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Increased ratio of high sensitivity C-reactive protein to interleukin-10 as a potential peripheral biomarker of schizophrenia and aggression

Qinting Zhang [a,b,c,1], Wu Hong [a,*,1], Haozhe Li [a,b], Fanglan Peng [a], Fan Wang [a], Ningning Li [a], Hui Xiang [a], Zongfeng Zhang [a], Yousong Su [a], Yueqi Huang [a,f], Shengyu Zhang [b], Guoqin Zhao [a], Rubai Zhou [a], Ling Mao [a,d], Zhiguang Lin [a], Weixiong Cai [b], Yiru Fang [a], Bin Xie [a], Min Zhao [a,c,e,*]

[a] Shanghai Mental Health Center, Shanghai Jiao Tong University School of Medicine, Shanghai 200030, China
[b] Shanghai Key Laboratory of Forensic Medicine, Shanghai Forensic Service Platform, Institute of Forensic Science, Ministry of Justice, Shanghai 200063, China
[c] Collaborative Innovation Center for Brain Science, Shanghai Mental Health Center, Shanghai Jiao Tong University School of Medicine, Shanghai 200030, China
[d] XuHui District Mental Health Center of Shanghai, Shanghai 200030, China
[e] Shanghai Key Laboratory of Psychotic Disorders, Shanghai Mental Health Center, Shanghai, China
[f] Hangzhou Seventh People's Hospital, Hanzhou 310007, China

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ABSTRACT

Background: Many studies have indicated that immune dysfunction might be involved in the physiopathology of schizophrenia and aggression. This study aimed to investigate the correlation between high-sensitivity C-reactive protein (hsCRP), interleukin (IL)-10 and clinical characteristics, especially aggression, and to explore the potential role of hsCRP and IL-10 as plasma biomarkers of schizophrenia.
Methods: Forty-one patients with schizophrenia and forty healthy individuals were enrolled. Psychopathological severity and aggression were assessed using the Positive and Negative Syndrome Scale (PANSS) and Modified Overt Aggression Scale (MOAS). Plasma concentrations of hsCRP and IL-10 were assessed by enzyme-linked immunosorbent assay (ELISA).
Results: (1) Higher levels of hsCRP ($p < 0.001$), lower levels of logIL-10 ($p < 0.001$) and higher ratio of hsCRP to IL-10 ($p < 0.001$) were observed in the plasma of patients with schizophrenia, compared to healthy controls; (2) ROC (receiver operating characteristic) curve analysis revealed that ratio of hsCRP/IL-10 (predictive value: 0.783, $p < 0.01$; sensitivity: 85.4%; specificity: 67.5%) was more applicable as a biomarker to distinguish patients with schizophrenia from the control group than hsCRP and IL-10 alone (predictive value: 0.718, $p < 0.01$; 0.275, $p < 0.001$, respectively); (3) we found positive correlations between hsCRP and the total score and verbal aggression score of MOAS ($r = 0.654$, $p < 0.01$; $r = 0.678$, $p < 0.05$), and between hsCRP/IL-10 and the total score of MOAS ($r = 0.636$, $p < 0.01$).
Conclusions: Our results suggest the possible function of hsCRP and IL-10 in the pathogenesis of schizophrenia and the possible value of hsCRP/IL-10 as a potential peripheral biomarker of schizophrenia. This finding also suggests a relationship between hsCRP, IL-10 and their ratio with aggression in patients with schizophrenia.

1. Introduction

Schizophrenia is a severe psychiatric illness with a variety of symptoms, including positive (delusions and hallucinations), negative (social withdrawal and apathy), and disorganised behaviours as well as altered emotional reactivity. Among the multiple symptoms of schizophrenia, aggression is common and results in serious clinical and societal consequences, which is the major reason for presentation to an emergency department and subsequent admission to a psychiatric inpatient unit. Aggression also leads to prolonged hospital stays and difficulty reintegrating into the community (Kageyama et al., 2015).

The hypothesis of immune dysfunction in schizophrenia was proposed over a century ago. A substantial body of evidence from different research areas suggests that immune dysfunction is involved in the pathogenesis of schizophrenia (Khandaker et al., 2015). Many immune-related diseases/problems, such as autoimmune thyroid diseases, cardiovascular disease, obesity, diabetes, hypertension, smoking, metabolic syndrome (Barnett et al., 2007) and infections (Blomstrom et al., 2014) have been found comorbidly with schizophrenia. People with high levels of pro-inflammatory biomarkers in plasma or serum have

Abbreviations: CRP, C-reactive protein; hsCRP, high-sensitivity C-reactive protein; IL, interleukin; PANSS, Positive and Negative Syndrome Scale; MOAS, Modified Overt Aggression Scale; ELISA, enzyme-linked immunosorbent assay; ROC, receiver operating characteristic.

* Corresponding authors at: Shanghai Mental Health Center, Shanghai Jiao Tong University School of Medicine, Shanghai 20003, China.
E-mail addresses: drhongwu@126.com (W. Hong), drminzhao@gmail.com (M. Zhao).
[1] These authors contributed equally to the paper.

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high risk of suffering from schizophrenia (Wium-Andersen et al., 2014). Patients with schizophrenia had significant inflammatory markers alterations (Asevedo et al., 2014; Dickerson et al., 2013). And, anti-inflammatory drugs, such as COX-2 inhibitors (Muller et al., 2010), anti-TNF (tumour necrosis factor) (Soczynska et al., 2009), aspirin (Laan et al., 2010) and anti-oxidants (Dodd et al., 2008) could improve the schizophrenia symptoms (Sommer et al., 2014). Additionally, it has been reported that some antipsychotic medications altered levels of cytokines in patients with schizophrenia (Sugino et al., 2009). Animals' studies have also indicated that cytokines can induce schizophrenia-like behaviour in animals (Luo et al., 2012). Furthermore, in the hypothesis of immune dysfunction in schizophrenia, immunological imbalance reportedly represented a key mechanism involved in the precipitation of schizophrenia-related pathology (Meyer et al., 2009).

C-reactive protein (CRP) is one of the most frequently used acute phase response immune markers, regulated by pro-inflammatory cytokines. The levels of CRP in the blood are normally very low, but increase rapidly with inflammation. Elevated CRP has been reported to be associated with increased risk of schizophrenia according to case-control (Joseph et al., 2015) and prospective studies (Wium-Andersen et al., 2014).

Interleukin-10 (IL-10) is a major player in the cellular and molecular suppression of inflammation (O'Farrell et al., 1998), which plays a regulatory role in the later phases of the immune response as a potential anti-inflammatory marker (Moore et al., 2001). In addition, IL-10 has been reported to maintain the balance between pro-and anti-inflammatory cytokine levels in the central nervous system (Sawada et al., 1999). Numerous studies have demonstrated that blood IL-10 levels were significantly decreased in patients with schizophrenia (Miller et al., 2011), and also associated with the severity of symptoms in patients with schizophrenia (Dimitrov et al., 2013). Studies have reported up-regulated IL-10 levels administration of atypical antipsychotics (Sugino et al., 2009).

With growing evidence supporting immune dysfunction in schizophrenia, the role of inflammation in behavioural and emotional symptoms is gaining credibility. And increasing number of studies have suggested a facilitatory role for inflammatory markers in aggression. Clinical studies have reported that inflammatory markers, such as CRP and IL-6 were positively correlated with anger, hostility, and aggression in community samples (Marsland et al., 2008), in psychiatric subjects with personality disorder (Coccaro, 2006) and in patients with intermittent explosive disorder (Coccaro et al., 2015). Patients have reported emerging anger when treated with pro-inflammatory agents (Kraus et al., 2003). Animal studies have also reported increasingly defensive aggressive behaviour in cats after the application of IL-1β and IL-2 to cells in the medial hypothalamus (MH) and in periaqueductal grey (PAG) (Pesce et al., 2011). However, mice deficient in inflammatory cytokine receptors fail to exhibit aggressive and defensive behaviour even when threatened (Patel et al., 2010).

The role of peripheral inflammatory markers as potential biomarkers for the diagnosis and treatment of schizophrenia and other mental illness (Goldstein et al., 2009; Li et al., 2015) has attracted the attentions of researchers. In addition, to our knowledge, little researches of peripheral inflammatory markers for aggression have been well studied in patients with schizophrenia. This study aimed to compare the plasma levels of hsCRP and IL-10 and ratio of hsCRP to IL-10 between patients with schizophrenia and healthy control subjects and to explore the correlations between levels of hsCRP, IL-10 and hsCRP/IL-10 with psychopathology and aggression in patients with schizophrenia, and the potential value of the above variables as diagnostic biomarkers.

2. Material and methods

2.1. Participants

Forty-one patients diagnosed with schizophrenia according to International Classification of Disease-10 (ICD-10) criteria, who were hospitalised in Shanghai Mental Health Center during 2014, were enrolled in the study. Diagnosis of schizophrenia was defined by a senior psychiatrist based on a semi-structured clinical interview and a review of medical records. The severity of schizophrenia symptoms was evaluated via the Positive and Negative Syndrome Scale (PANSS) by a trained clinical psychiatrist. Inclusion criteria were: (i) age between 18 and 65 years old; (ii) total score of PANSS ≥60; (iii) patients were medication naïve or medication free for at least 4 weeks before enrolment; (iv) ability to read the research content. Exclusion criteria were: (i) alcohol and/or substance dependence or ever diagnosed with other psychiatric disorders; (ii) pregnant or lactating; (iii) physical diseases (cardiac disease, significant organic brain disease, diabetes mellitus, thyroid and other immune related disease, or other serious medical condition); (iv) infectious disease in the preceding four weeks, using anti-inflammatory drugs, corticosteroids or antibiotics and autoimmune diseases; (v) infectious and autoimmune diseases one week after enrolment; (vi) lack of consensus on the diagnosis.

Forty age- and gender-matched healthy volunteers were enrolled in the control group, consisting of staff members and medical students at the Shanghai Mental Health Center. All the healthy controls were volunteers and met the following inclusion and exclusion criteria. Inclusion criteria were: (i) age between 18 and 65 years old; (ii) ability to read the research content. Exclusion criteria were: (i) alcohol and/or substance dependence or ever diagnosed with psychiatric disorders; (ii) family history of psychiatric disease; (iii) pregnant or lactating; (iv) physical diseases (cardiac disease, significant organic brain disease, diabetes mellitus, thyroid and other immune related disease, or other serious medical condition); (v) infectious disease in the preceding four weeks, using anti-inflammatory drugs, corticosteroids or antibiotics and autoimmune diseases; (vi) infectious and autoimmune diseases one week after enrolment.

The study conforms to the principles outlined in the Declaration of Helsinki and was approved by the Ethics Committee of Shanghai Mental Health Center, Shanghai, China. All patients and healthy volunteers gave their written informed consents.

2.2. Illness severity and clinical variables assessment

The symptoms and severity of patients were assessed by means of PANSS (Kay et al., 1987). This test was divided into positive, negative and general psychopathology subscales and three supplemental aggression risk items. The positive symptoms included seven symptoms: delusions, disorganisation, hallucinations, excitement, grandiosity, suspiciousness and hostility. The negative symptoms included seven symptoms: blunted affect, emotional and social withdrawal, poor rapport, difficulty in abstract thinking, lack of spontaneity and flow of conversation, and stereotyped thinking. The general symptoms included 16 symptoms: somatic concern, anxiety, guilt feelings, tension, mannerisms and posturing, depression, motor retardation, uncooperativeness, unusual thought content, disorientation, poor attention, lack of judgment and insight, disturbance of volition, poor impulse control, preoccupation, and active social avoidance. The three PANSS supplemental aggression risk items included: anger, difficulty in delaying gratification and affective lability (White et al., 1997). Every symptom was evaluated on a scale from 1 to 7, with 1 indicating an absence of the symptom and 7 representing the symptom at the maximum intensity. The total PANSS score was calculated by the sums of all positive, negative and general symptoms.

The aggressive symptoms were assessed using the PANSS Activation subscale and, The PANSS Supplemental Aggression Risk subscale (Buckley et al., 2007) and the Modified Overt Aggression Scale (MOAS) (Huang et al., 2009; Kay et al., 1988) by the same psychiatrist. The PANSS Activation subscale score was calculated by the sum of the following items: P4 (Excitement), P7 (Hostility), G4 (Tension), G8 (Uncooperativeness), G14 (Poor impulse control). The PANSS Supplemental Aggression Risk subscale score was calculated by the sum of