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Acute phase proteins as biological markers of negative psychopathology in paranoid schizophrenia

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Introduction. Acute inflammatory response is one of the pathophysiological elements involved in the etiology of schizophrenia. This paper aims to study the relationship between Acute Phase Proteins (APPs) and psychopathology in paranoid schizophrenia.

Method. Fifteen physically healthy inpatients meeting DSM-IV criteria for paranoid schizophrenia took part in the study. The Spanish version of the Positive and Negative Syndrome Scale (PANSS) was used in order to rate psychopathology. Ceruloplasmin, Complement's fraction 3 (C3) and fraction 4 (C4) levels were measured as APPs.

Results. Five out of seven items of the PANSS negative subscale showed a positive correlation with the APPs at a significant level. Poor Attention and Active Social Avoidance, two items of the general psychopathology subscale, correlated significantly with the APPs. No single item of the positive subscale correlated with the APPs.

Conclusions. Ceruloplasmin, C3 and C4 blood levels are useful peripheral biological markers of negative acute paranoid schizophrenic symptoms.

Key words:
Acute phase proteins. Schizophrenia. Psychopathology. Positive symptoms. Negative symptoms. Biological markers.

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Proteínas de fase aguda como marcadores biológicos de la psicopatología negativa en la esquizofrenia paranoide

Introducción. La respuesta inflamatoria aguda es uno de los elementos fisiopatológicos que se pueden alterar en la psicosis esquizofrénica. El objetivo de este trabajo consiste en estudiar las relaciones existentes entre psicopatología y proteínas de fase aguda (PFA) en la esquizofrenia paranoide.

Método. Se estudiaron 15 pacientes diagnosticados de esquizofrenia paranoide según el DSM-IV. A todos los sujetos se les administró la versión española de la Escala de síndromes Positivo y Negativo (PANSS) para cuantificar la psicopatología. Como PFA se midieron los niveles de ceruloplasmina y las fracciones 3 y 4 del complemento.

Resultados. Cinco de los siete ítems de la subescala negativa de la PANSS se correlacionaron de manera positiva y significativa con las PFA. Dos ítems de la escala de psicopatología general, Atención deficiente y Evitación social activa, se correlacionaron positiva y significativamente con las PFA. Ningún ítem de la subescala positiva se correlacionó significativamente con los niveles sanguíneos de las PFA.

Conclusiones. La cuantificación de los niveles plasmáticos de ceruloplasmina y las fracciones 3 y 4 del complemento puede consideralos como marcadores periféricos de la psicopatología negativa en la esquizofrenia paranoide aguda.

Palabras clave:
Proteínas de fase aguda. Esquizofrenia. Psicopatología. Síntomas positivos. Síntomas negativos. Marcadores biológicos.

INTRODUCTION

Schizophrenia is a psychiatric disease in which multiple etiopathogenic factors are involved. Viral infections, neuroendocrine and biochemical disorders and immune system disorders are found among these factors[1]. The relationships between schizophrenia and immunological factors are supported by the existence of psychotomimetic effects that cytokines produce in non-psychiatric patients[2] and the immunological alterations found in schizophrenic patients[3]. Acute Phase Proteins (APP) are proteins whose plasma level increases in response to inflammation[4]. Since the middle of the last century, alterations in the APP levels have been found in schizophrenia[5], although the mixture of psychopathology and clinical diagnoses does not make it possible to reach a definitive conclusion[6-8]. This present work aim is to study the relationships between psychopathology and APPs in acute paranoid schizophrenic psychosis.

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METHODS

The study sample is formed by patients admitted to the psychiatry ward of the University Hospital of Canary Islands. All the patients had to fulfill the DSM-IV criteria for paranoid type schizophrenic psychosis. The day after their admission, psychopathology was evaluated using the Spanish version of the Positive and Negative Syndrome Scale (PANSS)[9]. Blood was drawn at approximately 8 a.m., after a night of fasting. A urine sample was obtained at the same time. All patients who had a background of alcoholism, drug abuse, who were taking medicines that altered APP levels[10] or who had abnormal results in their laboratory tests were excluded from the study. The routine laboratory analysis included complete blood count and ESR, urea, creatinine, glucose, total cholesterol, uric acid, total bilirubin, total protein, GOT, GPT, GGT, urine sediment and abnormal elements. The APPs measured were ceruloplasmin and fractions 3 and 4 of the complement (C3 and C4). These proteins were quantified with nephelometry techniques. The SPSS program was used for the statistical analysis. The relationship between variables was studied with Pearson's correlation coefficient, accepting a likelihood under 0.05 as significant ($p < 0.05$).

Table 1 Sociodemographic and clinical characteristics of the sample

Age* (years)	25.27 ± 3.43 (20, 32)
Gender (man/woman)	13/2
Civil status (single/married)	15/0
Disease initial age* (years)	18.53 ± 3.0 (14, 23)
Disease duration* (years)	6.73 ± 4.23 (2, 16)
C3* (mg/dl)	115.53 ± 22.98 (79, 163)
C4* (mg/dl)	29.93 ± 10.12 (15, 52)
Ceruloplasmin* (mg/dl)	33.33 ± 8.05 (24, 52)

*The quantitative data are represented as mean ± standard deviation (minimun and maximum).

Table 2 Correlation matrix between acute phase proteins and PANSS

	C3	C4	Ceruloplasmin
C3	1		
C4	0.743 (0.002)	1	
Ceruloplasmin	0.379 (0.164)	0.579 (0.024)	1
Negative scale	0.577 (0.024)	0.508 (0.053)	0.616 (0.015)
General psychopathology	0.365 (0.181)	0.170 (0.545)	0.562 (0.029)
N1. Blunted affect	0.375 (0.169)	0.335 (0.223)	0.651 (0.009)
N3. Poor rapport	0.517 (0.049)	0.416 (0.123)	0.555 (0.032)
N4. Social withdrawal, passive apathy	0.746 (0.001)	0.629 (0.012)	0.387 (0.154)
N6. Lack of spontaneity and flow of conversation	0.437 (0.104)	0.416 (0.123)	0.753 (0.001)
N7. Stereotyped thinking	0.540 (0.038)	0.462 (0.083)	0.432 (0.108)
G11. Deficient attention	0.358 (0.190)	0.526 (0.044)	0.651 (0.009)
G16. Active social avoidance	0.590 (0.020)	0.365 (0.181)	0.092 (0.745)

The data are presented as correlation coefficient and p value in brackets. Only the significant correlations of PANSS (positive and negative syndrome scale) are presented.

RESULTS

The initial sample was made up of 18 patients, 3 of whom were excluded from the study, two because of urine infection and one because of elevated transaminases. The final sample was made up of 15 subjects. Table 1 shows the clinical and sociodemographic characteristics of the sample. Table 2 shows the correlation matrix between the different APPs and PANSS. No item of the positive scale significantly correlated with the APP levels (results not shown). Only two items Deficient Attention (PG11) and Active Social Avoidance (PG16), of the general psychopathology scale positively and significantly correlated with the APPs. Of the negative scale, five of the seven items show a positive and significant correlations with the APP. These items were: Blunted Affect, (N1), Poor Rapport (N3), Social Withdrawal, Passive Apathy (N4), Lack of Spontaneity and Flow of Conversation (N6) and Stereotyped Thinking (N7).

DISCUSSION

Inflammation is one of the pathophysiology elements involved in the etiopathogeny of schizophrenia. In this work, we have found that APPs, one of the main biological markers of inflammation, positively correlate with the PANSS negative scale while none of the positive scale items showed this relationship. There is still no total agreement on all the symptoms that should be included in the negative psychopathology, with at least 2 to 10 dimensional psychopathological structures of psychotic systems having been described[11-13]. Some authors have found that when the factorial structure of PANSS is analyzed, the Active Social Avoidance, an item on the general psychopathology scale, saturated in the negative scale[14]. The Deficient Attention item has also been considered as a negative symptom of the deficit syndrome[15]. Thus, we could consider that the two items of the general psychopathology scale that correlated positively with the APP may form a part of the negative psychopathology spectrum. The fact that the three APPs we evaluated in our study showed a significant correlation with the PANSS negative scale provides consistency to our results. The variance levels explained by these correlations are 38% for ceruloplasmin, 33% for C3 and 25% for C4. Most

of the investigations that studied the relationship between ceruloplasmin and schizophrenia have found elevated levels of ceruloplasmin in schizophrenic patients[6-8,16,17] although decreased levels (Bock et al., 1971; Domino et., al 1975)[18,19] or normal levels (Seal & Eist, 1966)[20] have also been found. The most likely cause that explains these differences is due to the different methods used and the different groups of patients[16,18,19] or different clinical pictures[6,8,20].

The literature that exists on the study of the relationships between schizophrenia and complement factors is limited. No differences have been found in C3 and C4 blood levels between schizophrenic and control patients. It has also been seen that schizophrenics have reduced total hemolytic activity of the complement[21,22]. On the other hand, it has also been found that untreated schizophrenic patients have higher C3a and C4 levels than schizophrenic patients under treatment, although the intensity of the psychopathology, measured with the Brief Psychiatric Rating Scale (BPRS), was the same in both patient groups[23]. Furthermore, no correlation was found between the APP levels and the BPRS scores. This difference of results may be explained by the different techniques used to quantify the different APPs. While some works[21,22] used radioimmunoanalysis techniques, other investigations[23] used nephelometry techniques.

Based on the immunology-inflammatory hypothesis of schizophrenia, some authors have treated schizophrenic patients with a combination of antipsychotics and antiinflammatories, obtaining a positive effect on psychopathology[24]. The APPs are the result of an acute phase reaction and some APPs have antioxidant properties[25]. Some *in vitro* studies have demonstrated that ceruloplasmin is a potent antioxidant, even more potent than albumin and superoxide dismutase[26]. Puzynski[17] demonstrated that ceruloplasmin blood levels positively correlated with the length of the disease. He considered that this was due to the disintoxicating role of ceruplasmin versus oxidative products of protein metabolism. Furthermore, he also found a reduced level of total antioxidant capacity and increase of lipid peroxidation in schizophrenic patients[27,28]. Other authors[29] have suggested that oxidative damage may be related with negative symptoms of schizophrenia. This agrees with the data found by other authors[30] who have seen that schizophrenic patients, with predominantly negative symptoms, have hyperproduction of free radicals. Given that ceruloplasmin has direct antioxidant effects, the possible correlation with negative symptoms found in our population of schizophrenic patients may be due to a compensatory mechanism that counteracts in oxidative stress in this type of patients.

The main inconvenience of our work is sample size. Thus these results must be interpreted with caution, since although the statistical likelihood of committing a type I error is low, it cannot be completely excluded. The existence of high correlations between the different APPs and most of the negative items of PANSS give internal consistency to our results.

From our point of view, this is the first time specific items of the schizophrenic psychopathology measured with the PANSS correlate with the APP. The positive correlation, mostly with the negative psychopathology and two items of the general psychopathology scale that could be within the spectrum of the negative/deficit symptoms, is important since a lesional anatomic base has been proposed for this type of psychopathology[10]. It is also interesting to indicate that the antiinflammatory and antioxidant hypotheses converge in our study. At present, we are conducting a follow-up study in which the APPs and oxidative status markers are being simultaneously measured.

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