

Role of family history and 5-HTTLPR polymorphism in female seasonal affective disorder patients with and without premenstrual dysphoric disorder

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Abstract

Seasonal affective disorder (SAD) and premenstrual dysphoric disorder (PMDD) share many clinical features, and have been associated with brain serotonin dysfunction. Females with SAD frequently fulfil the diagnostic criteria for PMDD. A polymorphism in the serotonin transporter promoter gene (5-HTTLPR) has been associated with SAD. We investigated the role of family history and 5-HTTLPR in female SAD patients with and without PMDD. Forty-four SAD females with, and 43 SAD females without PMDD, were genotyped for 5-HTTLPR. Family history of affective disorders in first degree relatives was assessed. An association between the presence of PMDD and family history ($P=0.0029$) and 5-HTTLPR long/short allele-heterozygosity ($P=0.033$) was found in females with SAD. PMDD and SAD may share genetic vulnerability factors, one candidate gene being 5-HTTLPR. The elevated rate of affective disorders in relatives of patients with SAD and PMDD suggests higher genetic vulnerability in this subgroup when compared to patients with SAD alone. © 2002 Elsevier Science B.V./ECNP All rights reserved.

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1. Introduction

Premenstrual dysphoric disorder (PMDD) and seasonal affective disorder/winter type (SAD) according to DSM IV (American Psychiatric Association, 1994), are cyclical disorders, and symptoms that recur and remit in both disorders are strikingly similar. Apart from depressed mood, poor concentration, irritability, loss of interest, and disruption of work or relationships, PMDD and SAD are typically manifested by so-called atypical or reverse vegetative symptoms, such as increased appetite, carbohy-

drate craving, fatigue, and hypersomnia. Many of the symptoms and behaviors characteristic of PMDD and SAD reflect disturbances in functions regulated by central serotonin (5-HT; Wurtman, 1990) which is known to play a key role in the regulation of circadian and seasonal rhythms, the control of food intake, and the mediation of mood (for review, see Wallin and Rissanen, 1994). Patients with SAD and women with severe premenstrual symptoms differ from normal controls in peripheral serotonergic measures (Smedh et al., 1999; Ashby et al., 1990) and neuroendocrine and behavioral responses to serotonergic challenge methods like tryptophan depletion (Neumeister et al., 1997; Lam et al., 1996; Menkes et al., 1994), and fenfluramine challenge (Coiro et al., 1993; FitzGerald et al., 1997). Serotonergic agents like L-tryptophan (Lam et al., 1997; Steinberg et al., 1999), and *m*-chloro-

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phenylpiperazine (*m*-CPP; Su et al., 1997; Joseph-Vanderpool et al., 1993; Garcia-Borreguero et al., 1995), have proven to rapidly alleviate PMDD and SAD symptoms, and selective serotonin re-uptake inhibitors (SSRIs) have proven to be effective treatments in both disorders (for review, see Partonen and Lonnqvist, 1998; Dimmock et al., 2000).

A recent epidemiological study investigating premenopausal females with SAD showed a prevalence rate as high as 46% for PMDD in comparison to a prevalence rate of 1% for PMDD in healthy controls (Praschak-Rieder et al., 2001) while the estimated prevalence rate in all menstruating women is 4 to 5% (Rivera-Tovar and Frank, 1990). Females with late luteal dysphoric disorder according to DSM-III-R (American Psychiatric Association, 1987) research criteria (LLPD) have shown high levels of seasonality, i.e. seasonal variation in mood, feeding behavior, energy and social activity, and a prevalence rate of 38% for SAD (Maskall et al., 1997). The prevalence rate of SAD in the general population varies with the latitude and is estimated to lie between 2 and 4% (Partonen and Lonnqvist, 1998).

The pathogenesis of both disorders is not fully explored so far. A number of studies have indicated that genetic factors play an important role in seasonality, and the etiology of SAD (Magnusson and Axelsson, 1993; Madden et al., 1996; Jang et al., 1997), and evidence from family and twin studies suggests a substantial heritability for premenstrual symptoms (Dalton et al., 1987; van den Akker et al., 1987, 1995; Condon, 1993; Kendler et al., 1992, 1998).

As both, SAD and PMDD, have been associated with brain serotonin dysfunction (for review, see Steiner and Pearlstein, 2000; Lam and Levitan, 2000), genes involved in the serotonergic neurotransmission are good candidates to explore the heritable tendency to, and the pathogenesis of PMDD and SAD. A polymorphism in the serotonin transporter promoter gene region (5-HTTLPR), has been associated with neuroticism and depression (Lesch et al., 1996). This polymorphism has two frequent alleles, designated long (*l*) and short (*s*). 5-HTTLPR has been shown to regulate the expression of the 5-HT transporter molecule in human cell lines (Lesch et al., 1996). Moreover, a recent study indicates that the short (*s*) allele may be a risk factor for both SAD and the trait of seasonality (Rosenthal et al., 1998).

In the present study we investigated the role of family history of affective disorders and the role of the 5-HTTLPR polymorphism as risk factors for PMDD in females with SAD. Based on the evidence that 5-HTTLPR plays an important role for 5-HT transporter function (Heils et al., 1996; Little et al., 1998; Greenberg et al., 1999), and based on the evidence for a heritable component in both, seasonal symptoms of mood and behaviour, and premenstrual complaints, we tested the hy-

pothesis that 5-HTTLPR genotype and family history of affective disorders are associated with vulnerability to PMDD in females with SAD.

2. Methods and materials

2.1. Patients

Premenopausal females who fulfilled DSM IV criteria for recurrent major depressive or bipolar disorder, and Rosenthal (Rosenthal et al., 1984) and DSM-IV criteria for SAD/winter type were recruited consecutively from our out-patient clinic for SAD in fall/winter 1998/1999 and 1999/2000. A self-rating questionnaire of PMDD symptoms according to the German version of DSM-IV was administered to patients at first presentation to our out-patient clinic in the fall/winter season. Patients with other current Axis I diagnoses or past or present substance abuse were not included in our study.

Forty-eight patients with and 39 patients without suspected PMDD according to the above mentioned screening questionnaire underwent prospective daily self-ratings during two consecutive menstrual cycles to verify the diagnosis of PMDD as requested by DSM-IV. These prospective ratings were performed during natural summer remission in order to exclude symptom overlap with SAD symptoms. PMDD could be verified in 44 females with SAD. In four females with suspected PMDD at first presentation, symptoms were not numerous or severe enough to fulfil diagnostic criteria for PMDD during summer. Thus, they were included into the group with SAD only subjects. Full remission of depressive symptoms during summer remission was ensured using the Structured Interview Guide for the Hamilton Depression Rating Scale, Seasonal Affective Disorder Version (SIGH-SAD, Williams et al., 1988).

Family history of affective disorders in first degree relatives was assessed in the index patient using the Family History Screen (FHS, Lish et al., 1995). All subjects gave written informed consent to participate in our study. The investigation of 5-HTTLPR polymorphism in SAD has been approved by the Ethics Committee of the University of Vienna.

2.2. Genotyping

Genomic DNA was isolated from peripheral nuclear blood cells according to standard procedures. Polymerase chain reaction (PCR) amplification was performed using the primers described by Deckert et al. (1997). PCR products were separated on a 3% agarose gel and visualized by ethidium bromide staining. All laboratory procedures were carried out blind to subject's status.

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