Inflammatory Response in Schizophrenia

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Abstract

Schizophrenia is a devastating disorder that affects approximately 1% of the world population. It is clearly that schizophrenia is a multifactorial disorder. Numerous theories have been proposed regarding the cause of schizophrenia ranging from developmental or neurodegenerative processes or neurotransmitter abnormalities to infectious or autoimmune process. However recent investigations suggest a strong relationship between immunological effects and the pathophysiology of schizophrenia. This study was carried out to evaluate the inflammatory response in schizophrenic patients by estimating some acute phase proteins. The study included 30 patients in acute episode and 34 controls. The results denoted that most of acute phase proteins were significantly higher in patients group than controls group. It is concluded that inflammatory response is manifested in schizophrenia.

Introduction

Acute-phase response is the systemic changes that may accompany inflammation occurring distant from the site or sites of inflammation and involving many organ systems. It has been referred to as the acute-phase response (APR) even though they accompany both acute and chronic inflammatory disorders ***(Kushner, 1993)***.

Acute-phase response changes may be divided into changes in the concentrations of many plasma proteins, known as the acute-phase proteins (reactant), and occurrence of other acute phase phenomena such as behavioural, physiologic, biochemical, and nutritional changes

Acute-phase proteins are plasma proteins whose concentration increases (positive acute-phase proteins) or decreases (negative acute-phase proteins) during inflammatory response (Table 1) ***(Morley & Kushner, 1982)***.

Substantial changes in the plasma concentrations of acute-phase proteins accompany infection, trauma, surgery, burns, tissue infarction, various immunologicaly mediated inflammatory conditions, and advanced cancer. Moderate changes occur after strenuous exercise, heatstroke, and childbirth. Small changes occur after psychological stress and in several psychiatric illnesses ***(Maes et al., 1997)***.

Table 1: Acute phase reactants

Group	*Individual proteins*
positive APRs	
Major APRs	Serum amyloid A, C-reactive protein, serum amyloid P component
Complement proteins	C2, C3, C4, C5, C9, B, C1 inhibitor, C4 binding protein
Coagulation proteins	Fibrinogen, von Willebrand factor
Proteinase inhibitors	α1-antitrypsin, α1-antichemotrypsin, α2-antiplasmin, heparin cofactor II, plasminogen activator inhibitor 1
Metal binding proteins	Haptoglobin, haemopexin, ceruloplasmin, manganese superoxide dismutase
Other proteins	α1-acid glycoprotein, haeme oxygenase, mannose binding protein, leucocyte protein I, lipoprotein (a), lipopolysaccharide-binding protein
Negative APRs	Albumin, pre-albumin, transferrin, apo AI, apo AII, HS glycoprotein, inter- α-trypsin inhibitor, histidine-rich-glycoprotein

Acute-phase proteins (APP) are produced by hepatocytes when exposed to certain cytokines or hormones. Cytokines are intercellular signalling polypeptides produced by activated cells mainly macrophages and monocytes at inflammatory sites. Most cytokines have multiple sources, multiple targets, and multiple functions. The cytokines that are produced during and participate in inflammatory processes are the chief stimulators of the production of acute-phase proteins. These inflammation-associated cytokines include interleukin-6, interleukin-1b, tumour necrosis factor A, interferon, transforming growth factor b and possibly interleukin-8 ***(Wigmore et al., 1997).***

Combinations of cytokines have been found to have additive, inhibitory, or synergistic effects ***(Mackiewicz et al., 1991)***. Thus, the induction of C-reactive protein and serum amyloid A in some models requires both interleukin-6 and either interleukin-1 or tumour necrosis factor A, and the induction of fibrinogen by interleukin-6 is inhibited by interleukin-1, tumour necrosis factor a, and transforming growth factor b. Interleukin-6 enhances the effect of interleukin-1b in inducing the expression of interleukin-1–receptor antagonist, ***(Gabay, et al., 1997)*** and interleukin-4 inhibits the induction of some acute-phase proteins by other cytokines ***(Loyer, et al., 1993)*** other soluble receptors, such as those for tumour necrosis factor a and interleukin-1, are inhibitory.

Glucocorticoids generally enhance the stimulatory effects of cytokines on the production of acute-phase proteins, ***(Baumann, et al., 1987)*** whereas insulin decreases their effects on the production of some acute-phase proteins ***(Campos, et al., 1994)***.

The expression of genes for acute-phase proteins is regulated mainly at the transcriptional level, but post-transcriptional mechanisms also participate ***(Jiang, et al., 1995)***. APRs have a wide range of activities that contribute to host defence: they can directly neutralize inflammatory agents, help to minimize the extent of local tissue damage, as well as participate in tissue repair and regeneration. There is a rapid increase in the plasma concentration of many complement cascade components, the activation of which ultimately results in the local accumulation of neutrophils, macrophages and plasma proteins. These participate in the killing of infectious agents, the clearance of foreign and host cellular debris, and the repair of damaged tissue. Coagulation components, such as fibrinogen, play an essential role in promoting wound healing. Proteinase inhibitors neutralize the lysosomal proteases released following the infiltration of activated neutrophils and macrophages, thus controlling the activity of the proinflammatory enzyme cascades. The increased plasma levels of some metal-binding proteins help prevent iron loss during infection and injury, also minimizing the level of haem iron avaible for uptake by bacteria and acting as scavenger for potentially damaging oxygen free radicals.

The major APRs include serum amyloid A (SAA) and either C-reactive protein (CRP) or serum amyloid P component SAP. Ironically the activities of these three are among the least well-known. Nevertheless, their interactions with other well-defined defence systems and the magnitude and rapidity of their induction following an acute phase stimulus, together with their short half-lives, suggest a particularly critical requirement for these proteins very early in the establishment of host defence.

Significantly, individuals unable to synthesize these proteins have not been described; these major APRs are therefore likely to be of considerable clinical importance.

Fever is representative of the neuroendocrine changes that characterize the acute-phase response. Although several cytokines may induce fever, interleukin-6 produced in the brain stem is required for the final steps leading to fever ***(Dinarello, 1997)***.

Other neuroendocrine changes reflect complex interactions among cytokines, the hypothalamic–pituitary–adrenal axis, and other components of the neuroendocrine system ***(Chrousos, 1995)***. For example, inflammation-associated cytokines stimulate the production of corticotropin-releasing hormone, with consequent stimulation of corticotropin and cortisol production, and also directly stimulate the adrenal gland. Stimulation of the production of arginine vasopressin by interleukin-6 can explain the hyponatremia that occurs during some inflammatory disorders. The behavioral changes that often accompany inflammation, including anorexia, somnolence, and lethargy, are similarly induced by cytokines. Neural mechanisms have also been implicated in anorexia ***(Sarraf, et al., 1997)***. Inflammation-associated cytokines have been implicated in the pathogenesis of anemia in chronic disease; thrombocytosis, cachexia, and impaired growth in children with chronic inflammatory conditions ***(De Benedetti, et al., 1997)***.

Recently an acute phase response has been reported in schizophrenia which is clearly a multifactorial disorder that must be considered from several perspectives. From the disease perspective, two central questions concern the pathogenesis and the pathophysiology of the illness ***(McHugh and Slavney, 1998)***. In terms of pathogenesis, what are the specific genetic and environmental factors that contribute to illness risk, and how do they act in combination to produce the biochemical and structural brain abnormalities that are characteristic of illness?. In terms of pathophysiology, how do these abnormalities alter brain function in order to give rise to the clinical syndrome that we recognize as schizophrenia?. Viewed from this perspective, unravelling the pathogenesis of schizophrenia is critical for the discovery of means of prevention and deciphering the pathophysiology of schizophrenia is essential for the identification of novel targets for therapeutic intervention ***(Muller et al., 2000)***.

Currently the problem of the aetiology of schizophrenia remains unsolved. The search? for the cause of this illness or group of illnesses has covered many areas of enquiry and we do not know how close we are to a fruitful approach.

The involvement of immunological and immunopathological mechanisms in the etiopathogenesis of schizophrenia has been a matter of research with recently increasing efforts ***(Lewis & Levitt 2002)***. Some data suggest an autoimmune component in schizophrenia and they are consistent with brain abnormalities of oligodendrocytes and myelinated fibres reported in the disease ***(Karry, et al., 2004)***.

So our aim in this study was to measure some acute phase proteins in cases of untreated schizophrenic patients to examine if acute phase response is present or not in a trial to unravel part of the secrets of etiopathogenesis of schizophrenia.

Subjects & Methods

The study was conducted at the institute of Psychiatry, Ain Shams University within the period of one year; the study included 30 patients & 34 healthy controls. The group of patients was further subdivided into 2 groups: group A including 18 patients with 1st episode of acute schizophrenia and group B including 12 patients in relapse after stopping treatment for at least 3 months.

- (1st episode: 2 weeks up to 6 month of presentation)
- (Relapse: 3 days up to 6 month of presentation)

Subjects:

A- Patient Group

Inclusion Criteria:

1. Out patients at the institute of Psychiatry
2. Never been treated in relapse and not receiving any treatments to the past 6 weeks.
3. Age between 22 and 50
4. Sex: both males and females
5. Fulfilling the criteria for diagnosis of Schizophrenia according to the ICD-10 diagnostic criteria for research.

Exclusion Criteria:

1. Presence having other psychiatric illness
2. Organic mental disorders
3. patients with substance abuse
4. Patients having symptoms and signs inflammation, infection or autoimmune disease.
5. Pregnant females or during menstruation or females on contraceptive pills.
6. Patients on steroid therapy or receiving contraceptive pills.
7. Patients with liver diseases, pancreatitis, Nephrotic Syndrome, or biliary obstruction.

B- Control group:

1. Normal individuals matched to age, sex, and other demographic variables of the patient group.
2. Physical illness was excluded by complete check-up lab investigations including complete blood count (CBC), liver function tests and kidney function tests.
3. Psychiatric morbidity was assessed by General Health Questioner ***(Goldberg & Williams 1998)***

Informed consent was taken from both controls and patients.

Methods:

A- Patient Group

The patients were diagnosed according to ICD-10 diagnostic criteria for research using the schedule to clinical assessment in neuropsychiatry (SCAN), ***(Abou Raya, 1998)***. Patients were not on medications or ECT for at least 6 weeks.

B- Control group:

The control group was subjected to the General Health Questioner ***(Goldeberg, 1998).*** The scale of 28 items was used in the Arabic version ***(Okasha et al., 1998)*** to exclude any mental disorders.

Sample Collection:

For each patient of control, 10 ml of blood were collected using routine venipuncture recautions, blood was divided into 3 parts:

1. Six ml collected blood o assay: ALT, AST, total proteins, urea creatinine, albumin, bilirubin and acute phase proteins:C3, C4, α1AT, α1glyc., HP and C-reactive protein.
2. Two ml. on EDTA for CBC

3. Two ml. anticoagulated with citrate 1:9 to estimate fibrinogen level in plasma.

All samples were transported to the lab within half an hour to be separated and stored at -20 C to be assayed within two weeks except for the CBC, ALT, AST, total proteins, albumin, bilirubin, urea and creatinine were estimated immediately. α1AT, HP, α1glyc., 3 and C4 were estimated by Radial Immune Diffusion technique (RID) using Bioscientifica S.A. plates. The diameter of the precipitation ring is measured by a magnifying glass lens and the results were evaluated by using tables of standard curves ***(Berne, 1974)***.

- CRP was detected by latex (Avitex) from omega diagnostics where latex suspension coated with serum; clear agglutination is seen in positive cases within 2 minutes. Serial dilutions were performed to estimate the titre.
- Fibrinogen was assayed by Hemosta fibrinogen (Human) using fibrin timer where thrombin is added to a pre-diluted plasma sample, the measured clotting time is inversely proportional to the fibrinogen concentration in specimen (Claus 1957) the clotting time is blotted on a calibration curve to estimated fibrinogen concentration.

Results

In our study, there was no significant difference between patient and control groups as regards the age and gender. The mean age for patients was 34.46 years while that of the controls was 33.64 years. Out of total 30 schizophrenic patients there was 8 females and 32 males, while in the control group out of 34 normal subjects there was 8 female and 26 males (Table 1).

The group of patients was further subdivided into 2 groups: group A including 18 patients with 1st episode of acute schizophrenia and group B including 12 patients in relapse after stopping treatment for at least 3 months (Table 5) (Figure 1):

Comparison of acute phase proteins between patients and controls (Table 2) (Figure 2):

Compliment 3 (C_3)

Comparing the mean value of C_3 in the patient group, it was 158.94 ± 94.9 mg/dl while it was 124.86 ± 50.6 mg/dl in the control group with a significant difference between the 2 groups ($p < 0.05$).

Compliment 4 (C_4)

As regards serum concentration of C_4, the mean value of the patient group was 39.53±21.2mg/dl and 28.92 ± 12.6 mg/dl in the control group with a significant difference between the 2 groups ($p < 0.05$).

Alpha1 Antitrypsin (α1AT)

The mean value of α1AT of the patient group was 104.5 ± 52.5 mg/dl while it was 120.81± 64.6 mg/dl in the control group with no significant difference between the 2 groups ($p >0.05$).

Haptoglobin (HP)

Regarding serum concentration of Haptoglobin there was a significant difference between the patient group and control group as the mean value of patient group was 158.95 ±124.8 mg/dl while that of the control group was 94.59 ± 60.1 mg/dl ($p <0.05$).

Alpha1 acidglycoprotein (α1glyc)

There was a highly significant difference in the mean value of α1glyc. of the patient group 196.40 ±117.4 mg/dl and control group 123.74 ± 59.5 mg/dl ($p <0.01$).

Fibrinogen (Fib)

Comparing fibrinogen level of the 2 groups, mean value of fibrinogen of the patient group was 280.80 ± 93.1 mg/dl while it was 242.18 ± 48.3 mg/dl of the control group with a significant difference ($p < 0.05$).

C- reactive protein (CRP)

Qualitative estimation of CRP showed that serum of all patients and control were negative for CRP with no difference between the 2 groups (Table 3).

When comparing the group of 1st episode and that of relapse, there was no significant difference in the acute phase proteins levels of the 2 subgroups (Table 4).

Table 2: Cases & Controls Distribution By Gender

Subjects	CASES		CONTROLS	
	No	%	No	%
Female	8	26.7	8	23.5
Male	22	73.3	26	76.5
Total	30	100	34	100

Table 3: Comparison of CRP in Patients & Controls

CASES		CONTROLS	
No	CRP	No	CRP
30	Negative	34	negative

Table 5: Frequency of 1st Episode Cases & Controls

	Schizophrenic Patients	
Patients	No	%
1st Episode	18	60
Relapse	12	40
Total	30	100

Table 2: Comparison of the Mean Level of Acute Phase Proteins between Schizophrenic Patients & Controls

APP	CASES			CONTROLS			t	P
	No	Range	Mean ±SD	No	Range	Mean ±SD		
C3	30	52.9-348.6	158.9±94.9	34	36.0-214.1	124.9±50.6	2.0	<0.05 S
C4	30	15.1-72.4	39.5±21.2	34	4.6-53.8	28.9±12.6	2.4	<0.05 S
HP	30	28.7-451.9	158.3±124.8	34	7.5-228.7	94.6±60.1	2.6	<0.05 S
α_1AT	30	52.0-222.9	104.5±52.4	34	15.0-252.9	120.8±64.6	1.0	>0.05 NS
α_1GLYC	30	37.4-500.0	196.4±117.4	34	39.4-243.5	123.7±59.5	3.1	<0.01 HS
FIBR	30	130.0-500.0	280.8±93.0	34	147.0-355.0	242.0±48.3	2.1	<0.05 S

Table 4: Acute Phase Proteins in Cases of 1st Episode versus Relapse

APP	1st Episode (n: 18) Mean ± SD	Relapse (n: 12) Mean ± SD	T	P
C3	177.5±97	131±88	1.3	>0.05 **NS**
C4	45.18±20	31±20.8	1.8	>0.05 **NS**
HP	168.6±140	142.8±90	0.5	>0.05 **NS**
α_1AT	106.9±65.5	99.2±23.8	0.5	>0.05 **NS**
α_1GLYC	223.2±114.6	114.3±114.3	1.5	>0.05 **NS**
FIBR	274±68.9	291±123.7	0.4	>0.05 **NS**

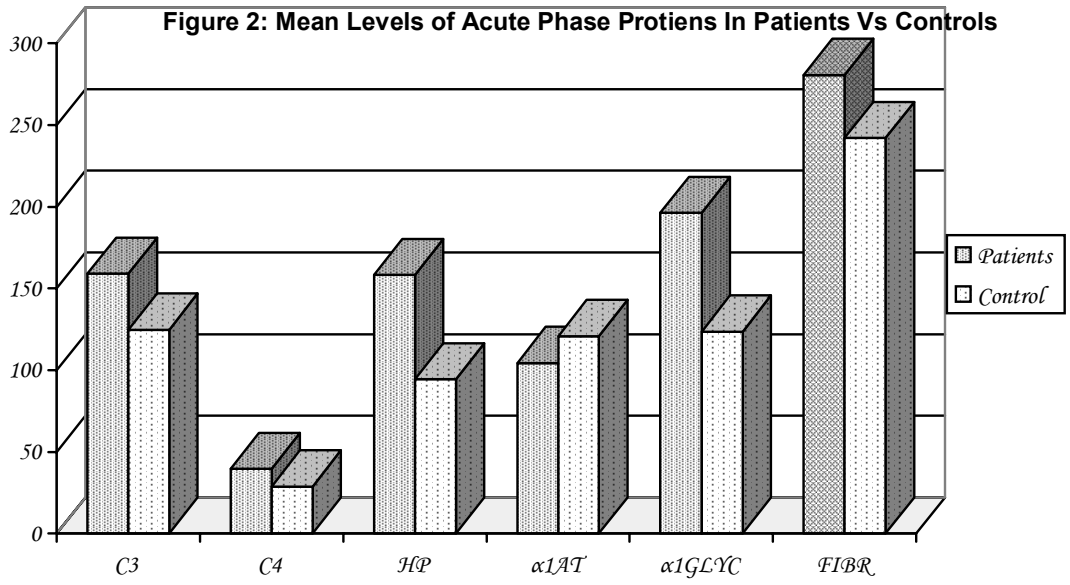
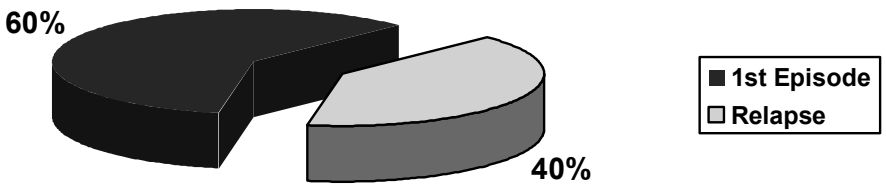


Figure 1: Distribution of Cases of 1st Episode & Relapse



Discussion

Immunological alterations have been described in the international literature since the beginning of this century. However, for several reasons the focus of interest turned away from the immune system. One reason was the introduction of neuroleptics into the therapy of schizophrenia leading to the dopamine hypothesis as the centre of research activities. Another reason was that the components and functions of the immune system have not been understood very well during those times. Schizophrenia is a heterogeneous disorder as regards the clinical symptomatology, the acuity of the symptoms, the course, the treatment response and probably also the etiology. A widespread heterogeneity can also be observed in the results of immunological studies in schizophrenia. However recent investigations suggest a strong relationship between immunological effects and the pathophysiology of schizophrenia ***(Müller et al., 2001)***.

The present study was undertaken to evaluate the acute phase response in schizophrenic patients as compared to normal controls by estimating some acute phase proteins in both groups. The acute phase proteins that have been studied are C3, C4, HP, α1AT, α1glyc., fibrinogen and C-reactive protein.

Our results denote that most of APP (C3, C4, HP, α1glyc. and fibrinogen) were significantly higher in patient group than the control group. In contrast, α1 AT showed no significant difference between the two groups.

This was in agreement with the study of Maes et al. 1997 who examined AP response in 27 schizophrenic, 23 manic, 29 major depressed and 21 normal subjects by measuring haptoglobin (Hp), immunoglobulin G (IgG), IgM, fibrinogen (Fb), complement component 3 (C3C), C4, α_1-antitrypsin (α_1AT), α_1-acid-glycoprotein (α_1S) and hemopexin (Hpx),. Schizophrenic patients had significantly higher plasma Hp,

Fb, C3C, C4, α_1S and Hpx than normal controls. Manic subjects showed significantly higher plasma Hp, Fb, α_1S and Hpx than normal controls. Depressed subjects had significantly higher plasma Hp, Fb, C3C, C4 and α_1S than normal controls. Overall, the above disorders in AP reactants were more pronounced in schizophrenic than in depressed subjects. They suggest that not only major depression but also schizophrenia and mania are accompanied by an AP response, and that the latter may be suppressed by chronic treatment with antipsychotic drugs.

In contrast to the study of Mazzarello et al. 2004 who reported increased s CRP in schizophrenic patients; there was no difference in CRP between schizophrenic patients and controls in our study. However elevated s levels of CRP may be associated with more severe psychopathology in a subgroup of patients with schizophrenia ***(Fan et al., 2007)***.

The difference between the results of our study and other studies as regards CRP may be due to the use of qualitative method for estimation and limited number of cases. Wan et al. 2007 focused on detecting schizophrenia related changes of plasma proteins using proteomic technology and examining the relation between schizophrenia and haptoglobin genotype. They investigated plasma proteins from schizophrenic subjects and healthy controls by two-dimensional gel electrophoresis (2-DE) in combination with mass spectrometry. To further reveal the genetic relationship between acute phase proteins and schizophrenia disease, they tested Hp α1/Hp α2 polymorphism and two single nucleotide polymorphisms of Hp. They found that four proteins in the family of positive APPs were all up regulated in patients and significant associations existing between schizophrenia and Hp polymorphisms. Schizophrenia is accompanied by both an altered expression of Hp protein and a different genotype distribution of Hp gene, demonstrating that Hp is associated with schizophrenia. Results indicate that acute phase reaction is likely to be an aetiological agent in the pathophysiology of schizophrenia, but not just an accompanying symptom.

In a previous study on Egyptian non paranoid schizophrenic patients, there was no significant difference in C3,CRP,α1 AT and ESR between patients and the controls ***(Okasha et al., 2006)***. They agreed with our study as regards CRP and α1 AT. However, the difference in C3 results may be due to different subgroup of schizophrenic and limited numbers of patients of the previous studies.

Conclusion

We concluded that inflammatory response is a series of immunological changes that are manifested in schizophrenia. It is reflected by the increase in the serum level of some positive acute phase proteins: C3, C4, α1 acid glycoprotein, fibrinogen and Haptoglobin.

Recommendations:

- Study of acute phase proteins in response to treatment.
- Study of other immune parameters in schizophrenia.
- Study the relation of acute phase proteins with different types of schizophrenia and the severity of illness.

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الأستجابة الألتهابية فى مرضى الفصا!

تبلغ نسبة داء الفصام ١% من سكان العالم وهو مرض متعدد العوامل ووجد من خلال الدراسات الحديثة علاقة قوية بين حدوث مرض الفصام والتأثيرات المناعية. من هنا أجريت هذه الدراسة لبحث الاستجابة الالتهابية فى مرضى الفصام من خلال دراسة بروتينات المرحلة الحادة وتضمنت الدراسة ĐČ مريض بالفصام الحاد و ٣Đ شخص طبيعىŎ. أوضحت نتائج الدراسة أن معظم بروتينات المرحلة الحادة التى تم قياسها كانت تركيزاتها بالدم فى مرضى الفصام عنها فى الأشخاص الطبيعيين ونستنج من ذلك وجود استجابة التهابية فى داء الفصام.