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The Correlations of Baseline Autonomic Nervous System Function and Hostility Score with Change Ratio of Treatment Response in Generalized Anxiety Disorder

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Abstract

The relationship between the autonomic nervous system (ANS) index, hostility scale and generalized anxiety disorder (GAD) in the long-term treatment outcome has been rarely studied. The aim of this study was to explore whether the ANS index and hostility scale at baseline are predictors of long-term outcome in GAD. Nine patients with GAD were recruited. At baseline (week 0), blood pressure (BP), heart rate (HR), and mean heart rate range (MHRR) were measured as ANS index; the Cook-Medley Hostility Scale was assessed as hostility. The Hamilton Anxiety Rating Scale (HAM-A) was administered at baseline, short-term (week 6) and long-term (week 52). The aggressive response subscale of the hostility scale was significantly negatively correlated with the HAM-A change ratio in short-term and long-term, while MHRR were significantly positively correlated with these change ratios. The MHRR and the aggressive response subscale at baseline could be predictors of long-term outcome in GAD.

Keywords: Autonomic nervous system function, Generalized anxiety disorder, Hostility, Predictors; Treatment response

Introduction

Generalized anxiety disorder (GAD) is one of the most common mental disorders, with a reported lifetime prevalence of 5-8%, and is associated with poorer adjustment and increased use of health services (Weisberg, 2009). In addition, GAD shares high comorbidity with several physical problems, especially cardiovascular risk (Chang et al., 2016). An elevated cortisol level is usually found in anxiety disorders. Hypothalamic -pituitary-adrenal axis dysregulation not only lead to anxiety symptoms, but may also influence the cardiovascular function. (Mantella, et al., 2008). Also, the symptoms of cardiovascular dysfunction will mimic the physical discomfort of GAD, such as short of breath, headache or chest

tightness, exaggerating worrisome or somatic symptoms in GAD patients. This serves as a reminder that cardiovascular function is related to GAD, which is influenced by the autonomic nervous system (ANS) (Chalmers, Quintana, Abbott, & Kemp, 2014). ANS dysfunction is often noted in GAD (Fisher & Newman, 2013). Examination of ANS function is broadly performed as an index of severity in patients with anxiety and depression (Alvares et al., 2013). Within the variables of the ANS, increased HR at baseline, low HR variability, and a low finger temperature have been observed in patients with GAD (Pittig, Arch, Lam, & Craske, 2013). A positive correlation between the severity of anxiety and ANS dysfunction was noted (Alvares et al., 2013). Biofeedback therapy, combining behavioral therapy and using the ANS index, has been reported to be a good treatment strategy in addition to medication in GAD (Canadian Agency for Drugs and Technologies in Health, 2014). Meanwhile, previous studies have shown that some psychological factors, such as hostility, are associated with anxiety and the ANS index (Deschenes, Dugas, Fracalanza, & Koerner, 2012; Virtanen et al., 2003). Additionally, the hostility score, assessed using a self - reported questionnaire, might be correlated with serotonin activity, which is part of the main action of pharmacological treatment of GAD (Park, Kim, Kim, Im, & Lee, 2010; Yang et al., 2007).

Objectives

Although patients with GAD present a chronic clinical course, most studies regarding the relationship between ANS and GAD have not assessed the long-term outcome following the recommended 12-month medical treatment period (Bereza, Machado, Ravindran, & Einarson, 2012). The aim of this study was to explore whether the ANS index and hostility are correlated with the long-term clinical treatment response in patients with GAD.

Methods

Participants

A total of 16 patients with GAD, 7 males and 9 females, were recruited from the psychiatric outpatient clinic of a university hospital from January 2012 to December 2016; however, 2 participants withdrew during the study, and 5 participants did not complete the one-year follow-up assessment. Only 9 patients with GAD, 4 males and 5 females, completed the one-year follow-up. No significant differences in terms of age, gender, or duration of illness were noted between the patients who did and did not complete the follow-up assessment (Table 1). All participants were assessed using the Hamilton Anxiety Rating Scale (HAM-A). The inclusion criteria for the participants with GAD were as follows: (i) patients should fulfill the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria for GAD; (ii) aged between 18 and 60 years; (iii) no physical illness and stable vital signs, and no evidence of substance abuse/dependence, as assessed during the clinical interview with the research psychiatrist, at the time of enrollment – all participants were confirmed by a senior psychiatrist to be free from any mental disorder except GAD by the MINI Neuropsychiatry Interview (MINI); (iv) free of any psychotropic medication, except benzodiazepines, during the three months prior to the time of testing. The exclusion criteria were as follows: (i) other comorbid psychiatric illnesses, substance abuse/dependence, or severe medical or neurological illnesses; (ii) mental retardation; (iii) pregnancy – all female participants underwent an instant urine pregnancy test prior to enrollment; (iv) patients deemed at risk of acute suicide/self-harm were excluded from the study for their safety.

Table 1: Comparisons between completed and uncompleted participants.

	Completed (N=9)					Uncompleted (N=7)					Statistic	
	N	Mean	SD	Median	Range	N	Mean	SD	Median	Range	χ2/Mann Whitney U	*p*
Gender (male/female)	4/5					3/4					0	0.95
Age (years)	9	41.1	13.9	43.0	23-59	7	35.3	11.9	36.0	22-48	0.90	0.37
Duration of illness (months)	9	52.0	76.3	4.0	1.0-180.0	6	21.9	23.0	12.2	3.2-62.0	0.47	0.64

Study protocol approved by the institutional review board of the National Cheng Kung University Hospital (NCKUH), which confirms to the provisions of the Declaration of Helsinki. Before any procedure was performed, written informed consent was obtained from each of the participants after a complete explanation of the study. This study was of a near-naturalistic design. After recruitment, most of the participants were prescribed sertraline (50–150 mg) with add-on benzodiazepines or other medications for the treatment of anxiety. The antidepressant could be changed to another based on clinical judgment. Hostility and ANS data were collected at baseline (week 0) and HAM-A was collected at baseline (week 0), short-term (week 6) and long-term (week 52). HAM-A change ratio was defined as (HAM-A after treatment – HAM-A at baseline)/ HAM-A at baseline.

Autonomic Nervous System (ANS) Activity during Resting

A full 20-minute period of recumbent acclimati zation preceded the cardiovascular measurements, which started at 10 AM. The beat-to-beat BP of the left radial artery and HR were monitored for 5 minutes while the subject remained in the supine position. BP and HR were continuously monitored using a Tonometry BP Monitor (Colin BP-508, Colin Co., Komaki-City, Aichi, Japan), which has been proven as a reliable instrument (Imholz, 1998), and input into a computer console. The referential BP was recorded by a sphygmomanometer cuff over the right brachial artery and measured at intervals of 2.5 minutes. Whenever the tonometry BP measurement was questionable or failed, cuff measurement automatically started for calibration.

Autonomic Function during the Respiratory Challenge Test

The participants were asked to take a deep breath and the HR was continuously recorded. Each deep breath cycle contained a five-second inspiration and five-second expiration, and 5 successive breath cycles were measured in one assessment. We subtracted the minimum HR during expiration from the maximum HR during inspiration, for each cycle of breathing, the time interval between two cycles being one minute, and then determined the mean of the differences. This was taken as the mean heart rate range (MHRR), which is one of the most widely-used methods by which to assess HRV under the respiratory challenge test (Low, 1977; Shaffer & Ginsberg, 2017; Shields, 2009). The MHRR can be changed by the practice of deep breathing. We adopted the two MHRR, from measurements of a total of three that were most similar, as MHRR 1 and MHRR 2.

Hostility

Hostility was measured using the Cook-Medley Hostility Scale (Cook, 1954). This scale is purported to measure cynical beliefs and mistrust of others, as well as neurotic and antagonistic hostility. Hostility has been used as a valid predictor of medical, psychological and interpersonal outcomes (Barefoot, 1994; Contrada & Jussim, 1992). This 39-item version contains items from the four subscales identified by Barefoot et al. (1995): cynicism (13 items), hostile attribution (12 items), hostile affect (5 items) and aggressive response (9 items).

Statistical Analysis

Because the sample size was small, the

Friedman Test was used to determine whether there was any improvement in the HAM-A score between visits, and the Wilcoxon signed ranks test was used for post-hoc analyses. Spearman's rho correlation was used to test the correlation between HAM-A score, hostility scale score and ANS score. The level of significance was set at $p < 0.05$.

Results

Results of the Friedman Test showed that there was a difference in HAM-A score between visits (baseline: 22.4±8.0, week 6: 11.9±6.3, week 52: 6.8±6.7, Friedman test = 16.22, $p < 0.001$). Post-hoc analyses showed that an improvement in the HAM-A score occurred at week 6 and at week 52 as compared with baseline ($p = 0.008$), but improvement was not observed between week 6 and week 52 ($p = 0.0504$).

The results of Spearman's rho correlation analysis showed that aggressive response was significantly negatively correlated with the HAM-A change ratio between baseline and week 6 and between baseline and week 52, while MHRR 1 and MHRR 2 were significantly positively correlated with these HAM-A change ratios (Table 2).

Table 2: Spearman's rho correlation was used to test the correlations between HAM-A score at different visits, hostility scale score at baseline and ANS score at baseline.

HAM-A	Baseline	Week 6	Week 52	HAM-A change ratio (baseline and week 6)[a]	HAM-A change ratio (baseline and week 52)[a]
	ρ	ρ	ρ	ρ	ρ
Hostility scale					
Cynicism	0.32	0.07	0.05	0.03	-0.07
Hostile affect	0.64	0.17	0.04	-0.11	-0.33
Aggressive response	0.57	-0.18	-0.64	-0.67*	-0.86**
Hostile attribution	0.37	0.17	0.09	-0.03	-0.07
ANS					
MHRR 1	0.14	0.77	0.81*	0.94**	0.81*
MHRR 2	-0.09	0.60	0.81*	0.89*	0.81*
SBP	-0.09	-0.09	0.23	0.09	0.23
DBP	-0.37	0.03	0.72	0.31	0.72
HR	0.71	0.83*	0.06	0.54	0.06

* $p < 0.05$; ** $p < 0.01$
a: the change ratio was computed as (after treatment – baseline)/baseline
HAM-A: Hamilton Anxiety Rating Scale
ANS: autonomic nervous system
MHRR: mean heart rate range
SBP: systolic blood pressure
DBP: diastolic blood pressure
HR: heart rate

Discussion

Early improvement in the HAM-A score has been reported to be a good predictor of treatment outcome in GAD patients (Rynn, Khalid-Khan, Garcia-Espana, Etemad, & Rickels, 2006). In this study, it showed non-improvement of HAM-A score in the longer follow-up between week 6 and week 52. Although there were no studies to investigate this result, it is possible that the residual symptoms of GAD might influence the improvement in the later treatment

course of GAD, and the augmentation of non-pharmacological intervention should be considered (Ravindran & Stein, 2010). Also, in previous studies, sleep disturbance, difficulty concentrating, restlessness, anxious mood, pain severity, neuroticism and psychosocial function have been reported to be strongly associated with outcome in patients with GAD (Bodkin et al., 2011; Pollack, Meoni, Otto, Simon & Hackett, 2003). However, these studies focused in the main on subjective symptomatic presentation, which could imply underlying ANS dysfunction. The results of our study showed that MHRR 1 and MHRR 2 were both significantly positively correlated with the change ratio of the HAM-A score during long-term treatment, but BP and the HR during the resting state were not. Resting ANS function is not sensitive enough to allow identification of autonomic dysfunction according to previous studies (Howorka, Pumprla, Jirkovska, Lacigova, & Nolan, 2010; Shields, 2009). As respiration has a significant effect on heart rate oscillations, the respiratory peak can be used as a quantitative measure of vagal control (Aysin & Aysin, 2006); furthermore, a physiological relationship between the vagal tone of the heart and the HRV with deep breathing has been reported (Shields, 2009), and estimates of ANS function differ during normal breathing and deep breathing (Aysin & Aysin, 2006). Therefore, deep breathing could be considered the most reliable test of parasympathetic functions (Low, 1977), meaning that the MHRR, an ANS index obtained under deep respiration challenge, could be a potential predictor of treatment response in GAD patients. Many researchers have applied different neurophysiological measurements to predict the change in severity of GAD after treatment (Connor & Davidson, 1998; Fisher & Newman, 2013; Makovac et al., 2016; Reeves, Fisher, Newman, & Granger, 2016). Clinically, ANS measurement could be an easily -obtainable and useful tool for the assessment of patients with GAD. It would also be useful to examine whether therapies that improve ANS function could improve the treatment response in GAD patients, such as biofeedback therapy, relaxation therapy or mindfulness therapy (Mankus, Aldao, Kerns, Mayville, & Mennin, 2013; Schoenberg & David, 2014). Also, a poor life quality with increasing stresses that could be correlated with the ANS dysfunction may worsen the severity of GAD (Brotman, Golden, & Wittstein, 2007). Lifestyle modification would be recommended for GAD patients (Sarris et al., 2012).

Hostility is similar to the characteristic of easy anger, which is a diagnostic criterion for GAD. High levels of anger and hostility are contributing factors in GAD (Deschenes et al., 2012). Previous studies have also reported that central serotonergic activities may play a role in hostility (Yang, Yao, Yeh, Lee, Chen & Lu, 2007). One of the neurobiological theories of GAD is related to serotonergic activity dysregulation (Connor & Davidson, 1998). In this study, it was confirmed that a subscale of the hostility scale, aggressive response, was significantly negatively correlated with the change ratio of the HAM-A score. The aggressive response items indicated the respondent's tendency to use anger and aggression as the instrumental response to problems, or endorse these behaviors as reasonable and justified (Barefoot, Dodge, Peterson, Dahlstrom, & Williams, 1989). In another study, intolerance of uncertainty mediated the association of GAD symptoms with anger expression, which also indirectly supported the correlation between hostility and the severity of GAD (Fracalanza, Koerner, Deschenes, & Dugas, 2014). Clinically, due to the high level of hostility and anger, intervention with cognitive or behavioral reconstruction such as cognitive -behavioral therapy will be helpful to these patients (Seligman & Ollendick, 2011).

Limitations

Several limitations should be considered. First, the number of participants was small. Second, a high dropout rate was noted. Third, other ANS indexes were not investigated in this study. Study in which the above limitations are negated could provide a more detailed

understanding of ANS function and hostility in GAD patients.

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Conflict of Interest Statement

The authors declare that they have no conflicts of interest in relation to this work. The funders had no role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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