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Research Article

Oligoclonal IgGs against DNA, Histones, and Myelin Basic Protein in the Cerebrospinal Fluid of Patients with Multiple Sclerosis

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Abstract

Multiple Sclerosis (MS) is known as a chronic demyelinating pathology of the central nervous system. The most accepted MS pathogenesis theory assigns the main role to demyelination of myelin-proteolipid shells due to inflammation-related with autoimmune reactions. One of the features of MS patients is the enhanced synthesis of oligoclonal IgGs in the bone marrow Cerebrospinal Fluid (CSF). By antigen-specific immunoblotting after isoelectrofocusing of IgGs, oligoclonal IgGs in CSF of MS patients were revealed only against the components of Epstein-Barr virus and Chlamydia. However, there was still unknown to which human auto-antigens in MS patients oligoclonal IgGs may be produced.

Here it was first shown that in the CSF of a narrow percentage of MS patients, oligoclonal IgGs are produced against their own antigens: DNA (24% patients), histones (20%), and myelin basic protein (12%). At the same time, the CSF of MS patients contains a very large amount of auto-IgGs-abzymes that hydrolyze DNA, histones, and myelin basic protein, which during isofocusing, are distributed throughout the gel from pH 3 to 10. It is concluded that these multiple IgGs-abzymes, which are dangerous to humans since stimulate development of MS, in the main are non-oligoclonal antibodies.

Keywords: Human cerebrospinal fluid; Multiple sclerosis; Catalytic IgGs; Oligoclonal IgGs against auto-antigens

Abbreviations

Abs: Antibodies; Abzs: Abzymes or Catalytically Active Antibodies; AIDs: Autoimmune Diseases; CSF: Cerebrospinal Fluid; BSA: Bovine Serum Albumin; HSCs: Hematopoietic Stem Cells; EAE: Experimental Autoimmune Encephalomyelitis; IEF: Isoelectrofocusing; FPLC: Fast Protein Liquid Chromatography; MS: Multiple Sclerosis; MBP: Myelin Basic Protein; oc-IgGs: oligoclonal IgGs; SDS-PAGE: SDS - Polyacrylamide Gel

Electrophoresis; SLE: Systemic Lupus Erythematosus; scDNA and relDNA: Supercoiled and Relaxed DNA

Introduction

Multiple Sclerosis (MS) presenting a serious social and medical problem is a chronic demyelinating pathology of the central nervous system. Its etiology remains still unclear, and the most accepted pathogenesis theory assigns the main role in demyelination to the axons myelin-proteolipid shell destruction due to inflammation-related Autoimmune (AI) reactions ([1], and refs therein). One of the features of MS patients is the enhanced synthesis of free light chains [1] and of oligoclonal IgGs in the bone marrow Cerebrospinal Fluid (CSF), showing themselves as oligoclonal bands after CSF proteins Isoelectrofocusing (IEF) [1-3].

However, the cloning IgGs from the active plaques and periplaque regions of the brain and the cerebrospinal fluid B-cells of MS patients were analyzed [4]. High-affinity IgGs against DNA were a major component of the intrathecal IgG response in multiple sclerosis patients.

Anti-DNA-specific Abs from MS and Systemic Lupus Erythematosus (SLE) patients were shown to interact efficiently with the surface of oligodendrocytes and neuronal cells. The results indicated that anti-DNA autoantibodies (auto-Abs) might promote momentous neuropathologic mechanisms not only in patients with SLE but also with MS [4].

It is believed that some different pathogens may be coupled with the development of MS, including several bacteria (*Chlamydia pneumoniae*, *Mycoplasma pneumoniae*, and, *Staphylococcus*) that produce different superantigens (for review see [5,6] and refs therein).

Besides, it is believed that people's infection with certain viruses (human herpesvirus, Epstein-Barr virus, and human endogenous retroviruses) can also lead to the development of MS. It is known that after people infection with viruses and bacteria, at first, there is a formation of Abs against their components, which may possess structural similarities with different proteins of human cells and blood [5,6]. Due to the mimicry of certain compounds of viruses and bacteria with those of humans, the protein epitope recognition and a halting of the immune system can lead to the production of Abs against its own compounds of the human body and, as a result, to the beginning and development of MS [5,6].

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Artificial abzymes (Abzs, antibodies to transition state analogues of chemical reactions with catalytic activities) and natural Abzs have been well described (reviewed in [10-15]).

Natural abzymes similar to artificial Abzs to different analogs of transition states can be produced directly against enzyme substrates acting as haptens with changed structure mimicking the transition states of chemical reactions. Abzs can also be second-antiidiotypic Abs against the active centers of many different enzymes. Natural abzymes hydrolyzing nucleotides, RNA, DNA, oligopeptides, proteins, and polysaccharides are revealed in the sera of patients with several autoimmune and viral diseases (e.g. SLE, MS, Hashimoto thyroiditis, polyarthritis, tick-borne encephalitis, and HIV-infected patients) [7-12]. Healthy humans do not usually develop Abzs with detectable catalytic activities; their levels are usually on the frontier of the sensitivity of the detection methods [7-12]. Nevertheless, germline antibodies of healthy peoples can demonstrate high level promiscuous, amyloid- or superantigen-directed activities [13].

Autoimmune Diseases (AIDs) have first been suggested may be originated from defects of Hematopoietic Stem Cells (HSC) [14]. Experimental autoimmune encephalomyelitis in C57BL/6 mice [15,16], as well as Systemic Lupus Erythematosus (SLE) in MRL-lpr/lpr mice [17-19], is beginning due to immune system-specific reorganization. Defects of the immune system include specific changes in the differentiation profile of bone marrow HSCs combined with the production of catalytic antibodies (abzymes) hydrolyzing DNA, polysaccharides, peptides, and proteins [15-19]. The statistically significant appearance of abzymes may be univocal detected at the earliest stages of different AIDs, when changes in Abs titers to specific antigens of various diseases, such as DNA (SLE, MS, etc.), thyroglobulin (Hashimoto thyroiditis), myelin basic protein (MS, SLE, etc.), and other compounds, still correspond to the range in the titers of these auto-Abs in healthy donors [7-12]. According to current data, the presence of Abzs in the blood is a clear significative of the beginning and progress of AI processes in humans and mammals [7-12].

It was shown that DNase, MBP-, and oligosaccharide-hydrolyzing activities are intrinsic properties of IgGs, IgMs, and IgAs from sera of SLE and MS patients [7-12]. The anti-MBP abzymes can attack and hydrolyze MBP of the myelin-proteolipid sheath of axons and play an important negatory role in MS pathogenesis [11]. Abzs with DNase activity are cytotoxic, cause hydrolysis of nuclear DNA, inducing cell death by apoptosis [12]. Interestingly, the relative specific catalytic activities of antibodies from the cerebrospinal fluid of patients with MS in the hydrolysis of DNA, MBP and oligosaccharides are about 30–60-fold higher than from the blood sera of the same patients [20-22].

Cuprizone induced demyelination is a widely used experimental model to analyze processes in the Central Nervous System (CNS) of re- and demyelination. The immunization of EAE-prone C57BL/6 mice with cuprizone results in a significant decrease of several indexes characterizing spontaneous and Myelin Oligodendrocyte Glycoprotein (MOG)-induced EAE: increased levels of titers of antibodies against DNA, MOG, and MBP, proteinuria, the generation of abzymes hydrolyzing these antigens [16]. The immunization of mice with cuprizone led to a significant decrease in the size of the brain corpus callosum compared with untreated mice but only slightly changed the level of proliferation and profile of differentiation of mice HSCs compared with mice treated with MOG. Extra 112 the data obtained indicate that treatment with cuprizone is associated with demyelination, which is not associated with significant changes in autoimmune processes compared with the spontaneous development of 112 EAE [16].

Histones, in addition to their various intranuclear cell functions, are damage-molecules in the extracellular space [23]. The increase in histones level in blood is associated with multiple contraventions of pathophysiological processes, including developing various inflammatory diseases and AIDs [23]. It was shown that in contrast to healthy humans, 100% of IgG preparations purified from the sera of HIV-infected patients hydrolyze efficiently from 1 to 5 human histones (H1, H2a, H2b, H3, and H4) [24]. The blood and cerebrospinal liquid of EAE C57BL/6 mice also contain autoantibodies against histones hydrolyzing these proteins effectively [25]. Many different Abs against DNA are directed against histone-DNA complexes appearing in the blood due to cell apoptosis [26]. Therefore, not only abzymes with DNase activity but also antibodies hydrolyzing five histones may be important for the development of MS, which is associated with demyelination.

Until recently, it was unknown if the cerebrospinal fluid of patients with MS can contain auto-Abs and abzymes against five histones. It was recently shown that the relative concentrations of IgGs against histones in MS patient's blood and CSF and their activity in the hydrolysis of all histones varied significantly from patient to patient [27]. However, all 28 IgG preparations from blood and CSF efficiently hydrolyze from one to five histones. It was shown that auto-IgGs from sera and cerebrospinal fluid of MS patients are usually extremely heterogeneous in their affinity to DNA, histones, and MBP. Affinity chromatographies of IgGs demonstrated the heterogeneity of Abs-abzymes hydrolyzing DNA, MBP, and histones from CSF and sera of MS patients on sorbents with immobilized DNA, MBP, and histones and by their isoelectrofocusing [27]. It was shown that antibodies that hydrolyze DNA, MBP, and histones are distributed over the entire profile of the IEF gel from pH 3 to 10. The data obtained indicated that the CSF of patients with MS contains many different abzymes with different isoelectric points. However, this work did not establish whether any of the antibodies are oligoclonal ones [27].

By using IEF and following antigen-specific immunoblotting, specific oligoclonal IgGs in CSF of some MS patients were revealed definitely against only components of Epstein-Barr virus [28] and Chlamydia [29]. However, it is still unknown to which human auto-antigens oligoclonal IgGs may be produced in MS patients.

We considered DNA, MBP, and histones as potential antigens for which oligoclonal auto-antibodies can probably be accumulated in the CSF of patients with MS. To confirm this assumption, we have carried out IEF of MS patients CSF IgGs and following transfer of separated IgGs to membranes saturated with these three antigens. It has been shown that in CSFs of only some patients may be oligoclonal IgGs against DNA, MBP, and histones.

Materials and Methods

Chemicals, patients, and ethical statement

Most chemicals, proteins were from Sigma (St. Louis, MO,

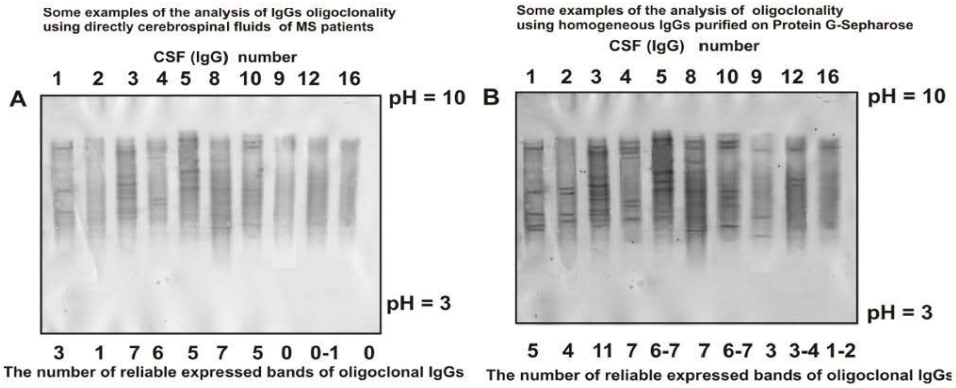

Figure 1: Typical examples of oligoclonal IgG analysis by standard isoelectric focusing. Some examples of oligoclonal bands analysis correspond directly cerebrospinal fluids of ten patients (A) and electrophoretically homogeneous IgGs purified from CSFs of the same ten patients (B).

USA). Protein G-Sepharose and Superdex 200 HR 10/30 column were from GE Healthcare (GE Healthcare, New York, USA). MS patients (28 patients; 8 men and 20 women; average age = 38.7±12.3 years), gratifying according to the classification of McDonald [30] the known criteria for definite MS were admitted at the period from January 2014 to October 2017 to the Multiple Sclerosis Center (the Ferrara University, Italy) and selected for the study. The blood and cerebrospinal fluid sampling protocols conformed to the hospital human ethics committee guidelines of the Multiple Sclerosis Center in accordance with Helsinki ethics committee guidelines. Informed consent was given by all 28 patients prior to inclusion. The design of this study was supported by the Regional Committee on Medical Ethics in Research.

Disease severity of 28 patients with multiple sclerosis was scored according to Kurtzke's Expanded Disability Status Scale (EDSS) [31] (range varied from 0.0 to 6.5, average value 2.6±1.3) at the time of sample collection. At entry, all patients had no any symptoms of acute infections.

Besides, none of the patients at the sample collection time had received before the study any anti-disease therapies during the six months. More detailed data are given in Supplementary Table S1.

Sample preparation

Samples of serum and CSF were collected in sterile conditions and survived in aliquots at -80°C until assay as in [27]. Samples of CSF were taken by atraumatic lumbar puncture, and then preparations free of cells were obtained by centrifugation for 15min at 12 thousand rpm at 20°C using an Eppendorf centrifuge (New York, USA). In parallel with CSF samples, blood preparations were obtained using puncture of the anterolateral vein; then, they were centrifuged for the cells removal as in [27].

Purification of IgGs

Electrophoretically homogeneous IgGs from CSF and sera were obtained using first affinity chromatography of samples proteins on protein G-Sepharose and then additionally by Fast Protein Liquid Chromatography (FPLC) - gel filtration as in [32-34]. The content of IgGs in CSF and serum of different patients, as well as their concentration after their purification, was estimated by standard immunochemical nephelometry as in [27].

Determination of IgG concentrations and antigen-mediated immunoblotting The content of IgGs in serum and CSF of different patients was estimated using standard immunochemical nephelometry using the Beckman Image 800 immunochemistry System (Beckman Instruments of Inc. Fullerton, CA. USA) according to the described procedure [3,28,29].

IgG oligoclonal bands against specific antigens were detected by antigen-mediated immunoblotting using CSF and purified IgG preparations according to [28,29]. First, directly CSF (10μl) or homogeneous IgG preparations (10μl; 3mg/ml) were put in the agarose gel pockets. After the IEF run, the gel was placed on top of nitrocellulose sheets previously coated for 12h at 22°C one of antigen: polymeric bovine DNA, MBP, or histones (all 0.15mg/ml) dissolved in PBS buffer. Then nitrocellulose membranes were washed three times with water and incubated in physiologic solutions containing 2% Bovine Serum Albumin (BSA) for 1h at weak shaking. Antigen-specific blotting was then carried out according to the manufacturer's instruction. After IEF, the gel was placed on top of a nitrocellulose membrane and, to improve the tight contact, was pinned down by a heavy object (1kg). Passive transfer of gel proteins to the membrane continued for 4h.

Nonspecific binding sites were then blocked using a buffer containing 2% BSA. The membrane was incubated for 30min at 22°C with rabbit anti-human IgGs solved in buffer containing 0.2% BSA and then washed twice with water. The blot was stained using a peroxidase substrate according to the manufacturer's instruction. Preparations containing no oligoclonal IgGs and a mixture of several proteins were used as controls. In these cases, the detection of stained spots was not achieved.

Results

Characterization of IgG antibodies used in this work

We have previously analyzed different parameters characterizing total IgGs from the sera and CSFs of 28 patients with MS [27]. The main characteristics of patients analyzed are given in Supplementary Table S1. The mean values of the total concentration of IgGs in the CSF (6.0±3.1 mg/dL) and blood (1166±178 mg/dL) of the patients were estimated; the average concentration of IgGs in sera was ~194-fold higher than in CSF. The average concentration of anti-DNA Abs

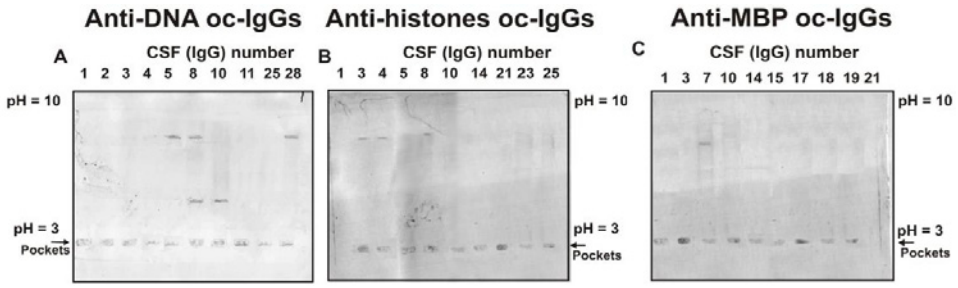

Figure 2: Typical examples of the determination of oligoclonal IgGs to different antigens. After the standard isoelectric focusing of homogeneous IgGs, they were analyze using immunoblotting by transfer of IgGs on nitrocellulose membranes treated with different antigens: polymeric DNA (A), five histones (B), and MBP (C). Nitrocellulose membranes were then treated using standard immunochemical nephelometry.

in CSF preparations (0.044±0.0026 A_{450}) was 2000-fold lower than that in the sera samples (8.8±6.5 A_{450}). The relative concentration of antibodies against MBP in serum (0.32±0.08 A_{450}) was 228 times higher than in CSF (1.4±0.72) $\times 10^{-3}$ A_{450}).

For 28 CSF preparations relative concentration of Abs against five histones (0.02±0.01 ME) was by a factor of 125 lower than in sera samples 2.5±0.87 ME) [27]. In addition, it was shown that electrophoretically and immunologically homogeneous IgG antibodies from the CSF and sera of MS patients effectively hydrolyze DNA, MBP, and five histones (H1, H2a, H2b, H3, and H4). Despite the lower content of antibodies in the CSF, their specific enzymatic activities were much higher in the hydrolysis of these substrates compared to antibodies from sera (-fold); DNase (45.0), MBP-hydrolyzing (55.6), and different histones-hydrolyzing: H1 (17.5), H2a (16.7), H2b (18.3), H3 (25.8), H4 (27.2) [27]. These data indicate that B-lymphocytes producing abzymes with different catalytic activities are already accumulated at the level of cerebrospinal fluid in MS patients. However, the data obtained did not make it possible to establish whether these enzymatic activities related to any oligoclonal IgGs of CSFs.

We have shown the exceptional heterogeneity of homogeneous IgG preparations in their affinity to substrates (DNA, MBP, and histones) using affinity chromatography of total IgGs from CSF and sera of MS patients on sorbets with immobilized DNA, MBP, and histones [27]. It was shown that when IgGs are eluted from these sorbents using different concentrations of NaCl and acidic buffer (pH 2.6), all antibodies and their catalytic activities are distributed over the entire chromatography profile (Supplementary Figure 1S). The character of the distribution of total IgGs from CSF and serum by isoelectric points using 18 cm long gels for IEF was individual for each MS patient (Supplementary Figure 2S) [27]. The heterogeneity of IgGs and their subfractions with catalytic activities (abzymes) hydrolyzing DNA, MBP, and histones was also demonstrated using 18cm long gels for IEF (Supplementary Figure 3S). It was shown that sera and CSFs of patients with MS could contain many abzymes with very different isoelectric points possessing DNase, MBP-, and histone-hydrolyzing activities. The polyclonal IgGs from CSF of various MS patients with three different enzymatic activities were distributed all over the gel for IEF from pH 3 to 10 (Supplementary Figure 3S). However, this approach did not permit to establish whether there are or not oligoclonal antibodies to any of the antigens (DNA, MBP, and histones) among the IgGs exposed to IEF.

On the whole, our data on the antibodies of the serum and cerebrospinal fluid indicated that it is impossible to exclude the formation of oligoclonal IgGs in the cerebrospinal fluids of some MS patients against their own components: DNA, MBP, and histones. As indicated above, using the antigen-specific immunoblotting approach, oligoclonal antibodies in CSF of MS patients were revealed only against Epstein-Barr virus [28] and Chlamydia [29] components using standard 6cm gels (Beckman Instruments of Inc. Fullerton, CA. USA).

Taking this into account, we used 28 IgGs described above for analysis of the potential possibility of the presence of oligoclonal antibodies in these preparations against DNA, MBP, and histones using antigen-specific immunoblotting methods as in [28,29].

Analysis of IgGs oligoclonality

First, the oligoclonal bands of IgGs (oc-IgGs) in the liquor and serum of MS patients was detected by a standard IEF procedure using directly the CSF and serum preparations [27].

Only one blood sample contained oc-IgGs in both liquor and sera (sample 1, Supplementary Table S1). According to data obtained, three liquor preparations did not contain clearly registered oc-IgGs, while the other 25 liquor preparations contained from one to seven oligoclonal IgGs (for example, several examples are given in Figure 1A). However, the presence of some bands cannot be revealed unequivocally using CSF and the standard approach. At the standard direct CSF assay, the sensitivity of the approach could be underestimated due to the presence of liquors in addition to IgGs of a large number of other proteins and the restriction of applying to the strip only 10μl of each sample. Taking this into account, we have compared oc-IgGs using preparations of liquors and homogeneous IgGs described above. Figure 1B demonstrates that several of the weakly visible bands of oc-IgGs when using CSF have become clearly visible at the analysis of purified homogeneous IgGs.

Depending on the preparation, the number of clearly detectable oc-IgGs becomes to be from one to 11 in some preparations (Figure 1B). Therefore, some CSF preparations can contain oc-IgGs in a minimum amount that does not allow detecting those unambiguously using liquor samples and standard approach.

Determination of specific oligoclonal IgGs to human auto-antigen First, we tried to detect in 25 CSFs of MS patients oc-IgGs against DNA, MBP, and histones using the CSF directly by analogy

with [28,29]. Unfortunately, the use of the standard approach and CSF directly did not lead to reliable detection of oc-IgGs against its own antigens. Therefore, for antigen-mediated immunoblotting, we have used purified homogeneous IgG preparations described above. Figure 2 shows several typical examples of the determination of oc-IgGs against DNA, MBP, and histones. Overall, anti-DNA oligoclonal IgGs were found in 6 of 25 IgG preparations (24%). Therewith, five preparations contain only one oc-IgGs, while one preparation - two anti-DNA oc-IgGs.

Five of 25 preparations demonstrated only one band of anti-histones oc-IgGs (20.0% of IgGs). Among the 25 preparations were found only three preparations containing oc-IgGs against MBP (12.0% of preparations). Herewith, to one IgG-8 preparation containing eleven oc-IgGs (Figure 1B) correspond two bands of oligoclonal IgGs against DNA and one band against histones. As one can see from Figure 1B, some polyclonal IgG preparations contain from 3 to 11 oligoclonal antibodies. However, some of them, even containing several oc-IgGs according to the data of common oligoclonal antibodies (Figure 1B), do not contain oligoclonal bands corresponding to own antigens of MS patients. Only from 12 to 24% of polyclonal antibodies demonstrate oc-IgGs against self-antigens of MS patients. This means that all other oc-IgGs (Figure 1B) are accumulated in the CSF of MS patients to some other, either their own or exogenous antigens. Nevertheless, in some MS patients can accumulate oligoclonal IgGs and to their own antigens.

Discussion

It was found previously that high-affinity anti-DNA Abs were one of the major components of the intrathecal IgG response in MS patients [4]. Taking this into account, one might expect that anti-DNA oligoclonal IgGs may be the main among all oc-IgGs of MS patients. However, anti-DNA oc-IgGs was found in the CSF of only 24% of MS patients. At the same time, it was previously shown that the IgGs with DNase activity are distributed over the entire profile of the gel for IEF from pH 3 to 10 (Supplementary Figure 3S) [27].

Consequently, in CSF of patients with MS, the most common - not oligoclonal IgGs against DNA are mainly accumulated, and there are a lot of them (Supplementary Figure 3S). A similar situation was found for oligoclonal IgGs against histones and MBP (Supplementary Figure 3S) [27]. Many different abzymes, specifically hydrolyzing these two substrates, were also distributed along the entire pH profile gradient from 3 to 10 when polyclonal IgGs were subjected to IEF. At the same time, we have shown that there are relatively few oligoclonal IgGs against histones (20%) and MBP (12%) in the CSF of MS patients.

Therefore, nevertheless, the formation of oligoclonal IgGs against the self-antigens of MS patients does not occur effectively in their CSFs. At the same time, the specific activity of very heterogeneous IgGs from CSF in the hydrolysis of DNA (45-fold), MBP (55.6-fold), and histones (16.7-27.2-fold) and is much higher than that of antibodies from the sera of the same MS patients [27]. Consequently, there are a lot of such abzymes with DNase, MBP- and histones-hydrolyzing IgGs in the CSF of MS patients, but they are generally not oligoclonal antibodies.

Conclusion

It has been shown that auto-IgGs of the cerebrospinal fluids of MS patients can contain many different oligoclonal antibodies having various isoelectric points. However, only a small percentage of multiple sclerosis patients contain oligoclonal antibodies against three own antigens: DNA (24.0%), histones (20%), and myelin basic protein (12%).

Supplementary Materials

Table S1: Several different characteristics of MS patients; Figures 1S, 2S and 3S demonstrating heterogeneity of IgGs from cerebrospinal fluids of patients with multiple sclerosis.

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