Single Centre Experience Of Testosterone Therapy For Boys With Hypogonadism

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Abstract

Background: Hypogonadism in boys is one of the commonest conditions encountered in paediatric endocrinology

Aims: To study variations in management in a contemporary group of boys at a single specialist centre.

Methods: Retrospective review of case records of all boys treated with testosterone at a tertiary endocrine service from 2012- 2017.

Results: Of the 358 boys reviewed for hypogonadism, 46 (13%) were initiated on testosterone therapy at a median age (range) of 14.2 years (12.1, 17.7). Indications for therapy included a functional delay of puberty that was constitutional in 17 (37%) or related to chronic disease in 10 (22%) or organic hypogonadism due to primary gonadal failure in 7 (15%), multiple pituitary hormone deficiency in 6 (13%), and isolated hypogonadotrophic hypogonadism in 6 (13%). Of the 46, 40 (89%) were started on intramuscular testosterone, 4 (9%) on oral testosterone and 1 (2%) on transdermal gel. Of the 19 boys (40%) with organic hypogonadism requiring long-term therapy, 12 (63%) had assessment of liver function, 6 (32%) had a haematocrit and 2 (11%) had a DXA scan in the year of commencing treatment.

Conclusions: Testosterone therapy is administered in about 13% of boys reviewed for hypogonadism and its monitoring requires standardisation.

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Introduction

Delayed puberty in boys is defined as the absence of testicular enlargement over 4ml after the age of 14 years or greater than 2 SD later than the population mean [1]. It is a common indication for referral to paediatric endocrine services, affecting approximately 2% of adolescents [2]. Boys with delayed puberty may present with significant psychosocial distress secondary to this, as well as long-term health consequences such as osteopaenia [3, 4]. In boys, hypogonadism can be categorised as functional or organic; common causes of functional hypogonadism in boys include constitutional delay of puberty and a delay secondary to chronic disease. These forms of hypogonadism often require short periods of testosterone therapy unlike organic hypogonadism secondary to conditions such as primary gonadal failure or hypogonadotrophic hypogonadism when testosterone therapy may be life-long [5]. Existing guidelines for testosterone replacement in adults recommend monitoring of testosterone levels during treatment for efficacy as well as for likely complications associated with testosterone therapy including cardiometabolic compromise, polycythaemia and derangement of liver enzymes [6]. The frequency of testosterone therapy in boys as well as the extent of variation in its monitoring has rarely been described [7]. The aim of the current study is to characterise the group of boys that present with suspected hypogonadism in adolescence and are subsequently treated with testosterone.

Patients & Methods

A retrospective review of case notes was conducted of all boys treated with testosterone for pubertal delay in the Royal Hospital for Children in Glasgow, UK from 2012 to 2017. Continuous variables are described as median and ranges and inter-group comparison for these variables was performed by Students T tests or one-way ANOVA as appropriate. Chi square analysis was performed to compare proportions in different groups. The level of $p<0.05$ was considered to be statistically significant and all analyses were performed using Microsoft Excel version 14.0 (USA) or GraphPad Prism version 4.0 (USA).

Results

Indications

Over the study period of 5 years, 358 boys, including 175 new referrals, were seen for review of boys with possible delayed puberty. Of these 358, 46 (13%) were treated with testosterone at a median age (range) of 14.2 years (12.1, 17.7). A median number of 7 boys (2, 15) were started on testosterone each year. Indications for treatment were constitutional delayed growth and puberty (CDGP) in 17 (37%), chronic disease related hypogonadism in 10 (22%), primary gonadal failure in 7 (15%), multiple pituitary hormone deficiency (MPHD) in 6 (13%), and isolated hypogonadotrophic hypogonadism in 6 (13%). Of those with chronic disease related hypogonadism, the underlying diagnosis was Duchenne Muscular Dystrophy in 5 (50%); Crohns disease in 1 (10%); HIV in 1 (10%); Juvenile Idiopathic Arthritis in 1 (10%); Addisons disease in 1 (10%) and immune dysregulation in 1 (10%). Age at starting treatment was similar, regardless of underlying diagnosis, with a median of 14.0 years (13.1, 17.7) in the 27 boys with a functional delay in puberty due to CDGP or chronic disease versus a median of 13.2 years (12.1, 17.4) in the 20 boys with organic hypogonadism (p=0.3) (Fig.1). Of the 28 boys with functional hypogonadism, 24, (86%) received only one 3 month course of testosterone whereas four received a 6-month course. All of the 19 boys with organic hypogonadism remain on current treatment.

Testosterone Therapy

Of the 46 boys, 3 (7%) were treated with oral testosterone; 1 (2%) with oral and intramuscular testosterone depot (IM); 1 (2%) with transdermal testosterone gel and IM and the rest (89%) with IM alone. Of the 4 boys on oral testosterone, 1 (25%) was on testosterone undecanoate 40mg on alternate days and the rest (75%) were on testosterone undecanoate 40mg daily. Of the 43 boys on IM, 2 (5%) were on 1g testosterone undecanoate as Nebido and the rest (95%) were on varying doses of testosterone enanthate as Sustanon (median starting dose 100 (range 50-250 mg)).

Investigations at Initiation of Testosterone Therapy

Of the 46 boys who were treated with testosterone, 40 (85%) had a bone age assessment, 12 (26%) had liver function tests (LFT), 6 (13%) had a haematocrit and 6 (13%) had an assessment of bone density by DXA within the year prior to starting testosterone. Of the 19 boys with organic hypogonadism, 12 (63%) had liver function tests; 6 (32%) had a haematocrit and 2 (11%) had a DXA scan prior to commencing treatment (Fig.2).

Monitoring of Testosterone Therapy

During therapy, of the 46 boys, LFTs were assessed in 6 (13%), blood pressure was recorded in 5 (11%) and a haematocrit was assessed in 3 (6%). In those who had LFTs or haematocrit performed, the indication for therapy was chronic disease related hypogonadism. Of the 6 boys who had LFTs, 4 (67%) had raised transaminases, which had previously been normal. None of the boys had any changes in testosterone dose based on the results of these investigations. Of the 46 boys, two (4%) reported a change in behaviour on testosterone therapy with increased aggression but did not require any change to treatment secondary to this. One of these boys had primary hypogonadism secondary to bilateral anorchia and was treated with IM testosterone therapy. The other had hypogonadotrophic hypogonadism and was on a treatment schedule with oral testosterone undecanoate.

Discussion

This study provides useful insight into the management of delayed puberty in boys, demonstrating that just over 10% of boys referred to a clinical paediatric endocrinology service receive testosterone therapy for induction of puberty. In actual numbers, this amounted to less than 10 cases per year. It is also interesting to note that despite the availability of several routes for administering testosterone therapy, the intramuscular depot form of testosterone remains the most popular. This may be related to difficulties in ensuring a continuous supply of oral testosterone undecanoate and a lack of an evidence base for the commonly available forms of transdermal testosterone. Approximately 60% of the cases that required testosterone therapy had a functional delay of puberty and required short-term therapy and the remainder had organic pathology requiring long-term testosterone therapy. Whilst categorising cases between functional and organic provides some insight into the indications of testosterone therapy, it is acknowledged that overlaps can exist within this classification. Although CDGP was the commonest presentation of functional delayed puberty [1, 8], in our cohort there was a high prevalence of hypogonadism secondary to chronic disease. Poor growth and delayed puberty are often associated with chronic disease [9, 10]. The frequency of testosterone therapy in these adolescents may depend on awareness and threshold for referral from clinicians who manage the boys' primary disease.

In adults, it is considered good practice to perform regular biochemical and haematological assessments to assess safety and efficacy of long term therapy [6]. In boys requiring testosterone therapy, previous studies have shown variable efficacy and pharmacodynamic profiles [11, 12]. Systematic monitoring of safety and efficacy other than assessment of virilisation and growth was not performed in the cohort of boys studied here and there is little evidence that this is performed elsewhere in similar cohorts [7]. Boys with chronic disease related hypogonadism were more likely in our cohort to have some form of monitoring probably because of the increased need for surveillance of their underlying condition. The lack of existing guidance for monitoring may be due to the fact that most boys require testosterone for a short period. In our cohort, over 50% of boys requiring testosterone did not have primary gonadal failure or a condition such as MPHD or hypogonadotrophic hypogonadism. Although in our cohort, testosterone therapy was well tolerated with only 4% of boys reporting a clinical adverse effect that could be attributed to the therapy there were some cases that displayed a derangement in liver function. Of note, this was observed in those who had a functional delay in puberty and were receiving testosterone therapy for a short period. Given that the indications and goals for testosterone therapy in adolescence are more variable than in adults, guidance for monitoring of therapy in adults cannot be simply replicated in adolescents and may be influenced by the underlying condition and/or the duration of therapy.

In conclusion, testosterone therapy for hypogonadism in boys is rare and given that it may be associated with adverse events, there is a need to consider clinical guidance that can be applied to monitor safety as well as efficacy of therapy in this age group.

Disclosures

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Legend To Figures

Figure 1. Age at starting testosterone therapy according to underlying diagnosis. The black line represents the median age. Abbreviations: CDGP: chronic disease related hypogonadism; hypog hypog: hypogonadotrophic hypogonadism; MPHD: multiple pituitary hormone disease.

Figure 2. Investigations performed in the year prior to treatment according to underlying diagnosis. Abbreviations: LFTs: liver function tests; CDGP: chronic disease related hypogonadism; hypog hypog: hypogonadotrophic hypogonadism; MPHD: multiple pituitary hormone disease.

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