufficient dosage [16].

Study limitations

KS is always challenging to identify, and most contemporary reports are based on clinic referrals. The follow-up of the newborn survey identified boys also encountered challenges getting complete data, so presented here are the best available outcomes from all datasets in 191 KS boys. In addition, although this report documents the results of the testosterone treatment, it is not absolutely clear whether the gynaecomastia would have resolved spontaneously without the intervention. Furthermore, the decision to recommend taking the testosterone in the morning was a pragmatic one, based on a careful understanding of the endocrine pathophysiology in KS and in adolescent gynaecomastia, but to be able to make firm recommendations, it would require a detailed large-scale study.

Conclusions

The incidence of gynaecomastia in KS boys (35.6%) is not different from that found in typically developing boys (34.0%) and is lower compared with the higher prevalence reported in adult KS men. This may be as a result of failure of the resolution of the breast enlargement consequent on the developing hypogonadism—the failure of the mid-pubertal rise in testosterone [2, 4, 5, 8–10]. The commencement of physiological testosterone replacement (here given orally or as transdermal gel) once significant breast enlargement is evident and continued until the completion of puberty appears to reduce the persistence of gynaecomastia in KS boys, in the majority avoiding the need for surgery. It is possible that the success of treatment may be aided by administering the testosterone in the morning, in a reverse diurnal rhythm, but this specific directive needs further research.

Note: Restandol was discontinued during 2020 leaving transdermal gel as the only available treatment option.

Abbreviations KS, Klinefelter syndrome; UCLH, University College London Hospital; MTV, Mean testis volume

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Author contributions The author designed the study, conducted the majority of the observations, analysed the data and wrote the manuscript with external expert scrutiny.

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Data availability Full - in UCLH medical records, Edinburgh study paper records archive

Code availability n/a

Declarations

Ethics approval Data from UCLH patients were collected retrospectively as observations from the clinical notes and did not require a separate ethics review according to a NHS Health Research Authority assessment. The Edinburgh newborn survey and follow-up programme were conducted in accord with the UK Medical Research Council guidelines for research in children.

Consent to participate UCLH patients attended a specialist clinic and knew data was collected anonymously for further research and understanding. Participants in the MRC Edinburgh study were enrolled by their parents with full consent.

Consent for publication n/a

Conflict of interest None

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