Long Term Therapy With Methylphenidate Induces Modest Effects on Growth in ADHD Children

Carla Balia[1], Alberto Anedda[1], Francesca Granitzio[1], Sara Carucci[1,2], Alessandro Zuddas[1,2]

Child Neuropsychiatry, [1]Dept Biomedical Science , University of Cagliari, [2] Cagliari University Hospital, Italy

INTRODUCTION

ADHD (Attention Deficit Hyperactivity Disorder) is a disorder that affects children and adolescents in their daily life. Although stimulants are the most effective medication for Attention Deficit Hyperactivity Disorder (ADHD), poor growth is a common concern, especially with children already on the lower growth percentiles. Studies providing longitudinal data indicate a reduction in both height and weight gain: these effects are usually minimal, but there is substantial variability with some children completely unaffected, whereas others shows significant growth suppression [1].

OBJECTIVES

To evaluate whether long term immediate release methylphenidate (IR-MPH) therapy (one or two years) interferes with the growth of ADHD children and to assess whether the effects on growth are related to the length of the treatment or to the daily dose.

METHODS

Data including growth parameters were collected from **89** ADHD **aged 6 to 14**, enrolled on the **Italian National Register for ADHD,** at the Centre for Pharmacological Therapies in Child and Adolescent NeuroPsychiatry (AOU Cagliari).

All patient were on **IR-MPH** and with a minimum follow-up of 12 months. **65** were Drug Naïve (DN), **24** were already on MPH since 1-3 years prior to enrollment in the Registry (prev-Mph).

Growth parameters were recorded at each follow-up visit (baseline and after 6, 12, 18, 24 months):

- **Weight** in Kg and its percentile based on age
- **Height** in cm and its percentile based on age
- **BMI** (Body Mass Index, kg/m^2) and its percentile based on age

In order to standardize the growth parameters on the basis of age and to allow a comparison at different times, **Height Z-score** and **BMI Z-score** were calculated. Z-score is obtained by subtracting the sample mean from our measured value, and dividing the result by the standard deviation of the sample: z = (x – X)/SD, where x = measurement value, X = mean of the distribution and SD = standard deviation of the distribution.

For the purposes of this study the following formula has been used:

$$Z = \frac{((X/M)^{**}L)-1}{LS}, L \neq 0 \text{ or } Z = \ln(X/M)/S, L = 0$$

where X = specific measure of height or BMI, M = median, S = generalized coefficient of variation and L = power in the Box-Cox transformation. M, S, and L were obtained from appropriate tables given in Centers for Disease Control and Prevention Growth Chart guidelines.

We also calculated growth velocity SDS, height deficit and BMI deficit, after 12 and 24 months:

- **Standard Deviation Score of growth velocity** defined as: (child's growth velocity – Mean of growth velocity by sex and age) / Standard Deviation of growth velocity.
- **Height deficit** (cm): Height measured at follow-up/ expected height (derived from correlation coefficient between baseline Z-score and follow-up Z-score)
- **BMI deficit** (kg/m^2): follow-up BMI/expected BMI (derived from correlation coefficient between baseline BMI Z-score and follow-up BMI Z-score)

STATISTICAL ANALYSIS

Categorical data were analyzed using contingency tables ($\chi 2$), continuous variables were compared **by one-way ANOVA**. Repeated measures ANOVA was performed for height and BMI Z scores at baseline, 6, 12, 18, 24 month follow up and for height velocity SDS at 12 and 24 months.

RESULTS

Sample Characteristics

		n	%
Sample Size		89	100
Male		79	88,8
Female		10	11,2
IQ	>80	59	66.3
	80-70	16	18
	69-55	10	11.2
	<55	4	4.5
Subtype	ADHD-C	86	96.6
	ADHD-I	3	3.4
	ADHD-H	0	0
Comorbidity	ODD	47	52.8
	Conduct Disorder	1	1.1
	Depression	0	0
	Anxiety	7	7.9
	Learning Disorder	26	29.2
	Tic	2	2.2
	PDD	2	2.2
Age at the start of therapy	6 yrs	2	2.2
	7 – 11 yrs	71	79.8
	11 – 14 yrs	16	18
Previous teraphy with MPH	Si	24	227
	No	65	773
Follow-Up	12 months	89	100
	18 months	65	73
	24 months	51	57.3

Basal auxologic Parameters in total sample

Sample Size	N= 89
Age (mean±DS) **Min max**	9.88 ± 2.13 6.52-14.68
Height (cm) mean (±DS) **Min max**	136.67 (±12.85) 115.0- 171.0
Weight (Kg) mean (±DS) **Min max**	36.62 (±11.05) 20.0-72.0
BMI mean (±DS) **Min Max**	19.28 (±3.55) 13.33-30.76
Basal height Zscore	-0.33±0.99
Basal BMI Z-score	0.19±1.15
Basal pro/kg Dose	0.48±0.21

Fig. 1a: Effects of MPH on height

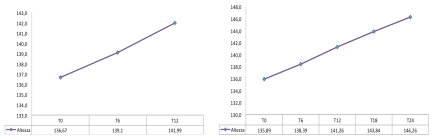

Fig. 1b: Effects of MPH on BMI

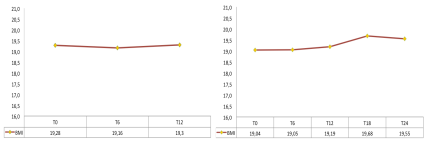

Fig. 1a,b: We observed an increase both in **height** and in **BMI absolute value** at month 12 and at month 24.

Fig. 2: Total sample Z-score during 12 m follow-up (n=89)

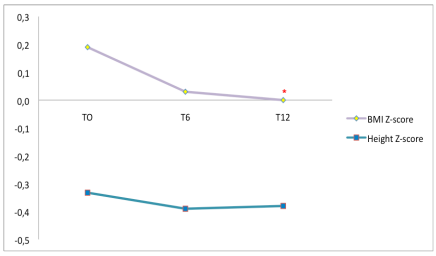

Fig. 2: We found that children in our study have a slightly higher weight than expected for age. A significant reduction in **BMI Z-score** after 12 months treatment was found (T0 to T12 p<0.001*). No significant change was found in **Height Z-score** T0 to T12.

Fig. 3: Total sample Z-score during 24 m follow-up (n=51)

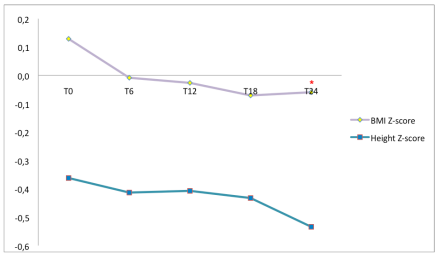

Fig. 3: We found a further slightly reduction in **BMI Z-score** after month 12, with a significant difference at 24 months (T0 to T24 p<0,05).
Height Z-score was slightly but not significantly reduced after 24 months (T0 to T24 p< 0.06; T12 to T24 p<0,062).

Drug Naïve and prev-Mph Characteristics

		Drug Naïve N=65 (%)	MPH PR N=24 (%)	p
Sample Size		89	100	n.s.
Male		57 (87.7)	22 (91.7)	n.s.
Female		8 (12.3)	2 (8.3)	
Age at the start of therapy	6 yrs	0 (0)	2 (8.3)	.002
	7 – 11 yrs	51 (78.5)	20 (83.3)	
	11 – 14 yrs	14 (21.5)	2 (8.3)	
Follow-Up	12 months	65 (100)	24 (100)	.003
	18 months	33 (66.15)	23 (91.6)	
	24 months	32 (49.2)	19 (79.1)	

Auxologic Parameters in Drug Naïve and prev-Mph

Sample Size	Drug Naïve N=65	MPH PR N=24	p
Age mean (±DS) **Min max**	9.78 (± 2.19) 6.52-14.7	10.06 (±1.99) 6.90-14.38	n.s.
Height (cm) mean (±DS) **Min max**	136.76 (±12.56) 115.0- 168.0	136.40 (±13.89) 118.3- 171.0	n.s.
Weight (Kg) mean (±DS) **Min max**	37.23 (±11.09) 20.0-72.0	34.97 (±11.03) 22.5-58.5	n.s.
BMI mean (±DS) **Min Max**	19.60 (±3.74) 13.33-30.76	18.39 (±2.87) 14.42-22.65	n.s.
Basal height Z-score (±DS)	-0.21 (±0.99)	-0.64 (±0.92)	.07
Basal BMI Z-score (±DS)	0.29 (±1.22)	-0.07 (±0.9)	n.s.
Basal pro/kg Dose: mean (±DS)	0.47 (±0.22)	0.51 (±0.18)	n.s.

Fig. 4: Height Z-score in Drug Naive and prev-Mph during 24 m follow-up

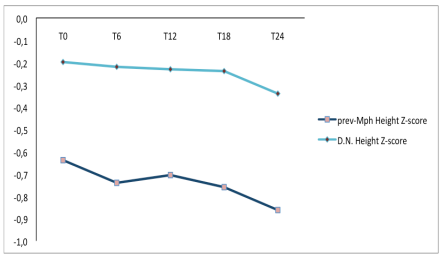

Fig. 4: Although no significant variations were found after 12 nor after 24 months, we recorded a slight reduction of **Height Z-score** both in D.N. sample and in PR sample. Moreover we found a significant decrease of **BMI Z-score** in D.N. sample after 12 months (T0 to T12 p<0,001). No significant variations were found after 24 months, even if we observed a slight increase of BMI Z-score in D.N. sample and a slight reduction in prev-Mph sample.

Fig. 5: Pro/die dose in Drug Naïve and in prev-Mph patients

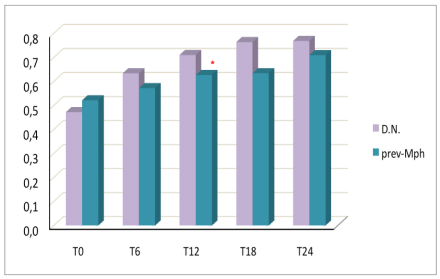

Fig. 5: The correlation of **BMI Z-score** with the per kg/die dose is statistically significant (p <.001).

Growth deficit

Sample Size	n	cm	DS
Height Deficit after 12 m	89	-0.47	2.74
Height Deficit after 24 m	52	-1.26	4.61
BMI Deficit after 12 m	89	-0.31	1.36
BMI Deficit after 24 m	52	-0.75	2.71

Fig. 6: Growth velocity SDS (n=51)

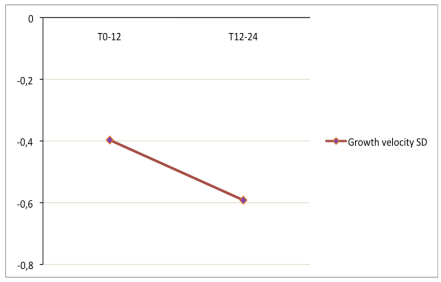

Fig. 6: Growth velocity DSS: The change in growth velocity DS recorded by T0 visit to T12 visit (-0.39) and by T12 visit to T24 visit (-0.59) was not statistically significant, although we recorded a slight decrease.

CONCLUSIONS

The findings of the present study suggest that the effects of MPH on growth are relatively small and unlikely to be of clinical concern for this population. Expected and actual deficit in growth should be considered in the context of the benefits the patient receives from the medication. More research is needed to better elucidate the mechanism of growth suppression and to implement specific treatment strategies for ADHD children.

References [1] Pliszka, S.R., Matthews, T.L., Braslow, K.J., Watson, M.A., 2006. Comparative Effects of Methylphenidate and Mixed Salts Amphetamine on Height and Weight in Children With Attention-Deficit/Hyperactivity Disorder. J Am Acad Child Adolesc Psychiatry 45, 520-526.

No potential conflict of interest to disclose