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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