

## Attention Deficit Hyperactivity Disorder and Growth

Aria Setoodeh<sup>\*1</sup>, MD; Sherida Teleffson<sup>2</sup>, MD

1. Pediatric Endocrinologist, Growth & Development Research Center, University of Tehran/ Medical Sciences, Tehran, IR Iran.
2. Pediatric Endocrinologist, Cardinal Glennon Hospital, Saint Louis School of Medicine, Missouri, USA

Received: 10/11/06; Accepted: 24/02/07

### Abstract

**Objective:** Attention deficit hyperactivity disorder (ADHD) is a common neuropsychiatric syndrome of childhood and adolescence in which stimulant medications are used to treat it. The evidence clearly indicates a temporary retardation in the rate of growth in weight and stature, with no effect on adult height.

**Case Presentation:** In this article we present a case with ADHD on stimulant therapy that had a catch up growth after the discontinuation of therapy, then review the literature on possible growth, and suppressing effects of these medications in the long term treatment.

**Conclusion:** Most of the previous studies suggest that the stimulant-associated height deficits in ADHD are temporary and early manifestation of ADHD itself and not complication of therapy, and the small risk of lost centimeters may be a price worth paying for many children to gain improved learning and social function.

**Key Words:** Attention deficit hyperactivity disorder, Short stature, Stimulant medication, Growth

### Introduction

Attention deficit hyperactivity disorder (ADHD) is one of the most commonly diagnosed childhood psychiatric disorders. Although psycho-stimulants have been used safely for more than 60 years, they have side

effects. The most common, include headache, abdominal discomfort, appetite suppression, and irritability. Particularly controversial has been the suppression of growth. The possible relationship of growth to ADHD may be mediated by several mechanisms including direct effect on cartilage, altered central nervous system growth factors, and altered hepatic

\* Correspondence author.

Address: Department of Pediatric Endocrinology, Children's Medical Center, Tehran University of Medical Sciences, Tehran, Iran.

E-mail: arset59@yahoo.com

growth factors; all of which may be either medication induced or disorder specific<sup>[1]</sup>.

### Case Presentation

We present a case to show the effect of stimulant therapy on growth. A 9.2 year-old white girl referred to the endocrinology unit of cardinal Glennon Hospital for growth failure. She was healthy except for ADHD which was diagnosed shortly after starting school about 3.5 years ago. The data from her previous chart showed that her weight and height were along the 5-10 and 10-25th percentile isopleths, respectively, until Dexedrine was started. There was no family history of short stature or constitutional delay in growth and puberty.

She was treated with Dexedrine (dextro-amphetamine sulfate) currently 22.5mg once daily during the school week, and 15 mg once daily during the weekend. At that time her weight was 17.3kg (less than 5 percentile) and her height 118.8 (2.5 SD below the mean).

Laboratory data including blood gas, thyroid function test and IGF1 were within normal limits and her karyotype was 46XX, her bone age was 6.8 years. She had poor appetite and had gained 5Kg weight when Dexedrine was stopped for a period of 6 weeks in the third grade. During several visits (as is shown in her growth chart) her weight was 5 percentile, and her height repeatedly 3-3.5SD below the mean.

The growth rate over the previous 3.5 years was about 3.8 cm in year. AT 12.6, years, the bone age was between 7.8 and 8.8 years. Right breast bud was noted but pubic hair was in stage of tanner 1. At this age Dexedrine was stopped and 6 months later she had good appetite, weight had an increase of 6.1 kg and height was 134.9 (increase of 3.1cm in 6 months); (Fig 1) sexual maturation at this point was stage 2 breast and pubic hair. She started her menstruation at the age of 14.6 years.

Our impression was that growth failure possibly was related to longstanding treatment with Dexedrine.

### Discussion

ADHD is a common neuropsychiatric syndrome of childhood and adolescence that pediatricians are often called upon to clinically evaluate and manage. Its prevalence is estimated at 3-5% of school aged children and is increasingly recognized in adolescents and adults.

The essential features of ADHD consist of persistent patterns of sustained attention deficits to repetitive or boring tasks such as schoolwork or reading, impulsivity and motor overactivity. Symptoms must be present in two or more settings, have an early age of onset (less than 7 years), have a chronic course and cause impairment to the child's development. Most researchers and clinicians use the framework in DMS IV for diagnostic approach.

The cause is unknown, but many believe that it is the result of a deficiency of specific neurotransmitters, norepinephrine or one of its precursors (dopa or dopamine) at the synapse of the nerves within specific brain circuits. Neuroimaging literature points to abnormalities in frontal networks (Frontostriatal dysfunction); these networks control attention and motor intentional behaviors. Also data from family-genetic, twin and adoption studies suggest a genetic origin for some forms of ADHD.

In the management of this disease, stimulants are drugs that produce excitation of CNS and have been used since 19430 s. Four types of these medications are considered the safest and are most frequently studied. These are methylphenidate, dextroamphetamine, mixed amphetamine salts and pemoline. The most important side effects of these drugs are appetite suppression, difficulty in falling asleep, irritability, sadness and hyperactivity as the medication wears off and hepatotoxicity with pemoline. But the major side effect that involves the pediatric endocrinologist is the growth issue in ADHD.

The potential mechanisms that underlie growth suppression in ADHD are many, including disorder-specific or medication

2 to 20 years: Girls  
Stature-for-age and Weight-for-age percentiles

NAME \_\_\_\_\_

RECORD # \_\_\_\_\_

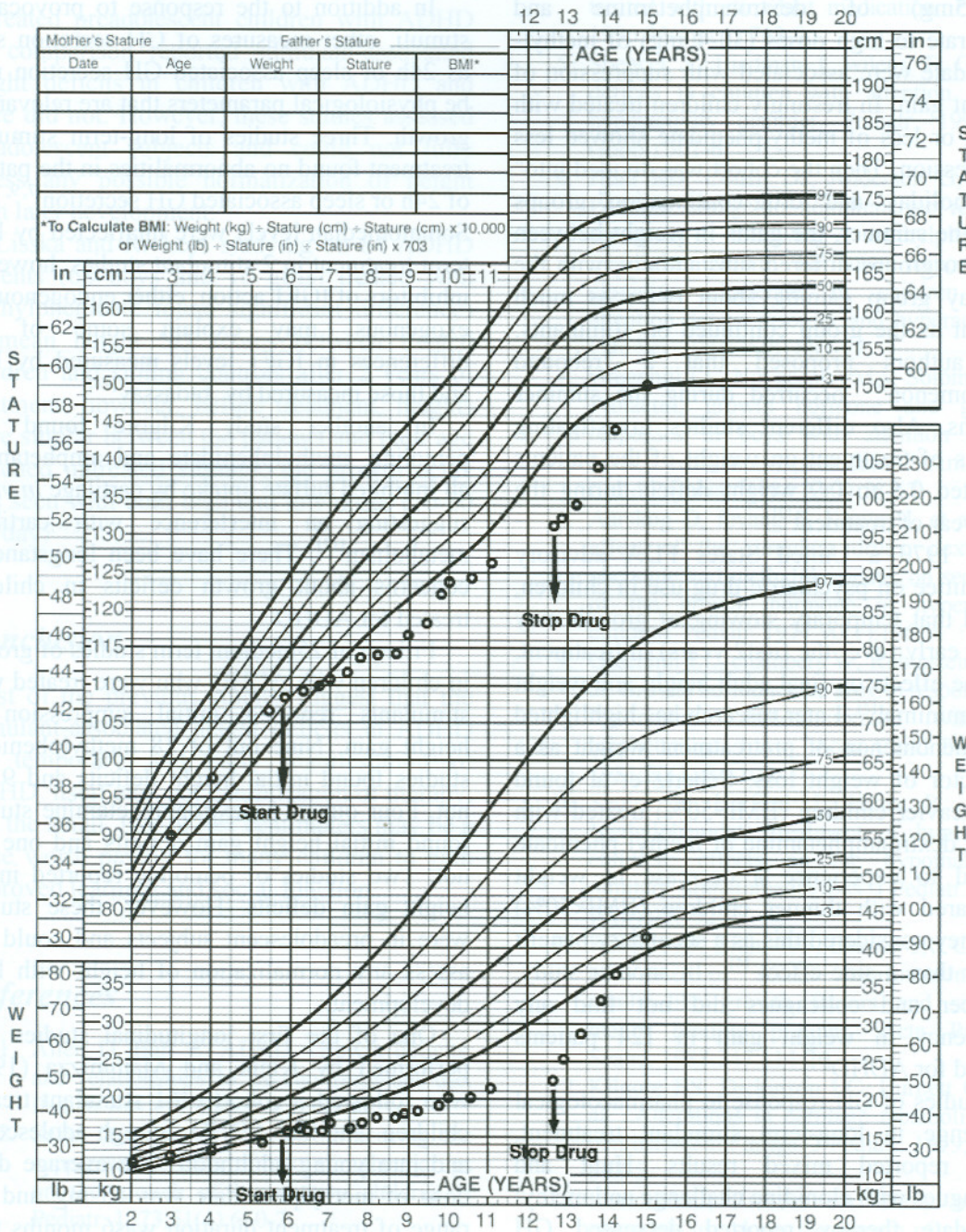


Fig 1: Growth chart of the our case with ADHD before and after treatment

effects on CNS growth factors, hepatic growth factors and direct cartilage effects. Weight gain can be suppressed by at least three mechanisms: decreased food intake, hyperactivity, and metabolic shifts. Psycho-

tropic treatment in children is commonly associated with loss of appetite and weight.

Among the first of many researchers to study the relationship between psychostimulants and growth deficit was Safer, Allen

and Barr (1972) who studied 29 hyperactive children, and found that moderate daily doses (10-15mg) of dextroamphetamine and moderate to high doses (30-40mg) of methylphenidate were associated with suppression of weight gain. In trestingly children treated with 20mg or less of methylphenidate showed less suppression. Then the cohort was divided into "drug holiday" and "drug continuation" groups over the summer, the gains in weight between the two groups differed substantially, with the holiday group gaining about twice as much weight as the group continued on stimulants; the authors proposed that a "rebound phenomenon" occurred during the summer months. Also different studies investigating effects of treatment on weight of the patients reported 0.5 to 0.9 weight deficit during the first year of treatment<sup>[2]</sup>.

In 1979 a United States FDA advisory committee on psychiatric drug use in children, found that temporary slowing of growth may occur early (over the first 2 years) in treatment, but the effects on final adult height and weight were minimal<sup>[3]</sup>. Later research has highlighted the phenomenon of pretreatment weight as a predictor of weight loss. Schertz et al found that heavier children (BMI>50%) treated with either dextroamphetamine or methyl phenidate tended to experience a decrease in weight compared with thinner children (BMI<50%) and they considered this as a secondary benefit rather than a side effect<sup>[4]</sup>. In another study, Spencer and colleagues did not find any deficiency in weight gain in 124 patients treated for ADHD<sup>[5]</sup>.

Studies of GH response to pharmacological challenge in long-term stimulant treatment, have reported mixed results. Hunt and colleagues with clonidine challenge and methyl phenidate therapy reported decreased GH response<sup>[6]</sup>.

In other studies, Greenhill et al with insulin provocation test for GH secretion during dextroamphetamine therapy<sup>[7]</sup>, Aarskog et al. with arginine, insulin tolerance and Methylphenidate therapy<sup>[8]</sup>, and Barter et al. with propranolol primed LDOPA GH

stimulation test during methylphenidate therapy showed normal GH responses.

In addition to the response to provocative stimuli, other measures of GH secretion such as 24h or sleep associated GH secretion may be physiological parameters that are relevant to growth. Three studies of long-term stimulant treatment found no abnormalities in the pattern of 24h or sleep associated GH secretion<sup>[7, 9, 10]</sup>. Somatomedian levels were unaffected by long term treatment in 2 stimulant studies, however, inhibitors of IGF1 action, either endogenous or exogenous, may explain some of the differences in IGF1 levels measured by RIA and those measured by bioassay<sup>[11]</sup>.

In another study Kilgore found that pemoline, methylphenidate and amphetamine all inhibited sulfate uptake by cartilage *in vitro*, suggesting an interference with cartilage metabolism<sup>[12]</sup>. There have been longstanding concerns about growth deficits in children treated for ADHD.

Fifteen of 25 medium term studies of growth in children with ADHD who were treated with stimulants reported initial suppression of height gain. Nine out of 18 methylphenidate studies found initial height deficits and 9 did not. Four out of 5 dextroamphetamine studies found initial height gain deficits and one did not. Two studies of pemoline reported initial height gain deficits. However, these studies were in preadolescent subjects and could not assess any normalization of height with later development.

One of the first longitudinal studies was performed by Klein and Mammizza (1988) who followed a cohort of 61 stimulant treated children who had ADHD through adolescence and into young adulthood. The average daily dose of methylphenidate was 45 mg and the range of treatment duration was 6 months to 5 years. They described a "growth-rebound phenomenon" upon cessation of medication and ultimately found no significant differences in final height between treated patients and the controls. Ultimately, the best way to differentiate disorder-related from medication-related effects would be to compare treated children who have ADHD with untreated

children who also have ADHD, rather than with unaffected control subjects.

Three of 6 previous studies that used untreated preadolescent children with ADHD for comparison reported stimulant-associated height deficits in children with ADHD and three did not. However, these studies assessed preadolescent subjects and could not fully assess any possible normalization of height with later development.

Lisska and Rivkees studying on 84 ADHD patients (68 boys and 16 girls) treated with methylphenidate found significant differences in mean height SD scores between treated children and sibling controls after 2 years of treatment; however, before treatment, heights were similar between the patients and their age matched untreated siblings, the growth delay was seen with both high and low doses (10-80 mg/day)<sup>[13]</sup>.

## Conclusion

Most of the previous studies suggest that the stimulant-associated height deficits in ADHD are temporary and early manifestation of ADHD itself and not complication of therapy, and the small risk of lost centimeters may be a price worth paying for many children to gain improved learning and social function.

## References

1. Allen D, Barr E. ADHD, Growth deficits, and relationships to psycho stimulant use. *Pediatr Review*. 2002;23(2):67-68.
2. Safar D, Allen R. Factors influencing the suppressant effects of two stimulant drugs on the growth of hyperactive children. *J Pediatr*. 1973;51(4):660-7.
3. Roche A, Lipman R, overall J, et al. The effects of stimulant medication on the growth of hyperkinetic children. *Pediatr*. 1979;63(6):847-50.
4. Schertz M, Adesman A, Alfieri N, et al. Predictors of weight loss in children with attention deficit hyperactivity disorder treated with stimulant medication. *Pediatr*. 1996;98(4 pt 1):763-9.
5. Spencer T, Biedman J, Wilens T. Growth deficits in children with attention deficit hyperactivity disorder. *Pediatr*. 1998;102 (suppl):501-6.
6. Hunt RD, Cohen DJ, Anderson G, et al. Possible change in noradrenergic receptor sensitivity following methylphenidate treatment: growth hormone response to clonidine challenge in children with attention deficit disorder and hyperactivity. *Life Sci*. 1984;35(8):885-97.
7. Greenhill LL, Novacenko MA, Solomon M. Prolactin, growth hormone and growth responses in boys with attention deficit treated with methylphenidate. *J Am Acad Child Psychiatr*. 1984;23(1):58-67.
8. Aarskog D, fevang F, Klove H, et al. The effect of the stimulant drugs, dextroamphetamine and methylphenidate, on secretion of the growth hormone in hyperactive children. *Pediatr*. 1977;90(1):136-9.
9. Greenhill LL, chambers W, Rubinstein B, et al. Growth hormone and growth responses in hyperkinetic males treated with d-amphetamine. *J Am. Acad Child Psychiatr*. 1981;20(1):84-103.
10. Shultz F, Harford J, Hintz R, et al. Methylphenidate treatment of hyperactive children: effects on the hypothalamic-pituitary-somatomedin axis. *J Pediatr*. 1982; 70(6):987-92.
11. Rande MB, Blum WF, Bierich JR. Clinical relevance of serum measurements of insulin-like growth factors and somatomedin binding proteins. *Acta Paediatr Scand*. 1988;347:114-26.
12. Kilgore BS, Dickinson LC, Burnett CR, et al. Alterations in cartilage metabolism by neurostimulant drugs. *J Pediatr*. 1979;94(4): 542-5.
13. Lisska MC, Rickees SA. Daily methylphenidate use slows the growth of children: a community based study. *J Pediatr Endocrinol Metabol*. 2003;16(5):711-8.