

ADHD and growth: questions still unanswered

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Submitted: 2014-01-05 Accepted: 2014-01-15 Published online: 2014-02-27

Key words: ADHD; attention deficit hyperactivity disorder;
growth changes; medication; stimulants

Neuroendocrinol Lett 2014; 35(1):1–6 PMID: 24625909 NEL350114R01 © 2014 Neuroendocrinology Letters • www.nel.edu

Abstract

Attention deficit hyperactivity disorder (ADHD) is one of the most commonly diagnosed childhood psychiatric disorders. It is manifested in every part of an affected child's behavior, with multiple symptomatology and heterogenous etiology. Published studies report that ADHD children may show changes in growth and development. Most of the studies on ADHD have been focused on connections between medication and growth changes and describe growth delays associated with medication. However, recent research results point to the low significance of the changes accompanying pharmacological treatment. Changes in growth may not only be a secondary effect of the treatment, but may also be specific characteristics of ADHD.

INTRODUCTION

Attention deficit hyperactivity disorder (ADHD) is one of the most studied psychiatric disorders. Genetical (Ptacek *et al.* 2011a,b; Kuzelova *et al.* 2010), biochemical, endocrinological (Kream *et al.* 2010, Husarova *et al.* 2009; Drtilkova *et al.* 2008), neurological (Foltyn *et al.* 2011; Paclt *et al.* 2011), and even neuroanatomical changes often appear in patients with ADHD (Macek *et al.* 2012a,b; Husarova *et al.* 2009). Specific changes in brain development of ADHD children may be caused by the disorder itself, or may be caused by other non-related factors (Hruby *et al.* 2013; Hasto *et al.* 2013; Takahashi 2013). In this connection and according to recent studies, children with ADHD show may exhibit changes in growth and development (Ptacek *et al.* 2009 a,b,c).

Many questions have been asked regarding growth in ADHD children. Efforts are mainly focused on determining if stimulants affect growth in ADHD children and how serious this effect may be. Early and recent studies have reported that stimulants may cause decreased growth hormone secretion, but due to the fast metabolic elimination, the influence may not be considered as significant. However, these conclusions have not yet been definitively confirmed because few longitudinal studies have adequately described these possible relations.

Although many studies have searched for connections between medication and growth changes, it is equally important to identify changes in growth connected with the disorder itself. Despite much effort, these questions have not been clearly answered.

This critical review summarizes findings to date and compares results of various studies on this topic.

STIMULANT MEDICATION AND GROWTH AND DEVELOPMENT

Although positive effects are well documented, treatment by stimulants may have adverse effects (Poulton & Nanan 2008; McAfee 2008). It was reported that long-term use of stimulants can seriously influence growth (Setoodeh *et al.* 2007). In this context, most of the available studies have reported high initial growth deficits after beginning treatment with stimulants (Poulton & Nanan 2008), as well as continuing changes in growth in height – a deficit of about 1 cm/year in comparison to norms (Poulton 2005). Treatment with stimulants in children is also commonly associated with weight loss (Setoodeh & Teleffson 2007). Swanson *et al.* (2006) reported deficits of 2.0 cm in height and 2.7 kg in weight in comparison to the non-medicated subgroup.

Deceleration of growth in medicated children was also confirmed by the MTA Cooperative Group (2004), which found that the medicated group had reduced growth in height compared with the group that had reported never taking stimulant medication. Further differences were reported by Lisska and Riv-

kees (2003), who found significant differences in mean height SD scores between treated children and sibling controls after 2 years of treatment. Faraone and Giefer (2007) showed that the treatment was associated with small but significant delays in growth, especially in height, weight, and BMI. Although numerous studies included only ADHD boys (in concordance with population prevalence), Biederman *et al.* (2003) also observed growth and weight differences in girls receiving stimulant medication. Comparison of these studies shows that changes in growth in ADHD children are not probably sex-dependent, but changes may be dose-dependent (Faraone *et al.* 2008)

However, these effects attenuate over time and some data suggest that ultimate adult growth parameters may not be affected (Faraone *et al.* 2008). Several studies suggest that stimulants do not affect long-term parameters. This was also confirmed by Zachor *et al.* (2006), who analyzed the effects of long-term psychostimulant medication on growth parameters in children with ADHD. Significant weight loss was documented, mostly during the first few months of treatment. Pre-pubertal children had more significant weight loss than pubescent children. According to their results, the growth changes in long-term stimulant therapy are not clinically significant. Renes *et al.* (2012) also found that stimulants have

Tab. 1. Comparison of the studies - medication.

Study	Type of stimulant and dose (mg/day)	Growth/Values of Body Height	Weight
Sund & Zeiner 2002	Mph: 23.9 mg Dex: 11.9 mg	NSD	NSD
Biederman <i>et al.</i> 2003	Mph: NS	NSD	NSD
Lisska & Rivkees 2003	Mph: 10–80 mg	growth suppression	NSD
Poulton & Cowell 2003	Mph: 27 mg Dex: 13.7 mg	growth suppression	NSD
MTA cooperative group 2004	Mph: 34.4 mg	growth suppression	NSD
Zhang <i>et al.</i> 2005	Mph: 27–64 mg	growth suppression	NSD
Charach <i>et al.</i> 2006	Mph: NS	NSD	weight loss
Zachor <i>et al.</i> 2006	Mph: NS	NSD	weight loss
Pliszka <i>et al.</i> 2006	Mph: NS Dex: NS	NSD	NSD
Faraone & Giefer 2007	Mph: NS	NSD	NSD
Swanson <i>et al.</i> 2006	Mph: NS	growth suppression	weight loss
Ptacek <i>et al.</i> 2008	Mph	NSD	NSD
Waring <i>et al.</i> 2008	Mph	NS	weight loss
Biederman <i>et al.</i> 2010	Mph Dex: NS	NSD	NS
Faraone <i>et al.</i> 2010	Dex	growth suppression	NS
Moungnoi, Maipang 2011	Mph: 0.41–0.49 mg/kg	NS	NSD

Legend: **NSD = no significant differences:** the study showed no effect of the treatment on growth parameters. **Weight loss:** the study showed statistically significant weight loss after medication. **Growth suppression:** the study showed statistically significant growth suppression in medicated children. **NS:** nonspecified or not available.

some negative effects on growth during the first years, but adult height is not affected. However, puberty could be a critical period during which stimulants can affect development. In contrast, Poulton *et al.* (2012) found that stimulant medication is associated with early fat loss and reduced bone turnover. They found that relatively minor reductions in weight of individuals on stimulant medication can be associated with long-term changes in body composition. In another study, Poulton *et al.* (2013) found that prolonged treatment (more than 3 years) with stimulant medication was associated with a slower rate of physical development during puberty.

Table 1 reviews effects of stimulants on development of height and weight according to currently available studies. As Poulton (2005) and Faraone *et al.* (2008) stated, many relevant studies were of poor quality and, despite the large number of studies, most failed to detect any adverse effect on growth due to stimulant medication. Although the reviews are detailed, they do not include concrete conclusions, recommendations, or explanations.

Although many studies found some differences in growth in medicated children, the results are not statistically significant in many cases and results are not completely clear and convincing. The above-mentioned reports of changes were not supported by Sund and Zeiner (2002), who found that treatment with amphetamine or methylphenidate did not have negative effects on growth. However, some children from the amphetamine-treated group showed weight loss during the first year of treatment. Changes in weight were also not confirmed by Zhang (2005), who found no statistically significant differences in height or weight.

According to numerous studies, height deficits in children treated with stimulants have been reported many times, but few longitudinal studies have been published. It is possible that the growth catch-up is related to ADHD-associated delayed maturation and is not a result of stimulant treatment. The long-effect of these changes has been monitored by only a few longitudinal studies or by studies including adults.

There may be several main mechanisms that can affect growth in children receiving stimulant medications. First, suppression of appetite and reduction in caloric intake can negatively affect growth in children (Cortese *et al.* 2013). Height and weight changes observed in medicated ADHD children could be caused by decreased appetite (Paclt *et al.* 2005). However, there may also be other reasons, such as endocrinological or dietary factors (Ptacek *et al.* 2010). Another proposed mechanism is associated with the dopaminergic effect of stimulants. Dopamine may suppress growth hormone secretion and directly affect growth in children. Some studies suggest that stimulants might slow the growth of cartilage tissue, thus affecting growth of bones (Faraone *et al.* 2008). The importance of the neuroendocrinological system in these changes was confirmed by Mostafavi *et al.* (2012), who found that administra-

tion of melatonin along with Ritalin improves growth of children. These effects may be attributed to circadian cycle modification, increasing sleep duration, and, consequently, more growth hormone release during sleep.

ADHD AND GROWTH AND DEVELOPMENT

ADHD is associated with a variety of biological changes and probably with some specific changes in physical development. These changes have long been studied, but only in connection with the use of medication. However, children with ADHD show some changes in growth and development independent of medication received (Ptacek *et al.* 2009a). It is possible that there are specific, and in some cases significant, differences in growth in children with ADHD, but these characteristics may be more typical of the disorder itself than of the treatment.

Most of the studies compared signs of nutrition such as body mass index or body weight in ADHD children in comparison to controls. Especially in the USA, attention has focused on the prevalence of obesity and identifying risk groups with a predisposition to obesity (Waring & Lapane 2008). Mustillo *et al.* (2003) found that there is a higher incidence of psychopathology among obese people, particularly conduct disorders and attention deficit disorder. Individuals with these disorders can have less success in weight reduction due to the characteristics of the disorders (Curtin *et al.* 2005). These individuals may be less persistent and successful in reducing body weight; however, dopaminergic or insulin receptor activity may play a role (Altafas 2002).

Hanc *et al.* (2012) showed a tendency for greater body weight and BMI in boys with ADHD in compari-

Tab. 2. Comparison of the studies measuring body mass index (BMI) in ADHD children.

Study	value of body mass index (in comparison to norms)
Holtkamp <i>et al.</i> 2004	higher
Altafas 2002	higher
Mustillo <i>et al.</i> 2003	not significantly higher
Curtin <i>et al.</i> 2005	not significantly higher
Lam & Yang 2007	not significantly higher
Waring <i>et al.</i> 2008	higher
Hubel <i>et al.</i> 2006	higher
Ptacek <i>et al.</i> 2008	higher
Bird <i>et al.</i> 2009	higher
Fuemmeler <i>et al.</i> 2011	higher
Hanc <i>et al.</i> 2012	higher
Gungor <i>et al.</i> 2013	higher
Choudhry <i>et al.</i> 2013	higher

son with the growth charts, which may also be manifested in greater risk of overweight and obesity in this group. Reports of higher BMI values and higher body fat percentage were later confirmed by other studies (Hubel *et al.* 2006; Waring *et al.* 2008; Bird *et al.* 2009) in children and adolescents (Lam & Yang 2007). Related characteristics such as greater abdominal circumference and percentage of fat in this area were also described (Ptacek *et al.* 2009).

Similarly, Gungor *et al.* (2013) found subjects with ADHD were more likely to be overweight or obese compared with a non-ADHD control group, according to weight for height (WFH) and body mass index scores. Individuals with ADHD were more likely to be overweight or obese compared with the non-ADHD control group.

Although BMI values are not statistically significant in some cases, the trend is obvious in the studied group (Lam & Yang 2007; Mustillo *et al.* 2003; Curtin *et al.* 2005).

It is clear that other factors need to be considered. Choudhry *et al.* (2013) stated that differences in weight or BMI are not accounted for by cognitive, motivational, or motor profiles, but socio-economic characteristics are strongly associated with overweight and obesity in ADHD children.

Numerous studies have dealt with questions of growth in connection to medication, but the question of height and weight changes connected with the disorder itself is unclear. Spencer *et al.* (1996) suggested that ADHD may be associated with temporary deficits in growth. Ptacek *et al.* (2009c) also found differences between an ADHD drug-naïve group and population norms in terms of body height. This finding of shorter height in ADHD children may be a manifestation of neuroendocrinological abnormalities connected with this disorder.

Hanc and Cieslik (2008) described changes in growth during various age stages and reported greater growth of boys in the prepubertal stage, the suppression of growth during prepubertal and pubertal periods, and earlier occurrence of growth spurt onset. However, Hanc *et al.* (2012) subsequently reported that the height of drug-naïve boys with ADHD was not significantly different from the norm.

The findings mentioned above may be very important for understanding ADHD. However, very few studies on this topic have been published and none have produced significant results or greater insight into the question.

DISCUSSION

The importance of growth changes in ADHD is still unclear. According to the current literature, children with ADHD appear to be different from non-ADHD children in physique, growth, and development. Although many studies have been done, the method-

ology and observed variables are very heterogeneous and inconsistent, and the reports do not lead to definite conclusions. In particular, the limited duration of the studies, a wide age distribution, and lack of selected parameters (e.g., BMI is very frequent parameter in many studies, however BMI value may not be particularly revealing parameter in childhood) do not allow clear conclusions.

Many studies found that the treatment with stimulants in childhood may reduce expected height and weight. Although these effects attenuate over time, according to current opinions, the ultimate adult growth parameters are probably not affected. However, a weakness of some recent findings could be that children receiving drugs to treat ADHD were not compared with untreated children but only with healthy control subjects. In this regard, such results could have no predictive value because they suggest that ADHD itself may lead to specific changes in growth and development. These characteristics may be more typical of the disorder itself than of the treatment. The nature of the neurochemical changes associated with ADHD and their effects are still not well understood and remain unclear.

If a decision is made to initiate pharmacotherapy with stimulants in children, monitoring of growth and other parameters should be mandatory throughout the entire process of pharmacotherapy. Examination of these children might be a helpful approach to understand the relationship between growth changes and the contribution of neurophysiological, psychological, and behavioral factors. The question of changes in growth during medication is still unanswered.

The inconsistency of results may arise from the possibility that the growth changes are really not so significant. However, what may be very important for clinical practice is that ADHD patients tend to be overweight or obese. This problem has not received enough attention. Overweight and obesity can lead to health complications such as high blood pressure (Fuemmeler *et al.* 2011) and other problems. The question of why ADHD patients have a higher predisposition to obesity remains unclear. It may be partly explained by specific behaviors such as chaotic eating patterns and possible higher caloric intake. However, the predictions of effect of eating patterns have not been definitively confirmed. Research should focus in this direction to find mechanisms connecting ADHD and higher predispositions to obesity. There have already been sufficient studies of changes during stimulant medication. Now it is necessary to investigate the possible pathological mechanisms that lead to specific changes in ADHD patients.

CONCLUSION

Growth in children with ADHD are controversial topics. Despite the large number of studies focused on ADHD and physical growth and development, the causes and context of these changes remain unclear.

Children with ADHD may be shorter, but may also have a higher body mass index, body weight, and fat percentage. Lower height or weight gain may thus occur in connection with the use of medication. However, we emphasize the low statistical significance of the changes reported to accompany pharmacological treatment. Changes in growth may not be just a secondary effect of the treatment with stimulant medication, but may also be a specific characteristic of ADHD.

ACKNOWLEDGEMENT

Supported by the Program of Charles University „PRVOUK P03 and P26“.

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