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Autonomic functions and HRV in Attention-deficit/hyperactivity disorder (ADHD)

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Abstract : *The present study was conceived with the objective to evaluate the literature on Autonomic functions and HRV (Heart Rate Variability) in patients with ADHD relative to controls and the effects of stimulant drugs on Autonomic functions and HRV. Underarousal of the sympathetic system has been proposed in patients of ADHD in several studies. Abnormality in the Autonomic functions is associated with increased cardiovascular morbidity as revealed by various studies. Stimulant drugs like methylphenidate alter the autonomic functions which could be attributed to the adrenergic effects of these drugs as well as the cardiac vagal modulation linked to the improvement in the disease condition. Monitoring of Autonomic functions in patients of ADHD at regular intervals may help in reducing the risk for cardiovascular disease and mortality.*
Keywords - *ADHD, Autonomic functions, HRV*

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I. Introduction

Attention-deficit/hyperactivity disorder (ADHD) is the commonest mental illnesses in childhood and adolescence with a worldwide prevalence of 7.2% [1]. The genetically mediated abnormalities in the neurotransmission could contribute to the discrete dysfunctions in the prefrontal cortex, limbic system, locus coeruleus-noradrenergic system and other related brain structures in patients of ADHD. These structures are also included in the neuro-cardiac complex regulation[2,3]. Spectral analysis of HRV allows non-invasive measurement of autonomic modulation of the sinoatrial node[4]. HRV is an index of central-peripheral neural feedback and CNS (Central Nervous System)-ANS (Autonomic Nervous System) integration[5]. Hence the HRV analysis can be used to study the possible links between mental disorders and cardiac autonomic regulation[6,7]. According to polyvagal theory, Respiratory Sinus Arrhythmia is considered as an index of cardiac vagal modulation and emotional regulation. As ADHD is associated with emotional dysregulation, a potential connection between ADHD-linked emotional dysregulation and reduced cardiovagal function might represent the possible mechanisms leading to the altered HRV in patients suffering from ADHD[8,9]. According to Thayer JF 2007, depressed HRV is a powerful predictor of arrhythmic events and mortality. Depressed HRV not only reflects the sympathetic overdrive or vagal withdrawal due to poor ventricular performance but also indicates depressed vagal activity which has a strong association with the pathogenesis of ventricular arrhythmias and sudden cardiac death[6]. HRV and autonomic functions have consistently been found to be impaired in ADHD in various studies. Underarousal of the sympathetic system has been proposed as a major pathophysiological mechanism in children with ADHD[10-13]. Methylphenidate affects the autonomic imbalance experienced by the children[14].

II. Methodology

Studies published in peer-reviewed journals at any time from databases of MEDLINE (PubMed) and Google Scholar search engines were searched. The keywords used were "ADHD," "Autonomic functions," "HRV," "Methylphenidate," and "treatment." The reference list of recently published relevant articles and reviews were also screened. Titles, abstracts, and full texts of peer-reviewed articles about related topics published were included. Only studies published in English were included.

Autonomic functions and HRV in ADHD

Autonomic function tests have been used extensively in clinical trials. They can be grouped into three general categories of autonomic activity: cardiovagal tests, adrenergic tests, and sudomotor tests[15].

Changes in HRV reflect the action of sympathetic and parasympathetic nervous systems. Analysis of the beat-to-beat interval variations in a continuous electrocardiogram (ECG) provides a non-invasive method of assessing the modulation of the autonomic nervous function. The separate contributions from sympathetic and

parasympathetic activity modulate the heart rate (RR) intervals of the QRS complexes in the ECG at distinct frequencies. Sympathetic activity is associated with low-frequency (LF) range while parasympathetic with higher frequency (HF) range. This difference in frequency ranges allows HRV analysis to separate sympathetic and parasympathetic contributions[16].

ADHD in is associated with abnormal parasympathetic mechanisms[10-12,17].

In a study conducted by Bianca Lee Negrao et al. in 2011, stimulant-free children with ADHD had a parasympathetic dominance of autonomic balance relative to the control subjects[10].

Malligurki Raghurama Rukmani et al. conducted a study at the National Institute of Mental Health and Neuro Sciences (NIMHANS), Bangalore, India on ten children with ADHD. In this study HF power was reduced, LF/HF ratio was higher, and SDNN(Square Root of the Variance of RR intervals), RMSSD(Square Root of Mean Squared Differences of the Successive RR intervals) & pNN50 were reduced in ADHD group as compared to the control group. A reduction in HF power signifies reduced parasympathetic activity. An increase in LF/HF ratio indicates that there was a sympathovagal imbalance with sympathetic dominance. The decrease in SDNN signifies a reduction in overall HRV while a decrease in RMSSD and pNN50 signifies a reduction in parasympathetic activity[18].

Carvalho et al. analyzed the time and frequency domains of HRV in stimulant-free children with ADHD and controls. They found that stimulant-free children with ADHD had parasympathetic dominance of the autonomic balance relative to control subjects[19].

Changes in Autonomic functions and HRV with Methylphenidate treatment

Psychostimulants are the first-line treatment for ADHD as they are more effective in treating ADHD symptoms than behavioral therapy alone. Methylphenidate is one of the most commonly used medications for ADHD treatment[20].

A study by Negaro et al. on HRV has shown that stimulant-free children with ADHD showed a sympathetic underarousal and parasympathetic overarousal relative to control subjects and methylphenidate shifted the autonomic balance of children with ADHD towards normal levels[10].

In a study conducted by Ingrid Tonhajzerova et al. in 2009, the mean R-R interval was significantly shorter in the ADHD group compared to controls. The parameters RMSSD, HF, log HF power, were substantially lower and LF/HF ratio was significantly higher in the ADHD group compared to controls. The parameters MSSD, CCVHF, log HF power, log TP were significantly lower in the ADHD group compared to controls. Patients with ADHD had decreased cardiac vagal activity and tachycardia in the supine position with abnormal activation of the autonomic nervous system in response to change in posture indicating changes in the cardiac autonomic regulation[7]. Tonhajzerova et al. proposed that assessment of early and subclinical abnormal signs of autonomic functions is essential in the psychopharmacological management of ADHD [21,22].

A study by Buchhorn R, 2012 shows that compared to healthy controls the ADHD children with and without methylphenidate treatment showed significantly higher mean heart rates. Moreover, RMSSD values were lowest in ADHD children without methylphenidate, middle in ADHD children with methylphenidate and highest in controls. SDNN values were not significantly different in the two groups. This study showed that there was a lower vagal tone with significantly diminished HRV and higher heart rates in unmedicated ADHD children. Methylphenidate treatment ameliorates these parameters of autonomic activation. No evidence for the negative impact of methylphenidate on HRV was detected in this study[23].

Kelly AS et al., 2014 detected that patients with ADHD had a greater low-frequency to high-frequency ratio and treatment with stimulant medication for ADHD altered cardiac autonomic function characterized by increased sympathetic tone[24].

After scrutiny of literature, it was observed that there is substantial literature on Autonomic dysfunction in ADHD. ADHD is characterized with sympathetic hyporesponsiveness which gets ameliorated with methylphenidate treatment. HRV and other autonomic functions could be an early predictor of individual patient's responsiveness and associated cardiac morbidity risk if any.

Sympathetic skin responses (SCR) is a sudomotor test wherein the recorded skin potential is derived from activated eccrine sweat glands. The amplitude and configuration are modulated by sweat gland epithelium and the overlying epidermis. The respiratory sinus arrhythmia is a primary cardiac-derived index of PNS (indexing resting PNS or vagal tone). Van Lang ND et al.[25] in 2006 showed that the ADHD children had similar skin conductance(SCL) responses as the anxiety disorder group. However, they showed less heart rate reactivity immediately after the stress task which may be due to a stronger parasympathetic than sympathetic activation.

Conzelmann et al. in 2013 reported a general autonomic hypoactivity in ADHD children at baseline and in response to low arousing neutral and highly arousing emotional stimuli. ADHD children without methylphenidate were characterized by reduced baseline SCL and overall reduced SCRs. ADHD children with methylphenidate never differed from control children and the authors hinted that methylphenidate normalizes this hypoactivity[26].

Anthony R et al. in 2015 reported that children with ADHD exhibited marginally higher parasympathetic activity as indexed by respiratory sinus arrhythmia (RSA) at resting baseline compared to controls[27].

Hayeon Jennifer Kim et al. inferred that patients of ADHD had parasympathetic dominance which can be altered by methylphenidate treatment as shown by a decrease in HF and RMSSD. They also suggested the possibility that HRV parameters can be used as psychophysiological markers in the treatment of ADHD[28].

III. Therapeutic Implications

The fact that methylphenidate is associated with a decrease in RMSSD which increases the risk of arrhythmias, cautious use of methylphenidate is warranted, more so in children with cardiac diseases. HRV and other autonomic functions could be an early predictor of individual patient's responsiveness and associated cardiac morbidity risk if any.

IV. Conclusion

The review highlights the importance of autonomic function testing in patients of ADHD whether being treated by stimulant drugs or not. The identification of vulnerable, at-risk patients will assist in preventing cardiovascular morbidity and mortality found to be associated with abnormal autonomic functions observed in patients with ADHD.

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