

Autonomic functions in Attention-deficit/hyperactivity disorder (ADHD) before and after Methylphenidate

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Abstract : ADHD is associated with autonomic dysfunction which gets further modulated with drug therapy. There are few prospective studies to evaluate the changes of Autonomic Function Tests before and after methylphenidate treatment in drug-naive patients with ADHD. The present study was conceived with the objective to study autonomic functions in children with Attention-deficit/hyperactivity disorder (ADHD) before and after treatment with Methylphenidate. Autonomic function tests were conducted on 52 drug-naive patients with ADHD. The patients then received methylphenidate medication for 12 weeks. The above parameters were repeated at 12 weeks of study period. On the Sympathetic reactivity tests, the increase in Systolic blood pressure and diastolic blood pressure on exposure to cold (Cold Pressor test) and sustained handgrip (Handgrip test) was significantly higher after Methylphenidate treatment which can be attributed to an activation of the sympathetic nervous system. The parasympathetic reactivity tests showed that there was a significant decrease of E: I ratio (Deep Breathing Test) after methylphenidate treatment. Changes in heart rate during deep breathing reflect parasympathetic modulation. However, there was no significant changes in 30:15 ratio (Heart response to standing). Hence methylphenidate increases the sympathetic domination, and reduces the parasympathetic domination, and tilts the sympathovagal balance towards the sympathetic arm.

Keywords: ADHD, autonomic function, methylphenidate.

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I. Introduction

Attention-deficit/hyperactivity disorder (ADHD) is one of the most common psychiatric disorders in children and adolescents with the worldwide prevalence of 7.2 %¹. Although the exact etiology of ADHD is yet to be determined, there is an increasing consensus that the condition involves functional and anatomical dysfunction in the brain's frontal cortex and basal ganglia segments of the cortico-basal ganglia-thalamo-cortical circuitry². The autonomic function has consistently been found to be impaired/ affected in ADHD in various studies. Underarousal of the sympathetic system has been observed in children with ADHD.³⁻⁷

II. Aim

To study in the ADHD children the Autonomic functions before and after the methylphenidate therapy. The study was carried out in the Department of Physiology in association with the Department of Psychiatry at Lady Hardinge Medical College and Smt Sucheta Kriplani Hospital, New Delhi and was approved by the institutional ethics committee for human research of Lady Hardinge Medical College, New Delhi.

III. Methods

Drug-naive cases of Attention-deficit/hyperactivity disorder (ADHD) diagnosed by a Psychiatrist as per American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM – V) criteria⁸ requiring methylphenidate treatment, 52 in number were recruited for the study. The subjects were

between 6 to 12 years of age. Known patients of hepatic, renal, cardiovascular diseases, diabetes mellitus systemic inflammatory disorders and patients having other psychiatric co-morbidities including autism, oppositional defiant disorder, conduct disorder and patients receiving medication known to affect autonomic function were excluded from the study. A parent or legal guardian of the patients provided the informed written consent in either Hindi or English.

All the participants were called to the Physiology department in the morning hours. The general physical examination and autonomic function tests were carried out. The ambient temperature in the laboratory was maintained at 23-25°C.

The following autonomic function tests were conducted on the subjects.

I. Sympathetic Reactivity tests

1. Cold pressor test^{9,10} :- In this test, the patient dipped one hand up to the wrist into cold water at 10 degrees Celsius for one minute. The Systolic and diastolic blood pressures were monitored from the other arm before the procedure and at one minute just before retracting the hand from cold water. The increase in the systolic and diastolic blood pressure was recorded as a response to cold stimulation.

2. Hand grip test^{11,12} :- The test was performed in sitting position. Resting blood pressure was recorded. First, the subject was instructed to grip the dynamometer with the dominant hand with and contract maximally. Three successive trials were performed at an interval of 30 seconds. The highest value of three contractions was taken as a maximum voluntary contraction. After an interval of five minutes, handgrip exercise was again done, but this time contraction was maintained steadily by the subject at 30% of maximum voluntary contraction for up to 4 minutes. During this maneuver, both systolic and diastolic blood pressure was recorded at first, 2nd and at the 4th minute from the non-exercising arm. The maximum rise in systolic and diastolic blood pressure was taken as an index of response to the hand grip.

II. Parasympathetic Reactivity tests

1. Deep breathing test-E:I ratio¹³⁻¹⁶ :- the ECG was recorded using BPL CARDIART 6208 ECG machine. The patient was instructed to take deep and steady breathing at six breaths per minute in lying position comprising of 5 seconds of inspiration and 5 seconds of expiration. During breathing, an electrocardiogram was recorded continuously. The point of beginning of inspiration and the point of expiration was marked on ECG. The E: I ratio was calculated from the formula-

$$\text{E: I ratio} = \frac{\text{Longest R-R interval during Expiration}}{\text{The shortest R-R interval during Inspiration}}$$

In very young children who were unable to follow the above instructions, the values were calculated from single breath cycle.

2. Standing lying test-30:15 ratio¹³⁻¹⁶ :- The ECG was recorded using BPL CARDIART 6208 ECG machine. The subject was instructed to lie down quietly for 10 minutes, while a continuous electrocardiogram was recorded and then the patient was instructed to stand up and remain motionless. The point of standing was recorded. The 30:15 ratio was calculated as-

$$30:15 \text{ ratio} = \frac{\text{R-R interval at beat 30 after assuming an erect posture}}{\text{R-R interval at beat 15 after assuming an erect posture}}$$

The patients were then put on methylphenidate for 12 weeks. Mean dose of methylphenidate at the endpoint of the study was 20.58 ± 3.52 mg and mean dose per kg of body weight at the endpoint of the study was 0.70 ± 0.09 mg/ Kg.

Autonomic function tests were repeated at 12 weeks of study period.

Data obtained were subjected to statistical evaluation using Graph Pad Prism Version 7 software. The mean and standard error of the mean (Mean \pm SEM) were calculated after testing for normal Gaussian distribution. Wilcoxon matched-pairs signed rank test was used to compare the difference from baseline to 12 weeks after methylphenidate treatment.

IV. Results

In the comparison of sympathetic reactivity tests (**Table1**) before and after methylphenidate treatment, there was an increase in Systolic blood pressure & diastolic blood pressure on exposure to cold (Cold Pressor test) and sustained handgrip (Handgrip test) after Methylphenidate treatment. The parasympathetic reactivity tests (**Table2**) showed that there was a significant decrease of E: I ratio (Deep Breathing Test) after methylphenidate treatment. However, there was no significant change in 30:15 ratio (Heart response to standing).

V. Discussion

The increase in blood pressure following the cold pressor test is attributed to activation of sympathetic nervous system¹⁷.

The maximum increase in the systolic and diastolic blood pressure in response to sustained handgrip significantly higher after Methylphenidate treatment. Sustained isometric muscular contractions are known to produce marked increases in systemic arterial blood pressure, heart rate, and cardiac output. The hemodynamic responses to the static effort are related to an activation of the adrenergic system¹⁷. The increments in SBP and DBP here again show the increased sympathetic responsiveness as evident in CPT.

Changes in heart rate during deep breathing reflect parasympathetic modulation^{13, 15} and in this study decrease in E: I ratio could signify decreasing parasympathetic modulation after the methylphenidate therapy.

Our study is in concordance with studies by various authors. In a study conducted in 2011 by Negrao et al.⁴, it was found that stimulant-free children with ADHD had a sympathetic underarousal and parasympathetic overarousal of the autonomic system as compared to control subjects and that methylphenidate shifted the autonomic balance of children with ADHD towards normal levels. In a recent study by Hayeon Jennifer Kim in 2015¹⁸, it was reported that children with ADHD show parasympathetic dominance and that methylphenidate treatment changes this parasympathetic dominance into an autonomic balance. Thus, there was a shift away from parasympathetic dominance post-therapy with methylphenidate.

Thus, in our study ADHD children showed an increase in sympathetic activity with methylphenidate treatment.

In our study, no serious adverse events were reported during the study period. But the increase in sympathetic activity warrants a cautious use of Methylphenidate. Hence patients should be screened carefully for cardiac diseases before initiating methylphenidate treatment.

Our study has a few limitations. No control group was recruited in our study to compare the autonomic functions with patients of ADHD. Only male patients were recruited in our study as no female patient met our inclusion and exclusion criteria. The sample size was small (only 52 patients).

Table 1: Changes in cold pressor test (CPT) and Hand grip test (HGT) from baseline to 12 weeks after methylphenidate treatment in the study group (Mean ± S.E.M values)

Parameters			Baseline	After Treatment	p-value
CPT	SBP (mm Hg.)	Basal	104.30±0.45	104.8±0.49	0.0001
		After 1 min	113.10±0.60	117.0±0.61	0.0001
		Difference	8.85±0.37	12.23±0.47	0.0001
	DBP (mm Hg.)	Basal	67.46±0.50	68.15±0.43	0.0001
		After 1 min	75.96±0.67	79.23±0.61	0.0001
		Difference	8.50±0.40	11.08±0.48	0.0001
HGT	SBP (mm Hg.)	Basal	104.10±0.49	105.0±0.55	0.0001
		Max increase	111.6±0.59	115.1±0.73	0.0001
		Difference	7.50±0.32	10.35±0.43	0.0001
	DBP (mm Hg.)	Basal	67.38±0.48	68.19±0.42	0.0001
		Max increase	74.81±0.57	77.46±0.59	0.0001
		Difference	7.42±0.33	9.27±0.41	0.0001

p value- > 0.05-Non-Significant (NS), <0.05-Significant, <0.01-Very Significant, <0.001-Highly Significant. Wilcoxon matched-pairs signed rank test

Table 2: Changes in E: I, 30:15 from baseline to 12 weeks after methylphenidate treatment in the study group (Mean ± S.E.M values)

Parameters	Baseline	After treatment	p-value
E: I ratio	1.27 ± 0.03	1.21 ± 0.02	0.0065
30: 15 ratio	1.03 ± 0.01	1.07 ± 0.01	0.0720

p value- > 0.05-Non-Significant (NS), <0.05-Significant, <0.01-Very Significant, <0.001-Highly Significant. Wilcoxon matched-pairs signed rank test

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