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Chapter 7

Immune System Dysregulation and Autoimmunity in Schizophrenia: IgGs from Sera of Patients with Several Catalytic Activities

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Additional information is available at the end of the chapter

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Abstract

Schizophrenia is usually a progressive mental illness with very different polymorphic symptoms. Several different theories of schizophrenia were discussed; the causes of this disease are not yet clear. Destruction of DNA, RNA, and myelin basic protein (MBP) by inflammation caused by autoimmune reactions has been revealed. Healthy humans usually do not develop abzymes. It was shown that DNase, RNase, and MBP-hydrolyzing abzymes are easily detectable at the beginning of different autoimmune diseases (AIDs). During the development of spontaneous and induced AIDs in mice, a specific reorganization of their immune system associated with the generation of abzymes hydrolyzing different autoantigens was revealed. SCZ is currently not assigned to classical autoimmune diseases. However, the sera of approximately 30% of SCZ patients demonstrated a high level of anti-DNA Abs (comparing to 37% of SLE patients); abzymes hydrolyzing DNA, RNA, and MBP were revealed in 80–100% of SCZ patients. The site-specific hydrolysis of four known SCZ-specific microRNA playing an important role in the regulation of several genes functioning was revealed. Anti-MBP IgGs hydrolyze specifically only MBP but not other proteins. The data indicate that SCZ patients may to a certain extent show similar to SLE and MS patients' typical signs of autoimmune processes.

Keywords: schizophrenia, autoimmunity, catalytic antibodies, hydrolysis of autoantigens

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1. Introduction

Schizophrenia (SCZ) is a highly heritable brain disorder, and it is one of the most relevant problems of psychiatry [1]. The prevalence of SCZ in the human population is approximately 1%, and this disease is the most severe mental diseases [2]. Schizophrenia is a progressive mental illness demonstrating polymorphic symptomatology and resulting in the persistent violation of social adaptation and ability to work. In SCZ, a violation of synaptic transmission resulting in neuronal damage and severe dysfunction was observed [3–5]. These changes often may begin to arise in utero or early childhood [6, 7].

Several different theories of SCZ were discussed, but all of them cannot be definitively concluded for or against the degenerative or neurodevelopmental hypothesis and did not provide clarity concerning the mechanism of schizophrenia development [8].

The dopamine hypothesis of schizophrenia is a model, attributing symptoms of SCZ to a disturbed and hyperactive dopaminergic signal transduction. Since dysfunction of the glutamatergic system is a widely known fact in SCZ [9–12], it is possible that misbalance of dopamine-glutamate homeostasis can lead to the patient's development of generalized oxidative stress [13, 14]. The known theory, however, does not posit dopamine overabundance as a complete explanation of SCZ. Rather, the overactivation of D2 receptors, specifically, is one effect of the global chemical synaptic dysregulation observed in this disorder.

Detection of neurotropic effect which was postulated is associated with the damages of cell membranes [15, 16]. It is believed that the brain cell membranes damage causes the formation of autoantigens and as the consequence autoantibodies (Abs) [17–19]. Interestingly, Abs to glutamate receptors were revealed in SCZ and many other diseases including typical autoimmune ones [20]. Anti-NMDA-NR1, anti-AMPA-GluR3, anti-NMDA-NR2A/B, and anti-mGluR1 or anti-mGluR5 antibodies were found in subpopulations of patients not only with SCZ but also with encephalitis, epilepsy, SLE, neuropsychiatric SLE, cerebellar ataxia, Sjogren's syndrome, and mania or stroke [20]. These autoimmune Abs against anti-glutamate receptors can bind neurons in few brain regions, activate receptors of glutamate, decrease glutamate receptor's expression, activate blood-brain barrier endothelial cells, damage the brain, impair glutamate-induced signaling and function, kill neurons, and induce psychiatric/behavioral/cognitive abnormalities [20]. The association between SCZ and various inflammatory-autoimmune diseases was reported in several epidemiological surveys. Several studies demonstrated that individuals with SCZ are somehow less likely to have rheumatoid arthritis [21]. Some other autoimmune (AI) disorders have also been linked to schizophrenia, particularly Hashimoto's thyroiditis and celiac disease [22, 23].

During the last decade, new data about increasing recognition of central nervous system (CNS) syndromes associated with autoimmune processes leading to the production of autoantibodies to CNS cell surface antigens were obtained [24]. Most of these syndromes present outstanding mental and cognitive symptoms, among the variety of neurological manifestations such as seizures, movement disorders, and autonomic dysfunction, and is best described as "autoimmune encephalopathy."

The causes of schizophrenia include environmental and genetic factors [25]. Recently, a genome-wide microarray study in postmortem brains of SCZ patients has explored expression profiling of immune-modulatory genes [26]. Genetic factors in SCZ include a variety of common and rare genetic variants [27]. It was shown that SCZ is a multifactorial disease, the pathogenesis of which can contribute to numerous genes and the products of their transcription [28]. Therefore, in research of schizophrenia pathogenesis, understanding a possible role of microRNAs may be important. Short non-coding microRNAs (18–25 nucleotides) can individually regulate up to several hundred genes. Disturbances in microRNA (microRNA-regulated gene network) lead to alteration in the expression of many genes. The expression of different microRNAs in plasma [29, 30], mononuclear cells of peripheral blood [31] as well as in various brain regions [32, 33] in patients with SCZ was detected. In addition, genome-wide association study shows, in SCZ, a close association of a single-nucleotide polymorphism of miR-137 and miR-9-5p [34–36]. MicroRNA miR-137 plays an important role in the differentiation of embryonic stem cells, proliferation, and differentiation of neurons, the maturation of the synapses [37]. The miR-137 inhibits AMPA receptor-mediated synaptic transmission by decreasing the expression of the GluA1 subunit of this receptor [38]; influences the release of neurotransmitters from synaptic vesicles and disrupts synaptic plasticity [39]. Interestingly, one of the genes regulating the expression of miR-137, is a protein zinc finger 804A (zinc finger protein 804 A-ZNF804A), which in turn inhibits the expression of catechol-O-methyltransferase (catechol-O-methyltransferase), and D2 receptor of dopamine [37], which leads to a disruption in dopamine neurotransmission. In the regulation of expression of the D2 receptor of dopamine is also involved in the miR-9-5p [36]. It is shown that miR-9-5p is involved in neuronal migration and that the expression of miR-9-5p in patients with schizophrenia is reduced in neuronal cells precursors (neural progenitor cells) [40]. It was also found that miR-219 plays an important role in the differentiation of oligodendrocytes and myelination of axons of neuronal cells [41].

It is known that enzymes can play important role in the pathogenesis of different diseases: dysfunction of enzymes systems involved in the metabolism of biogenic amines (indolamine, catecholamines) during mental disorders including SCZ [23, 42].

The above data testify to the fact that some patients with SCZ are clearly showing signs of typical autoimmune pathologies. However, the importance of immunological changes resulting in the loss of the tolerance to self-antigens in the pathogenesis of SCZ is currently not accepted. Summarizing all existing hypotheses, one can say that SCZ is a very multifactorial disease including some variations in the functioning of neurotransmitter systems associated with the changes in the rate of synthesis or breakdown of the neurotransmitter, possible modifications of the structure of the relevant receptors, genetic predisposition and a dysregulation between the immune and nervous systems, important role of genetic factors and microRNAs, as well as enzymatic systems.

Despite the fact that SCZ is not currently attributed to typical autoimmune diseases, the immune system and dysregulation of immune cells, including autoimmune processes in this disease, are not to be excluded [17–20, 24]. Schizophrenia, autoimmunity and immune system dysregulation are reviewed in [43, 44]. Thus, the search of the importance of different mechanisms of SCZ development including possible autoimmune factors is undoubtedly actual. In this

connection, some literature data should be mentioned. Catalytically active artificial antibodies or abzymes (Abzs) against transition chemical reaction states were well studied (reviewed in [45–47]). In the last three decades, it was shown that auto-antibodies from the blood of patients with different AIDs can possess enzymatic activities and that their occurrence is a specific feature of these pathologies (reviewed in [47–53]). Similarly to artificial Abzs to transition states of chemical reactions [45–47], natural abzymes are Abs raised directly against enzyme substrates acting as haptens of proteins mimicking transition states of catalytic reactions. In addition, anti-idiotypic Abs against catalytic centers of enzymes can be induced in AIDs, and they also possess catalytic activities [47–56].

Even in the sera of healthy mammals, auto-antibodies to different peptides, proteins, DNA, and RNA are detectable, and their titers vary significantly [47–57]. The sera of SLE patients usually contain DNA and anti-DNA Abs in increased concentrations, and SLE is usually considered to be associated with the autoimmunization of patients with DNA. However, the sera of patients with several different autoimmune diseases contain DNA and anti-DNA Abs [57], as well as RNA and anti-RNA Abs in high concentrations [58–61]. Many anti-DNA Abs are directed against histone-DNA nucleosomal complexes appearing from internucleosomal cleavage during apoptosis [62].

Despite the fact that the blood of healthy donors usually contains autoantibodies to DNA, RNA, and many different proteins, these Abs usually do not possess catalytic activities [47–56]. It was shown, that in the case of different autoimmune patients, experimental mice abzymes with DNase, protease, and amylase activities are the earliest and statistically significant markers of autoimmune pathology onset and following development [63–69]. Enzymatic activities of Abs are detectable even at the stage of pre-disease when there is no visible markers of autoimmune diseases and changes in proteinuria, and the anti-antigen titers including DNA and proteins are within the typical ranges of these indicators for healthy humans and experimental mice [63–69]. Therefore, a detectable level of Ab activities can be considered as valuable index even at the beginning of the pathology (pre-disease) and obvious pathology conditions of spontaneous or induced autoimmune diseases [63–69].

Natural polyclonal IgGs and/or IgAs and IgMs hydrolyzing mononucleotides, DNA, RNA, oligopeptides, proteins, and polysaccharides, from the sera of patients with several AIDs and several viral diseases with significant autoimmune reactions were revealed (reviewed in [47–56]). Bence-Jones proteins of multiple myeloma patients [70], DNase abzymes from SLE [71] and MS [51] are cytotoxic, induce nuclear DNA fragmentation and cause cell death by apoptosis, leading to increase in the concentration of many different cell components including DNA, RNA, and proteins in patients with various AIDS. Abzymes with RNase activity in autoimmune diseases are of particular interest. The same polyclonal preparations of Abzs hydrolyzed RNA approximately 10-fold to 300-fold faster than DNA [72–74].

It has been recently shown that myelin basic protein (MBP)-hydrolyzing activity is an intrinsic property of IgGs of SLE patients [75–78] as well as IgGs, IgMs, and IgAs from the sera of MS patients [79–82]. In MS and SLE, anti-MBP abzymes with protease activity can attack MBP of the myelin-proteolipid sheath of axons and can play an important harmful role in MS and SLE pathogenesis [75–82].

In this review, an analysis of the catalytic activities of currently described abzymes in the blood of patients with SCZ was carried out. These abzymes of SCZ with different catalytic activities are compared with other Abzs in AIDs. In addition, a possible role of defects of immune systems leading to the production of abzymes is discussed.

Taking into accoIn this review, an analysis of the catalytic activities of currently described abzymes in the blood of patients with SCZ. These abzymes of SCZ with different catalytic activities are compared with other Abzs in AIDs. In addition, a possible role of defects of immune systems leading to the production of abzymes is discussed.unt the ability of autoimmune patient's abzymes to hydrolyze RNA together with the important role of microRNAs in proliferation, differentiation, and maturation of neuronal cells and the relationship of microRNAs with the development of SCZ, the aim of present chapter was to analyze the RNA-hydrolyzing activity of Abs of schizophrenia patients. In addition, we have described substrate specificity antibodies in the hydrolysis of specific for schizophrenia microRNA.

As mentioned above, schizophrenia is not attributed to the classic autoimmune diseases. At the same time, it was recently shown that the sera of ~30% of SCZ patients showed a higher content of anti-DNA Abs (comparing to 37% of SLE patients), while DNase abzymes were revealed in 80% of SCZ patients [83]. In addition, it was shown that abzymes hydrolyzing MBP were revealed in 82% of the SC patients. These data can indicate for at least a pronounced autoimmune component in patients with SCZ. Interestingly, the researchers of the London medical Institute Oliver House advanced theory, according to which schizophrenia is the result of a lesion of immune system of the brain (http://the-newspapers.com/2017/11/08/schizophrenia-has-announced-a-disease-of-the-immune-system).

2. Abzymes with DNase activity

The generation of auto-Abs to DNA usually occurs not only in patients with AI, viral, and bacterial diseases but also in healthy humans [23, 24, 32–35, 55]. We have compared the relative levels of Abs interacting with DNA in sera of 20 SCZ patients and 20 healthy donors. The levels of Abs interacting with single-stranded (ss) DNA (A_{450}/ml) for 20 healthy donors were detectable; they varied from 0.07 to 0.14 specific units (average value—0.13 ± 0.02) and, on average, they were 1.3-fold higher ($P = 6.3 \times 10^{-4}$) than those interacting with double-stranded (ds) DNA varying from 0.1 to 0.18 (0.1 ± 0.02) [83, 84]. The average level of Abs (A_{450}/ml) for the total group of patients with SCZ interacting with ssDNA (range from 0.1 to 1.4; average value 0.23 ± 0.13) was only 1.1-fold lower ($P = 6.9 \times 10^{-4}$) than that for interacting with dsDNA (range from 0.15 to 0.44; average value 0.25 ± 0.07). The average level of Abs interacting with dsDNA for healthy donors is 2.5-fold lower ($P = 1.0 \times 10^{-6}$) than that for SCZ patients, while for antibodies interacting with ssDNA, it is lower only 1.8-fold ($P = 0.05$). Several SCZ patients are characterized by very high levels of Abs interacting with ssDNA and dsDNA (0.31–1.4 A_{450}/ml) characterizing patients with SLE (0.51 ± 0.50 and 0.66 ± 0.48 A_{450}/ml, respectively) and with MS (0.22 ± 0.18 and 0.39 ± 0.26 A_{450}/ml, respectively) [53–56].

The average relative level of Abs interacting with dsDNA (0.23 ± 0.05 A_{450}/ml) for SCZ patients with positive symptoms was 1.2-fold lower than that for patients with negative symptoms

(0.28 ± 0.07 A_{450}/ml) (**Table 2**). At the same time, the average level of Abs interacting with ssDNA (0.3 ± 0.22 A_{450}/ml) for patients with positive symptoms was 1.9-fold higher than that for SCZ patients demonstrating negative symptoms (0.16 ± 0.07 A_{450}/ml). It was accepted that increased concentration of anti-DNA Abs is a characteristic of patients with SLE. However, concentration of anti-DNA Abs compared with healthy donors is higher in patients with SLE (37% of patients), MS (17–18%), Sjogren's syndrome (18%), Hashimoto thyroiditis (23%), rheumatoid arthritis (7% of patients), and myasthenia gravis (6%) [57]. Overall, ~30% of SCZ patients (comparable with SLE patients 37% [57]) displayed higher content of Abs interacting with ss- and dsDNA when compared to healthy donors.

As mentioned above, polyclonal natural DNA-hydrolyzing IgGs and/or IgAs and IgMs were revealed in blood sera of patients with several AI and viral diseases (reviewed in [47–57]). Electrophoretically and immunologically homogeneous IgGs were obtained from the sera of 20 SCZ patients and 20 healthy volunteers by sequential chromatography of the serum proteins on Protein A-Sepharose using conditions providing removing non-specifically bound proteins, followed by FPLC gel filtration in an acidic buffer destroying immune complexes as in [75–81]. For some experiments, equimolar mixtures of 20 IgG preparations of SCZ patients (scz-IgG_{mix}) and 20 preparations of healthy donors (healthy-IgG_{mix}) were used [83]. To show that IgGs of SCZ patients possess DNase activity, we have checked several known strict criteria [52–56, 85]. The following main criteria were used [83]: (a) Abs should be electrophoretically homogeneous (**Figure 1A**); (b) Abs after gel filtration in an acidic buffer (pH 2.6) dissociating strong noncovalent complexes IgGs must possess DNase activity and the peak of the activity should tracked exactly with the intact Abs (**Figure 1B**); (c) immobilized polyclonal antibodies against the human Abs should completely absorb the DNase activity; (d) among criteria, there is an hardest one; if it is carried out, all other criteria are also met. To exclude any possible artifacts due to hypothetical traces of contaminating canonical DNases, scz-IgG_{mix} preparation was subjected to SDS-PAGE in a gel containing polymeric DNA, and its DNase activity was analyzed after gel incubation in the standard reaction buffer (**Figure 1C**). Ethidium bromide staining of the gels revealed sharp dark bands against a fluorescent DNA background only in the position of intact IgG_{mix} before (lane 3) and only in the position of light chains after Abs reduction with DTT (lane 4). There was no revealed DNase activity of healthy-IgG_{mix} before (lane 5) and after Abs reduction with DTT (lane 6).

The intact IgGs have molecular masses (~150 kDa) significantly higher than for all canonical human DNases (35–36 kDa), while DNases have higher molecular masses than light chains of IgGs (22–25 kDa). SDS usually dissociates all protein complexes. The detection of DNase activity only in the gel zones of intact IgGs and their light chains as well as the absence of any other activity and protein bands (**Figure 1C**) ensure direct evidence that SCZ IgGs hydrolyze DNA and are not contaminated with canonical DNases. Several other strict criteria were also fulfilled (see below).

We have shown that the DNase activity of IgGs purified by chromatography on Protein G-Sepharose followed by FPLC gel filtration can be used for the evaluation of their relative activity (RA) without additional purification. The RAs of SCZ patients IgGs were significantly varied from patient to patient. However, 16 of 20 samples (80%) had high or detectable DNase activity. The distributions of the RAs for IgGs of different SCZ patients with positive and

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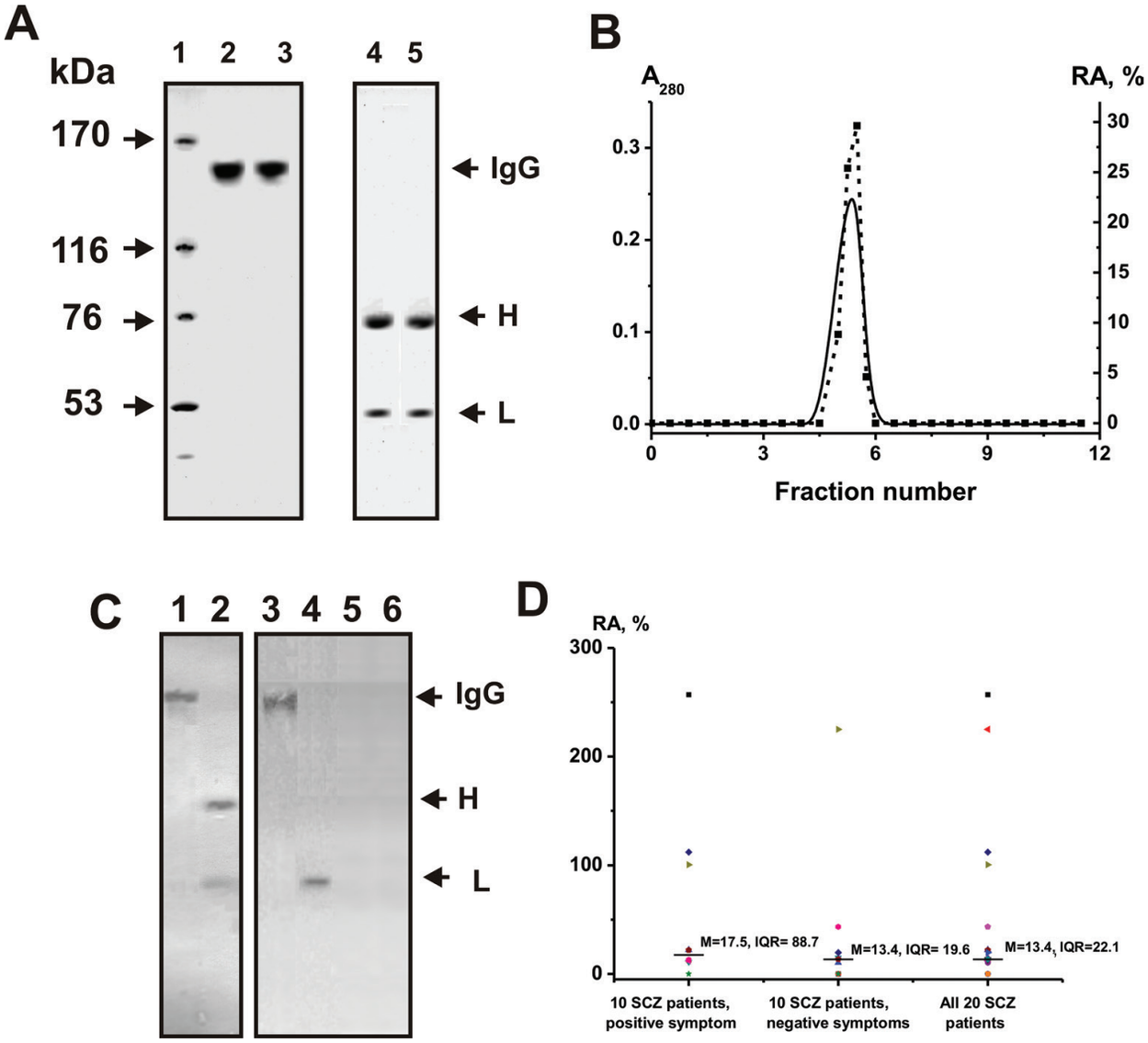


Figure 1. SDS-PAGE analysis of IgG_{mix} (7 μg) corresponding to the mixtures of scz-IgG_{mix} (lane 2) from the sera of 20 patients with SCZ and healthy-IgG_{mix} (lane 3) corresponding to 20 healthy donors in a nonreducing 3–16% gradient gel or in a reducing 12% gel (lanes 4 and 5, respectively) followed by silver staining (A); the lane 1 arrows indicate the positions of molecular mass markers. The application of the strict criteria is to prove that the DNase activity of Abs is the intrinsic property of scz-IgG_{mix}. FPLC gel filtration of scz-IgG_{mix} on a Superdex 200 column using an acidic buffer (pH 2.6) after IgGs pre-incubation in the same buffer (B): (■), relative activity (RA, %) of IgGs in the hydrolysis of supercoiled DNA; (—), absorbance at 280 nm (A280). A complete hydrolysis of 18 μg/ml scDNA for 2 h was taken for 100%. The initial rate determination error from three experiments in each case did not exceed 7–10%. Assay of DNase activity of scz-IgG_{mix} from schizophrenia patients in-gel containing thymus DNA before (lane 3) and after IgGs reduction with DTT (lane 4); lane 5 corresponds to healthy-IgGmix before treatment with DTT (C). DNase activity was revealed after gel staining with ethidium bromide as a dark band on the fluorescent background. There was no revealed catalytic activity of healthy-IgG_{mix} before its reduction (lane 5). A part of the used gel was stained with Coomassie R250 to find the position of intact scz-IgG_{mix} before (lane 1) as well as its free heavy and light chains after Ab reduction (lane 2). The distribution of the RAs (in the hydrolysis of scDNA) corresponding to SCZ patients with positive and negative symptoms within different ranges (D). The median (M; solid lines) and interquartile ranges (IQR) were estimated using the Mann-Whitney test.

negative symptoms are shown in **Figure 1D**. Finally, to compare RAs of DNase IgGs of SCZ patients with those for patients with other diseases, the values of apparent k_{cat} in the hydrolysis of DNA for every IgG preparation (k_{cat} = V (M/min)/ [IgGs] (M) and average values of parameters were calculated (**Table 1**) [83].

One of the criteria of Abs' activity is their higher affinity for substrates comparing with canonical DNases. The K_m and k_{cat} values for scDNA hydrolysis were estimated. First, IgG-19 corresponds to the patient with negative symptoms (NS) of SCZ, while IgG-1 and IgG-6 to patients with positive symptoms (**Table 1**). The K_m value for IgG-19 (K_m = 95 ± 18 nM) was comparable with that for IgG-1 (K_m = 85.0 ± 12.0 nM) and IgG-6 (K_m = 80.0 ± 12.0 nM), while k_{cat} for IgG-19 ((2.7 ± 0.3) × 10^{-3} min^{-1}) and IgG-6 ((3.0 ± 0.3) × 10^{-3} min^{-1}) were comparable, but lower than that for IgG-1 ((7.9 ± 0.5) × 10^{-3} min^{-1}). Thus, the affinity of scDNA for SCZ IgGs was in the range 80–95 nM, which corresponds to typical K_d (and K_m) values for interactions of antibodies with antigens; it is approximately 3–4 orders of magnitude higher than affinity of DNase I for scDNA (K_m = 46–58 μM) [86].

Number of patients (sex)	**Abs to dsDNA, A_{450}/ml**	**Abs to ssDNA, A_{450}/ml**	**Relative hydrolysis of DNA, %**	**k_{cat} ×10^5,min^{-1}**
	1	**2**	**3**	**4**
	Positive symptoms (PS)			
1 (M)	0.35	1.4	257[μ]	39.6[***]
2 (M)	0.19	0.11	11.7	1.8
3 (M)	0.2	0.31	22.2	3.4
4 (M)	0.19	0.16	11	1.7
5 (M)	0.24	0.19	12	1.9
6 (M)	0.15	0.11	100.4	15.5
7 (M)	0.21	0.14	112	17.3
8 (F)	0.2	0.23	22	3.4
9 (F)	0.34	0.25	13	2.0
10 (F)	0.18	0.11	0	0
Average (PS)	0.23±0.05	0.30±0.22	56.1±60.2	8.7±9.3
M (IQR) (PS)ϒ	0.20 (0.05)	0.18 (0.14)	17.5 (88.7)	2.7 (13.7)
Correl. coeff. (PS)	Groups 1–2 (0.71)		1–3 (0.46)	2–3 (0.84)
Negative symptoms (NS)				
11 (M)	0.48	0.23	0[μ]	0
12 (M)	0.28	0.2	0	0
13 (M)	0.21	0.13	10.4	1.6
14 (M)	0.22	0.16	15.0	2.3
15 (M)	0.23	0.1	13.3	2.1
16 (F)	0.44	0.12	225	34.7
17 (F)	0.24	0.11	19.6	3.0
18 (F)	0.17	0.19	13.6	2.1
19 (F)	0.25	0.16	43.4	6.7

Number of patients (sex)	Abs to dsDNA, A_{450}/ml	Abs to ssDNA, A_{450}/ml	Relative hydrolysis of DNA, %	k_{cat} ×10^5,min^{-1}
	1	2	3	4
	Positive symptoms (PS)			
20 (F)	0.24	0.15	0	0
Average (NS)**	0.28±0.07	0.16±0.03	34.0±40.1	5.3±6.2
M (IQR) (NS)	0.24 (0.06)	0.16 (0.07)	13.4 (19.6)	2.1 (3.0)
Average, total group	0.25±0.07	0.23±0.13	45.1±50.4	7.0 (7.9)
M (IQR), total groupϒ	0.23 (0.07)	0.16±0.1	13.4 (22.1)	2.1 (3.4)
Correl. coeff. (NS)	1–2 (0.3)	1–3 (0.5)	2–3 (0.35)	
Correl. coeff., complete group	1–2 (0.3)	1–3 (0.4)	2–3 (0.62)	

*For each value, a mean of three measurements is reported; the error of the determination of values did not exceed 7–10%.

**Average values are reported as mean ± S.E; they were recalculated to standard conditions and complete hydrolysis of 18 μg/ml scDNA after 1 h of incubation in the presence of 0.1 mg/ml IgG was taken for 100%.

***The average apparent k_{cat} values of the reaction of DNA hydrolysis were calculated using average RA values: k_{cat} = V (M/min)/ [IgGs] (M), 18 μg/ml scDNA was used.

μStatistical significance of differences in DNase activity between schizophrenia patients with positive and negative symptoms (P = 0.026).

ϒThe median (M) and interquartile ranges (IQR) were calculated using the Mann-Whitney test.

Table 1. The relative concentration of fnti-DNA Abs, RAs (%), and the apparent k_{cat} values characterizing hydrolysis of scDNA by IgGs from the sera of SCZ patients.*

3. Abzymes with RNase activity

It was shown in several articles that IgGs from the sera of healthy humans cannot hydrolyze RNA [87–90]. At the same time, IgGs from the sera of patients with SLE, MS, Hashimoto's thyroiditis and some other autoimmune pathologies effectively hydrolyze different ribopolynucleotides and tRNAs [87–90].

Electrophoretically and immunologically homogeneous IgGs purified from the sera of 35 SCZ patients according to [75–83] as described above were used [91]. On the first step, we used a mixture of equal amounts of 35 polyclonal IgGs (scz-IgG_{mix}) and 15 healthy donors. Then, we checked the fulfillment of the strict criteria described above. The homogeneity of the typical 150-kDa IgG_{mix} was confirmed by SDS-PAGE with silver staining similar to **Figure 1**. The activity peak of the IgG_{mix} treated with acidic buffer (pH 2.6) coincided under gel filtration exactly with the peak of intact Abs (**Figure 2A**) Immobilized polyclonal mouse IgGs against the light chains of human IgGs completely bind the RNase activity. Scz-IgG_{mix} was subjected to SDS-PAGE in a gel co-polymerized with polymeric yeast RNA, and its RNase activity was revealed after the gel incubation in the standard reaction buffer only in the position of intact scz-IgG_{mix}. (**Figure 2B**). Canonical human RNases have significantly lower molecular masses (13–15 kDa) than the intact IgGs (150 kDa). Therefore, the activity detection in the gel zones

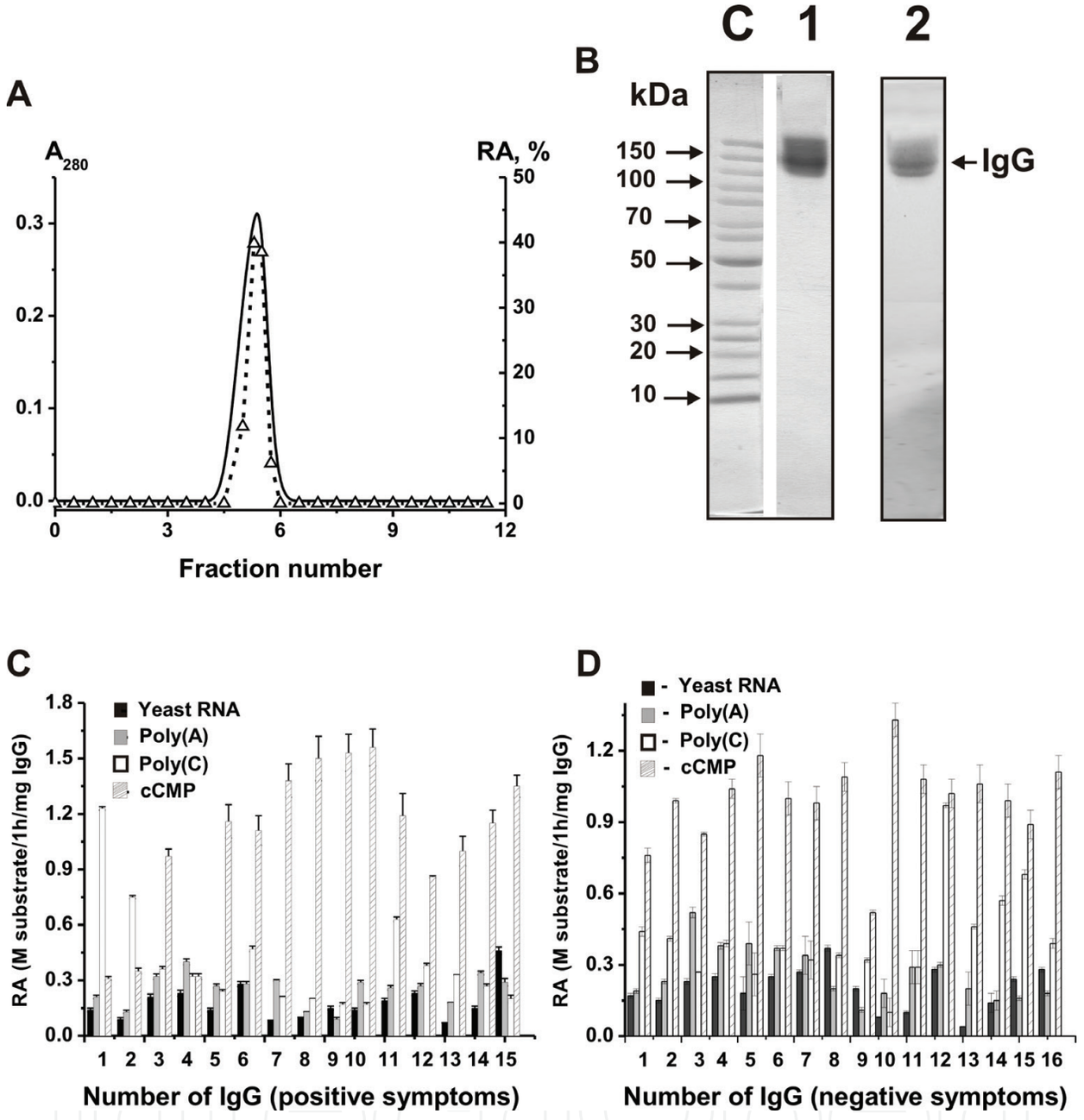


Figure 2. Verification of the strict criteria to prove that the RNase activity of IgGs is an intrinsic property of IgG_{mix}. FPLC gel filtration of scz-IgG_{mix} on a Superdex 200 column equilibrated with an acidic buffer (pH 2.6) after its pre-incubation in the same buffer (A): (—), absorbance at 280 nm (A_{280}); (Δ), relative activity (RA, %) of IgG_{mix} in the cleavage of RNA. A complete hydrolysis of poly(C) for 7 h was taken for 100%. The error in the initial rate estimation from two experiments in each case did not exceed 7–10%. Assay of RNase activity of scz-IgG_{mix} in-gel containing polymeric yeast RNA (lane 2). RNase activity was detected after gel staining with ethidium bromide as a dark band on the fluorescent background. A gel part was stained with Coomassie R250 to show the position of intact scz-IgG_{mix} (lane 1). Lane C corresponds to molecular mass markers. Relative activity of individual IgGs of patients with positive (C) and negative (D) symptoms of SCZ in the hydrolysis of yeast RNA, poly(A), poly(C), and cCMP.

of only intact scz-IgG_{mix} together with the absence of any other activity and protein bands (**Figure 2B**) guarantee direct evidence that schizophrenia IgGs cleave RNA and IgGs are not contaminated by canonical RNases. Several other strict criteria were also fulfilled (see below).

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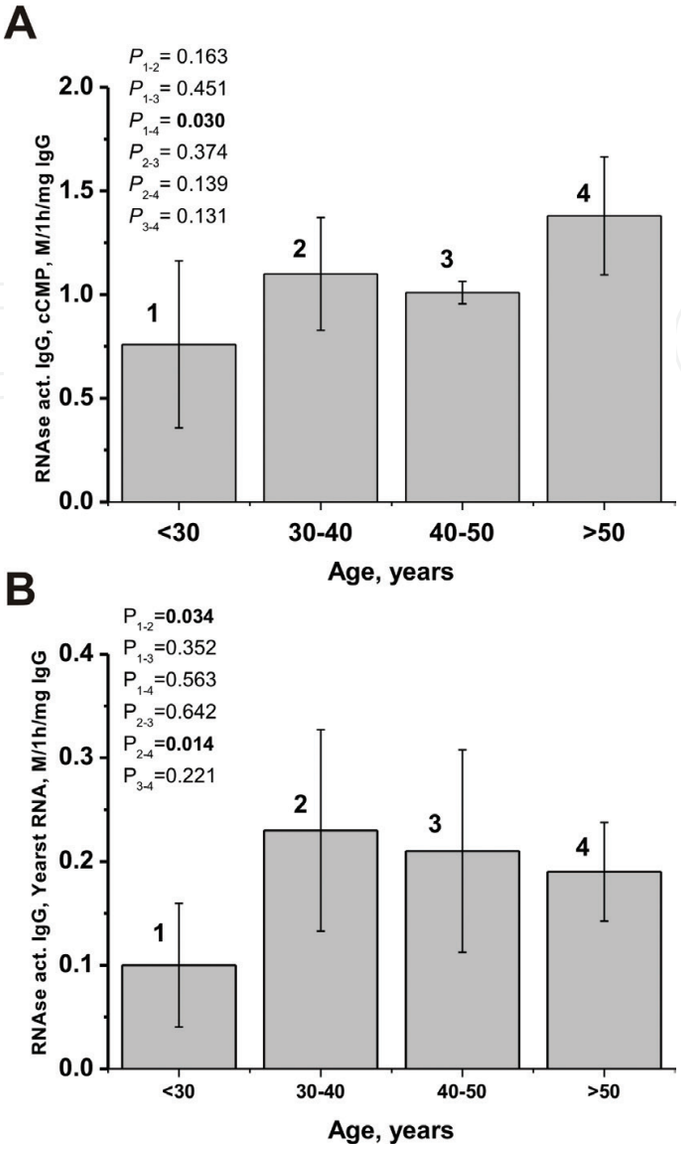


Figure 3. Dependencies of average activities of IgGs of four groups of SCZ patients with different age in the hydrolysis of cCMP (A) and poly(C) (B).

The relative activities of IgGs significantly varied from patient to patient. However, all 15 samples of patients with positive and 16 ones with negative symptoms of SCZ demonstrated detectable or high RNase activity (**Figure 2C** and **D**). The relative average activity for patients with SCZ positive symptoms varied essentially (M/1 h/mg IgG): cCMP (0.31–1.56; average value (AV) = 1.05 ± 0.43), poly(C) (0.17–1.23 AV = 0.4 ± 0.29), poly(A) (0.09–0.4; AV = 0.25 ± 0.09), and yeast total RNA (0.08–0.46 AV = 0.18 ± 0.1) (**Figure 2C**). Similar situation was observed for patients with negative symptoms (M/1 h/mg IgG): cCMP (0.52–1.18; AV = 0.99 ± 0.18), poly(C) (0.1–0.68, AV = 0.41 ± 0.2), poly(A) (0.11–0.52; AV = 0.20 ± 0.11), and yeast total RNA (0.4–3.1 AV = 1.68 ± 0.71) (**Figure 2D**). The difference in average activities of IgGs from patients with positive and negative symptoms was very small: cCMP (1.1-fold), poly(C) (1.03-fold), poly(A) (1.3-fold), and yeast total RNA (1.1-fold). According to non-parametric Kruskal-Wallis analysis,

in none of these cases, there was a statistically significant difference ($P > 0.2$). Interestingly, a clear correlation of the RNase RAs with the duration of SCZ was not observed ($P = -0.015 \pm 0.14$) except with activity of IgGs in poly(C) hydrolysis (+ 0.47). The tendency of increase in activity of IgGs in the hydrolysis of cCMP and poly(C) with age of SCZ patients was revealed (**Figure 3**). A statistically significant difference in the mean values of the relative activity in the case of cCMP hydrolysis was observed for a group of patients younger than 30 and over 50 years old ($P = 0.03$) (**Figure 3A**). For activity in poly(C) hydrolysis, statistically significant difference was revealed between the groups younger 30 and 30–40 ($P = 0.034$) as well as group of patients over 50 years old ($P = 0.014$) (**Figure 3B**). In addition, a good statistically significant correlation was observed between the activity in hydrolysis of cCMP (CC = + 0.896) and composite index of SCZ, demonstrating a difference between parameters of positive symptoms and negative symptoms and showing the prevailing symptoms. Interestingly, a moderate but statistically significant negative correlation was observed between the efficiency of poly(C) hydrolysis and PANSS + (or PANSS Positive scale) evaluating signs that are redundant in relation to normal mental status (−0.43).

4. Hydrolysis of microRNAs

As mentioned above, some microRNAs regulate up to several hundred genes in the pathogenesis of SCZ [34–41]. We have analyzed the hydrolysis by SCZ abzymes' four known microRNAs playing an important role in SCZ [91]. **Figures 4–7** demonstrate typical patterns of miR-137, miR-9-5p, miR-219-2-3p, and miR-219a-5p hydrolysis; specific % of the hydrolysis for each IgG and the average percent of microRNAs hydrolysis by 21 different Abs were estimated. Percentage of the microRNA hydrolysis by different IgGs in the same conditions varied and average values decreased in the following order: miR-219a-5p (the range: 7.4–99.7%, AV = 71.0 ± 32.7%) ≥ miR-137 (14.9–99.9%, AV = 66.2 ± 29.2%) ≥ miR-9-5p (3.1–99.9%, AV = 56.7 ± 32.9%) ≥ miR-219a-2-3p (7.4–99.7%, AV = 52.4 ± 34.5%) (**Figures 2–5**). The correlation coefficients between sets of RAs in the hydrolysis of all 4 microRNAs are quite high, 0.84–0.93.

Spatial structures of microRNAs having minimal energy were calculated; **Figure 8A–D** show position of major, moderate, and minor sites of four microRNA hydrolysis by different IgGs (average % of the RNAs hydrolysis by 21 IgG preparations) [91]. One can see that three major sites of microRNAs hydrolysis are located in their loops or duplex parts directly articulated with the loops. The major sites of the hydrolysis of four microRNAs are different, but more often the cleavages occur after or before G-base: miR-219a-5p—6G-7U; 13C-14G, and 8C-9C; miR-137—5 U-6G, 8 U–9 U, and 10A-11A; miR-9-5p—6G-7G, 8 U–9 U, and 13 U-14A; miR-219a-2-3p—5 U-6 U, 8 U-9G, and 13G–14G (**Figure 8**).

We have estimated the K_m and V_{max} (k_{cat}) values for microRNA hydrolysis using different preparations [91]. The dependencies of the initial rate on the microRNA concentration in the reaction catalyzed by IgGs were consistent with Michaelis-Menten kinetics. The K_m and k_{cat} values were to some extent comparable for all microRNAs: miR-137, K_m = 3.5 ± 0.2 μM,

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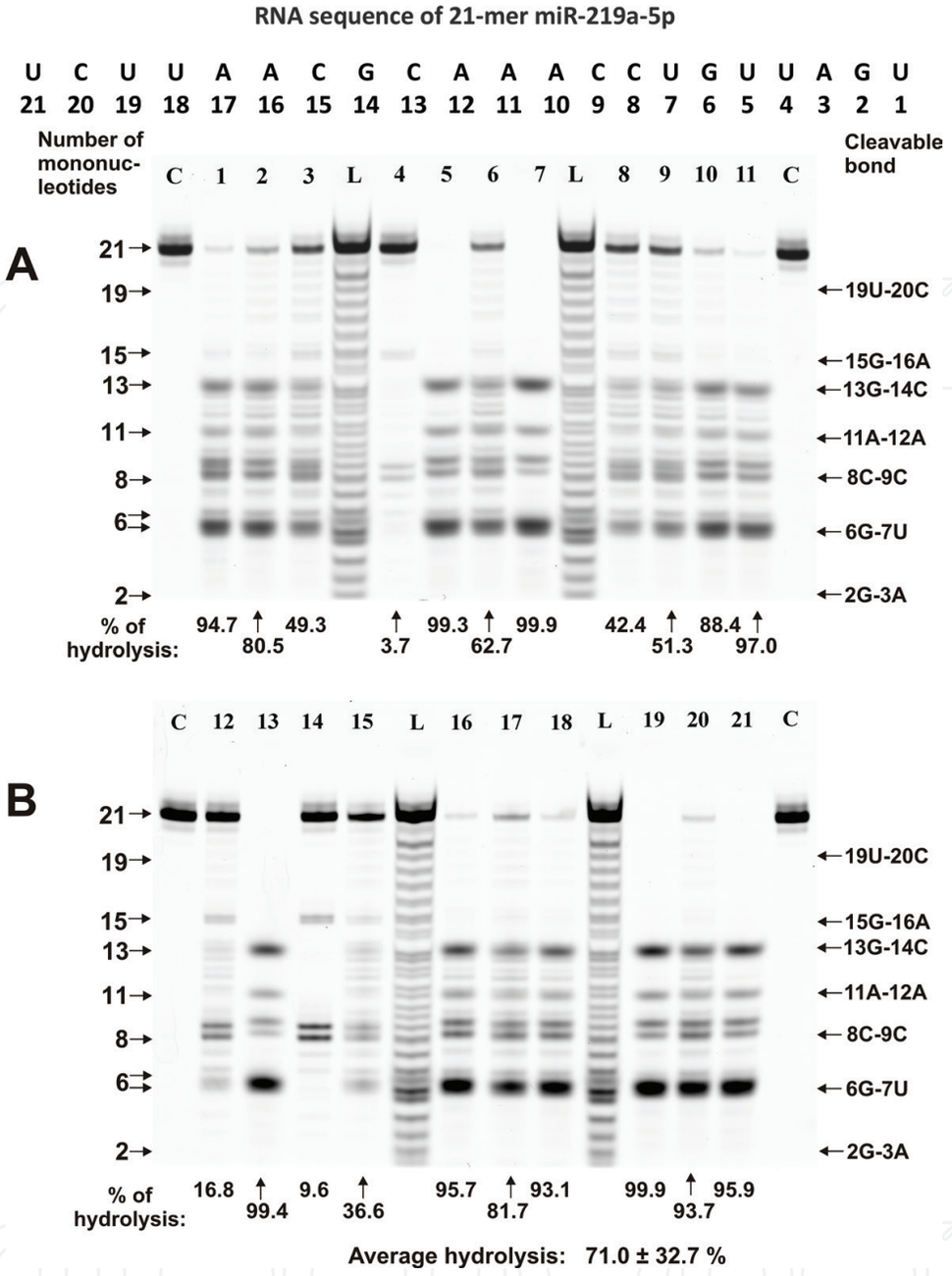


Figure 4. The patterns of flu- miR-219a-5p (0.01 mg/ml) hydrolysis by IgGs (0.1 mg/ml) from sera of 21 SCZ patients. The hydrolysis products were detected by their fluorescence due to the fluorescent residue (flu) on their 5′-ends. The numbers of antibodies, lengths of the products, and the percentage of microRNA hydrolysis by each preparation are indicated in panels A and B.

k_{cat} = 0.14 ± 0.009 min^{-1}; miR-9-5p, K_m = 2.4 ± 0.13 μM, k_{cat} = 0.083 ± 0.003 min^{-1}; miR-219-2-3p. K_m = 1.7 ± 0.12 μM, k_{cat} = 0.10 ± 0.008 min^{-1}; miR-219a-5p K_m = 4.5 ± 0.2 μM, k_{cat} = 0.17 ± 0.02 min^{-1}.

Many anti-DNA Abs are directed against histone-DNA nucleosomal complexes appearing from internucleosomal cleavage during apoptosis [62]. In addition, cell apoptosis leads to the increase in blood the concentration of different nucleases, RNA and its complexes with various

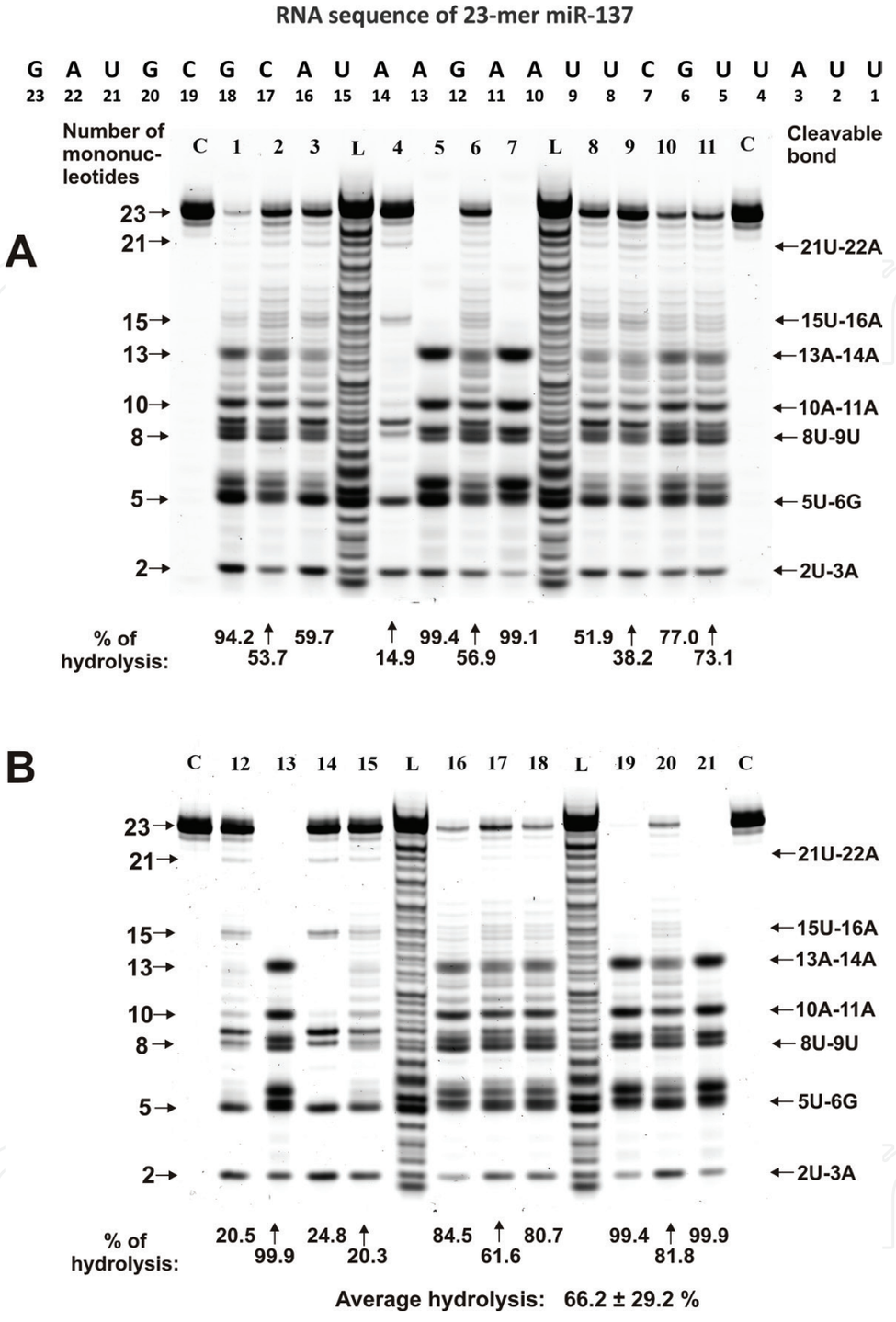


Figure 5. The patterns of Flu-miR-9-5p (0.01 mg/ml) hydrolysis by IgGs (0.1 mg/ml) from sera of 21 different SCZ patients. The hydrolysis products were detected by their fluorescence due to the fluorescent residue (Flu) on their 5′-ends. The numbers of antibodies, lengths of the products, and the percentage of microRNA hydrolysis by each preparation are indicated in panels A and B.

proteins. It was shown that the formation of DNA- and RNA-hydrolyzing Abs occurs after immunization of rabbits with RNA, DNA, DNase I, DNase II, and pancreatic RNase [92–96]. In addition, several monoclonal IgGs against B-DNA of different sequences (from SLE mice) efficiently hydrolyze ss- and dsRNA and DNA in a sequence-independent manner and the

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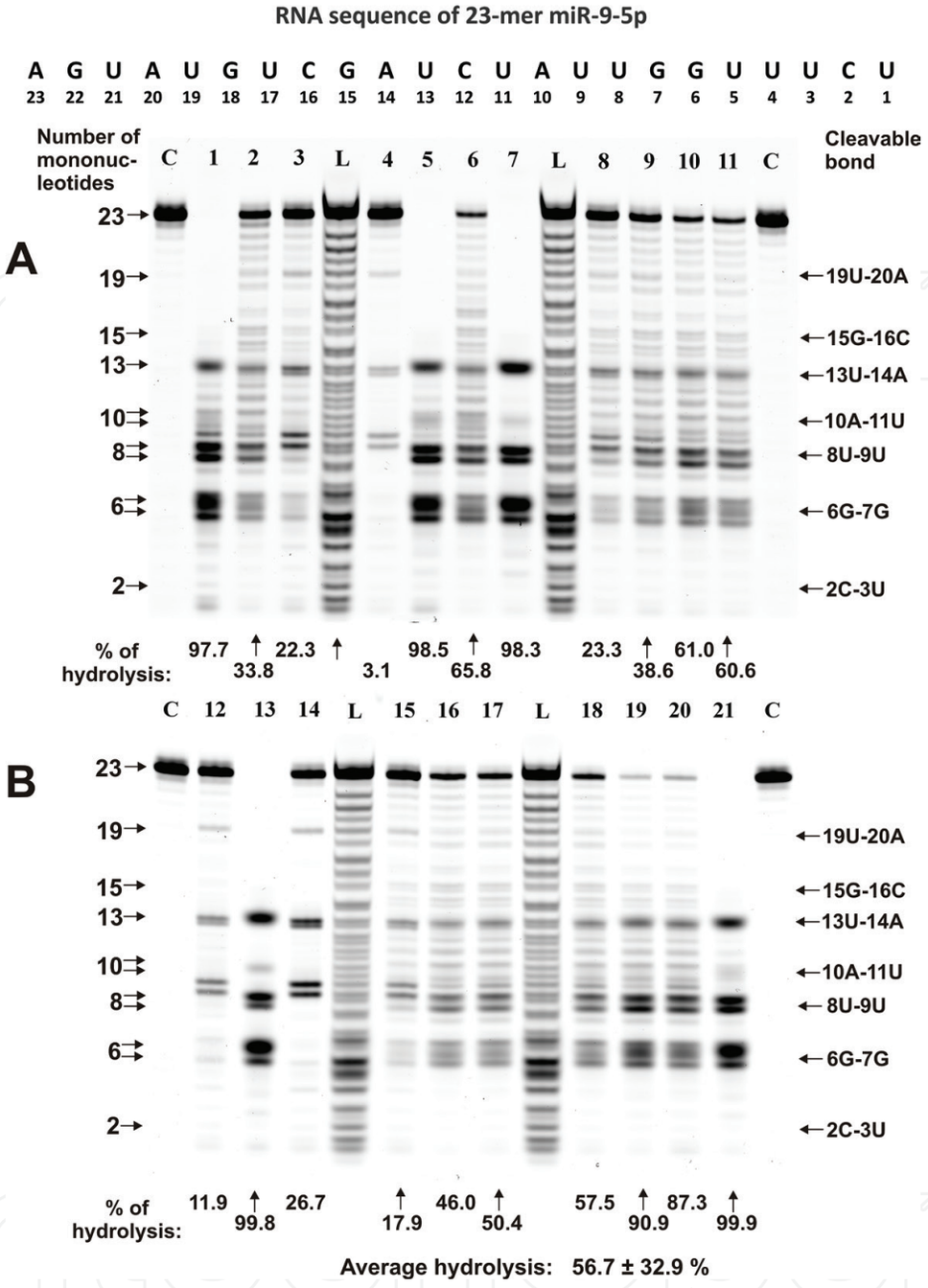


Figure 6. The patterns of Flu-miR-137 (0.01 mg/ml) hydrolysis by IgGs (0.1 mg/ml) from sera of 21 different SCZ patients. The hydrolysis products were detected by their fluorescence due to the fluorescent residue (Flu) on their 5′-ends. The numbers of antibodies, lengths of the products, and the percentage of microRNA hydrolysis by each preparation are indicated in panels A and B.

RNase activity was by a factor of 30–100 higher than that of DNA [97]. Thus, DNase and RNase abzymes can appear in the blood of autoimmune patients due to several very different ways. Since IgGs hydrolyze different homo-polynucleotides and cleavage of four microRNA is site-specific (**Figures 4–8**), one can assume that some sets of RNase abzymes may be specific for some RNAs, while others are not.

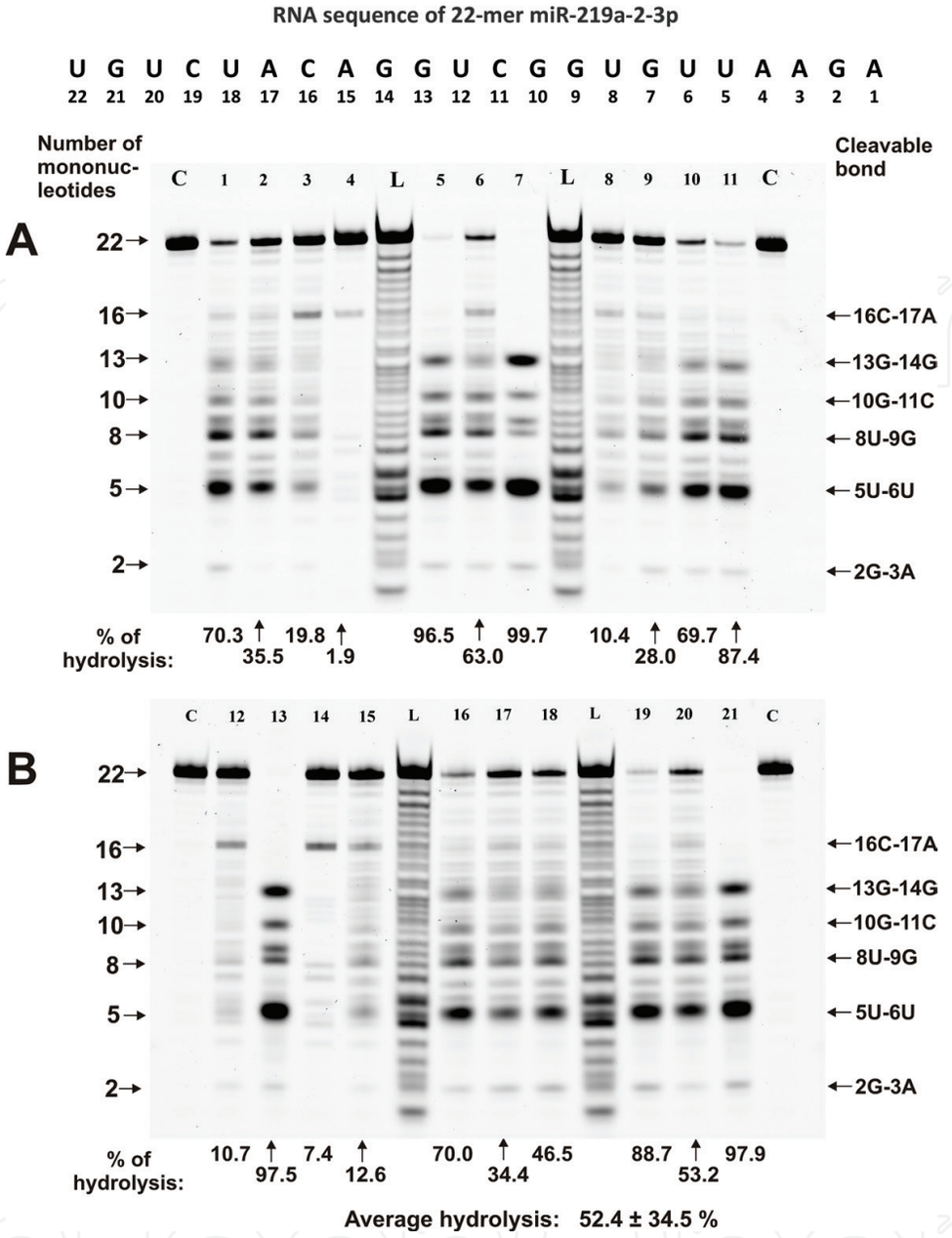


Figure 7. The patterns of Flu-miR-219a-2-3p (0.01 mg/ml) hydrolysis by IgGs (0.1 mg/ml) from sera of 21 different SCZ patients. The hydrolysis products were detected by their fluorescence due to the fluorescent residue (Flu) on their 5′-ends. The numbers of antibodies, lengths of the products, and the percentage of microRNA hydrolysis by each preparation are indicated in panels A and B.

It was shown that 90–95% of Abs SLE and MS patients effectively hydrolyze DNA [47–56]. It was shown that a very high percent IgGs of SCZ patients (80–82%) are active the hydrolysis of DNA [83]. At the same time, similar to SLE and MS [47–56], all 100% schizophrenia IgGs effectively hydrolyze different RNAs [91]. It was shown previously that the appearance of abzymes hydrolyzing DNA and RNA is among the clear and earliest signs of autoimmune reactions [47–56]. In addition, light chains of IgGs from schizophrenia patients are similar to

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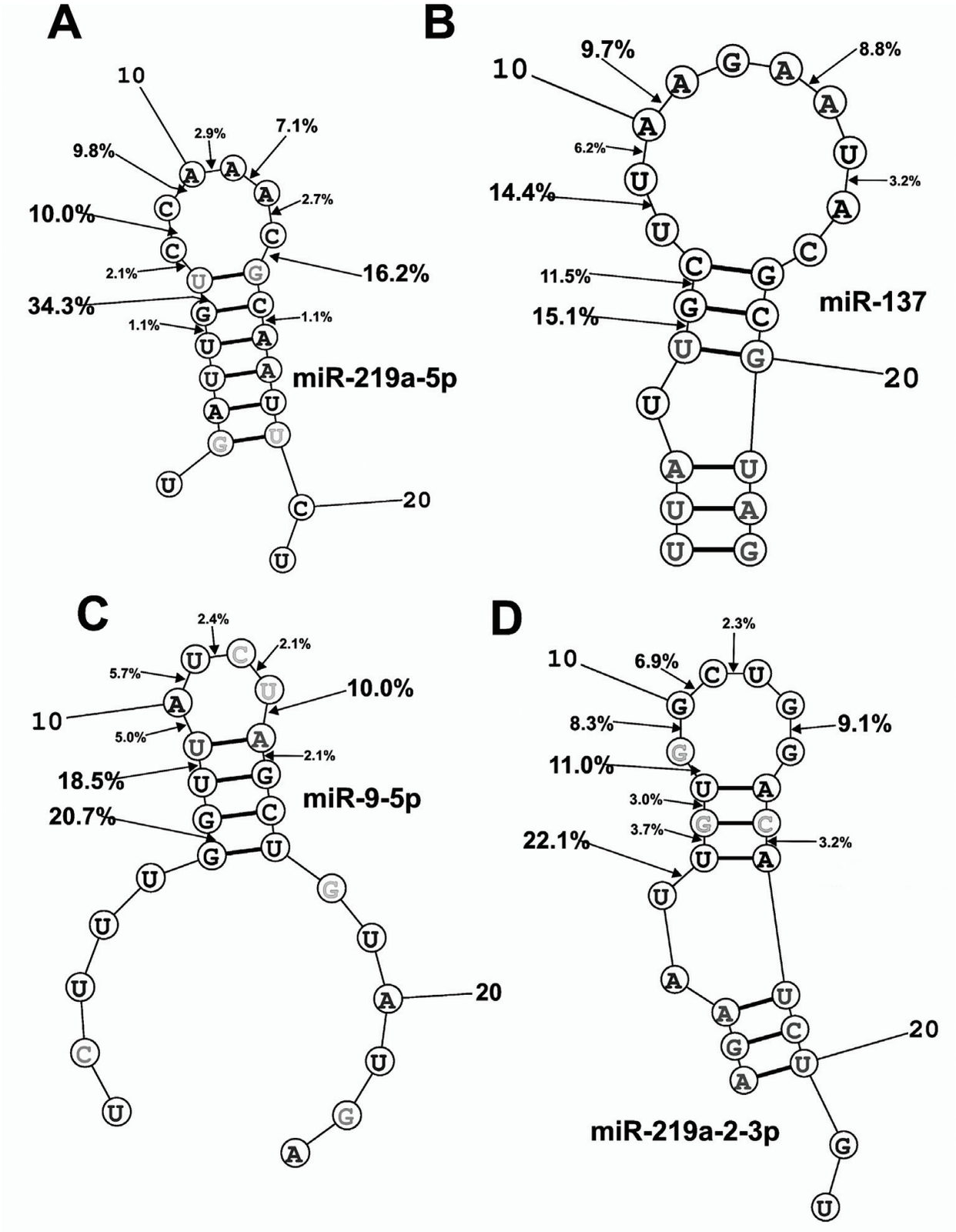


Figure 8. The average efficiency of four micro-RNAs hydrolysis by 21 IgG preparations in all sites of their cleavage (A–D). The position of major and moderate sites of different RNAs hydrolysis is shown.

those of SLE patients, but not to these chains of healthy donors [83]. These data indicate that in patients with SCZ similar to SLE, MS, and other AIDS, there is a trespassing of the immune system leading to the production of abzymes with DNase and RNase activities.

5. Hydrolysis of myelin basic protein

Serum anti-MBP Abs in MS and SLE patients were reported in several articles [75, 76, 79–81, 98, 99]. The relative levels of antibodies against MBP in the sera of 28 patients with SCZ and 15 healthy donors were compared by ELISA (**Table 2**). The concentrations of auto-Abs against MBP for healthy donors were not zero and changed from 0.02 to 0.16 A_{450} units, in average 0.09 ± 0.04 A_{450} units [75, 76, 79–81, 100, 101]. Relative indexes of anti-MBP Abs for 28 SCZ patients varied from 0.04 to 0.26 A_{450} units, in average 0.16 ± 0.068 A_{450} units. For patients with positive symptoms of SCZ, average value (0.18 ± 0.066 A_{450} units) was 1.3-fold higher than that for patients with negative symptoms (0.14 ± 0.067 A_{450} units), but this difference was statistically

Number of patients (Sex)	**Abs to MBP, A_{450}/ml**	**Relative % of hydrolysis**	**$k_{cat} \times 10^3$, min^{-1}**
	Positive symptoms of SCZ		
	Parameters 1	**Parameters 2**	
1 (M)	0.32*	10.5**	9.8***
2 (M)	0.24	50.0	46.8
3 (M)	0.13	20.5	19.2
4 (M)	0.07	0.5	0.5
5 (F)	0.13	1.0	1.0
6 (F)	0.18	18.5	17.3
7 (F)	0.15	15.0	14.0
8 (F)	0.09	0.5	0.5
9 (F)	0.17	17.5	16.4
10 (F)	0.20	4.5	4.2
11 (F)	0.18	15.0	14.0
12 (M)	0.14	0	0
13 (F)	0.20	0	0
14 (M)	0.26	0	0
Average value	0.18 ± 0.066	11.0 ± 13.7	10.3 ± 12.9
	Negative symptoms of SCZ		
	Parameters 3	Parameters 4	
15 (M)	0.17*	50.0**	46.8***

Number of patients (Sex)	Abs to MBP, A_{450}/ml	Relative % of hydrolysis	$k_{cat} \times 10^3$, min^{-1}
	Positive symptoms of SCZ		
	Parameters 1	**Parameters 2**	
16 (M)	0.19	49.5	46.3
17 (F)	0.22	13.5	12.6
18 (M)	0.17	47.0	44.0
19 (M)	0.08	50.0	46.8
20 (F)	0.04	25.0	23.4
21 (F)	0.17	10.5	9.8
22 (M)	0.26	14.0	13.1
23 (F)	0.03	26.5	24.8
24 (M)	0.11	6.5	6.1
25 (F)	0.18	43.5	40.7
26(F)	0.16	43.5	40.7
27 (F)	0.08	0.0	0.0
28 (M)	0.12	0.0	0.0
Average value	0.14 ± 0.067	27.1 ± 19.6	25.4 ± 18.4
Correl. coefficient	Parameters 1 and 2 (0.28), Parameters 3 and 4 (0.10); Parameters 1 + 3 and 2 + 4 (0.04)		

*For each value, a mean of three measurements is reported; the error of the determination of values did not exceed 7–10%.

**Average values are reported as mean ± S.E; they were recalculated to standard conditions and complete hydrolysis of 0.33 mg/ml MBP after 5 h of incubation in the presence of 0.1 mg/ml IgG was taken for 100%.

***The average apparent k_{cat} values in the reaction of MBP hydrolysis were calculated using average RA values (% of the hydrolysis at fixed concentration of MBP**): k_{cat} = V (M/min)/ [IgGs] (M).

Table 2. Numbers of SCZ patients, their sex, and relative characteristics of patients antibodies.

insignificant ($P = 0.27$). Using the same approach and test system, it was previously shown that average index of anti-MBP antibodies for 25 MS patients is 0.8 ± 0.1 A_{450} units [79] and, for SLE patients, it is 0.38 ± 0.08 A_{450} units [75]. Thus, all SCZ patients analyzed by us demonstrated ~1.8-fold higher level of serum anti-MBP Abs than healthy individuals, but ~2.4-fold and 5.0-fold lower level than SLE and MS patients, respectively.

Electrophoretically and immunologically homogeneous polyclonal IgGs were separated from the sera of 28 SCZ patients and 15 healthy donors as described above. The homogeneity of the 150 kDa scz-IgG_{mix} and healthy-IgGmix (mixtures of equal amounts IgGs from the sera of 28 SCZ patients and 15 healthy volunteers, respectively) was confirmed by SDS-PAGE similar to [83] **Figure 1A**.

We have applied several of known rigid criteria described above. The most important of these criteria are given below: (1) electrophoretic homogeneity of scz-IgG_{mix} (**Figure 1A**); (2) complete

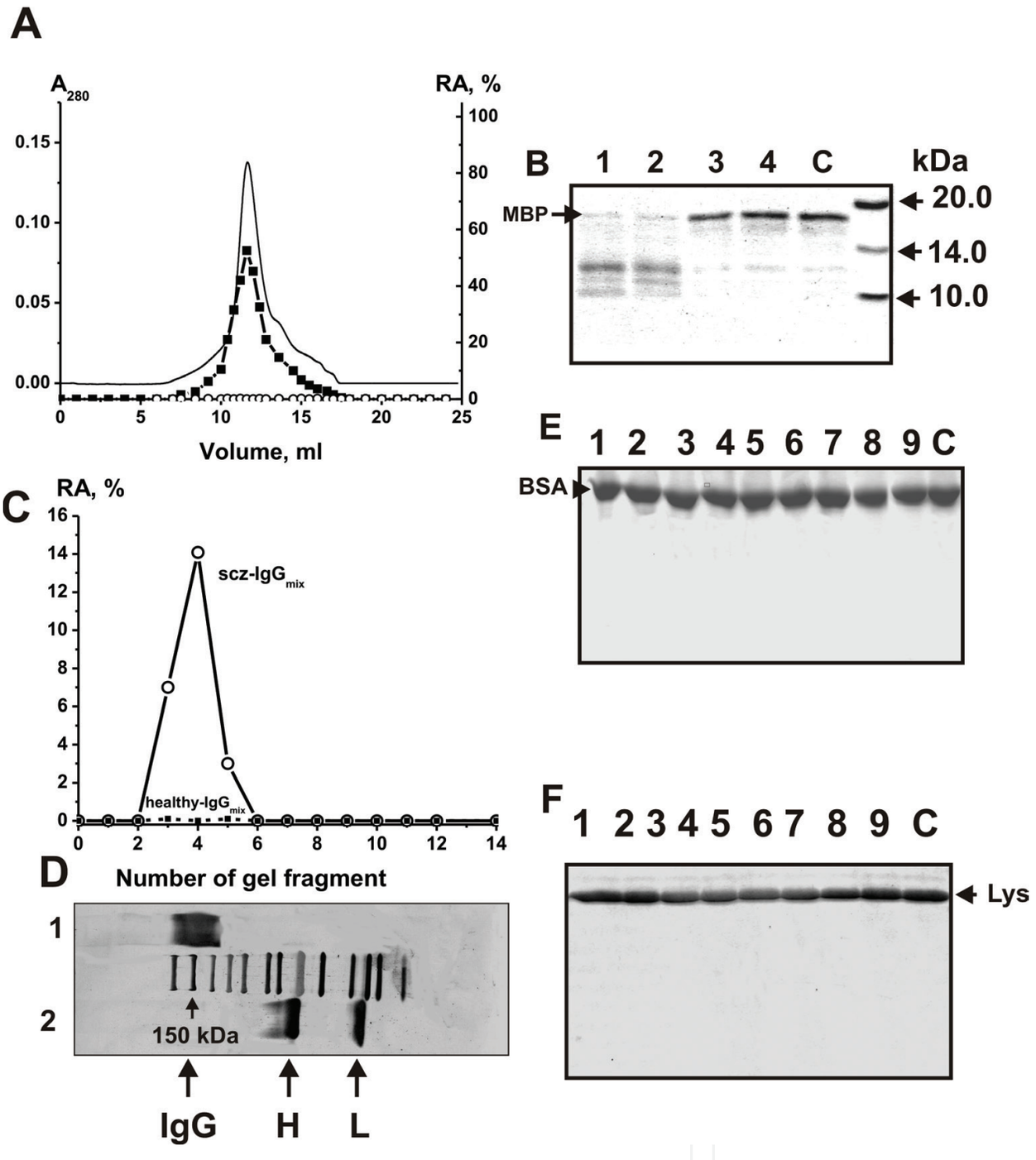


Figure 9. FPLC gel filtration of scz-IgG_{mix} on a Superdex 200 column in an acidic buffer (pH 2.6) after IgGs pre-incubation in the same buffer (A): (—), absorbance at 280 nm (A_{280}); (■), relative activity (RA, %) of IgGs in the hydrolysis MBP. A complete hydrolysis of MBP for 5 h was taken for 100%. Assay of MBP-hydrolyzing activity of purified scz-IgG_{mix} after SDS-PAGE in gradient 4-15 % gel, the gel was incubated under special conditions for renaturation of Abs (B). MBP (0.4 mg/ml) was incubated with 0.1 mg/ml scz-IgG_{mix} for 24 h (lane 1) or scz-IgG-1 (lane 2) and with healthy-IgG_{mix} (lane 3) or individual healthy-IgG-1 (lane 4), as well as in the absence of Abs (lane C). The RA (%) was revealed using the extracts of 2-3-mm many fragments of one longitudinal slice of the gel (C). The second control longitudinal slices of the same gels corresponding to IgG_{mix} before (lane 1) and after (lane 2) treatment with DTT were stained with Coomassie R250 (D). Analysis of possible hydrolysis of bovine serum albumin (BSA) (E) and hen egg lysozyme (Lys) (F) by scz-IgG_{mix} purified on MBP-Sepharose (lanes 1). Lanes 2-9 correspond to nine individual scz-IgGs, while lanes C to the proteins incubated in the absence of Abs (E and F).

adsorption of IgG_{mix} hydrolyzing MBP by anti-IgG Sepharose leading to a disappearance of the catalytic activity of the solution; (3) FPLC gel-filtration of scz-IgG_{mix} under conditions of "acidic shock" (pH 2.6) lead to revealing of the activity only in the peak corresponding exactly to 150 kDa IgGs (**Figure 9A**); (4) in contrast to scz-IgG_{mix}, healthy-IgG_{mix} did not hydrolyze MBP (**Figure 9B**); (5) Scz-IgG_{mix} purified on MBP-Sepharose hydrolyzed only MBP and was inactive in the hydrolysis of control proteins, bovine serum albumin (**Figure 9C**), and lactoferrin (**Figure 9D**); (6) scz-IgG_{mix} was separated by SDS-PAGE, and their MBP-hydrolyzing activity was estimated after the extraction of proteins from the separated gel slices (**Figure 9E** and **F**). The electrophoretic mobility of low molecular mass canonical proteases (24–25 kDa) cannot coincide with that of intact IgGs (150 kDa). Therefore, the detection of protease activity in the gel fragments corresponding only to intact IgGs together with the absence of any other proteins and activity bands (**Figure 9E** and **F**) provides direct evidence that SCZ IgGs possess MBP-hydrolyzing activity.

The RAs of SCZ IgGs in the cleavage MBP was estimated from the decrease in the intensity of Coomassie-stained MBP band after electrophoresis according to [76–81]. For quantitative estimation of the proteolytic activity, we have found a relatively low concentration of each IgG sample (0.05–0.3 mg/ml) corresponding to the reaction of the first order (1–24 h; 15–45% of conversion). This approach allowed us to normalize the relative activity, like in the case of determination of the specific activity of enzymes [102], to standard condition; relative % of MBP hydrolysis after incubation for 5 h in the presence of 0.1 mg/ml (0.66 μM) IgGs.

Among 28 individual SCZ patients, the RAs of IgGs at a fixed concentration of MBP (0.33 mg/ml) were absent for five patients (17.9%): 3 of 14 patients (21.4%) with positive symptoms and 2 of 14 patients (14.3%) with negative symptoms (**Table 1**). The average relative activity (RA, %) and apparent k_{cat} values (k_{cat} = V/[IgG]) at fixed concentration of MBP (0.33 mg/ml; 18.3 μM) were calculated (**Table 2**). The apparent k_{cat} values characterizing hydrolysis of MBP by 14 IgGs of patients with positive symptoms varied in the range 0–46.8 × 10^{-3} min^{-1} (average 10.3 ± 12.9) × 10^{-3} min^{-1}; M = 0.7 × 10^{-3}, IQR = (0.5–16.4) × 10^{-3}). The apparent k_{cat} values for 14 IgGs of patients with negative symptoms also varied in the range 0–46.8.0 × 10^{-3} min^{-1} (average (25.4 ± 18.4) × 10^{-3} min^{-1}; M = 24.1 × 10^{-3}, IQR = (9.8–44.0) × 10^{-3}). Overall, the average k_{cat} value of IgGs from patients with negative symptoms was approximately 2.5-fold higher than that for Abs of patients with positive symptoms (**Table 2**). The coefficient of correlation (CC) between the anti-MBP Abs titers (A_{450}) and RAs of 28 Abs was very low, 0.04. At the same time, CC for these values in the case of patients with positive symptoms (0.28) was 2.8-fold higher than that for patients with negative symptoms (0.10) (**Table 2**). According to Wald-Wolfowitz test, there is a statistically significant difference between k_{cat} value of IgGs from patients with negative and positive symptoms (P = 0.034). Interestingly, the CC (0.7–0.79) between the anti-MBP Abs titers (A_{450}) and RAs of Abs from SLE patients [8] was significantly higher than for SCZ patients.

It has been recently shown that abzymes against MBP from the sera of MS patients hydrolyze MBP at several clustered sites localized within four known antigenic determinants of human MBP and that four oligopeptides corresponding to these determinants of MBP are encephalytogenic and can play a negative role in the MS pathogenesis [79–82]. It is important that anti-MBP abzymes from the sera of SLE, MS, and SCZ patients hydrolyze MBP at the same four

sites of antigenic determinants and effectively cleavage all four 17–25-mer OPs corresponding to these four determinants [75–80]. It was shown, that anti-MBP abzymes of SCZ patients can also cleavage these four OPs: OP21 and OP25 were the best substrates of SCZ abzymes.

We have estimated the K_m and k_{cat} values for the hydrolysis of MBP, OP21 (YLASASTM-DHARHGFLPRRHR) and OP25 (AQGTLSKIFKLGGRDSRSGSPMARR) in the case of two individual preparations of SCZ patients. The initial rate data obtained at increasing MBP, OP21, and OP25 concentrations were consistent with the Michaelis-Menten kinetics. Different abzymes usually demonstrate a significantly higher affinity to substrates in comparison with canonical proteases [45–56]. The affinity of intact MBP for SCZ IgGs was (in terms of K_m values) in the range of 4.3–12.4 μM (**Table 2**), which corresponds to typical K_d (and K_m) values for Ab-antigen interactions. These K_m values for MBP of SCZ abzymes are to some extent comparable with the K_m for MBP (~0.6–2.7 μM) reported previously for IgGs from SLE [75–78] and MS (0.9–5.0 μM) [81] patients. Interestingly, the K_m values for scz-IgGs in the case OP21 and OP25 (49–770 μM) are to some extent lower compared with those for four OPs in the case of SLE. As it mentioned above, a detectable level of MBP-hydrolyzing abzymes was shown to be as an indicator of pre-disease, while increase in the activity of obvious pathology conditions of typical spontaneous or induced autoimmune diseases [63–68].

It was shown that DNase and RNase abzymes of autoimmune patients present a "cocktail" of Abs directly to DNA and RNA or their complexes with proteins and anti-idiotypic Abs against active centers of DNase I, DNase II, RNase and other enzymes hydrolyzing nucleic acids [92–96]. MBP-hydrolyzing Abs are produced from animals immunization with MBP and its encephalytogenic peptides [66–68]. In addition, immunization of experimental autoimmune encephalomyelitis (EAE) mice, a model of human MS, with myelin oligodendrocyte glycoprotein ($MOG_{35–55}$) leads to the production of both MBP- and DNA-hydrolyzing abzymes [66–68].

6. Abzymes with oxidation-reduction activities

Several publications show that some abzymes may form not only in patients with autoimmune pathologies but also in healthy humans. However, it is not currently clear which antigens can stimulate the formation of these abzymes in autoimmune patients and healthy donors.

Human organisms are constantly exposed to oxidative stress and various toxic components. The partially reduced oxygen species (O^{2-}, H_2O_2, and $OH^{\bullet}$) produced in all higher organisms and appeared in bodies through exposure to different compounds to ionizing radiation. They act as dangerous oxidants attacking lipids, proteins, DNA, and other different cellular components [103–107]. Oxidative damage of many cells has been considered as a very important pathophysiological factor in the development of many different diseases such as carcinogenesis, aging, multiple sclerosis (MS), and SCZ. It is believed that MS and SCZ have different pathogenetic mechanisms. MS is a neurodegenerative chronic disease of AI nature, associated with structural damage to the nerve fibers myelin sheath, while SCZ has neurotransmitter nature. It was, however, demonstrated that the oxidative stress activation is a major factor in the MS and SCZ [108–114]. In the case of SCZ, the cellular metabolism changes associated with alteration in the activity of enzymes including antioxidant enzymes were revealed [109, 112].

Several enzymes protecting various organisms from oxidative stress are known. Mammalian, plant, and bacterial peroxidases, glutathione peroxidases, oxidoreductases, oxidases, and dismutases are mostly metal ions-dependent enzymes [107, 115–118]. Metal ions having the variable valence (more often: Fe_{2+}, Cu^{2+}, and Mn^{2+}) participate in a transfer of electrons in the reactions of oxidation-reduction, catalyzed by enzymes [118].

A comparison of catalase, superoxide dismutase, H_2O_2-dependent peroxidase, and H_2O_2-independent oxidoreductase activities of polyclonal IgGs obtained from the sera of healthy Wistar rats have been carried out [119]. Approximately, 83% of IgGs possess superoxide dismutase activity, but all IgGs oxidized 3,3′-diaminobenzidine in the presence (peroxidase activity) and the absence of hydrogen peroxide (oxidoreductase activity). Only 17% of rat IgGs were shown to possess catalase activity. It was shown that small fractions of IgGs and their $F(ab)_2$ and Fab fragments of IgGs from sera healthy humans oxidize 3,3′-diaminobenzidine in the presence of H_2O_2 through a peroxidase and in the absence of H_2O_2 through an oxidoreductase activity [120, 121].

It was shown that some electrophoretically homogeneous IgGs (and their F(ab) and $F(ab)_2$ fragments) from the sera of patients with SCZ (36.4%) and from healthy donors (33.3%) possess catalase activity [122]. As in the case of the abzymes described above, it was shown that the catalase activity of all IgGs is their intrinsic property (**Figure 10**). The catalase RA of IgGs from the sera of individual of SCZ patients on average was 15.8-fold higher than that of healthy volunteers. After extensive dialysis against EDTA chelating metal ions of IgGs, the catalase RA of IgGs, on average decreases approximately 2.5–3.7-fold; all IgGs possess metal-independent and dependent catalase activity.

External Me^{2+} ions added to non-dialyzed and dialyzed IgGs significantly increase their activity (**Figure 11**). $Co^{2+}$is the best activator of non-dialyzed and dialyzed IgGs, the activation of IgGs by Mn^{2+}, Cu^{2+}, and Ni^{2+} ions is substantially lower than by Co^{2+}. All IgGs demonstrate several individual different expressed pH optima in the pH range from 4.0 to 9.5. These data speak for the individual repertoire of catalase IgGs in every person and an extreme diversity of abzymes in their pH optima and activation by different metal ions.

In this connection, it should be marked that polyclonal IgGs against different antigens from the blood sera of patients with AI diseases and with different activities are usually very heterogeneous in their affinity for specific antigens and can be separated into many subfractions by chromatography on antigens-Sepharoses [75, 76, 79, 123]. Pools of polyclonal abzymes can contain different proportions of light chains of κ- and λ-types, Abs demonstrating different pH optima, having different net charges, metal-independent or activated by different metal ions, and characterized by different substrate affinities and specificities [17, 39–43, 124]. It was shown that small fractions of IgGs of all four subclasses (IgG1–IgG4) from autoimmune patients are catalytically active in the hydrolysis of different substrates [47–56]. For analysis of myelin basic protein- and DNA-hydrolyzing activities of monoclonal light chains (MLChs) corresponding to SLE phagemid library of kappa MLChs were used [125–129]. It was shown that some hundreds of different monoclonal light chains hydrolyze DNA and other ones cleavage myelin basic protein; all MLChs demonstrated very different physicochemical and enzymatic properties [125–129]. It should be assumed that the extraordinary diversity of these

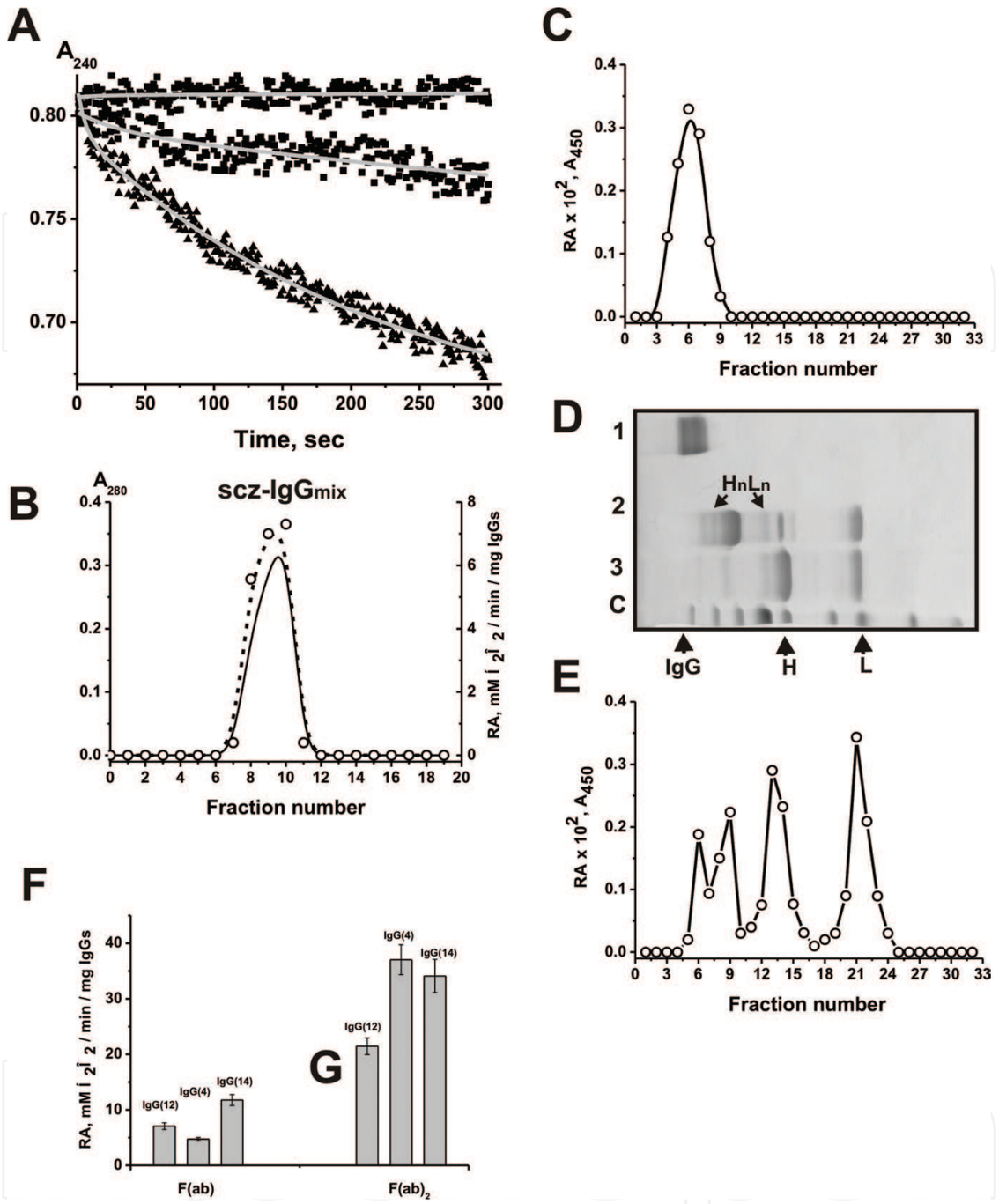


Figure 10. Typical time-dependencies of the decrease in 30 mM H_2O_2 absorbance at 240 nm (A_{240}) in the presence of 200 nM IgG-1 and IgG-11 as well as 2 nM IgG-8 corresponding to different individual patients (A). Checking of strict criteria proving that the catalase activity is intrinsic properties of scz-IgG_{mix}. Preparations of scz-IgG_{mix} (equimolar mixture of 22 samples) were separated by FPLC gel filtration on a Superdex 200 column in an acidic buffer Gly-HCl pH 2.6 after Abs pre-incubation using the same buffer (B): (o), relative activity (RA) of the IgG_{mix} in the degradation of H_2O_2; (—), absorbance at 280 nm (A_{280}); SDS-PAGE analysis of catalase activity of intact scz-IgG_{mix} (C) as well as separated H, L chains and their L_nH_n oligomers (E) in non-reducing SDS-PAGE using gradient 4–15%: Scz-IgGmix before (C) and after treatment of IgG_{mix} with DTT (E); lane 1 of panel D corresponds to panel C and lane 2 to panel E. The RAs (A_{240}/min) were revealed using the extracts of 2–3-mm fragments of one gel longitudinal slice of corresponding IgG_{mix} before (C) and after treatment with DTT (E). The control longitudinal slices of the same gels were stained with Coomassie R250 (D): lane 1 corresponds to intact IgG_{mix}, lane 2 to IgG_{mix} incubated with 40 mM DTT for 10 min at 30° C, lane 3 to IgG_{mix} boiled with DTT. Lane C (D) shows the positions of molecular mass standard markers. The relative activity of F(ab) and $F(ab)_2$ fragments of individual IgG-4, IgG-12, and IgG-14 (F). The average error of the initial rate determination from two experiments did not exceed 10–15%.

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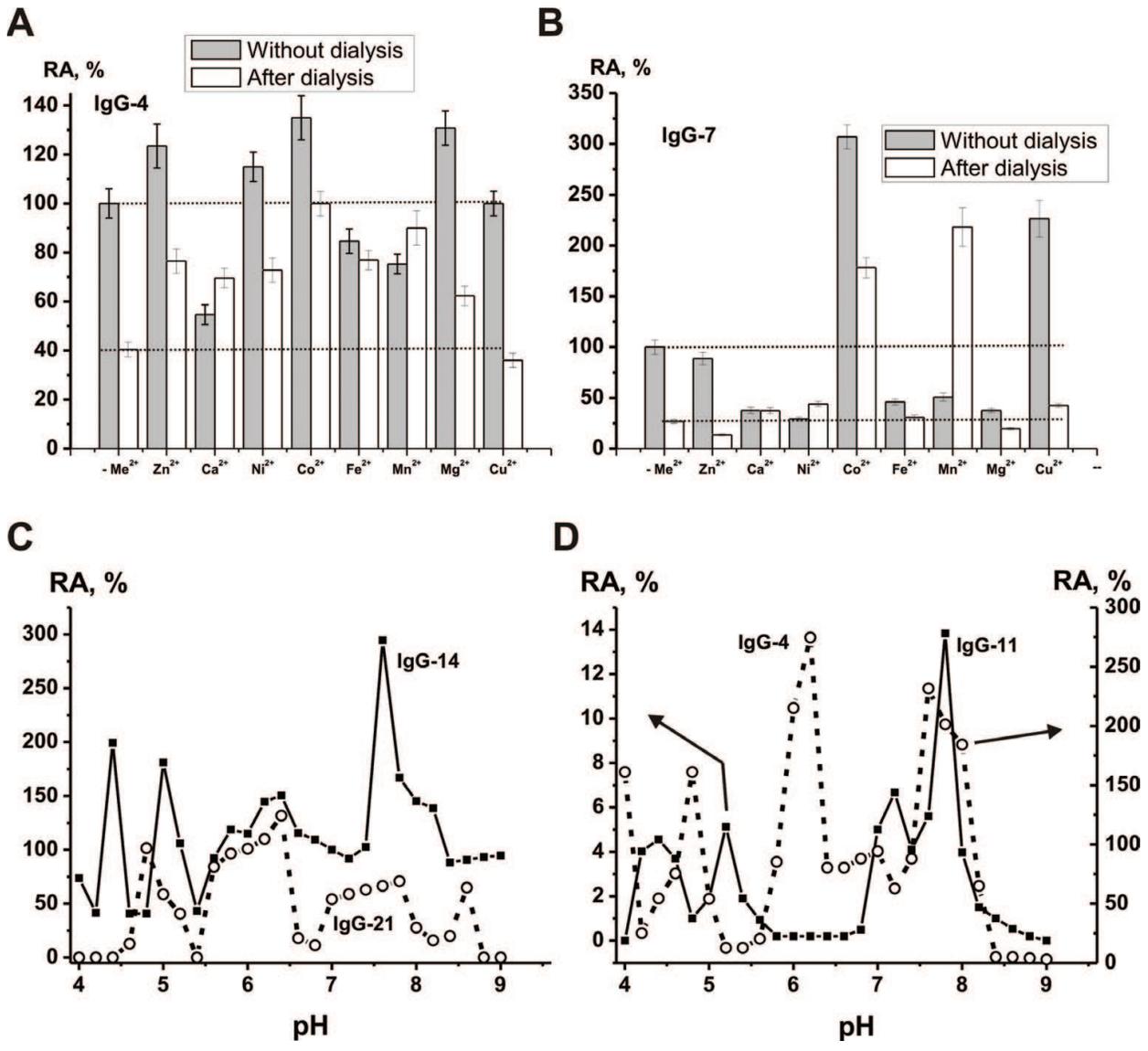


Figure 11. Effect of the dialysis of IgGs against EDTA for two individual scz-IgGs and different metal ions on the relative activity (RA, %) of dialyzed and non-dialyzed preparations (A and B). The RA of every non-dialyzed preparation was taken for 100%. Dependencies of the relative catalase activity of scz-IgGs on pH of the reaction mixture (C and D). All RAs of Abs before its preincubation were taken for 100%. The relative activity of IgG-14 at pH 7.0 was taken for 100%. All IgG preparations, metal ions, and conditions used marked on panels A–D. The errors in the determination of initial rate from three experiments in each case did not exceed 7–10%.

monoclonal light chains is mainly due to the significant differences in their variable regions responsible for substrate specificity and catalysis [125–129]. Heterogeneity is also observed in intact catalytic IgGs with kappa light chains, and it was shown that structural diversity (heterogeneity) might exist due to the constant region domain and specific role of metal ions of the catalytic light chains [130, 131]. A similar result of extreme catalytic heterogeneity is observed for abzymes with catalase activity.

It has been shown that immunoglobulins from humans and various animals have superoxide dismutase activity; they convert singlet oxygen $^1O^2$ into its reduced form $O^{2\bullet}$ [132, 133]. These abzymes use H_2O as an electron source and attach it to $^1O^{2*}$ to form H_2O_3 as the first intermediate of several consecutive stages leading to the formation of H_2O_2. These data are believed to

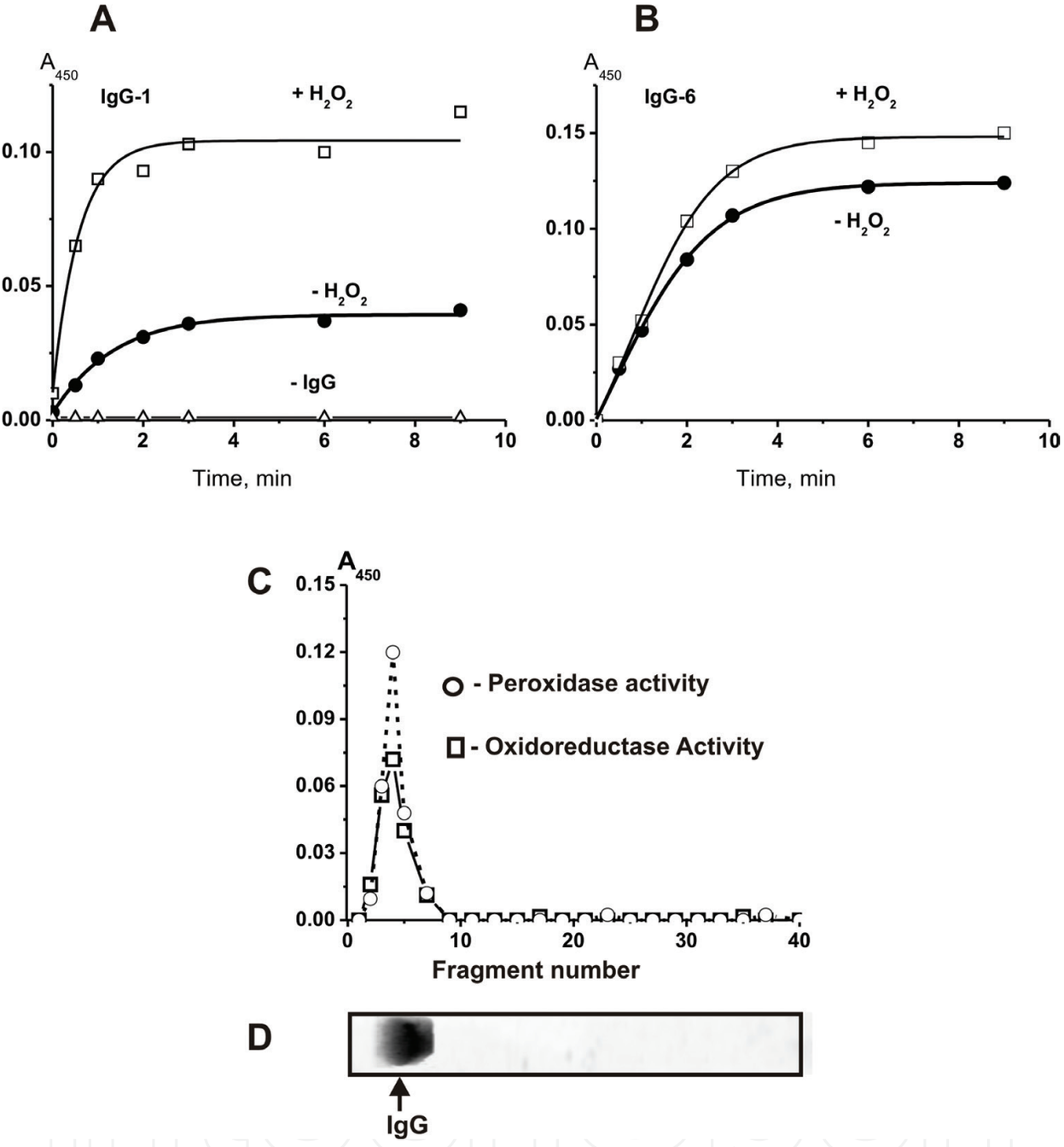


Figure 12. Typical kinetic curves of accumulation of a colored product (A_{450}) after DAB substrate oxidation by IgGs with peroxidase (in the presence of H_2O_2) (A) and with oxidoreductase (in the absence of H_2O_2) (B); activities in the oxidation of 3,3′-diaminobenzidine (0.2 mg/ml) in the case of 670 nM IgG-1 and IgG-6. Curve - IgG corresponds to the oxidation of the substrate in the absence of IgGs. SDS-PAGE analysis of peroxidase (o) and oxidoreductase (□) activities of IgG_{mix} (20 μg) (C and D). After electrophoresis, the 4–15% gradient gel was treated using special conditions for renaturation of IgG_{mix}. The RAs were evaluated using extracts of 40 gel fragments (2–3 mm); 20 μl of extracts were added to the standard mixtures and incubated for 24 h. The second band of the same gel was used to determine the position of intact IgG_{mix} (D); the gel was stained with Coomassie R250.

indicate the possibility of protecting mammalian organisms from $^1O^{2*}$ with Abs and raise the question of the possibility of a special evolution of immunoglobulins as a specific antioxidants of blood [132, 133]. For immunoglobulins, a mechanism has been discovered by which oxygen can be recovered and reused in phagocytosis, which indicates the possibility of the

involvement of the immune system in microbial regulation. Even more surprising is the discovery of abzymes of higher eukaryotes that catalyze the formation of ozone used by cells in phagocytosis [134]. Taking this into account, one can put that Abs with superoxide dismutase activity can catalyze the conversion of the superoxide radical into hydrogen peroxide, and the abzymes with catalase activity neutralize the harmful effect of H_2O_2.

It was shown that IgGs from the blood of healthy Wistar rats possess high H_2O_2-dependent peroxidase (hereinafter peroxidase) and H_2O_2-independent oxidoreductase (hereinafter oxidoreductase) activities in the oxidation of horseradish peroxidase substrate—3,3′-diaminobenzidine and some other aromatic amines, phenols, and quinones [135–138]. Interestingly, the same activities were detected in IgG from the blood of healthy people [120, 121]. The relative peroxidase activity of IgG of healthy people in the absence of external metal ions varies very much from donor to donor, but on average, it is about five times lower than in rat IgGs [120, 121].

Electrophoretically and immunologically homogeneous preparations of IgG antibodies were isolated from blood sera of 18 patients with SCZ and 14 healthy donors by affinity chromatography on Protein G-Sepharose followed by high-efficiency gel filtration as described above. Using rigid criteria, it was shown that the oxidation of substrates is an intrinsic property of these polyclonal antibodies (**Figure 12**). The comparison of H_2O_2-dependent peroxidase and H_2O_2-independent oxidoreductase activities of IgGs of SCZ patients and healthy donors in the oxidation of 3,3′-diaminobenzidine was carried. All IgG preparations of SCZ patients and healthy donors had these activities, but the apparent k_{cat} values varied in a very wide range (16.2–355.8 min^{-1}).

On average, the rate of oxidation of the substrate in the presence of H_2O_2 from the sera of SCZ patients and healthy donors was 1.3–1.5 times higher than in the absence of H_2O_2. The difference between the average peroxidase (1.8-fold) and oxidoreductase (1.5-fold) IgG activity from the sera of SCZ patients and healthy donors was statistically significant ($P = 0.008$). At the same time, the correlation coefficient of peroxidase and oxidoreductase activity of abzymes of SCZ patients was significantly higher (0.66) than for healthy donors (0.27).

The blood of healthy donors and patients with various autoimmune diseases including SLE and MS usually contains abzymes with amylase and ATPase activities [47–56]. In addition, the spontaneous and DNA-induced development of deep SLE-like pathology associated with a specific reorganization of the immune system in the case of autoimmune-prone MRL-lpr/lpr mice, leads to a production of IgGs hydrolyzing DNA, ATP, and polysaccharides [64, 65]. It was surprising that in the case of 18 patients with SCZ, amylase activity was detected only in IgG antibodies from one patient, but all 18 preparations were inactive in ATP hydrolysis. This indicates the possibility of the production of abzymes to various antigens in the case different autoimmune diseases.

7. Comparison of abzymes of patients with SCZ and other pathologies

It has been shown that antibodies hydrolyzing DNA, proteins, ATP, and polysaccharides can be considered the earliest and statistically significant markers of autoimmune pathologies in

human patients and experimental mice with autoimmune diseases [47–56, 64–69]. Abzymes are found already in the early stages of different diseases when there are no visible markers of specific AIDs, and changes in proteinuria, auto-antibodies titers correspond to typical ranges of these indicators for healthy individuals. The detection of abzymes is significantly more sensitive than the detectable ELISA markers since catalysis is characterized by the development of the reaction product due to a large number of enzyme turns and the possibility of increasing the catalyst turnover due to the increase in the reaction time. It makes possible to detect even small amounts of abzymes in preparations of polyclonal Abs with a relatively low but reliably tested activity.

Antibodies against DNA were detected in an increased concentration, compared with that in healthy donors, in only 17–18% of patients with MS and 37% of patients with SLE [57], while DNA-hydrolyzing Abs in 90–95% of patients with MS [74] and SLE [72, 73]. This is because the increase in auto-Abs titers in patients with AIDs occurs only in the late stages or with exacerbations of these diseases. Thus, reliable detection of abzymes, from our point of view, can be considered as an indicator of even a painful condition (the onset of pathology), and even more development of spontaneous or induced AIDS [47–56, 64–69].

To diagnose MS, a number of medical Poseur criteria are usually used [139, 140], but the final reliable diagnosis is made after the tomography showing "plaques" in the brain that appear in the late stages of the disease. The presence of anti-DNA Abs in patients with MS traditionally was considered only as one of the additional evidences of a system imbalance in immunoregulation, which has no independent pathogenetic significance. However, only anti-DNA Abs as the main component of the intracerebral IgG response was found directly in the brain plaques and the cerebrospinal fluid, and they bind to the surface of neuronal cells and oligodendrocytes [141]. These data were interpreted as evidence of the leading role of anti-DNA Abs in the pathogenesis of MS [141].

Despite the absence of signs that meet the criteria of Poseur, we assumed a preliminary diagnosis of the "initial stage of MS" in the case of three patients [69], since they demonstrated Abs with high DNase activity in their blood. Approximately 1.5 years later, the indicators of these patients began to meet the criteria of Poseur and after 2–3 years, the patients had "plaques" in the brain.

In this connection, it should be mentioned that the sera of healthy donors do not contain Abs with DNase, RNase, and MBP-hydrolyzing activities [47–56]. In addition, there were no detected abzymes with such activities in patients with weak autoimmune reactions. Currently, IgGs and/or IgAs and IgMs hydrolyzing DNA/RNA have been revealed in the sera of patients with SLE [72, 73, 142, 143], Hashimoto thyroiditis [144], diabetes mellitus [53], MS [74, 145, 146], tick-borne encephalitis [147], and HIV infection [148] demonstrating strong autoimmune reactions. As it was shown on the example of Hashimoto thyroiditis, the typical therapy of patients with thyroxine resulted only in a temporary change of the hormone concentration in the blood but did not affect the level of DNase abzymes. However, treatment of patients with an immunosuppressive drug Plaquenil leads to a significant decrease in DNase antibodies associated with an increase in concentrations of thyroid hormone, elevation of the thyroid gland functional activity, and improvement of the patient's clinical state [144].

It should be mentioned that the average concentration of Abs interacting with dsDNA for SCZ patients (0.25 ± 0.07 A_{450}/ml) is 2.5-fold higher than that for healthy donors (0.1 ± 0.02 A_{450}/ml), but lower than for MS (0.39 ± 0.26 A_{450}/ml) and SLE (0.66 ± 0.48 A_{450}/ml) patients [53–56]. At the same time, concentrations of anti-DNA antibodies in comparison with healthy donors are higher in 30% patients with SCZ, which is comparable with that for SLE patients (37%) [83]. In addition, 80% IgGs of SCZ patients possess detectable or high DNase activity. Moreover, all 100% of IgGs of SCZ patients have RNase activity, and they can hydrolyze not only different polynucleotides and cCMP, but also specific for this pathology microRNAs [83]. Thus, these data point to the development of autoimmune processes in patients with schizophrenia similar to those of classical AIDS: SLE and MS [83].

Interestingly, SCZ patients demonstrated ~1.8-fold higher level of serum anti-MBP Abs than healthy individuals, but ~2.4- and 5..50-fold lower than those for SLE and MS patients, respectively [75]. A feature people with MS and SLE is the development of abzymes hydrolyzing not only DNA, but also MBP and polysaccharides [75–82]. It was shown that IgGs from the sera and cerebrospinal fluid (CSF) of MS patients are active in the hydrolysis of MBP, DNA, and polysaccharides [149–151]. In contrast to healthy donors, Abs from the sera of 82% of patients with SCZ showed a reliably tested or high activity in the hydrolysis of MBP [100, 101]. As mentioned above, the researchers of the London medical Institute Oliver House advanced theory, according to which schizophrenia is the result of a lesion of immune system of the brain. The set forth above data reveals a number of similarities between SCZ and MS.

In this connection, it should be mentioned that development of SLE in autoimmune-prone MRL-lpr/lpr mice and changes in EAE-like (experimental autoimmune encephalomyelitis) parameters in C57BL/6 mice can occur spontaneously and may be accelerated by immunization of mice with DNA [63–65] or with MOG [66–68], respectively. It was shown that IgGs from the sera of control C57BL/6 mice are catalytically inactive. During spontaneous development of EAE, a specific reorganization of the immune system of mice occurred leading to a condition which was associated with the generation of catalytically active IgGs hydrolyzing MBP, MOG (myelin oligodendrocyte glycoprotein) and DNA. These processes are associated with increased proteinuria, changes in the differentiation of mice bone marrow hematopoietic stem cells and an increase in proliferation of lymphocytes in bone marrow, spleen, and thymus as well as a significant suppression of cell apoptosis in these organs. The strongest alterations were found after mice immunization with MOG. Thus, a significant increase in DNase and protease activities of abzymes were shown to be the earliest statistically significant marker of EAE development. In connection with these, it is important to note that abzymes hydrolyzing DNA, MBP, and oligosaccharides were found in cerebrospinal fluid of MS patients and their activity on average approximately from 30 to 60-fold higher than those from the sera of the same patients [149–151]. This may indicate that the development of autoimmune processes can begin already in the human brain.

In MS, SLE, and SCZ, anti-MBP abzymes can attack MBP of the myelin-proteolipid sheath of axons leading to a disturbance of conduction of nerve impulses [53–56]. Overall, the destruction of the myelin sheath and the production of MBP-hydrolyzing Abs can be a common phenomenon for some different diseases including SCZ. Interestingly, neuropsychiatric involvement to some extent similar to MS and SCZ patients occurs in approximately 50%

patients with SLE and carries a poor forecast [152]. SLE mostly affects the central neural system, and within its cerebral complications, it has a particular propensity—perhaps more than any other systemic inflammatory disease—to cause psychiatric disorders. Some similar neuropsychiatric indicators of disease common to SLE, MS, and SCZ were observed [152]. The production of abzymes hydrolyzing MBP as well as DNA and RNA even more powerful indicate the development of significant autoimmune reactions in patients with SCZ. Thus, in different patients with SCZ, SLE, and MS, there are, in some extent, similarities in the violation of the immune system, production of abzymes, and neuropsychiatric disorders.

As it indicated above, the sera of healthy donors contain abzymes with different oxidation-reduction activities. Therefore, at first glance, the detection of abzymes with such activities in patients with SCZ may not have a pathophysiological significance. However, in SCZ patients, a dysfunction of the glutamatergic system is shown [9–12], while misbalance of dopamine-glutamate homeostasis can result in the patient's development of generalized oxidative stress [13, 14]. In SCZ patients, the cellular metabolism changes are associated with alteration in the activity of enzymes, including antioxidant enzymes [109, 112].

The difference between the average peroxidase (1.8-fold) and oxidoreductase (1.5-fold) IgG activity in the oxidation of 3,3′-diaminobenzidine from the sera of SCZ patients and healthy donors was moderate but statistically significant ($P = 0.008$). At the same time, the average relative catalase activity of IgGs from the sera of SCZ patients was 15.8-fold higher than from healthy donors. These data on the oxidation-reduction enzymatic activities of antibodies seem to be important for understanding the possibility of protecting a person from oxidative stress with the help of blood immunoglobulins.

8. Conclusion

It was shown that similar to patients with typical autoimmune pathologies, SLE and MS, sera of SCZ patients contain IgGs hydrolyzing DNA, RNA, MBP, and abzymes with catalase, peroxidase, and oxidoreductase activities. As mentioned above, an appearance of abzymes with nuclease and protease activities, which are absent in the blood of healthy donors, may be used as the earliest markers of autoimmune reactions in patients with different autoimmune diseases. Therefore, one cannot exclude that abzymes with these activities may in addition to other different important factors cooperatively promote activation of neuropathologic and psychiatric mechanisms in SCZ pathogenesis.

SCZ patients show some similarity with MS and SLE patients in the development of the same medical, biochemical, and immunological indexes appearing especially in late stages of these diseases. Thus, it is obvious that early diagnostics of SCZ requires the use of all known independent methods to exclude SLE, MS, and probably other possible diseases leading to a formation of MBP-, DNA-, and RNA-hydrolyzing abzymes. However, even revealing of these abzymes on early stages of SCZ may be very useful for detecting of autoimmune reactions in such patients. It is known that SLE, MS, and SCZ patients are usually treated with different drugs. SCZ is known as the progressive mental illness with very different polymorphic symptoms, which are similar to typical autoimmune diseases associated in addition with

autoimmune reactions. Taking this into account, one cannot exclude that for a more effective treatment of schizophrenia, patients may be necessary to use some kind of medications suppressing the autoimmune reactions in this pathology. For example, it should be emphasized that the activity of MBP-hydrolyzing Abs attacking myelin-proteolipid shell of axons may be inhibited by MS therapeutic Copaxone [82].

DNase abzymes form SLE and MS patients are cytotoxic and induce apoptotic cell death. The decrease in activity of Abs with nuclease activities was achieved after treatment of patients with Hashimoto thyroiditis with Plaquenil [144]. It cannot be ruled out that any other drugs that are used to treat patients with other different autoimmune diseases can be effective in suppressing the autoimmune component in patients with schizophrenia.

In summary, as mentioned above, schizophrenia is not currently attributed to the typical autoimmune diseases. However, we have shown for the first time in several articles that polyclonal IgGs from the sera of schizophrenia patients possess DNase, RNase, MBP-hydrolyzing, catalase, peroxidase, and oxidoreductase catalytic activities, which are the earliest markers of autoimmune reactions. It means that immune system dysregulation including autoimmunity together with other factors can be important for the development of schizophrenia.

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Conflict of interest

The authors declare that they have no conflict of interest.

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