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A serotonin transporter gene polymorphism predicts peripartum depressive symptoms in an at-risk psychiatric cohort

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ABSTRACT

Backgroud: Peripartum major depressive disorder (MDD) is a prevalent psychiatric disorder with potential detrimental consequences for both mother and child. Despite its enormous health care relevance, data regarding genetic predictors of peripartum depression are sparse. The aim of this study was to investigate associations of the serotonin-transporter linked polymorphic region (5-HTTLPR) genotype with peripartum MDD in an at-risk population.
Methods: Two hundred and seventy four women with a prior history of MDD were genotyped for 5-HTTLPR and serially evaluated in late pregnancy (gestational weeks 31–40), early post-partum (week 1–8) and late post-partum (week 9–24) for diagnosis of a current major depressive episode (MDE) and depressive symptom severity.
Results: 5-HTTLPR S-allele carrier status predicted the occurrence of a MDE in the early post-partum period only (OR = 5.13, $p = 0.017$). This association persisted despite continued antidepressant treatment.
Conclusions: The 5-HTTLPR genotype may be a clinically relevant predictor of early post-partum depression in an at-risk population.
Objective: Peripartum major depressive disorder is a prevalent psychiatric disorder with potential detrimental consequences for both mother and child. Despite its enormous health care relevance, data regarding genetic predictors of peripartum depression are sparse. The aim of this study was to investigate associations of the serotonin-transporter linked polymorphic region (5-HTTLPR) genotype with peripartum MDD in an at-risk population.

1. Introduction

Major depressive disorder (MDD) during pregnancy and the post-partum period (peripartum MDD) are common, with estimates of point prevalence ranging between 8% and 13% (CDC, 2008; Cox et al., 1993; Dietz et al., 2007; Evans et al., 2001; Gavin et al., 2005; O'Hara et al., 1991). Moreover, a burgeoning clinical and preclinical literature demonstrates an array of adverse sequelae of maternal MDD and stress during pregnancy and the post-partum period including potential life-long effects on the offspring (Brennan et al., 2008; Hammen and Brennan, 2003; Murray et al., 1996; Newport et al., 2002a,b). Some have suggested these enduring effects may be epigenetically mediated (Oberlander et al., 2008). Similar to non-puerperal MDD, psychological stress and family or personal histories of MDD increase the risk of peripartum MDD (Gotlib et al., 1991; Murphy-Eberenz et al., 2006; Paykel et al., 1980). Despite the high prevalence and negative impact on the child, the biological underpinnings of peripartum MDD are not well-defined. Alterations in stress hormones, gonadal steroids, and serotonergic activity have all been implicated in the etiology of this disorder (Bloch et al., 2000; Jolley et al., 2007; Maes et al., 2002; Newport et al., 2004; Steiner et al., 2003).

Family studies suggest a genetic contribution to the risk for peripartum MDD (Forty et al., 2006; Murphy-Eberenz et al., 2006). To date, genetic studies of peripartum MDD have emphasized polymorphisms in genes within the serotonin system, including the serotonin transporter gene (Jones et al., 2000; Sanjuan et al., 2008; Scheid et al., 2007; Sun et al., 2004). The serotonin-transporter linked polymorphic region (5-HTTLPR) is one of the best investigated polymorphisms in psychiatric genetics. Briefly,

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5-HTTLPR (Lesch et al., 1996), a repeat polymorphism in the promoter region of the serotonin transporter gene (SLC6A4) on chromosome 17, has been associated with functional differences in serotonin reuptake. Compared to the long version (16 incomplete 22 base pair repeats), the short version (14 repeats) of the 5-HTTLPR is linked to reduced serotonin transporter gene expression and serotonin uptake (Heils et al., 1996). A single nucleotide polymorphism, rs25531, within the long allele has been shown to moderate the functional impact of this genetic variant further (Hu et al., 2006).

While case-control associations of the 5-HTTLPR with MDD are largely negative (Lasky-Su et al., 2005), an increasing literature supports its interaction with adverse life events to heighten the risk for MDD. While several studies support, at least partially, the initial report of such an interaction by Caspi et al. (2003), some studies report negative results (see Uher and McGuffin (2008) for a recent review; Risch et al., 2009 for a meta-analysis). The 5-HTTLPR has also been associated with antidepressant therapeutic response (Serretti et al., 2007) but see also (Hu et al., 2007). It is thus not surprising that the 5-HTTLPR has also been chosen as a candidate polymorphism in peripartum MDD.

Two existing investigations have reported on the association of the 5-HTTLPR and peripartum MDD, one examining it's influence on post-partum MDD (Sanjuan et al., 2008) and the other gene-environment interactions contributing to mid-pregnancy MDD (Scheid et al., 2007). Replicating previously reported gene-environment interactions in non-peripartum populations (Caspi et al., 2003), Scheid et al. (2007) reported a higher level of depressive symptoms in mid-pregnancy among women with the 5-HTTLPR short (s-) allele and a history of abuse but no main effects of the polymorphism on depressive symptoms. Sanjuan et al. (2008), investigating not the 5-HTTLPR genotype alone but a combined genotype of the 5-HTTLPR and a second tandem repeat polymorphism in intron 2 of the gene, reported that homozygosity of the long (l-) allele (present in high and medium expressing groups but not a low expressing group) was associated with greater depressive symptoms at 8 but not 32 weeks post-partum. Because post-partum depression has been associated with decreased tryptophan bioavailability (Kohl et al., 2005; Maes et al., 2002), the authors contend that this finding is congruent with the heightened sensitivity of high function serotonin transporter gene carriers to the depressogenic effects of tryptophan depletion (Moreno et al., 2002; Neumeister et al., 2006). It is noteworthy, however, that increased sensitivity to tryptophan depletion has also been reported for women carrying the low-expressing S-allele of this polymorphism, especially in combination with a family history of mood disorders (Neumeister et al., 2002). Because the two existing investigations of the impact of the 5-HTTLPR on the risk for peripartum MDD have focused on very different phenotypes, no independent replication of either study has yet been reported. In addition, both studies used a non-psychiatric sample.

The goal of the current study was to conduct a prospective longitudinal investigation of the association of the 5-HTTLPR on depressive symptoms in late pregnancy and the post-partum period in an at-risk cohort of women with prior histories of MDD, ascertaining whether this genetic variant might serve to identify women at highest risk for recurrent depressive illness during pregnancy or the post-partum period. We examined both the 5-HTTLPR alone and the functional classification including rs25531 (Hu et al., 2006), which has not yet been investigated in peripartum MDD. Our study thus explores mechanisms whereby the previous findings (i.e., interaction of the 5-HTTLPR with a history of abuse to predict MDD during pregnancy and a main effect of this polymorphism on post-partum MDD (Scheid et al., 2007; Sanjuan et al., 2008)), may be related to an at-risk clinical cohort. Furthermore, the current study adds a longitudinal prospective component utilizing serial data collection from late pregnancy through the post-partum period.

2. Materials and methods

2.1. Patients and psychometric assessments

Pregnant women (age $\geqslant$ 18 years) with lifetime histories of MDD, presenting to the Emory Women's Mental Health Program (WMHP), were enrolled prior to 20 weeks gestation in a prospective observational study of the perinatal course of MDD. Women were excluded from the present study if they were actively suicidal, exhibited current psychotic symptoms, were severely anemic, had a positive urine drug screen, had an abnormal plasma TSH concentration, or were actively abusing alcohol or drugs within the past 12 months. Failure to extract high-quality DNA from blood samples was also an exclusion criterion. Written informed consent for study participation was obtained, and the Institutional Review Board of the Emory University School of Medicine approved the study.

At study entry, current and lifetime psychiatric diagnoses were assessed using the Structured Clinical Interview for DSM-IV (SCID) (First et al., 1995).

At the baseline and all subsequent follow-up visits, depressive symptom severity was assessed using the 17-item Hamilton Rating Scale for Depression ($HRSD_{17}$) (Hamilton, 1960), and the presence of a current MDE was determined using the SCID Mood Module. For women agreeing to participate in the genetic analyses, mood was assessed during late pregnancy ($\geqslant$30 weeks gestation), early post-partum ($\leqslant$8 weeks), and later post-partum (9–24 weeks). Finally, all medications, maternal daily dose, and self-reported adherence were prospectively recorded at each study visit and at delivery.

2.2. DNA extraction and 5-HTTLPR genotyping

DNA was extracted from whole blood using the Qiagen M48 biorobot (Qiagen Inc.). Genotyping of the 5-HTTLPR used the following primers (forward: 5′-Hex-TGAATGCCAGCACCTAACC-3′; reverse: 5′-ATACTGCGAGGGGTGCAG-3′). PCR was carried out in 384 well plates in a 10 μl volume with 10 ng DNA. Each PCR reaction contained 0.5 μM of each primer, 0.08 μM of dATP, dCTP and dTTP and 0.04 uM of dGTP, 0.2 μM of 7-deaza GTP (Amersham Biosciences), 5% DMSO and 1.25 units of AmpliTaq Gold (Applied Biosystems). The cycling parameters were as follows: 95 °C for 5 min, then 94 °C for 30 s, 63 °C for 30 s and 72 °C for 1 min for 1 cycle, then the annealing temperature was reduced to 62 °C for one more cycle and then to 59.5 °C for 38 cycles. 5 μl of the resulting PCR products was then digested with 5 U MspI (New England Biolabs) in a total volume of 10 μl for 90 min at 37 °C to detect the A/G SNP rs25531 shown to influence the functional effects of the long and short alleles (Hu et al., 2006). The digested PCR products were then separated using an Applied Biosystems 3100 genetic analyzer and analyzed with Applied Biosystems Genemapper 4.0 software. Fragment lengths for the L_A-allele are 291 bp, 148 for the L_G and 247 bp for the S-allele. The VL fragment is 335 bp and the XL fragment 375 bp. The L-VL or L-XL genotypes were each observed in one participant; both were excluded from the analysis.

For quality control, the runs included duplicated samples and positive controls established through re-sequencing.

2.3. Statistical analysis

Statistical analyses were performed using SPSS version 15.0. We used contingency tables and logistic regression to evaluate