CLINICAL STUDY

Cognitive effects of aromatase inhibitor therapy in peripubertal boys

M Hero*, S Maury^{1,*}, E Luotonen¹, E Service^{1,2,†} and L Dunkel^{3,†}*Hospital for Children and Adolescents, University of Helsinki and Helsinki University Central Hospital, PO Box 448, FIN-00029 HUS Helsinki, Finland,**¹Department of Psychology, University of Helsinki, PO Box 9, FIN-00014 Helsinki, Finland, ²Department of Psychology and McMaster University, University of Helsinki, Hamilton, Ontario L8S4L8, Canada and ³Department of Paediatrics, Kuopio University Hospital and University of Eastern Finland, PO Box 1777, FIN-70210 Kuopio, Finland**(Correspondence should be addressed to M Hero; Email: matti.hero@hus.fi)*

*(M Hero and S Maury are joint first authors)

†(E Service and L Dunkel are joint last authors)

Abstract

Objective: Aromatase inhibitors, blockers of oestrogen biosynthesis, have emerged as a new potential treatment modality for boys with short stature. The cognitive effects of such therapy are unknown. In this study, we explored the effects of aromatase inhibition on cognitive performance in peripubertal boys.

Design: Prospective, double-blind, randomised, placebo-controlled clinical study.

Methods: Twenty-eight boys, aged 9.0–14.5 years, with idiopathic short stature were treated with the aromatase inhibitor letrozole (2.5 mg/day) or placebo, for 2 years. During the treatment, the progression of physical signs of puberty and the concentrations of sex hormones were followed up. A selection of cognitive tests, focusing on memory function, was administered to the participants at entry, at 12 months and at 24 months after the start of the treatment.

Results: Letrozole effectively inhibited the conversion of androgen to oestrogen, as indicated by high serum testosterone and low serum oestradiol concentrations in letrozole-treated boys who progressed into puberty. In both the groups, there was a gain in performance during the follow-up period in tests of verbal performance, in most of the tests of visuospatial performance and in some tests of verbal memory. No significant differences between the letrozole- and placebo-treated boys in development of cognitive performance were found in any of the tests during the follow-up period.

Conclusions: Our results suggest that blockade of oestrogen biosynthesis with an aromatase inhibitor does not influence cognitive performance in peripubertal males.

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Introduction

Several lines of evidence suggest that oestrogen is involved in the regulation of cognitive function. Previous studies with premenopausal women after ovariectomy and with postmenopausal women have suggested that oestrogen replacement therapy may improve memory (1–4) and decrease the risk of dementia (5, 6). The most extensive studies to date have, however, failed to confirm these associations (7, 8). While some observational studies have reported global improvement in cognitive function after oestrogen replacement therapy (9, 10), most commonly, improvements have been found on measures of verbal memory (4, 11). Further supporting a role for oestrogen in the modulation of verbal functions, performance in some verbal tasks and oestrogen levels have been observed to change in parallel in women during the menstrual cycle (12).

Data from recent neuroanatomical and neurophysiological studies add plausibility to findings in

interventional and observational studies in females. Oestrogen receptors (ERs) are present in the telencephalic regions of the brain, and particularly, ER β has been localised in the hippocampus, a brain area known to be important in memory function (13). In addition, temporal lobe neurons are capable of synthesising oestrogen locally through aromatisation of circulating androgenic precursors (14).

Relatively few studies have assessed the significance of oestrogen in the regulation of cognitive function in males. In one study, testosterone treatment improved spatial and verbal memory function in healthy old males, whereas the combination of testosterone and the aromatase inhibitor anastrozole treatment was associated with improved spatial memory, but no change was associated with verbal memory (15). Thus, in men, direct androgen effects may be more important in the regulation of spatial memory functioning, and oestrogen effects appear to be more important in the regulation of verbal memory (15).

The role of oestrogen in the regulation of cognitive function in males during childhood or adolescence is currently unknown. In the present randomised, placebo-controlled, double-blind study, peripubertal boys with idiopathic short stature (ISS) were treated for 2 years with the aromatase inhibitor letrozole, a potent blocker of oestrogen biosynthesis. As there was a concern that suppression of oestrogen production could affect cognitive abilities, particularly verbal memory, the boys' performance in cognitive tests focusing on memory function was followed up during the treatment. The primary goal for the hormonal intervention was to study whether inhibition of oestrogen biosynthesis results in increased growth potential.

Participants and methods

Participants

The study population consisted of boys with ISS, who had been followed up at the outpatient clinic for paediatric endocrinology at the Hospital for Children and Adolescents, University of Helsinki, Finland. The selection of participants and study protocol has been reported in detail previously (16). In short, the inclusion criteria were calendar age of 9.0–14.5 years, height ≤ -2 s.d. or height at least 2 s.d. below the midparental target height. The exclusion criteria were bone age of more than 14 years, signs or symptoms of chronic illness or endocrine disorder.

Participants were classified prepubertal, if their testis volume was ≤ 2 ml at the end of the study, and pubertal if their testis volume was > 2 ml at 18 months after the onset of treatment. According to these criteria, 6 out of 15 and 5 out of 13 boys remained prepubertal, while 9 out of 15 and 8 out of 13 boys progressed into puberty in the letrozole and placebo groups respectively. At 24 months, the letrozole-treated pubertal boys had reached a median Tanner G-stage of 4 (range 2–5) and Tanner P-stage of 4 (1–5). At the same time-point, the placebo-treated pubertal boys had reached the Tanner G-stage of 3 (2–4) and the P-stage of 2 (1–4). Initially, 31 boys with ISS were recruited, with 28 boys completing the 24-month follow-up of cognitive performance. One boy was diagnosed with diabetes mellitus 6 months after the start of treatment, one boy was excluded due to poor compliance, and another was excluded due to poor reading skills.

At baseline, no differences in calendar age, bone age, pubertal stage, testis volume, serum testosterone or serum oestrogen concentrations were observed between the letrozole- and placebo-treated boys (Table 1). In the group receiving letrozole, one boy needed remedial education due to learning difficulties. In the placebo group, one boy had results suggesting mild intellectual disability in the neuropsychological tests, and one boy was suspected of having foetal alcohol syndrome. The remaining 25 boys attended normal school and had no

Table 1 Baseline characteristics in study participants. Values are means (s.d.), except for Tanner pubertal stage, which is median (range).

	Letrozole (n=15)	Placebo (n=13)
Age (years)	11.1 (1.7)	11.1 (1.5)
Bone age (years)	9.1 (2.4)	9.0 (1.8)
Stage of puberty		
G	1 (1–3)	1 (1–2)
P	1 (1–2)	1 (1)
Testis volume (ml)	1.3 (1.1)	0.9 (0.5)
S-testosterone (nmol/l)	1.1 (1.6)	0.4 (0.4)
S-oestradiol (pmol/l)	12.5 (5.4)	16.2 (5.8)

No statistically significant differences between the groups were found. G (Tanner genital stage), P (Tanner pubic hair stage).

findings suggestive of neurological or psychological difficulties. All the 28 participants were included in the analyses in order to gain sufficient statistical power. The results remain essentially the same if the three boys suffering from neuropsychological symptoms are excluded.

As reported previously (16), letrozole treatment in participants who reached puberty during the study resulted in high testosterone concentrations, while the pubertal increase in oestradiol was inhibited (Table 2). In contrast, in prepubertal boys, the concentrations of circulating sex steroids remained low, and did not differ between the letrozole and placebo groups (Table 2).

Study protocol

The boys were randomised in a double-blind manner to receive either aromatase inhibitor letrozole (Lz, Femara, Novartis AG), a potent inhibitor of oestrogen synthesis (17), 2.5 mg orally once daily, or placebo (Pl) orally once daily for 24 months. The participants were examined at entry and every 6 months thereafter. Follow-up visits included a physical examination, evaluation of pubertal stage according to Tanner (18), and venous blood sampling for measurement of serum testosterone and oestradiol. A selection of cognitive tests (see below), focusing on memory function, was administered to the participants at entry, at 12 months and at 24 months after the start of follow-up. The researchers and participants were blinded to treatment assignment for the duration of the study. The study protocol was approved by the ethical committee of the Hospital for Children and Adolescents, and by the National Agency for Medicines. Before the initiation of treatment, written informed consent was obtained from each participant and his guardian(s).

Biochemical measurements

The venous blood samples were drawn between 0730 and 1000 h. Serum testosterone and serum oestradiol concentrations were measured from sera stored at -20°C until required. Serum testosterone

Table 2 Serum concentrations of testosterone and oestradiol in boys who progressed in puberty and in those who remained prepubertal during the follow-up. Values are mean (s.d.).

	Letrozole			Placebo			<i>P</i>
	Months						
	0	12	24	0	12	24	
Pubertal boys							
Testosterone (nmol/l)	1.7 (2) (<i>n</i> =9)	24.9 (16)	30.9 (17)	0.5 (1) (<i>n</i> =8)	2.6 (3)	8.9 (6)	<0.05
Oestradiol (pmol/l)	11.6 (5) (<i>n</i> =9)	11.9 (4)	13.0 (6)	15.4 (5) (<i>n</i> =8)	14.2 (7)	22.1 (12)	0.06
Prepubertal boys							
Testosterone (nmol/l)	0.1 (0.1) (<i>n</i> =6)	0.2 (0.1)	0.5 (0.4)	0.2 (0.02) (<i>n</i> =5)	0.2 (0.1)	0.8 (0.8)	NS
Oestradiol (pmol/l)	13.7 (5.7) (<i>n</i> =6)	11.4 (4.4)	9.8 (3.6)	17.6 (6.8) (<i>n</i> =5)	13.3 (3.0)	10.1 (8.4)	NS

P value refers to difference between the groups, as analysed by ANOVAs. Values of the pubertal boys have been previously published (16).

concentrations were determined using a modified RIA, as described previously (19). The sensitivity of the assay was 0.03 nmol/l. The inter-assay coefficient of variation (CV) was 16% for a concentration of 0.2 nmol/l, and below 10% for concentrations above 0.8 nmol/l. The intra-assay CV was 11% for a concentration of 0.2 nmol/l, and below 7% for concentrations above 0.4 nmol/l. Serum oestradiol concentrations were quantified using a modified RIA (Spectria E2, ORION Diagnostica, Espoo, Finland) with a detection limit of 4.5 pmol/l, as described previously (20).

Cognitive test materials

Cognitive tests of verbal and visuospatial performance as well as of verbal and visuospatial memory and working memory were administered. Four graduate psychology students with testing experience performed the testing.

Verbal performance was measured using two subtests, Similarities and Comprehension, from the Finnish version of the Wechsler Intelligence Scale for Children-III (WISC-III) (21, 22). The WISC-III is a widely used, individually administered test battery for cognitive assessment of children between ages of 6 and 16 years.

Visuospatial performance was assessed with the Block design subtest from the WISC-III (22), immediate copying of the Rey-Osterrieth Complex Figure and a mental rotation task. In the latter, the participants were shown rotated letters on a computer screen and were instructed to indicate by pressing one of two keys on the keyboard whether the letters were presented correctly or as mirror images. Accuracy (hit rate) and reaction time were recorded.

Verbal memory was evaluated with the List Learning subtest of the Finnish version of the NEPSY Developmental Neuropsychological Assessment (23, 24), where the participants had to recall over five trials an auditorily presented 15-item wordlist. In addition, immediate and delayed recall of a story were assessed by administering the Story subtest from the WMS-R (25, 26) for the participants who were 11 years or older at the beginning of the follow-up period. For the participants under the age of 10 years, a similar subtest,

Narrative Memory, from the NEPSY (23) was used. This was done, because the NEPSY test is aimed at children between 3 and 12 years old, and the story was thought to be too simple and childish for the older participants, whereas the WMS-III Story subtest was assumed to be too complicated for the younger children. Scoring followed respective test manuals.

Two different aspects of verbal working memory were evaluated. Phonological short-term memory was first assessed with auditory forward and backward Digit Spans from the WISC-III (21, 22) following the prescribed scoring procedure. It was further investigated in a pseudoword span task (modified from (27); see (28)) by administration of two-syllable pseudowords in lists of increasing length for immediate serial recall. Testing was stopped at the longest sequence for which the participant got at least three of five trials correct. The score was the number of correctly recalled sequences. In a complex span task (modified by Numminen *et al.* (29) from Daneman & Carpenter (30)) and loading on the executive functions of working memory, the participants had to indicate whether a sentence that they heard was true or false in relation to a picture presented on a computer screen, while, simultaneously, trying to memorise the last words of the sentences. Set size, i.e. number of sentences (and last words) increased from two to six, with four trials at each set size. Testing was stopped when participants failed to remember at least two sequences out of four at a certain set size. The score was the number of correctly recalled last word sequences.

Visuospatial memory was assessed by delayed memory reproduction of the Rey-Osterrieth Complex Figure, following an intervening verbal task. Both copying and recall were scored for number of reproduced units (max. 36), so that the perception and memory components could be differentiated (31).

Statistical analysis

In order to analyse group differences in hormone levels as well as the neuropsychological tests over time, mixed ANOVAs were used, with treatment group (letrozole/placebo) as a between-subjects variable and observation

time (baseline/1 year/2 years) as a within-subjects factor. Bidirectional P values of <0.05 were considered statistically significant. Differences in baseline characteristics between the treatment groups were analysed by t -tests.

Results

Performance in cognitive tests

Results from mixed ANOVAs for tests in visuospatial and verbal performance are summarised in Table 3. For comparability with tasks lacking age norms, raw values were used in analyses unless otherwise stated. Analysis of age-adjusted cognitive test data produced similar results.

The letrozole- and placebo-treated groups differed overall in verbal performance, the letrozole group scoring lower at baseline and throughout the observation interval. This difference was significant ($P<0.05$) for the Similarities test and approached significance for the Comprehension test ($P<0.1$). Verbal performance improved in both the groups during the follow-up period (main effect of treatment time $P<0.001$ and $P<0.05$ for the Similarities and Comprehension tests respectively). No significant group-treatment-time interactions were observed.

In none of the visuospatial performance tests, significant differences were found in overall performance between the groups. Neither were there any significant interactions between group and treatment time. Performance in both the groups improved significantly during the follow-up period in Block design ($P<0.0001$) and the Rey-Osterrieth Complex Figure Copying tasks ($P<0.05$). The accuracy score (hit-rate) for the Rotation task increased slightly only in the letrozole group. However, reaction times in the Rotation task got faster for both the groups ($P<0.005$).

Effect sizes (Cohen's d) for group differences in change over time were in the low range with two exceptions. In Block design, a moderate effect size ($d=0.58$) suggested slightly greater improvement in the placebo group. However, accuracy in the Rotation task showed the opposite pattern with greater improvement for the letrozole group ($d=0.51$), suggesting that both small effects were spurious.

Raw scores from the tests of verbal and visual memory are depicted in Fig. 1. For the Story test only standard scores were available because different versions of the test were administered to boys of different ages. A mixed ANOVA, with treatment group as a between-subjects variable and observation time as within-subjects factor, did not reveal a significant main effect of group for any of the memory tests, nor were there group-observation time interactions. In both the groups there were significant gains in performance in List Learning ($P<0.01$), recall of the Rey-Osterrieth Complex Figure ($P<0.01$), Digit Span forwards ($P<0.001$) and Digit Span total points ($P<0.05$) during the follow-up period. In the Complex Span, Pseudoword Span, Story and Digit Span backwards tasks, neither of the groups showed significant improvement. Effect sizes (Cohen's d) for differences between groups in change over time were in the low range except for Digit span total points, which showed an effect size of $d=0.50$, indicating slightly greater improvement in the letrozole group.

Spearman correlations between change in the performance of cognitive tests (baseline measures subtracted from the 24-month follow-up performance) and serum testosterone and oestradiol concentrations were also tested. Neither the hormonal levels at the 24-month follow-up, nor the change in hormonal concentrations during the observation interval, correlated significantly with change in cognitive test performance.

Table 3 Cognitive performance during 2-year treatment with letrozole or placebo. Values are mean (s.d.).

	Letrozole			Placebo			P^a
	Baseline	Year 1	Year 2	Baseline	Year 1	Year 2	
Verbal performance							
Similarities (WISC-III)	13.7 (4.7) ($n=15$)	14.7 (4.3) ($n=15$)	16.3 (4.1) ($n=15$)	17.5 (4.9) ($n=13$)	17.6 (4.3) ($n=12$)	20.0 (5.5) ($n=13$)	0.70 ($n=27$)
Comprehension (WISC-III)	15.7 (5.3) ($n=15$)	15.9 (6.4) ($n=15$)	18.3 (4.8) ($n=15$)	19.3 (7.1) ($n=13$)	21.3 (6.7) ($n=12$)	21.2 (6.3) ($n=13$)	0.22 ($n=27$)
Visuospatial performance							
Rotation task hits	66.1 (14.5) ($n=15$)	67.3 (14.0) ($n=15$)	70.0 (11.6) ($n=14$)	72.2 (13.7) ($n=13$)	73.9 (13.0) ($n=11$)	71.5 (11.1) ($n=12$)	0.61 ($n=25$)
Rotation task RT (ms)	1706 (579) ($n=14$)	1433 (731) ($n=14$)	1212 (405) ($n=14$)	1684 (579) ($n=10$)	1417 (434) ($n=10$)	1032 (214) ($n=10$)	0.82 ($n=24$)
Block design (WISC-III)	44.0 (9.0) ($n=15$)	46.9 (9.0) ($n=15$)	54.3 (7.9) ($n=15$)	38.8 (13.6) ($n=13$)	46.4 (15.1) ($n=12$)	53.3 (13.8) ($n=13$)	0.16 ($n=27$)
Rey-Osterrieth (copying)	29.1 (5.2) ($n=15$)	30.5 (4.1) ($n=15$)	30.4 (4.2) ($n=15$)	25.4 (9.9) ($n=13$)	28.5 (7.9) ($n=12$)	29.3 (7.5) ($n=13$)	0.35 ($n=27$)

^aANOVA comparing Lz and placebo groups.

Figure 1 Mean cognitive performance in tests of verbal (1–4) and visuospatial (5) memory in peripubertal letrozole (black squares)-versus placebo (white diamonds)-treated boys with idiopathic short stature, at the beginning of treatment, and after 12 and 24 months. Error bars indicate S.E.M.

Discussion

In the present randomised, double-blind, placebo controlled study, cognitive performance during modulation of sex hormone milieu with an aromatase inhibitor was examined for the first time in boys during childhood and adolescence. Despite significant blockade of the aromatase enzyme, we could not detect any treatment-associated deterioration of cognitive performance in the aromatase inhibitor letrozole-treated boys compared with a placebo group. In particular, no significant differences in verbal memory development were found between the treatment groups. Thus, blockade of oestrogen biosynthesis may not impair cognitive abilities in peripubertal boys. This finding is of clinical relevance, since aromatase inhibition is a potential new treatment modality for short stature (32), and therefore there is a need to characterise the safety of such treatment during childhood and adolescence.

To our knowledge, to date only three other studies have addressed the influence of aromatase inhibitor treatment on cognitive function in humans. In a cross-sectional pilot study of postmenopausal women with breast cancer, treatment with the aromatase inhibitor anastrozole was associated with a specific deficit in verbal memory performance (33). In contrast, a prospective, double-blind, placebo-controlled study of the same compound in a comparable cohort of patients found no difference in cognitive performance between the placebo and anastrozole groups (34). A recent study of healthy older men receiving testosterone in combination with anastrozole, or placebo, found that testosterone treatment enhanced verbal memory performance only in those who received placebo (15). Thus, although available data is limited and controversial, it is reasonable to postulate that inhibition of oestrogen biosynthesis adversely influences verbal memory function in both sexes, at least at the older age. Indeed evidence from recent basic research suggests that oestrogen exerts significant neuromodulatory, neurotrophic and neuroprotective effects on the brain (35–37). Furthermore, recent studies with mice have indicated that oestrogen improves hippocampus-dependent memory functions, regulates hippocampal synaptic plasticity and increases synaptic proteins specifically through activation of $ER\beta$ (ESR2) (38). These findings provide a physiological background to studies of oestrogen-related modulation of cognitive performance also in humans, since $ER\beta$ is abundant also in the hippocampus of the human brain (39). According to the manufacturer's information, letrozole also diffuses to the brain and may therefore inhibit *in situ* aromatisation of androgenic precursors.

Resulting from enhanced gonadotrophin secretion (16), letrozole treatment in our sample of boys with ISS was associated with significant stimulation of gonadal testosterone production after the start of puberty. Interestingly, this did not seem to influence their spatial

abilities. Based on findings in healthy older men treated with testosterone and anastrozole (15), androgens are positively associated with spatial performance. Moreover, findings in a previous study of androgen treatment in men with either idiopathic or acquired hypogonadotropic hypogonadism suggest that androgens favourably influence spatial abilities through a permanent organising effect on the brain before or at puberty (40).

The strength of the current study is its prospective, placebo-controlled, double-blind study design and relatively long duration of treatment and follow-up of cognitive performance. Despite the relatively small sample size, our results justify optimism concerning the absence of negative effects of aromatase inhibitor treatment as such effects were not only statistically non-significant, but the absolute effect sizes were very small or favoured the treatment group. However, treatment effect on cognitive performance in males particularly during late puberty cannot be ruled out, considering the heterogeneity in pubertal maturation in our population. In our study, 86% of the boys were prepubertal at the start, and 39% remained prepubertal after 2 years of treatment. Despite the neutral findings of the current study, letrozole remains an experimental treatment for growth disorders, particularly due to its possible adverse effects on bone. Letrozole appears to suppress bone turnover and stimulate cortical bone growth in pubertal males (41), and the treatment may predispose boys to vertebral deformities (42).

In conclusion, our findings suggest that treatment with the aromatase inhibitor letrozole has no significant influence on cognitive performance in peripubertal boys. However, further studies with larger sample size and adequate power are needed to conclusively establish the impact of oestrogen on cognitive functions in males during adolescence.

Declaration of interest

All authors declare that there is no financial or other conflict of interest.

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