Psychiatry Research 169 (2009) 149–153

Contents lists available at ScienceDirect

Psychiatry Research

journal homepage: www.elsevier.com/locate/psychres

Panic disorder and social anxiety disorder subtypes in a caffeine challenge test

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ARTICLE INFO

Article history:
Received 1 May 2007
Received in revised form 29 July 2007
Accepted 12 June 2008

Keywords:
Panic attacks
Phobias
Social phobia
Anxiety disorder
Caffeine
Caffeine challenge test

ABSTRACT

Studies have demonstrated the vulnerability of anxiety disorder patients to challenge tests. Our aim was to observe if panic disorder (PD) patients and generalized social anxiety disorder (GSAD) and performance social anxiety disorder (PSAD) patients respond in a similar way to the induction of anxiety symptoms and panic attacks by an oral caffeine challenge test. We compared 28 PD patients, 25 GSAD patients, 19 PSAD, and 26 control subjects after a 480-mg caffeine test. The patients had not received psychotropic drugs for at least a 4-week period. In a randomized double-blind experiment performed in two occasions 7 days apart, 480 mg of caffeine and a caffeine-free solution were administered and anxiety scales were administered before and after each test. A panic attack was induced in 17 (60.7%) PD patients, 4 (16.0%) GSAD patients, and 10 (52.6%) PSAD patients, during the caffeine test. None of the control subjects had a panic attack after the caffeine intake. Neither patients nor any control subject had a panic attack after drinking the caffeine-free solution. Our data suggest that there is an association between PD and PSAD hyperreactivity to an oral caffeine challenge test. The PD and PSAD patients had a higher number of induced panic attacks, some specific anxiety symptoms, and a more severe anxiety response than GSAD patients and normal volunteers.

1. Introduction

Some studies have demonstrated the vulnerability of different groups of patients with anxiety disorders to biochemical and respiratory challenge tests, and have confirmed that patients with panic disorder (PD) are particularly prone to experience panic attacks in response to these tests (Gorman et al., 1981; Perna et al., 1994; Verburg et al., 1998).

Caffeine is one of the most widely consumed psychoactive substances in the world as it is found in beverages, foods, and medications, although most caffeine consumed is derived from coffee, tea, and soft drinks (Uhde, 1990). It is a xanthine derivative that is used worldwide as a psychostimulant, and it may provide a useful biological model of an induced panic attack (Lee et al., 1988; Uhde, 1990). In PD patients, oral administration of caffeine produces a significant increase in subject-rated anxiety, nervousness, fear, nausea, palpitations, restlessness and tremors (Charney et al., 1985), as well as significantly increased reactivity with respect to N2-P2 auditory evoked potential amplitude, N2 latency and electroencephalographic alpha waves (Bruce et al., 1992). Caffeine-induced panic attacks are relatively specific to PD, as healthy volunteers rarely panic with this agent (Nickell and Uhde, 1994–1995). In addition to panic attacks, long-lasting anxiety induced by caffeine includes insomnia and an increase in blood pressure. These symptoms occur at an increased rate and intensity in PD relative to healthy volunteers (Charney et al., 1985; Uhde, 1990).

Caffeine-induced anxiety symptoms did not appear to differ in social anxiety disorder (SAD) versus normal control subjects, and the symptoms induced by caffeine challenge in the SAD group did not mimic their naturally occurring symptoms (Tancer et al., 1995). Tancer et al. (1991) studied 11 subjects in each of three groups: SAD, PD, and normal controls. They found that cortisol levels, but not lactate levels, in SAD patients increased similarly to caffeine-induced increments found in patients with PD.

The generalized subtype of social anxiety disorder (GSAD) is defined by the fear of most social situations, with the remainder of SAD described by various terms such as “discrete”, “circumscribed”, “performance” or “nongeneralized” (Mannuzza et al., 1995). The SAD group usually fears “performance” situations such as public speaking, eating, or writing in public. Persons with GSAD often complain of similar fears, but they also fear social interactions, such as informal conversation, speaking to authority figures, and attending social gatherings (Liebowitz et al., 1985; Mannuzza et al., 1995). Mannuzza et al. (1995) reported that SAD subtypes could be distinguished reliably in a clinical sample of 129 SAD patients, even though the GSAD

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doi:10.1016/j.psychres.2008.06.023

definition (fear of "most social situations") is not fully operationalized. They found that persons with GSAD were often single, had earlier onsets of the disorder, were more often characterized by fear of interpersonal interactions, and had higher rates of major depression and alcoholism and lower rates of PD. Persons with performance social anxiety disorder (PSAD) seem to be responsive to β-blockers, usually have a sudden onset of symptoms, have an onset of disorder that is laterr than that of the GSAD, and seems to have few-ercomorbidities (Liebowitz et al., 1985, 1992; Heimberg et al., 1993; Mannuzza et al., 1995; Nardi, 1996). The studies examining the subtype differences in response to various treatment modalities are few and inconclusive (Liebowitz et al., 1992; Heimberg et al., 1993).

Our research team has been focusing on challenge tests in anxiety and mood disorders, and the caffeine challenge test has been a major focus of our research (Nardi et al., 2007a,b, 2008). Our samples have no overlap in these different trials. Each patient can participate only once in a challenge trial and even the control groups change in each trial for methodological, ethical, and therapeutic reasons. We decided to compare the response of PD patients, GSAD patients, PSAD patients, and a normal volunteers group to an oral caffeine challenge test. We hypothesized that PD and PSAD patients would have more panic attacks and a greater increase in anxiety levels during the test, and that the GSAD and the control group would react to caffeine in a similar way. All the tests were done without using any medication.

2. Methods

We consecutively selected patients with the diagnosis of PD with agoraphobia and SAD, as they presented themselves spontaneously to the Laboratory of Panic and Respiration from the Federal University of Rio de Janeiro. After receiving a clinical diagnosis of PD with agoraphobia, GSAD or PSAD, made by a study psychiatrist, the subjects were interviewed by a second clinician with the Structured Clinical Interview Diagnostic — SCID (First et al., 1997) for DSM-IV (American Psychiatric Association, 1994). If the two clinicians disagreed on the diagnosis, they met to confer, and if a consensus on the diagnosis could not be reached, the subject was not enrolled. Patients who met the DSM-IV criteria for current major depression, bipolar disorder, obsessive–compulsive disorder, schizophrenia, delusional or psychotic disorders, organic brain syndrome, severe personality disorder, epilepsy, or substance abuse or dependence (during the previous year) were excluded. Patients with comorbid dysthymia, generalized anxiety disorder, or past major depression were included if PD or SAD was judged to be the principal diagnosis. For the patients with SAD, the presence of PD comorbidity was an exclusion criterion. During the period of selection for our research program, all PD and SAD patients received a diary in which they recorded any panic attack that occurred between the screen visit and the visits for the caffeine test. The objective of the diary was to check the spontaneous symptoms associated with anticipatory anxiety, panic attacks, and avoidance/agoraphobia.

The protocol was explained to the subjects, who signed a voluntary written consent to participate in the study. The subjects were informed that the procedures were not dangerous and that anxiety symptoms could occur during the tests. Our local Ethics Committee approved the protocol, which complied with the principles of the Declaration of Helsinki.

The inclusion criteria were as follows: 18 to 55 years of age, occurrence of at least three panic attacks in 2 weeks before the first challenge test day for the PD patients, no use of any antipsychotic, antidepressant, benzodiazepine or nonbenzodiazepine anxiolytic medication for at least 4 weeks, or fluoxetine for 5 weeks, before the first test by any subject, and a negative urine test for benzodiazepines and other medications just before each challenge test. Exclusion criteria were: unstable medical condition, cognitive-behavior psychotherapy during the study, or the presence of suicidal risk. Subjects with a history of respiratory disease and smokers were also excluded.

All subjects underwent a physical examination and laboratory examinations to ensure they were healthy to participate in challenge tests. They had no respiratory or cardiovascular abnormalities and were free of caffeine ingestion for 1 week. All the subjects received a list containing the main soft drinks, coffee and tea presentations, and over-the shelf drugs that contain caffeine in order to avoid them during this period. The compliance was obtained by their retrospective report.

In the day of the first caffeine challenge test, the subjects were explained what they were expected to do and an additional 10 min of relaxation was given to them after which we gave them the coffee solution. In a randomized double-blind experiment performed on two occasions 7 days apart, an oral dose of 480 mg of caffeine or a caffeine-free solution was administered in the form of instant coffee, produced regularly by a commercial coffee company. All procedures were conducted during the morning between 8 and 11 am. The decaffeinated coffee contained some small amount of caffeine as more than 97% of the caffeine was removed resulting in less than 5 mg of caffeine intake. The source of caffeine used does not guarantee that the doses given in the challenges were accurate. Most of the caffeine products (e.g. caffeine citrate) are quite bitter. In order to deal with the caffeine-free drink (placebo), we used two tablets of a low calorie sweetener sucralose (0.2 cal/tablet) in the caffeine and in the caffeine-free drinks. The patient was requested to drink the coffee solution within a period of 15 min, after which a 30-min period followed before the measurements procedures, so that the caffeine could reach its peak levels in the blood (Blanchard and Sawers, 1983).

To measure the baseline anxiety level, subjects were asked before each challenge test to complete the Subjective Units of Disturbance Scale (SUDS). A semiquantitative evaluation method ranging from 0 s–no anxiety to 10 s maximum anxiety level (Bech et al., 1986), and the Diagnostic Symptom Questionnaire (Sanderson et al., 1989) was adapted for DSM-IV in which the presence and level of discomfort of panic symptoms experienced after the solutions were rated on a 0- to 4- point scale ranging from 0 s=none to 4 s=very severe. On the basis of the Diagnostic Symptom Questionnaire, an induced panic attack was defined as the following: 1. the presence of four or more DSM-IV panic attack symptoms where either the presence or the increase in DSM-IV symptomatology was used for diagnosis; 2. at least one DSM-IV cognitive panic symptom, i.e., fear of dying, losing control, or going crazy; 3. patient's description of the sensation of panic or fear, resembling real-life panic attacks; and 4. an agreement of two medical doctors that the patient had a clinical panic attack. The SUDS scores were not used to diagnose a panic attack. All these criteria made the diagnosis of a panic attack reliable and clinically significant.

The family history data were collected during the interview with the patient. We also interviewed a first-degree relative of every patient to compare and check the information collected.

2.1. Statistical analysis

Panic rates of symptoms for the four groups were compared by the chi-square test. Data concerning the effects of the tests and time of observation were tested by two-way analysis of variance (ANOVA) with repeated measures for time and independent groups for SUDS (before and after). Age and the age when the disorder started were compared with the Mann–Whitney test. Gender was compared by χ^2 test. Pairwise comparisons of the groups were performed by applying Fisher's protected least significant difference method. The level of significance was set at 5%.

3. Results

We selected 28 PD patients (19 women; mean age 37.4 years ± 8.6); 25 GSAD patients (14 women; mean age 41.5 years ± 10.2), 19 PSAD patients (9 women; mean age 38.2 years ± 9.7), and 26 subjects for the control group (13 women; mean age 35.5 years ± 12.1). There were no gender, age, educational level, marital status, occupation, or previous psychiatric treatment differences among the groups. We compared some clinical aspects of our groups (Table 1). The PD and the PSAD patients had a higher family history of PD; the disorder started significantly later than in the GSAD patients; and they had less history of previous alcohol abuse.

The PD (71.4%) and GSAD groups (60.0%) had more previous depressive episodes than the PSAD group (26.3%) — Table 1. No patient fulfilled the criteria for major depressive episode during our study, but this comorbidity is quite common in anxiety disorder, and PSAD patients seem to have a lower probability of cormorbid depression than PD and GSAD patients.

There were no heavy or moderate-to-heavy caffeine users in our study's sample. The consumption pattern of caffeine of all subjects was as follows: 75.0% consumed soft drinks regularly, 69.4% chocolate products, 65.3% coffee, and 27.8% tea. The average and median potential daily intakes of caffeine by the sample were 2.51 ± 0.86 for PD, 2.44 ± 1.05 for GSAD, 2.67 ± 0.96 for PSAD, and 2.13 ± 1.15 mg/kg for the control group (Mann–Whitney, $P=0.803$). No patient mentioned any problem/symptom that appeared to be associated with abstinence from caffeine during the period preceding the caffeine testing.

A panic attack was induced in 17 (60.7%) PD patients, in 10 (52.6%) PSAD patients, and in 4 (16.0%) GSAD patients after the caffeine test ($\chi^2=25.4$, $df=2$, $P<0.001$). None of the control subjects had a panic attack after the 480-mg caffeine intake ($\chi^2=75.4$, $df=3$, $P<0.001$). Neither patients nor control subjects had a panic attack after drinking the caffeine-free solution.

The self-rating of SUDS before the caffeine test was 2.4 ± 1.8 for PD; 2.1 ± 1.5 for GSAD; 2.2 ± 1.2 for PSAD, and 2.4 ± 2.0 for the control group. After the test the ratings were 8.3 ± 5.6 for PD; 7.9 ± 5.0 for PSAD; 3.6 ± 3.5 for GSAD; and 3.8 ± 3.2 for the control group. All