SHORT COMMUNICATION

Assessment of major mental disorders in a German peripartum cardiomyopathy cohort

Tobias J. Pfeffer[1]*, Julian Herrmann[2], Dominik Berliner[1], Tobias König[1], Lotta Winter[2], Melanie Ricke-Hoch[1], Evgeni Ponimaskin[3], Sven Schuchardt[4], Thomas Thum[5], Denise Hilfiker-Kleiner[1]*, Johann Bauersachs[1] and Kai G. Kahl[2]

[1]*Department of Cardiology and Angiology, Hannover Medical School, Carl-Neuberg-Str. 1, Hannover, 30625, Germany;* [2]*Department of Psychiatry, Social Psychiatry and Psychotherapy, Hannover Medical School, Hannover, Germany;* [3]*Cellular Neurophysiology, Hannover Medical School, Hannover, Germany;* [4]*Department of Bio and Environmental Analytics, Fraunhofer Institute for Toxicology and Experimental Medicine, Hannover, Germany;* [5]*Institute of Molecular and Translational Therapeutic Strategies, Hannover Medical School, Hannover, Germany*

Abstract

Aims   Peripartum cardiomyopathy (PPCM) is a heart disease affecting women during the last month of pregnancy or in the first months after delivery. The impact of the disease on mental health is largely unknown.

Methods and results   Major mental disorders were assessed by a structured clinical interview in 40 patients with a confirmed PPCM diagnosis, and the data were compared with published prevalence in postpartum women. Circulating biomarkers associated with mental health, such as kynurenine, serotonin, and microRNA (miR)-30e, were evaluated in PPCM and compared with matched healthy pregnancy-matched postpartum controls (PP-Ctrl). Major mental disorders were diagnosed in 65% (26/40) of the PPCM cohort. The prevalence for major depressive disorders was 4-fold, for post-traumatic stress disorder 14-fold, and for panic disorder 6-fold higher in PPCM patients compared with postpartum women without a PPCM diagnosis. Compared with PP-Ctrl, PPCM patients displayed elevated levels of serum kynurenine ($P < 0.01$), reduced levels of serum serotonin ($P < 0.05$), and elevated levels of plasma miR-30e ($P < 0.05$).

Conclusions   The majority of PPCM patients in the present cohort displayed mental disorders with a higher prevalence of major depressive disorders, post-traumatic stress disorder (PTBS), and panic disorder, compared with postpartum women without a PPCM diagnosis. This higher prevalence was associated with an impaired tryptophan metabolism and elevated levels of the depression-associated miR-30e, suggesting a potential predisposition for mental disorders at the time of PPCM diagnosis. Consequently, physicians should be aware of the increased risk for mental disorders in PPCM patients, and psychiatric assessment should be included in the diagnosis and management of PPCM patients.

Background

Peripartum cardiomyopathy (PPCM) is characterized by heart failure with reduced ejection fraction [left ventricular ejection fraction (LVEF) <45%] during the last month of pregnancy or in the first months after delivery in previously heart-healthy women.[1] PPCM affects about 1:1000 pregnancies worldwide.[1,2] The clinical course ranges from mild symptoms of heart failure to severe forms with cardiogenic shock and presents a dramatic situation for the patient and her family.[3] However, the chance for cardiac recovery is good, even for PPCM patients with severe heart failure.[4,5] In the majority of PPCM patients, cardiac recovery is stable but is frequently accompanied by co-morbidities, including other cardiovascular disease and cancer.[4,5] Recent self-rating screening questionnaires reported a high prevalence of depressive symptoms in 32%[6] and symptoms of generalized anxiety disorder in 53% of PPCM patients.[7]

Mental disorders including depression have been linked to impaired tryptophan metabolism with reduced levels of the anti-depressive neurotransmitter serotonin[8] and increased production of the pro-inflammatory and mental disorders promoting kynurenine.[9] MicroRNA (miR)-30e has emerged as a biomarker causally linked with mental disorders including severe depression and suicide risk because it reduces the signalling functions of the serotonin 1A receptor 5-HT1AR.[10]

In the present study, we systematically performed face-to-face interviews to address the prevalence and type of mental disorders in newly diagnosed PPCM patients and analysed levels of circulating serotonin, kynurenine, and miR-30e as potential biomarkers for mental disorders.

Aims

This study aims to examine the incidence of mental disorders in PPCM patients using expert face-to-face interviews and compare findings with published prevalence of mental disorders in peripartum women.[11,12] Further, the study aims to analyse potential alterations of circulating serotonin, kynurenine, and the depression-associated miR-30e[8,10] in PPCM patients compared with pregnancy-matched postpartum controls (PP-Ctrl).

Methods

The study was approved by the local ethics committee and complies in full with the Declaration of Helsinki. All PPCM patients gave written informed consent. Forty PPCM patients were included, of whom 37 were recruited during outpatient treatment and three during acute inpatient treatment at the heart failure unit.

Psychological assessment

Diagnostic assessment was performed by senior physicians using the Structured Clinical Interview for DSM-IV, an expert face-to-face interview format that is considered to be the gold standard of psychiatric assessment.[13] Using Structured Clinical Interview for DSM-IV, current and lifetime diagnoses of major mental disorders are assessed and can be attributed to severe life events. Further instruments used in the assessment included anthropometric data, the Beck Depression Inventory-2, and the World Health Organization Quality of Life Questionnaire (short form: WHOQoL BREF).

Mental disorder incidence rates in PPCM were compared with published incidence rates of mental disorders in peripartum women (n = 310, *Table 1*)[11] and documented prevalences for common postpartum mental disorders.[12] In the cited study,[11] mental disorders were similarly assessed using a structured clinical interview according to DSM-IV, and study participants were of similar age (34 ± 6 vs. 36 ± 6 years in PPCM).

Assessment of blood-based markers for mental disorders

Blood samples were collected from PPCM patients at diagnosis (PPCM bsl.; time of blood sampling, 1 day to 6 months postpartum) and from heart-healthy (LVEF >50%) postpartum controls (blood sampling, 1 day to 10.5 months postpartum). Concentrations of kynurenine, serotonin (AbsoluteIDQ™ p180 Kit, BIOCRATES Life Sciences AG), and miR-30e were measured (miR-30e, 384-well microfluid card, Thermo Fisher Scientific). MiR-30e levels were analysed by the relative quantification (ΔΔCt) method normalized to cel-miR-39. Statistical analysis was performed using SPSS version 25 for Windows (Armonk, NY) and GraphPad Prism version 8.0 for Mac OS X (GraphPad Software, San Diego, CA, USA). The comparison of incidence rates of mental disorders between PPCM patients and healthy peripartum women was performed using the χ^2 test. Clinical characteristics of PPCM patients *with* vs. *without* mental disorders as well as the plasma levels of blood-based biomarkers in PPCM patients and PP-Ctrl were compared using the Mann–Whitney U test, the t-test, and the χ^2 test where appropriate. The normality of distribution was tested using D'Agostino and Pearson test. A P-value <0.05 was considered significant.

Table 1 Incidence of mental disorders in peripartum cardiomyopathy patients compared with published incidence rates of mental disorders in peripartum women without diagnosed peripartum cardiomyopathy[11]

	PPCM (N = 40)	Peripartum mental disorder without PPCM (N = 310)[a]	P-value
Major depressive disorder	22.5% (N = 9)	5.8% (N = 18)	<0.001
Panic disorder	10% (N = 4)	1.6% (N = 5)	0.002
Post-traumatic stress disorder	10% (N = 4)	0.7% (N = 2)	<0.001
Generalized anxiety disorder	5% (N = 2)	3.6% (N = 11)	0.562

PPCM, peripartum cardiomyopathy.
Reported values in postpartum women from additional studies are in a similar range.[14–16]
[a]Peripartum mental disorder values derive from the study of Fairbrother *et al*.[11]

Results

Sixty-five per cent (26/40) of the studied PPCM suffered from a major mental disorder following diagnosis of PPCM. Patients with vs. without major mental disorders were similar regarding age [with: 34 ± 5 years, without: 36 ± 6 years, not significant (n.s.)], school years (with: 12 ± 1, without: 12 ± 1, n.s.), partner status (with: 9/9 partnered, without: 30/31 partnered, n.s.), parity [with: 1 (1–5), without: 2 (1–4), n.s.], and LVEF (with: 28 ± 10%, without: 26 ± 3%, n.s.), as well as smoking (with: 12%, without: 14%, n.s.) and alcohol consumption status (low in both groups, data not shown).

Peripartum cardiomyopathy patients with mental disorders displayed significantly lower global quality of life compared with PPCM patients without mental disorders (59.5 ± 24.8 vs. 74.1 ± 15.8; $P < 0.05$) and were more afflicted by depressive symptoms (Beck Depression Inventory sum score 11.4 ± 8.4 vs. 4.0 ± 3.8; $P < 0.05$). Among the diagnosed mental disorders were major depressive disorders (MDD) in 23% (9/40) followed by adjustment disorder (AD) in 20% (8/40), post-traumatic stress disorder (PTSD) in 10% (4/40), panic disorder (PD) in 10% (4/40), and generalized anxiety disorder in 5% (2/40) of PPCM patients (*Table 1*). *Table 1* shows that the prevalence of generalized anxiety disorder was similar between PPCM patients and a comparable collective of postpartum women without diagnosed PPCM ($n = 310$).[11] In contrast, the prevalence of MDD ($X^2 = 13.868$; df = 1; $P < 0.001$), of PTSD ($X^2 = 18.401$; df = 1; $P < 0.001$), and of PD ($X^2 = 9.948$; df = 1; $P < 0.01$) was significantly higher in PPCM patients compared with postpartum women without diagnosed PPCM ($n = 310$)[11] (*Table 1*). It is important to note that the prevalence of the aforementioned mental problems in peripartum women is consistent in several studies.[14–16]

Blood-based markers associated with mental disorders are impaired in PPCM patients compared with age and pregnancy-matched PP-Ctrl, with reduced serotonin and increased kynurenine and miR-30e levels in PPCM patients (*Figure 1*).

Conclusions

In the present study, we report a high incidence of mental disorders in a cohort of well-characterized German PPCM patients. Particularly, MDD, PTSD, and PD were more frequently observed in PPCM patients compared with postpartum women without a PPCM diagnosis.[11,14–16] Patients with heart failure disorders other than PPCM also display increased rates of mental disorders, particularly MDD,[17] and patients with MDD and PTSD display a higher risk for cardiovascular disease and heart failure[18] supporting a connection between heart failure and mental disorders.

Peripartum cardiomyopathy patients afflicted by mental disorders had a significantly reduced quality of life and higher depression scores compared with PPCM patients without mental disorders. Consequently, mental disorders appear to be more common in patients with PPCM and further reduce quality of life.

Stress reactions due to critical life events such as PPCM are to some extent a normal adaptive response. Milder forms of AD and ASD are common disorders that overlap with the so-called baby blues in postpartum women.[12] Typically, ASD and AD remit when the stressor is eliminated. However, chronic AD may develop in psychiatric disorders, in particular MDD, generalized anxiety disorder, and PTSD.[19]

The high rate of mental disorders in PPCM may result from several factors, including the threat of a potentially life-threatening disease, concerns about caring for a newborn, and anxiety concerning the relationship with a partner, leading to a combination of physical and psychological distress.

FIGURE 1 Measurement of tryptophan metabolites kynurenine, serotonin, and miR-30e in peripartum cardiomyopathy (PPCM) patients and PP-Ctrl. The graphs summarize the serum levels of (A) kynurenine and (B) serotonin in PPCM patients at diagnosis (bsl., $n = 29$) and PP-Ctrl ($n = 19$). (C) Graph summarizing the plasma levels of miR-30e in PPCM (bsl., $n = 33$) and PP-Ctrl ($n = 36$). Unpaired *t*-test (A) or Mann–Whitney *U* test (B, C) depending on the normality of distribution; $^*P < 0.05$; $^{**}P < 0.01$.
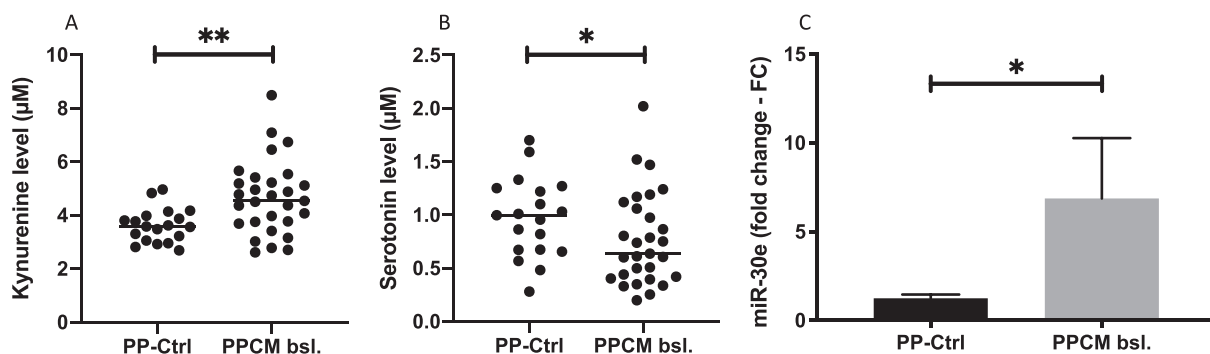
Peripartum cardiomyopathy patients displayed an impaired tryptophan metabolism with reduced levels of the anti-depressive neurotransmitter serotonin[8] and increased levels of kynurenine, a pro-inflammatory factor associated with schizophrenia and other mental disorders.[9] The recently discovered miR-30e, which has been found to promote severe depression,[10] was also elevated in PPCM patients, suggesting that the pathophysiology of PPCM may predispose for postpartum mental disorders. In addition, all PPCM patients in the present study had obtained low-dose bromocriptine, a dopamine receptor D2 agonist that may impact on mental health.[20,21] Although other retrospective studies, in which PPCM patient did not routinely obtain bromocriptine, also reported a high prevalence of depressive disorders,[6,7] a connection between bromocriptine treatment and psychiatric disorders cannot be excluded and should be evaluated in larger cohorts and registries.

Awareness of mental disorders in PPCM is important, because depression and anxiety disorders are associated with the progression of heart failure and increased mortality in the patient, but may also affect the whole family, and have a large impact on the mother–child relationship.[22] Indeed, postpartum mental disorders exert an unfavourable effect on hospitalization and mortality in children up to 1 year of age, increase the risk for maternal neonaticide, negatively influence academic achievement during adolescence, and increase the risk for adolescent depression.[23–26]

Given the overlap between cardiac and psychiatric symptoms, accurately diagnosing mental disorders, in particular major depression and anxiety disorders, can be challenging. We therefore recommend assessment via interdisciplinary diagnostic teams that also include psychiatrists. Biomarker profiling, that is, for serotonin, kynurenine, and miR-30e, may also be helpful for risk assessment and diagnosis. Psychosocial support and psychopharmacological interventions should be considered in patients with psychological problems and/or co-morbid psychiatric disorders. However, additional larger studies are necessary to evaluate the complex connection between mental disorders and PPCM.

Conflict of interest

On behalf of all authors, the corresponding author states that there are no relationships of relevance to the topic of the submitted article with industry or other relevant entities.

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