Antibodies to Heat Shock Protein 70kDa and 90kDa in the Patients with Schizophrenia, and Their Relationship with Clinical Variables

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ABSTRACT

Schizophrenia has many clinical expressions and probably different etiologic factors. Infections, autoimmune mechanism and related neurodevelopmental abnormalities have been suggested as possible etiologic factors of schizophrenia. It has been reported that immunoreactivity to heat shock proteins, which play a protective role against environmental stresses in a cell, might be related to the pathogenesis of schizophrenia. Therefore, we examined the immunoreactivity to heat shock protein 70kDa and 90kDa(HSP70 and 90) in 91 patients with schizophrenia and 83 normal controls.

Ig G antibodies to HSP70 and 90 of sera were quantitated by ELISA. The optical density(OD) was measured by an automated microplate reader at a wavelength of 490nm. The amounts of antibodies to HSPs were expressed as arbitrary units(AU)/ml related to a standard serum. The limit for elevated antibody titers(anti-HSPs positive or negative) was set at two standard deviations added to the mean of the normal controls.

Twenty nine(31.9%) of the 91 patients showed anti-HSP70 positive and 19(20.9%) of those showed anti-HSP90 positive. On the other hand, only 1(1.4%) of the normal controls and 4(4.8%) of those showed anti-HSP70 positive and anti-HSP90 positive, respectively. The titers of anti-HSP70 positive were related with BPRS scores, while those of anti-HSP90 positive were not. There were no relationship between antibody titers and clinical variables including age at onset, duration of illness, family history of schizophrenia or number of admission. The titers of anti-HSP70 positive were significantly associated with anti-HSP90 positive.

Our results suggest the presence of abnormal immune reactivity involving HSP70 and HSP90 in a subset of patients with schizophrenia.

KEY WORDS : Schizophrenia · Heat shock protein · Antibody · Autoimmune mechanism.

Introduction

It has been known that schizophrenia has varied clinical manifestations and probably different etiologic factors including genetic, environmental, biochemical, immunologic and endocrine factors(Wyatt *et al*. 1995). Schizophrenia also resembles some clinical features of autoimmune diseases. Its symptoms appear usually during adolescent period, tend to be worsening in association with a variety of stresses, and have clinical course of remissions and relapses(Knight 1982). Therefore, autoimmune mechanism has been suggested as one of possible pathogenetic factors of schizophrenia(Sirota 1990). Numerous studies have been examined to probe target antigen and immunological abnormalities in the patients with schizophrenia. Among them, there were antibodies to brain tissues(Baron *et al*. 1977 ; Pandey *et al*. 1981), altered interleukin-2 production(Ganguli *et al*. 1992), increased interleukin-1 and interleukin-3 like activity(Sirota *et al*. 1995), and delayed-type hypersensitivity to myelin basic protein and normal human brain tissue(Sirota 1990). Also, some investigations examined antibodies to heat shock proteins(HSPs), mainly HSP 60, in the patients with

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schizophrenia(Killidreas *et al*. 1992 ; Mazeh *et al*. 1998 ; Schwarz *et al*. 1998 ; Schwarz *et al*. 1999).

HSPs play a protective role against environmental stresses, such as infection, high temperature, chemical or mechanical insults in a mammalian cell(Linquist 1986 ; Kauffmann 1990 ; Nagao *et al*. 1990 ; Walsh *et al*. 1991 ; Welch 1992). The HSPs function in the repair, maintenance, and removal of cellular proteins during stresses(Nagao *et al*. 1990 ; Welch 1992). Expression of HSPs, especially HSP70, in the central nervous system(CNS) has been observed following stresses such as hyperthermia, hypoxia, traumatic injury, status epilepticus, and other pathological conditions(Satoh *et al*. 1994). Also, as HSPs are expressed constitutively in normal cells and demonstrate increased expression at specific stages of development of cells, they have critical roles in normal mammalian cells during normal growth and differentiation(Linquist 1986 ; Nagao *et al*. 1990 ; Walsh *et al*. 1991 ; Wolgemuth & Gruppi 1991). And they could be targets for immunological insults leading to autoimmune phenomena(Young 1990).

Infections during pregnancy, autoimmune mechanism and related neurodevelopmental abnormalities have been suggested as possible etiologic factors of schizophrenia(Ganguli *et al*. 1987 ; Lyon *et al*. 1989 ; Kirch 1993 ; Wright P & Murray RM 1993 ; O'Reilly 1994). Maternal stresses such as influenza malnutrition, perinatal complications have been reported to be related with abnormalities of central nervous system and schizophrenia(Lewis & Murray 1987 ; Mednick *et al*. 1988). Therefore, schizophrenia may be due to the defective production of HSPs to environmental stresses to embryo(Bates *et al*. 1996). Regarding autoimmune hypothesis of schizophrenia, antibodies to HSPs could be a factor associated with the pathogenesis of schizophrenia.

As HSP70 and HSP90 are observed at stage-dependent manners during normal development(Wolgemuth & Gruppi 1991), it is hypothesized that antibodies to HSP70 and 90 might be related with the neurodevelopmental abnormalities and pathogenesis of schizophrenia. To date, there was only one report which demonstrates antibodies to HSP70 in the patients with schizophrenia(Schwarz *et al*. 1999). In the patients with schizophrenia, antibodies to HSP90 were not examined yet.

With theses aspects in mind, the levels of antibodies to HSP70 and HSP90 in the patients with schizophrenia and normal controls were measured in this study. Their relationship with severity of schizophrenic symptoms and other clinical variables including age at onset, duration of illness, family history of schizophrenia and number of admission were also examined.

Methods

1. Subjects

We investigated 91 patients with schizophrenia who were admitted to the department of psychiatry, Kangnam St. Mary's Hospital, College of Medicine, the Catholic University of Korea, from March, 1997 to May, 1999. They were under the acute state of illness. Forty four were males and 49 were females. Mean age was 30.3±8.6 years(16 - 64 years). All patients fulfilled the DSM-Ⅳ criteria for schizophrenia. They were diagnosed by two independent psychiatrists, who also evaluated psychopathology using the brief psychiatric rating scale(BPRS) scores before blood sampling and the interrater reliability was above 0.7. Normal control sera were obtained from 83 healthy volunteers who visited health screening center of Kangnam St. Mary's Hospital. Forty two were males and 41 were females. Mean age was 41.4±11.6 years(21 - 64 years). All of the subjects who had autoimmune diseases, neurologic diseases or substance abuse were excluded. They were not in acute infectious state and not taken any psychotropic drugs for at least 6 weeks prior to this study. Informed consent was obtained from the 91 patients of schizophrenia. Age at onset, duration of illness, family history of schizophrenia and number of admission were also examined as clinical variables.

2. Laboratory methods

The serum samples were obtained from peripheral blood of patients with schizophrenia and volunteers, and stored at -20℃ until used. IgG antibodies to HSP70 and HSP90 of sera were quantitated by enzyme-linked immunosorbent assay(ELISA). The laboratory personnel were blinded with regard to two groups.

Microtiter plates(Nunc, Naperville, Illinois, U.S.A.) were coated with a 1.0 μg/ml suspension of recombinant human HSP70 or HSP90(StressGen, Victoria, Canada) diluted in potassium phosphate buffer, pH 7.6 at 4℃ overnight, adding 100 μl/well. The plates were washed with 0.05% PBS-Tween 20 and then blocked the nonspecific binding sites with 100 μl of 100% normal goat serum(NGS, Jackson Immuno-Research Lab., West Grove, PN, U.S.A.) for 2 hours at room temperature. After additional washing, 100 μl of aliquots of sera, diluted 1 : 50 for

HSP70 or 1 : 100 for HSP90 in 100% NGS buffered with crystalline Tris(0.1 M) and NaCl(0.15 M), pH 8.0, are added to the microtiter plates in duplicates, and reacted with antigen for 2 hours at room temperature. The plates were washed again and then incubated with biotinylated antihuman IgG(Fabspecific, Jackson ImmunoResearch Lab.), diluted 1 : 20,000 for HSP70 or 1 : 5000 for HSP90 in 25% NGS in 0.1 M Tris-0.15 M NaCl buffer, pH 8.0, for 2 hours at room temperature. After further washing, avidin-conjugated peroxidase(Jackson ImmunoResearch Lab.), diluted 1 : 32,000 for HSP70 and for HSP90 in 0.1 M Tris-0.15 M NaCl buffer, pH 7.5, containing 0.5% ovalbumin and 0.05% Tween-20, was reacted with the plates at room temperature for 2 hours. After washing, color development was induced by the addition of o-phenylenediamine-H_2O_2 dissolved in phosphate citrate buffer, pH 5.0 to the plates and was stopped 30 min later by adding 2.5 N H_2SO_4. The optical density(OD) was measured by an automated microplate reader(SpectraMax 250 ELISA reader, Molecular Devices, Palo Alto, CA) at a wavelength of 490nm.

Means of duplicate wells were calculated and the optical densities of the uncoated wells were subtracted from the mean values. The amounts of antibodies to HSP70 and HSP90 were expressed as arbitrary units(AU)/ml related to a standard serum that showed relatively high antibody titers to HSP70 or HSP90 in a preliminary study. The standard curve was made by a serial dilution of a standard serum. The unknown values for each sample were compared with the corresponding linear standard curve and expressed as AU defining the 1 : 50(HSP70) or 1 : 100(HSP90) dilution of the standards as 100 AU. The function of the curve was carried out with softmaxPro 2.61 program and calculated by an semilog function. To compare the rate of immunoreactivity between schizophrenics and controls, the antibody titers were divided into anti-HSP positive or anti-HSP negative groups for each antibodies, according to cut-off values, which mean the limit of elevated titers between normal and high antibody titers defined by a two-fold standard deviation of the mean value of controls.

All samples were tested in two independent assays. The average intra- and interplate coefficients of variation were below 10%. The specificity of the assays was tested by inhibition experiments. Standard serum was diluted in NGS and incubated with 0, 1.25, 2.5, 5, 10 and 20 μg/ml of HSPs at 37℃ for 2hours and tested by ELISA.

3. Statistical analysis

Statistical analysis was calculated using SPSS for Windows V7.5(SPSS Inc.). Differences of antibody titer of HSP90 and HSP70 between the means of groups were calculated using the t test. The frequencies of elevated antibody titers between the patient group and the control group were analyzed by χ^2 test. The clinical variables of elevated antibody group and normal antibody group were assessed using Mann-Whitney U test. Correlations of antibody titers and clinical variables were calculated using the Pearson's correlation test. The changes of the distributions of elevated antibody titer after medication were analyzed by McNemar test. A p value of less than 0.05 was considered as statistically significant.

Results

Serum levels of antibodies to HSP70 and HSP90 were expressed as an arbitrary unit(AU) which were calculated by the comparison with the standard curves(Fig. 1 & 2). The levels of antibodies to HSP70 were significantly higher in the patients with schizophrenia than normal controls(Fig. 3). The mean values of the levels of the antibodies to HSP70 were 106.98±255.73 AU(5.079 AU-868.105 AU) in the patients with schizophrenia, and 18.02±26.13 AU(0.336 AU-218.360 AU) in normal controls. Also, the levels of antibodies to HSP90 were significantly higher in the patients with schizophrenia than normal controls(Fig. 4). The mean values of the levels of antibodies to HSP90 were 34.73±82.89 AU(2.002 AU-172.315 AU) in the patients with schizophrenia, and 13.92±13.01 AU

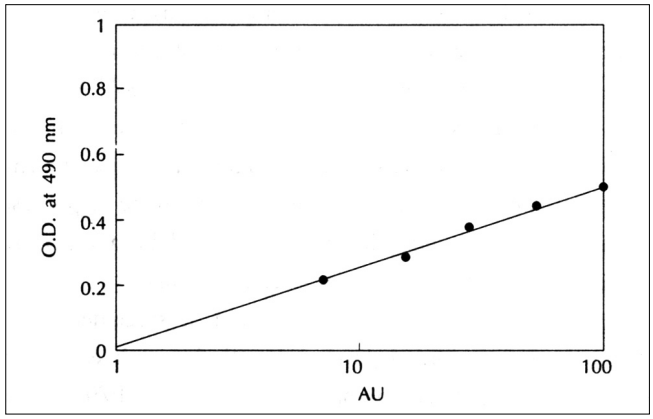

Fig. 1. Standard curve for heat shock protein 70. Antibody levels of the serially diluted standard serum were measured by ELISA as described in Materials and Methods, and O.D. of fifty-fold diluted sample was defined as 100 arbitrary unit(AU).

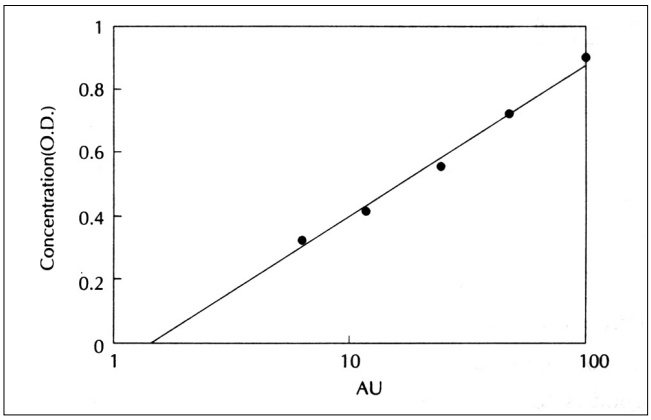

Fig. 2. Standard curve for heat shock protein 90. Antibody levels of the serially diluted standard serum were measured by ELISA as described in Materials and Methods, and O.D. of one hundred-fold diluted sample was defined as 100 arbitrary unit(AU).

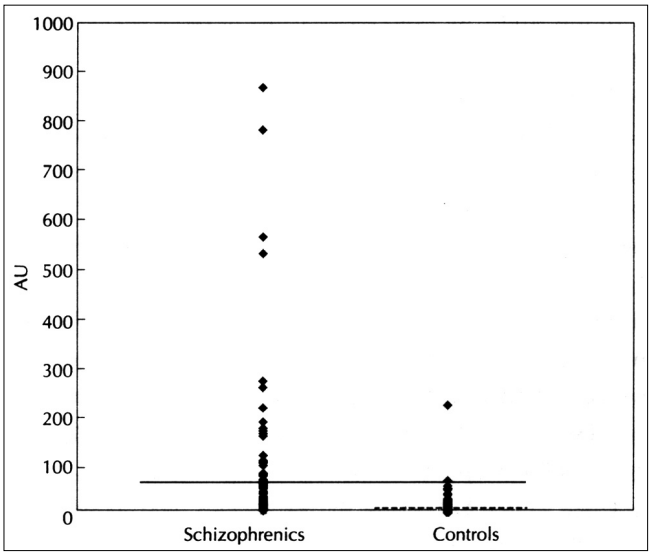

Fig. 3. Distribution of HSP70 antibody titers in the patients with schizophrenia and normal controls. Sera were collected from schizophrenics(n=91) and normal controls(n=83), and titers of antibody to HSP70 were measured and expressed as arbitrary units(AU) as described in Materials and Methods. The broken line indicates the mean of the controls(18.02 AU), and the solid line shows the cut-off value to high antibody titers (70.28 AU).

(2.734 AU -69.693 AU) in normal controls. There were no differences of antibody titers according to age and sex in both groups. Cut-off values were 70.28 AU for HSP70 and 39.94 AU for HSP90(Fig. 3 & 4).

The frequencies of anti-HSP70 antibodies were significantly different between the patients with schizophrenia and normal controls(χ^2=25.208, df=1, p=0.00). Twenty nine(31.9%) of the 91 patients showed anti-HSP70 positive. Otherwise, only 1(1.3%) of 83 normal controls showed anti-HSP70 positive (Table 1). Also, the frequencies of anti-HSP90 antibodies were

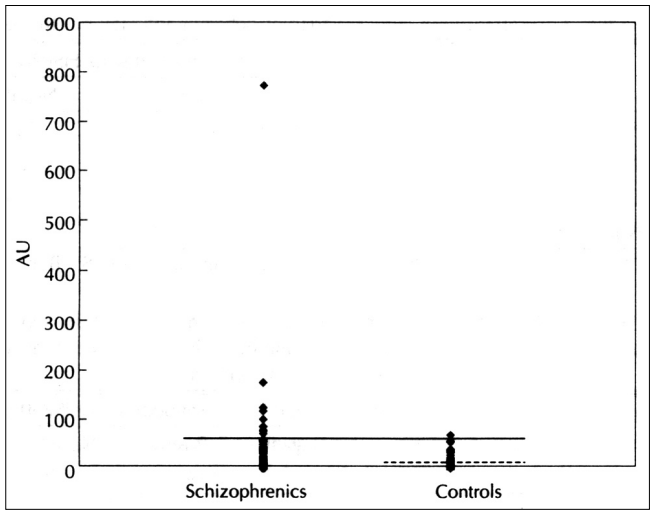

Fig. 4. Distribution of HSP90 antibody titers in the patients with schizophrenia and normal controls. Sera were collected from schizophrenics(n=91) and normal controls(n=83), and titers of antibody to HSP90 were measured and expressed as arbitrary units(AU) as described in Materials and Methods. The broken line indicates the mean of the controls(13.92 AU), and the solid line shows the cut-off value to high antibody titers(39.94 AU).

Table 1. Frequency of the immunoreactivity to heat shock protein 70(HSP70) and heat shock protein 90(HSP90) in the patients with schizophrenia and normal controls

	Antibodies to HSP70		Antibodies to HSP90	
	Positive n,(%)	Negative n,(%)	Positive n,(%)	Negative n,(%)
Patients(n=91)	29(31.9)*	62(68.1)	19(20.9)*	72(79.1)
Controls(n=83)	1(1.3)	82(98.7)	4(4.8)	79(95.2)

*p<0.05, compared with that of controls in each group

significantly different between the patients with schizophrenia and normal controls(χ^2=6.704, df=1, p=0.01). Nineteen (20.9%) of the 91 patients showed anti-HSP90 positive. However, only 4(4.8%) of 83 normal controls showed anti-HSP90 positive(Table 1). There were no differences in age and sex between the patients with schizophrenia who demonstrated anti-HSP70 positive or anti-HSP90 positive and those who did not.

Anti-HSP70 antibodies were related with BPRS scores in the patients with schizophrenia(p=0.034), while those against HSP90 were not. The BPRS scores were higher in the anti-HSP70 positive group. Between the patients who showed anti-HSP70 positive or anti-HSP90 positive and those who did not, the antibody titers to HSP70 or HSP90 were not different in accordance with clinical variables, such as age at onset, duration of illness, or number of admission(Table 2). Family history was obtained from 66 patients of schizophrenia, and there were no differences between the patients who showed anti-HSP70 posi-

Table 2. Comparison of clinical variables between anti-HSP positive group and anti-HSP negative group

	Antibodies to HSP70		Antibodies to HSP90	
	Positive (n=29)	Negative (n=62)	Positive (n=19)	Negative (n=72)
BPRS	37.79±7.45*	34.89±8.27	36.53±7.14	35.53±8.35
Age at onset(year)	27.3 ±7.3	25.8 ±6.6	27.1 ±7.1	26.0 ±6.8
Duration of illness(year)	4.31±6.16	3.83±3.88	3.30±4.11	4.51±6.48
Number of admission	2.39±1.77	3.84±1.86	1.40±0.84	2.17±3.43

*p<0.05, compared with that of the negative group BPRS : Brief Psychiatric Rating Scale Values are expressed as means±SD.

Table 3. Comparison of family history between the anti-heat shock protein(HSP) positive and anti-heat shock protein negative groups in the patients with schizophrenia

	Antibodies to HSP70		Antibodies to HSP90	
	Positive n,(%)	Negative n,(%)	Positive n,(%)	Negative n,(%)
Family History				
Positive(n=18)	8(12.1)	10(23.3)	2(3.0)	16(24.2)
Negative(n=48)	15(22.7)	33(50.0)	7(10.6)	41(62.1)

tive or anti-HSP90 positive and those who did not(Table 3).

The titers of anti-HSP70 were significantly associated with the titers of anti-HSP90(χ^2=6.186, p=0.013, df=1). Contingency Coefficient was 0.254. Seven(7.8%) of 91 patients had both anti-HSP70 positive and anti-HSP90 positive. Between the patients who showed both anti-HSP70 positive and anti-HSP90 positive and those who did not, the antibody titers were not different in accordance with clinical variables, such as age at onset, duration of illness, family history of schizophrenia, number of admission or BPRS scores.

Discussion

There are many reports that suggested neurodevelopmental etiology of schizophrenia ; environmental factors affecting fetal development induce the abnormalities of central nervous system of schizophrenia(Weinberger 1987). HSPs function in the prevention of developmental defects(Petersen 1990 ; Walsh *et al*. 1991). If a stress, such as an increase in maternal temperature or abnormal intrauterine environment, is inflicted upon a developing embryo during early neuronal development, this may result in minor physical anomalies or structural and functional abnormalities observed in schizophrenic individuals(German 1984 ; Englen & Finnell 1991 ; Bates *et al*. 1996). The HSPs play an important role in the protection of a cell, and the amount of HSPs, especially HSP70, is relatively high during the initial stages of development(Nagao *et al*. 1990). Therefore, autoantibodies to HSPs could be a good indicator to probe the etiology of the neurodevelopmental abnormality of schizophrenia. The antibodies to HSP70 and HSP90 were detected in other autoimmune diseases such as systemic lupus erythematosus(Tishler & Shoenfeld 1996 ; Minota *et al*. 1988 ; Conroy *et al*. 1994 ; Conroy *et al*. 1996). Also, antibodies to HSP70 were found in multiple sclerosis(Birnbaum 1996).

In this study, we observed that the levels of the antibodies to HSP70 and HSP90. Unlike previous studies, we examined the larger sample size and adopted highly sensitive ELISA with avidinbiotin system for detecting antibodies to HSPs. We found that the titers of the antibodies to HSP70 and HSP90 were significantly higher in the sera of the patients with schizophrenia than those of normal controls. Anti-HSP70 antibodies were related with BPRS scores in the patients with schizophrenia, while those against HSP90 were not. The titers of anti-HSP70 were significantly associated with the titers of anti-HSP90. It suggests that autoimmunity to HSP70 and HSP90 might be related with the pathogenesis of schizophrenia in a subset of patients.

There were 29(31.9%) of the 91 patients who showed anti-HSP70 positive in this study. Otherwise, only 1(1.3%) of 83 normal controls showed anti-HSP70 positive. This is in agreement with previous report(Schwarz *et al*. 1999), which demonstrate 23% of the patients but 3% of normal controls showed anti-HSP70 positive using ELISA.

To our knowledge, this is the first report which demonstrate antibody to HSP90 might be involved in the pathogenesis of schizophrenia. In the previous study, which examined antibodies to HSPs to neuroblastoma cell line proteins in patients with schizophrenia using western blot analysis, they observed that 30.71% of immunoglobulins of patients reacted with 80 - 85 kDa proteins while the sera of all the patients and normal controls reacted with 60 kDa proteins(Mazeh *et al*. 1998). They suggested that this 80 - 85 kDa proteins might be belonged to the HSP90 family. HSP90 is one of endogenous peptides bound to the human class I MHC molecule, HLA-B27(Jardetzky *et al*

1991), which was suggested as a marker for vulnerability to schizophrenia(Gattaz 1981). Further research focusing on this issue is needed. There have been no reports which detected antibodies to HSP90 in normal controls, but 4.8% of normal controls showed high antibody titers against HSP90 in this study. This might be related with more sensitive method used in this study.

In this study, the titers of anti-HSP70 positive were significantly associated with the titers of anti-HSP90 positive. Unlike other groups of heat shock protein, HSP70 and HSP90 interact with glucocorticoid receptors which play a role as a transcription factor when activated by appropriate steroid hormone (Smith & Toft 1993). Although the role of glucocorticoid receptor in schizophrenia has not been thoroughly examined, there was a report which suggest the association of the glucocorticoid receptor polymorphism and schizophrenia(Kennedy *et al*. 1988).

Our results showed that the titers of anti-HSP70 positive were related with BPRS scores. It suggest that antibodies to HSP70 might be related with the severity of symptoms. In Olney and Farber's study(1995), HSP70 is overexpressed in corticolimbic neurons after administration of an N-methyl-D-aspartic acid (NMDA) receptor antagonist, which is engaged in the production of symptoms of schizophrenia(Tsai *et al* 1995). This might support the finding that antibodies to HSP70 were related with psychopathology in this study. Otherwise, the titers of anti-HSP90 positive were not related with BPRS scores. HSP70 and HSP90 are observed at stage-dependent manners during normal development(Wolgemuth & Gruppi 1991). In this regard, the pathogenetic mechanisms of HSP70 and HSP90 on the neurodevelopmental abnormalities of schizophrenia might be different from each other.

As all the subjects were drug-free for 6 weeks before this study, these results were not the effect of a drug. The antibody titers to HSP70 were reported to be decreased after medication (Schwarz 1999). Therefore further research investigating the change of antibodies to HSP70 and HSP90 after medication is needed.

It might be possible that the immunoreactivity to HSPs could be an unspecific reaction for other biological manifestations of schizophrenia. Therefore, comparison of antibodies to HSPs with other psychiatric disorders and follow-up study on the patients who showed immunoreactivity to HSPs should be examined.

To confirm the exact role of HSPs in CNS and their association with neurodevelopmental abnormality in schizophrenia, detection of antibodies to HSPs in CSF of the patients with schizophrenia and in the children who have a high vulnerability to schizophrenia must be investigated.

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