

Persistent intrathecal secretion of oligoclonal, *Borrelia burgdorferi*-specific IgG in chronic meningoradiculomyelitis

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Summary. In the cerebrospinal fluid IgG of five patients with lymphomeningoradiculitis (Bannwarth's syndrome) and radiculomyelitis studied by immunoblot technique an oligoclonal pattern was found. Most of these oligoclonal bands were specific for *Borrelia burgdorferi*. In patients suffering from chronic meningoradiculomyelitis, repeated CSF examination by this technique showed persistent secretion of identical IgG bands. Thus, the specific humoral immune response and the disease activity could be documented over the course of the disease.

Key words: Lyme disease – Lymphomeningoradiculitis – *Borrelia burgdorferi* – Cerebrospinal fluid – Immunoblot technique

Lyme disease is a tick-borne spirochetal infection which, particularly in Europe, often involves the central nervous system (CNS). In most cases, the disease starts with a characteristic skin rash, erythema chronicum migrans (ECM), and symptoms of general illness such as fever, headache and arthralgia (stage 1) [3, 4]. Weeks or months later, specific organs such as heart, joints and CNS are involved (stage 2) [3, 14]. Without appropriate treatment by antibiotics the disease may then progress into a subacute or chronic stage in which there may be acrodermatitis chronica atrophicans, chronic oligoarthritis or progressive encephalomyelitis (stage 3) [1, 3, 14]. Neurological manifestations of Lyme disease include lymphomeningoradiculitis, radiculomyelitis or even progressive encephalomyelitis [1, 10, 14, 18, 19]. Characteristic cerebrospinal fluid (CSF) findings are lymphocyte and monocyte pleocytosis, increased total protein and immunoglobulins. Investigations of CSF immunoglobulins during different stages consistently show the restricted heterogeneity of CSF IgG by the presence of oligoclonal bands [8, 11, 24]. The diagnosis is confirmed by high titres of serum and CSF antibodies, specific for *Borrelia burgdorferi*, which has recently been identified as the aetiological agent of Lyme disease and Bannwarth's syndrome [2].

The purpose of our study was to answer the questions whether the CSF immunoglobulin G (IgG) in lymphomeningoradiculitis is locally produced, whether its antigen specificity can be determined, and whether the persistence of a specific distribution pattern can be recorded over the course of the disease. The recently described immunoblot technique [6], which combines isoelectric focusing (IEF) of unconcentrated or diluted CSF with blotting to an antigen-loaded nitrocellulose filter, was used.

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Patients and methods

The five patients studied were treated in our clinic in 1986. Their ages ranged between 34 and 67 years. Three of the patients remembered a tick bite and/or ECM. The clinical diagnosis of meningoradiculitis or radiculomyelitis was confirmed by antibodies against *B. burgdorferi* [immunofluorescence test (IFT): significant positive serum IgG titre >1:64; significant positive CSF IgG titre >1:16; ELISA: significant positive CSF IgG titre >1:10] in the serum and the CSF, elevated total protein and IgG of CSF and a lymphocytic CSF pleocytosis. All five patients suffered from either meningitis with accompanying radiculoneuritis or from meningomyelitis (Table 1) and were treated with 20×10^6 units/day penicillin G for 14 days either once or repeatedly, according to the persistence of clinical symptoms. According to the course of the disease and the persistence of pathological CSF findings, we only used the term chronic meningoradiculitis or radiculomyelitis when both clinical and laboratory findings were present for longer than 6 months without any improvement. Relevant laboratory findings of the sera and CSF, which were always collected on the same day, are shown in Table 2. Patient C had already been treated by corticosteroids and antibiotics when CSF and serum were collected. The antibody titre was therefore comparatively low. In this patient, proliferative testing of peripheral blood lymphocytes with *B. burgdorferi* antigen further confirmed the diagnosis. All CSF and serum samples were drawn with informed consent of the patients. As a positive control, monoclonal antibody H 9724 specific for *B. burgdorferi* (kind gift of Dr. A. Barbour, University of Texas, San Antonio, USA) was used. Sera and CSF samples of patients suffering from either meningoencephalomyelitis or multiple sclerosis (both seronegative for *B. burgdorferi*-specific antibodies) were taken (data not shown).

Determination of CSF and serum protein concentrations. All protein and IgG concentrations were determined by laser-nephelometry (Behring Laser Nephelometer, Behring-Werke, Marburg, FRG) and expressed in milligrams per decilitre (mg/dl). Antibodies to *B. burgdorferi* were tested by IFT and ELISA as described previously [13]. The IgG coefficient was calculated according to the method of Delpech and Lichtblau [5].

***B. burgdorferi* antigen preparation.** Lyme disease spirochetes (*B. burgdorferi* strain M34; kind gift of Dr. R. Ackermann, Department of Neurology, University of Cologne, FRG) were prepared as described by Pachner et al. [17]. Briefly, the

Table 1. Age distribution, clinical findings and disease course of five patients (A–E) suffering from chronic lymphomeningoradiculitis or radiculomyelitis

	A	B	C	D	E
Age (years)	34	63	67	66	57
Sex	Female	Female	Female	Female	Female
ECM	–	–	+	+	+
Meningoradiculitis	+	+	+	+	+
Radiculomyelitis	–	+	+	–	+
Pretreatment	–	–	+ ^a	–	–
Treatment courses ^b	2	1	2	2	4
Duration of symptoms (months) ^c	7	4	6	4	15

ECM = erythema chronicum migrans

^a Pretreatment by antibiotics and corticosteroids

^b Treatment courses: 20 × 10⁶ units/day penicillin G for 14 days; in patient E corticosteroids were added during the fourth course

^c Persistent symptoms consisted of radicular pain, mono- and paraparesis, spastic-atactic gait and vegetative symptoms

spirochetes were pelleted four times (10000 g; 20 min; 4°C) and washed in 0.01 M PBS/5 mM magnesium chloride (pH 7.3) and sonicated on ice. The protein concentration was determined by Biorad protein assay (Biorad, Munich, FRG).

Immunoblotting procedure. A modification of the technique described by Dörries and ter Meulen [6] was used. Nitrocellulose filters (BA 85, Schleicher and Schüll, Dassel, FRG) were cut to 70 × 180 mm sheets and loaded either with rabbit anti-human IgG (25 ml, 0.1 mg/ml in PBS; Dakopatts, Hamburg, FRG) or *B. burgdorferi* antigen (20 ml, 0.15 mg/ml in PBS), prepared as described above. The filters were incubated at room temperature overnight on a rocker platform and then rinsed in PBS for 10 min. Unoccupied protein binding sites were blocked by incubation in 5% bovine serum albumin (BSA; Serva, Munich, FRG) in PBS (pH 7.4) for 1 h. After washing in PBS, 0.5% NP40 (Sigma, Taufkirchen, FRG) in PBS and PBS (10 min each cycle), the filters were ready for blotting.

IEF of CSF and serum was carried out on the following agarose gel: 1% agarose (IEF grade, Pharmacia, Freiburg, FRG) containing 12% sorbitol (Sigma, Taufkirchen, FRG), 1 ml pharmalyte, pH 3–10, 0.2 ml pharmalyte, pH 8–10.5 (Pharmacia, Freiburg, FRG). The dimensions of the gels were 200 × 110 × 0.5 mm (length, width, height). CSF samples were adjusted to 20 µg IgG/ml by dilution with saline (0.9%) and 7.5 µl aliquots were applied to the gel with application strips (Serva, Munich, FRG; 3.5 × 2 mm). IEF was performed at 18 W constant power in an LKB Ultrophor Electrofocusing Unit (LKB, Bromma, Sweden) at 18°C for 1 h.

Blotting of immunoglobulins to nitrocellulose filters was accomplished by affinity-driven transfer. For this purpose, the moist filter was laid on top of the gel to avoid air bubbles. Then it was covered with a PBS-moistened filter paper (LKB), three sheets of dry filter paper, a glass plate and 2 × 200 g weight. After 1 h, three washing cycles (as described above) followed.

The filters were now incubated in 25 ml PBS containing 0.1 mg/ml peroxidase-labelled rabbit anti-human IgG (Dakopatts, Hamburg, FRG) for 1 h. After three washing cycles the filters were stained in a solution of 40 mg 3-amino-9-ethylcarbazole (Sigma, Taufkirchen, FRG), 2.5 ml dimethylformamide (Sigma), 47.5 ml 50 mM sodium acetate solution (pH 4.5) and 50 µl hydrogen peroxide 30%. After staining for 15 min a final washing in distilled water was performed.

Results

The five patients with typical clinical and laboratory findings of meningoradiculitis and radiculomyelitis showed raised total CSF protein and elevated CSF immunoglobulins with IgG ranging up to 85 mg/dl. As shown by IFT (Table 2), antibodies specific for *B. burgdorferi* were present both in the sera and the CSF. Although IgG coefficients according to Delpech and Lichtblau were elevated in all cases, *B. burgdorferi* specific IgG, determined by IFT, was always lower in the CSF (Table 2). For the determination of a restricted pattern of intrathecally produced IgG, immunoblotting of diluted CSF and serum was performed using filters precoated with rabbit anti-human

Table 2. Laboratory findings (CSF and serum) of five patients (A–E) suffering from chronic lymphomeningoradiculitis or radiculomyelitis

	A	B	C	D	E
CSF					
Total protein (mg/dl)	102	357	59	156	230
Albumin (mg/dl)	44	151	35	72	137
IgG (mg/dl)	25	85	8	32	39
IgA (mg/dl)	2.5	9	0.8	2.9	2.7
IgM (mg/dl)	7.6	3	0.5	19.5	2.3
IgG index ^a	1.6	1.8	0.7	1.5	1.0
IFT titre (IgG)	1:256	1:256	1:32	1:128	1:64
Cells					
Total leucocytes (cells/µl)	400	46	170	280	190
% Lymphocytes	91	92	93	86	92
% Monocytes	5	4	0	10	8
% Plasma cells	3	1	2	4	0
% Other cells	1	3	5	0	0
Serum					
IgG (mg/dl)	1600	1000	1270	1090	1036
Albumin (mg/dl)	4600	3210	3560	3630	3820
IFT-titre (IgG)	1:1024	1:2048	1:64	1:512	1:256

IFT = immunofluorescence test

^a According to Delpech and Lichtblau [5]; normal values ranging from 0.3 to 0.7

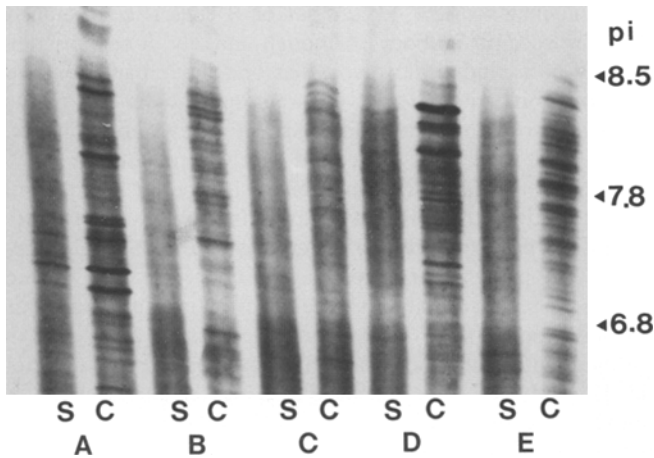


Fig. 1. Immunoblot analysis for total IgG of serum (S) and CSF (C) of patients A-E. An individual pattern of oligoclonal IgG bands can be seen in all CSF samples (C) whereas only some weak bands are found in the sera (see patient A). *pI*, isoelectric point

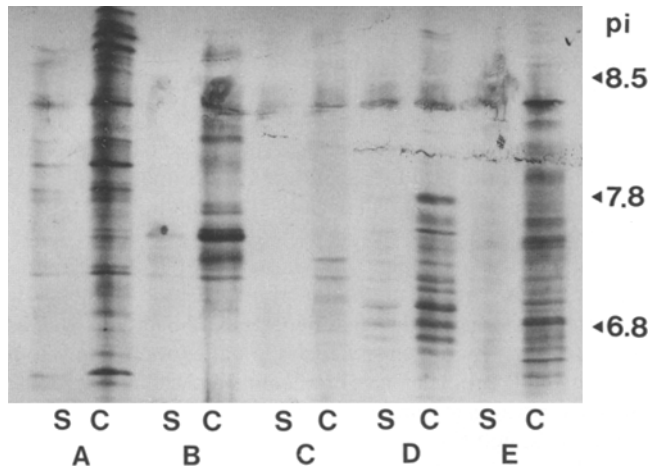


Fig. 2. Immunoblot analysis for *Borrelia burgdorferi*-specific IgG in the sera (S) and CSF (C) of patients A-E. Oligoclonal, *B. burgdorferi*-specific bands can be seen in all CSF samples (C) and some faint bands also in the sera (S) of patients A, B and D. *pI*, isoelectric point

IgG. Thus, the oligoclonal nature of CSF IgG could be demonstrated. In Fig. 1 the IgG distribution patterns within the sera and the CSF are shown in parallel. The CSF of each patient demonstrates an individual distribution of IgG bands which cannot be compared with one another. In the sera, however, only homogeneous staining or single faint bands could be seen. It should be noted that sera and CSF samples were adjusted to the same IgG concentration of 20 $\mu\text{g}/\text{ml}$.

In a further step, we tried to identify the antigen specificity of the oligoclonal IgG bands found. For this purpose, *B. burgdorferi* coated nitrocellulose filters were used for the immunoblotting procedure. Figure 2 shows the results of the immunoblotting to *B. burgdorferi* antigen for both serum and CSF of all five patients. Thus, it can be seen that the majority of oligoclonal bands were specific for *B. burgdorferi*. Comparing the lanes of individual patients, the same heterogeneity of antibody bands is noted. Patient C, who had only a low IFT titre of serum and CSF, showed very weak *B. burgdorferi*-specific bands. In patients A, B and D some specific IgG bands could be seen in the CSF and, to a minor extent, also in the

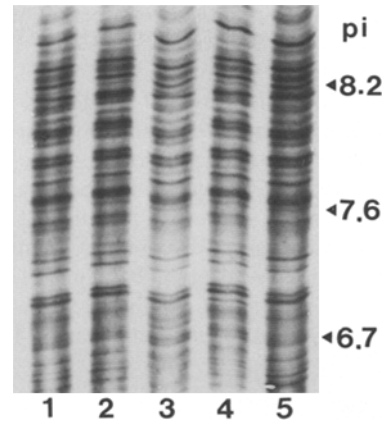


Fig. 3. Oligoclonal total IgG bands in five consecutively collected CSF samples of patient E (tracks 1-5). Over a period of 12 months the distribution pattern of IgG bands remained stable. *pI*, isoelectric point

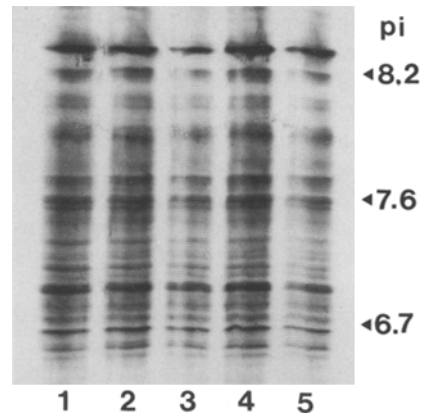


Fig. 4. Oligoclonal, *B. burgdorferi*-specific IgG bands in five CSF samples consecutively collected over a period of 12 months (tracks 1-5). The stable distribution pattern demonstrates the persistent secretion of specific antibodies by single B-cell clones. For the corresponding immunoblot for total IgG, see Fig. 3. *pI*, isoelectric point

Table 3. Protein, IgG concentrations and *Borrelia burgdorferi* antibody titres of five CSF samples (patient E) consecutively collected at 3-month intervals

	1	2	3	4	5
Albumin (CSF) (mg/dl)	39.1	25.1	19.5	20.9	18.1
IgG (CSF) (mg/dl)	30.8	17.5	11.8	9.3	8.9
IgA (CSF) (mg/dl)	2.7	1.8	1.1	0.9	0.8
IgM (CSF) (mg/dl)	2.3	1.6	<0.2	0.5	0.3
IgG index ^a	2.9	2.3	1.9	1.9	1.5
IFT titre (CSF)	1:64	1:32	1:32	1:32	1:32
ELISA titre (CSF)	>1:80	1:80	1:80	1:80	>1:80

IFT = immunofluorescence test

^a According to Delpech and Lichtblau [5]; normal values ranging from 0.3 to 0.7

serum tracks. The control patients did not show oligoclonal bands either for total IgG or for *B. burgdorferi* (data not shown).

In addition, we studied the distribution pattern of intrathecally produced IgG in one patient (E), who continuously

suffered from radicular pain and paraparesis, over a period of 12 months. Laboratory values of five CSF samples collected at approximately 3-month intervals are summarized in Table 3. The IgG concentration continuously dropped with time, whereas the IFT titre for *B. burgdorferi*-specific antibodies remained the same. Figure 3 shows the configuration of oligoclonal total IgG bands in all five CSF samples of this patient. The corresponding immunoblot of *B. burgdorferi*-specific CSF IgG is demonstrated in Fig. 4. Both figures reveal that, during the 12-month period, no overt differences in the banding pattern could be detected, although the patient had three courses of treatment with penicillin G (20×10^6 units/day over 14 days) in the meantime.

Discussion

In the present study, we used a rapid and sensitive immunoblotting technique [6] to detect and characterize intrathecally produced IgG in five patients suffering from chronic meningo-radicularitis (Bannwarth's syndrome) or radiculomyelitis. In earlier reports it was shown that the determination of *B. burgdorferi*-specific antibodies of either IgG or IgM type is a useful diagnostic criterion for Lyme disease and Bannwarth's syndrome [4]. The patients studied in this report suffered from meningo-radicularitis or radiculomyelitis in either a subacute or chronic stage. Three patients (A, C, E) are still suffering from persistent clinical symptoms such as radicular pain, brisk tendon reflexes and positive Babinski sign; for this reason the term "chronic" should only be used for these patients. After treatment by antibiotics patients B and D markedly improved within 4 months and we would therefore prefer to consider these disease courses as subacute. All of them exhibited oligoclonal IgG shown by both IEF of unconcentrated CSF and blotting to nitrocellulose filters coupled with rabbit anti-human IgG. This observation is also well documented in other viral or bacterial CNS infections such as tuberculous meningitis, neurosyphilis, subacute sclerosing panencephalitis and mumps meningitis [9, 12, 16, 23]. In a further step the antigen specificity of CSF IgG for the aetiological agent *B. burgdorferi* was shown by using the same blotting technique, but coupling *B. burgdorferi* antigen to the nitrocellulose filters. Thus, we found oligoclonal, *B. burgdorferi*-specific IgG bands in the CSF samples of all patients. The presence in three patients of minor bands in the sera which had been adjusted to the same IgG content can be taken as an indicator of the intrathecal production of specific antibodies. This is confirmed by the high IgG indices which had been calculated according to the method of Delpech and Lichtblau [5]. The presence of weak bands seen in the serum track at the same position as the corresponding CSF bands may either be due to parallel formation of the antibodies in the CSF and the peripheral blood or to passive diffusion of CSF IgG to the peripheral blood via the blood-CSF barrier. Apart from the demonstration of the antigen specificity of oligoclonal IgG bands, this highly sensitive method can also be used to follow the persistent secretion of specific IgG in single B cells. This issue was pursued by repeated immunoblotting of CSF samples which had been collected over a longer period of time. Owing to the restriction of space, the blots are only shown for patient E over a period of 12 months. It is clearly demonstrated that the distribution pattern of both total IgG and *B. burgdorferi*-specific IgG remained exactly the same (Figs. 3, 4; tracks 1–5). This is an in-

dication that a restricted number of B cells is continuously forming specific antibody. Although unlikely, it cannot completely be excluded, however, that one single band contains two or more antibodies of different specificities but of the same electrophoretic mobility. As IFT titres were comparatively low, it may be postulated that the persistence of *B. burgdorferi*-specific oligoclonal bands is a better indicator of disease activity than IFT titres alone. In our patients, this notion is further supported by the co-existence of clinical symptoms. The presence of oligoclonal IgG bands in the CSF and not in the serum of patients suffering from meningo-radicularitis or radiculomyelitis strongly favours the intrathecal production of these antibodies and was firstly demonstrated by Krüger et al. [11]. Murray et al. [15] also investigated the question of antigen specificity of oligoclonal CSF IgG by staining IEF bands with ^{125}I -labelled *B. burgdorferi* antigen. In addition, they immunoprecipitated ^{125}I -labelled *B. burgdorferi* antigen by either serum or CSF and used this mixture for SDS gel electrophoresis. Applying such techniques, they detected *B. burgdorferi*-specific oligoclonal bands only in the CSF of one out of nine patients. Because few clinical data are given in their report, we cannot explain whether this difference resulted from a difference in disease severity or stage or whether their technique was less sensitive. Henriksson et al. [8] investigated IgG-, IgM- and IgA-producing B-cells in the serum and CSF, Ig indices and also oligoclonal total IgG bands over the course of lymphocytic meningo-radicularitis. Apart from a high proportion of IgG-, IgM- and IgA-secreting B-cells and a prolonged IgM response, they found oligoclonal IgG bands in the CSF of all patients.

Comparing our results with those reported in the literature, it seems that our method is more sensitive; it is rapidly performed and easily detects oligoclonal CSF IgG as well as characterizing its antigen specificity in patients suffering from subacute and chronic meningo-radicularitis and radiculomyelitis. Obvious advantages are the possibility of using unconcentrated or diluted CSF and the rapid application with no need for radioactive substances. The technique can easily be used for the detection of intrathecally produced, *B. burgdorferi*-specific IgG because IEF of CSF is a standard procedure for the diagnosis of multiple sclerosis in most neurology clinics. The disadvantages of the immunoblot technique are the large amount of antigen necessary and the difficulty of identifying simultaneously the specificity of CSF IgG for subfractions of the *B. burgdorferi* antigen. For this purpose, Western blot analysis, as described by Wilske et al. [25], should be used. It should also be mentioned that the direct comparison of the patterns of oligoclonal IgG bands with those specific for *B. burgdorferi* antigen may be difficult because the transfer conditions for total IgG and *B. burgdorferi* specific IgG are different, as already noted by Dörries and ter Meulen [6].

In all patients, we were able to demonstrate prominent, oligoclonal IgG bands in the CSF but not in the serum. Most of these bands were specific for *B. burgdorferi*, with only a few weak bands seen in the sera. The persistent secretion of specific IgG is paralleled by the presence of clinical symptoms such as radicular pain, mono- and paraparesis over long periods of time. This is not a unique finding in meningo-radicularitis, but can also be demonstrated after recovery from acute herpes virus encephalitis, mumps virus and varicella zoster meningoencephalitis [20–22] and in relapsing subacute encephalomyelitis induced by corona virus in rats [7]. In all these cases of persistent antibody secretion within the CSF,

the question arises whether live bacteria or viruses or only antigen fragments persist within the CNS or whether the immune response against the invading pathogen cannot be suppressed in certain individuals. To elucidate further the cause of persistent CSF antibody secretion, it will be necessary to isolate *B. burgdorferi* antigen from the CSF and to characterize the cellular immune response within the CNS, in patients suffering from chronic meningoradiculitis and radiculomyelitis, in more detail.

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