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Regular article

Long-term effects of oxandrolone treatment in childhood on neurocognition, quality of life and social–emotional functioning in young adults with Turner syndrome

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ABSTRACT

Turner syndrome (TS) is the result of (partial) absence of one X-chromosome. Besides short stature, gonadal dysgenesis and other physical aspects, TS women have typical psychological features. Since psychological effects of androgen exposure in childhood probably are long-lasting, we explored long-term psychological functioning after oxandrolone (Ox) therapy during childhood in adults with TS in terms of neurocognition, quality of life and social–emotional functioning. During the initial study, girls were treated with growth hormone (GH) combined with placebo (Pl), Ox 0.03 mg/kg/day, or Ox 0.06 mg/kg/day from the age of eight, and estrogen from the age of twelve. Sixty-eight women participated in the current double-blinded follow-up study (mean age 24.0 years, mean time since stopping GH/Ox 8.7 years). We found no effects on neurocognition. Concerning quality of life women treated with Ox had higher anxiety levels (STAI 37.4 ± 8.4 vs 31.8 ± 5.0, $p = 0.002$) and higher scores on the depression subscale of the SCL-90-R (25.7 ± 10.7 vs 20.5 ± 4.7, $p = 0.01$). Regarding social–emotional functioning, emotion perception for fearful faces was lower in the Ox-treated patients, without effect on interpersonal behavior. Our exploratory study is the first to suggest that androgen treatment in adolescence possibly has long-term effects on adult quality of life and social–emotional functioning. However, differences are small and clinical implications of our results seem limited. Therefore we would not recommend against the use of Ox in light of psychological consequences.

Introduction

Turner syndrome (TS) is the result of total or partial absence of one X chromosome and has an incidence of approximately 1:2000 in live born girls (Nielsen and Wohlert, 1990). In addition to short stature, gonadal dysgenesis – with infertility in the majority of the women – and dysmorphic features, TS is associated with a wide range of abnormalities affecting nearly every organ system. Apart from these physical aspects, psychological problems including neurocognitive dysfunction, diminished quality of life and social–emotional deficits have been reported.

Regarding neurocognition, women with TS have a distinct profile characterized by a normal to high verbal intelligence quotient (VIQ) and a decreased performance IQ (PIQ) (Nijhuis-van der Sanden et al., 2003; Ross et al., 2002). Cognitive problems commonly persist into adulthood and adult women with TS are prone to impairments in visual–motor integration, attention, (working) memory, executive function and spatial cognition (Nijhuis-van der Sanden et al., 2003; Ross et al., 2002).

Quality of life in TS is generally considered to be unaffected, although some studies reported diminished scores on especially

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physical functioning subscales (Amundson et al., 2010; Nadeem and Roche, 2013; Ros et al., 2013; Taback and Van Vliet, 2011). Sexual functioning may be impacted and women with TS have a higher rate of lifetime depression (Cardoso et al., 2004; Ros et al., 2013). Furthermore, women with TS report more social isolation, shyness, social anxiety and problems in relationships (Amundson et al., 2010; Rolstad et al., 2007; Schmidt et al., 2006). Infertility may be one of the main contributing factors, since similar problems have been reported in women with premature ovarian failure (Cardoso et al., 2004; Ros et al., 2013; Schmidt et al., 2006). In addition to health-related problems, social interaction is probably influenced by difficulties in interpreting non-verbal communication, that is, recognizing facial expression of certain emotions (especially fear) (Lawrence et al., 2003a,b; Mazzola et al., 2006).

In general, girls with TS are treated with growth hormone (GH) to increase adult height (Bondy, 2007). In order to improve the growth-enhancing effect of GH in TS, the addition of the weak synthetic androgen oxandrolone (Ox) has recently been investigated in three placebo (Pl) controlled trials, including ours (Gault et al., 2011; Menke et al., 2010a; Zeger et al., 2011). We investigated the additional growth-enhancing effect of Ox in two different dosages (Menke et al., 2010a). Compared with GH + Pl, GH + Ox in a dose of 0.03 mg/kg/day (Ox 0.03) significantly increased adult height gain (9.5 vs. 7.2 cm in Pl) at the cost of mild deceleration of breast development. At a higher dose of 0.06 mg/kg/day (GH + Ox 0.06), no significant increase in height gain was found and significantly more girls reported virilization (Menke et al., 2010a). In the Ox groups a decrease in fat mass, an increase in muscle mass and lowering of the voice was found (Menke et al., 2010c, 2011). During the same study a psychological survey (testing emotional and behavioral problems, sexual aspects of quality of life and gender role) revealed no differences between the Ox and Pl treated groups (Menke et al., 2010b).

Others found that during methyltestosterone treatment in TS quality of life, including general health, and sexual desire improved (Zuckerman-Levin et al., 2009). In the same study androgen treatment was associated with neuro-cognitive functioning in terms of improved selective attention and verbal episodic memory, and a decline in some of the executive functions including working memory (Zuckerman-Levin et al., 2009). Strikingly, other researchers treated TS girls with Ox for 2 years and found significant improvement of working memory and measures of immediate recall, but no effects on verbal abilities, spatial cognition, and executive function (Ross et al., 2003). Four years of Ox treatment resulted in slight improvement of mathematical learning disabilities, but no effect was found on reading learning disability (Ross et al., 2009).

Conventionally, the effects of androgens on psychological functioning are divided into activational (temporary, during exposure) and organizational (permanent) (Arnold and Breedlove, 1985). While research on organizational effects has primarily focused on the prenatal and neonatal period, the timeframe in which cerebral function can be permanently influenced by external hormonal influences possibly last into puberty (Berenbaum and Beltz, 2011).

Taking together the susceptibility to (neuro)psychological problems in TS and the potentially permanent psychological effects of exposure to exogenous androgens during childhood and adolescence, this raises important questions regarding the safety of growth-enhancing treatment with Ox in these patients. The aim of this exploratory follow-up study was to determine the long-term effects of Ox on neuro-cognitive functioning (i.e., 'traditional' cognitive functions related to information processing), quality of life and social–emotional functioning.

Methods

Participants and previous treatment

The current study is a follow-up evaluation of the pediatric multi-center randomized, placebo-controlled, double-blind Turner Oxandrolone Study. The initial study started in 1991. In this study 133 girls with TS were treated with GH (1.33 mg/m^2 body surface/day) from baseline combined with Pl, Ox 0.03, or Ox 0.06 mg/kg body weight/day from the age of eight and estrogen from the age of twelve. More detailed participant information and treatment modalities, including inclusion and exclusion criteria, were reported previously (Menke et al., 2010a).

For the current study all patients and investigators remained blinded for the study medication and the patients who discontinued GH treatment at least six months before entry were invited. Additional exclusion criteria of this study were participation in another drug study within two months of entry, malignant or severely disabling disease, suspicion of major psychiatric disorder and pregnancy or current fertility treatment.

Assessments

All neuropsychological tests and psychological questionnaires were performed during a whole-day program, which included medical assessments as well. The questionnaires were computerized and set out in a quiet room without any company. All neuropsychological tests were performed by two well-trained assistant psychologists.

Neurocognition and intelligence

Intelligence (total IQ, verbal and performance IQ) was assessed using the abbreviated version of the Wechsler Adult Intelligence Scale (WAIS-III), consisting of the 7 subtests Arithmetic, Information, Digit Span, Similarities, Picture Completion, Block Design and Symbol Substitution (Axelrod et al., 2000). Executive function was measured using the Brixton Spatial Anticipation Test (Brixton) as an index of rule detection and concept shifting and the Zoo Map subtest of the Behavioral Assessment of the Dysexecutive Syndrome (BADS) as a test for visuospatial planning (Lezak et al., 2012). Visuospatial working memory was addressed with the Box Task, a computerized paradigm to assess visuospatial efficiency and working memory (Van Asselen et al., 2005). The Box Task consists of different trials with increasing difficulty (4, 6, 8 and 10 boxes). Outcome measures are within-search errors (errors within a single search reflecting the ability to keep visuospatial information active), between-search errors (errors between several search trials, reflecting the ability to maintain visuospatial information over longer periods of time) and a strategy score (reflecting search efficiency) (Van Asselen et al., 2005).

Quality of life

Health-related quality of life was assessed with the RAND 36 adapted from the MOS 36-item short-form health survey (Aaronson et al., 1998). The original RAND consists of 8 subscales: Physical Functioning, Social Functioning, Limitations due to Physical Problems, Limitations due to Emotional Problems, Mental Health, Vitality, Bodily Pain and General Health. A ninth subscale 'Health change' was added.

The Dutch revised version of the Symptom Checklist (SCL-90-R) was performed to estimate general psychological, somatic and cognitive wellbeing (Arrindell and Ettema, 2003). The test consists of 90 items that have to be rated on a five-point scale. Eight subscales are defined as Agoraphobia, Somatization, Anger-Hostility, Depression, Interpersonal Sensitivity and Paranoid Ideation, Anxiety, Cognitive Performance Difficulty, and Sleep Disturbance.

More detailed information about depression and anxiety was collected by two additional questionnaires. The level of depressive symptoms was measured using the Beck Depression Inventory — 2nd Edition (Dutch version, BDI-II-NL) (Beck et al., 1996; Van der Does, 2002). The scores for the 21 items range from 0 to 3 and are divided into three categories: Cognitive, Somatic and Affective. We considered a score above 16 as indicative for depression. Anxiety was measured using the Spielberger State Trait Anxiety Inventory (Dutch version, STAI) (Van der Ploeg et al., 1980). The STAI measures the Trait Anxiety

(a general tendency of an individual to be anxious) and the State Anxiety (the level of anxiety on a certain moment). Both measures include 20 items which scores range from 1 to 4.

To examine women's evaluation of the impact of TS in their life (cognitive coping), the Illness Cognition Questionnaire (ICQ) was used (Evers et al., 2001). A score was computed for each of the three subscales: Helplessness, Acceptance and Disease Benefits.

Five items of the Inventory Social Involvement (ISI) – the social dimension of the Arthritis Impact Measurement Scales – were used to assess the participant's own perception of social support in the past six months (Dam-Baggen and Kraaimaat, 1992; Meenan et al., 1980).

To assess the thoughts and emotions concerning sexuality we used the Dutch version adapted from the Women's Sexual Self-Concept Scale (WSSCS) (Johnson Vickberg and Deaux, 2005). The three different subscales of the WSSCS are defined as Agentic Sexuality (women's interest and active role in sexuality), Negative Associations (sexual coercion, negative emotions and concerns about sexuality) and Reserved Approach (responsibility, carefulness and faithfulness) (Johnson Vickberg and Deaux, 2005).

Social and emotional functioning

We assessed three different aspects of social–emotional functioning: understanding of emotions, interpersonal distress, and recognition of emotions.

To assess the ability to understand and process emotions the Bermond–Vorst Alexithymia Questionnaire (BVAQ) was administered (Vorst and Bermond, 2001). The five sub-scales differentiate between cognitive (Identifying, Verbalizing and Analyzing) and affective (Emotionalizing, Fantasizing) dimensions of alexithymia.

As an index for social behavior and the associated experience of stress, the Scale for Interpersonal Behavior (SIB) was administered (Arrindell et al., 2001). The SIB consists of two different scales (50 items): one for the frequency of engagement in a specific social situation (SIB-F) and one for the degree of experienced discomfort (SIB-G). The index provides four subscales named Negative Assertion (disclosure of negative feelings), Insecurity (expression of and dealing with personal limitations), Initiating Assertiveness (social assertiveness and expressing one's own opinion) and Positive Assertion (praising others and the ability to deal with compliments).

To examine the ability to perceive and label emotional expressions the short form of the Emotion Recognition Test (ERT) was administered (Kessels et al., 2014). This is a computerized test for the recognition of the six basic facial emotional expressions: anger, disgust, fear, happiness, sadness and surprise. The emotions are mimicked by two male and two female actors. Morphed video clips show a neutral face gradually changing into different emotions at different levels of intensities (40, 60, 80 and 100%). After each video clip, the participant is asked to make a forced choice between the six emotional expressions. Each emotion in each intensity is presented four times, each by a different actor.

Statistical analyses

We performed a 'modified intention to treat analysis' including only those patients who took at least one dose of the study medication (Pl or Ox). For comparison between the three groups (Pl, Ox 0.03, Ox 0.06) ANOVA or Chi-square test were used where appropriate. Only in the case of significant main effects post-hoc comparisons were performed. ERT and Box Task were analyzed using a general linear model repeated-measures analysis. For comparison between Pl and the total Ox group (Ox 0.03 and Ox 0.06 together) we used ANOVA and unpaired T-tests. To correct for multiple testing, alpha was set at 0.01 for comparison of the three treatment modalities. We used Statistical Package for the Social Sciences version 16.0 (SPSS, Inc., Chicago, Illinois). Effect sizes have been calculated using the Effect Size Calculator (www.cognitiveflexibility.org/effectsize/).

The study was performed in accordance with the Declaration of Helsinki and approved by the ethics committee of the Radboud University Medical Center. Written informed consent was obtained from all participants.

Results

Recruitment

Of the original 133 patients, 68 patients participated in the follow-up study. For recruitment and participation details see Fig. 1. Between the three groups there were no differences in education level, employment and living situation. One patient in the Ox 0.06 group was excluded because of a serious psychiatric disorder. Three patients were under regular care of a psychiatrist and/or psychologist, all three had been treated with Ox 0.03.

Two patients did not complete the psychological questionnaires because their parents considered them incapable (IQ 63 and 74, respectively) and another patient because of anxiety to fail. The fourth patient was excluded because of too many missing values. Three other patients did not undergo neuropsychological examination: one patient refused to participate and in two patients data could not be collected due to logistic reasons. According to the modified intention to treat analysis, two patients were excluded in the Ox 0.03 group because they had never started Ox.

Table 1 summarizes the main patient characteristics and physical outcome measures. More detailed information about growth, body composition and virilization has been reported in a previous paper (Freriks et al., 2013). The mean time ± SD interval since the end of GH/Ox was 8.7 ± 3.3 years. The timing and duration of GH/Ox was not different between the three treatment modalities. Estrogen therapy was equal in all groups.

Neurocognition and intelligence

All neurocognitive results are summarized in Table 2. We found no main effect of treatment modality on intellectual ability (TIQ, PIQ, VIQ: all F values < 0.8). No differences between the treatment groups were found on visuospatial planning (Zoo Map: all F values < 1.9) and rule detection and concept shifting (Brixton: $F_{2,62} = 1.8$). Repeated-measures analyses revealed no effect of Ox on visuospatial working memory (Box Task between-search errors). No strategy differences were observed on this task either (all F values < 2.0).

Quality of life

All results are summarized in Table 3.

Concerning quality of life the RAND-36 showed no main effect of Ox (all F-values < 2.7). When comparing the Pl group with both Ox treated groups taken together no significant differences on the subscales were found. In addition, the SCL-90-R subscales did not reveal any significant differences when comparing the Ox 0.03 and Ox 0.06 groups with Pl separately (all F-values < 2.4). When combining the two Ox groups, the patients using Ox reported significantly more complaints compared to Pl on the subscale Depression (25.7 vs 20.5, $p = 0.01$). None of the other subscales showed a treatment effect.

Focusing on depression and anxiety, no main effect of the study medication was found on the different subscales of the BDI-II (all F-values < 1.4). Mean values in all three groups indicate low levels of depressive symptoms. When comparing the Pl group with the Ox treated groups together no significant differences were found. Eight patients had a total score of >16: one in the Pl group, four in the Ox 0.03 group and three in the Ox 0.06 group, but no significant differences were found in frequency of occurrence across the three groups. Testing anxiety with the STAI, we demonstrated no main effect of Ox compared to Pl for both current anxiety and anxiety predisposition.

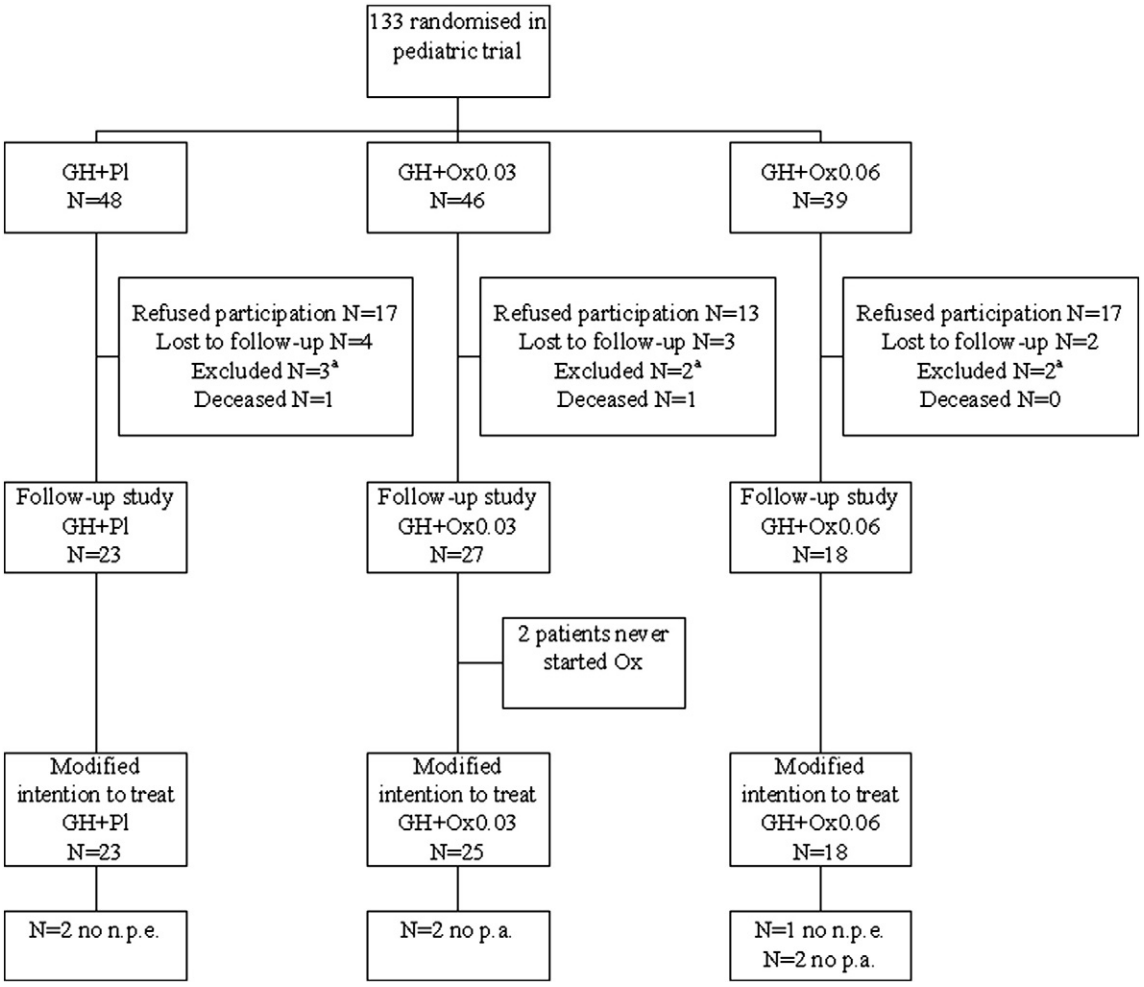

Fig. 1. Flow chart of patient inclusion. n.p.e. neuropsychological examination, p.a. psychological assessment. [a]Exclusion due to current GH treatment (n = 5), multiple handicaps (n = 1) or psychiatric illness (n = 1). The patient with psychiatric illness was in the Ox 0.06 group.

When combining the Ox treated groups for both subscales a significant effect was found when compared to Pl: current anxiety (37.4 vs 31.8, $p = 0.002$) and anxiety predisposition (40.2 vs 33.4, $p = 0.002$), indicating higher levels of anxiety in the Ox treated groups.

Testing cognitive coping, no significant main effect of treatment condition on the ICQ was found (all three F values < 1.5). A comparison between the Pl group and both Ox groups together showed no significant differences as well.

We found no main effect for Ox on the total ISI score ($F_{2,61} = 2.41$, $p = 0.1$), meaning that self reported social support is comparable between the treatment modalities. Comparing the Ox groups together revealed no differences with Pl.

Concerning psychosexual wellbeing mean scores of the WSSCS subscales were 4.3 ± 1.1 for Agentic Sexuality, 2.1 ± 0.7 for Negative Associations and 5.4 ± 1.2 for Reserved Approach, without any differences between the treatment modalities.

Table 1
Patient characteristics (modified intention to treat, n = 66).

	GH + Pl (n = 23)	GH + Ox 0.03 (n = 25)	GH + Ox 0.03 vs GH + Pl p value	GH + Ox 0.06 (n = 18)	GH + Ox 0.06 vs GH + Pl p value
Age	24.6 ± 4.2	24.2 ± 3.4	0.707	23.6 ± 3.4	0.414
Percentage 45, X	14/23 = 60.9%	8/25 = 31.0%	0.045	8/18 = 44.4%	0.295
Age at start Ox/Pl	10.7 ± 2.5	10.4 ± 2.2	0.593	9.7 ± 1.7	0.140
Duration of Ox/Pl therapy	5.1 ± 1.6	4.7 ± 1.5	0.315	5.0 ± 1.3	0.709
Adult height (cm)	156.7 ± 4.7	159.0 ± 6.7	0.171	157.9 ± 5.2	0.531
Adult height gain (cm)	8.0 ± 4.6	10.0 ± 4.9	0.144	9.7 ± 4.4	0.258
BMI (kg/m^2)	26.9 ± 5.2	28.0 ± 6.9	0.487	26.6 ± 4.2	0.879
Breast size (cm)[a]	13.5 ± 3.6	13.9 ± 4.3	0.730	12.7 ± 3.1	0.518
Tanner breast stage	4.5 ± 0.7	4.6 ± 0.5	0.619	4.7 ± 0.4	0.398
Ferriman & Gallwey score[b]	0.09 ± 0.3	3.5 ± 8.8	0.039	1.7 ± 2.2	0.372
One or more virilizing complaints[c]	8/23 = 34.8%	13/25 = 52.0%	0.230	15/18 = 83.3%	0.002

[a] Breast size was estimated by subtraction of the widest chest circumference (at the level of the nipples) minus the smallest chest circumference (under the breasts) with the patient in supine position. Six patients were excluded for breast size measurements: two patients refused measurement without underwear and four had a history of breast surgery.
[b] Ferriman & Gallwey score is a score for excessive, androgen dependent, body hair.
[c] Excessive hair growth, acne, greasy skin, large clitoral size and/or lowering of the voice.

Table 2
Neurocognition and intelligence.

	Placebo (n = 23) Mean ± SD	Ox 0.03 (n = 23) Mean ± SD	Effect size Ox 0.03 Cohen's *d*	Ox 0.06 (n = 17) Mean ± SD	Effect size Ox 0.06 Cohen's *d*	Total Ox group (n = 40) Mean ± SD	Effect size Total Ox group Cohen's *d*
WAIS III							
Total IQ	87.1 ± 12.0	90.5 ± 13.6	−0.27	86.7 ± 10.6	0.04	88.9 ± 12.4	−0.15
Verbal IQ	91.7 ± 12.6	95.0 ± 14.5	−0.24	91.8 ± 14.2	−0.01	93.7 ± 14.3	−0.15
Performance IQ	83.3 ± 12.2	86.6 ± 12.5	−0.27	82.5 ± 8.7	0.08	84.9 ± 11.1	−0.14
Brixton	11.1 ± 4.2	13.0 ± 5.6	−0.39	14.2 ± 6.1	−0.60	13.5 ± 5.8	−0.48
Zoo Map (BADS)							
Score (condition 1)	3.5 ± 4.9	3.7 ± 4.4	−0.04	2.9 ± 5.3	0.12	3.4 ± 4.8	0.02
Planning time (sec)	111.6 ± 163.1	79.5 ± 64.1	0.28	110.2 ± 119.6	0.01	92.6 ± 91.8	0.15
Total time (sec)	209.4 ± 153.1	186.0 ± 85.4	0.20	252.3 ± 162.5	−0.27	214.2 ± 126.7	−0.03
Score (condition 2)	7.4 ± 1.8	6.6 ± 2.2	0.40	7.6 ± 1.2	−0.13	7.0 ± 1.9	0.22
Planning time (sec)	10.3 ± 10.2	15.2 ± 25.2	−0.28	14.2 ± 19.6	−0.26	14.8 ± 22.7	−0.27
Total time (sec)	63.8 ± 24.1	69.4 ± 28.9	−0.21	72.2 ± 31.5	−0.30	70.6 ± 29.7	−0.25
Box Task							
Between search error							
4 boxes	0.2 ± 0.3	0.2 ± 0.3	0.00	0.3 ± 0.4	−0.29	0.2 ± 0.4	0.00
6 boxes	0.8 ± 1.0	0.8 ± 1.2	0.00	0.4 ± 0.7	0.47	0.7 ± 1.0	0.10
8 boxes	3.6 ± 3.9	3.2 ± 2.5	0.13	4.0 ± 3.6	−0.11	3.5 ± 3.0	0.03
10 boxes	10.0 ± 4.3	10.0 ± 4.4	0.00	9.2 ± 3.5	0.21	9.7 ± 4.0	0.07
Strategy score							
4 boxes	1.9 ± 0.7	1.8 ± 0.6	0.15	2.1 ± 0.6	−0.31	1.9 ± 0.5	0.00
6 boxes	3.2 ± 1.1	3.4 ± 0.7	−0.22	3.5 ± 1.0	−0.29	3.5 ± 0.8	−0.32
8 boxes	4.4 ± 1.3	4.7 ± 1.1	−0.25	4.6 ± 1.0	−0.17	4.7 ± 1.1	−0.25
10 boxes	6.5 ± 2.0	6.7 ± 1.1	−0.13	6.8 ± 1.6	−0.17	6.7 ± 1.3	−0.12

WAIS, Wechsler Adult Intelligence Scale; IQ, intelligence quotient; BADS, Behavioral Assessment of the Dysexecutive Syndrome; SD, standard deviation. Higher scores on the WAIS indicate a higher IQ. More errors for the Brixton reflect more problems in executive function. For the Zoo Map higher scores correlate with better visuospatial planning. Concerning the Box Task an increasing number of errors reflect problems in visuospatial efficiency and working memory, where a lower score on strategy indicates more efficient use of strategy.

Social and emotional functioning

Table 3 shows the results of the various tests. Concerning alexithymia, we found a main effect of Ox on the BVAQ subscale Emotionalizing ($F_{2,61} = 6.29$, $p = 0.003$). Post-hoc analysis however, showed no significant differences between the three treatment modalities.

Scores on the SIB did not differ between the different treatment modalities on both SIB-F (all F values < 1.4) and SIB-G (all F values < 1.3). Comparing combined Ox groups with Pl revealed no significant differences for social behavior and associated stress.

Fig. 2 shows the results of the ERT for the three treatment groups. Main effects for emotion type ($F_{5,300} = 103.5$, $p < 0.0001$) and intensity ($F_{3,180} = 68.1$, $p < 0.0001$) were found. ERT revealed no main effect of Ox ($F_{2,60} = 0.56$, $p = 0.57$). We found an interaction between treatment group and intensity ($F_{6,180} = 3.3$, $p = 0.004$). Subsequent analyses revealed a main effect of treatment condition only on intensity 40% ($F_{2,60} = 6.3$, $p = 0.003$). Combining both Ox groups, Ox treated patients performed worse on fear (0.83 vs 1.61, $p = 0.001$) for the 40% intensity trials.

Correlation physical aspects and quality of life

No significant correlations between adult height, adult height gain, Ferriman and Gallwey score, BMI, breast size and Tanner breast stage and quality of life were found (all Pearson correlation (r) ≤ 0.2). When comparing women with subjective virilization to women without subjective virilization no difference in quality of life was found (mean RAND score 77.6 ± 14.3 and 82.5 ± 14.9 respectively). Furthermore, no difference in quality of life was found when comparing women satisfied with adult height to women who were not satisfied (mean RAND score 80.3 ± 15.1 and 77.9 ± 13.2 respectively).

Discussion

We present the psychological and neuropsychological long-term follow-up data of the Dutch randomized double blind placebo controlled study on Ox in GH treated girls with TS at a mean of 8.7 years after discontinuation of Ox. Our exploratory study shows that women previously treated with Ox may have more feelings of anxiety and depression compared to those who had received Pl, although an overall effect on quality of life was not found. We found no long-term effect of Ox on neurocognition (i.e., intelligence, working memory and executive function). Regarding social–emotional functioning, only emotion perception for fearful faces was lower in the Ox groups, without affecting social functioning in daily life.

Our study is the first to explore quality of life using a follow-up assessment after discontinuation of Ox. We observed a trend towards lower quality of life in the Ox treated groups, which is likely related to the higher frequency of depressive complaints and the higher anxiety levels in the Ox groups. With respect to anxiety, the Ox treated groups taken together reported higher levels of anxiety (measured with the STAI) with a large effect size and a moderate, yet statistically not significant, effect on the anxiety subscale of the SCL-90-R. Considering depressive symptoms we observed a moderate significant effect on the depression subscale of the SCL-90-R, but depression measured with the BDI was not more common.

Studies on quality of life in relation to androgen use in TS are scarce. One previous study showed that during testosterone treatment in adult women with TS the quality of life improved (Zuckerman-Levin et al., 2009). Also in other patient groups androgen substitution has positive effects on well-being: for example in postmenopausal women after oophorectomy transdermal testosterone resulted in an improvement of well-being (Shifren et al., 2000). However, it is yet unclear if testosterone and Ox have comparable effects, since Ox is nonaromatizable (Fox et al., 1962). Moreover, we do not know the exact effect of Ox on quality of life during treatment in our pediatric study, since quality of life was not measured in childhood. We cannot rule out that previous Ox treatment changed some aspects of quality of life with permanent effects years after treatment. A long-lasting effect of Ox on the endogenous androgen production is unlikely, because androgen levels during this follow-up were similar between the three treatment modalities (data not shown).

Additionally, we found no correlation between quality of life and certain physical effects of androgen treatment. First of all, objective and subjective virilizing effects were more frequently found in the Ox

Table 3
Questionnaires concerning quality of life and social and emotional functioning.

	Placebo (n = 21)	Ox 0.03 (n = 25)	Effect size Ox 0.03	Ox 0.06 (n = 16)	Effect size Ox 0.06	Total Ox group (n = 41)	Effect size Total Ox group
	Mean ± SD	Mean ± SD	Cohen's *d*	Mean ± SD	Cohen's *d*	Mean ± SD	Cohen's *d*
Quality of life							
RAND (mean)	84.8 ± 8.9	79.0 ± 15.7	0.47	74.4 ± 17.7	0.78	77.2 ± 16.4	0.60
Physical functioning	93.4 ± 7.9	89.2 ± 17.2	0.33	88.8 ± 16.5	0.38	89.0 ± 16.7	0.36
Social functioning	92.5 ± 10.0	86.4 ± 20.1	0.41	78.8 ± 24.1	0.80	83.4 ± 21.8	0.57
Role limitation — physical	88.6 ± 22.8	87.0 ± 29.0	0.06	68.8 ± 41.3	0.62	79.9 ± 35.0	0.30
Role limitation — emotional	90.8 ± 18.6	77.2 ± 38.2	0.48	79.1 ± 36.3	0.43	78.0 ± 37.0	0.46
Mental health	77.6 ± 9.6	74.6 ± 15.8	0.24	71.8 ± 15.0	0.47	73.5 ± 15.4	0.33
Vitality	66.4 ± 12.6	58.4 ± 20.6	0.48	56.6 ± 22.9	0.55	57.7 ± 21.2	0.51
Bodily pain	95.5 ± 8.8	88.4 ± 17.4	0.54	86.9 ± 15.5	0.71	87.8 ± 16.5	0.61
General health	73.4 ± 15.3	70.4 ± 18.1	0.18	64.7 ± 17.4	0.53	68.2 ± 17.8	0.31
SCL-90-R (total)	117.7 ± 24.6	135.6 ± 50.2	−0.48	135.2 ± 38.9	−0.55	135.4 ± 45.6	−0.50
Anxiety	12.0 ± 2.7	14.5 ± 6.3	−0.56	13.8 ± 4.0	−0.54	14.2 ± 5.5	−0.54
Agoraphobia	7.4 ± 0.7	8.7 ± 3.3	−0.65	8.4 ± 2.4	−0.65	8.6 ± 2.9	−0.67
Depression	20.5 ± 4.7	26.3 ± 12.4	−0.68	24.7 ± 7.6	−0.68	25.7 ± 10.7*	−0.68
Somatization	15.3 ± 3.6	16.4 ± 5.5	−0.24	17.0 ± 4.6	−0.41	16.6 ± 5.1	−0.30
Cognitive performance difficulty	13.7 ± 4.8	16.3 ± 7.0	−0.44	16.8 ± 6.7	−0.54	16.5 ± 6.8	−0.48
Interpersonal sensitivity	26.3 ± 8.4	28.8 ± 11.8	−0.25	29.8 ± 11.2	−0.36	29.2 ± 11.4	−0.29
Anger-hostility	7.1 ± 1.4	7.6 ± 1.7	−0.32	7.6 ± 2.1	−0.29	7.6 ± 1.8	−0.31
Sleep disturbance	4.4 ± 1.7	4.5 ± 1.8	−0.06	4.8 ± 1.9	−0.22	4.6 ± 1.8	−0.11
BDI-II-NL (total)	4.4 ± 5.4	7.0 ± 8.3	−0.38	6.9 ± 7.9	−0.38	7.0 ± 8.0	−0.39
Affection	0.4 ± 0.9	0.9 ± 1.8	−0.37	1.3 ± 2.1	−0.60	1.1 ± 1.9	−0.50
Cognition	1.5 ± 2.4	2.9 ± 3.8	−0.45	2.3 ± 2.7	−0.31	2.7 ± 3.4	−0.41
Somatic	2.5 ± 2.5	3.2 ± 3.9	−0.22	3.4 ± 3.9	−0.28	3.3 ± 3.8	−0.25
STAI							
Current anxiety	31.8 ± 5.0	37.4 ± 9.1	−0.79	37.5 ± 7.4	−0.92	37.4 ± 8.4**	−0.84
Anxiety predisposition	33.4 ± 5.6	40.3 ± 11.9	−0.79	39.9 ± 9.2	−0.88	40.2 ± 10.8**	−0.83
ICQ							
Helplessness	7.6 ± 2.5	8.6 ± 2.7	−0.38	8.7 ± 2.7	−0.42	8.6 ± 2.7	−0.38
Acceptance	21.4 ± 2.5	19.5 ± 4.1	0.58	19.8 ± 4.7	0.44	19.6 ± 4.3	0.53
Perceived benefits	14.8 ± 4.5	15.4 ± 4.7	−0.13	15.1 ± 4.7	−0.07	15.3 ± 4.6	−0.11
ISI	17.2 ± 3.6	16.8 ± 3.2	0.12	14.8 ± 3.9	0.64	16.0 ± 3.6	0.33
Social and emotional functioning							
BVAQ							
Emotionalizing	26.5 ± 3.3	29.8 ± 3.9	−0.92	26.4 ± 3.8	0.03	28.5 ± 4.2	−0.53
Fantasizing	22.6 ± 7.3	24.5 ± 6.6	−0.27	23.4 ± 7.3	−0.11	24.1 ± 6.8	−0.21
Identifying	30.6 ± 4.4	29.8 ± 6.0	0.15	30.1 ± 5.1	0.11	29.9 ± 5.6	0.14
Analyzing	30.6 ± 4.6	29.3 ± 5.2	0.27	29.4 ± 3.8	0.29	29.4 ± 4.6	0.26
Verbalizing	24.8 ± 5.8	24.6 ± 6.6	0.03	24.8 ± 5.3	0.00	24.7 ± 6.0	0.02
SIB-G							
Express negative feelings	36.7 ± 11.4	38.4 ± 12.7	−0.14	37.4 ± 9.2	−0.07	38.0 ± 11.4	−0.11
Express uncertainty	26.0 ± 9.5	26.3 ± 8.5	−0.03	30.4 ± 9.4	−0.47	27.9 ± 9.0	−0.21
Make yourself noticed	20.4 ± 7.2	22.2 ± 7.7	−0.24	22.7 ± 6.8	−0.33	22.4 ± 7.3	−0.28
Express positive feelings	17.8 ± 7.4	16.8 ± 5.8	0.15	17.9 ± 7.0	−0.01	17.2 ± 6.2	0.09
SIB-F							
Express negative feelings	40.4 ± 10.3	40.6 ± 8.1	−0.02	38.7 ± 7.7	0.19	39.8 ± 7.9	0.07
Express uncertainty	51.8 ± 10.4	51.4 ± 6.5	0.05	47.8 ± 5.1	0.52	50.0 ± 6.2	0.22
Make yourself noticed	26.5 ± 6.2	27.2 ± 5.3	−0.12	25.1 ± 3.4	0.29	26.4 ± 4.7	0.02
Express positive feelings	24.7 ± 6.3	25.2 ± 5.9	−0.08	25.1 ± 4.8	−0.07	25.1 ± 5.5	−0.07

BDI-II-NL, Beck Depression Inventory — 2nd Edition; SCL-90-R, Symptom Checklist-90 Revised; STAI, Spielberger State Trait Anxiety Inventory; ICQ, Illness Cognition Questionnaire; ISI, Inventory Social Involvement; SD, standard deviation; BVAQ, Bermond–Vorst Alexithymia Questionnaire; SIB, Scale for Interpersonal Behavior; SD, standard deviation. A higher score for the RAND corresponds with a better quality of life. Higher scores on the SCL-90-R reflect more complaints. Higher scores on the BDI and STAI correspond with more depressive symptoms and a higher anxiety level respectively. For the ICQ higher scores indicate more feelings of helplessness, higher levels of acceptance and more perceived benefits. The higher the score on the ISI, the better the perception of social support. Concerning BVAQ increased scores on the affective dimension reflect problems in the conscious experience of arousal (Emotionalizing, Fantasizing), while a high score on the cognitive dimension is supposed to refer to difficulties in Identifying, Verbalizing and Analyzing emotions. For the SIB higher scores correspond with more discomfort (SIB-G) and a higher frequency of complaints (SIB-F).

* p value when compared to placebo ≤ 0.01.

** p value compared to placebo ≤ 0.002.

treated women (Freriks et al., 2013). We did neither find any differences in quality of life when comparing women with and without subjective virilization, nor a correlation between quality of life and the Ferriman and Gallwey score for hirsutism. Secondly, in our pediatric study we found that breast development was decelerated in the Ox treated groups (Menke et al., 2010a). One could hypothesize a negative effect of this experience on quality of life. However, the follow-up study after several years of treatment with adult estrogen dosages, did not reveal any differences in breast size. The current breast size did not correlate with quality of life and the women who reported a subjective delay of breast development during puberty as compared to peers were equally distributed over the Pl and Ox groups. Thirdly, we speculated about a positive effect of height (gain) on quality of life, but in our study height was not correlated with quality of life. This is in line with previous studies in TS showing no positive effects of GH treatment and/or increased height on quality of life (Amundson et al., 2010; Boman et al., 2004; Carel et al., 2005). Previously Bannink et al. reported that patient satisfaction with adult height correlated positively with quality of life (Bannink et al., 2006). We could not confirm this observation, since we found no differences in quality of life between patients with and without satisfaction with their adult height.

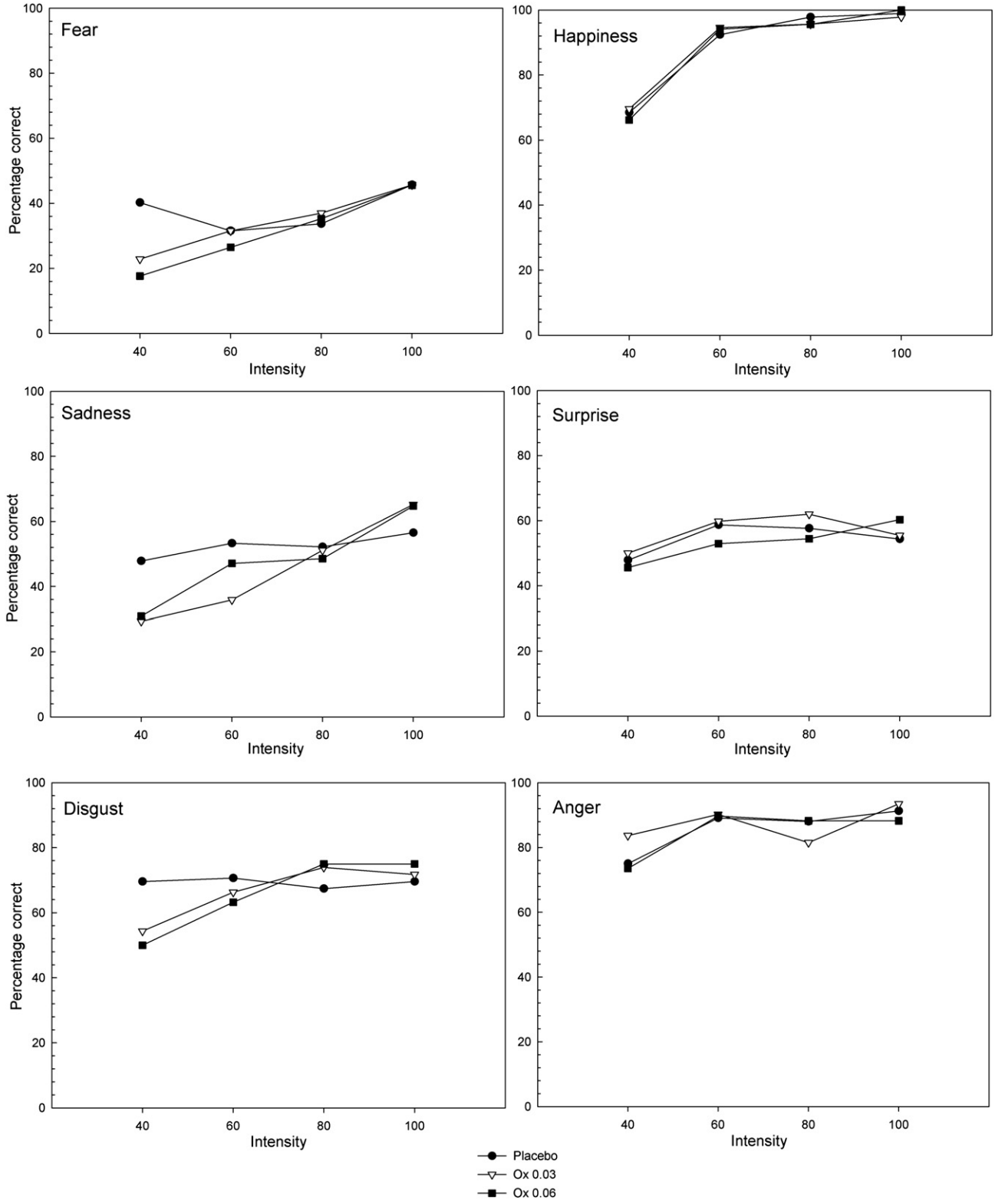

Fig. 2. Emotion recognition task performance. Mean performance of the three different treatment modalities (Pl, Ox 0.03 and Ox 0.06) for the six emotions and the four intensities (percentage emotional expression 40, 60, 80 and 100% respectively).

In this study, we found that Ox treated women only performed worse on the perception and labeling of fearful faces at low intensity with a large effect size for both the Ox 0.03 and 0.06 group. Previous studies showed that a typical female and male emotion perception profile can be defined: females typically recognized the emotions happiness, fear and sadness more easily, where male participants were more accurate in recognizing anger (Montagne et al., 2005). Although the effects of Ox in our study were small (besides the effect on the emotion fear, only a non-significant trend for the emotions sadness and disgust), Ox may induce a slight shift towards a less 'feminine' emotion perception (Montagne et al., 2005). An alternative explanation for the difference in emotion perception could be the

higher levels of anxious and depressive symptoms in the Ox treated groups, since it is known that these factors negatively influence the emotion perception (Demenescu et al., 2010). However, the differences in emotion perception found in the current study are small and these outcomes did not affect the interpersonal behavior as assessed with the SIB. Still, future studies using larger samples should include measure of emotion perception to examine these hypotheses in more detail.

In this follow-up study we found no effect on PIQ, nor on VIQ and TIQ. Furthermore, we found no effect on executive function and working memory, constructs that show conceptual overlap with performance intelligence tests that assess fluid intelligence (Roca et al., 2010). Probably the effect of Ox and other androgens on fluid intelligence tasks is only apparent during treatment, since others found differences during or directly after treatment (Ross et al., 2003, 2009; Zuckerman-Levin et al., 2009).

A higher frequency of sexual problems in adult TS women was previously reported (Sylven et al., 1993). In this study, we found no differences in sexual self-concept between the treatment groups. Consequently, Ox treatment during childhood does not seem to have a long-lasting effect on sexuality in adulthood.

A limitation of this study is the relatively small sample of patients, since not all participants of the original study participated in the follow-up study. In this light, selection bias might have occurred towards 'psychologically better performing' women. However, loss to follow-up did not differ between the treatment groups.

This is the first study to explore the long-term (neuro)psychological effects of Ox treatment in childhood and the effects seem to be limited. Our findings suggest that during late childhood and adolescence androgen treatment may influence cerebral function in an organizational way. Although even small differences may be of greatest interest from a scientific point of view, their clinical relevance is probably limited. As a result, we certainly would not advice against the use of Ox – in low doses – in clinical practice. However, awareness of potential psychological consequences of androgen use in girls with TS is encouraged. Future studies in larger cohorts should include evaluation of quality of life and social–emotional functioning. These studies will hopefully also shed light on the differential effects on aspects of quality of life in TS.

In conclusion, our exploratory data show that treatment with Ox in childhood and adolescence has only limited long-term effects on feelings of anxiety and depression, and emotion perception of fearful faces. No late effects on overall quality of life or neurocognition were present. Therefore, we would not advise against the use of Ox in girls with TS as a growth-enhancing drug. Future research during and after androgen treatment in larger samples is necessary to establish the exact effect of Ox and to improve the understanding of the underlying pathophysiology.

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