Eur Arch Psychiatry Clin Neurosci (1998) 248 : 282–288

ORIGINAL PAPER

M. J. Schwarz · M. Riedel · R. Gruber · N. Müller
M. Ackenheil

Autoantibodies against 60-kDa heat shock protein in schizophrenia

Received: 13 November 1997 / Accepted: 15 September 1998

Abstract Immunological abnormalities in schizophrenic patients have been reported for many years. However, the question of whether these parameters are involved in the pathophysiology of the disorder or represent treatment effects is still not answered. We investigated a combination of humoral and soluble immune parameters in 30 unmedicated schizophrenic patients before and during antipsychotic treatment and in 31 healthy controls. The aim of our study was to unravel an underlying immune process, to elucidate the influence of neuroleptic treatment and to identify a subgroup of schizophrenics. Antibodies against human 60-kDa heat-shock protein (HSP60), serum levels of soluble ICAM-1 and IL-2R were determined and correlated with parameters of blood–brain barrier and of psychopathology. In 10% of the drug-free but in 20% of the medicated schizophrenics, especially in females, we observed immunoreactivity against HSP60, high levels of IgG in CSF and a blood–brain barrier impairment. The high HSP antibody titres correlated with high levels of sIL-2R and sICAM-1. Only one of the controls showed antibodies against HSP60. Our results suggest that the observed immunological alterations are more pronounced during neuroleptic treatment than in the drug-free state. Whether or not this differential response to treatment with altered antibody production represents a subgroup of patients has yet to be determined.

Key words Schizophrenia · Immunology · 60 kDa heat-shock protein · IL-2R; subgroup

M. J. Schwarz (✉) · M. Ackenheil
Neurochemische Abteilung der Psychiatrischen Klinik und Poliklinik der Universität München, Nussbaumstrasse 7, D-80336 Munich, Germany

M. Riedel · N. Müller
Psychiatrische Klinik und Poliklinik der Universität München, Nussbaumstrasse 7, D-80336 Munich, Germany

R. Gruber
Institut für Immunologie der Universität München, Nussbaumstrasse 7, D-80336 Munich, Germany

Introduction

A variety of immunological abnormalities in schizophrenic patients have been reported during several decades. Early findings on high-affinity binding of serum immunoglobulins to brain structures of schizophrenic patients (Pandey et al. 1981; Baron et al. 1977) were followed by more detailed studies, as of increased serum levels of the soluble IL-2 receptor (McAllister et al. 1991, Müller et al. 1997), altered IL-2 production (Ganguli et al. 1992), IFN-γ production by in vitro stimulated lymphocytes (Arolt et al. 1997; Wilke et al. 1996) or serum antibodies binding to the 60-kDa heat-shock protein (Kilidireas et al. 1992). Most of these studies have been discussed as being suggestive for an immunological abnormality or even an autoimmune process in schizophrenia.

The soluble interleukin-2 receptor (sIL-2R) has become one of the standard parameters of immunological investigations in schizophrenia. Elevated levels of sIL-2R have been found repeatedly (Wilke et al. 1996; Maes et al. 1995; Rapaport et al. 1994a, b), and it has been suggested that antipsychotic medication is causative for this effect (Pollmächer et al. 1995). Soluble forms of cytokine receptors are generated by proteolytic cleavage of the extracellular domain of the membrane-bound receptor or by alternative splicing (Fernandez-Botran et al. 1996). Although it is well known that the level of sIL-2R correlates with cellular activation and disease activity in inflammatory, autoreactive and other diseases, its possible influence on the pathophysiology of schizophrenia is still not established.

Two other immune parameters could also be of interest in schizophrenia research: antibodies against heat-shock proteins (HSP) and soluble intercellular adhesion molecule-1 (sICAM-1). For antibodies against HSP it is known that they are frequently involved in autoimmune disorders with neuropsychiatric manifestations such as systemic lupus erythematosus (Panchapakesan et al. 1992) and multiple sclerosis (Prabhakar et al. 1994; Birnbaum 1996). Heat shock proteins – especially HSP60 – are expressed

in neuronal, glial and microglial cells (Mutis et al. 1994; Freedman et al. 1992; Brown and Rush 1990) and can be used as markers of nervous system injury (Higashi et al. 1994) and neurodegenerative processes (Harrison et al. 1993). Further findings suggest that these proteins are able to protect cells from damaging effects (Lowenstein et al. 1991) and apoptosis (Mailhos et al. 1993) by preservation of cellular proteins during cellular stress.

sICAM-1 serves as a significant parameter of blood-cerebral spinal fluid (CSF) barrier damage and intrathecal immune activation (Rieckmann et al. 1993; Sharief et al. 1993). In multiple sclerosis there has been found an correlation between sICAM-1 and clinical activity (Dore-Duffy et al. 1995). sICAM-1 plays a role in inflammatory and autoimmune disorders and may possibly induce signal transduction by its leucocyte standing ligand, resulting in a functional change (van de Stolpe 1996). ICAM-1 is expressed in immune cells and endothelial cells as well as in neurons and astrocytes (Hampel et al. 1996). Regulation and function of sICAM-1 are yet unclear, and no reports of sICAM-1 in schizophrenia have been published until now.

In our preliminary study with schizophrenic patients we measured common immune parameters of the humoral immune system, supplemented by soluble parameters indicating an immune activation in unmedicated schizophrenic patients and in gender- and age-related control individuals. The patients were re-investigated after a period of antipsychotic treatment. Based on the findings of Kilidireas et al. (1992) we investigated titres of autoantibodies against 60-kDa heat shock protein (HSP60) together with levels of soluble cytokine receptor sIL-2R and soluble adhesion molecule sICAM-1.

The reason to combine different parameters was the hypothesis that identification of a schizophrenic subgroup depends on the valid combination of significant and relevant parameters. The three parameters were chosen to consider autoantibody production (anti-HSP60 antibodies), cellular activation (sIL-2R) and intrathecal immune activation (sICAM-1).

Table 1 Patients' age, gender, diagnoses according to ICD-10 and DSM-III-R, duration of treatment and illness, age at onset, number of exacerbation of psychosis together with the global value of the PANSS score at the beginning (*uPA_glo*) and at the end (*mPA_glo*) of the study

Age (years)	Gender	ICD diagnosis	DSM-III-R diagnosis	Duration of treatment	Duration of illness	Age at onset (years)	No. of exacerbations of psychosis	uPA_glo	mPA_glo
18	M	F21	295.40	2	2	18	1	34	19
27	M	F20.1	295.14	4	28	24	2	45	45
36	F	F20.0	295.34	3	12	35	1	41	37
26	M	F20.0	295.34	1	1	26	1	56	51
24	M	F20.0	295.31	2	2	24	1	35	21
33	M	F20.0	295.34	0.5	48	29	1	29	27
30	M	F20.0	295.34	2.5	2.5	30	2	51	34
33	M	F20.0	295.34	2	120	23	5	40	20
23	M	F20.1	295.14	4	11	22	3	47	69
28	M	F20.5	295.62	2	60	23	2	58	58
62	F	F20.0	295.34	2.5	372	31	7	33	22
33	M	F20.0	295.34	3	87	25	3	66	56
45	F	F20.5	295.62	1.5	48	41	1	46	27
35	M	F20.0	295.34	2.5	84	28	3	52	47
35	M	F20.1	295.14	3	12	34	2	55	62
32	M	F20.0	295.34	4	12	30	2	37	33
63	F	F20.0	295.34	1	288	39	2	19	19
30	M	F20.1	295.14	1	24	28	4	36	36
39	M	F21	295.40	1	10	38	1	37	53
20	M	F20.1	295.12	2	5	19	1	45	37
22	F	F20.0	295.34	1.5	3	22	1	53	29
31	M	F20.0	295.34	7	132	20	8	46	41
27	F	F21	295.9	2	0.5	26	1	35	18
33	F	F20.0	295.33	2	2	33	1	54	21
31	F	F20.0	295.34	1.5	48	27	1	47	22
44	F	F20.0	295.34	3	240	24	5	40	35
22	F	F20.0	295.33	3	3	22	1	39	31
39	F	F20.0	295.34	1	120	29	2	31	21
29	F	F20.0	295.34	4	48	25	2	47	42
36	F	F20.0	295.34	2	228	19	4	44	19

Materials and methods

Patients

Serum samples were obtained from 30 unmedicated schizophrenics (15 females and 15 males; mean age 32.9 ± 10 years, age range 18–63 years) with a mean duration of illness of 68 ± 95.8 months (range of duration of illness 0.5–372 months). All patients fulfilled the DSM-III-R and ICD-10 criteria for schizophrenia and were diagnosed by two independent psychiatrists. Thirteen of the patients were suffering from a first episode of schizophrenia and had never been medicated with neuroleptics. The remaining 17 patients had a wash-out period of at least 4 months. Psychopathology was monitored using the PANSS score before treatment (first blood sampling) and at the second point of investigation, two days before discharge from hospital. The mean duration of treatment between the two sample collections was 2.4 months (SD 1.3 months, range 0.5–7 months). Two thirds of the patients were treated with classical neuroleptics (mainly haloperidol), and one third with either clozapine or olanzapine. Informed consent was obtained from all subjects. Detailed patient characteristics are given in Table 1.

Fifteen of the patients underwent a lumbar puncture with investigation of the CSF in order to exclude underlying organic disorders. The total protein concentration, cell count and the CSF/serum albumin and immunoglobulin G ratio were determined. The CSF was further screened for the presence/absence of oligoclones.

Controls

Control serum samples were taken from 31 age- and gender-related healthy subjects (14 females and 17 males; mean age 28.6 ± 6.47 years, age range 21–53 years). Individuals suffering from infectious or autoimmune disorders or alcohol abuse were excluded from the study; abuse of nicotine was listed. To exclude any additional disease, blood count, blood sedimentation rate or C-reactive protein were measured in all serum samples.

Laboratory methods

The serum samples of all patients were investigated for HSP60-antibody concentrations before and after treatment with neuroleptics. Depending on the volume of serum samples of each patient, ICAM-1 was measured in 24 of these patients and IL-2R in 28 patients. The laboratory personnel were blinded with regard to subject and diagnosis of the serum probes.

For determination of anti-HSP60 antibodies NUNC PolySorp U96 microtitre plates were incubated with 50-µl recombinant human HSP60 (Stressgen SPP 749) at concentration of 5.0 µg/ml. Blocking was done with 1% BSA in PBS. After washing, standards and samples were added in triplicates, whereas always one of the wells was uncoated and just blocked to exclude unspecific reactions. Serum probes were diluted 1 : 4. The plates were washed and a 1 : 8,000 dilution of peroxidase-conjugated rabbit anti-human IgA, IgG, IgM (Dako P212) was incubated. After washing, the substrate OPD was added. The colour development was stopped after 15 min and measured at 490 and 620 nm. The optical densities of the uncoated wells were subtracted from the mean of the corresponding duplicates. The standard curve was made by a serial dilution of a serum that had high titres of anti-HSP60. The values of the samples were compared with the corresponding linear standard curve and expressed as arbitrary units (AU) defining the 1:4 dilution of the standards as 500 AU and 1 : 256 dilution as 4 AU, whereas the function of the curve was calculated by an exponential function. The limit for "elevated antibody titres" was set at two standard deviations added to the mean of the controls.

The soluble proteins sIL-2R and sICAM-1 were estimated by the following commercially available ELISA kits: T cell Diagnostics IL-2R Test Kit (Cellfree sIL-2R Test Kit, T Cell Diagnostics, USA), ICAM-1 (Cellfree sICAM-1 ELISA, Endogen, USA).

For CSF investigations albumin and immunoglobulin G concentrations were determined by means of an immunonephelometric method using a Behring nephelometer (Behringwerke, Germany). The reference values of CSF albumin and CSF IgG were chosen according to the values published by Reiber and Felgenhauer (1987). The CSF/serum albumin ratio was assessed according to the indices of Tibbling et al. (1977) and Reiber and Felgenhauer (1987).

Statistics

Calculation of the standard curve function were carried out with GraphPad Prism 1.0. Statistical analysis was calculated using SPSS 6.1.3 (SPSS Inc.). For statistical evaluation we used the chi-square test, Pearson's correlation test, *t*-test for independent samples, *t*-test for paired samples and Mann-Whitney U-Wilcoxon rank sum W test.

Results

Serum HSP60-antibody concentrations were determined in 30 schizophrenic patients before and after a period of neuroleptic treatment (0.5–7 months) and compared with those of healthy controls. In Fig. 1 the individual data of untreated patients, treated patients and controls are presented as arbitrary units (AU). A threshold value of 23 AU between normal and elevated antibody titres was defined by a twofold standard deviation of the mean value of controls. Individuals with elevated anti-HSP60 titres are herein described as anti-HSP60 positive.

Considering the proportion of patients off and on antipsychotic treatment, only three (10%) of the unmedicated but six (20%) of the medicated patients were anti-HSP60 positive. The duration of treatment in these six patients with elevated levels ranged from 1.5 to 4 months; two of them were suffering from the first episode of schizophrenia. In two patients the anti-HSP60 titres were elevated at both investigations. In one patient the titre decreased below the threshold value during treatment. Concerning the control population, only in one was the titre above the threshold range. As expected, chi-square calculation showed no significant difference in the number of anti-HSP60 positives between unmedicated and medicated patients and between unmedicated patients and controls. However, the difference between the medicated and the controls trended towards significance (Pearson's $r = 4.2$, $p = 0.040$; Fisher's exact test: two-tail significance $p = 0.053$).

The correlation of the antibody titres with clinical data showed interesting associations. Comparing the anti-HSP60 titres with gender, high titres were found mainly in female patients: Two of the three unmedicated patients with elevated anti-HSP60 titres and all who were anti-HSP60 positive under treatment were females (Pearson's $r = 7.5$, $p = 0.006$; Fisher's exact test: two-tail significance $p = 0.017$). The male patient with elevated titres in the unmedicated state became normal during treatment.

As far as psychopathology was concerned in the unmedicated patients, the PANSS item for positive symptoms was lower in the anti-HSP60-positive patients (mean 15.3 ± 0.6 in patients with elevated titres vs 21.4 ± 6.3;

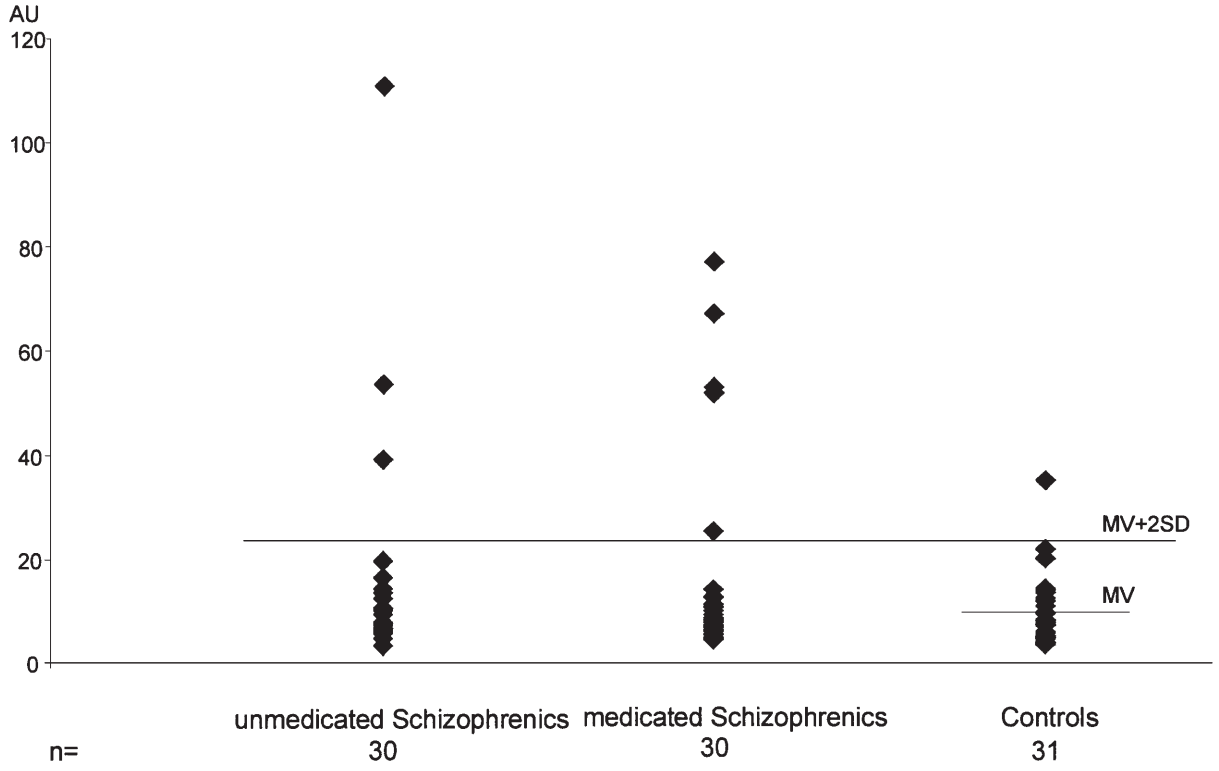

Fig. 1 Results of the anti-HSP60 antibody measurements in serum from patients off and on antipsychotic medication and from controls. Antibody levels are presented in arbitrary units (*AU*). The *short line* indicates the mean of the controls (9.5 AU), and the *long line* shows the threshold value to "elevated titres" (22.96 AU)

statistical calculation was not recommended due to the low number of individuals).

In all patients we observed an effect of treatment on serum sIL-2R concentrations, which increased during antipsychotic medication (paired sample's *t*-test, mean of unmedicated: 473.0 ± 220.9 U/ml; mean of medicated: 634.8 ± 345.4 U/ml; $p = 0.035$) and thus became different from the control values (independent sample's *t*-test, mean of controls: 393 ± 178.6 U/ml; $p = 0.005$). In those patients who were anti-HSP60 positive under medication, the sIL-2R levels increased markedly during treatment (from 506.5 ± 132.2 U/ml to 993.0 ± 515.6 U/ml) with only a slight overlap in the standard deviations; with respect to the small number of individuals (six), no statistical calculations were carried out. Data of sIL-2R are shown in Fig. 2, comparing the unmedicated and the medicated patients with controls as total groups and after splitting into anti-HSP60 normal and positive ones.

In contrast to the sIL-2R levels which were significantly higher in medicated schizophrenics than in controls, levels of sICAM-1 were lower in both, unmedicated (249.6 ± 118.5 ng/ml, $p = 0.042$) and medicated schizophrenics, (242.6 ± 86.4 ng/ml; $p = 0.009$) as compared with controls (301.4 ± 57.0 ng/ml). Comparing the groups of patients with elevated vs normal antibody titres, levels of sICAM-1 appear to be higher in the anti-HSP60-positive patients (anti-HSP60 negative mean: 217.6 ± 51.4 ng/ml; anti-HSP60 positive mean: 337.4 ± 129.6 ng/ml); again, statistical calculation was not recommended.

We found additional correlations between serum concentrations of anti-HSP60 antibodies and the CSF/serum albumin ratio ($r = 0.561$, $p = 0.029$) as well as to IgG in CSF ($r = 0.610$, $p = 0.016$) in medicated patients. Even stronger relations were found to the serum concentrations of sICAM-1 ($r = 0.641$, $p = 0.001$) and of sIL-2R ($r = 0.527$, $p = 0.004$). A Mann-Whitney test comparing patients with high vs normal anti-HSP60 titres underlined the difference of sIL-2R levels ($U = 12.0$, $p = 0.001$) and sICAM-1 levels ($U = 20.5$, $p = 0.053$) between the subgroups.

Discussion

The aim of our study was to identify a subgroup of schizophrenic patients by immune parameters. For that purpose we measured the immunoreactivity against human 60-kDa HSP in serum of patients before and during antipsychotic medication. Additionally, we estimated the soluble immune parameters sICAM-1 and sIL-2R.

Our finding of autoantibodies against human HSP60 reproduces the results of Kilidireas et al. (1992) using a more specific method. The method of Kilidireas and colleagues was based on the binding of serum antibodies to electrophoretically separated proteins from neuroblastoma cells. In their study 14 of 32 schizophrenic patients (44%) showed antibodies to a 60-kDa protein of the

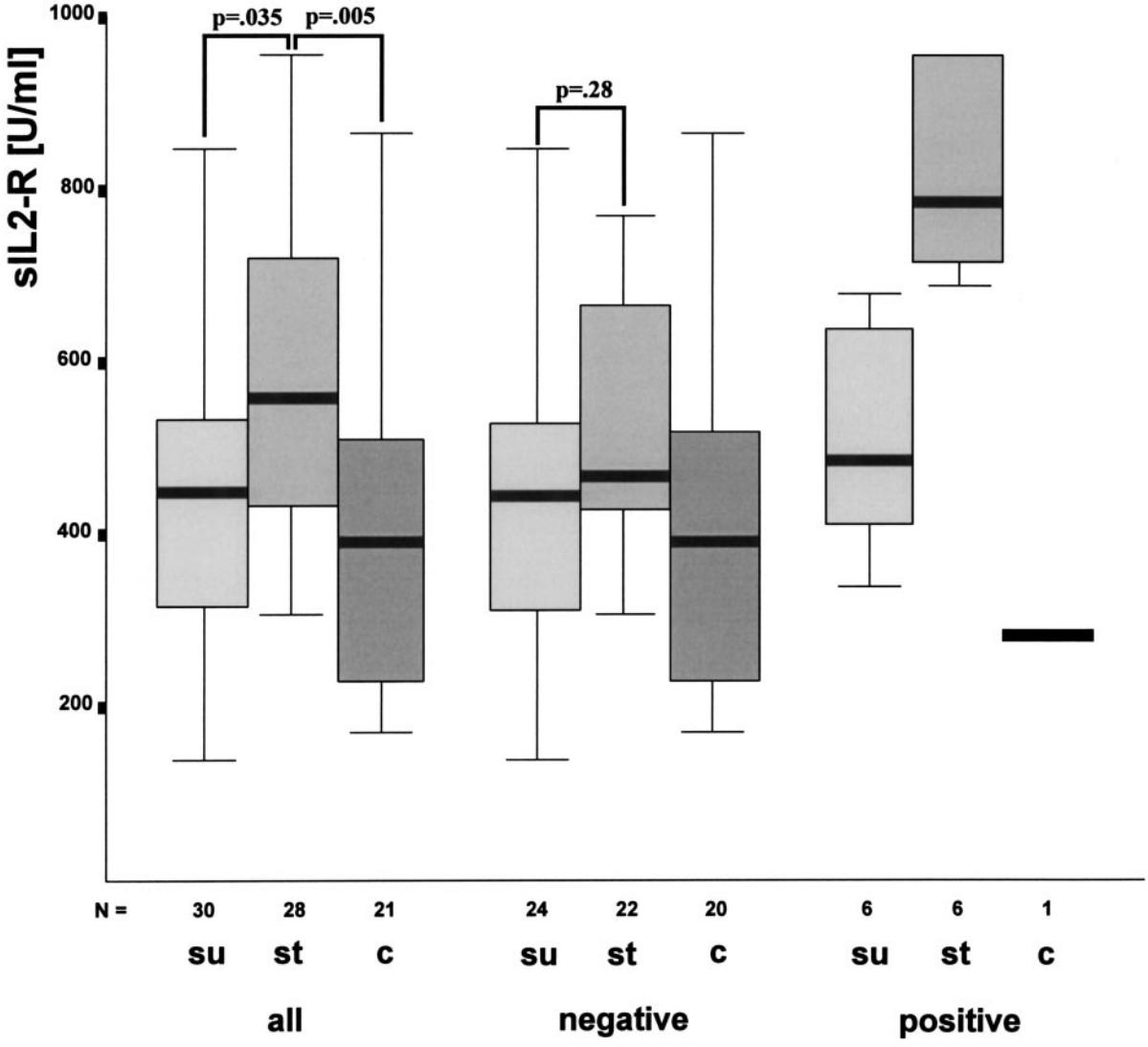

Fig. 2 Means of concentration of soluble interleukin-2 receptor (*sIL-2R*) in patients before (*su*) and during antipsychotic medication (*st*) and in controls (*c*). The *left part* of the figure shows the whole group of schizophrenics and controls, and the right part shows those patients and controls that did not have elevated antibody titres. The numbers indicated by *an asterisk* show the p-values after *t*-test for independent samples, and those marked by *a double asterisk* show the *p*-values after *t*-test for paired samples

lysate, but only in 8 of 100 non-schizophrenic controls were these antibodies observed. The 60-kDa protein was identified as HSP60. There was no consideration for a treatment effect or other clinical and laboratory parameters.

In our study 10% of the 30 unmedicated and 20% of the medicated patients, but only 3% of the healthy controls, had elevated anti-HSP60 titres; thus, only patients under antipsychotic medication showed a significant difference to controls, but not the unmedicated patients.

The increase in the proportion of patients showing elevated anti-HSP60 titres could be explained by different hypotheses. Firstly, the non-significant increase may represent a nonspecific epiphenomenon by chance. Secondly, if treatment over several weeks results in a double increase in the proportion of anit-HSP60-positive patients, treatment over a longer period, maybe even over years, could lead to a significant proportion of anti-HSP60-positive patients similar to that obtained by Kilidireas and colleagues (Kilidireas et al. 1992). Thirdly, since in almost half of our patients it was the first episode of the disorder, the slight increase in the number of patients with elevated titres might be explained by the course of schizophrenia. After a longer duration of disease, a much higher proportion of schizophrenic patients might have elevated antibody titres.

Further investigations with a longer period between the measurements have to prove the hypotheses.

Another question is, in which way are antibodies against HSP60 involved in the pathophysiology of schizophrenia. One explanation could be a cross-reactivity of HSP with other proteins, as observed in multiple sclerosis as cross-reaction between mycobacterial HSP65 and an enzyme involved in metabolism of myelin (Birnbaum et al. 1994). On the other hand, the neuroprotective protein

activity-dependent neurotrophic factor (ADNF) has been described, which shows strong sequence homology to HSP60 (Brenneman and Gozes 1996); therefore, the principal disease-related effect of anti-HSP60 still has to be clarified.

The prerequisite for an involvement of these antibodies in the pathophysiology of schizophrenia is the presence of the antibodies in the CSF as well. A useful method to elucidate the question as to whether serum antibodies may act intrathecally is the comparison of serum/CSF albumin ratio and IgG content of the CSF with the serum antibody titres, since the serum/CSF albumin ratio is a marker of blood–brain barrier impairment. The correlation of this quotient with high anti-HSP60 titres point out that the serum antibodies may penetrate the blood–brain barrier and then react with structures within the CNS. The correlation of IgG in CSF with high anti-HSP60 titres might thus be an indicator for the relatively higher concentration of the anti-HSP60 antibodies in CSF than in serum. In a different population of schizophrenic patients we evaluated the relationship between anti-HSP60 antibody titres in serum and CSF ($r = 0.644$, $p = 0.033$; manuscript in preparation). This suggests that the results of antibody measurement in serum could be transferred to the CSF, thus indicating a possible activity of these antibodies in the CNS.

The comparison of the antibody titres with clinical and immunological data yielded some interesting associations. Especially women showed high antibody titres. This is in agreement with findings in the literature that females have a higher susceptibility for autoimmune reactions than males (Beeson 1994). The observation of a lower score of unmedicated, antibody-positive patients in the positive symptoms scale should not be overrated, because of the small number of patients, but it could give a valuable hint for further investigations.

Elevated CSF/serum albumin ratio correlated with high anti-HSP60 concentrations as well as with high concentrations of CSF IgG. These findings could indicate a disturbed blood–brain barrier and an autologous IgG production associated with increased immunoreactivity against HSP60, i.e. the higher the anti-HSP60 titres, the more marked the blood–brain barrier impairment.

The strong correlation between anti-HSP60 and soluble ICAM-1 or IL-2R and the higher levels of these immune markers in the subgroup of anti-HSP60-positive patients gives additional hints to the immunological relevance of these antibodies. Elevated levels of circulating IL-2R in schizophrenic patients have already been described and discussed as being associated with autoreactive diseases (McAllister et al. 1991; Müller et al. 1997).

Elevation of sICAM-1 has been reported in inflammatory and autoimmune diseases (van de Stolpe 1996). Data with schizophrenic patients are still missing. Interestingly, in our study the mean sICAM-1 levels were decreased in schizophrenic patients as compared with controls. Only the subgroup of anti-HSP60-positive patients had markedly higher ICAM-1 levels. Additionally, this group of patients had a treatment effect on the levels of sIL-2R and sICAM-1, in contrast to the other patients. This could indicate a differential reaction on neuroleptic therapy in those patients, who have elevated anti-HSP60 titres.

Although our number of patients and controls investigated is small, the consistency of the data indicate an activation of the immune system at least in some of the patients. The anti-HSP antibodies could be a nonspecific sign of an altered immune reactivity, but together with the altered levels of sICAM-1, sIL-2R and of IgG in the CSF, as well as the blood–brain barrier impairment, this could be a useful tool for the identification of a schizophrenic subgroup. This suggestion is further underlined by the effects of treatment upon antibody titres. The final identification of a subgroup with altered immunoreactivity would imply a different treatment strategy in these patients.

Acknowledgement This article reflects part of M.J. Schwarz's dissertation. The authors thank the Volkswagen Foundation for supporting this work.

References

Arolt V, Weitzsch C, Wilke I, Nolte A, Pinnow M, Rothermundt M, Kirchner H (1997) Production of interferon-gamma in families with multiple occurrence of schizophrenia. Psychiatry Res 66:145–152

Baron M, Stern M, Anavi R, Witz IP (1977) Tissue-binding factor in schizophrenic sera: a clinical and genetic study. Biol Psychiatry 12: 199–219

Beeson PB (1994) Age and sex associations of 40 autoimmune diseases. Am J Med 96: 457–462

Birnbaum G (1996) Stress proteins: their role in the normal central nervous system and in disease states, especially multiple sclerosis. In: Chofflon M, Steinman L (eds) Immunoneurology. Springer, Berlin Heidelberg New York

Birnbaum G, Kotilinek L, Schlievert P, Clark HB, Trotter J, Horvath E, Gao E, Cox M, Braun PE (1994) Immunologic cross-reactivity between a mycobacterial heat shock protein and myelin 2′, 3′ cyclic nucleotide 3′ phosphodiesterase. Neurology 44 [Suppl 2]: A146

Brenneman DE, Gozes I (1996) A femtomolar-acting neuroprotective peptide. J Clin Invest 97: 2299–2307

Brown IR, Rush SJ (1990) Expression of heat shock genes (HSP70) in the mammalian brain: distinguishing constitutively expressed and hyperthermia-inducible mRNA species. J Neurosci Res 25: 14

Dore-Duffy P, Newman W, Balabanov R, Lisak RP, Mainolfi E, Rothlein R, Peterson M (1995) Circulating soluble adhesion proteins in cerebrospinal fluid and serum of patients with multiple sclerosis: correlation with clinical activity. Ann Neurol 37: 55–62

Fernandez Botran R (1991) Soluble cytokine receptors: their role in immunoregulation. FASEB J 5: 2567–2574

Freedman MS, Buu NN, Ruijs TC, Williams K, Antel JP (1992) Differential expression of heat shock proteins by human glial cells. J Neuroimmunol 41: 231–238

Ganguli R, Brar JS, Solomon W, Chengappa KNR, Rabin BS (1992) Altered interleukin-2 production in schizophrenia: association between clinical state and autoantibody production. Psychiatry Res 44: 113–123

Hampel H, Schwarz MJ, Kötter HU, Schneider C, Müller N (1996) Cell adhesion molecules in the central nervous system. Drug News Perspect 9: 69–81

Harrison PJ, Procter AW, Exworthy T, Roberts GW, Najlerahim A, Barton AJ, Pearson RC (1993) Heat shock protein (HSP70) mRNA expression in human brain: effects of neurodegenerative disease and agonal state. Neuropathol Appl Neurobiol 19: 10

Higashi T, Takechi H, Uemura Y, Kikuchi H, Nagata K (1994) Differential induction of messenger-RNA species encoding several classes of stress proteins following focal cerebral ischemia in rats. Brain Res 650: 239

Kilidireas K, Latov N, Strauss DH, Aviva DG, Hashim GA, Gorman J M, Sadiq SA (1992) Antibodies to human 60 kD heat-shock protein in patients with schizophrenia. Lancet 340: 569–572

Lowenstein DH, Chan PH, Miles MF (1991) The stress protein response in cultured neurons: characterization and evidence for a protective role in excitotoxicity. Neuron 7: 1053–1060

Maes M, Bosmans E, Calabrese J, Smith R, Meltzer HY (1995) Interleukin-2 and interleukin-6 in schizophrenia and mania: effects of neuroleptics and mood stabilizers. J Psychiatr Res 29: 141–152

Mailhos C, Howard MK, Latchman DS (1993) Heat shock protects neuronal cells from programmed cell death by apoptosis. Neuroscience 55: 621–627

McAllister CG, Rapaport MH, Pickar D, Paul SM (1991) Autoimmunity and schizophrenia. In: Tamminga CA, Schulz SC (eds) Advances in neuropsychiatry and psychopharmacology, vol 1. Schizophrenia research. Raven Press, New York, pp 111–118

Müller N, Empl M, Putz A, Schwarz M, Ackenheil M (1997) Immunological effects of treatment in schizophrenia. In: Henneberg AE, Kaschka WP (eds) Immunological alterations in psychiatric diseases. Adv Biol Psychiatry 18: 78–84

Mutis T, Corneliss YE, Datema G, van den Elsen PJ, Ottenhoff THM, Vries RRP de (1994) Definition of a human suppressor T-cell epitope. Proc Natl Acad Sci USA 91: 9456

Panchapakesan J, Daglis M, Gatenby P (1992) Antibodies to 65 kD and 70 kD heat shock proteins in rheumatoid arthritis and systemic lupus erythematosus. Immunol Cell Biol 70: 295–300

Pandey RS, Gupta AK, Chaturvedi VC (1981) Autoimmune model of schizophrenia with special reference to anti-brain antibodies. Biol Psychiatry 16: 1123–1136

Pollmächer T, Hinze SD, Mullington J, Holsboer F (1995) Clozapine-induced increase in plasma levels of soluble interleukin-2 receptors (letter). Arch Gen Psychiatry 52: 877–878

Prabhakar S, Kurien E, Gupta RS, Zielinski S, Friedman MS (1994) Heat shock protein immunoreactivity in CSF: correlation with oligoclonal banding and demyelinating disease. Neurology 44: 1644

Rapaport MH, Lohr JB (1994a) Serum-soluble interleukin-2 receptors in neuroleptic-naive schizophrenic subjects and in medicated schizophrenic subjects with and without tardive dyskinesia. Acta Psychiatr Scand 90: 311–315

Rapaport MH, McAllister CG, Kim YS, Han JH, Pickar D, Nelson DL, Kirch DG, Paul SM (1994b) Increased serum soluble interleukin-2 receptors in Caucasian and Korean schizophrenic patients. Biol Psychiatry 35: 767–771

Reiber H, Felgenhauer K (1987) Protein transfer at the blood cerebrospinal fluid barrier and the quantitation of the humoral immune response within the central nervous system. Clin Chem Acta 163: 319–328

Rieckmann P, Nunke K, Burchhardt M, Albrecht M, Wiltfang J, Ulrich M, Felgenhauer K (1993) Soluble intercellular adhesion molecule-1 in cerebrospinal fluid: an indicator for the inflammatory impairment of the blood–cerebrospinal fluid barrier. J Neuroimmunol 47: 133–140

Sharief MK, Noori MA, Ciardi M, Cirelli A, Thompson EJ (1993) Increased levels of circulating ICAM-1 in serum and cerebrospinal fluid of patients with active multiple sclerosis. Correlation with TNF-alpha and blood–brain barrier damage. J Neuroimmunol 43: 15–21

Tibbling G, Link H, Ohmann S (1977) Principles of albumin and IgG analyses in neurological disorders. I. Establishment of reference values. Scand J Clin Lab Invest 37: 385–390

van de Stolpe A, van der Saag PT (1996) Intercellular adhesion molecule-1. J Mol Med 74: 13–33

Vass K, Welch WJ, Nowak TSJ (1988) Localization of 70-kDa stress protein induction in gerbil brain after ischemia. Acta Neuropathol 77: 128

Wilke I, Arolt V, Rothermund M, Weitzsch C, Hornberg M, Kirchner H (1996) Investigations of cytokine production in whole blood cultures of paranoid and residual schizophrenic patients. Eur Arch Psychiatry Clin Neurosci 246: 279–284