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The 5HTT and MAO-A polymorphisms associate with depressive mood and climacteric symptoms in postmenopausal women

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ABSTRACT

Objective: The aim of this study was to assess the influence of the 44-bp polymorphism in the 5HTTLPR (SLC 6A4) (serotonin-transporter-linked polymorphic region, solute carrier family 6 member 4) promoter region and the 30-bpVNTR (variable number of tandem repeats) polymorphism in the MAO-A (monoamine oxidase A) promoter region on the prevalence of depressive mood and the severity of climacteric symptoms in postmenopausal women.
Material and methods: The study involved 630 women from northern Poland who had their last menstrual period at least one year before the study. The women did not abuse alcohol or cigarettes, had not been diagnosed as having endocrinological, cancerous or mental diseases, and had not received psychiatric treatment by the time. This survey-based study was performed using the following research instruments: the Beck Depression Inventory (BDI), to evaluate depressive symptoms, and the Blatt–Kupperman Menopausal Index, to measure the severity of climacteric symptoms.
Results: The average age of the women was 57.5 ± 6.4 years. Depressive symptoms of different severity according to the BDI were diagnosed in 29.2% of the women (minor—18.6%, moderate—7.1%, severe—3.5%) and according to the Blatt–Kupperman Menopausal Index were diagnosed in 42% of the women (minor—24.1%, moderate—9.2%, severe—8.7%). Allele 'l' was significantly more common in the women without climacteric symptoms than those with minor, moderate or severe climacteric complaints ($p \leq 0.05$). There was a significant correlation between the severity of climacteric and depressive symptoms ($p \leq 0.05$). The women who had severe climacteric symptoms also had more severe depressive symptoms.
Conclusions: 1. The 5HTTLPR gene polymorphism contributes to climacteric symptoms in postmenopausal women. 2. The Blatt–Kupperman Menopausal Index is an instrument which can not only be used for the measurement of the severity of climacteric symptoms but also the early detection of perimenopausal women at the risk of developing depressive symptoms.

1. Introduction

As a consequence of longer life spans, today's women spend 30% of their lives in the postmenopausal period. The health problems that they experience after their last menstrual cycle have become a serious challenge for modern medicine and the social sciences (Broekmans et al., 2009; Henderson and Sherwin, 2007; Thurston et al., 2008). The climacteric period is a transitional period, starting several years before and ending a few years after menopause, i.e., after the last normal menstrual cycle in a woman's life. Menopause usually occurs between the ages of 48 and 52, as a consequence of the complete loss of ovarian follicles, and is followed by the cessation of menstrual bleeding for at least one year (Word Health Organization, 1996).

Hormonal changes, especially estrogen deficiency, in menopausal women are responsible for numerous clinical symptoms, mainly hot flashes and excessive sweating (Broekmans et al., 2009; Grycewicz and Cypryk, 2008). Their occurrence is associated with changes in neurotransmitter concentrations (mostly adrenaline, serotonin, dopamine, opioids and prostaglandin acting locally on the central nervous system), which result from a lack of estrogen receptor stimulation in the limbic system (Chakraborty et al., 2007; Thurston et al., 2008). Approximately 90% of women suffer from mental disorders manifesting as sudden mood changes, problems coping with

Abbreviations: 5HTT, serotonin transporter; 5HTTLPR, serotonin-transporter-linked polymorphic region; BDI, Beck Depression Inventory; ICD-10, International Statistical Classification of Diseases and Related Health Problems; MAO-A, monoamine oxidase A; MHT, menopause hormone therapy; PCR, polymerase chain reaction; SLC6A4, solute carrier family 6 member 4; VNTR, variable number of tandem repeats.

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everyday stress, fatigue, nervousness, irritability, poor concentration, memory impairments, somatic complaints that do not respond to treatment, and full-blown depression (Jagielska et al., 2007; Pertyński and Stachowiak, 2006; Sprawka et al., 2008).

Although efforts to identify biological, mental and social risk factors have been made, the mechanism through which depressive symptoms develop during the perimenopausal period is not yet completely understood. It is estimated that about 40–50% of personality difference result from genetic predisposition (Pełka-Wysiecka et al., 2012). It is believed that changes in the monoaminergic system, which affect the expression of personality traits, mental functions and behavior, may play a large role in the development of mood disorders (Jabbi et al., 2007). It has been demonstrated that the monoamine imbalance may contribute to depressive symptoms in women (Newport et al., 2004). Pharmacological treatment, which is based on medications that contribute to the monoamine reuptake and metabolism, has profound therapeutic effects (Nonacs et al., 2005). The genes bearing the greatest responsibility for the functioning of the monoamine neurotransmitter system have been identified. They include monoamine oxidase A (MAO-A) inhibitors and the serotonin transporter (5HTT). The expression of these genes depends on the type of polymorphism they contain, which may predispose the occurrence of particular mood disorders (Jabbi et al., 2008). One of the most commonly studied genes from this group is SLC6A4, a gene encoding the serotonin transporter (Caspi et al., 2003; Serretti et al., 2006). The 5HTT is an integral membrane protein that moves the serotonin neurotransmitter from the synaptic cleft to presynaptic neurons. The 5HTT protein is encoded by a single gene on the 17q12 chromosome. This gene has a polymorphism that is characterized by the insertion or deletion of a 44-bp fragment, resulting in either a short or a long allele and the diversification of gene transcriptional activity. A short allele confers reduced ability to reuptake serotonin compared to a long allele (Heils et al., 1996).

Genes involved in serotoninergic routes are regarded as candidate genes due to the documented role of serotonin (5HT) in the etiopathogenesis of mood disorders. Available research results suggest that the presence of allele 's' of this gene is related to higher neuroticism and the development of mood and anxiety disorders (Stein et al., 2009). Carriers of allele 's' of this gene are more susceptible to affective and anxiety disorders (Ebstein, 2006; Hauser et al., 2003; Lesch et al., 1996). The expression of the 5HTT gene is crucial for neuroticism development (Lesch and Gutknecht, 2005).

Monoamine oxidase A (MAO-A) is essential for the degradation of monoamines such as dopamine, serotonin and noradrenalin, which play a role in the development of depression (Berry et al., 1994). The MAO-A gene may also be responsible for a tendency to develop depression. Sabol et al. (1998) were the first to describe the MAO-A polymorphism, which is a VNTR polymorphism in the MAO-A promoter region. It consists of a 30-bp repeated sequence, which can be present in 3, 3.5, 4 and 5 copies (Black et al., 1991). Allele '3' is associated with lower gene transcriptional activity, while alleles '3.5', '4' and '5' are related to the higher MAO-A activity (Denney et al., 1999). The research carried out by Sabol and Deckert revealed significant differences in the enzyme activity conferred by these alleles. It was noted in in vitro studies that alleles with 3.5 or 4 copies of the repeated sequence are transcribed more efficiently than allele '3'. The research results regarding allele '5R' are ambiguous (Deckert et al., 1999; Sabol et al., 1998).

The authors of this study maintain that the available literature lacks analyses of the correlations between genetic markers and the development of depressive symptoms in the postmenopausal period.

1.1. Aim of the study

The aim of this study was to assess the influence of the 44-bp polymorphism in the 5HTTLPR (SLC 6A4) promoter region and the 30-bp VNTR polymorphism in the MAO-A promoter region on the prevalence of depressive mood and the severity of climacteric symptoms in postmenopausal women.

2. Material and methods

2.1. Subjects

The study involved 630 women from northern Poland who had their last menstrual period at least one year before the study. These women did not abuse alcohol (Grochans et al., 2011), cigarettes, benzodiazepines (Konopka et al., 2013), had not been diagnosed as having endocrinological, cancerous or mental diseases, and had not received psychiatric treatment by the time.

The study was conducted with the consent of the Bioethical Commission of the Pomeranian Medical University in Szczecin (permission number KB-0080/187/09).

2.2. Assessments

The first stage of the study was based on a diagnostic survey performed using standard research instruments, namely the Beck Depression Inventory (BDI) for the assessment of depressive symptoms (Beck et al., 1961), and the Blatt–Kupperman Menopausal Index for the measurement of the severity of climacteric symptoms (Kupperman et al., 1953). A statistical analysis was performed on women without depressive symptoms (up to 10 points in the Beck Depression Inventory) and women with minor, moderate or severe depressive symptoms (over 20 points in the Beck Depression Inventory).

Women with Axis I mental disorders according to the ICD-10 classification were excluded from the analysis by means of the PRIME-MD questionnaire and a psychiatric examination (Spitzer et al., 1999).

The second stage of the study was based on genetic tests; DNA was isolated from whole blood by a salting-out method according to Miller et al. (1988). Polymerase chain reaction (PCR) was used to identify DNA polymorphisms. The aim of the analysis was to amplify the fragment consisting of 2–5 repetitions of the 30-bp VNTR polymorphism in the MAO-A promoter region. The following primer sequences were used: MAO-A F, 5′ CCC AGG CTG CTC CAG AAA 3′; and MAO-A R, 5′ GGA CCT GGG TTG TGC 3′. The sizes of the amplified fragments were as follows: 239, 209, 226, and 269 bp. In the 5HTT polymorphism analysis, the fragment, including the 44-bp ins/del in the regulatory sequence (the presence or the lack of 44-bp), was amplified. The following primer sequences were used: HTT F, 5′ GGC GTT GCC GCT CTG AAT GC 3′; and HTT R, GAG GGA CTG AGC TGG ACA ACC AC 3′. The sizes of the amplified fragments were 484 and 528 bp.

2.3. Statistical analyses

The statistical analysis was performed using STATISTICA 7.1 PL. The chi-squared independence test was applied to verify the null hypothesis regarding the independence of the analyzed variables. Spearman's rank R correlation coefficient was used to identify and test the strength of a relationship between the ordinal variables. The accepted significance level was $\alpha = 0.05$. The power calculated for all of the genetic tests exceeded 0.95 (power > 0.95).

3. Results

The authors of this study investigated two groups of potential contributors to the prevalence of depressive symptoms in postmenopausal women.

1. The 44-bp polymorphism in the 5HTTLPR (SLC 6A4) promoter region and the 30-bp VNTR polymorphism in the MAO-A promoter region:
   - 1.1. With reference to the prevalence of depressive symptoms according to the Beck Depression Inventory (BDI)
   - 1.2. With reference to the severity of climacteric symptoms according to the Blatt–Kupperman Menopausal Index