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Elevated serum immunoinflammation-related protein complexes are associated with psychosis

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ABSTRACT

Emerging evidence suggests an underlying immune and inflammatory response for a variety of psychiatric disorders. Herein, we employed an optimized native-polyacrylamide gel electrophoresis to isolate psychosis-related serum immunoinflammation-related protein complexes (IIRPCs) from 147 patients with schizophrenia (SCH), 158 patients with bipolar disorder (BPD), 132 patients with other psychosis, and 145 normal controls. All participants could be classified into four categories based on serum IIRPCs, which correspond to 290, 215, 70, and 7 serum samples, correspondingly. For each category, significantly enhanced levels of serum IIRPCs in patients with SCH, BPD, and other psychosis groups were observed compared with normal controls. Receiver operating characteristic analysis indicated that serum IIRPCs have excellent diagnostic performance to differentiate SCH, BPD, and other psychosis groups from normal controls, with high sensitivities and specificities of $>85\%$. Total serum amounts of IgG, IgA, and IgM in all patients were significantly decreased compared with normal controls.

1. Introduction

Psychosis is a severe mental disorder characterized by a loss of contact with reality. Several types of psychosis are classified based on psychopathological features, such as schizophrenia (SCH) which is applied to a syndrome with long duration, bizarre delusions, negative symptoms, and few affective symptoms (van Os and Kapur, 2009) and bipolar disorder (BPD) which is characterized by recurrent mania or hypomania and depressive episodes that impair overall function and quality of life (Labrie et al., 2012). Psychiatric disorder is a main contributor to global disease burden and has the risk of suicide which needs more research to resolve these problems (Collins et al., 2011; Nordentoft et al., 2015; Pompili et al., 2011). However, the biological mechanisms underlying the pathophysiology of these disorders still remain challenging.

The immunity and inflammation are new and important aspects to understand the pathogenesis of psychosis and can be potential therapeutic targets for psychosis. Previous studies have indicated that inflammation and immunity are closely correlated with the molecular pathogenesis of SCH and BPD (Bergink et al., 2014; Fan et al., 2007; Hamdani et al., 2013; Kirkpatrick and Miller, 2013; Leboyer et al., 2012; Muller et al., 2012). For SCH patients, C-reactive protein (CRP) and many cytokines, including IL-1β, sIL-2R, IL2, IL6, IL8, and TNF-α, were elevated (Borovcanin et al., 2012; Erbagci et al., 2001; Fillman et al., 2014; Miller et al., 2011, 2014; Singh and Chaudhuri, 2014; Zhang et al., 2002). For BPD patients, previous studies indicated that pro-inflammatory cytokines, such as IL2, IL6, and TNF-α, as well as CRP, were also significantly increased (Brietzke et al., 2009; Dickerson et al., 2013; Kim et al., 2007; Modabbernia et al., 2013; Munkholm et al., 2013).

Our previous study has indicated that elevated serum immunoinflammation-related protein complexes (IIRPCs) are significantly associated with chronic diseases including benign diseases and cancers (Wang et al., 2014) and disease progression of lung cancer (Song et al., 2015). In this study, we employed an optimized native-polyacrylamide gel electrophoresis (native-PAGE) to isolate serum IIRPCs from 147 patients with SCH, 158 patients with BPD, 132 patients with other psychosis, and 145 normal controls to investigate the relationships between the levels of serum IIRPCs and psychiatric status.

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2. Methods

2.1. Participants and serum sample collection

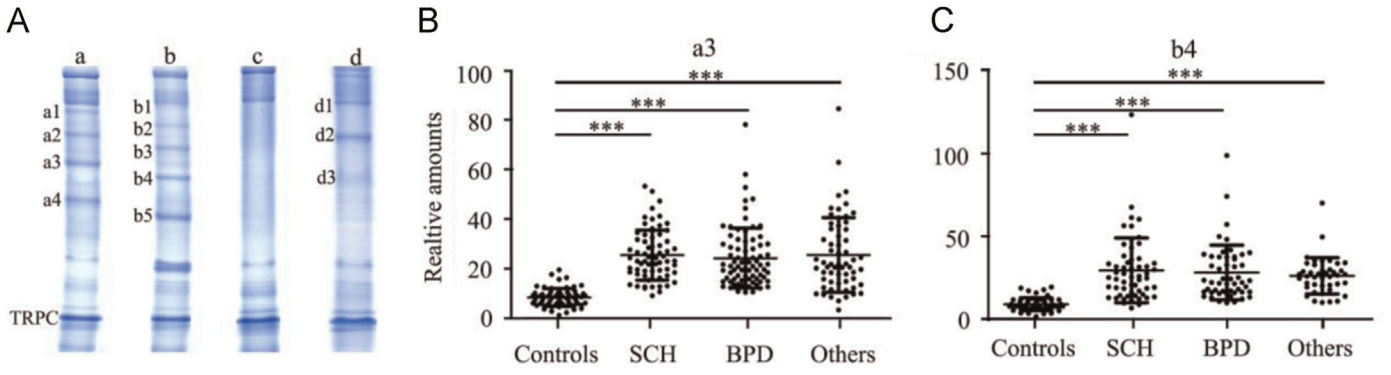
In this study, a total of 582 participants were recruited from January 2011 through May 2014 without medical treatment records in past two months. They are 147 patients with SCH, 158 patients with BPD, 132 patients with other psychosis (other psychosis groups) (*i.e.* depressive disorder, 71; dysthymia, 5; schizoaffective psychosis, 11; acute and transient psychotic disorder,15; major depression with psychotic symptoms, 15; delusional disorder, 15), and 145 healthy controls with normal psychiatric histories and physiological indices determined by physical and laboratory examinations, Psychiatric diagnoses were performed based on the Diagnostic and Statistical Manual of Mental Disorders, 4th. Edition (DSM-IV). Serum samples were collected at diagnosis after about 10 h overnight fast. The study was conducted in accordance with the most recent version of the Declaration of Helsinki. The protocol was approved by the ethical committee at Beijing An Ding Hospital and the Institute of Basic Medical Sciences, Chinese Academy of Medical Sciences, and the informed consent was obtained from each participant.

2.2. Native-PAGE separation and pattern assignment of serum IIRPCs

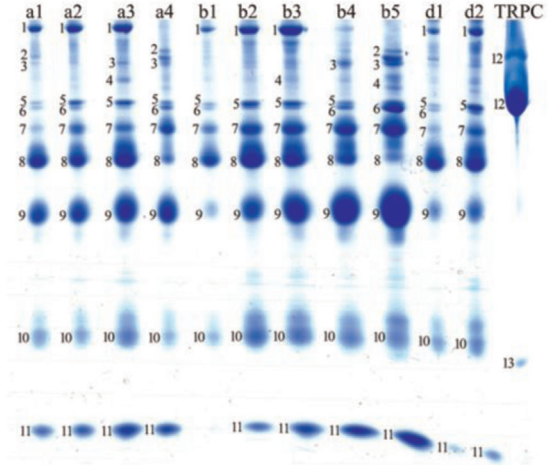
Serum IIRPCs were isolated using the native-PAGE as described previously (Wang et al., 2014). Briefly, 4–10% linear gradient acrylamide gel and 4% acrylamide gel were used as separating gel and stacking gel, respectively. 2 μL of serum sample mixed with 8 μL 1 × native loading buffer (25% v/v 50 mM Tris–HCl pH 7.5; 50% v/v glycerol; 0.1% w/v XYlene cyanol FF) was loaded into one lane. Electrophoresis was run at 10 mA per gel for 1.5 h and then at 25 mA for 3 h, followed by staining with Coomassie blue G250. The background was destained with water, and then the gels were either scanned with an UMAX PowerLook 2100XL scanner (Techville, Inc., USA) for optical densitometry-based quantification, or were immediately separated using SDS-PAGE to identify the components of these protein complexes. In terms of the positions and the number of serum IIRPCs in each lane of the gels, the serum samples were classified into four categories (*i.e.,* patterns a, b, c, and d) (Fig. 1A). For pattern a, four specific IIRPCs were observed (a1, a2, a3, and a4); for pattern b, five specific IIRPCs (b1, b2, b3, b4, and b5); for pattern c, no specific IIRPCs; and for pattern d, three specific IIRPCs.

2.3. Quantification of serum IIRPCs

Nine serum samples and one quality control (QC) sample as an external reference were separated on one native-PAGE gel. The QC sample was a mixed serum from three random healthy control sera. The gray values of the gel bands of these protein complexes were calculated using Quantity One software (version 4.6.3, Bio-Rad). The gray value of the transferring-related protein complexes (TRPC) was normalized to 100 (Fig. 1A), and the amounts of serum IIRPCs relative to serum TRPC in each gel were quantified.



D



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band number	proteins name	mass weight	calculated pI value	sequence coverage	mascot score
1	α-2-macroglobulin	164614	6.00	29%	125
	complement factor H	143680	6.21	21%	55
2	complement C3-α	112956	6.02	36%	99
3	complement C3-α	112956	6.02	18%	66
4	complement C4-A-α	84131	6.65	17%	60
5	complement C4-A-β	71634	6.65	28%	89
6	complement C3-β	71272	6.02	33%	93
7	Igα-1 chain C region	38486	6.08	22%	23
8	Igγ-1 chain C	36596	8.46	36%	44
9	haptoglobin-β	27248	6.13	55%	87
10	Igκ chain C	11773	5.58	58%	52
11	haptoglobin-α2	15837	6.13	58%	45
12	transferrin	79280	6.81	24%	81
13	apolipoprotein A-I	30759	5.56	47%	130

Fig. 1. Patterns a (protein complexes a1, a2, a3, and a4), b (b1, b2, b3, b4, and b5), c (no IIRPCs), and d (d1, d2, and d3) of serum IIRPCs (A). Scatter plots of serum amount of a3 relative to the TRPC (B), b4 relative to the TRPC (C) . SDS-PAGE separation of protein complexes a1, a2, a3, a4, b1, b2, b3, b4, b5, d1, and d2 from patterns a, b, and d, respectively and TRPC. The number (1–13) represents the main components of serum IIRPCs and TRPC (D). Information on the identified proteins from serum IIRPCs and TRPC in D (E). ***, $p < 0.001$.

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