IMMEDIATE POSTPARTUM DEPRESSION AND THE NT-3 GENE

Valeria Velazquez Jaramillo*, Arturo Gonzalez Santana, Araceli Consuelo Hinojosa Juarez**, Joel Alberto Vargas Hernandez** and Hugo Mendieta Zeron◇,1**

*Universidad Colegio Mayor de Antioquia, Transversal 78 65 - 46, Medelln, Antioquia, Colombia, **Faculty of Medicine, Autonomous University of the State of Mexico UAEMex, Av Paseo Tollocan, Calle Jess Carranza, Moderna de la Cruz, 50180, Toluca, Mexico, ◇Faculty of Medicine, Autonomous University of the State of Mexico (UAEMex), "Mónica Pretelini Sáenz" Maternal-Perinatal Hospital (HMPMPS), Paseo Tollocan 201 Poniente, Col. Universidad, Toluca, México

ABSTRACT Introduction: Postpartum depression has a prevalence range from 6.5% to 12.9%. The NT-3 gene is involved in alterations in patients with mood disorders. **Purpose:** The aim was to describe a possible correlation between the NT-3 expression and the Edinburgh Postnatal Depression Scale (EPDS). **Material and Methods:** It was a clinical, comparative, prospective, and cross-sectional study. Puerperal women were asked to answer the EPDS while mRNA was extracted from peripheral blood and through the qPCR the relative expression of NT-3 was determined using the delta-delta-(CT) method (2-ΔΔCT). **Results and Discussion:** The NT-3 expression was quantified in 5 patients with depression and 6 healthy women. A fold change of 1.7 was obtained when the NT-3 is present in the group with depression in relation to the control group. Also, a positive significant correlation was found between the gene relative expression and the EPDS score (r2 = 0.60516, p = 0.04853). The fold change when the NT-3 is expressed means a risk to develop puerperal depression in our population, which is visualized as an inevitable disease for a wide range of patients. **Conclusion:** It was concluded that the NT-3 gene is effectively correlated with the EPDS score and explains, in part, a subgroup of patients that will develop this health complication.

KEYWORDS Edinburgh Postnatal Depression Scale, NT-3, postpartum depression.

Introduction

Postpartum depression (PPD) is a common disabling mental disorder with options to be treated correctly but underdiagnosed [1]; it is defined by the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) of the American Psychiatric Association, as a major depressive episode "with peripartum onset if the onset of mood symptoms occurs during the pregnancy or within 4 weeks after delivery" [2]. However, some authors consider PPD up to 12 months after delivery with the potential to cause important damage to the woman's health [3]. The estimated prevalence of PPD ranges from 6.5% to 12.9% [4], with some discrepancies in the rates of depression among new generations of parents [5]. The main symptoms are anxiety, irritability, and sleep disturbances. The strongest risk factor for PPD is a history of mood and anxiety problems and, in particular, untreated depression and anxiety during pregnancy [3].

The specific pathogenesis of PPD is unknown, but the rapid decrease in the level of reproductive hormones after childbirth probably contributes to depression development in susceptible women [6]; other proposed contributors include genetics [7] and social factors [8].

The association between maternal depression and breastfeeding duration has been explored previously [9]. Adding to this, Forster et al. demonstrated that women who had depressive symptoms at six months postpartum had significantly lower rates of breastfeeding [10].

The natural course of PPD is variable, with cases of spontaneous remission within weeks after its onset or a permanent state of depression. Furthermore, PPD results in maternal distress leading to diminished functioning, and beyond the interpersonal conflicts, there is a deterioration in the attachment of baby caregivers, as well as an increased risk of emotional, social, and cognitive impairment in the child [11], and in rare cases, suicide or infanticide [12].

The risk of PPD in women who have untreated depression during pregnancy is more than seven times higher than that of women who do not have prenatal symptoms of depression; making it mandatory to start a treatment of prenatal depression

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[1]Faculty of Medicine, Autonomous University of the State of Mexico (UAEMex), "Mónica Pretelini Sáenz" Maternal-Perinatal Hospital (HMPMPS), Paseo Tollocan 201 Poniente, Col. Universidad, Toluca, México, Email: drmendietaz@yahoo.com

as soon as possible [13].

Lastly, genetic studies have identified some genes, which take part in the growth axonal, the regulation of ion channels, the traffic of synaptic vesicles, and the release of neurotransmitters, whose expression is altered in cases of prenatal stress [14]. It has also been shown the altered expression of several genes in the placenta associated with depression [15]. This whole field of susceptibility genes for depression in pregnancy has been little studied and deserves our contribution. For example, the NT-3 gene located on chromosome 12 at position 12p13.31 synthesizes a neurotrophic factor of the neurotrophin family, which is involved in alterations in patients with mood disorders [16].

Clinically, the Edinburgh Postpartum Depression Scale (EPDS) is a ten-item self-report scale designed to identify women who experience depressive symptoms in the postnatal period [17]. The aim of this survey was to describe a possible correlation between the NT-3 expression and the EPDS score.

Materials and methods

In this prospective, comparative and cross-sectional study pregnant women with an age range between 15 and 38 years, attended in the Gynecology-Obstetric service of the "Mónica Pretelini Sáenz" Maternal-Perinatal Hospital (HMPMPS), of the Health Institute of the State of Mexico (ISEM), Toluca, Mexico, were invited to participate. Two groups were conformed: A) With depression and B) Without depression. Women with pre-pregnancy depression, affected by autoimmune, cardiovascular, or renal diseases were excluded, and thus with unsuitable samples were discarded from the final analysis.

Sociodemographic data and depression test

The general information of the patients, including demographics data, was obtained from the Clinical History used in the Hospital. The EPDS was used in all cases. This scale has proved valid as a screening tool for perinatal psychiatric morbidity, with good sensitivity (85.5) and specificity (85.5) [18]. In this survey, a validated Mexican version of the EPDS was used with a cut-off point of 9/10 to detect depression [19].

Sampling

After a fasting period of 8 hours, samples were taken by venipuncture in the forearm, extracting peripheral blood by the vacutainer method. Laboratory analysis performed were cholesterol (mg/dl), creatinine (mg/dl), glucose (mg/dl), triglycerides (mg/dl) and urea (mg/dl) (Dimension R × L Max, Dade Behring, USA). For the genetic analysis, it was collected 1 tube of total blood with EDTA anticoagulant that was kept at -20°C until analysis.

Gene expression

Oligos

The oligos were purchased from the Institute of Biotechnology of the National Autonomous University of Mexico (UNAM) according to the NT-3 sequence previously used by Otsuki et al. [20]. The genes were contrasted against GADPH, and the delta-delta- (CT) method (2-ΔΔCT). was used to obtain the relative expression.

RNA extraction

In the Genetics Laboratory of the Faculty of Medicine of the UAEMex, RNA was obtained using the quick-RNA miniprep Plus kit. The purity and integrity of total RNA were assessed using a NanoPhotometer (Implen GmbH, Germany).

NT-3 expression

In the Research Laboratory of Ciprés Grupo Médico S.C. (CGM) the NT-3 expression was determined by the real-time PCR technique, using the QuantiNova SYBR Green RT-PCR Kit Kit in 8-PRIME-Q equipment (Techne, UK). The oligos used were: for GADPH 5'CTTGGTATCGTGGAAGGACTC3', 3' GTAGAGGCAGGGATGATGTTCT5' and for NT-3 were 5' GAAACGCGATGTAAGGAAGC3' and 3'CCAGCCCACGAGTTTATTGT5'. Cycling was programmed in the following way: a) Retro transcription: 50°C 10 minutes x 1 cycle, b) Activation of the enzyme: 95°C 2 minutes x 1 cycle, c) Denaturation: 95°C 5 seconds x 35 cycles, d) Alignment: 60°C 10 seconds x 35 cycles, e) Extension: 60°C 10 seconds x 35 cycles, f) Melting curve: 72°C, 1 minute x 62 cycles.

Ethical implications

This study was authorized by the Ethics and Research Committees of the HMPMPS (code: 2017-06-528) and was carried out following the ethical standards established in the Declaration of Helsinki (Fortaleza, Brazil). The informed consent was obtained from the patient, her spouse, or the designated legal guardian in case of being a minor.

Statistical analysis

Quantitative variables were represented by measures of central tendency. Using the SPSS software version 23 (IBM, USA), Mann Whitney U test was used to compare the variables between the two groups, and the association between the EPDS score and the NT-3 relative expression was evaluated through the Spearman correlation test. A P value equal to or less than 0.05 was considered as statistically significant.

Results

The mean age of 11 puerperal women was 24.3 ± 6.88 years old. Table 1 shows the general characteristics of the patients without finding significant statistical differences among the studied variables.

When carrying out the PCR to identify the NT-3 gene, a fold change of 1.7 was obtained when the NT-3 gene is present in the group with depression in relation to the control group, and a positive correlation was found between the relative expression of the tested gene and the score obtained with the EPDS ($r2 = 0.60516$, $P = 0.04853$).

Discusión

A differentiating aspect of our study is that we apply the questionnaires in the immediate puerperium, with the theoretical support that after pregnancy termination is when hormonal changes occur and in abrupt biochemical signals that may be associated with different diseases.

Emerging researchers have endeavored to explore genetic causes of PPD (Table 2). Following this line of research, neurotrophins play a critical role in brain development and continue

Table 1 General characteristics of the patients

Variable	Without depression (N = 5) Mean (range)	With depression (N = 6) Mean (range)
Age (years)	25.2 (15-37)	26.8 (20-38)
EPDS (score)	6.2 (4-8)	9.6 (9-12)
Glucose (mg/dl)	91.5 (66-169)	96.1 (70-161)
Cholesterol (mg/dL)	196.7 (147-274)	215 (168-280)
Triglycerides (mg/dL)	233.6 (15120-370)	277 (70-480)
Creatinine (mg/dL)	0.65 (0.51-0.85)	0.59 (0.5-0.86)
Urea (mg/dL)	21.4 (10.7-40.66)	16.26 (8.56-32.1)

to exert their action importantly in the mature nervous system plasticity, and changes in the expression levels of NT-3 mRNA in peripheral white blood cells could be dependent on the state of depression [27].

As a result of this pilot clinical survey, the fold change of NT-3 in this first approach reflects a higher risk to develop this obstetrical complication, adding to the neurotrophin hypothesis of depression, which claims that this mental disease is caused by reduced neurotrophic activity in the brain [28].

Because of the seriousness of this condition, all puerperal women should be screened for PPD, being the generalization of the EPDS application during pregnancy a commonly used tool. Of course, there are important challenges to overcome this last recommendation. First, clinicians who provide obstetrical care may not have the expertise or time during clinical visits to perform the required assessments [29]. In addition, the patients themselves may not recognize a clinical problem mistakenly attributing discomfort as part of the pregnancy process.

To attend appropriately the above-mentioned problems, a practical solution should be for the obstetrical services of any hospital or clinic, to have EPDS in print and with a link to the internet to be answered by all pregnant women when they have time. With the result that they can sum in paper or find automatically with the online questionnaire, the patient can ask for more information in case of a score compatible with PPD.

A main concern is that the benefit of establishing a timely diagnosis of PPD can be diluted if there is a delay in the start of a specific treatment. Fortunately, there is a route to improve the symptoms of the affected women [30].

Finally, studies of susceptibility genes to develop puerperal depression are useful to lay the foundations of specific molecular interventions in the future; and while it is true that, currently they are not available to the poorest countries, which is where hypothetically there would be more cases, due to the stressful environmental factors faced by a pregnant woman, designing a national or regional strategy to set up units of Molecular medicine, progress could be made in studies of gene quantification in this and other diseases.

Table 2 Genes and polymorphism associated with puerperal depression

Genes and polymorphism	Effect
5-HTTLPR polymorphism [21]	protective
ESR1 polymorphisms [22]	risk
ARAP3, CD97, NKG7, RIN1 and TBC1D8 up regulated and HIST1H3D, HIST1H4E, TRIM58 and IGJ down regulated as compared to the control group [23]	risk
Polymorphisms in OXT rs2740210 [24]	risk
The BclI and ER22/23EK polymorphisms of the glucocorticoid receptor and the haplotype-tagged rs1876828, rs242939 and rs242941 SNPs of the CRHR1 [25]	risk
Polymorphisms in FADS1/FADS2 [26]	protective

The most obvious limitation of the present study was the low number of patients. However, patients' indisposition to answer questionnaires in the immediate puerperium can be argued. In conclusion, it is postulated a positive correlation between the EPDS score and the NT-3 relative expression.

Ethics committee approval

This study was authorized by the Ethics and Research Committees.

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Conflict of interest

The authors declared that this project was done independently without any conflict of interest.

Author's Contribution Author contributions

All authors attest that they meet the current International Committee of Medical Journal Editors (ICMJE) criteria for Authorship.

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