Asian Journal of Psychiatry 42 (2019) 74–78

Contents lists available at ScienceDirect

Asian Journal of Psychiatry

journal homepage: www.elsevier.com/locate/ajp

Cytokine alterations in first-onset postpartum psychosis-clues for underlying immune dysregulation

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ARTICLE INFO

Keywords:
Postpartum psychosis
Mania
Depression
Acute Psychosis
Immune
Cytokine
Chemokine

ABSTRACT

Background: Emerging evidence suggests a possible role for immune system dysregulation in the pathogenesis of postpartum psychosis (PP) but the evidence is limited. The current study sought to determine the serum cytokines/ chemokine changes associated with first-onset PP.

Methods: Women with first onset PP were recruited as cases and the cytokines/ chemokine changes were compared against healthy postpartum (HP) and healthy non-postpartum (HNP) women.There were 20 subjects in each of the three groups. Levels of serum cytokines and Monocyte Chemoattractant Protein-1 (MCP-1) were estimated with a cytometric beadarray assay.

Results: HP group showed significantly elevated levels of interleukin (IL)-6 as compared to HNP group. Whereas, the first onset PP group showed significantly elevated levels of both IL-6 and IL-8 as compared to HNP group.

Conclusion: Postpartum period appears to be a state of altered immune functioning considering the elevated level of IL-6 in both HP and PP group. Additionally, IL-8 appears to play a role in the manifestation of PP. Our study highlights the immune alterations associated with first-onset PP.

1. Introduction

Postpartum psychosis (PP) is a severe form of psychiatric disorder occurring within the first few weeks following childbirth. The reported prevalence of PP is 1–2/1000 deliveries and the condition is characterized by an acute onset of symptoms along with significant risks to the mother and infant (Sit et al., 2002). PP is possibly a presentation of underlying bipolar illness with some patients experiencing symptoms only during the postpartum period (Chaudron and Pies, 2003). Several psychosocial and biological factors have been identified as possible risk factors for PP. Biological factors such as sudden drop in oestrogen levels in the immediate postpartum period, sleep and circadian rhythm disruption, dopamine receptor hypersensitivity along with contributing genetic factors have been suggested as possible factors that play a role in the manifestation of PP (Bergink et al., 2013; Kumar et al., 2007; Lewis et al., 2016; Sharma et al., 2004).

Patients with PP have been reported to have higher rates of autoimmune thyroiditis and pre-eclampsia, both of which have an immunological basis (Bergink et al., 2011, 2015). Various autoimmune diseases like rheumatoid arthritis (RA), multiple sclerosis (MS) and autoimmune thyroiditis frequently remit during pregnancy and exacerbate or have their onset in the postpartum period (Häupl et al., 2008; Hughes et al., 2014; Weetman, 2010). Such fluctuations in the clinical course of various autoimmune disorders during pregnancy and postpartum period suggest the underlying changes in the immune system during these periods. Thus far, the possible mechanism suggested to this varying manifestation of the autoimmune diseases, is differential neuroendocrine regulation of T-helper cells type 1 (Th1) and T-helper cells type 2 (Th2) cytokine production (Elenkov et al., 1997). It is reported that during normal pregnancy, there is reduced Th1 function leading to an immunosuppressive state (Marzi et al., 1996; Russell et al., 1997). The rebound activation of the immune system following the delivery plays a vital role in the manifestation of various autoimmune diseases (Elenkov et al., 2001; Weetman, 2010). Also, evidence links the pathogenesis of bipolar illness to an underlying immune dysfunction, characterized by an elevation in pro-inflammatory cytokines (Luo et al., 2016; Munkholm et al., 2013, 2015). In view of the above findings and also because of the link between bipolar disorder and postpartum psychosis, it is likely that immune factors may play a role in the manifestation of PP.

A study that examined the association between immune system activation and first-onset PP found that chemokine MCP-1/CCL2

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https://doi.org/10.1016/j.ajp.2019.03.012
Received 8 December 2018; Received in revised form 16 February 2019; Accepted 25 March 2019

Table 1
Comparison of First Onset Postpartum Psychosis (PP), Healthy Postpartum (HP), and Healthy Non-Postpartum (HNP) Groups on Socio-Demographic Variables.

Variable	PP (N = 20) (Mean ± S.D)	HP (N = 20) (Mean ± S.D)	HNP (N = 20) (Mean ± S.D)	F/Chi	p
Age in Years	22.85 ± 3.63	22.90 ± 3.27	25.25 ± 2.33	3.84	0.027*
Years of Education	10.60 ± 5.12	10.10 ± 3.99	15.30 ± 4.5	7.89	0.001*
Years of marriage	3.02 ± 1.95	3.35 ± 2.58	1.53 ± 0.60	1.63	0.206
Area	10 (50%)	5 (25%)	8 (40%)	2.69	0.262
Rural	10 (50%)	15 (75%)	12 (60%)		
Urban					
Socioeconomic Status	14 (70%)	14 (70%)	12 (60%)	0.60	0.741
Low	6 (30%)	6 (30%)	8 (40%)		
Mid					

* $p \leq 0.05$.

(chemokine (C-C motif) ligand 2) was significantly upregulated and glucocorticoid receptors-alpha (GR-α) with an anti-inflammatory role were downregulated in women with PP as compared to healthy postpartum and non-postpartum women (Bergink et al., 2013).

The research in the area of immune system dysregulation in PP is sparse and the current limited understanding has come mainly from studies involving populations in western countries. The variations in the immune system with geographical factors, socioeconomic factors, and dietary habits are being increasingly recognised (Graham-Rowe, 2011; Logan et al., 2016). Hence, there is a need for further research in the area of immune dysfunction in PP from diverse sociocultural backgrounds. In this study from the southern part of India, we have explored the cytokine and chemokine changes associated with first onset PP.

2. Materials and methods

It is a cross sectional exploratory study conducted at the mother-baby psychiatry inpatient unit, NIMHANS, INDIA over a period of one and half years.

2.1. Participants and procedures

Twenty patients with first-onset PP, defined in the study as acute onset of psychotic symptoms within 6 weeks of delivery of a baby were recruited as cases. Subjects were diagnosed using The International Classification of Diseases, 10th edition (ICD-10). The past history was unremarkable in all the cases. Healthy postpartum women (HP) and healthy non-postpartum women (HNP), twenty in each group were included as controls. Nearly, 50 HP subjects were recruited for the study, but only 20 participants provided consent for the study. Hence, HP subjects were recruited up to 3 months postpartum. Subjects with a diagnosis of schizophrenia, autoimmune disorders and those having clinical signs of infections were excluded from the study. The study protocol was approved by the Institute Ethics Committee and informed consent was obtained from all the participants. Sociodemographic, clinical details and infant related variables were collected by a trained clinician within first few days of admission to the hospital. The clinical severity of the condition was rated using Brief Psychiatric Rating Scale (BPRS). All serum samples were collected in the morning and preserved at -80^0 C. Multiple serum cytokines and a chemokine were measured on a FACS Verse flow cytometer (BD Biosciences, USA) using BD Cytometric Bead Array kit. The following cytokines were measured:

i *Monocytes/ Macrophages/ Dendritic Cells Panel:* IL-1α (Interleukin), IL-1ß, IL-6, IL-8, IL-12p70, TNF-α (Tumor Necrosis Factor-alpha), TGF-β1 (Transforming Growth Factor-beta 1);
ii *Th1/ Th2/ Th17 panel:* IFN-γ, IL-2, IL-4, IL-5, IL-10, IL-13, IL-17A;
iii *Chemokine panel:* MCP-1 (Monocyte Chemoattractant Protein-1).

2.2. Statistical analysis

One-way ANOVA was used to compare normally distributed continuous variables between groups followed by post-hoc analysis. Chi-square test was used to compare categorical variables between groups. Mann-Whitney U, two-independent sample test was applied for comparison of cytokine levels as the data was not normally distributed. All tests of significance were two-tailed and a P value of ≤ 0.05 was considered as statistically significant. Statistical analysis was done with the SPSS software package (version 20.0).

3. Results

3.1. Sample characteristics

The comparison of PP, HP, and HNP groups on sociodemographic variables is shown in Table 1. The comparison of mean body-mass index (BMI) scores among HP (21.47 ± 3.93), PP (22.77 ± 2.55), and HNP (23.95 ± 4.96) groups did not show any significant difference. The comparison of PP and HP subjects on obstetric and infant related parameters is shown in Table 2. The mean duration of the postpartum period in days at the time of sample collection between PP (38.35 ± 25.36) and HP (51.60 ± 30.62) groups was not statistically significant. All the women in HP group provided exclusive breastfeed to their infants. However, women in PP group provided formula feeds in addition to breastfeeds, when considered necessary. Patients had received second-generation antipsychotics such as risperidone, olanzapine for variable durations. None of the patients received clozapine. Nineteen out of 20 cases (95%) were diagnosed to be suffering from acute polymorphic psychosis and one subject (5%) was diagnosed to have mania with psychotic symptoms.

Table 2
Comparison of First Onset Postpartum Psychosis (PP) and Healthy Postpartum (HP) Groups on Obstetric and Infant Related Variables.

Variable	PP (N = 20)	HP (N = 20)	Chi/t	p
Parity	9 (45%)	11 (55%)	0.400	0.527
Primipara	11 (55%)	9 (45%)		
Multipara				
Gestation Age	20 (100%)	17 (85%)	3.24	0.07
Term	–	3 (15%)		
Preterm				
PIH	17 (85%)	19 (95%)	1.11	0.292
Absent	3 (15%)	1 (5%)		
Present				
Mode of delivery	15 (75%)	19 (95%)	3.13	0.07
Normal	5 (25%)	1 (5%)		
Instrumental				
Gender of Baby	8 (40%)	12 (60%)	1.60	0.206
Male	12 (60%)	8 (40%)		
Female				
Birthweight (Kg)	2.67 ± 0.56	2.69 ± 0.76	−0.078	0.939

Table 3
Cytokines Levels in Patients with First Onset Postpartum Psychosis Measured By BD Cytometric Bead Array (CBA) Assay Compared With Healthy Postpartum and Non-Postpartum Controls.

Cytokines *[pg/mL]*	PP *n = 20* Median (Range) [Interquartile Range]	HP *n = 20* Median (Range) [Interquartile Range]	HNP *n = 20* Median (Range) [Interquartile Range]	*p*-Value*		
				PP Vs HP	PP Vs HNP	HP Vs HNP
IL-6	0 (0- 387.31) [0-13.3]	1.31 (0- 767.13) [0-22.41]	0 (0 – 48.14) [0-0]	0.66	**0.05***	**0.03***
IL-8	62.90 (0-7766.29) [24.7 – 155.6]	25.32 (0 – 1465.09) [21.0 - 402.6]	25.86 (0 - 1157.28) [5.3 – 47.4]	0.79	**0.03***	0.12

* Values in bold indicate statistical significance ($p \leq 0.05$).

3.2. Serum cytokines and chemokine analysis

The comparison of serum cytokine levels that were significant are presented in Table 3. We specifically abstained from presenting the comparison of serum cytokine and chemokine levels that were not detectable and also non-significant. PP group was found to have significantly increased levels of IL-8 (p = 0.03*) as compared to HNP group as demonstrated in Fig. 1. However, there were no significant differences noted between PP vs HP groups (p = 0.79) and HP vs HNP groups (p = 0.12). With respect to IL-6, both the PP and the HP groups were found to have significantly elevated levels as compared to the HNP group (p = 0.05 and p = 0.03) as demonstrated in Fig. 2. However, no significant difference was noted between PP vs HP groups (p = 0.66).

4. Discussion

Our study assessed the cytokine and chemokine changes associated with first onset PP as compared to HP and HNP groups. In the monocytes/ macrophages/ dendritic cells panel, IL-6 levels were found to be significantly elevated in both HP and PP groups when compared with HNP group. Earlier studies have reported increased IL-6 levels during the immediate postpartum period in healthy postpartum women (Groer et al., 2015; Ishikawa et al., 2004). Levels of IL–6 tend to increase during pregnancy and come down to the pre-pregnancy levels by 8–10 weeks postpartum (Gillespie et al., 2016). Therefore, the increased levels of IL-6 in both the HP and PP groups could be possibly suggestive of a normal postpartum physiological response. These findings probably suggest that pro-inflammatory cytokine IL-6 may not have an independent role in the pathogenesis of PP as it remains elevated in both the postpartum groups i.e., HP and PP.

In our study, PP group as compared to HNP group showed significantly elevated levels of IL-8, while the levels in HP group were

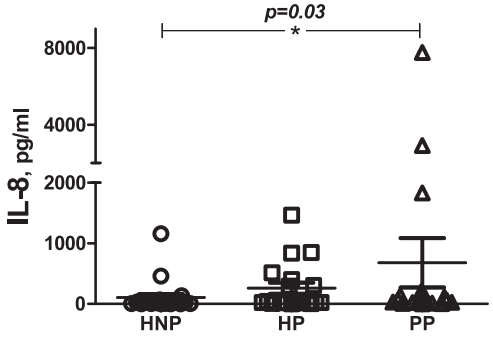

Fig. 1. Serum IL-8 Cytokine Levels in HNP, HP & PP Groups.

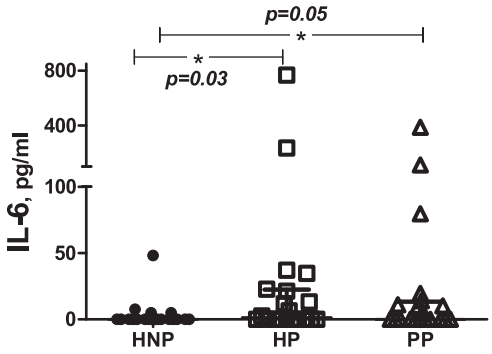

Fig. 2. Serum IL-6 Cytokine Levels in HNP, HP & PP Groups.

almost similar to that of the HNP group. This observation suggests a possible association of IL-8 with manifestation of PP. The literature about the role of IL-8 in PP is sparse. IL-8 has been found to be involved in the recruitment and activation of neutrophils, thereby playing an important role in acute inflammation (Harada et al., 1994). Evidence suggests that IL-8 levels have been significantly elevated in various psychiatric disorders including psychosis (Gariup et al., 2015). IL-8 has also been found to be associated with perinatal depression, first-episode acute psychosis and schizophrenia along with other proinflammatory cytokines (Di Nicola et al., 2013a; Osborne and Monk, 2013; Yang et al., 2002). Individuals with first episode acute psychosis having higher baseline levels of IL-8 responded well to antipsychotic medications (Di Nicola et al., 2013b; Mondelli et al., 2015). It is important to note that our patients were exposed to atypical antipsychotics, which are reported to have both pro- and anti-inflammatory effects in patients with psychosis (Sherer et al., 2017). Haring et al. studied the role of various antipsychotic medications on the cytokine levels in individuals with first-episode psychosis and demonstrated a significant reduction in the serum cytokine levels of IL-8 along with IL-1α IL-2, IL-4, IL-6 and IFN-γ (Haring et al., 2015). Hence, an elevation of IL-8 levels in PP group while being on antipsychotics as compared to HNP merits a further investigation into the relationship between atypical antipsychotics, postpartum psychosis, and IL-8 levels.

A study by Bergink et al. reported elevated levels of IL-1β in the healthy postpartum control subjects as compared to healthy non-postpartum controls and also women in the first onset PP group had higher expression of MCP1 levels as compared to the other two groups i.e healthy postpartum and non-postpartum controls (Bergink et al., 2013). However, we did not find any such associations regarding the IL-1β levels and MCP1 levels in our study.

Study of immune dysfunction has been an active area of interest in the pathophysiology of major psychiatric disorders. Peripheral cytokines level remains the main stay of assessment because of the ethical considerations involved in obtaining the cerebrospinal fluid or brain tissue. Peripheral cytokine levels may not exactly reflect the brain cytokine levels but can affect the production of cytokines in the brain. Further, these cytokines can act as mediators for synaptic plasticity at the tripartite synapse-astrocytes, pre-and post-synaptic neurons that serve as the relay system for immune-CNS interaction (Besedovsky and del Rey, 2011). A metanalysis of various cytokines in schizophrenia reports of elevated levels of IL-1β, IL- 6, IL-12, TGF-β, IFN- γ and sIL-2R (Soluble interleukin 2 receptor). IL- 6, TGF-β and IL-1β are considered as state markers for acute exacerbation of schizophrenia as they tend to normalize with antipsychotic treatment, whereas IL-12, IFN- γ and sIL-2R are considered more as trait marker (Miller et al., 2011). Similarly, a metanalysis of cytokine status in bipolar disorder reveals elevated levels of IL-1β, IL-4, IL- 6, IL-10 and TNF-α in mania (Modabbernia et al., 2013). Failure to detect similar associations among the cytokines that were examined in our study could suggest that first onset PP may have a different immune pathophysiology. However, this observation needs to

be viewed with caution considering the fact that we did not include patients with schizophrenia and mania as controls in our study.

Taken together, the elevated levels of both the pro-inflammatory cytokines IL-6 and IL-8 in PP observed in our study may point towards a synergy between these two cytokines in the immune-mediated pathogenesis of PP. On the other hand, the exclusive elevation of IL-8 in the PP group as compared to HP may suggest an independent role for this cytokine. It is important to note the small sample size, effect of outliers, and also that 14 cytokines were measured in the study. A conservative Bonferroni correction would have required a p value lesser than 0.0035 to be considered as significant. The subject groups in our study were comparable in terms of sociodemographic, obstetric and infant related variables except for differences in age and years of education.

Further studies to investigate the interplay between IL-6 and IL-8 along with other related cytokines and chemokines may provide key insights into the pathophysiology of PP.

5. Conclusion

Our study suggests a possible association between first-onset PP and proinflammatory cytokine IL-8. The role of inflammatory cytokines in the pathogenesis of first onset PP and also the effect of antipsychotics on cytokine levels needs to be examined in future studies.

Limitations

First, we acknowledge the small sample size as a limitation of the study. Second, PP subjects were recruited up to 6 weeks postpartum, whereas HP subjects were recruited up to three months postpartum. The details of antipsychotic dosages and duration of the drug were not recorded.

Conflict of interest

All the authors declare no conflict of interest.

Financial disclosure

The research was supported by National Institute of Mental Health and Neuro Sciences (NIMHANS)Intramural Research Grant ID NIMH/PROJ-RSM/545/2014-15. India.

Acknowledgments

None

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