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Dysregulation of cardiac autonomic function in offspring exposed to alcohol during antenatal period

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ABSTRACT

Several lines of investigations have shown the deleterious effect of an alcohol on the autonomic nervous system. Recent evidence shows that infants exposed to alcohol during the antenatal period displayed aberration in the cardiac autonomic function after the birth. However, there is dearth of literature on the long term influence of antenatal alcohol exposure. In this study we measured the cardiac autonomic functions in children who were exposed to alcohol in the antenatal period and compared them with non-exposed control children. Twenty eight children (age: 9 ± 2 years) in the antenatal alcohol exposed group and age, gender matched 30 non exposed healthy volunteers as a control (age: 10 ± 2 years) were recruited. Electrocardiogram was recorded in all subjects at rest in the supine position. HRV parameters were analyzed in the time and frequency domains using customized software. The average heart rate was similar between both the groups. There was no statistical significant difference in the time domain measures between the groups. However, the low frequency power, normalized units and low frequency to high frequency ratio were significantly higher in the antenatal alcohol exposed children compared to the controls. This suggests sympathetic predominance in children who were exposed to alcohol in the antenatal period. In this study we provide evidence for the deleterious long lasting effect of antenatal exposure of alcohol on cardiac autonomic regulation. Further prospective studies are needed to confirm the causal relationship between antenatal alcohol exposure and autonomic dysregulation.

1. Introduction

Heart rate variability (HRV) is a non invasive tool to characterize the cardiac autonomic regulation. HRV is extensively used to assess the cardiac autonomic function in various psychiatric and neurological illnesses (Abhishekh et al., 2013; Dhargave et al., 2014; Puneeth et al., 2013; Udupa et al., 2007). Acute and habitual consumption of alcohol have been shown to alter the autonomic functions in adults (Murata et al., 1994; Zambelis et al., 2005). Further, recent metaanalysis confirmed deleterious effect of alcohol on cardiac autonomic functions as assessed by HRV (Quintana et al., 2013). Finding of structural brain changes in chronic alcoholics suggests a possible link between the structural brain changes and autonomic functions (Fein et al., 2013; Medina et al., 2008; Taki et al., 2006). The alterations in autonomic neuronal connections by alcohol and its metabolites, particularly in the central autonomic network, may be the reason for the alterations in autonomic nervous output in these individuals. The brain stem neural connections have been particularly shown to be critical in the development and maintenance of dependence in chronic alcoholics suggesting closer link between central autonomic network and alcohol related autonomic damage (CB, 2004; EB, 1997).

Antenatal environment is crucial for the proper development of the fetus. Any alterations can have lifelong implications for the child from that pregnancy. In that sense, exposure of alcohol to the developing fetus, when the mother consumes alcohol poses further threat to the development of organ systems particularly the brain. It is interesting to note that infants exposed to alcohol during antenatal period shown to have aberration in autonomic regulation shortly after birth (Oberlander et al., 2010; Fifer et al., 2009). However, it remains elusive whether such dysregulation of autonomic function is long lasting. This study intends to measure the cardiac autonomic function in children who are exposed to alcohol in the antenatal period and compare them with non exposed control children.

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2. Methods

The study has been approved by the Institute Ethics Committee. Children between 6 and 16 years of age were recruited for the study after obtaining written informed consent from the guardian. Parents of these children were interviewed about alcohol intake history. Alcohol consumption status was confirmed from the relatives and social workers in the particular area. Field workers working with Self Help Groups (SHG) in the low economic strata population were contacted first and information collected about the specific population required for the study. Health workers working among the population were also contacted to identify families using alcohol, particularly females consuming alcohol. A total of 132 families were interviewed with particular history based on the field worker's information (areas inside Bangalore city limits) for mothers consuming alcohol having child in the specified age group of the study (6–16 yrs). Families thus identified were interviewed. Twenty eight children, whose mother consumed alcohol during pregnancy, were finally available for the study (Age range 6–14 years, average-10 years). Thirty age matched children, with a history from their mothers regarding alcohol abstinence during pregnancy, were recruited from the same socioeconomic background as controls. The children recruited for the study were screened by detailed history and physical examination. Demographic data of the recruited children were collected. Any history of continuous drug intake by the child or mother during pregnancy, neurological abnormalities, or hereditary neurological disorders were criteria's for exclusion from the study. Specifically, we excluded children with fetal alcohol spectrum disorder. The autonomic function tests were conducted in the Autonomic lab, Department of Neurophysiology, NIMHANS, Bengaluru in presence of subject's guardian. All the tests were conducted between 9.00am and 12.00noon under standard conditions. After familiarizing with lab atmosphere ECG recordings were done after 15 min of supine rest. Lead II electrocardiogram (ECG) and breathing signals were conveyed through analog digital converter (Power lab, 16 channe[i]ls data acquisition system, AD Instruments, Australia) with a sampling rate of 1024 Hz. MLS 310 Module was used to analyze the different HRV measures. HRV was recorded and analyzed as per the guidelines of Task force report (1996). As far as possible it was ensured that children were breathing at their normal respiratory pattern. Twenty minutes basal recordings were recorded and later, a 5 min artifact/ectopic free segment was analyzed to obtain time domain (mean normal to normal (NN) interval, heart rate, standard deviation of NN interval—SDNN, root mean square of successive differences of NN interval—RMSSD) and frequency domain (total power—TP, very low frequency power—VLF power, low frequency power—LF power, low frequency normalized units—LFnu, high frequency power—HF power, High frequency normalized unit—HFnu, sympathovagal balance—LF/HF ratio), parameters of HRV (Malik, 1996; Abhishekh et al., 2014; Dhargave et al., 2014; Udupa et al., 2007).

2.1. Statistical analysis

The autonomic parameters were square root transformed to achieve normal distribution. Independent sample '*t*' test was used for the comparison of the continuous variables.

3. Results

Table 1 provides demographic details of study participants. Twenty eight children (Age: 9 ± 2 yrs, M:F—9:19) in the antenatal alcohol exposed group and 30 children (Age: 10 ± 2 yrs, M:F—16:14) in the control group completed the study. Educational and socioeconomic strata of the both groups were comparable.

Table 1
Comparison of demographic profiles between the alcohol exposed subjects and non-exposed subjects.

	Alcohol exposed children ($n=28$)	Non exposed children($n=30$)	p Value
Age (years)	9 ± 2	10 ± 2	0.463
Gender (M:F)	9:19	16:14	0.134
Height (cm)	122.8 ± 5.4	123.2 ± 6.9	0.785
Weight (kg)	21.9 ± 4.7	22.4 ± 4.3	0.721
Mid arm circumference (cm)	17.8 ± 1.5	17.9 ± 1.4	0.862
Head circumference (cm)	49.5 ± 1.2	49.6 ± 1.3	0.700

Table 2
Comparison of time domain measures of HRV between the alcohol exposed children and their non-exposed counterparts. Values expressed as mean ± SEM.

Parameter	Alcohol exposed ($n=28$)	Non exposed ($n=30$)	p Value
Average heart rate	711.3 ± 17.4	712.1 ± 12.3	0.97
Mean NN (ms)	85.8 ± 2.1	85 ± 1.4	0.74
SDNN (ms)	61 ± 5.9	57.2 ± 4.3	0.67
RMSSD (ms)	50.8 ± 4.6	57.7 ± 5.6	0.41

Alcohol exposed–children exposed to alcohol in-utero/mother consumed alcohol during pregnancy. Non exposed–children not exposed to alcohol in utero/mother not consumed alcohol during pregnancy.
NN—R-R interval (ms); SDNN—standard deviation of NN intervals (ms); RMSSD—square root of the mean of the sum of squares of differences between adjacent NN intervals (ms).

Table 3
Comparison of frequency domain measures of HRV between the alcohol exposed children and their non-exposed counterparts. Values expressed as mean ± SEM.

	Alcohol exposed ($n=28$)	Non exposed ($n=30$)	p Value
Total power (ms^2)	3165.4 ± 403.4	3760.5 ± 533.9	0.55
LF power (ms^2)	954.8 ± 127.3	675.2 ± 95.9	0.09
HF power (ms^2)	1389.9 ± 247.2	1609.9 ± 279.1	0.59
LF nu	36.8 ± 2.8	27.2 ± 1.9	0.01**
HF nu	46.6 ± 2.9	53.3 ± 2.8	0.10
LF–HF ratio (sympathovagal balance)	1.01 ± 0.15	0.60 ± 0.07	0.01**

TP—total power (ms^2); LF—low frequency power (ms^2); HF—high frequency power (ms^2); nu—normalized units.
** $p < 0.05$.

The average heart rate was similar between both the groups. There was no statistical significant difference in the time domain parameters in the antenatal alcohol exposed children compared to controls (Table 2).

The low frequency power and normalized units (LF and LFnu) were significantly more in the antenatal alcohol exposed children compared to controls. The high frequency component of HRV was less in the antenatal alcohol exposed children though there was no significant difference. The LF/HF ratio denoting the sympathovagal balance showed a tilt towards increased sympathetic output in the antenatal alcohol exposed children compared to the non exposed controls. The spectral analysis showed an overall decrease in power in the antenatal alcohol exposed children although it did not attain statistical significance (Table 3 and Fig. 1).

4. Discussion

To our knowledge this is first study investigating the cardiac autonomic measures in older children exposed to alcohol during antenatal period. In this study, there was significant increase in the low frequency and LF/HF parameters denoting sympathetic