Psychiatry Research 246 (2016) 89–94

Contents lists available at ScienceDirect

Psychiatry Research

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

Serum high-sensitivity C-reactive protein: A delicate sentinel elevated in drug-free acutely agitated patients with schizophrenia

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ARTICLE INFO

Article history:
Received 19 January 2016
Received in revised form
4 September 2016
Accepted 20 September 2016
Available online 21 September 2016

Keywords:
Acute agitation
Schizophrenia
High-sensitivity C-reactive protein
White blood cell counts

ABSTRACT

Increased levels of high-sensitivity C reactive protein (hsCRP) have been reported in schizophrenia, but to date, no study is designed to examine serum hsCRP in acutely agitated patients with schizophrenia, an extreme state that requires immediate diagnosis and medical treatment. Serum hsCRP levels were assessed in 32 clinically acutely agitated patients and 42 healthy control subjects matched for demographic properties. Further, serum hsCRP levels in acutely agitated patients were compared with control subjects and with the levels after the patients were treated with anti-psychiatric medications. Meanwhile, the influence of clinical subtypes, family history, and gender, as well as the levels of white blood cell (WBC) counts were also considered. In results, serum hsCRP levels were significantly higher in acutely agitated patients with schizophrenia than in healthy subjects. The elevation of serum hsCRP in patients was not affected by gender, family history ($P > 0.05$), and clinical classification of schizophrenia ($P > 0.05$). However, the elevation of hsCRP was suppressed by the medical treatment for schizophrenia with acute agitation ($P < 0.05$). In addition, WBC counts, another inflammation-related indicator, were also increased significantly in acutely agitated patients compared with healthy subjects, consistent with the elevation of serum hsCRP. In conclusion, hsCRP is an important indicator of immune alterations in the pathogenesis of schizophrenia and has potential to be developed into a sensitive marker for the acute agitation in schizophrenia.

1. Introduction

Schizophrenia is a psychiatric illness characterized by a variety of psychotic symptoms, including delusions and hallucinations, altered emotional reactivity, and disorganized behavior (Porteous, 2008). Schizophrenia usually is divided into two common types: paranoid and non-paranoid (Huang and Wu, 2000; Segal et al., 2007). Despite its 1% prevalence, schizophrenia has drawn attention as a leading public health problem and exerts enormous personal and economic costs worldwide (Singh and Chaudhuri, 2014). Even after the ongoing tireless research efforts, the etiology of schizophrenia is not yet clearly understood. Importantly, many studies reveal that the alteration of the immune system and inflammatory processes are associated with the pathogenesis of schizophrenia (Boyajyan et al., 2008; Bilbo and Schwarz, 2009; Monji et al., 2009; Singh et al., 2009).

Agitation has been considered as a syndrome of behaviors, such as verbal aggression, physical aggression, purposeless motor behaviors, heightened arousal, and disruption of patient functioning (Allen et al., 2005). Severe agitation is frequently reported to accompany the acute states of schizophrenia, with the symptoms of super excitement, physical and verbal hyperactivity, hostility, tension, and aggression. The situation of agitation causes extreme distress and could be a considerable risk to patients and their environment; therefore, it requires immediate diagnosis and medical treatment (Thomas et al., 2009).

High-sensitivity C-reactive protein (hsCRP) is a pentameric protein generated largely in the liver and secreted into the circulation. The measurement of hsCRP in the blood provides a reliable marker of chronic inflammation caused by infectious and other proinflammatory agents. Increased levels of hsCRP have been associated with chronic infections and inflammatory reactions as well as with increased risk of inflammatory, cardiovascular or metabolic disorders (Lowe, 2005).

Previous studies in schizophrenia have repeatedly reported that hsCRP levels is higher in people with schizophrenia than in comparison subjects (Akanji et al., 2009; Fawzi et al., 2011; Dickerson et al., 2013; Miller et al., 2014; Joseph et al., 2015; Fernandes et al., 2016; Inoshita et al., 2016), but few studies have examined

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http://dx.doi.org/10.1016/j.psychres.2016.09.033
0165-1781/

the immune alterations or inflammatory reactions in the condition of acutely agitated patients with schizophrenia without the treatment of antipsychotic drugs. Therefore, the present study is designed to investigate the levels of serum hsCRP in acutely agitated patients in comparison with healthy controls, as well as the relationship of serum hsCRP levels with the demographic characteristics, clinical classification of schizophrenia, and family history in clinically acutely agitated patients with schizophrenia. The findings will not only give some insight into the pathogenesis of schizophrenia, but also provide a scientific basis for the diagnosis and treatment of the acute phase of the disease.

2. Methods

2.1. Subjects

Thirty-two newly admitted patients (male/female = 17/15) were randomly recruited for the study from the Beijing HuiLongGuan Hospital, China during January 2015 to October 2015. All patients met the following inclusion criteria: (1) Han Chinese 20–65 years of age; (2) DSM-IV criteria for diagnosis of schizophrenia confirmed by two psychiatrists based on the Structured Clinical Interview for DSM-IV (SCID); (3) diagnosis as in an acute agitation state confirmed by two psychiatrists; PANSS excitement component (PANSS-EC) $\geq$ 14; (4) conformity to the disease- and health-related question classification Tenth Edition (ICD-10) schizophrenia diagnosis standard; (5) not receiving any doses of antipsychotic drugs for $\geq$ 3 months. Patients diagnosed with a major affective disease (i.e. schizoaffective, bipolar disorder, major depression, and mania) were excluded. We also excluded patients suffering from any acute physical illness, patients with fever $>$ 37.9 °C, or those who were treated with antibiotics, steroids, antipyretics, or anti-inflammatory medications. Serum hsCRP levels and PNASS-EC scores were measured upon admission and after 2 weeks of treatments with haloperidol (15–30 mg/Day) to control acute agitation, in combination with olanzapine (10 mg/Day), or quetiapine (200–400 mg/Day).

Forty-two normal controls (male/female = 19/23) were recruited from the local community, were 20–65 years old, were Han Chinese, and were matched for age and sex. A complete medical history, physical examination, and laboratory tests were obtained from all subjects to screen out those with evidence of any acute or chronic general medical or psychiatric condition. Potential control subjects who had history of psychiatric or physical illness, trauma or surgical intervention in the preceding 6 months were also excluded.

All subjects gave written informed consent. The study did not interfere with the treatment of the patients and was approved by the Institutional Ethical Committee of Beijing HuiLongGuan Hospital.

2.2. Data on demographic characteristics

The clinical data retrieved included sex, marital status, education, body mass index (BMI) and smoking status. Psychiatric scales including PANSS-EC score were routinely completed in Beijing HuiLongGuan Hospital. PANSS-EC score was determined by the patient's attending psychiatrist following an interview conducted within 48 h after admission and again 2 weeks later as a routine practice of the inpatient unit. PANSS-EC score was used as a measure of agitation (Lindenmayer et al., 2004; Huber et al., 2008; Montoya et al., 2011). Demographic and clinical characteristics of the sample are presented in Table 1.

2.3. Laboratory procedures

Venous blood from forearm vein was collected into tubes containing coagulation accelerator thrombin, centrifuged at 4000 rpm/min for 5 min. Serum samples from patients were collected within 1 h after admission and between 7 and 9 A.M. after 2 weeks of treatment with anti-psychiatric medication. Healthy controls also had serum samples collected between 7 and 9 A.M. The concentrations of serum hsCRP were determined by enhanced immunoturbidimetric method. The kits were provided by Mindray Company (Beijing, China), and MINDRAY BS-800 automatic biochemical analyzer was applied for determination. All samples were assayed by the same investigator, who was blind to the sample sources. The reference ranges of serum hsCRP are 0.11–3.01 mg/L. Another indicator associated with inflammation was the white blood cells (WBC) counts. Venous blood from forearm vein was collected into tubes containing anticoagulant EDTA-K_2 and the WBC counts were measured using Sysmex XT-1800i. The kits used in measuring WBC counts were provided by Sysmex Company (Japan). The reference ranges of WBC counts are $(3.50–9.50) \times 10^9$/L.

2.4. Statistical analysis

All data were statistically analyzed by SPSS 20.0 software. Descriptive statistics were expressed as (MEAN $\pm$ SD) or rate (%). The quantitative data were analyzed with non-parametric Mann–Whitney U test or Kruskal–Wallis test as appropriate. The count data were described by case number (percent) and two groups were compared by using x^2 test. Statistical significance was considered when $P < 0.05$.

3. Results

3.1. Demographic data

The two groups are similar in terms of age and sex (patients: 46.9% women, 53.1% men; Healthy subjects: 54.8% women, 45.2% men). The mean age of healthy subjects is 41.2 years old and the mean age of patients is 40.6 years old. Relative to the control subjects, the group of patients with schizophrenia is also similar in terms of education and marital status (single or married), current smoking habits, and BMI. The percentage of clinical subtypes of schizophrenia is shown as follows: paranoid (13, 40.6%) and non-paranoid schizophrenia (19, 59.4%). Family history of patients with schizophrenia is as follows: present (12, 37.5%) and absent (20, 62.5%). As expected, the acutely agitated patients with schizophrenia have worse psychopathology symptoms, with an average PANSS-EC score of 23.3 $\pm$ 4.5. After medical treatment for 2 weeks, their average PANSS-EC score is reduced to 10.3 $\pm$ 2.4 ($P < 0.001$, $Z = -6.886$). Sociodemographic features of the groups are shown in Table 1.

3.2. hsCRP levels and WBC counts in acutely agitated patients with schizophrenia and normal controls

Serum hsCRP levels are significantly higher in acutely agitated patients with schizophrenia than in comparison subjects (9.79 $\pm$ 7.64 vs. 0.96 $\pm$ 0.82 mg/L) ($P < 0.001$, $Z = -5.828$) (Fig. 1). After medical treatment for 2 weeks, serum hsCRP levels are decreased statistically (2.83 $\pm$ 2.74 mg/L) ($P < 0.001$, $Z = -3.935$) (Fig. 2). The reduction of serum hsCRP levels after treatment is consistent with the decrease of PANSS-EC scores of the patients (Table 1).

In the following, the influence of gender, family history, and