Journal of Psychosomatic Research 111 (2018) 58–68

Contents lists available at ScienceDirect

Journal of Psychosomatic Research

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

Review article

Interleukin, tumor necrosis factor-α and C-reactive protein profiles in melancholic and non-melancholic depression: A systematic review

Chenghao Yang[a,b,c], Kim M. Tiemessen[b], Fokko J. Bosker[b,c,*], Klaas J. Wardenaar[d], Jie Lie[a], Robert A. Schoevers[b,c]

[a] Tianjin Mental Health Institute, Tianjin Anding Hospital, Tianjin, China
[b] University Centre of Psychiatry, University Medical Centre Groningen, University of Groningen, Groningen, The Netherlands
[c] University of Groningen, Research School Behavioral and Cognitive Neurosciences (BCN), Groningen, The Netherlands
[d] University of Groningen, University Medical Center Groningen, Department of Psychiatry, Interdisciplinary Center Psychopathology and Emotion regulation (ICPE), Groningen, The Netherlands

ARTICLE INFO

Keywords:
Biochemical profiling
Inflammatory markers
MDD subtypes
Melancholic
Non-melancholic
Atypical

ABSTRACT

Objective: The current diagnostic criteria for major depressive disorder (MDD) do not allow prediction of prognosis and therapeutic response. A possible strategy to improve this situation is the identification of depression subtypes on the bases of biomarkers reflecting underlying pathological processes such as neuro-inflammation.

Methods: The PubMed/Medline database was searched until Apr 25th, 2017. In the initial search 1018 articles were retrieved, which were subsequently screened and only selected when the inclusion and exclusion criteria were fulfilled.

Results: Eight eligible studies were found. Overall, serum interleukin-6 and 1β values were increased in the melancholic MDD subtype compared to controls and the non-melancholic MDD subtype. C-reactive protein was increased in non-melancholic MDD in 2 out of 4 studies, while there was no difference for tumor necrosis factor-α and interleukin-2 and 10.

Conclusion: Given the paucity of eligible studies the tentative conclusion must be drawn that peripheral inflammation markers have limited added value thus far to distinguish between melancholic and non-melancholic depression. To allow for a more definitive conclusion, further research is warranted using a broader panel of inflammatory markers in MDD subtypes, preferably based on a general consensus regarding diagnostic criteria and subtype definitions.

1. Introduction

Depression is one of the most prevailing illnesses in the world, with > 300 million people falling under this category [1]. Major depressive disorder (MDD) has been estimated to account for a total of 63.2 million disability adjusted life years (DALYs) worldwide [2], making it a high cost burden for the society. MDD is a syndrome with a broad spectrum of varying symptoms. On the basis of symptom profiles the diagnostic statistical manual (DSM) has classified MDD into several clinical subtypes. However, field trials for DSM-5 mood disorders diagnoses have shown that 6-month test-retest reliability was poor to fair (kappa 0.20–0.39) for MDD [3] and even poor using the DSM-IV criteria [4]. So, attempts to improve the reliability of these diagnoses are called for. Moreover, such classification appeared to have little predictive power with respect to prognosis and treatment outcome [5–7]. Still, this is what the field has been working with for many years despite many trials to improve it. To the best of our knowledge, no such data is available regarding the subtypes of MDD, but as subtypes are mostly based on symptoms that are also assessed in MDD diagnosis they will probably be in the same range. A more fruitful approach could be a classification of MDD and it subtypes on the basis of underlying pathological processes. Arguably, this will provide a more rational and suitable basis for improving antidepressant treatment.

Several major hypotheses of pathophysiological processes involved in MDD have been raised in the past, including dysfunctions of the monoamine system, the immune-inflammatory system, the hypothalamic-pituitary-adrenal axis and neurogenesis/neuroplasticity related processes. Previously we have proposed a theoretical model linking clinical presentations of depression to these pathophysiological processes [8]. The present review is focused on the immune-inflammation

* Corresponding author at: University Centre of Psychiatry, UMCG, Hanzeplein 1, 9700 RB Groningen, the Netherlands.
E-mail address: f.j.bosker@umcg.nl (F.J. Bosker).

https://doi.org/10.1016/j.jpsychores.2018.05.008
Received 8 February 2018; Received in revised form 10 May 2018; Accepted 12 May 2018

hypothesis. It postulates that monocytes, T-lymphocytes and cytokines are involved in the pathogenesis of MDD [9,10]. According to this theory pro-inflammatory cytokines such as tumor necrosis factor alpha (TNF-α), interferon-gamma (IFN-γ) and interleukin-1 (IL-1) play a key role in the control of neuro-endocrine and behavioral characteristics of MDD. Growing evidence suggests indeed that the pathophysiology of depression is associated with dysregulated inflammatory processes and cytokine imbalance [11–17]. Following this line of thought, research into a possible relation of peripheral inflammatory markers with subtypes of MDD might help to pave the way for a more physiologically oriented approach to diagnosis, prognosis and treatment outcome [18,19]. In addition, it could contribute to developing preventative measures and adjuvant pharmacological treatment strategies [19].

A challenging problem with biomarker research is the heterogeneous character of MDD [7]. Currently, most biomarker research involves patients with divergent symptom profiles. As a consequence the results may be mixed and possibly delude one another. The biological dysregulations found in patients with MDD have indeed varied across studies [20,21]. This variability could be due to differences in sample size and composition (such as age and ethnicity) or to methodological differences, but it might also be attributable to the heterogeneity of MDD [22]. It is thus important to identify biological correlates of MDD subtypes, which may also enable the identification of patients "at-risk" for MDD, for instance those with silent chronic inflammation, to enable preventative measures to be taken. Yet attempts to predict antidepressant treatment response in the STAR*D and iSPOT-D trials [7,23] on the basis of subtypes such as melancholic depression, atypical depression and anxious depression appeared far from successful. Moreover both trials reported a considerable overlap between these subtypes while 25–33% of the patients could not be categorized through any of them. Given the generally poorer prognosis with the anxious form of depression [24], it can also be argued that this is not a subtype but a comorbid disorder with two distinct biological correlates. In terms of clinical subtypes the only distinction that has remained over time is between melancholic and atypical depression. These subtypes have a different clinical presentation and may also differ in course and treatment outcome [25–27]. It is important to note here that atypical depression falls under non-melancholic depression The DSM classifications categorize atypical depression by means of specific symptoms, and it often has a chronic course [28,29], which contrasts with what is often concerned as the typical melancholic form of depression. Both subtypes of depression are relatively common among patients diagnosed with MDD, with 15 to 30% of patients displaying atypical features [30,31] and 25 to 30% displaying melancholic features [31]. Several studies have suggested that melancholic and atypical depression also differ in biological characteristics, which is promising as these two subtypes have remained relatively stable and distinct from one another over time [22,32,33]. The biomarkers investigated in this review include interleukin-2 (IL-2), interleukin-6 (IL-6), interleukin-10 (IL-10), interleukin-1 beta (IL-1β), TNF-α, and C-reactive protein (CRP/hsCRP), and are all important players in the human immune system (see Table 1). The aim of this systematic review is to investigate whether these peripheral markers provide relevant information regarding inflammatory processes in the melancholic and non-melancholic forms of depression.

2. Materials and methods

The database used was Pubmed (Medline). The search string included the following terms: ((((((((((“Biological Markers”[Mesh]) OR “C-Reactive Protein”[Mesh])) OR “Interferon-gamma”[Mesh])) OR “Interleukins”[Mesh])) OR “Tumor Necrosis Factor-alpha”[Mesh])) OR (biomarker*[tw] OR “inflammatory marker*”[tw] OR c-reactive protein[tw] OR CRP[tw] OR high-sensitive CRP[tw] OR hsCRP[tw] OR interferon gamma[tw] OR interleukin[tw] OR tumor necrosis factor [tw])) AND (“Depressive Disorder, Major”[Mesh] OR atypical depress*[tw] OR melancholic*[tw]).

The PubMed search was performed on Apr 25th 2017, and yielded 1018 articles (8 studies in non-human species were excluded; see Fig. 1 below). The titles and abstracts of the articles were scanned to see if they met the inclusion criteria. If there were any doubts whether an article should be included or not, the whole text was read. Previous review studies, including meta-analyses, were not used for this review, but their reference list was scanned for articles that might have been missed by the PubMed search. Articles that primarily focused on somatic diseases (such as cardiovascular disease, cancer or autoimmune disease) with co-morbid depression were also excluded from the study. An exception to this exclusion criterion was made for depression with co-morbid anxiety disorder as these very often co-occur [35]. It is important to note that only studies reporting baseline serum values of biomarkers were taken into consideration, thus excluding challenge studies to assess the cytokine production capacity. Some antidepressants can alter the immune response [36,37]. Yet we have also included studies wherein part of the patients was treated with antidepressants, as long as co-variate analyses indicated that antidepressant treatment did not appreciably influence the outcome. Finally, it was required that studies included both melancholic and non-melancholic subtypes in relation to biomarker levels. References in all included studies were screened for cross references of eligible studies possibly missed by the PubMed search. The articles were then evaluated whether useful information was provided regarding inflammatory processes in the two subtypes. It is also important to note that a study not making a distinction between IL-1α and IL-1β has been excluded in this respect [38]. Finally, on the basis of the reported sample size, mean value and standard deviation Forest plots were constructed showing the Hedges'g effect sizes for the markers. Given the small sample size of some of the studies ($n < 20$) we have used the Hedges'g formula instead of the simpler one from Cohen.

3. Results

In the 8 studies eligible for analysis, 6307 persons were included. In total, 5455 controls were compared to 852 MDD patients. Most studies used the symptom-based DSM-IV criteria to diagnose MDD and to define the subtypes, although a few used alternative methods such as the sign-based CORE measure, which assesses psychomotor and neuroendocrine disturbances instead of symptoms. Other assessments included the Diagnostic Interview for Genetic Studies (DIGS) combined with the General Health Questionnaire-12 items (GHQ-12), the Composite International Diagnostic Interview-version 2.1 (CIDI-2.1) or Latent Class Analysis (LCA). A summary of the results can be found in Table 2, while the statistically significant findings are summarized in the text below. Only 6 out of 8 studies were suitable to construct Forest plots, depicting the Hedges'g effect sizes. These are shown in Fig. 2 together with the number of patients, mean values and standard deviations.

3.1. IL-2 in melancholic and non-melancholic depression

Spanemberg et al. found no statistically significant difference between melancholic and non-melancholic groups for IL-2 ($p > 0.05$) [39]. Overall, there is no tendency for IL-2 to be increased in patients suffering from non-melancholic MDD (including atypical depression).

3.2. IL-6 in melancholic and non-melancholic depression

Dunjic-Kostic et al. found a tendency for increased IL-6 levels in melancholic patients [40]. The serum concentration of IL-6 was found to be higher in the melancholic subtype compared to the atypical subtype, although Fisher's least significant difference (LSD) showed no difference in IL-6 between the two groups [40]. The only statistically significant difference was between melancholic depression and controls