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Cytokine function in medication-naive first episode psychosis: A systematic review and meta-analysis

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ABSTRACT

This systematic review sets out to give a comprehensive overview of the cytokine profile at the onset of psychosis un-confounded by medication. We aim to provide insight into the early pathophysiological process of psychosis and areas for future research of potential biomarkers able to chart the extent of illness or effectiveness of treatment.

Following PRISMA guidelines, a systematic primary search identified 4638 citations, 4651 studies were retrieved and screened, and 23 studies met the inclusion criteria (published in English before June 2013, patients with neuroleptic naive first episode psychosis, and assessed circulating cytokines). These reported 570 patients, 683 healthy control subjects, and 20 cytokine/cytokine receptors. Papers that contained sufficient stratified data were included in a random-effects pooled effect size meta-analysis.

Highly significant effect sizes were found for elevated IL-1β, sIL-2r, IL-6, and TNF-α. Non-significant effect size estimates were obtained for IL-2, IL-4, and IFN-γ.

Thus, we found significant elevation in pro-inflammatory cytokine levels in the serum of patients with medication-naive first episode psychosis. This adds to the evidence of a pro-inflammatory immune deregulation in schizophrenia and suggests these cytokines should be the focus for further research in biomarkers of progress and extent of illness. Future studies should focus on the medication-naive group at the early stages of illness with numbers large enough to allow for the control of other potential confounding factors.

1. Introduction

Schizophrenia is currently understood as a debilitating neurodevelopmental disorder that appears at a critical period in early adulthood (Gilmore and Murray, 2006; van Os and Kapur, 2009). In recent times, there has been an increased interest into the study of prodromal stages of this disorder and the evolution to clinically significant psychosis (Malla et al., 2002). However, the underlying pathophysiological cause of schizophrenia in its early stages is essentially unknown. The vast majority of biological research into the pathogenesis of schizophrenia has focused on neurotransmitter abnormalities in established disorder (Aghajanian and Marek, 2000; Jones et al., 2005). There is also evidence for genetic predisposition (Craddock and Owen, 2005), viral infections (Bradbury and Miller, 1985), and obstetric complication (Gilmore and Murray, 2006). Increasing evidence, however, also suggests a role of immunological processes. Indeed, schizophrenia has been associated with an abnormal activation of the immune system for many years (Dameshek, 1930; Schwarz, 2007; Miller et al., 2011; Müller, 2011).

The immune response is a highly coordinated process involving an array of cell types, normally protecting the body from harm, such as from pathogens or cancerous cells, while maintaining tolerance to harmless or beneficial organisms. The first arm is our "innate" defence mechanism, which is older in evolutionary terms and considered to be a first line defence. Its cellular components include neutrophils, basophils, eosinophils, monocytes macrophages, dendritic cells, and natural killer (NK) cells. These recognize and promote defence against pathogens but lack the sophistication to adapt compared to other more recent additions to the immune system. The innate humoral component is made up of acute phase proteins and the compliment cascade, which allow phagocytic cells to clear pathogens from an organism and various cytokines. The second arm of our immune system is the "adaptive" system, which is often considered more highly advanced and organized. This arm acts on memory, re-exposure, and the ability

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to be conditioned. The prime cellular components of the adaptive system include T cells and B cells. T cells comprise key components of the T helper 1 (Th1) system and the T helper 2 system (Th2). The Th1 system is polarised towards the production of pro-inflammatory cytokines such as interleukin 2 (IL-2), interferon ϒ (IF-ϒ), and tumor necrosis factor (TNF-α). The Th2 system promotes the generation and maintenance of antibody-mediated immune responses and the production of anti-inflammatory cytokines such as interleukin 4 (IL-4), interleukin 10 (IL-10) and interleukin 13 (IL-13). The humoral component of the adaptive system includes these various circulating cytokines and specific antibodies. A more recently recognized addition to the adaptive immune system includes regulatory T cells ("suppressor" T cells) and other specialised T helper cells (e.g., Th17 and Th22)(Meredith et al., 2005).

There is also considerable "cross talk" between the two major arms of the immune system (Upthegrove and Barnes, 2014). Cytokines are the key signalling molecules that coordinate the innate and adaptive arms of the immune system, and they can exert effects peripherally and in the brain. Recently, changes in cytokines levels, their receptors and cytokine activity modifiers have been found in blood and cerebrospinal fluid (CSF) of schizophrenic patients. Evidence includes the presence of antibodies in serum, an altered distribution of T-cell subsets and altered serum levels of Th1- and Th2-related cytokines (Müller and Schwarz, 2010; Upthegrove and Barnes, 2014). It had been initially proposed that patients with psychosis may have an impaired production of Th1 cytokines and an overactivation of the Th2 system, leading to a dysfunction in the normal Th1/Th2 balance (Müller, 2011). In contrast, some investigations point to an overactivation of the Th1 activity in schizophrenia (Kim et al., 2004). It would therefore appear that an imbalance between Th1 and Th2 cytokines may play a role in schizophrenia, but the data reported are variable, inconsistent or even contradictory. Likely contributing factors to this disarray include studies sampling patients at different stage of illness, differing illness course, acutely unwell or in remission. Use of illicit drugs, differences in age, gender, smoking, body mass, and recent infections will also have significant impact yet are not controlled for (Upthegrove and Barnes, 2014). Most significantly, however, is the role of antipsychotic medication, as we now know its ability to impact the immune system is clear (Drzyzga et al., 2006). For instance, studies *in vitro* confirm that the antipsychotic drug effects on immune cell function is widespread and often occurs very shortly after initial exposure—indicating some direct effects of the drugs upon immune cell subsets. However, mixed results and differing effects are evident, including either stimulatory or inhibitory actions, particularly with regard to interferon (INF-ϒ). It is of further interest that recent studies *in vitro* suggest that, in part, the efficacy of some antipsychotics arises through the suppression of cytokine-mediated microglial activity (Bian et al., 2008), for instance, aripiprazole suppressing the apoptosis of rodent oligodendrocytes by IFN-γ-activated microglia and the inhibition of tumor necrosis factor-alpha (TNF-α) secretion from IFN-γ-activated microglia (Seki et al., 2013).

Some newer clinical studies have begun to take account of confounding factors, yet antipsychotic medication has not been controlled for regularly, and therefore it is not clear whether results presented are at least in part a product of medication effects (Potvin et al.,2008). In studies investigating first episode psychosis, the vast majority have sampled patients on medication, or in a drug-free status variously defined as neuroleptic naive, free of medication for a period of time, or recently commenced on medication. In a comprehensive meta-analysis, Miller et al. (2011) explored cytokine function in first episode psychosis, with significant results, yet their analysis included groups with mixed neuroleptic exposure and naive status combined.

Therefore, in order to re-assess recent advances and conclusions, we performed a review of studies investigating serum cytokine levels in a medication-naive status and first episode psychosis. The present review article aimed to give a comprehensive and up-to-date overview of the cytokine profile at the onset of first episode psychosis un-confounded by medication. We hope to provide insights into early pathophysiological processes moderating progression of illness and potentially forward avenues of research to identify biomarkers able to judge the extent of disease or the effectiveness of treatment.

2. Methods

2.1. Study selection

First, published and supplementary material from Miller et al. (2011), which describes a comprehensive systematic search of studies on cytokine function in schizophrenia, was accessed. This included studies published between years 1989 and 2010. Second, in order to ensure all available data were robustly gathered during the peak growth of studies on immune dysfunction, studies on cytokines in first episode schizophrenia published after 2001 were systematically searched via computerized literature databases using PRISMA guidelines (Moher et al., 2009). Pubmed, EMBASE, PsycINFO, and Cochrane were searched, last run on June 17, 2013, with the following key words: immune, inflammat*, cytokines and schizophrenia, psychosis, "first psychotic episode," "first episode," "early onset," or "early intervention." The reference lists of identified articles were reviewed for additional studies. A consensus was reached among authors on the studies retained or discarded on the basis of the following inclusion and exclusion criteria.

Inclusion criteria were as follows:

1. Published in English before June 2013
2. Patients with a first episode psychosis (FEP) including the following schizophrenia spectrum disorder: schizophrenia, schizoaffective disorder, and schizophreniform disorder.
3. Assessed circulating cytokines levels with plasma or serum samples (in vivo studies)
4. Included data on neuroleptic naive subjects
5. Comprising a control group of healthy volunteers

Exclusion criteria were as follows:

1. Studies assessing cytokine genes
2. *In vitro* studies
3. Review articles
4. Studies assessing immune markers other than cytokines
5. Animal studies

Data extraction and meta-analysis

Information was extracted by two authors (RU and NT) from each included study trial, including patient demographics, inclusion and exclusion criteria, control group, and type of study. For studies that included patients with different clinical status (e.g., both first episode, early and late stage of schizophrenia, drug free, or medication naive), we examined stratified data to ascertain whether neuroleptic naive first episode patients were reported on. If this was not presented in the manuscript, we attempted to contact study authors for further data. Publications pertaining to the same research group and studying the same cytokine were checked for potential data overlap.

Sample size, mean, and standard deviation for schizophrenia and control subjects for every individual cytokine (or cytokine receptor or antagonist) assessed in each study were recorded. Results were converted to standard units (pg/ml) where necessary. We recorded data on medication-naive FEP and normal controls. We then calculated effect size estimates (Hedges' *g*) for every individual cytokine (or cytokine receptor or antagonist) reported in more than one study. Random-effects pooled effect size estimates and 95% confidence intervals were calculated using the method of DerSimonian and Laird (1986). The random-effects model was chosen as more conservative than the fixed effects model, giving a lower type I error and wider confidence intervals. Its use was indicated by the considerable heterogeneity in the studies included.

3. Results

3.1. Study characteristics

The results of the search are shown in Fig. 1.

Primary search identified 4638 citations; 4651 studies were retrieved and screened. Articles were selected for full-text review if the inclusion criteria were met or if either reviewer considered them potentially relevant. Full articles were pulled and assessed for eligibility for 136 of these studies. After full text review, 14 studies did not include first episode participants, 49 studies were genetic studies, 28 studies were review articles, 11 studies were not written in English, 5 studies did not assess cytokines, 5 studies were only *in vitro* studies, and 1 study did not report a normal control group. These were excluded. Thus, 23 studies met our inclusion criteria (see Table 1). Individual authors were contacted where stratified data were not reported for additional data. For 8 papers, these data were not available (i.e., reported samples were a mixture of medication naive + treated), and one paper reported on a previously reported medication-naive sample (Borovcanin et al., 2013).

Fourteen papers were thus included in the meta-analysis (Rapaport et al., 1989; Becker et al., 1990; Gattaz et al., 1992; Ganguli et al., 1994; Akiyama, 1999; Theodoropoulou et al., 2001; Sirota et al., 2005; Crespo-Facorro et al., 2008; Xiu et al., 2008; Fernandez-Egea et al., 2009; Song et al., 2009; Borovcanin et al., 2012; Di Nicola et al., 2012; Xiu et al., 2012). There was universal agreement on the included studies. The 14 studies included 570 patients with drug-naive first episode psychosis and 683 healthy control subjects. Within the FEP group, varying measures of diagnostic status were used; PANSS, SCAN, OPCRIT, ICD-10 RDC, and DSM-IV SCID-1 and participants ranged in diagnosis from schizophrenia, schizophreniform disorder, delusional disorder, and brief reactive psychosis. The majority diagnosis was schizophrenia or schizophreniform disorder (81%).

Twenty cytokine/cytokine receptors were reported on. The most frequently assessed cytokines were IL-1β, IL-2, sIL-2 r, IL-4, IL-6, TNF-α, and IFN-γ. These were reported on in more than one study

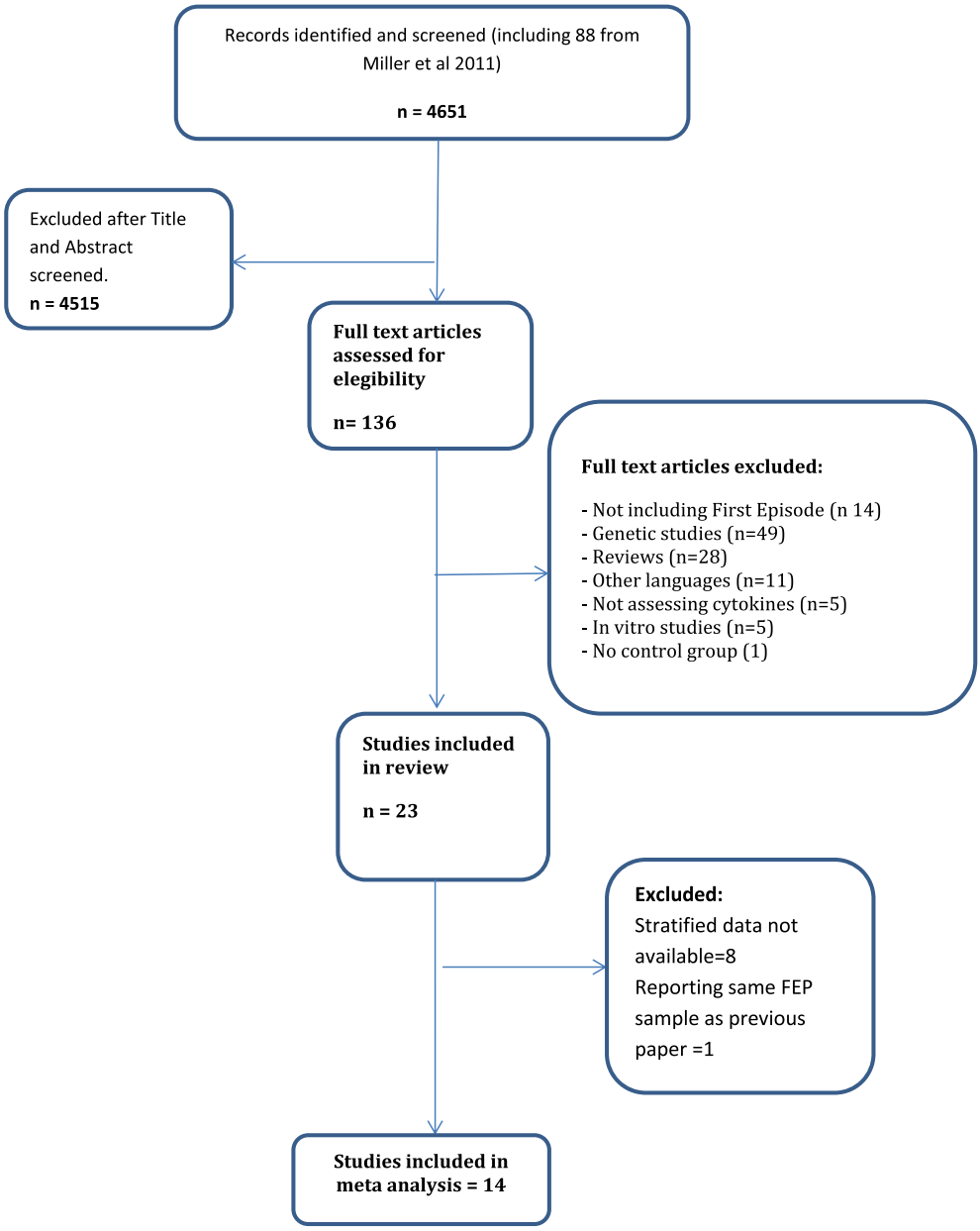


Fig. 1. Study selection process.

Table 1
Studies included in review.

	Cytokines	Assay	n Drug Naive	Country	Comments
Akiyama, 1999	sIL-2R, IL-6, IL-1-RA	Sandwich	14	Japan	Included in analysis
Becker et al.,1990	IFN	Semimiroassay	34	Israel	Included in analysis
Borovcanin et al., 2012	TNF-α, IFN-γ, IL-4, IL-10, IL-17, TGF-β IL-27, IL-6	ELISA	88	Serbia	Included in analysis
Borovcanin et al.,2013	TNF-α, IFN-γ, IL-4, IL-10, IL-17, TGF-β, IL-27, IL-6	ELISA	88	Serbia	Same drug-naive sample as 2012 - not-included
Cazzullo et al.,2002	IL-2, IL-4, IL-10, INF-γ	ELISA	3	Italy	stratified data not available for medication naive status
Crespo-Facorro et al., 2008	IL-12	SMA	56	Spain	Included in analysis
Di Nicola et al.,2012	IL-1α, IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, TNF-α, IFN-γ	SMA	5	UK	Data requested received and included
Fernandez-Egea et al.,2009	IL-6	ELISA	50	Spain	Included in analysis
Ganguli et al., 1994	sIL-2R, IL-6	ELISA	24	US	Included in analysis
Gattaz et al.,1992	IL-2, IFN-γ, IFN-α	ELISA	10	Germany	Included in analysis
Garcia-Rizo et al.,2012	IL-6	ELISA	20	Spain	No normal control group- not included
Kim et al., 2000	IL-1β, IL-2, IL-6	ELISA	25	Korea	stratified data not available for medication naive status
Kim et al., 2004	TGF-β	ELISA	43	Korea	stratified data not available for medication naive status
Kim et al., 2009	IL-2, IL-4, IL-6, TNF-α, TGF-β	ELISA	38	Korea	stratified data not available for medication naive status
Kim (2002)	IL-12	ELISA	43	Korea	stratified data not available for medication naive status
Kowalski et al., 2001	IL-1β, TNF-α	ELISA	4	Poland	stratified data not available for medication naive status
Rapaport and Lohr,1994	sIL-2R	ELISA	12	US	Included in analysis
Reale et al., 2011	IL-8, IL-18, INF-γ	ELISA	51	Italy	In vitro sample: not included
Sirota et al.,2005	IL-1-RA, sIL-2R	ELISA	32	Israel	Included in analysis
Song et al.,2009	IL-1β, TNF-α	ELISA	83	China	Included in analysis
Theodoropoulou et al.,2001	IL-1β, IL-2, TNF-α	ELISA	53	Greece	Included in analysis
Xiong et al., 2011	NGF, IL-2	ELISA	30	China	stratified data not available for medication naive status
Xiu et al.,2008	IL-3	ELISA	24	China	Included in analysis
Xiu et al.,2012	IL-1β	ELISA	78	China	Included in analysis

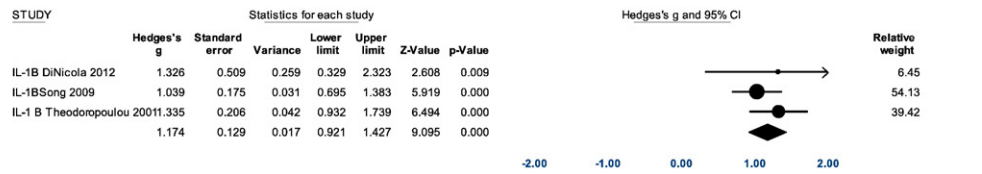
and were included in the random-effects pooled effect size analysis (see Table 2).

IL-17 and IL-27 were reported on in one study with non-significant differences found between FEP and control groups (Borovcanin et al., 2012). IL-12 was reported on in only one study (Crespo-Facorro et al., 2008) with levels found to be significantly higher before starting medication in 56 patients compared to controls and increased further after treatment with antipsychotic medication. Xiu et al. (2008, 2012)

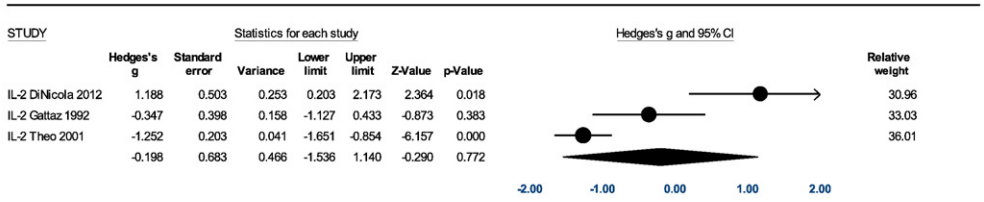
Table 2
Serum cytokines in drug-naive FEP included in meta-analysis.

Cytokine	Study	Patient mean (pg/ml)	SD	*n*	Control mean (pg/ml)	SD	*n*	% change
IL-1β	Di Nicola et al.,(2012)	17.57	29.44	5	2.1	0.4	24	737
IL-1 β	Song et al.,(2009)	25.93	13.3	83	14.19	7.86	65	83
IL-1 β	Theodoropoulou et al.,(2001)	21.4	8	53	12	6	62	56
Summary % change IL-1 β								292
IL-2	Di Nicola et al.,(2012)	50.21	97.11	5	4.5	1.3	24	1015
IL-2	Gattaz et al.,(1992)	0.49	0.37	10	0.68	0.61	15	38
IL-2	Theodoropoulou et al.,(2001)	220	25	53	271	50	62	-18
Summary % change IL-2								345
sIL2-R	Rapoport and Lohr,(1994)	1705.7	1124.2	12	739.8	325.5	14	131
sIL2-R	Akiyama, (1999)	739.3	217.2	14	520.9	162.5	27	42
sIL-2Rα	Sirota et al.,(2005)	1760	325.2	6	1114.6	316.6	22	60
Summary % change sIL-R								78
IL-4	Borovcanin et al.,(2012)	25.1	10.73	88	12.09	8	34	107
IL-4	Di Nicola et al.,(2012)	3.7	1.31	5	4.6	0.8	24	-20
Summary % change IL-4								44
IL-6	Di Nicola et al.,(2012)	3.75	5.8	5	1.5	0.5	24	150
IL-6	Akiyama, (1999)	2.165	2.029	14	0.999	0.495	27	112
IL-6	Borovcanin et al.,(2012)	27.86	27.86	88	8.14	3.47	36	242
IL-6	Fernandez-Ega	3.63	6.91	50	1.02	1.02	50	255
IL-6	Ganguli et al., (1994)	10	1.07	24	1.05	1.11	110	800
Summary % change IL-6								281
IFN-γ	Borovcanin et al.,(2012)	78.51	37.28	88	29.06	10.68	34	170
IFN-γ	Di Nicola et al.,(2012)	1.5	0.83	5	3.7	1.8	24	-59
IFN-γ	Gattaz et al.,(1992)	20.8	32.4	10	13	16.9	15	60
Summary % change IFN-γ								57
TNF-α	Di Nicola et al.,(2012)	54.88	109.17	5	15.9	5	24	245
TNF-α	Song et al.,(2009)	31.01	13.82	83	21.33	8.9	65	45
TNF-α	Theodoropoulou et al.,(2001)	24	8	53	16	6	62	50
Summary % change TNF-α								113

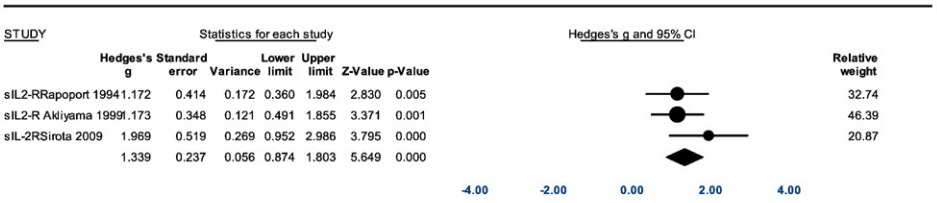
IL-1β



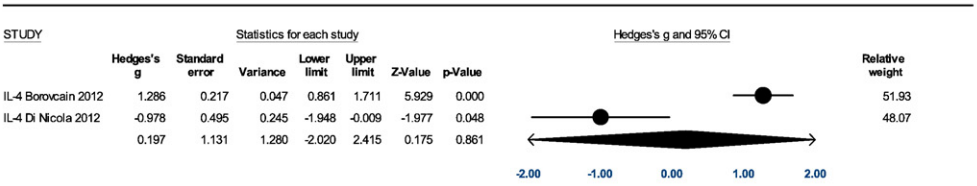
IL-2



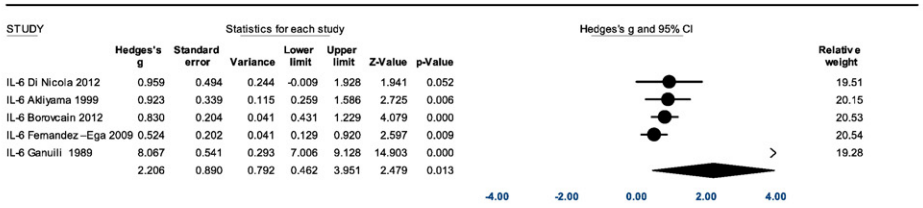
sIL-2r



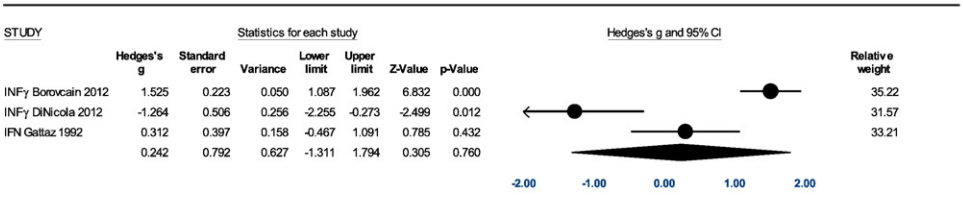
IL-4



IL-6



IFN-γ



TNFα

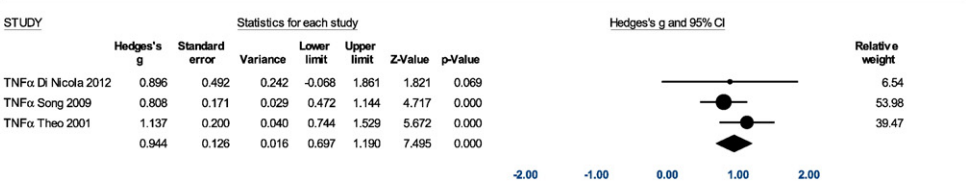


Fig. 2. Random-effects meta-analysis serum cytokines in medication-naive FEP versus control.

reported IL-3 and IL-18 in medication-naive FEP, finding a decrease in IL-3 in patients with medication-naive FEP and an increase in IL-18 compared to controls. These two studies have not been replicated to date in our search.

3.2. Meta-analysis

Highly significant effect sizes emerged for IL-1β (3 studies total n 99), sIL-2R (3 studies, total n58), IL-6 (5 studies total n 181), and TNF-α (3 studies, total n 99), suggesting an increase in these cytokines in first episode psychosis that is unrelated to medication effects (see Fig. 2).

Non-significant effect size estimates were obtained for IL-2 (3 studies, n 26), IL-4 (2 studies, n 93), and IFN-γ (3 studies, n 103).

4. Discussion

Questions regarding the effect of antipsychotic medication on serum cytokine levels have been repeatedly raised. Previous studies acknowledge this potential confounding factor (Drzyzga et al., 2006). Results of many studies with mixed populations have previously been understood with the knowledge that antipsychotic medication has not been controlled for, yet is likely to impact on immune cell function. We have now been able to demonstrate that significant elevations in IL-1β, sIL-2r, IL-6, and TNF-α occur in truly medication-naive samples of patients with FEP. Previous individual papers have often reported drug naive/drug free and brief exposure with psychotropic medication as though these are a homogenous group.

The strength of this present review is our strict definitions of absolute medication naivety, the additional data made available from some authors, and the use of random-effects model. The fixed effect model assumes that all studies in the meta-analysis are drawn from a common population. Given the diagnostic uncertainty within FEP and the varied study teams and countries from which data are pooled, it cannot be assumed that our population of first episode schizophrenia is common. In a fixed effect model, the observed effect size in individual studies may still be the result of random error inherent in each study. In a random-effects model, the assumption is that the studies were drawn from populations that differ from each other in ways that could impact on the effect. This potential for random error is controlled for in the present analysis, which adds confidence in the detected increase in IL-1β, sIL-2r, IL-6, and TNF-α levels in FEP.

These cytokines and circulating cytokine receptor (sIL2r) have in common a pro-inflammatory role in the adaptive immune system. IL-1β induces both acute phase proteins and stimulates the excretion of IL-6, which in turn induces acute phase proteins and late B-cell differentiation. sIL-2r flows into the blood during T-cell activation and is a common marker for cell-mediated immune activation. TNF-α is a key player in the inflammatory response and induces acute phase proteins. Miller et al. (2011) reported their large meta-analysis in 2011 and included studies in FEP and chronic schizophrenia with a mixture or medication free and treated patients. They proposed that the inflammatory cytokines IL-1β, IL-6, and TGF-β may be successful treatment biomarkers (i.e., elevated in acute illness and reduce in line with treatment), while IL-12, INF-ϒ, TNF-α, and IL-2R are trait like biomarkers that remain elevated throughout the illness course (Miller et al., 2011). Our results are in keeping with this proposal in part; IL-1β, sIL-2r, IL-6, and TNF-α being elevated in medication-naive FEP. However, non-significant results were found for INF-ϒ. Clarity will only come on the state/trait questions when robust longitudinal studies beginning with FEP patients who are absolutely drug naive are available. The lack of significant elevation of INF-ϒ is also notable given their reported role in stimulating the release of nitric oxide and microglia shown with studies *in vitro* (Bian et al., 2008; Kato et al., 2011). However, it is highly possible that circulating cytokine levels may not recapitulate local levels evident in the CNS.

The results we present are in keeping with some, but not all, of the main theories of immune dysfunction in schizophrenia. Maternal viral infection, producing a later overactive inflammatory response, has been proposed for a number of years. Animal studies indicate that it may not be a certain virus exposure but the subsequent immune response that determines risk (Müller, 2011). Cytokines are essential for synaptogenesis during early development and in periods of neuronal plasticity in adult life. The disruption of the relative balance of cytokines, for example, by early maternal infection, may have direct effects but also more nuanced changes visible later in development. Infectious agents such as influenza, bornavirus, chlamydia, toxoplasma gondii, and others have been proposed involved in risk of later developing schizophrenia (Müller and Schwarz,2010). Prenatal exposure to an early inflammatory response may also lead to a priming of immune reactions, subsequently leading to a more vigorous or atypical response to later environmental challenges later during a time of heightened neuronal plasticity and change, in late adolescence, bringing the development of illness. A clear indication of excessive pro-inflammatory cytokines in adaptive immunity supports this theory. In addition, the common and increasingly recognized occurrence of affective symptoms in schizophrenia may also be explained by shared immune and inflammatory processes, including an increase in cytokines and immune response (Upthegrove et al., 2010; Fineberg and Ellman, 2013). It is proposed that chronically activated immune cell subsets (e.g., macrophages and lymphocytes) and related cells (e.g., microglia) release inflammatory cytokines that over time contribute to the structural and functional neuronal changes seen in schizophrenia. Monocytes carrying CD54 markers bind to intracellular molecules, leading to the migration of further monocytes through endothelial cells in the blood vessels (Cazzullo et al., 2001). Chronic excessive cytokine secretion could be the cause of the neurotransmitter dopamine and gamma-amino butyric acid (GABA) abnormalities seen in schizophrenia (Smith and Maes, 1995).

In contrast, our results do not wholly support a proposed Th1/Th2 imbalance, as no significant decrease in key Th1 cytokines (IL-2 or IFN-γ) was found. However, IL-6 is also product of the innate immune system, and Potvin suggests a primary alteration in this arm of the immune system may be relevant (Potvin et al., 2008). Our results were also mixed with regard to the microglial hypothesis, which states that inflammatory cytokines such as IFN-γ activate microglia in the central nervous system. Microglia are the mononuclear phagocytes of the brain and play a major role in brain development, synaptogenesis, and synaptic pruning. Microglial activation results in their production of pro-inflammatory cytokines such as IL-6 and TNF-α (Monji et al., 2009). However, microgial cells also have a role in neuroprotection. Microglia-mediated neuroprotection and neurogenesis have been shown to occur with to exposure to IL-4 and low levels of IFN-γ. Our results did not show significant differences in these two cytokines when compared to controls—suggesting there may well be a lack of neuroprotection at the crucial stage of development that coincides with FEP. Indeed this need for neuroprotection is a key driver in newer therapeutic options in schizophrenia, with some good evidence of their effectiveness (Chaudhry et al., 2012).

5. Summary

In summary, this meta-analysis has therefore demonstrated clear evidence for elevation in IL-1β, sIL-2r, IL-6, and TNF-α in medication-naive first episode psychosis and forwards clear evidence of a pro-inflammatory effect. Potentially significant findings of elevation in cytokines IL-12 and IL-18 from single studies, subject to independent validation, suggest intriguing cytokine inter-play. Alternatively, our secondary research did not find evidence to support alterations in IL-2, IL-4, or IFN-γ, suggesting a lack of neuroprotection in this early phase of illness.

There remain significant limitations as to the conclusions that can be drawn. Within our own meta-analysis, while all participants were

medication naive and first episode psychosis, severity of illness, diagnostic group, age, gender, and body mass were not controlled for. Thus, although results do pertain to medication-naive first episode psychosis, the patient group remained largely heterogeneous. In addition, stratified data were not available from 8 studies, which may have added statistical weight to the results.

In conclusion, however, we have found significant elevations in pro-inflammatory cytokine levels in the serum of patients with medication-naive first episode psychosis. This adds to the evidence of a clear indication of pro-inflammatory immune deregulation in schizophrenia. Future studies should focus on the medication-naive group at the early stages of illness with longitudinal follow up and numbers large enough to allow for other factors to be controlled. Further knowledge in this area has the most potential in decades to translate into effective treatment options so desperately needed in this group.

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Contributors

RU and NMT conducted literature search and retrieved articles. All authors drew up inclusion criteria and reviewed final articles. RU completed data extraction and statistical analysis. All authors contributed to write up.

Conflict of interest

Professor Barnes is the principal founder, director, and major shareholder in Celentyx Ltd, a pharmaceutical research and development company that seeks to treat disorders of the human immune system.

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