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SCHIZOPHRENIA AND OTHER PSYCHOTIC DISORDERS (AK PANDURANGI, SECTION EDITOR)

Neuroinflammation and Schizophrenia

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Abstract

Purpose of Review There are longstanding, intriguing findings of immune dysfunction in schizophrenia. These findings span peripheral immune markers, especially cytokine abnormalities.

Recent Findings This review describes recent genetic and immune marker studies and emergent treatment studies.

Summary Collectively, this provides a synthesis and current appraisal of the neuroimmune hypothesis of schizophrenia.

Keywords Schizophrenia · Immune markers · Genetics · Cytokines

Introduction

Chance findings often lead to later robust scientific discovery. In 2017, Miyaoka and colleagues observed how a patient with treatment-refractory schizophrenia went into remission of his psychosis contemporaneously with the bone marrow treatment he received for leukemia [1••]. His 7-year remission of psychosis was considered to be the result of immune cellular therapy. Provocative indeed.

However, the notion of immune dysfunction in schizophrenia is not new and there exists an earlier and somewhat perplexing literature on immune abnormalities in schizophrenia—largely based on alterations in peripheral blood immune markers—both antibodies and selective cytokines [2]. This field of research has undergone a resurgence of interest in recent years and the neuroimmune hypothesis of schizophrenia has been reinvigorated—buttressed further by early treatment studies [3••]. This review, while not exhaustive, seeks to inform readers of the general direction of this work—focusing most pertinently on reports that have been recently published.

This article is part of the Topical Collection on *Schizophrenia and Other Psychotic Disorders*

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Genetics

Central to the immune hypothesis is the notion of some genetic disturbance that cascades and raises the vulnerability for psychosis. The seminal paper in Nature detailing 108 genetic "hits" for schizophrenia also distinguished substantial overlap with genes for immune function. This propelled interest in immune-related genes and schizophrenia, as detailed in the review paper by Pouget [4]. The immune hypothesis also offers a unifying theory across many medical conditions, including several psychiatric disorders. Several large genetics studies have also now pointed to a convergence across psychiatric conditions [5,6,7••]. A seminal study by Gandal and colleagues found strong convergence in post-mortem brain samples for schizophrenia-bipolar disorders ($r = 0.75$), schizophrenia-autism spectrum disorder ($r = 0.48$), bipolar disorder-autism spectrum disorder ($r = 0.38$), and schizophrenia-major depression ($r = 0.25$) [7••].

Similarly, Plano-Ripoll and colleagues in a Danish registry study point to a shared risk across mental disorders, with a compelling co-occurrence, overlap, and convergence over time across psychiatric disorders including schizophrenia, mood disorders, substance misuse disorders, intellectual disabilities, and developmental disorders [8]. As Hyman points out in a commentary on this Danish study [9•], the confluence across psychiatric disorders now observed speaks to more singular underlying pathology—and immune dysfunction is certainly under consideration.

Antibodies and Cytokines

In addition to genetics, physiological studies of immune markers have been foundational to the immune hypothesis of schizophrenia [2]. The study of immune markers continues to this day and some recent examples are now highlighted below. Oviedo-Salcedo and colleagues examined for autoimmune encephalitis antibodies in a first episode schizophrenia study [10]. Only 4% of patients had positive antibody titers in their cerebrospinal fluid. Dahan and colleagues found elevated levels of several cytokines, some that appeared to correlate with symptom severity among an Israeli sample with schizophrenia [11]. Kelly and colleagues reported strong relationships between anti-gliadin antibodies and TNF-α in schizophrenia [12]. Melbourne and colleagues reported elevated expression of RNAs in relation to cytokine MRNA expression in blood cells from patients with schizophrenia [13].

Elevated anti-gliadin antibodies are associated with gluten sensitivity and heightened gluten sensitivity is one of those longstanding curious associations with schizophrenia. Cihakova and colleagues also reported elevated anti-gliadin antibodies in a sample of 160 patients with schizophrenia [14]. Garcia-Alvarez and colleagues [15] report elevated levels of several immune markers in patients with schizophrenia, a pattern that differed from the bipolar disorder patient group. Misiak and colleagues [16] also examined the pattern of immune markers across schizophrenia and bipolar disorder, with a focus on cognitive impairment. Their authoritative review of this suggests that elevation of C-reactive protein is associated with greater cognitive impairment in schizophrenia. They did not find a similar relationship for cytokines in schizophrenia or for either cytokines or C-reactive protein with respect to cognitive performance in patients with bipolar disorder. In one of the most comprehensive studies of immune markers in the field of schizophrenia research, Jeffries and colleagues explore the typology of immune-related protein expression in the North American Prodrome Longitudinal Study (NAPLS) [17]. NAPLS is a major collaborative study that included 765 individuals who had demonstrated mild/attenuated psychotic symptoms—though no patients were psychotic. They were followed over time and evaluated for conversion to psychosis. They observed a differential network of serum proteins implicated in inflammation between individuals with prodrome of psychosis who converted to florid psychosis compared with individuals who did not experience a psychosis. The discriminatory power of inflammatory cytokines was not as robust in their sample. This is important as it illustrates that, at least at this juncture, this approach is neither sensitive nor specific enough to form the basis for a biomarker screening for psychosis. Time will tell how this biomarker battery approach evolves over time and whether either more detailed and discriminatory immune assays alone or in combination with genetic and other related biomarkers might offer greater discriminatory power in the assessment of psychosis.

Treatment Options

In contrast to the relatively longstanding literature on immune abnormalities in schizophrenia, the translation of this work into treatment options is relatively recent. There are now several studies that document some benefit on positive symptoms through the addition of non-steroidal anti-inflammatory drugs (NSAIDS) to antipsychotic therapy [2]. Somewhat more speculatively, there are a handful of studies that have evaluated vaccine therapies for schizophrenia. The results are inconclusive, at best. There are also several studies of immune modulators—that work at various discrete sites of action—that have been published. Deakin and colleagues conducted a large multi-center British study (BeneMin) of minocycline—a known dermatologic treatment that has both neuroprotective and anti-inflammatory effects—in just over 200 patients with schizophrenia who were selected for persistent negative symptoms [18••]. The methodology of this 1-year double-blind placebo controlled trial was exemplary. The results were clear: there was no effect of minocycline on symptoms—either positive or negative symptoms—or on either the brain imaging, neurocognitive, or peripheral inflammatory markers. In contrast, Zhang and colleagues did find an effect of minocycline upon negative symptoms in a smaller ($n = 75$) double-blind, placebo controlled trial of 3 months' duration. Patients receiving minocycline had clinical improvements in both positive and negative symptoms, as well as showing reductions in peripheral immune markers [19].

Following upon the success of antibody therapies in rheumatoid arthritis and related immunological disorders, there has been a growing interest in evaluating selective antibody approaches as adjunctive therapies for schizophrenia. Several review papers attest to the rationale, potential, as well as pitfalls of this highly innovative approach [2, 20]. A recent study by Girgis and colleagues is also illustrative [21]. In a 2-week trial among 36 patients with chronic schizophrenia, Girgis and colleagues tested the efficacy of tocilizumab—an interleukin 6 antibody—that is FDA approved as an intravenous (infusion) treatment for rheumatoid arthritis. The methodology of this study was robust. The authors found no effect of tocilizumab. They postulated that the absence of effect was because tocilizumab does not cross the blood brain barrier. They did however observe a modest reduction in the peripheral immune marker—plasma C-reactive protein.

Conclusions

The study of immune dysfunction in schizophrenia has a long history and is confounded by comorbidities, potential effects of antipsychotic medications. That said, recent genetics studies are suggestive of an overlap in genetic markers for immune functions and genetic abnormalities in schizophrenia. Several large

studies are either completed of underway evaluating immune antibody strategies as potential adjunctive therapies for schizophrenia. The results to date are mixed. Time will tell whether immune dysfunction is a primary mechanism or a secondary consequence in the neurobiology of schizophrenia. How our field will evolve in a manner analogous to other medical conditions and toward personalized medicine is hopefully ahead of us [22].

Compliance with Ethical Standards

Conflict of Interest Peter F. Buckley is a co-investigator on research grants supporting the study of immunologic drugs for schizophrenia for the Stanley Foundation and the Brain & Behavior Research Foundation.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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