Mood changes after delivery: role of the serotonin transporter gene


Background
Polymorphic variations in the serotonin transporter gene (5-HTT) moderate the depressogenic effects of tryptophan depletion. After childbirth there is a sharp reduction in brain tryptophan availability, thus polymorphic variations in 5-HTT may play a similar role in the post-partum period.

Aims
To study the role of 5-HTT polymorphic variations in mood changes after delivery.

Method
One thousand, eight hundred and four depression-free Spanish women were studied post-partum. We evaluated depressive symptoms at 2–3 days, 8 weeks and 32 weeks post-partum. We used diagnostic interview to confirm major depression for all probable cases. Based on two polymorphisms of 5-HTT (5-HTTLPR and Stin2 VNTR), three genotype combinations were created to reflect different levels of 5-HTT expression.

Results
One hundred and seventy-three women (12.7%) experienced major depression during the 32-week post-partum period. Depressive symptoms were associated with the high-expression 5-HTT genotypes in a dose-response fashion at 8 weeks post-partum, but not at 32 weeks.

Conclusions
High-expression 5-HTT genotypes may render women more vulnerable to depressive symptoms after childbirth.

Declaration of Interest
None. Funding detailed in Acknowledgements.

The most likely time for a woman to become depressed is after childbirth.1 Post-partum depression affects approximately 13% of women.2,3 Post-partum depression has a great impact on the family and economy, and is considered a major public health problem.4,5 There is general agreement that the dramatic physiological changes that occur post-partum increase a woman’s vulnerability to depressive symptoms, including post-partum depression.6,7

Pregnancy and delivery are accompanied by hormonal changes as well as lower plasma tryptophan levels, both of which are thought to be etiologically relevant to the mood changes that follow childbirth.6,8,9 Although plasma tryptophan availability is not directly related to mood changes,8 the brain tryptophan availability index is decreased after delivery and is related to depressive symptoms.10 The mood-lowering effects of experimental tryptophan depletion are controversial,11 perhaps because of differences in 5-HTT genotype–tryptophan interaction. In women with previous depressive episodes, 5-HTT genotype may moderate the risk for depressive symptoms after tryptophan depletion.12,13 If childbirth is considered an environmental factor, there may be a strong pathophysiological link between post-partum mood changes and the genes that moderate 5-hydroxytryptamine (5-HT) signalling.

Jans et al14 have proposed the concept of ‘serotonergic vulnerability’. Disruption of the serotonergic system may occur at several levels, including tryptophan availability, 5-HT synthesis, release, reuptake or metabolism, and/or pre- or post-synaptic 5-HT receptors. 5-HTT has received special attention because it plays a crucial role in the regulation of serotonergic function.15,16

In the light of these findings, we designed a prospective longitudinal multicentre study to evaluate interactions between 5-HTT genotype and post-partum mood changes. We hypothesised that 5-HTT genotype would shape the risk for depressive symptoms in post-partum women. We considered three genotype combinations of 5-HTTLPR and Stin2 VNTR polymorphisms that predict differential 5-HTT expression.17 Given that the acute decline in tryptophan availability that follows childbirth resembles experimental tryptophan depletion, we hypothesised that high-expression 5-HTT genotypes would be associated with depressive symptoms in the weeks following childbirth.

Method
Participants
Between December 2003 and October 2004 women (2–3 days post-partum) were recruited in seven acute care teaching hospitals in Spain and invited to participate in a 32-week follow-up study. All participants were Spanish, not under psychiatric care during pregnancy, and able to understand and answer the clinical questionnaire. Women whose children died after birth were excluded. This study was approved by the institutional review boards of the participating hospitals. All women gave written informed consent.

Measures
All participants completed a semi-structured interview that included socio-demographic data: age, education level, marital status, number of children and employment status during pregnancy. Personal and family history of psychiatric illness was also recorded.

Depression
Depressive symptoms were assessed using the total score of the Edinburgh Postnatal Depression Scale (EPDS)18 with a Spanish validated version.19 The EPDS is a 10-item self-report scale with

four possible responses and a total score from 0 to 30. The EPDS was administered at baseline (2–3 days post-partum), 8 weeks and 32 weeks post-partum. All women who scored 9/10 in the EPDS were defined as probable cases of major depression. The cut-off of 9/10 for major depression maximises the sensitivity to 100% and reaches a specificity of 89%.26 All probable cases of major depression were evaluated using the Spanish version of the Diagnostic Interview for Genetics Studies (DIGS)20,21 adapted for post-partum depression. All interviews were conducted by clinical psychologists who were previously trained in DIGS using the same video case records. A high level of reliability (kappa>0.8) was obtained among interviewers.

Genotyping
The Puregene DNA purification kit (Gentra Systems) was used to extract genomic DNA from peripheral blood samples. Two polymorphisms of 5-HTTLPR were analysed, both of which affect 5-HTT expression: 5-HTTLPR, a 44-base pair insertion/deletion in the promoter region, and STin2, a multi-allelic 17-base pair variable number of tandem repeats (VNTR) within intron 2. Alleles of the 5-HTTLPR polymorphism were termed S (short allele with the deletion) and L (long allele with the insertion); the L allele shows higher basal transcription than the S allele.22 Two main alleles of the STin2 VNTR polymorphism have been described: STin2.10 and STin2.12, with 10 or 12 repeats respectively. STin2.12 displays higher transcriptional activity than STin2.10.23,24 STin2 alleles with seven and nine repeats occur at very low frequencies, and thus they were eliminated from the statistical analysis. Linked to 5-HTTLPR deletion insertion of a single nucleotide polymorphism (A/G) has been described.25 This single nucleotide polymorphism somehow modulates the functional effect on 5-HTTLPR promoter polymorphisms on gene expression. However, the STin2 VNTR polymorphism acts as an enhancer having a dramatic effect on gene expression. Moreover, it has been experimentally showed that the combination of both polymorphisms (5-HTTLPR and STin2 VNTR) strongly affect the transcriptional level of the 5-HTT gene.17 So, it seems more relevant to take into consideration the effect of both polymorphisms as a whole.

Taking into account the combined effect of both polymorphisms, significant differences in expression levels could be established based on high expression at one, both or neither of the loci.17 Three types of 5-HTT expression genotype combinations were used for the statistical analysis: no low-expressing genotype at either of the loci (LL/12.12); low-expressing genotype at one of the loci (LL/12.10, LL/10.10, LS/12.12, SS/12.12); and low-expressing genotypes at both loci (LS/12.10, LS/10.10, SS/12.10, SS/10.10).

Statistical methods
Outcomes were the EPDS score and major depression diagnosis at 8 weeks and 32 weeks post-partum. The independent variable was the expression level genotype.

Multiple regression analysis was used to determine whether expression level genotype was associated with EPDS scores. The linear trends were assessed in relation to the degree of genotype loading. The regression model of EPDS score at 8 weeks was corrected using the EPDS score at baseline, and the regression model of EPDS score at 32 weeks was corrected with the EPDS score at 8 weeks. The chi-squared test was used to estimate the significance of association between expression level genotype and major depression at 8 and 32 weeks post-partum. A likelihood ratio test for interaction was used to test whether the association between expression level genotype and depression at 8 weeks differed from expression level genotype at 32 weeks. Given the low power of these tests, a P-value of 0.1 was considered suggestive of differences in effect size at 8 and 32 weeks. STATA version 9.2 was used for the statistical analyses. Two-sided statistical significance was set at P<0.05.

Results
Participants
There were 1974 women who fitted the inclusion criteria for the study, 94 (5%) women refused to participate and 76 (3.8%) women were excluded because their EPDS questionnaires were incomplete. Thus, the final sample comprised 1804 women. At the 8-week follow-up, 1407 (78%) women remained in the study. At 32 weeks, 1337 (74.1%) women were evaluated (Fig. 1). Those women who dropped out during the follow-up period were compared with the final sample, revealing that women from lower social classes were the most likely to drop out (P=0.005). The mean age of the participants was 31.7 years (s.d.=4.6), range 18–46. Of the participants, 32% had attended primary school, 41% finished secondary school and 27% had a college degree. Most participants (68%) were employed, 9% were homemakers or students, 12% were unemployed and 11% were on sick leave or maternity leave. Forty-six per cent of the women were primiparous. Thirty-one per cent of the total sample has a family history of previous psychiatric treatment. Sixteen per cent had a previous personal history of psychiatric treatment.

Clinical variables
Of the 1407 women studied at 8 weeks post-partum, 214 scored 9/10 on the EPDS scale. A diagnosis of major depression was confirmed by DIGS in 112 (7.9%) women. At 32 weeks post-partum, 323 of 1337 women scored 9/10 on the EPDS, but only 61 (4.5%) new cases of major depression were confirmed by DIGS. Overall, 173 women (12.7%) had a major depression episode during the first 32 post-partum weeks (Fig. 1). There were no differences in socio-demographic variables (i.e. age, educational level, employment) between women diagnosed with major depression at 8 weeks post-partum and women diagnosed at 32 weeks post-partum.

Edinburgh Postnatal Depression Scale scores declined over the post-partum period. The mean EPDS score was 6.1 (s.d.=4.5) at baseline, 5.3 (s.d.=4.6) at 8 weeks post-partum and 4.4 (s.d.=4.7) at 32 weeks post-partum (Fig. 2).

Frequency of polymorphisms
Genotype analysis of 5-HTTLPR and STin2 VNTR polymorphisms in the 1804 women revealed the following frequencies: 0.28 LL, 0.48 LL, and 0.24 SS for 5-HTTLPR, and 0.46 STin2.12/STin2.12, 0.42 STin2.12/STin2.10, 0.10 STin2.10/STin2.10, 0.1 STin2.12/STin2.9, and 0.1 STin2.10/STin2.9 for STin2 VNTR. Allele frequencies for the 5-HTTLPR polymorphism were 0.52 for L and 0.48 for S. For the STin2 VNTR polymorphism, STin2.12, STin2.10, and STin2.9 alleles occurred at a frequency of 0.67, 0.32 and 0.01 respectively. Both polymorphisms were in Hardy–Weinberg equilibrium (5-HTTLPR P=0.19; STin2 VNTR P=0.62). No significant differences in the two polymorphisms were observed between samples from the seven different centres, and frequencies were similar to those reported for other Caucasian populations.26 The frequencies of the expression genotypes were: no low-expressing genotype at either of the loci L12;088;
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Genotype frequencies according to serotonin transporter expression

No significant difference in the distribution of major depression according to genotype combination was observed at 8 weeks (P=0.089) or 32 weeks (P=0.125) post-partum.

At baseline, genotype was not a predictor of EPDS score. At 8 weeks after childbirth, EPDS scores were related to 5-HTT expression levels in a dose–response fashion (regression coefficient B=0.45, 95% CI 0.09 to 0.82, P=0.015). At 32 weeks post-partum, EPDS was not related to genotype (B=0.14, 95% CI −0.53 to 0.26, P=0.49) (Table 1, Fig. 2). The test for interaction between time and expression level genotype suggested the difference between 8 and 32 weeks was not due to chance (\(\chi^2=2.7, \text{d.f.}=1, P=0.11\)).

The differences remains significant after correcting for multiple comparison using Bonferroni correction between high expression (no low-expressing genotype at either of the loci) and low expression groups (low-expressing genotypes at both loci and low-expressing genotype at one of the loci) (P=0.045). We also introduce age in our linear regression model with not significant effect on the results (P=0.069).

Discussion

The incidence of post-partum depression in this study (12.7%) is in concordance with previous reports. Although there was a trend (P=0.089), no significant interaction between the expression level genotype and major depression was found. The EPDS score at 8 weeks post-partum was associated with the high-expression genotype. These results are in agreement with our hypothesis that 5-HTT genotype may modulate the mood changes, mainly depressive symptoms, that women experience just after delivery.

A number of factors may explain why the 5-HTT genotype was significantly associated with the EPDS score at 8 weeks, but not with major depression. First, it could be that the lack of significance (P=0.089) may be a statistical problem related to the relatively small sample size of women with major depression (n=173) and/or a weak effect of the 5-HTT genotype. High-expression 5-HTT polymorphisms may promote tryptophan depletion and induce major depression post-partum, but only when other genetic and/or environmental factors are present (e.g. lack of social support or life events). It seems unlikely that EPDS score at 8 weeks may reflect the ‘blues’, a transient emotional liability that affects about 50% of post-partum women. The ‘blues’ are quantitatively and qualitatively different from depression; they emerge during the first post-partum week and disappear by the second week. Moreover, there is some evidence that the DSM–IV or ICD–10 definition of major depression.

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**Fig. 1** Follow-up study of post-partum depression; EPDS, Edinburgh Postpartum Depression Scale; MD, major depression: DSM–IV major depression episode; DIGS, Diagnostic Interview for Genetics Studies; PPD, post-partum depression.

**Fig. 2** Edinburgh Postnatal Depression Scale (EPDS) score over time (2–3 days, 8 weeks and 32-weeks post-partum) in relation to the different 5-HTT genotype combinations. HE, no low-expressing genotype at either of the loci; ME, low-expressing genotype at one of the loci; LE, low-expressing genotypes at both loci.
Table 1: Frequency of different 5-HTT genotype combinations (5-HTT-GC) and Edinburgh Postnatal Depression Scale (EPDS) score at baseline (2–3 days post-partum), 8 weeks post-partum, and 32 weeks post-partum.

<table>
<thead>
<tr>
<th>Expression level genotypes</th>
<th>Baseline</th>
<th>8 weeks</th>
<th>32 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>Regression coefficient (95% CI)</td>
<td>P</td>
</tr>
<tr>
<td>LE</td>
<td>5.85</td>
<td>0.00</td>
<td>4.89</td>
</tr>
<tr>
<td>ME</td>
<td>6.29</td>
<td>0.44 (–0.00 to 0.88) 0.052</td>
<td>5.49</td>
</tr>
<tr>
<td>HE</td>
<td>6.08</td>
<td>0.23 (–0.54 to 1.00) 0.56</td>
<td>6.00</td>
</tr>
</tbody>
</table>

Regression coefficient linear trend: 0.24 (–0.10 to 0.58) 0.16
0.45 (0.09 to 0.82) 0.015
–0.14 (–0.53 to 0.26) 0.49

1. LE: low expressing genotype at either of the loci; ME: low-expressing genotype at one of the loci; LE, low-expressing genotypes at both loci.

2. Summary increase in EPDS score with one unit change in genotypic loading. *P values refer to the differences of ME and HE genotype with LE genotype as reference group.

depression is an arbitrary diagnostic convention imposed upon a continuum of depressive symptoms.31–34 Reduced availability of brain tryptophan during the post-partum period may explain the high (>9) EPDS scores. Experimental tryptophan depletion frequently leads to transient symptoms of depression in vulnerable individuals.35 The brain tryptophan availability index decreases by 15% after delivery and is associated with depressive symptoms.10 This reduction in the early post-partum period is not associated with plasma tryptophan levels8 but rather with a dramatic increase in circulating tryptophan levels during the post-partum period, such as familiality, are in agreement with the above observation, the genotype effect disappears by 32 weeks post-partum.

In summary, our results suggest that there are no ‘bad’ or ‘good’ 5-HTT genotypes in relation to depression. High-expression 5-HTT genotypes might be a risk factor under certain environmental conditions such as tryptophan depletion after childbirth. This study supports a new hypothesis for understanding the biological mechanisms underlying depressive symptoms after delivery and encourages further study of gene–tryptophan interactions in mood disorders.
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In 1986 the British Journal of Psychiatry published a report ‘A case of anorexia nervosa with Klinefelter’s syndrome’ (Hindler CG, Norris, DL. Br J Psychiatry, 149: 659–660). The case was of interest as it was the first documented case of anorexia nervosa in a male associated with Klinefelter’s syndrome. The patient had initially been diagnosed as having ‘atypical anorexia nervosa’ and the Klinefelter’s syndrome was cytogenetically proven. No other associated organic pathology was diagnosed at that time. Specifically, computed tomography (CT) scans were reported within normal limits.

Clinically, the patient had presented (in 1985) with significant weight loss, from 50 kg to 39.9 kg over the preceding 2 years. He had a history of prior admission to the unit (7 years earlier, at the age of 13) with a diagnosis of anorexia nervosa. In addition to the weight loss, he reported vomiting five times per week in the 2 months before the admission, but not as a consequence of binge eating or guilt following perceived overeating. The vomiting was not self-induced. The patient denied any fear of fatness, reporting a loss of appetite, excessive fluid intake and persistently feeling cold (features not inconsistent with anorexia nervosa). His limb length, sexual characteristics and delayed puberty suggested he had Klinefelter’s syndrome.

Following the admission in 1985, a magnetic resonance image (MRI) scan was undertaken due to the onset of an ataxic gait, tremor and noticeable nystagmus. A cerebellar tumour was diagnosed, identified as an ‘atypical teratoma’ during a subsequent neurosurgery. Because of local infiltration and incomplete tumour excision, a course of radiotherapy followed the surgery. Thereafter, the patient gained 5.5 kg over the first 3 months and a further 3.5 kg in the next 6 months to weigh 51 kg. His recovery was generally satisfactory. However, in January 1988 his speech began to slur and he became uncoordinated. A CT scan revealed a tumour in the right frontal lobe. Following surgery (with adjuvant radiotherapy), a germinoma was diagnosed. Review of the pathology findings concluded that both tumours had indeed been germinomas.

Between 1988 and 2000 a number of MRI scans did not reveal any recurrent tumour growth. The patient’s last gadolinium-enhanced MRI scan (2005) showed no evidence of tumour recurrence in either the right frontal lobe or posterior fossa, and generalised cerebral and cerebellar involutional changes, possibly secondary to previous radiotherapy. At the most recent consultation (2006), the patient reported no eating-related concerns and he had no symptoms of an eating disorder.

Given that both tumours (frontal and cerebellar) were diagnosed as germinomas, it may be that although the cerebellar tumour had been the one initially diagnosed, the one in the frontal lobe had been there all along. With hindsight it appears possible that the initial clinical features were more harbingers of the pathology that was ultimately diagnosed, rather than of an eating disorder. Features of a developing neurological disturbance were noted during the various admissions to the eating disorders unit. However, they were not as prominent as the weight loss and vomiting which, together with the diagnosis of Klinefelter’s syndrome and the initial negative CT scans, may have deflected attention. The reported absence of the more complex features of psychopathology usually associated with an eating disorder further suggests a more likely primarily neurological pathology in evolution.

The case highlights a specific clinical issue – the clinical interpretation of disordered eating and the distinction of such behaviour from an eating disorder.
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