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Puberty-Promoting Treatment and Psychosocial Well-Being in Boys With Constitutional Delay of Puberty: A Randomized Controlled Trial

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Keywords: delayed puberty | hormone replacement therapy | letrozole | male adolescents | psychological distress | temperament | testosterone

ABSTRACT

Objective: In boys, constitutional delay of growth and puberty (CDGP) has been associated with diverse negative psychosocial effects. Albeit alleviating distress is one of the main reasons for inducing pubertal development, the impact of puberty-promoting treatment on psychosocial wellbeing is under-researched. Our objective was to investigate the impact of puberty-promoting therapies on the behavioural patterns as defined by the temperament characteristics emotionality, activity, and sociability (EAS) in boys with CDGP.

Design: The study is a randomized, controlled, open-label trial.

Patients: Thirty boys were randomized to receive either aromatase inhibitor letrozole (2.5 mg/day) ($n = 15$) or intramuscular testosterone (1 mg/kg/every 4 weeks) ($n = 15$) for 6 months and followed up to 12 months. To compare our results with healthy peers, an age- and postal-code matched, and a national reference population were collected.

Measurements: Temperament characteristics were evaluated with a standardized and validated questionnaire at 0-, 6-, and 12-month visits.

Results: In comparison to local peers, boys with CDGP were more withdrawn ($p = 0.02$) and experienced less anger ($p = 0.02$) and fear ($p = 0.02$). Compared to both local and national controls, there was a significant difference in emotionality, CDGP boys being less negatively emotional than peers ($p = 0.04$). Sociability was higher in the Lz-group in comparison to the T-group both

after the 6-month treatment period (−0.48, 95% CI: 0.89; −0.08, $p = 0.019$) and at 12-month follow-up (−0.72, CI: 95%, −1.12; −0.32, $p = 0.001$).

Conclusion: Overall, boys with CDGP exhibited a generally docile temperament. The administration of puberty-promoting treatments did not result in any adverse psychosocial effects on the temperament characteristics assessed.

1 | Introduction

Approximately 2%–2.5% of healthy male adolescents experience delayed puberty, which is defined as absence of pubertal maturation (testicular growth) at an age 2–2.5 SD later than the population mean [1]. The most common cause for delayed puberty is constitutionally delayed growth and puberty (CDGP), which is a self-limited condition [2, 3]. In boys, CDGP accounts for 63%–82% of cases of delayed puberty [3, 4], and is most often consistent with autosomal dominant inheritance in the family. Despite its self-limited nature, CDGP or late pubertal timing has been associated with diverse negative psychosocial effects, such as lower self-esteem, lower ego development, risk for depression, increased lifetime prevalence rates of disruptive behaviour disorder, stress from and social problems with peers and therefore, social withdrawal and risk for substance use [5–9]. Delayed pubertal maturation may also lead to development of unhealthy defense mechanisms and unfavourable development of temperament, personality and sexuality [8].

In boys with CDGP and significant psychosocial burden, puberty-promoting treatment, typically low-dose testosterone (T) is commonly started to alleviate the stressful situation instead of 'watch-and-wait' only. We have recently introduced a possible alternative to testosterone, per oral aromatase inhibitor letrozole (Lz), to induce pubertal development in selected boys with CDGP [10]. Letrozole inhibits the conversion of androstenedione to estrone and testosterone to estradiol [11]. Letrozole thus lowers estrogen concentrations, which activates gonadotropin secretion leading to elevated testosterone levels if the central 'brake' on HPG-axis has loosened [12].

During puberty, there is an approximate 30-fold increase in testosterone levels in males [13]. This elevation is not only responsible for rapid changes in physical characteristics but also known to affect certain behaviours. Higher testosterone levels have been linked to some behavioural patterns such as lack of frustration tolerance, aggression, impulsive personality and increased risk-taking [14, 15]. Some of these behavioural patterns represent normative developmental trajectories of adolescent males but may especially in the long-term develop to potentially detrimental behavioural patterns. However, there is a lack of sufficient data on the impact of testosterone treatment on mood and behaviour [16], and the impact of aromatase inhibition on psychosocial endpoints during adolescence has not been studied before.

Physical growth and maturation during puberty are associated with emotional well-being [17, 18] and thus short stature and lack of secondary sexual characteristics may appear as the main issues for psychosocial distress in delayed puberty. Body image is related to self-esteem and late maturation has been associated with less favourable body image among boys, although the impact of pubertal timing on body image seems to vary across racial-ethnic groups [19]. Previously, self-limited delayed puberty mainly affected dissatisfaction with physical appearance, while overall health-related quality of life remained unaffected in adolescents [20]. Puberty-promoting therapy was associated with positive changes in experience of dimensions of physical appearance and vitality, and effects of low-dose testosterone and letrozole treatments were similar [20].

The main indication for puberty-promoting treatment for CDGP boys is psychological distress but little is known of the psychological profile of CDGP boys. This study investigates the impact of puberty-promoting therapies on the behavioural patterns as defined by temperament characteristics emotionality, activity and sociability (EAS) in boys with CDGP. We focused on changes in the temperament characteristics during a 6-month randomized clinical trial of puberty-promoting treatment with Lz or T in boys with CDGP. In addition, we compare the results of the treatment groups to an age-, sex- and postal code-/living area-matched general population sample (referred later to as local controls). A second control group was obtained from the Young Finns Study (YFS) (https://youngfinnsstudy.utu.fi/index.html) (later referred to as YFS-controls).

We hypothesized that Lz, an aromatase inhibitor that blocks estrogen synthesis and promotes gonadotropin and endogenous testosterone secretion, is non-inferior to conventional low-dose testosterone in promoting positive behavioural patterns and that puberty-promoting therapy does not have a negative impact on behavioural patterns.

2 | Materials and Methods

This study included 30 boys with CDGP who participated in a randomized controlled trial in four Finnish pediatric endocrinology outpatient clinics between 2013 and 2017 [10]. Study inclusion criteria were age of 14 years or older, delayed puberty but with the first signs of HPG axis activation detectable, a mean testicular volume 2.5−4 mL and serum testosterone concentration of less than 5 nmol/L or Tanner genital stage 2 and serum testosterone concentration < 3 nmol/L. Exclusion criteria were chronic diseases, known chromosomal anomalies, primary or hypogonadotropic hypogonadism and chronic medication that could potentially adversely affect bone mineralization. The detailed study design has been reported before [10]. The boys were randomized to receive either aromatase inhibitor letrozole (2.5 mg/day) ($n = 15$) or intramuscular testosterone (1 mg/kg/every 4 weeks) ($n = 15$) for 6 months and followed up to 12 months. In brief, the boys were evaluated at 0-, 6-, and 12-month visits. Their height, weight, growth velocity and testicular volume were measured, and pubertal stage was recorded. Morning blood samples were drawn at each visit. For the baseline characteristics see Table 1.

TABLE 1 | Baseline characteristics.

	Letrozole ($n = 15$)	Testosterone ($n = 15$)
Age (years)	14.8 (14.2–16.0)	15.0 (14.1–16.2)
Testicular volume (mL)	2.9 (1.2–4.8)	3.4 (2.2–4.9)
Height (cm)	153.7 (141.1–165.4)	157.5 (149.0–168.3)
Height (SDS)	−2.2 (−3.6 to −0.5)	−1.83 (−2.8 to −0.5)
Tanner G-stage distribution (*n* stages 1–5)	4/11/0/0/0	3/12/0/0/0
Tanner P-stage distribution (*n* stages 1–5)	10/5/0/0/0	6/9/0/0/0
Serum testosterone (nmol/l)	1.9 (0.7–4.5)	2.3 (0.3–4.5)

Note: Data mean and range (min and max).

Lz and low-dose testosterone had differential effects on circulating sex steroid concentrations. In the Lz group, serum testosterone rose substantially as the mean serum testosterone was 21 and 30 nmol/L at 3 and 6 months after the start, respectively, whereas serum estradiol remained low, at 6.9 and 15.7 nmol/L at 3 and 6 months after the start. In the T-group, serum testosterone increased less as the mean serum testosterone was 9.7 and 5.7 nmol/L at 3 and 6 months, and serum estradiol increased in parallel, 39 and 22 nmol/L at 3 and 6 months.

2.1 | Behavioural Patterns/Temperament Characteristics

We evaluated temperament characteristics with a standardized and validated questionnaire at 0-, 6-, and 12-month visits. The effects of the treatments were assessed in three aspects: emotionality, activity, and sociability. At 0-, 6-, and 12-month patients were interviewed for psychiatric symptoms, and they completed a battery of questionnaires, usually during the waiting time before the physical examination buy the study doctor. The questionnaire consisted of 101 questions; multiple choice on a 5-scale of 1 (*totally disagree*) to 5 (*totally agree*) where the boys chose the number best describing the suitability of the sentence on themselves, multiple choice on a 4-scale (four different claims in which the boys chose the most suitable description) as well as straightforward yes/no questions.

In studying the impact of puberty-promoting therapies on the behavioural patterns, in this paper we focused on temperament characteristics defined by the Buss-Plomin adulthood emotionality-activity-sociability (EAS) temperament model [21, 22]. The EAS-model is one of the most widely used measures within the field of developmental psychology and has been broadly used across different age ranges, also for adolescents [23]. Emotionality refers to experiencing and showing intense negative behaviours such as aggression, anger, distress and fear and can be divided into two measured components, anger and fear. Activity refers to hyperactive behaviours such as impatience and impulsivity and sociability reflects a preference for being with people and to interacting. High scores in negative emotionality have been associated with increased risk of mental health problems. Activity is also correlated to a temperament associated with adverse health-related outcomes. A high score in sociability refers to a more agreeable temperament, the person seeks and enjoys the company of others, whereas low sociability has been linked to depressive symptoms and negative affectivity [24, 25]. Although temperament characteristics are often seen as relatively stable, they have been shown to change throughout life as a person matures [26]. Emotionality was assessed in 12 items, activity by 11 items and sociability by 5 items. Two questionnaires were uncompleted, for one boy the 6-month questionnaire was missing and for another boy the 12-month questionnaire was missing.

To compare our results with healthy peers, we aimed to select a control group that would match as close to the cases as possible, including not only chronological age but also the environment they were living in. Finland being a country large by area, there could be differences in how local manners, traits and culture impact on how variations from normal development are experienced. We thus collected an age- and postal-code matched reference population from The Finnish Digital and Population Data Services Agency. Based on the power calculation we aimed to find 120 age- and post number matched peers ($n = 32$ 1 SD, $n = 126$ 0.5 SD). However, insufficient age- and postal-code matched reference population were found in two living-areas. In the first round we sent the questionnaire to 114 boys and got 16 answers (response rate 14%). After 98 new requests and 13 new responses (response rate of 13%), a total of 29 boys were used as the reference population (local controls). Our co-authors had used the same questionnaire in the large national YFS study, and we were kindly offered to utilize this part of their data in our study to increase our control population sample size. The other control-group comprised of 57 14-15-year-old (14 years $n = 48$ (56%), 15 years $n = 38$ (44%)) healthy boys from the national YFS. The data is collected between 2018 and 2020 in the 3-generational YFS. The control boys are offspring of the original cohort members that were recruited in the study in 1980. The YFS is a population-based study, originally established to study cardiovascular risk in the youth [27]. The latest generational field study was conducted in 2018–2020 and included a questionnaire based on the EAS-temperament model. CDGP-boys in our study came from urban areas and to minimize potential confounding factors related to differences in social dynamics, including educational opportunities and access to hobbies, that might exist between urban and rural settings, only boys living in urban areas were included.

Our study protocol was registered to ClinicalTrials.gov (registration number: NCT01797718) and approved by the Finnish National Committee on Medical Research Ethics and the Finnish Medicines Agency. Written informed consent was obtained from all subjects.

2.2 | Statistical Analyses

We present the data using means and ranges for the Lz and T groups. We investigated correlations between testicular volume, testosterone level, height SDS and the psychological dimensions at 0–6 months (during the treatment) and at 0–12 months (baseline to follow-up).

The EAS variables were modelled using ordinary least squares regression (ols) to compare the cases to our own controls and to a pooled set of YFS-controls combined to our own controls.

The changes in time for the cases were investigated using general least squares (gls) regression to account for the repeated measurements by including random intercepts for each subject. We then further investigated the differences between the Lz and T groups by also fitting models allowing potential differences between the groups for each time point (baseline, 6 months and 12 months).

Missing values, approximately 2%, were imputed using MICE (Multivariate Imputation by Chained Equations). We created ten imputed sets. Spearman correlation was used to select 15–25 variables, as recommended by the mice-package, for each variable to be imputed. Score sums were not imputed directly, instead the components were imputed and then summed up. The estimates from the imputed sets were pooled using Rubin's rule. Repeating the analyses without data imputation yielded results that were nearly identical to those with imputation, with only minimal differences likely due to chance.

We considered $p < 0.05$ statistically significant. Statistical analyses were done with SPSS for Windows and R software version 4.4.2 using mice, rms and Hmisc packages.

3 | Results

In comparison to the pooled control group (local and YFS-controls), CDGP boys had a lower score in emotionality at the baseline (−0.25, 95% CI: −0.49; −0.01, $p = 0.040$), a borderline difference in activity (−0.25, 95% CI: −0.51; 0.00, $p = 0.055$) and no difference in sociability (−0.11, CI: 95% −0.39; 0.16, $p = 0.418$) between the groups. In comparison to the local controls only, at baseline/before puberty-promoting treatment, CDGP boys had a lower score in activity (−0.34, 95% CI: −0.63; −0.05, $p = 0.024$), in both parts of emotion: fear (−0.34, 95% CI: −0.63; −0.05, $p = 0.023$) and anger (−0.44, 95% CI: −0.80; −0.07, $p = 0.020$), as well as in emotion in total (−0.40, 95% CI: −0.67; −0.12, $p = 0.006$) (Figure 1). Compared only to the national YFS-control group, CDGP-boys had lower values in the dimensions emotionality (anger and fear), activity and sociability, matching results with the original controls, but the differences were not statistically significant ($p = 0.145$–0.615).

None of the EAS-parameters changed significantly during the study period in CDGP boys (Figure 2). In contrast to what could be expected, activity and emotionality decreased slightly although the testosterone levels increased during puberty-promoting treatment. When compared to the pooled control group (local controls and YFS controls combined), activity and anger were significantly lower in CDGP boys at both the 6- and 12-month time points, and fear was significantly lower at 12 months. There was a small trend towards increasing effect sizes over time. Detailed estimates are provided in Table S1.

Anger was slightly more common at baseline (0.52, CI: 95% 0.03; 1.01, $p = 0.041$) and at 12-months (0.50, CI: 95% 0.00; 0.99, $p = 0.049$) in the T-group. There was a protocol violation in one

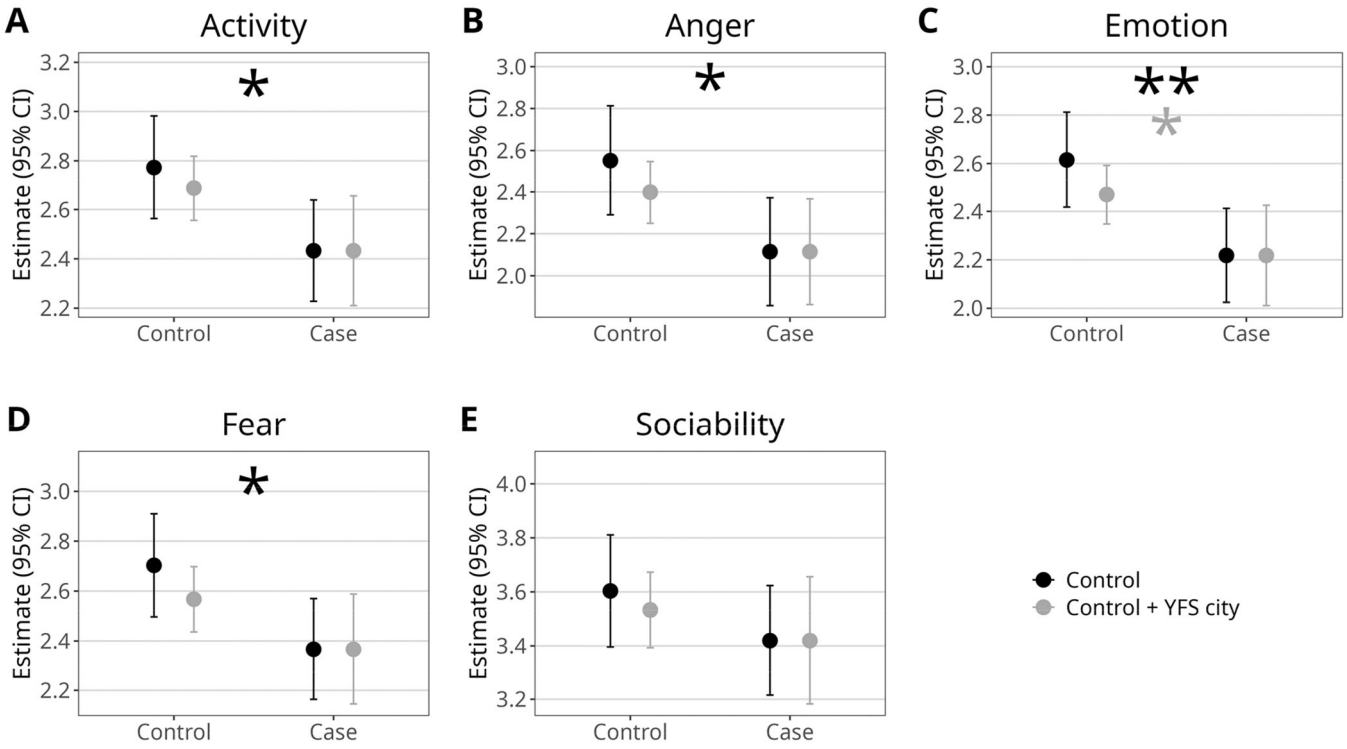

FIGURE 1 | Charts A-E, EAS-dimensions, cases vs local controls (black) and cases versus pooled controls (grey) at baseline. Anger and Fear are the two parts of the dimension Emotion, here shown also separated. The results are from ols regression models. *$p < 0.05$ and **$p < 0.01$.

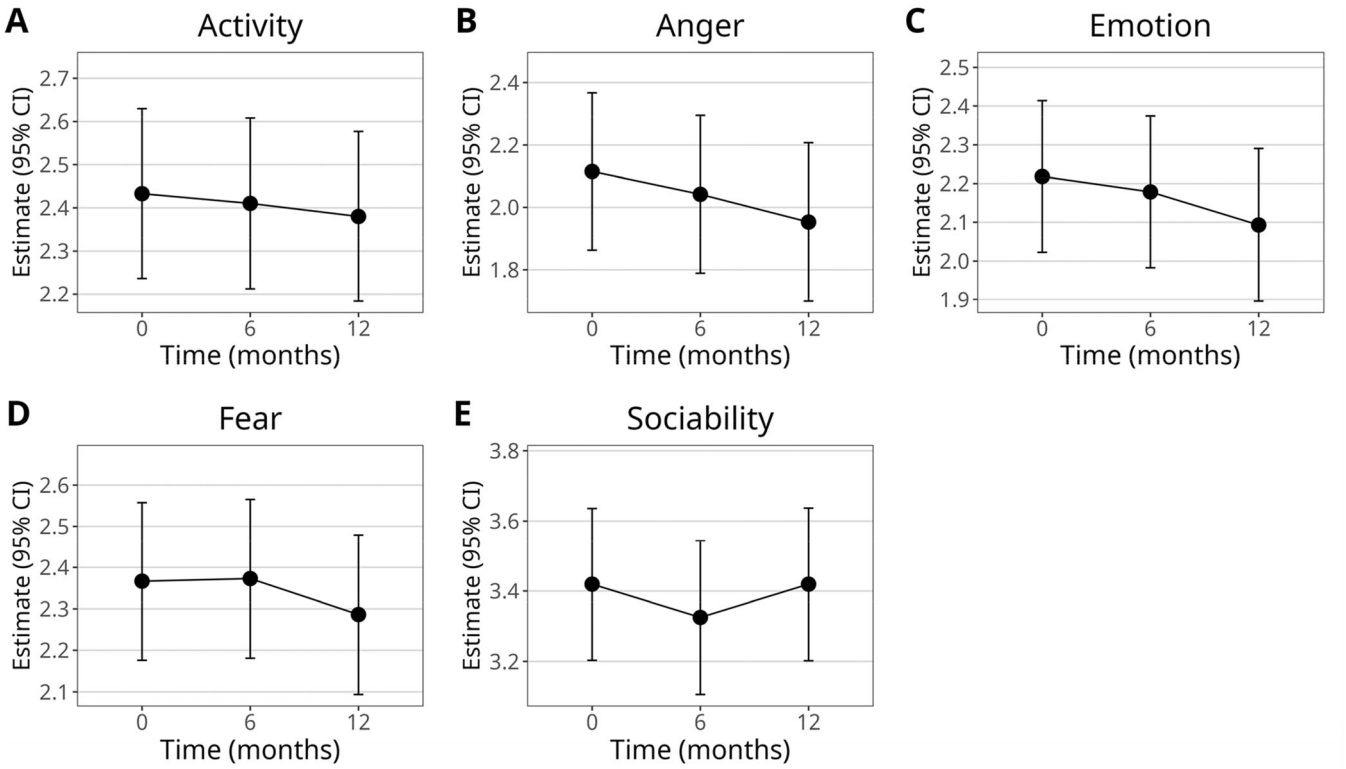

FIGURE 2 | Charts A-E, Changes in EAS parameters during the study period in CDGP boys treated with Lz or T (pooled results). Estimates are from gls regression models.

of the boys in the T-group, receiving a larger testosterone-dose. Excluding this case from the analysis had no effect on the results. No significant differences between the treatment groups were evident in activity and emotionality (in total) during the study. In sociability, Lz and T treated boys showed opposing trends (Figure 3). After the 6-month treatment period (−0.48 CI: 95% −0.89; −0.08, $p = 0.019$) and at 12-month follow-up (−0.72 CI: 95% −1.12; −0.32, $p = 0.001$), boys treated with Lz had higher scores in sociability compared to the T-group.

Positive correlations were observed between testes volume and emotionality ($r = 0.43$, 95% Cl: 0.08;0.69, $p = 0.016$) as well as between testes volume and anger ($r = 0.45$, 95% Cl: 0.11;0.70, $p = 0.012$) during the treatment period (0–6 months, comparing changes over this period). Interestingly, testosterone level showed no correlation with anger or emotionality ($r = 0.30$, 95% Cl: −0.07;0.59, $p = 0.110$ vs. $r = 0.31$, 95% Cl: −0.06;0.60, $p = 0.096$). We found no correlation with sociability and the other tested measures (testosterone level, testes volume, length SDS).

4 | Discussion

Before puberty-promoting treatment, boys with CDGP reported lower negative emotionality than their peers (local and YFS-controls). In comparison to local controls, the difference was even greater. CDGP boys reported lower negative emotionality (fear and anger) and less negative activity. There were no significant differences in sociability. CDGP boys in our study were docile, they did not seem to be severely emotionally distressed in comparison to peers and their social circle was not diminished even though, as we have shown before [20], there was dissatisfaction with physical appearance. Puberty-promoting treatment with either T or Lz showed no negative psychosocial impact. Instead, compared with the pooled control group at 6 and 12 months, lower estimates in activity and anger became significant, and fear was lower at 12 months, with a small trend toward increasing effect sizes. Thus, despite induced pubertal progression and elevated testosterone levels during treatment, the gap in these temperament characteristics did not narrow, suggesting relative stability of these traits or persistence of patterns shaped before treatment.

Based on previous studies, it seems that if the state of delayed puberty continues and especially if the peer relationships are stressful, more substantial psychological problems may arise [5–9, 28]. The results, however, are divergent, and the studies differ in study design and aims, and very few concentrate specifically on CDGP boys. Crowne et al. followed 43 CDGP boys up to final height (1976–1986) and found no significant differences in self-esteem, marital, or employment state between the CDGP boys and the control group [29]. Twenty (53%) subjects reported, however, that they would have preferred puberty-promoting treatment and 25 (65%) felt that delayed growth impacted their success at school, work or social life, thus supporting a more active use of puberty-promoting treatment [29]. Lindfors et al. [8] studied 23 boys with delayed puberty and found that there was a significant negative correlation between late maturation and ego development and sexuality. Simmons et al. [30] investigated the impact of pubertal timing and school context and found no relation between pubertal status and

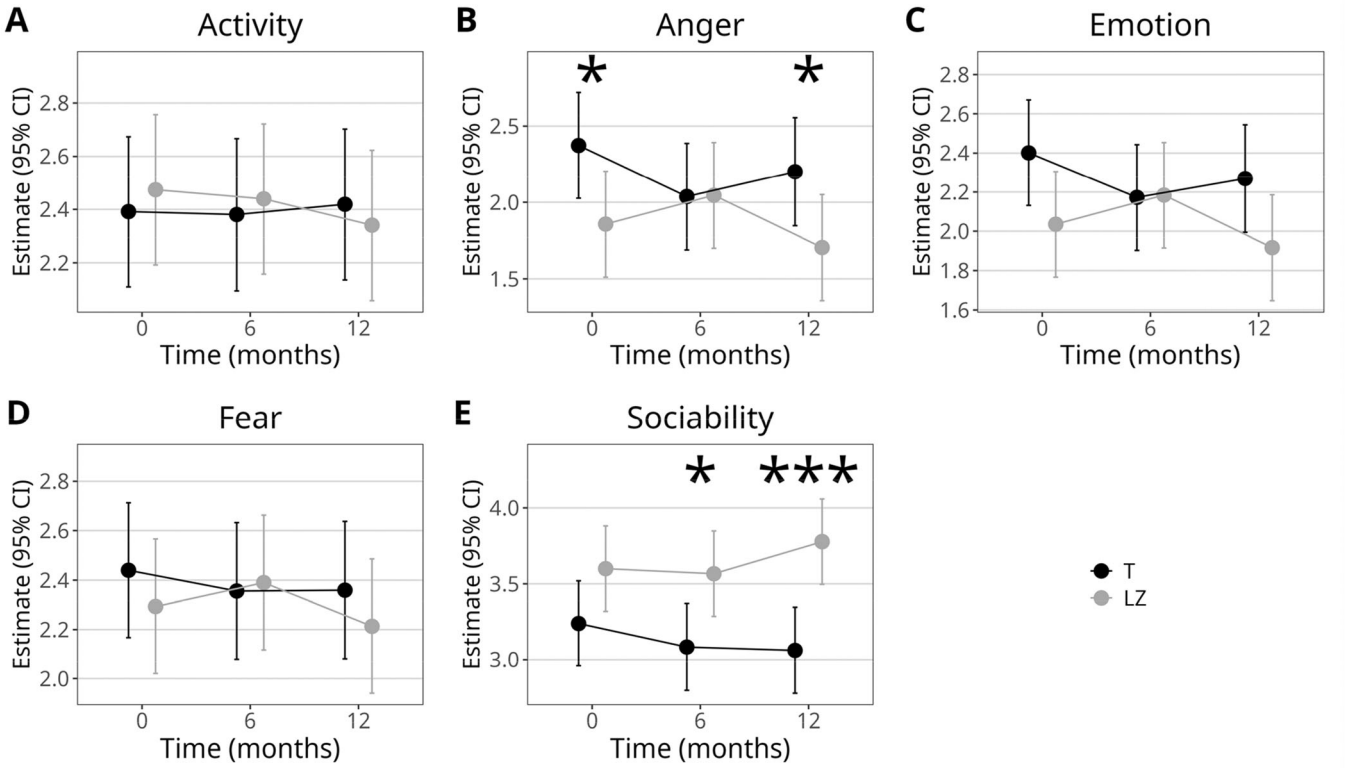

FIGURE 3 | Charts A-E, Between-group (T vs. Lz) differences in EAS parameters during the study period. Estimates obtained from gls regression models $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p \leq 0.001$.

aggressive behaviour. Although there is evidence that testosterone increases emotionality and risk-taking, perceived as part of normal male adolescent psychosocial development, the impact of sex steroids on the developing brain still seems to be an under-investigated area. According to a systematic review of 27 studies [16] the evidence was insufficient to confirm a significant association between testosterone and mood and behaviour in adolescent males. Recently, another systematic review of 55 studies reported toward a positive association between testosterone and aggressive and rule-breaking behaviours, such as substance-use, in males [31].

We found no negative changes in the EAS-phenotype and thus, no proof of negative psychosocial effects, such as aggression, increased impatience or impulsivity or distinct social withdrawal in boys who opted for puberty-promoting treatment in this study. Within-person changes in salivary testosterone levels have been associated with higher affect fluctuation in the life of adolescents [32]. Testes volume did correlate with anger and emotionality during the 6-month treatment-period, but this was not reflected in the EAS-profile. Supporting our hypothesis, treatment with Lz seems to have a positive effect on sociability, which is generally seen as an essential part of well-being, the preference to be with people and to interact with others. T-treatment did not affect sociability in this study. Boys in the T-group reported higher levels of anger at baseline and 12-month follow-up. There was a slight nonsignificant difference between the treatment groups considering testosterone-levels at baseline and follow-up. On the other hand, the changes in testosterone levels during the treatment and follow-up were larger in the Lz-group than in the T-group and there was no detectable difference in anger at 6 months and therefore fluctuation of testosterone levels is unlikely to explain the difference in anger over time between the treatment-groups. Thus, between-group difference in anger likely results from random effect.

To the best of our knowledge, only two randomized controlled trials have previously assessed the impact of puberty-promoting treatment on psychosocial endpoints. In a randomized, double-blind, placebo-controlled, cross-over trial ($n = 35$ males, 24/35 had CDGP) Susman and colleagues found no abnormal patterns of behaviour problems during sex hormone replacement therapy (depo-testosterone) as indexed by parent and self-report in boys with delayed puberty [33]. On the other hand, measured by The Olweus Multifaceted Aggression Inventory [15] there was a significant testosterone effect on hypogonadal adolescents on self-reported physical aggressive behaviour [34]. In the same data, depo-testosterone had a significant positive effect on self-perceived athletic and job competence but no other domains of social competence [35]. In another study, after 1 year of oxandrolone therapy growth velocity increased significantly while self-image or social competence showed no change in boys with CDGP ($n = 40$ boys) [36]. In our previous study, puberty-promoting treatment with T or Lz was related to improved perceived physical appearance and vitality of CDGP boys [20].

The main strength of the current study is the well characterized study population in terms of physical and hormonal markers of puberty. Further, the EAS-temperament model is well documented and has been used for adolescents in multiple studies. Limitations of the current study include the limited number of

participants (resulting in a concern about statistical power and potential selection bias) and use of self-reports (although self-reports are in general thought to represent accurate reporting), resulting in modest power to detect subtle differences in EAS-dimensions. Psychosocial wellbeing is a broad concept which includes subjective feelings as well as both genetically programmed and learned traits and operating models with impact from the surrounding environment. The EAS-model lack measures of self-esteem and depression. Other models might be useful for a comprehensive evaluation of psychosocial wellbeing of CDGP boys. Further, difference in EAS results between the local and national control groups is challenging to interpret. Potential explanatory factors are differences in social environment and culture as the local controls lived in urban setting mainly in the Finnish capital and the national controls likely in a more suburban setting in smaller cities. We acknowledge that the Covid-19 pandemic may have had psychosocial effects on adolescents of the local control group, collected in spring 2021, at the time of the pandemic. However, findings from the Finnish School Health Promotion Study from spring 2021 (organized by the Finnish institute for Health and Welfare every second year in primary school, including junior high school classes 8 and 9, in other words 14–15-year-old adolescents) among adolescent males showed only moderate increase in anxiety by 2% from 2019, and in contrast to girls, boys reported increased general positive mental health (https://urn.fi/URN:NBN:fi-fe2021112557144). Finally, a longer follow-up time might be needed to detect psychological changes related to increasing levels of sex hormones.

In conclusion, puberty-promoting treatment with either T or Lz showed no negative psychosocial impact in the form of aggressiveness or increased negative emotionality among CDGP boys. Despite the limited sample size, this study provides novel insights into temperament characteristics in CDGP boys undergoing puberty-promoting treatment. Given the lack of prior randomized interventional studies focusing on emotionality, activity, and sociability in this population, our findings serve as a foundation for generating hypotheses in future research with larger cohort. Our study should be replicated in a larger sample of CDGP boys. In future studies, it would be valuable to include control groups matched not only by chronological age but also by bone age, to better account for maturational differences driven by cumulative sex steroid exposure. Such comparisons could further help to distinguish whether psychosocial differences are more closely related to biological maturation status rather than age per se.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request. Data will be shared according to the EU General Data Protection Regulation and national and hospital data protection regulations.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.
Supplementary table 1 CDGP vs Combined Controls 6 and 12 mo.