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Correlation between Vanderbilt Parent Rating Scale and Autonomic Functions in ADHD Before and After Methylphenidate

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Abstract: The present study was planned with the objective to evaluate the correlation between autonomic function tests and disease severity as assessed on Vanderbilt Parent Rating Scale(VPRS) in drug naïve patients of ADHD before and after treatment with methylphenidate. Dysfunction in the prefrontal cortex, limbic system, locus coeruleus-noradrenergic system and other related brain structures involving dopaminergic and noradrenergic dysregulation has been proposed as the primary pathophysiological mechanism of the disease. These structures are also included in the neuro-cardiac complex regulation leading to autonomic dysfunction in these patients. Sympathetic underarousal and parasympathetic dominance have been observed in drug naïve patients of ADHD in various studies. Abnormalities in autonomic functions are associated with increased risk of arrhythmias and cardiac mortality. Methylphenidate affects the autonomic functions due to its adrenergic effects. The autonomic functions also get modulated as the disease condition improves. Autonomic function tests (E: I ratio, 30:15 ratio, Cold pressor test, Handgrip test) were performed, and VPRS combined score was assessed on 52 patients of ADHD before and after 12 weeks of methylphenidate treatment. A significant Negative correlation between the E: I ratio(Deep breathing test) and systolic blood pressure change in CPT(Cold pressor test) with Vanderbilt combined score after 12 weeks of methylphenidate treatment was observed. Sympathovagal balance shifts towards the sympathetic arm independent of the adrenergic action of methylphenidate.

Keywords: ADHD, autonomic functions, methylphenidate, Vanderbilt ADHD Parent Rating Scale.

INTRODUCTION

ADHD is characterized by a decreased sustained attention and higher levels of impulsivity in a child or adolescent than expected for someone of that age and developmental level [1]. Studies on HRV have shown that stimulant-free children with ADHD showed a sympathetic under arousal and parasympathetic overarousal relative to control subjects[2-4]. Vanderbilt ADHD Rating Scale, designed by the Association for Academic Psychiatry and National Institute for Children's Healthcare Quality was administered to capture standardized ADHD symptom information from parents and teachers. VPRS can reliably, validly, and efficiently measure ADHD symptoms in patients[5,6]. The scale also has symptom screens for three other co-morbidities:-oppositional-defiant disorder, conduct disorder, and anxiety/ depression. The ADHD Rating Scales can be used as a scored tool for assessment of the severity of ADHD symptoms [7]. Heart-rate variation measured as the ratio of the heart rate at expiration to that at inspiration, the so-called E: I ratio (Deep breathing test) reflects parasympathetic modulation [8,9]. In 30:15 ratio test the change from lying to standing is characterized by an immediate rapid increase in heart rate which occurs maximally at about the 15th beat after standing. Relative overshoot bradycardia then occurs, maximal at about the 30th beat. Immediate heart-rate response to standing is a simple test for the assessment of parasympathetic arm of the autonomic system [10]. Cold pressor test (CPT)is

a well-known method to induce ischemic pain associated with cold water stimulation. CPT can identify sympathetic activity deficiency [11,12]. Sustained hand grip associated muscle contraction results in increased cardiac output, blood pressure, and heart rate. This autonomic manoeuvre has been adopted as a clinical test of sympathetic autonomic function [13].

METHODOLOGY

The ethics committee for human research of Lady Hardinge Medical College, New Delhi approved the study (LHMC/ECHR/2015/151 dated 03/11/2015). Consenting drug-naive patients meeting the inclusion criteria were recruited from the Psychiatry OPD of Smt Sucheta Kriplani Hospital, New Delhi. The patients included in the study group were diagnosed using the DSM-V (5th edition of the Diagnostic and Statistical Manual of Mental Disorders) criteria[14]. Only male patients were recruited for the study as no female patient met the inclusion criteria during the study period. The subjects were 52 in number, in the age group of 6 to 12 years. Patients with other psychiatric co-morbidities including autism, oppositional defiant disorder, conduct disorder were excluded from the study. Patients receiving psychotropic medicines other than methylphenidate were also excluded. Consumption of tea and caffeinated drinks was not allowed on the day of the tests and tests were performed in the morning hours. The ambient temperature in the laboratory was maintained at 23-25°C.

The following autonomic function tests were conducted on the subjects.

Parasympathetic Reactivity tests

The electrocardiogram (ECG) was recorded with BPL CARDIART 6208 ECG machine for Parasympathetic Reactivity tests.

E: I ratio (Deep breathing test):- The subjects were asked to take deep and steady breathing at six breaths per minute in lying position, with 5 seconds of inspiration and expiration each. During breathing, an ECG was recorded continuously. The point of beginning of inspiration and expiration was marked on ECG. The E: I ratio was calculated by dividing the Longest R-R interval during Expiration with the shortest R-R interval during Inspiration.

30:15 ratio (Standing lying test):–. The patients were instructed to lie down quietly for 10 minutes, while a continuous ECG was recorded and then the patient was asked to stand up and remain motionless. The point of standing was marked. The 30:15 ratio was determined by dividing the R-R interval at beat 30 with the R-R interval at beat 15 after assuming an upright posture.

Sympathetic Reactivity tests

Cold pressor test (CPT): - In this test, the patients dipped one hand up to the wrist into cold water at 10 degrees Celsius(as per the guidelines for CPT testing in children) for one minute[15]. The Systolic(S) and diastolic (D) 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.

Handgrip test (HGT): - The test was performed in the sitting position. Resting blood pressure was recorded. First, the subjects were instructed to grip the dynamometer with the dominant hand and were asked to 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 manoeuvre, both systolic and diastolic blood pressures were 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.

Vanderbilt ADHD Diagnostic Rating Scale (VADRS)

The symptom screens part of the scale comprises of 18 questions to screen ADHD symptoms for both inattentive (items 1–9) and hyperactive (items 10–18) types. The questions were read to the parents one by one, and the responses were marked accordingly. A positive response was rated as “often” and “very often” for that particular symptom as assessed by the parents in the last one month. The number of positives in each sub-segment was added for the combined score.

The patients were then put on methylphenidate for 12 weeks. Mean dose of methylphenidate at the endpoint of the study was 0.70 ± 0.09 mg/ Kg body weight. Autonomic function tests and Vanderbilt Parent Rating Scale were repeated at 12 weeks of study period.

Statistical evaluation was done by using the Version 7 of the Graph Pad Prism software. Gaussian distribution was tested by applying The D'Agostino & Pearson normality test, Shapiro-Wilk normality test and KS normality test. Correlation between Vanderbilt Parent Rating Scale and Autonomic Function Tests were assessed with Spearman correlation coefficient.

OBSERVATIONS

The Spearman's Correlation test did not yield any significant correlation between Vanderbilt Parent Rating Scale and autonomic reactivity tests at baseline (Table 1).

There was a significant Negative correlation between the E: I ratio and CPT Systolic Blood Pressure (CPT SBP) with Vanderbilt combined score after 12 weeks of methylphenidate treatment. The Spearman's Correlation test did not yield any significant correlation in the other parameters between Vanderbilt Parent Rating Scale and autonomic reactivity tests after 12 weeks of methylphenidate treatment (Table 2, Figure1 and Figure2).

DISCUSSION

Vanderbilt combined score showed a negative correlation with E: I ratio and CPT SBP changes after 12 weeks of methylphenidate treatment indicating decreased parasympathetic dominance post-therapy in children with lower Vanderbilt score (which signifies clinical improvement).

Autonomic functions are an index of central-peripheral neural feedback and CNS (Central Nervous System)-ANS (Autonomic Nervous System) integration [16]. Hence the autonomic function analysis can be used to study the possible links between mental disorders and cardiac autonomic regulation [17,18]. As ADHD is associated with emotional dysregulation, a potential connection between ADHD-linked emotional dysregulation and reduced cardio vagal function might represent the possible mechanisms leading to the altered autonomic functions in patients who have ADHD [19,20]. A negative correlation between disease severity and parasympathetic reactivity tests shows that autonomic dysfunction improves with improvement in disease condition independent of the adrenergic action of methylphenidate.

LIMITATIONS

The first limitation of our study is the lack of control group hence we are unable to determine whether methylphenidate brings the autonomic balance to normal or not. The sample size was small constituting only 52 patients as patients receiving other psychotropic drugs were excluded from the study. Only male patients were recruited for this study as no female patient met our inclusion criteria during the study period. Patients were started on tablet methylphenidate (immediate release) 5-10 mg as per Clinical Practice Guidelines of the Indian Psychiatric Society, and the dose was increased gradually every 15 days or one month [21]. So the patients were on a lower dose during the initial duration of the study compared to the endpoint. Hence more extended duration studies should be carried out on the correlation between autonomic functions and disease severity in patients treated with a full therapeutic dose of methylphenidate. Vanderbilt ADHD Teacher rating scale was not used in our study which could have revealed more information about the patient's symptoms in school.

Table-1: Correlation between baseline autonomic reactivity tests with Vanderbilt Parent Rating Scale (combined score) in ADHD patients (n=52)

PARAMETERS	Vanderbilt combined(CM) score	
	Correlation Coefficient(r)	P value
E : I ratio	0.036	0.898
30:15 ratio	-0.184	0.303
CPT S	-0.285	0.293
CPT D	-0.293	0.889
HGT S	-0.278	0.428
HGT D	-0.148	0.211

* Significant p value

Table-2: Correlation between autonomic reactivity tests with Vanderbilt Parent Rating Scale (combined score) after 12 weeks of methylphenidate treatment in ADHD patients (n=52)

PARAMETERS	Vanderbilt combined(CM) score	
	Correlation Co-efficient(r)	P value
E : I ratio	-0.497	0.0002*
30:15 ratio	0.103	0.467
CPT S	-0.306	0.027*
CPT D	-0.094	0.505
HGT S	-0.259	0.063
HGT D	-0.112	0.427

* Significant p value

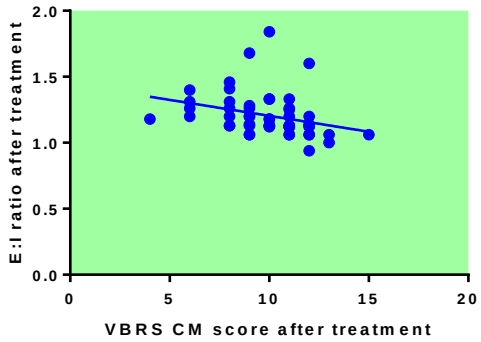

Fig-1: Graph showing significant correlation between E: I ratio (Deep breathing test) with Vanderbilt combined (CM) score after 12 weeks of methylphenidate treatment

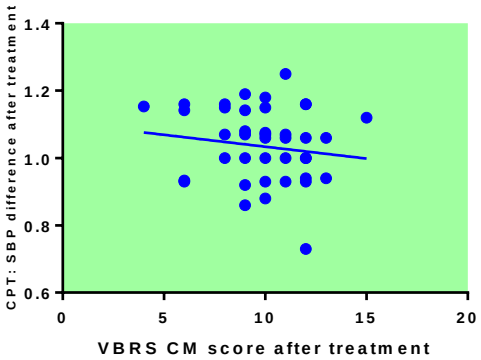

Fig-2: Graph showing significant correlation CPT Systolic Blood Pressure difference with Vanderbilt combined (CM) score after 12 weeks of methylphenidate treatment

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