

Associations of IGF-1 and adrenal androgens with cognition in childhood

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Short title: Associations of IGF-1 and adrenal androgens with cognition

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1. Abstract

Background: Little is known about the association between adrenarche and cognition in general populations of children. We therefore studied the associations of dehydroepiandrosterone sulfate (DHEAS), androstenedione (A4), testosterone, insulin-like growth factor-1 (IGF-1), and adrenarche with cognition among prepubertal children.

Methods: These cross-sectional analyses are based on baseline data of the Physical Activity and Nutrition in Children Study. A total of 387 children (183 girls, 204 boys) were included in the analyses. The Raven's Coloured Progressive Matrices (CPM) score was used to assess non-verbal reasoning. Serum adrenal androgens and IGF-1 concentrations were measured and clinical signs of androgen action were evaluated.

Results: Higher IGF-1 among boys ($\beta = 0.149$, $P = 0.033$) was related to a better Raven's CPM score after adjustment for age and parental education. Adrenal androgens in girls or boys or IGF-1 in girls were not associated with the score. There were no differences in Raven's CPM score between children with biochemical adrenarche (DHEAS ≥ 1.08 $\mu\text{mol/L}$; ≥ 40 $\mu\text{g/dL}$) or with clinical signs of androgen action and children without them.

Conclusion: The results suggest that higher serum IGF-1 among boys is related to better cognition in prepubertal children. We could not provide evidence for the associations of adrenal maturation with cognition in prepubertal children.

Clinical Trial Registration Number: NCT01803776

2. Introduction

Dehydroepiandrosterone (DHEA) and its sulfate (DHEAS) are abundant steroid hormones and androgen precursors produced by adrenal cortex. DHEAS has been suggested as an important neurosteroid that promotes neuroneogenesis, neuronal growth, and neuronal survival by its antioxidative, anti-inflammatory, and antiglucocorticoid effects [1,2] Serum DHEAS levels have been positively correlated with global cognition, working memory, attention, and verbal fluency in some studies among adults [3,4]. However, studies on DHEA supplementation have failed to improve cognitive function in adults [1], except one study in young men who were treated with high doses of DHEA [5]. Moreover, DHEA treatment has not improved cognitive function in Addison`s disease patients [6].

Adrenarche refers to an increase in the secretion of DHEA and DHEAS during maturation in mid-childhood [7]. It occurs at the same time as the growth in brain volume ceases [8] and the cortical brain maturation begins [9]. There are few studies on the association between DHEAS and cognition in children. There is some evidence that higher salivary DHEA levels are associated with better visual attention [10] and better working memory but lower performance in spatial working memory [11] in children and adolescents. However, prepubertal girls with premature adrenarche had no differences in cognitive measures such as intelligence quotient (IQ) and executive functioning compared to on-time girls [12]. It has also been suggested that an increased serum concentration of DHEA at around seven years of age enables maintaining synaptic plasticity [2,13].

Major adrenocortical androgens are DHEA, DHEAS, and androstenedione (A4), of which a small portion is converted further to testosterone [14]. Prepubertal children with premature adrenarche demonstrate also elevated serum insulin-like growth factor-1 (IGF-1) levels [15]. IGF-1 has been found to increase the production of adrenal androgens, such as DHEAS, in cultured human adrenocortical cells [16]. Increased circulating IGF-1 concentration has been associated with enhanced neurogenesis, learning, and memory [17]. Serum IGF-1 levels have been directly associated with an IQ in children

aged 7-8 years [18]. Moreover, there is some evidence that a decrease in serum IGF-1 levels is associated with a decline in cognition among older adults [19].

Androgens may play an important role in cortical maturation and cognitive development during mid-childhood [2,8,9] . However, little is known about the association between adrenarche and cognition in general populations of children. Therefore, we studied the associations of serum DHEAS, serum A4, serum testosterone, serum IGF-1, biochemical adrenarche, and clinical signs of androgen action with cognition among prepubertal children aged 6–8 years.

3. Material and methods

3.1. Study design and population

The present analyses are based on baseline data of the Physical Activity and Nutrition in Children (PANIC) Study which is a physical activity and dietary intervention study in a population sample of primary school children from the city of Kuopio in Finland (Clinical Trial Registration Number: NCT01803776).

Altogether 736 children 6-8 years of age from 16 schools of the city of Kuopio were invited to participate in the study. Of these children, 512 (70%) participated in the baseline examinations in 2007-2009. The participants did not differ in age, sex distribution, or body mass index standard deviation score (BMI SDS) from all children who started the first grade in the primary schools of Kuopio in 2007–2009 based on comprehensive data obtained from school health examinations.

The exclusion criteria for the present analyses were central puberty, acute or major illness, and any long-term medication that could have an effect on adrenal function. We also excluded one child who had a serious delay in cognitive function observed by a physician, 21 children who were born before gestational age < 37 weeks, and 12 children with a birth weight standard deviation score (SDS) ≤ -2.0 . A total of 387 children (183 girls, 204 boys) had data on variables used and were included in the present analyses.

3.2. Assessment of cognition

Raven's Coloured Progressive Matrices (CPM) was used to assess non-verbal reasoning [20]. One trained researcher administered the assessments. Raven's CPM includes 36 large figures with a part missing. The children were asked to select a correct part that completes the figure from six alternatives presented beneath the large figure. Raven's CPM requires the ability to find similarities, differences, and discrete patterns, does not depend on acquired knowledge or language skills [20], and has been suggested to represent all-core components of executive functions, such as inhibition and interference

control, working memory, and cognitive flexibility [21]. The Raven's CPM score was the number of correct answers, ranging from 0 to 36, a higher score indicating better cognition. A majority of children (87.3%) performed the Raven's test between 12 am and 4 pm.

3.3. Assessment of body size and pubertal signs

Body weight was measured twice after an overnight fast, bladder emptied, and standing in light underwear by InBody[®]720 bioelectrical impedance device (Biospace Co. Ltd., Seoul, Southern Korea) to accuracy of 0.1 kg. The mean of these two values was used in the analyses. Height was measured three times in the Frankfurt plane without shoes using a wall-mounted stadiometer to accuracy of 0.1 cm. The mean of the two nearest values was used in the analyses. BMI was calculated as weight (kg) divided by height (m) squared. Height SDS and BMI SDS were calculated according to the Finnish growth references [22]. Information on gestational age at birth, birth length and weight were obtained from Kuopio University Hospital records and birth weight SDS and birth height SDS were calculated according to Finnish growth reference data [23].

Central gonadotropin-dependent puberty was defined by a clinical examination as breast development at ≥ 2 for girls and testicular volume ≥ 4 ml assessed using an orchidometer for boys. Clinical signs of androgen action, including adult type body odor, oily hair, acne, comedones, and pubic or axillary hair, were evaluated by a specifically trained physician; body odor and oiliness of the hair were also assessed by asking about them from the parents.

3.4. Assessment of IGF-1 and adrenal androgens

Serum samples were taken after an overnight fast and kept deep frozen until analyzed. Serum DHEAS concentrations were determined using an ELISA kit (Alpha Diagnostic International, San Antonio, TX, USA). The intra-assay coefficient of variation (CV) of the DHEAS method was 7.5-11.5% and the inter-

assay CV was 7.0-11.0%. Serum IGF-1 concentrations were determined using an ELISA kit (Mediagnost, Reutlingen, Germany). The intra-assay CV of the IGF-1 method was 5.1-6.6% and the inter-assay CV was 7.7-9.2%. A4 and testosterone were determined by liquid chromatography-tandem mass spectrometry as previously reported [24].

3.5. Assessment of parental education

The parents were asked to report their highest completed or ongoing educational degree (vocational school or less, polytechnic, or university). The degree of the more educated parent was used in the analyses.

3.6. Statistical methods

The SPSS statistical analysis software, Version 24.0 (IBM Corp., Armonk, NY, USA), was used in the statistical analyses. We compared basic characteristics between girls and boys using the Student's *t* test, the Mann-Whitney's *U* test, or the Chi-square test. The associations of IGF-1, DHEAS, A4 and testosterone with the Raven's CPM score were investigated using the linear regression analysis adjusted for age, sex, and parental education in all children and adjusted for age and parental education in girls and boys separately. The associations of IGF-1 and adrenal androgens with the Raven's CPM score were adjusted further for BMI SDS or birth weight SDS in all analyses. We compared the Raven's CPM score between children with higher serum DHEAS levels $\geq 1.08 \mu\text{mol/L}$ ($\geq 40 \mu\text{g/dL}$), which has been suggested as the definition for biochemical adrenarche [25], and children with lower DHEAS levels $< 1.08 \mu\text{mol/L}$ ($< 40 \mu\text{g/dL}$) using the general linear model adjusted for age, sex, parental education, and birth weight SDS in all children and adjusted for age, parental education, and birth weight SDS in girls and boys separately. We used the general linear model to compare the Raven's CPM score between children with clinical signs of adrenarche and children without them adjusted for age, sex, parental education, and birth weight SDS in all children and adjusted for age, parental education, and birth weight SDS in girls and boys separately. There were only 10 children with premature adrenarche [DHEAS $\geq 1.08 \mu\text{mol/L}$ ($\geq 40 \mu\text{g/dL}$)] and clinical signs of androgen action in a

girl aged < 8 years or in a boy < 9 years in our study population. Therefore, we did not compare the Raven's CPM score between children with premature adrenarche and those without it. Associations with $P < 0.05$ were considered statistically significant.

4. Results

Boys were heavier and taller than girls at the age of 6-8 years and at birth (Table 1). Serum IGF-1 and testosterone were higher in girls than in boys, but serum DHEAS and A4 did not differ between sexes (Table 1).

Serum DHEAS, A4, or testosterone were not associated with the Raven's CPM score in all children adjusted for age, sex, and parental education or in girls or boys adjusted for age and parental education (Table 2). Further adjustment for BMI SDS or birth weight SDS did not change the result in all children, girls, or boys (Table 2).

Altogether 50 children (22 girls, 28 boys) had serum DHEAS $\geq 1.08 \mu\text{mol/L}$ ($\geq 40 \mu\text{g/dL}$). The Raven's CPM score did not differ between children with serum DHEAS $\geq 1.08 \mu\text{mol/L}$ [$\geq 40 \mu\text{g/dL}$ (mean 25, 95% confidence interval (CI) 23-24)] and children with serum DHEAS $< 1.08 \mu\text{mol/L}$ [$< 40 \mu\text{g/dL}$ (mean 24, 95% CI 24-26)] after adjustment for age, sex and parental education in all children ($P = 0.436$) or further for birth weight SDS ($P = 0.457$). Neither did the Raven's CPM score differ between these two groups in girls ($P = 0.868$) or boys ($P = 0.412$) after adjustment for age and parental education or further for birth weight SDS ($P = 0.855$ for girls and 0.430 for boys).

Altogether 62 children (43 girls, 19 boys) had clinical signs of adrenarche. The Raven's CPM score did not differ between children with clinical signs of adrenarche (mean 24, 95% CI 24-25) and children without them (mean 24, 95% CI 23-25) after adjustment for age, sex, and parental education ($P = 0.818$), or further for birth weight SDS ($P = 0.858$). Neither did the Raven's CPM score differ between these two groups in girls ($P = 0.574$) or boys ($P = 0.835$) after adjustment for age and parental education, or further for birth weight SDS ($P = 0.545$ for girls and 0.902 for boys).

Serum IGF-1 was not associated with the Raven's CPM score in all children adjusted for age, sex, and parental education or in girls after adjustment for age and parental education (Table 2). However, higher serum IGF-1 was related to a better Raven's CPM score in boys after adjustment for age and parental education ($\beta = 0.149$, $P = 0.033$). The association between serum IGF-1 and the Raven's CPM

score in boys was even stronger after further adjustment for BMI SDS ($\beta = 0.179$, $P = 0.016$; Table 2).

Adjustment for birth weight SDS instead of BMI SDS did not change the significance (Table 2).

5. Discussion and conclusion

We found that higher serum IGF-1 but not adrenal androgens were related to a better Raven's CPM score among boys. Neither IGF-1 nor adrenal androgens were related to the Raven's CPM score in girls. Furthermore, there were no differences in the Raven's CPM score between children with adrenarche and those without it.

Our observations on the association between higher IGF-1 and better cognition in boys is in line with the results of a previous study suggesting a positive association between IGF-1 and a verbal IQ in children aged 7-8 years [18]. Furthermore, increased serum IGF-1 concentration was related to improved executive functions measured by the Block design test and IQ in seven-year-old children undergoing a long-term growth hormone therapy [26].

An explanation for these findings may be that IGF-1 is widely expressed in the central nervous system and the growth hormone/IGF-1 axis is involved in brain growth, development, myelination, and plasticity [27]. IGF-1 has been found to increase the proliferation of progenitor cells and the formation of new neurons in hippocampus in experimental animal and in vitro studies [27,28]. Moreover, cerebral cortex has been suggested to be especially sensitive to the actions of IGF-1 [27]. IGF-1 could thereby improve learning and memory [17]. It has been suggested that the effects of IGF-1 on cognition are mediated by brain-derived neurotrophic factor (BDNF) and vascular endothelial derived growth factor (VEGF) interacting with energy supply, estrogen, and corticosterone [29,30]. However, the exact mechanisms behind the association between the growth hormone/IGF-1 axis and various cognitive functions during growth and maturation are still unknown.

We found that a higher serum IGF-1 concentration was related to a better Raven's CPM score among boys. Contrary to our results, the positive association between IGF-1 and cognition among children with a mean age of eight years in the Avon Longitudinal Study of Parents and Children (ALSPAC) study was stronger in girls than in boys. Children in the ALSPAC study were slightly older than children in our study. In addition puberty was not taken into account in the ALSPAC study. Boys reach peak cortical

thickness in the frontal area, which is involved in planning, organizing, and executive functions, approximately one year later than girls [31], at 12 years in boys and at 11 years in girls. Similarly, grey matter volume in parietal cortex reaches its peak volume about 1.5 years later in boys than in girls [31]. Serum IGF-1 was higher in girls than in boys in the present study among prepubertal children which is in line with the observations of previous studies [32,33]. Because IGF-1 stimulates cellular proliferation in the development of central nervous system [27], it is possible that boys with higher IGF-1 have more advanced brain maturation and better cognitive abilities than other boys.

The results of the ALSPAC study suggest that the link between IGF-1 and IQ in children, particularly in girls, is largely explained by parental education and socioeconomic position [18]. However, in the present study higher IGF-1 was related to better cognition in boys even after adjustment for parental education. We adjusted the results also for family income instead of parental education and this did not change the results (data not shown). Our findings may be due to a homogenous childhood environment and free higher education in Finland.

Increased circulating DHEAS levels have been linked to improved brain plasticity during growth and maturation [2,13]. Some earlier studies have found a positive association between salivary DHEA levels measured before a cognitive task and working memory in young women [34]. Higher DHEA levels in saliva have also been associated with better visual attention [10] and better working memory but lower performance in spatial working memory tasks in children and adolescents [11]. Moreover, higher serum DHEAS levels were associated with better executive function and working memory in women aged 18-75 years [3]. However, we observed no association between DHEAS or other adrenal androgens and cognition in girls or boys. This is in line with the observation of a previous study among 129 children five years of age that there was no correlation between DHEA in saliva and cognition [35]. The reason for not finding an association between DHEAS and cognition may be that we studied younger individuals and used different measures of cognition than other studies [3,10,34].

The results of our study are in accordance with Azurmendi et al. who found no association of A4 or testosterone with cognition in prepubertal children [35]. On the other hand, testosterone

concentrations have been associated with cerebral development, the findings being different in prepubertal girls and postpubertal boys, suggesting that central nervous system effects of androgens are sex-, age-, and also dose-specific [36].

There was no difference in the Raven's CPM score between children with clinical signs of adrenarche and children without them in the present study. In accordance with our findings, there was no difference in cognition between children with early adrenarche, defined by levels of DHEA and testosterone in saliva, and children with later adrenarche in one previous study [37] or in another study on girls with premature and on-time pubarche [12]. Nevertheless, girls with premature adrenarche have been observed to have better attention but poorer performance in verbal, working memory, and visuospatial tasks than girls with on-time adrenarche [38].

A strength of the present study is the relatively large population sample of girls and boys. We also had the opportunity to take parental education into account in the analyses. Although we used a well-defined method to measure cognition, a more comprehensive testing of different components of cognitive functions would have provided more information on the associations of adrenal androgens and IGF-1 with different aspects of cognition. The study had a cross-sectional design that does not allow us to make conclusions about causality of the relationships. Earlier results have been based on DHEA rather than DHEAS. It has been indicated that DHEA levels in brain are influenced by peripheral levels of both DHEA and DHEAS [39], although these hormones are produced also within the brain [1,40]. The blood-brain barrier is easily penetrable for DHEA but not for its sulfate form [40]. The activity of steroid sulfatase and the opposite influence of sulfotransferase have a significance for effects on the brain [40]. We did not study urinary steroid profile for overall adrenal androgen secretion neither did we measure insulin-like growth binding proteins (IGFBP), which can either inhibit or enhance the binding of IGF-1 to its receptor [27].

The results of the present study suggest that higher serum IGF-1 is related to better cognition among prepubertal boys. We could not provide evidence for the associations of DHEAS or clinical signs of adrenarche with cognition in prepubertal children.

6. Statements

6.1. Acknowledgements

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6.2. Ethics Statement

The study protocol was approved by the Research Ethics Committee of the Hospital District of Northern Savo. All children participating in the study and their parents gave their informed written consent. All experiments on human participants were conducted with the Declaration of Helsinki.

6.3. Disclosure statement

The authors have no conflicts of interest to disclose.

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interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

6.5. Author Contributions

Aino Mäntyselkä: data curation, formal analysis, investigation, methodology, validation, visualization, writing the original draft, and reviewing and editing. Eero Haapala: data curation, methodology, validation, and reviewing and editing. Virpi Lindi: data curation, funding acquisition, methodology, supervision, validation, visualization, reviewing and editing, and project administration. Merja R. Häkkinen: data curation, investigation, methodology, validation and reviewing and editing. Seppo Auriola: data curation, investigation, methodology, validation and reviewing and editing. Jarmo Jääskeläinen: methodology, funding acquisition, resources, supervision, validation, and reviewing and editing. Timo A. Lakka: funding acquisition, methodology, project administration, resources, software, supervision, validation, and reviewing and editing.

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