Schizophrenia Research xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Schizophrenia Research

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

# Cytokines dysregulation in schizophrenia: A systematic review of psychoneuroimmune relationship

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ARTICLE INFO

*Article history:*
Received 31 July 2017
Received in revised form 15 November 2017
Accepted 18 November 2017
Available online xxxx

*Keywords:*
Schizophrenia
Cytokines
Cytokine polymorphisms
Cytokine mRNAs
Proinflammatory cytokines
Psychoneuroimmunology

ABSTRACT

Introduction: Schizophrenia is a multifactorial psychiatric disease with complex interactions among the brain and the immune system. A psycho-immune relationship underling schizophrenia is supported by several studies and integrates a specific area of knowledge - psychoneuroimmunology.
*Methods:* A systematic review was performed by 2009 Preferred Reporting Items (PRISMA) recommendations. Based on the inclusion/exclusion criteria, publications with relevant information (evaluated by the Joanna Briggs Institute Critical Appraisals tools to quality assessment) were included.
*Results:* In this review, we considered the inflammatory activity promoted by cytokine alterations in schizophrenia aetiology, which reflects the systemic comprehension of this disease in opposition to the traditional approach focused solely on the brain. We focus on the analysis of several specific outcomes, such as proinflammatory cytokines, sample sort, laboratory techniques, diagnosis scales and results of each publication.
*Conclusion:* This systematic review confirms the existence of cytokines abnormalities in schizophrenia disease. Immune imbalances such as increased levels of some cytokines (either at protein level or at mRNA expression), cytokine mRNAs, as well as cytokine gene polymorphisms have been reported with a large support in schizophrenia. These findings provide a strong evidence of a concomitant process of inflammatory activity in schizophrenia illness course.



## 1. Introduction

Schizophrenia is a severe psychotic disorder, which pathogenesis is still partially understood (van Kesteren et al., 2017). Given the multiple interaction between the brain and other organ systems that may have an incidence in the development of aberrant behavioural phenotypes, the aetiology of schizophrenia remains, in part, uncertain. One suggested mechanism that may putatively underlie schizophrenia development, implies disturbances of the immune system and their complex interactions with the nervous system, which may give a new insight on the pathogenesis and pathophysiology of this psychotic disorder (Khandaker et al., 2017; van Kesteren et al., 2017). This relationship was hypothesized over a century ago, and is reinforced by genetic and epidemiological studies linking infection and inflammation with brain disorders (Khandaker et al., 2015). Evidence demonstrates that the pathophysiology of schizophrenia could be associated with cytokine abnormalities (Hope et al., 2013; Pandey et al., 2015; Potvin et al., 2008). Specifically, proinflammatory cytokines are involved in central nervous system (CNS) inflammation processes, disturbing the homeostasis and contributing to additional tissues injury (Müller et al., 2015). The increase of proinflammatory cytokines levels and their soluble receptors in human samples such as serum, plasma or cerebrospinal fluid (CSF) was reported in several studies (Debnath and Berk, 2014; Potvin et al., 2008; Wu et al., 2016). In the other hand, anti-inflammatory cytokines that down-regulate the inflammatory response are also altered in schizophrenia (Müller and Schwarz, 2010). Another important aspect pointing towards the involvement of immune system abnormalities in schizophrenia vulnerability is the presence of specific cytokine gene polymorphisms that may results in inflammatory events that putatively modulate the development of the schizophrenia syndrome by neurodevelopmental or neurodegenerative abnormalities (Fan et al., 2007). For example, the polymorphisms in the interleukin-1 (IL-1) or IL-6 genes have been associated to schizophrenia, with increasing blood levels of both cytokines (Debnath and Berk, 2014; Katila et al., 1999). In particular, evidence suggest an unequivocal role of the IL-6

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https://doi.org/10.1016/j.schres.2017.11.023
0920-9964/

in the pathogenesis of schizophrenia, whose levels of IL-6 and sIL-6R (receptor) are elevated in the serum of patients with schizophrenia (Chase et al., 2016; Potvin et al., 2008; Upthegrove et al., 2014). Furthermore, analysis of mRNA expression levels of pro-inflammatory cytokines indicates that mRNAs upregulation, bring about the changes in cytokine levels observed in schizophrenia (Pandey et al., 2015). Schizophrenia is recognized as a systemic syndrome, involving not only the nervous system, but also the immune system, as well as originating from a combination of environmental and genetic factors. Based on these findings, the purpose of this review is to analyse and synthetize clinical and laboratory data, allowing a functional knowledge of the role of inflammatory activity of cytokines in schizophrenia. Therefore, the integrated data will help to understand the connection between alterations of the immune system (related with cytokines, their gene polymorphisms and mRNAs) and clinical data (e.g. stress, severity of symptomatology, cognitive and functional performance, etc.) in the context of psychotic diseases such as schizophrenia.

## 2. Methodology

A systematic review of literature was achieved, using the 2009 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations and the Joanna Briggs Institute (JBI) Critical Appraisal to quality assessment.

### 2.1. Study design

This is a descriptive and qualitative systematic review, which explores the role of the immune system in schizophrenia aetiology. This review was realized following the guidelines of the 2009 Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement (Liberati et al., 2009; Moher et al., 2009).

### 2.2. Eligibility criteria for selection

This search was performed based on all studies published until 18/05/2017, in English and focused on humans with schizophrenia disease, which diagnosis was based on mental, cognitive or functional scales (inclusion criteria). The exclusion criteria comprise studies of patients with other psychiatric/neurological diseases such as depression, bipolar disorder, autism, Parkinson's, Alzheimer's, autoimmune or chronic inflammatory diseases and trauma. Also, studies focused in the anti-inflammatory response and anti-inflammatory cytokines are excluded because it is not the outcome/objective of this review. Studies were included if they were prospective or retrospective case-control and cohort, systematic reviews or other qualitative research that investigated the correlation between schizophrenia and cytokines involved in inflammatory processes (upregulation and downregulation of cytokines and their genes).

### 2.3. Data sources

We electronically examined publications in the PubMed, Medline, PsycINFO and Cochrane databases, introducing the search terms "proinflammatory cytokines and schizophrenia", "proinflammatory cytokines and psychosis" and "inflammation and schizophrenia". To make the searching process more specific and efficient, we resorted to PubMed filters, detailed in the inclusion criteria.

### 2.4. Data selection

Three researchers (DRA, TRB and RAB) independently screened the titles and abstracts, resulting 586 reports. Full text of all relevant publications was reviewed and 99 studies were selected. All selected studies complied the schizophrenia diagnosis requirement based on mental assessment scales. Specifically, Diagnostic and Statistical Manual of Mental Disorders (DSM) by American Psychiatric Association, and International Classification of Diseases (ICD) by World Health Organization. Additionally, other scales were applied such as Scale for the Assessment of Positive or Negative Symptoms (SAPS or SANS), Positive and Negative Syndrome Scale (PANSS), cognitive scales as Wechsler Adult Intelligence Scale (WAIS), and functional scales as Global Assessment of Functioning (GAF) to cross specific clinical data with laboratorial findings. Discrepancies were resolved by deliberations among the authors.

### 2.5. Data synthesis

After eligibility, 99 studies were included in the qualitative synthesis (Fig. 1), and the pertinent information was recompiled in a table after create a folder with the selected articles in the Mendeley organizer. This review analyses qualitative data, correlating the inflammatory cytokines profile, genetic polymorphisms and mRNA levels of cytokines, laboratory procedures, samples sort and evaluation scales used in schizophrenia diagnosis.

## 3. Results

### 3.1. Search results

After search, using the terms: "proinflammatory cytokines and schizophrenia", "proinflammatory cytokines and psychosis" or "inflammation and schizophrenia", 1003 studies were identified. Implementing the limits and eliminating the duplicate items, we selected 586 studies for further screening. From this collection, 420 studies were excluded because after screening the title and abstract, these studies clearly did not fulfil the criteria. Finally, we carefully examined the full text of the 166 studies selected, and discarded 67 studies because they did not meet the requirements. Thereby, 99 studies were included in the present report (Fig. 1). The search strategy was executed without publications dates limit. The purpose of this review is to identify the role of inflammation in schizophrenia pathophysiology, applying a methodology based on recommendations that reduce the bias risk (PRISMA recommendations and JBI appraisals).

### 3.2. Study characteristics

Eligible studies analysed the association between proinflammatory cytokines, inflammation and schizophrenia. The characteristics of each study were examined individually. These studies were categorized based on the cytokines profile (involved in inflammatory processes), gene polymorphisms and mRNA levels. The final sample of reviewed publications involving 8234 participants (4529 male and 3601 female; age range: 6 to 75 years, and 111 participants whose gender was not differentiated in the studies). The majority of the studies used serum (n = 42; 42.42%) to measure the cytokine levels. However, other types of samples were utilized such as plasma (n = 16; 16.16%), blood (n = 11; 11.11%), CSF (n = 5; 5.05%), peripheral blood leukocytes (n = 11, 11.11%), saliva (n = 1; 1.01%), post-mortem tissue (n = 1; 1.01%), and studies including more than one sample (ex: serum and CFS; serum and peripheral blood leukocytes, etc.) (n = 12; 12.12%). A concomitant examination was performed by some studies, which measured the cytokine levels and gene polymorphisms (Frydecka et al., 2015) or the cytokine and mRNAs levels (Pandey et al., 2015). We investigated 42 different cytokines, 33 gene polymorphisms, and 11 cytokine mRNAs (Supplementary Fig. 1).

Some of these cytokines, gene polymorphisms or mRNA levels were measured in more than two studies: IL-6, tumor necrosis factor alpha (TNF-α), IL-10, IL-2, interferon-gamma (IFN-γ), IL-4, sTNFR1, IL-1Ra, IL-18, sIL-2R, IL-1β, IL-6R, IL-17, IL-8, IL-12, TNF-α gene -308G/A and IL-6 mRNA (Table 2). Several techniques were used, being the enzyme-linked immunosorbent assay (ELISA) the most widely used for measuring the cytokine levels. Others techniques such as Luminex

Please cite this article as: Rodrigues-Amorim, D., et al., Cytokines dysregulation in schizophrenia: A systematic review of psychoneuroimmune relationship, Schizophr. Res. (2017), https://doi.org/10.1016/j.schres.2017.11.023