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Endocrine Dysfunction and Growth in Attention Deficit Hyperactivity Disorder

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1. Introduction

Scientific literature contains numerous accounts of possible hypothalamic - pituitary axis dysfunction in pediatric patients with various behavioral disorders and/or psychopathology. However, demonstrating any consistent pattern of endocrine dysfunction in these behavioral areas, if indeed such even exists, remains elusive. This chapter will review the literature regarding possible endocrine dysfunction in pediatric patients with ADHD and will focus on the two areas where publications have been the most prolific regarding possible interactions of hormones and behavior: (1) the hypothalamic - pituitary - adrenocortical axis and ADHD and (2) growth in children with Attention Deficit Hyperactivity Disorder. The chapter will conclude with a review of growth hormone therapy in children with ADHD, focusing primarily on ADHD children referred for poor growth and growth evaluation to a pediatric endocrine practice.

2. Hypothalamic - Pituitary - Adrenocortical Axis (HPAA) in behavior and ADHD

Variations in hypothalamic - pituitary - adrenocortical axis (HPAA) activity have been associated with or implied as a potential causative factor in a variety of psychopathology. Higher cortisol levels may be seen with aggressive/impulsive behavior whereas lower cortisol levels correlate more often with callous unemotional (CU) behavior. For example, significantly higher adrenal activity, both baseline and stress challenged, is found in five year old boys exhibiting hyperactivity, impulsivity and emotional difficulties than is found in boys without such behavior (Hatzinger et al., 2007). In reviewing older children and adolescents, Barzman et al also found higher cortisol levels to occur more often in conjunction with impulsive aggressive behavior, and lower cortisol levels with CU traits (Barzman et al., 2010). Similarly, Stadler et al. found lower stressed salivary cortisol responses in ADHD children who exhibited CU traits compared to ADHD children with lower CU traits (Stadler et al., 2011).

2.1 Dysregulation of Hypothalamic - Pituitary - Adrenocortical Axis Activity in behavior and ADHD

Hypothalamic - Pituitary - Adrenocortical Axis (HPAA) activity is known to vary with gender and age; gender specific differences in HPAA activity are found in children as young

as five years old, with girls having higher baseline and stressed adrenal activity compared to boys (Hatzinger et al., 2007). Recent studies increasingly support the idea that at least some varieties of ADHD are associated with dysregulation of the HPAA axis, particularly a reduced response to stressful stimuli (Ma et al., 2011, Anu-Katriina et al., 2011). Interestingly, similar reduced HPAA activity may be also found in people following significant acute traumatic events or with chronic stress (Anu-Katriina et al., 2011).

In some studies, ADHD subtypes are found to have both decreased baseline, wakening cortisol levels and a decreased response to stressful stimuli (Freitag et al., 2009). Freitag et. al. found these decreased wakening cortisol levels in ADHD children only when ADHD was also associated with comorbid oppositional defiant disorder (ODD). Diminished wakening cortisol was not observed in children with ADHD only or in children with ADHD plus conduct disorder or anxiety disorder (Freitag et al., 2009). In other studies, in this case 170 elementary school-age ADHD males, no differences in baseline, waking cortisol levels between ADHD subtypes could be demonstrated (Hastings et al., 2009).

In another study of 128 ADHD male children, age 6 – 14 years, Ma et. al. found that ADHD children with hyperactive impulsive traits (ADHD-HI) had significantly lower baseline (8:00 am) cortisol levels than in children with either ADHD-predominantly inattention type (ADHD-I) or ADHD-combined type (ADHD-C) (Ma et al., 2011). Further, the ADHD group as a whole had significantly lower baseline (8:00 am) cortisol levels compared to non-ADHD controls (226.47±129.12 nmol/L ADHD vs. 384.53±141.43 nmol/L controls, $P<0.001$. Despite these differences in cortisol levels, there were no significant corresponding differences in ACTH levels between the ADHD group as a whole vs. the non-ADHD control group ($P>0.05$).

Cortisol, a hormonal product of the adrenal glands, can be used as an indicator of hypothalamic - pituitary - adrenal -axis (HPAA) activity. In the above referenced study, lower cortisol levels in the ADHD group compared to non-ADHD controls without concurrent differences in ACTH secretion suggest a general disinhibition or dysfunction (under-reactivity) of HPAA activity in ADHD children as opposed to the general population. Finally, no differences were found in ACTH values between the various sub-groups of ADHD ($P>0.05$), despite the lower cortisol values found in the ADHD-HI subgroup, suggesting that even among patients with ADHD, some exhibit greater HPAA disinhibition than others (Ma et al., 2011).

Mothers of 272 eight-year-old children with ADHD were asked to rate their child's ADHD related behavior using such standard methods as the ADHD-IV Rating Scale and the Child Behavior Checklist (CBCL). The mothers' responses were then compared to diurnal salivary cortisol levels from the children in an attempt to correlate behavior with baseline, unstressed salivary cortisol. In contrast to some of the previously referenced studies, no correlations nor significant associations were found between unstressed diurnal cortisol levels and behavioral symptoms. Stressed, salivary cortisol responses to the Trier Social Stress Test for Children (TSST-C) were next evaluated, and differential stress responses were found, again suggesting dysregulated HPAA activity. Lower cortisol stress responses were seen in ADHD males with higher degrees of inattentive symptoms (ADHD-I) than in other ADHD males. Similarly, ADHD-I females had a more rapid fall in stress cortisol response than did other non-ADHD-I females (Anu-Katriina et al., 2011).

Perhaps not surprising and again emphasizing mind-body connection. increased stressed cortisol levels in response to venipuncture are greater in some ADHD children with

coexisting anxiety disorders than in those with comorbid disruptive behavior or oppositional problems (Hastings et al., 2009).

A summary of selected studies of the hypothalamic - pituitary - adrenocortical axis activity and associated behavior is presented in Table 1. The table compares the patient populations studied, the endocrine activity measured, associated diagnosis or behavioral traits selected by the researchers, and the qualitative results. Qualitative results are presented, rather than quantitative findings, in order to better compare and appreciate the differences in the studies.

2.2 Summary and therapeutic considerations

In summary, studies of hypothalamic - pituitary - adrenocortical axis activity in ADHD children have yielded conflicting results, likely due to the confounding variables of comorbidities, subtypes and heterogeneity of ADHD (Hastings et al., 2009); the variety of methods used to assess stress hormone activity; and current psychosocial conflicts such as parenting issues, family conflicts and stressful, acute life events, all of which can increase cortisol levels (Freitag et al., 2009) and affect the outcome of studies of hormonal levels and behavior. If further research is able to better clarify this complex interaction, measurements of hormonal levels may become a useful diagnostic adjunct to help select the most appropriate treatment modalities for pediatric behavioral disorders and aggression (Barzman et al., 2010).

Reference	Patient Population	Endocrine	Diagnosis or Associated Behavioral Traits	Result
Hatzinger et al., 2007	102 five-year olds, (59 boys, 43 girls)	Baseline adrenal activity	hyperactivity, impulsivity and emotional problems (boys); positive emotions (girls)	Increased adrenal activity vs. controls
	102 five-year olds, (59 boys, 43 girls)	Stress challenged adrenal activity	hyperactivity, impulsivity and emotional problems (boys); positive emotions (girls)	Increased adrenal activity vs. controls
Freitag et al., 2009	128 ADHD age 6–13 years; 96 control age 6–12 years	Cortisol awakening response	ADHD with and without comorbid oppositional defiant (ODD), conduct, or anxiety disorders	Decreased cortisol in ADHD with ODD group vs all other subgroups or controls
	128 ADHD age 6–13 years	Cortisol awakening response	ADHD with and without current psychosocial risk / stress factors	Increased cortisol with adverse parenting, family conflicts, acute life events
Hastings et al., 2009	170 ADHD boys, elementary school-age	Salivary cortisol at waking, baseline	ADHD with and without comorbid disruptive behavior and anxiety disorders	No differences in wakening, baseline cortisol levels between subgroups

	170 ADHD boys, elementary school-age	Salivary cortisol post stress	ADHD with and without comorbid disruptive behavior and anxiety disorders	Increased post stress cortisol in ADHD with anxiety disorders
Barzman et al., 2010	children and adolescents	Cortisol	impulsive, aggressive traits	Increased cortisol concentrations
	children and adolescents	Cortisol	callous, unemotional traits	Decreased cortisol concentrations
Stadler et al., 2011	36 boys with ADHD, age 8– 14 years	Salivary cortisol, pre and post stress	higher callous, unemotional traits vs. lower CU traits	Decreased HPAA activity in higher ADHD-CU vs. lower ADHD-CU
Ma et al., 2011	boys with ADHD, 6–14 years old	Baseline 8:00 am Cortisol	ADHD with hyperactive (HI); inattention (I); or combined traits	Lowest baseline cortisol in ADHD-HI vs. ADHD-I or ADHD combined traits
	boys with ADHD, 6–14 years old	ACTH levels	ADHD with hyperactive (HI); inattention (I); or combined traits	No difference in ACTH between subgroups
	boys age 6–14 years old	Baseline 8:00 am Cortisol	ADHD vs. non-ADHD controls	Lower baseline cortisol in ADHD vs. non-ADHD
	boys age 6–14 years old	ACTH levels	ADHD vs. non-ADHD controls	No difference in ACTH in ADHD vs. controls
Anu-Katriina et al., 2011	272 ADHD, age eight years	Diurnal salivary cortisol	ADHD-IV Rating Scale and the Child Behavior Checklist (CBCL)	No associations between behavioral symptoms and diurnal cortisol levels.
	272 ADHD, age eight years	Salivary cortisol post stress	ADHD-IV Rating Scale, CBCL, Trier Social Stress Test for Children (TSST-C)	Lower stressed cortisol in boys and girls with predominant ADHD-I

Abbreviations: ADHD = attention deficit hyperactivity disorder; ADHD-CU = ADHD with callous unemotional traits; ADHD-HI = ADHD with hyperactive impulsive traits; ADHD-I = ADHD-predominantly inattention type; ADHD-C = ADHD-combined type

Table 1. Hypothalamic - Pituitary - Adrenocortical Axis (HPAA) Activity in Behavior and ADHD

3. Growth in children with ADHD

3.1 Growth in non-medically treated ADHD children

Children with ADHD, with or without stimulant therapy, may have significantly decreased height, head circumference, percent body fat, and abdominal circumference,(Ptacek et al., 2009a, 2009b). In two studies Ptacek and colleagues demonstrated decreased nutritional status and lower stature in ADHD children compared to population normals. First, a comparison of non-medicated ADHD boys (n=46, average age 11.03 years) found significantly decreased percent body fat and height in a non-treated ADHD population (Ptacek et al., 2009a). Next, anthropometric measurements, including height, head circumference, percent body fat, and abdominal circumference, were determined in both medically-treated and non-treated ADHD boys (n=104, age 4-16 years). These measurements in the treated and non-treated groups were compared to a normal, non-ADHD population and demonstrated decreased percent body fat and abdominal circumference (markers for nutritional status) as well as decreased height and head circumference in the ADHD population vs. the population norms ($p<0.01$) regardless of treatment status (Ptacek et al., 2009b), suggesting that dysregulated growth may be caused by or at least associated with ADHD itself, independent of other factors.

In a review of 124 ADHD boys, height deficits were found only in early adolescent aged boys with ADHD. This early adolescent decline in growth then spontaneously improved by later adolescence or adulthood with no apparent effect on adult height. Although 89% of the ADHD patients had a history of pharmacologic therapy at some point, height deficits were unrelated to stimulant medication use or weight loss. The mean height SDS of the ADHD group was 0.21 compared to 0.47 in the controls ($p = 0.03$), and the adolescent aged related decline amounted to a mean height deficit of 2.1 cm compared to controls (Spencer et al., 1998).

3.2 Growth in stimulant medication treated ADHD children

Reductions in height, weight and / or body mass index are commonly reported with stimulant therapy use for ADHD (Faraone et al., 2008, Negrao & Viljoen, 2011), and may be worse in larger children, those who are naive to therapy or who have a greater cumulative exposure to stimulants (Faraone et al., 2010). Ptacek et al. found a lower percent body fat in medically treated ADHD males (age 4 – 16 years) as compared to non-treated peers (Ptacek et al., 2009b).

A quantitative review of published, longitudinal studies of stimulant-treated ADHD children found significant delays in height and weight over at least of year of treatment time (Faraone et al., 2008). To determine if such decreased growth also occurs in typical clinical scenarios in which patients are treated for longer periods of time in outpatient settings, the heights and weights of 84 ADHD children treated for two - three years continuously with methylphenidate from two community pediatric practices were examined. Growth parameters in treated ADHD children were compared to those of near-same age-matched, healthy siblings who did not have ADHD nor any other chronic condition. Height standard deviation (SD) scores were determined from at least one year prior to starting therapy and thereafter during therapy. Heights were similar pretreatment between boys with ADHD and their age-matched, non-ADHD siblings. During treatment, the height SD scores and

growth velocity of the methylphenidate treated boys declined while those of their siblings did not decline and remained constant or even increased. Methylphenidate treated girls showed similar decline in growth. Over time, treated ADHD boys lost about 0.5 SD in height (roughly 3-4 cm), and treated girls lost about 0.6 SD (3-4 cm) in height compared to age-, time- and gender-matched siblings. A clear dose-response curve of methylphenidate dose vs. growth decline was not found, and the authors did not address growth in non-stimulant medication treated ADHD children. However, this study did document a clear decline in growth over time in treated children seen in general practice (Lisska & Rivkees, 2003).

Other studies have found more mild and transient growth disruptions in ADHD children (Negrao & Viljoen 2011), and that even with stimulant treatment, associated growth deceleration and loss of expected height may amount to only a one to two centimeter deficit per year during treatment (Poulton, 2005, Drappatz et al., 2006). Comparison of paired height measurements, before and after ADHD treatment, suggest a height deficit of only about 1 cm/year during the first 1 to 3 years of ADHD treatment (Pliszka, 1998). Growth delay may also be dose dependent during treatment, normalizing afterwards (Faraone et al., 2008) with no long-term adverse effect even with high dose, aggressive stimulant therapy (Pliszka, 1998).

3.3 Side effects of stimulant medications and possible causes of growth delay

One of the most frequently reported side effects of stimulant medication use for ADHD is loss of appetite. Other commonly reported and usually relatively minor complaints include headaches, disturbances in mood and other emotional problems, stomach upset, sleep disturbances, and rashes (Tobaiqy et al., 2011). Far less common, but obviously more serious, concerns regarding stimulant medication use include suicidal ideation and sudden cardiac death (Graham et al., 2011).

Interestingly, although a controversial area among physicians and the subject of multiple scientific studies, growth delay was not a reported concern in a survey of parents of children and adolescents receiving stimulant medical therapy (methylphenidate) for ADHD (Tobaiqy et al., 2011).

The exact mechanism by which stimulant medication affects growth is unclear, but possibly includes decreased appetite with subsequent poor weight gain (Poulton, 2005). Since decreased or loss of appetite is a common complaint, It is tempting to ascribe decreased stature as a secondary consequence of stimulant-induced malnutrition. However, despite loss of appetite being reported in as many as 34.3% of treated ADHD patients (Tobaiqy et al., 2011), actual weight loss is not a consistent finding among ADHD studies. While varying degrees of weight loss are found in some patient populations, other studies report no weight loss. Similarly, it has not been possible to convincingly demonstrate an association between decreased nutrition and subsequent poor height growth in ADHD reports (Spencer et al., 1998).

Other possible mechanisms for poor growth include decreased bone mineralization, maturation and linear growth (Lahat et al., 2000), or a medication-induced disruption of the hypothalamic - pituitary - IGF-I axis (Negrao & Viljoen, 2011). Adrenergic stimulants are known to increase dopamine and noradrenaline in neural synapses. Increased dopamine and noradrenaline may in turn inhibit the secretion of growth hormone (GH) and other

growth-related peptides including thyroid hormones, sex hormones, prolactin and insulin, ultimately resulting in growth suppression (Negrao & Viljoen, 2011). However, studies of growth hormone have not shown a consistent altered pattern of GH secretion in association with stimulant treatment (Spencer et al.,1998). Finally, dysregulation of various neurotransmitters, in particular the catecholamines, is associated with ADHD itself. Such dysregulation may alter hypothalamic - pituitary function and cause growth delay, even in the absence of stimulant treatment (Spencer et al.,1998).

3.4 Concerns regarding growth studies in ADHD

Despite many, and at times, conflicting reports of slow growth in children and adolescents with ADHD (Frindik et al., 2009) and theoretical concerns of adverse interactions between ADHD and the hypothalamic-pituitary-IGF-I axis (Jensen & Garfinkel, 1988), no intrinsic defect or consistent dysfunction in this axis in ADHD has been identified. However, the following caveats regarding studies of growth in ADHD must be kept in mind. Rigorous scientific investigations of growth in children with ADHD have been relatively rare, the majority of ADHD studies are of a retrospective nature and lack significant power, adequate controls, sufficient follow up time, or stringent statistical analysis to draw firm conclusions (Poulton, 2005, Drappatz et al., 2006). Identifying appropriate age, gender, socio-economic, and diagnosis-matched control populations to study growth in ADHD patients with and without stimulant treatment may be especially problematic due to inherent treatment bias. The use of stimulant medication in children with ADHD varies by gender, race, age, language spoken in the home, insurance status, and contact with health care providers (Visser et al., 2007). The frequency with which ADHD medication is used for any reason also varies by geographic location, ranging from 2.1% of the general pediatric population in California to 6.5% in Arkansas (CDC, 2003). ADHD medical treatment is more likely to be used in males than females of all ages, and used more often in non-Hispanic, English-speaking, insured children than other groups (CDC, 2003, Visser et al., 2007). Cognizant of these difficulties, Drappatz and colleagues in 2006 reviewed 845 published articles on ADHD and growth, and concluded that usable data for a meta-analysis review could be extracted from only 22 (2.6%) of published studies (Drappatz et al., 2006).

The pathophysiology of ADHD itself is poorly understood (Spencer et al.,1998). It is likely therefore that the ADHD population in many studies is actually fairly heterogenous, further adding to the problems of patient selection for population studies and the selection of appropriate controls.

Because of the difficulties sited above, the actual long-term growth effects, if any, of ADHD or its treatment have remained unclear and controversial (Spencer et al.,1998, Pliszka, 1998, Poulton, 2005, Negrao & Viljoen, 2011). Recently, however, long-term, case control data have begun to emerge on final adult heights in ADHD. Biederman and colleagues studied the effect of ADHD and stimulant treatment using longitudinal, case-control studies of male and female children with ADHD (n = 137) compared to control children without ADHD (n = 124) followed for 10–11 years into adulthood. Compared to the control children, there were no differences in any growth outcomes in the ADHD group, regardless of stimulant treatment or the lack thereof (Biederman et al., 2010). A summary of growth studies in ADHD children and adolescents, some with no medical treatment and some treated with psychostimulant medications, is presented in table 2.

	Reference	Patient Population	Study Details	Result
ADHD, No Stimulant Treatment				
	Lisska & Rivkees, 2003	ADHD vs. age- and gender-matched, non ADHD siblings,	Height, weight, and BMI prior to ADHD stimulant treatment	No significant differences in height SDS between matched ADHD and non-ADHD siblings
	Ptacek et al., 2009a	ADHD males (n=46, ave. age 11.03 years) vs. control, non-ADHD	Anthropometric measurements	Decreased percent body fat and height in ADHD vs. non-ADHD
	Biederman et al., 2010	ADHD males and females (n=137) vs. control, non-ADHD (n=124)	Case-controlled study, longitudinal 10-11 year follow-up	No differences in height trajectories or in any growth parameters at follow-up
	Ptacek et al., 2009b	ADHD males (treated and non-treated, n=104, age 4-16 years) vs. control, non-ADHD	Anthropometric measurements	Decreased percent body fat, abdominal circumference, height, head circumference, ADHD vs. non-ADHD
ADHD with Stimulant Treatment				
	Spencer et al.,1998	ADHD males (89% treated at some time and 11% non-treated, n=124) vs. control, non-ADHD (n=109)	Anthropometric measurements	Mean height deficit of 2.1 cm in early adolescent ADHD males vs. controls. Mean height SDS 0.21 (ADHD) vs. 0.47 (controls), p = 0.03
	Lahat et al., 2000	Methylphenidate treated ADHD vs. control, non ADHD, 1-2 years of treatment	Dual photon absorptiometry, serum alkaline phosphatase, urinary deoxypyridinoline	No differences in bone mineral density turnover in treated ADHD vs. controls

	Lisska & Rivkees, 2003	Methylphenidate treated ADHD vs. age- and gender-matched, non ADHD siblings, 2-3 years treatment duration	Height, weight and BMI; pre-treatment and up to 3 years during treatment	Decreased height velocity during treatment; overall loss of 0.5 SDS height (boys) and 0.6 SDS height (girls)
	Drappatz et al., 2006	Variable age ranges	Meta-analysis review of 22 studies	1 - 2 cm / year height deficit per year of ADHD treatment
	Poulton, 2005	Variable age ranges	Medline search and review of 29 studies	One cm / year height deficit, during 1-3 three years of ADHD treatment
	Frindik et al., 2009	Prepubertal, male and female, treated ADHD vs. non - ADHD	Retrospective review of GH registry, pre-GH treatment data	Decreased BMI in treated ADHD; No difference in mean height SDS or growth rates prior to GH treatment
	Biederman et al., 2010	Males and females; psychostimulant treatment ADHD vs. control, non-ADHD	Longitudinal, case-controlled study, linear growth, 10-11 year follow-up	No differences in growth in ADHD with psychostimulant treatment vs. controls
	Faraone et al., 2010	LDX treated ADHD children (n=281), ages 6 to 13 years	Longitudinal, height, weight, BMI, up to 15 months treatment	Decreased gains in height, weight, BMI vs. expected from CDC standards
	Rose et al., 2011	Treated ADHD (n=1055) vs. non - ADHD (n= 6319)	Review of GH registry, pre-GH treatment data	No difference in mean height SDS treated ADHD vs. non-ADHD prior to GH treatment

Abbreviations: ADHD, attention deficit hyperactivity disorder; n = number, BMI, body mass index; GH, growth hormone; SDS, standard deviation score, LDX = .lisdexamfetamine dimesylate, CDC = Centers for Disease Control.

Table 2. Growth in Children with ADHD

4. Growth hormone treatment of ADHD associated short stature

As the preceding section discusses, the majority of children with ADHD have, at worst, mild, perhaps stimulant therapy-related, growth delays, ultimately achieving normal heights and weights. However, a subgroup of ADHD patients seems to exist that does have clinically significant and concerning growth delay. Spencer and colleagues found that 10% of ADHD boys in their review of 124 patients had height SD scores of more than 2 SD's below the mean. Using the same height SD cutoff criteria, only 1% of their control non-ADHD population was this short (Spencer et al.,1998).

The characteristics and natural history of this more growth delayed ADHD subgroup are not well defined. Their documented existence, however, supports our clinical impressions that at least some ADHD-treated children have growth delays that are sufficient to warrant investigation by a pediatric endocrinologist. In point of fact, our pediatric endocrine practice has seen a steadily increasing number of ADHD-treated children referred for evaluation of delayed growth and possible growth hormone therapy. Anecdotally, such children, if treated with recombinant human growth hormone (GH), did not seem to respond as well to GH therapy as children receiving GH therapy alone, suggesting that ADHD treatment might be a relative contraindication to GH therapy.

We undertook a retrospective analysis of children enrolled in a national growth hormone patient registry (Genentech's National Cooperative Growth Study (NCGS)) database (1985-2005) to determine (1) the frequency of ADHD treatment among children who are also receiving GH, (2) if any differences existed in either biochemical testing or anthropometrics between ADHD and non-ADHD, and (3) the first-year growth response in children receiving GH therapy only vs. those receiving GH therapy plus an ADHD medication (Frindik et al., 2009).

4.1 Frequency of ADHD medication use in growth hormone treated children

Both the absolute number of children receiving both ADHD treatment and growth hormone and the percentage of such enrolled in the national growth registry increased over a twenty year period. During the first year of the NCGS registry (1985), out of 850 patients receiving GH therapy, only 7 (0.8%) were receiving concurrent ADHD medications. Twenty years later (2005), of 12,113 enrolled patients on GH therapy, 752 (5.8%) were also receiving ADHD treatment. Reasons for this increase were felt to include: 1) an increased incidence of ADHD and/or an increased use of ADHD medication within the general pediatric population (CDC 2003, Froehlich et al., 2007) that could then be reflected in the NCGS database and 2) a referral bias in growth registries (Finkelstein et al., 1998, Kemp, 2006) that possibly leading to some overlap between the GH-treated and the ADHD-treated populations (Visser et al., 2007).

4.2 Endocrine function and growth in ADHD children prior to GH treatment

To examine differences in hypothalamic - pituitary - growth hormone axis activity in non-ADHD as compared to ADHD children, children were divided into two groups on the basis of their response to GH stimulation testing. Children were considered to have idiopathic GH deficiency (IGHD) if their maximum stimulated growth hormone (MSGH) response to

provocative stimuli was less than 10 ng/ml, or idiopathic short stature (ISS) if the MSGH response was equal to or greater than 10 ng/ml and no other syndrome or diagnosis given. Once divided into these two groups (IGHD and ISS), we found no distinguishing characteristics in hypothalamic - pituitary - growth hormone axis activity: mean MSGH (ng/ml) responses were similar in both the ADHD-treated and non-ADHD-treated groups.

4.3 Anthropometrics

The two groups were also similar as regards pre-treatment anthropometric measurements, although the ADHD-treated populations, both IGHD and ISS, were thinner (mean –0.4 BMI standard deviation scores (SDS) for IGHD and –0.4 BMI SDS for ISS) than the non–ADHD-treated, presumably an effect of the ADHD medication on appetite and weight. This difference in BMI was not reflected in height, as there was no statistically significant difference between mean baseline height SDS with and without ADHD treatment. Mean baseline height SDS with ADHD treatment was –2.6 and without ADHD treatment –2.7.

4.4 Response to GH treatment

When adjusted for age, sex, and enrollment body mass index, the difference in first-year GH-treatment response for children with IGHD was similar regardless of ADHD therapy. Mean first year growth rate for ADHD-treated IGHD was 8.5±2.0 cm/yr vs 9.4±2.6 cm/yr for non-ADHD-treated IGHD, a slightly less, but clinically insignificant difference. Similarly, first-year growth response was clinically indistinguishable between the ISS groups: 8.1±1.9 cm/yr (ADHD treatment) vs 8.6±2.1 cm/yr (ISS without ADHD treatment).

4.4.1 Other GH registry based studies of GH treatment in ADHD

Rao and colleagues reviewed the impact of ADHD treatment on the response to GH therapy over a longer treatment time, comparing IGHD and ISS children receiving GH plus either methylphenidate and pemoline to the response to GH alone over a mean treatment time of 2.7 to 3.0 years. Enrollment, pre-GH treatment height SD scores were similar in the ADHD treated groups and non-ADHD groups. Treatment with methylphenidate and pemoline had a minor effect on the change in height SDS with GH treatment in the IGHD group. However, not only was this negative effect minor in the first place, but the degree of differential response between the ADHD-IGHD-GH group and the IGHD-GH only group decreased the longer GH treatment was used. No differences were seen in the response to GH therapy in the two ISS groups. Enrollment heights and responses to GH therapy are presented in Table 3.

Another GH registry review of ADHD treated children followed for 3 years of GH therapy also demonstrated a similar response to GH therapy regardless of the status of ADHD treatment.

Children naive to GH therapy were divided into two groups: those receiving concomitant ADHD medication (ADHDm) and those receiving GH only. Diagnoses of patients receiving GH only included GH deficiency, multiple pituitary hormone deficiency, Turner syndrome, Noonan syndrome, small for gestational age, and idiopathic or other short stature. Mean height standard deviation scores (SDS) in the two groups were similar at

Reference	Patient Population	Treatment Status	Study Parameters	Published Results mean ± SD
Rao et al., 1998	IGHD with treated ADHD vs. non-ADHD IGHD	methylphenidate or pemoline in ADHD	Pre-GH treatment height SDS	– 2.8 ± 0.7 (ADHD) vs. – 3.0 ± 0.9 (non-ADHD)
	n=184 (ADHD); n=2313 (IGHD)	methylphenidate or pemoline in ADHD plus GH	Change in height SDS after GH treatment	1.2 ± 0.8 (ADHD) vs. 1.3 ± 0.9 (non-ADHD)
	ISS with treated ADHD vs. non-ADHD ISS	methylphenidate or pemoline in ADHD	Pre-GH treatment height SDS	– 2.8 ± 0.7 (ADHD) vs. – 2.9 ± 0.7 (non-ADHD)
	n=117 (ADHD); n=1283 (ISS)	methylphenidate or pemoline in ADHD plus GH	Change in height SDS after GH treatment	1.0 ± 0.7 (ADHD) vs. 1.1 ± 0.7 (non-ADHD)
Frindik et al., 2009	IGHD with treated ADHD vs. non-ADHD IGHD	stimulant treatment in ADHD	Pre-GH growth rate cm/yr	3.8 ± 1.8 (ADHD) vs. 4.4 ± 2.3 (non-ADHD)
	n= 263 (ADHD); n=6223 (IGHD)	stimulant treatment in ADHD plus GH	Growth Rate cm/yr after one year of GH	8.5 ± 2.0 (ADHD) vs. 9.4 ± 2.6 (non-ADHD)
	ISS with treated ADHD vs. non-ADHD ISS	stimulant treatment in ADHD	Pre-GH growth rate cm/yr	4.1 ± 1.9 (ADHD) vs. 4.4 ± 2.0 (non-ADHD)
	n= 121 (ADHD); n=2695 (ISS)	stimulant treatment in ADHD plus GH	Growth Rate cm/yr after one year of GH	8.1 ± 1.9 (ADHD) vs. 8.6 ± 2.1 (non-ADHD)
Rose et al., 2011	Patients receiving up to 3 years of GH treatment; n = 314 (ADHD); n = 1583 (GH only)	stimulant treatment in ADHD plus GH vs. non-ADHD with GH only	Change in height SDS after 3 years GH	1.14 ± 0.60 (ADHD + GH) vs. 1.26 ± 0.79 (non-ADHD)

Abbreviations: ADHD = attention deficit hyperactivity disorder; IGHD = idiopathic growth hormone deficiency; ISS = idiopathic short stature; n = number; SD = Standard Deviation; SDS = Standard Deviation Score.

Table 3. Effects of Growth Hormone (GH) on Growth in ADHD from Retrospective Reviews of GH Registries

start of therapy: –2.3 ADHDm group vs. –2.2 GH only group. Mean BMI was also comparable between the groups both at enrollment and during treatment. The ADHDm had lower mean change (improvement) in height SDS at 4 months, 1 year, 2 years and 3 years of GH therapy compared to the GH-only group, but the differences were minor and felt to be of no clinical significance. After three years of GH treatment, the change in mean height SDS of the ADHDm group was 1.14 compared to 1.26 of the GH-only group. Furthermore, 83% of patients on GH therapy plus concomitant ADHD medical treatment achieved a height in the normal range (greater than – 2 SDS), a response similar to the non-ADHD, GH-only group in whom 85% of children achieved a height greater than – 2 SDS (Rose et al., 2011).

See Table 3 for a summation of pretreatment data (either enrollment heights or growth velocity, when available) and the effects of GH therapy (either change in height or growth rate) in these three reviews.

5. Conclusion

The retrospective nature and referral bias of growth registries (Blethen et al., 1996) prevent extrapolation of these results to the general ADHD population. However, matched, ADHD-treated and non-treated populations are similar enough as regards pre-treatment anthropometric measurements, growth hormone stimulation results, and overall response to GH therapy to support the idea that there is no inherent hypothalamic - pituitary - growth hormone dysfunction in ADHD that would interfere significantly with GH therapy.

Finally, ADHD medical therapy should not exclude GH treatment if a child is otherwise an appropriate candidate for GH therapy. Such children should be expected to respond to GH regardless of concurrent ADHD treatment, many with first-year growth rates very similar to matched, non-ADHD children (Frindik et al., 2009). While it is true that some children with concurrent ADHD treatment may have a slightly decreased response during GH therapy, the effect is minor and of little clinical significance (Rao et al., 1998), and the overwhelming majority ultimately achieve heights in the normal range with GH therapy (Rose et al., 2011).

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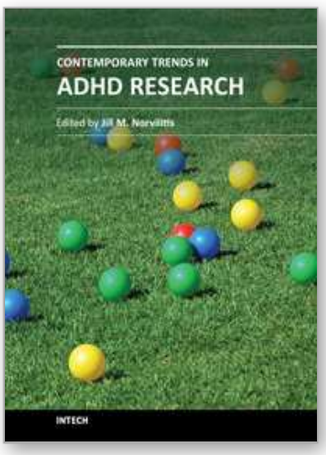
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With many children and adults affected by Attention Deficit Hyperactivity Disorder, researchers strive to understand the underpinnings of ADHD and associated factors on both a basic and applied level. The goal of this volume is to explore some of the broad array of research in the field of ADHD. The 12 chapters cover a variety of topics as varied as postural control, endocrine dysfunction, juvenile justice, and academic outcomes. These chapters will provide valuable insights for students reading about ADHD for the first time, researchers wishing to learn about the latest advances, and practitioners seeking new insight in the field.

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