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Heart rate variability in adolescents with functional hypothalamic amenorrhea and anorexia nervosa

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ABSTRACT

Aim of this study consisted in assessing the 24-h heart rate variability (HRV), a measure of autonomic nervous system (ANS) imbalance, in 21 adolescents with functional hypothalamic amenorrhea (FHA, 11 normogonadotropic, N-FHA, and 10 hypogonadotropic, Hy-FHA) compared to 21 patients with anorexia nervosa (AN) and 21 controls. As expected, subjects with AN showed a significant dysregulation in multiple HRV parameters, while Hy-FHA patients presented with a dysregulation in a few domains (SDNN, HFr), which was not present in girls with N-FHA, who showed values largely similar to controls. FHA might represent part of the AN biological spectrum, and a link between these two conditions might exist, possibly related to the degree of psychological and/or hormonal dysfunction.

1. Introduction

Functional hypothalamic amenorrhea (FHA) is a common and reversible endocrine pathology due to the suppression of hypothalamic-pituitary-ovarian axis, without any identifiable organic cause. This disorder is characterized by anovulation and amenorrhea (almost 6 months of duration) in previously normal cycling women (Couzinet et al., 1999). FHA is common in adolescents and represents the 15–55% of cases of secondary amenorrhea (Couzinet et al., 1999). FHA is determined by the disruption of GnRH drive (Speroff et al., 1999) with low or normal gonadotropin and prolactin levels, increased cortisol secretion and mild or severe hypoestrogenism (Speroff et al., 1999). Thus, patients with FHA are categorized as normogonadotropic (N-FHA, also called "defect of the positive feed-back") if LH and FSH levels are similar to those seen in the early follicular phase of a normal menstrual cycle, and hypogonadotropic (Hy-FHA) if gonadotropin levels are very low. Interestingly, adolescents with FHA, in particular the Hy-FHA, show a higher incidence of subclinical symptoms of anorexia nervosa (AN) of the "restrictive type", including psychosomatic discomfort, and mild depressive traits (Bomba et al., 2007, 2013). This allows to hypothesize the presence of common features between the two conditions and prompts to design further research on putative common phenotypic features.

A wide range of autonomic system disturbances are described in patients with AN (bradycardia, low arterial blood pressure, and QT-prolongation) (Mazurak et al., 2011). In particular, in adolescents with AN, the evaluation of the autonomic function through the analysis of the heart rate variability (HRV) shows a generalized dysregulation. In particular, the impairment of the sympathetic/parasympathetic balance and the increased parasympathetic tone has been reported in literature, although there is no consensus about this finding (Bär et al., 2006; Lachish et al., 2009; Mazurak et al., 2011). It is still being discussed whether these alterations are reversible with weight restoration (Bär et al., 2006), or not (Lachish et al., 2009), and they probably represent a substrate for cardiac arrhythmias in AN patients. Despite the presence of similarities between the clinical features of AN and FHA (Bomba et al., 2007, 2013), the function of the autonomic system has never been studied in subjects with FHA. Therefore, our aim in this paper was to analyze HRV in a case-control study that compared subjects with FHA (both N-FHA and Hy-FHA), AN, and healthy matched

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controls. In fact, autonomic and endocrine dysfunctions are strictly intertwined and they might contribute to each other's expression (Di Domenico et al., 2013).

2. Materials and methods

2.1. Subject recruitment

Twenty-one adolescent girls with FHA were enrolled and subjects' and parents' informed consent was obtained. A complete patients' history was gained to identify the possible causes of FHA; moreover, all girls underwent a clinical examination and the calculation of body mass index (BMI), blood routine and hormone assays and a radiological evaluation of the sella turcica. Furthermore, the girls underwent a psychiatric evaluation with a specialist in neuropsychiatry, expert in adolescent disorders. FHA was then diagnosed by clinical (amenorrhea for a period ≥ 6 months) and hormonal findings (low or normal levels of gonadotropins and estradiol), and the negativity of the radiological evaluation. Hormonal assays were assessed in fasting conditions between 8:00 and 9:00 A.M. in duplicate. Based on the hormonal profile and history, no FHA patient had polycystic ovary syndrome, Cushing or Addison disease, premature ovarian failure, hyperprolactinemia, hypo/hypertiroidism, and no patient had a history of drug abuse, or had used any medication in the 6 months preceding admission. Anorexia nervosa was excluded in these subjects and none met the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) criteria. The recruited teenagers with FHA were divided into two subgroups on the basis of the hormonal profile (Speroff et al., 1999): 11N-FHA and 10 Hy-FHA (see Table 1).

Twenty-one age-matched (± 1 year) girls with AN of the restrictive type were recruited. The diagnosis of AN was made by a specialist in neuropsychiatry expert in adolescent disorders, according to the DSM-IV criteria (American Psychiatric Association, 2000); blood assessments were performed and the BMI calculated. Finally, the control group (CTRL) was made up of 21 school girls (community volunteers known to the hospital personnel), age-matched (± 1 year), with normal BMI and regular ovulatory menstrual cycles. All CTRL girls had no history of neurological or psychiatric disorders, thyroid diseases, showed absence of androgenic symptoms and they had not taken steroid hormones in the last 12 months. Specifically, eating disorder traits or excessive physical activity were denied both by CTRL subjects and their parents. Blood determinations were not performed on the CTRL group. All the recruited subjects were drug-free and denied substance abuse.

2.2. Heart rate variability (HRV)

Measurement and physiological interpretation of HRV parameters were performed according to the standards of the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology (1996) and all the patients were asked to avoid caffeine, cigarettes or alcohol on the study day and on the previous day from 10.00 P.M onwards. A 24-h ECG recording (Accuplus 363, Del Mar Avionics, Irvine, CA) with implemented software was used to analyze HRV (Zulli et al., 2005). All the ECG recordings started at 09.00 A.M.

ECG records were analyzed according to time-domain methods (i.e., related to the variability of beat-to-beat, or NN intervals) and to frequency-domain methods as previously reported (Zulli et al., 2005). For time-domain, the following variables were assessed: (t1) SDNN, the standard deviation of NN intervals (in milliseconds, ms); (t2) SDANN, the standard deviation of the average NN intervals (in ms); (t3) rMSSD, the square root of the mean squared difference of successive NN (in ms); (t4) pNN50, numbers of pairs of adjacent normal beat (NN) intervals differing by more than 50 ms (NN50) given as the percentage of the total number of NN intervals. For frequency domain, spectral analysis was performed by Fast Fourier Transform analysis of 5-min periods with resting and awake patients and two frequency components assessed: (f1) LF, low frequency (0.04–0.15 Hz), and (f2) HF, high frequency (0.15–0.40 Hz); moreover, (f3) the LF/HF ratio (LFHFr) was calculated.

Patients were asked to stay awake in a supine position between 03.00 P.M. and 04.00 P.M. and to maintain uniform behavior during the 24-h period. Accurate editing was performed by the operator before analysis.

Table 1
Clinical and socio-demographic features of the enrolled subjects.

	AN ($n=21$)	Hy-FHA ($n=10$)	N-FHA ($n=11$)	CTRL ($n=21$)
Age, years	15.9 (1.1)	16.5 (0.8)	15.9 (0.9)	16.2 (1.0)
SES	30.8 (16.7)	32.6 (16.7)	35.6 (16.4)	32.0 (15.8)
BMI	15.1 (2.6)*,#	18.1 (1.1)	18.7 (1.1)	19.7 (1.8)
Amenorrhea, months	15.1 (12.3)	10.3 (4.2)	11.6 (5.9)	N/A
LH, mIU/mL	1.37 (1.4)°	1.8 (0.74)°	2.7 (1.7)	N/P
FSH, mIU/mL	3.2 (2.6)	4.6 (0.46)	5.0 (0.61)	N/P

Analysis of variance (ANOVA) followed by Bonferroni *post hoc* test was used for assessing differences among the four groups. Values are expressed as: mean (SD). AN, anorexia nervosa; Hy-FHA, hypogonadotropic functional hypothalamic amenorrea; N-FHA, normogonadotropic FHA; CTRL, healthy matched controls.
SES, socio-economic status according to Hollingshead's 4-factors index (Hollingshead, 1975); BMI, body mass index. N/A, not applicable. N/P, not performed.

* $p < 0.01$ vs. N-FHA and CTRL;
# $p=0.055$ vs. Hy-FHA; °$p < 0.001$ vs. N-FHA.

2.3. Statistical analysis

Values were expressed as mean $\pm$ standard error (SEM), except where specifically noted. Since the low BMI is a clinical criteria for the diagnosis of AN, firstly Spearman's non-parametric test was performed to study possible correlations between BMI and the HRV variables considered/evaluated. As a second step, an ANCOVA test and Bonferroni Post Hoc test for multiple comparisons were performed to compare HRV scores, obtained in the four groups, including the BMI in the model as a covariate to control its influence on the dependent variables (HRV scores). Moreover, since amenorrhea duration, and LH levels were quite variable in the groups of AN, Hy-FHA and N-FHA subjects, an ANCOVA was performed considering these as covariates to control their possible influence on the dependent variables (HRV scores). In order to integrate the information obtained, a multivariate analysis was then performed including LH, amenorrhea duration and BMI as covariates, to control their possible combined effects on HRV values in the three clinical groups.

Correlation between variables was assessed by two-tailed Pearson's coefficient. Statistical analysis was performed by SPSS (16.0).

3. Results

Clinical and socio-demographic features of all the recruited subjects are shown in Table 1. The groups were comparable in age, socio-economic status, and number of months of amenorrhea (for FHA and AN). The BMI was lower in patients with AN (15.1 ± 2.6 kg/m^2) compared to that of N-FHA (18.7 ± 1.1 kg/m^2; $p < 0.01$), CTRL (19.7 ± 1.8 kg/m^2; $p < 0.01$), and to that of Hy-FHA, even if only in terms of absolute values (18.1 ± 1.1 kg/m^2; $p=0.055$). Patients with AN and Hy-FHA had significantly lower levels of LH when compared to subjects with N-FHA. Both BMI and age were not statistically correlated to any of the reported findings.

The 24-h HRV records were analyzed according to different time- and frequency-domain methods (see above) in the four enrolled groups (see Fig. 1). AN subjects showed a dysregulation of several variables of the time-domain (NN intervals), since higher values were shown for both, SDNN (+22% and +40%), and rMSSD (+40% and +45%), when compared to CTRL and N-FHA

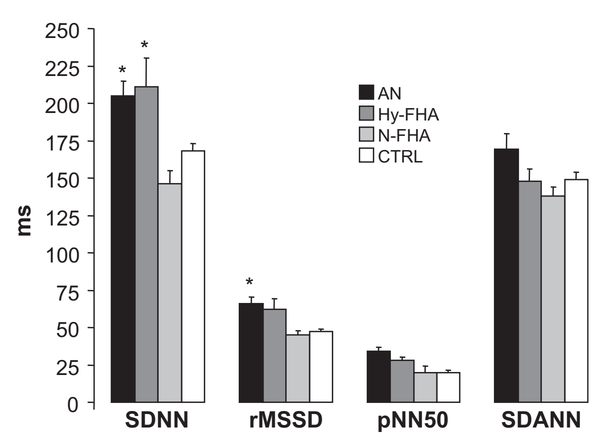

Fig. 1. HRV analysis of time-domain variables. For abbreviations see text. $p < 0.03$ at ANCOVA for both SDNN e rMMSD, followed by Bonferroni *post hoc* analysis, *$p < 0.05$ vs. both N-FHA and CTRL.