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ORIGINAL COMMUNICATION

The presence of oligoclonal IgG bands in human CSF during the course of neurological diseases

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Abstract The analysis of cerebrospinal fluid (CSF) is an important tool for the diagnosis of neurological diseases. However, there is limited knowledge about the representativity of a single oligoclonal band (OCB) analysis for a neurological disease during its clinical course. In this study, we analyzed the presence of OCB in the CSF of patients who underwent lumbar puncture more than once. We retrospectively analyzed anonymized data from serial 17,002 CSF analyses done in the CSF laboratory of the Department of Neurology, University Hospital Zurich. We included cases with documented diagnosis in whom OCB were determined more than once. We included 144 patients. The median time span between the first and second OCB analysis was 274 days (range, 1–3,533 days). The result of the second OCB analysis was identical in 109 cases, and different in 35 (24 %). Twenty-five patients acquired and ten patients lost OCB over time. Three of 24 MS patients did not show OCB at the first CSF analysis, but in the second. In the entire group, newly occurring OCB were often associated with new symptoms or occurred after the acute phase of CNS infectious diseases, supposedly as a consequence of the immune reaction. A loss of OCB was often associated with remissions from diseases, e.g., during effective treatment. In patients with neurological diseases, both initially positive and negative OCB results may change over time, which often parallels the clinical condition. Such variability must be taken into account for the interpretation of OCB results.

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Introduction

The primary function of cerebrospinal fluid (CSF) is protecting the central nervous system (CNS) from mechanical injury. Moreover, it is important for homeostatic regulation, helps in maintaining intracerebral pressure at a constant level, circulates nutrients, and rinses waste products from the brain parenchyma. In humans, the majority of CSF originates from the four choroid plexus in the ventricles, from parenchyma of the brain and of the spinal cord, and from ependymal lining of the ventricles [1, 2]. CSF is constantly produced and mainly drained through cisternae, subarachnoid space, and arachnoid villi into the venous blood. The transfer of proteins, such as albumin, antibodies, or complement, from blood into CSF follows passive diffusion as a function of molecular size. Restriction of this transfer from blood into the CSF is called the blood–CSF fluid barrier [3, 4]. While leukocytes can cross vessel walls to reach the perivascular space (PVS) as part of normal immune surveillance, their progression across the glia limitans into the brain parenchyma depends on perivascular antigen recognition, inducing ectoenzymes such as metalloproteinases [5–7]. In neurological disorders, CSF analysis is an important tool for diagnosis [4]. Typical CSF signs of an acute CNS disease include increased CSF cell count and increased albumin CSF/serum concentration quotient, the latter indicating an impairment of the blood–CSF barrier, as albumin is exclusively produced in the liver and thus can only occur in the CNS by passing the barrier. Immune reactions in the CNS include an intrathecal antibody synthesis of immunoglobulins originating from

perivascular infiltrates of B-lymphocytes. Beneath the synthesis of specific antibodies in infectious diseases, the humoral immune response in the CNS may lead to polyspecific/unspecific IgG/IgA/IgM patterns. Oligoclonal IgG detected as oligoclonal bands (OCB) upon isoelectric CSF focusing with or without corresponding OCB in the serum reflect an intrathecal humoral immune response with or without a corresponding systemic immune reaction and is often seen in autoimmune CNS inflammation including multiple sclerosis (MS), Sjögren's syndrome, systemic lupus erythematosus (SLE), or neurosarcoidosis, but also in CNS infections [8–10]. Due to an improvement of MRI techniques, decreasing emphasis is placed on the value of CSF OCB in the diagnosis and study of MS [11]. Nevertheless, beneath the value of standard CSF analysis for the exclusion of differential diagnoses, OCB analysis may provide relevant information in the diagnostic process of autoimmune diseases. Positive OCB provide direct evidence of immune reactions in the CNS while imaging provides only indirect information. OCB are present in approximately 90–95 % of MS patients, and thereby a positive result supports the diagnosis of MS against, for example, vascular lesions [12, 13]. Also, within the group of autoimmune inflammatory diseases, the analysis of OCB may be helpful for differential diagnoses. For example, neuromyelitis optica (NMO) may resemble MS. OCB might be positive in NMO, but much less often than in MS, and therefore the determination of OCB could be helpful in distinguishing MS from NMO [14, 15].

CSF analysis is usually performed for diagnostic purposes and by lumbar puncture (LP). As it is painful and invasive, it is only performed when clearly indicated. Therefore, longitudinal data on changes of OCB synthesis during the clinical course of an autoimmune disease are limited [16–18]. The aim of this study was to examine to what extent OCB results change intraindividually over time and with which clinical conditions such changes might be associated.

Methods

Patients

We retrospectively analyzed 17,002 anonymized serial lumbar punctures documented in the CSF database, Department of Neurology, University Hospital Zurich, after pseudonymization. This database includes demographic (age, gender), clinical (confirmed or suspected diagnosis), and CSF data from 1992 on. Cases were included when ≥2 paired CSF and serum samples were analyzed for OCB and the diagnosis was documented in the database.

OCB definitions

OCB were assessed by isoelectric focusing electrophoresis with anti-human-IgG and silver stain (PhastSystem, GE Healthcare, Heidelberg, Germany). OCB were identified by two experienced raters in consensus reading and, in rare case of differences, by the laboratory supervisor. *OCB negative* (*OCB neg*) was defined as no OCB detection in CSF and serum (Fig. 1a). *OCB positive* (*OCB pos*) was defined as ≥1 OCB in the CSF, but no OCB in corresponding serum (Fig. 1a). *OCB pos/pos* was defined as ≥1

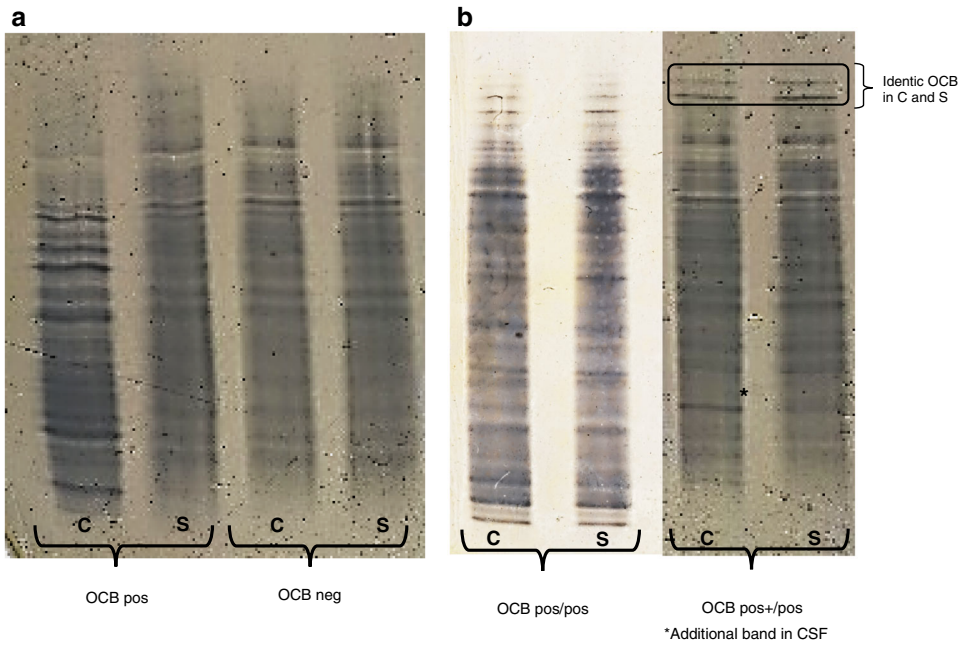

Fig. 1 Paired CSF and serum samples of OCB. **a** Two sets of paired CSF (*C*) and serum samples (*S*) showing the patterns of *OCB pos*, *OCB neg*. **b** Two sets of paired CSF and serum sample illustrating the pattern of *OCB pos/pos* and *OCB pos+/pos*. Isoelectric focusing electrophoresis with anti-human-IgG and silver stain. The lower image quality can be explained because we work with microgels that subsequently were scanned in

identic OCB in CSF and serum (Fig. 1b). *OCB pos+/pos* was defined as identical OCB in CSF and serum plus additional OCB in the CSF (Fig. 1b).

Results

OCB analyses were done at least twice in 144 patients with confirmed diagnoses (2× in 115 patients, 3× in 16 patients, 4× in four patients, 5× in two patients, 6× in four patients, 7× in one patient, and 10× in two patients). There was no change in the result of OCB in 109 cases. In 16 of them, OCB were analyzed more often than twice, and the results were also unchanged in those analyses. In 35 cases, OCB changed over time. In 13 of these cases, OCB were analyzed more than twice.

The group of patients with stable OCB included 43 women and 66 men. At the date of the first LP, the age of

Table 1 Overview of the change of OCBs

Diagnosis	N	Time between CSF analysis (days), mean (range)		Column 1 (C1) Unchanged OCB neg	Column 2 (C2) Unchanged OCB pos	Column 3 (C3) Unchanged OCB pos/pos	Column 4 (C4) OCB neg-> pos	Column 5 (C5) OCB neg-> pos+/ pos	Column 6 (C6) OCB neg-> pos/ pos	Column 7 (C7) OCB pos-> pos+/ pos	Column 8 (C8) OCB pos-> pos/ pos	Column 9 (C9) OCB pos/pos-> pos+/pos	Column 10 (C10) OCB pos+/ pos-> pos	Column 11 (C11) OCB pos-> neg	Reason for further LP, if available
Autoimmune	62	750 (5-3256)	CIDP	3 [1+1b; 2]			1 [1a+1b+2a]								C1: clinical deterioration; C4: follow-up, later on, multiple sclerosis is the additional suspected diagnosis (suspected diagnosis was already made when OCBs were still negative)
			Collagenosis	1									1 [1a+1c]	1 [1a+1c]	C10 and 11: clinical deterioration/ new symptoms
			GBS	2 [2]											
			Morbus Behcet						1 [1a+1c]						C6: follow-up
			MS		16 [1b+4a, 1c+4a : 6; 1c+4a; 1c+7; 1b+4a; 1c+4a; 1c; 1c; 1c; 1c]		1 [5]	1	1	3 [4a; 1b+4; 1b+4a]				2 [1a+1c; 1a]	C2: two cases in the context of a study, C5: diagnosis, C6: follow-up/ diagnosis; C7: follow-up; C11: clinical deterioration, follow-up
			CIS	3	3		2 [1a+1b]								C2: follow-up for exclusion of neuroborreliosis (positive serologic testing for borreliosis); C4: follow-up
			Mononeuritis multiplex	2											
			Myelitis	2 [1c]	2 [8; 1c+6]		1								C4: clinical deterioration
			Narcolepsy/ Cataplexy	2											
			NMO	1 [1b]			2 [1+1b]								C4: clinical deterioration
			Neuro-sarcoidosis		2 [1a+1c; 1c]									2 [1b; 1a+1b]	C2: clinical deterioration
			Paraneoplasm							1 [1c]		1 [1c+2]		1 [1c]	C7 and C11: follow-up
			Vasculitis		1 [1a+1b]										
Infectious	27	459 (6-2122)	HIV	2	2										
			Meningitis/ Meningo-encephalitis	3 [6]	3 [1b+6, 3+6]		4 [1+1b+3, 6, 6]								C1 and C4: follow-up
			Myelo-radiculitis	3 [1b; 1b+6]										1 [1c]	C1: new symptoms, follow-up, C11: follow-up (clinical improvement)
			PML				1 [1]							1 [1]	C4: clinical deterioration
			SSP		2										
			Neuro-borreliosis	2 [6; 1c+6]			1 [1b+6]								
			Neurolues	1 [6]	1 [6]										C1 and C2: follow-up

Table 1 continued

Diagnosis	N	Time between CSF analysis (days), mean (range)		Column 1 (C1) Unchanged OCB neg	Column 2 (C2) Unchanged OCB pos	Column 3 (C3) Unchanged OCB pos/pos	Column 4 (C4) OCB neg-> pos	Column 5 (C5) OCB neg-> pos+/ pos	Column 6 (C6) OCB neg-> pos/ pos	Column 7 (C7) OCB pos-> pos+/ pos	Column 8 (C8) OCB pos-> pos/ pos	Column 9 (C9) OCB pos/pos-> pos+/pos	Column 10 (C10) OCB pos+/ pos-> pos	Column 11 (C11) OCB pos-> neg	Reason for further LP, if available
Neuro-degenerative	16	457 (8-2740)	Dementia	3	1				1		1 [1]				C1: follow-up, clinical deterioration; C6: occurrence of an autoimmune disease at the date of the second LP; C8: follow-up, JC Virus positive at the date of 1. LP, negative at 2. LP
			Motor neuron disease	1		1									
			MSA	1											
			Neuro-degenerative	3 [1a+2]											C1: follow-up
			disease												
			Spinal canal stenosis	2											
			Spino-cerebellar ataxia						1						C6: follow-up
Neuro-vascular	6	806 (7-2699)	Encephalo-pathy vascular	3	1										C1: follow-up, exclusion of NPH
			Hemorrhage			1									
			Ischemia	1											
Neuro-oncological	6	52 (1-138)	Lymphoma CNS				1								C4: follow-up/ diagnosis, clinical deterioration
			Meningeoma	1											
			Metastasis/ Meningeosis carcinomatosa	1	1										
			Tumour mass	1	1										
Others	27	181 (88-274)	Facial nerve paresis		2 [1c+6]										C2: follow-up, no clear clinical recovery
		550 (12-1614)	Headache	3											C1: clinical deterioration
		1052 (13-2091)	Mitochondrial disease	2											
		1643	Morbus Fahr	1											
		249 (223-274)	Myelopathy	2											
		17	Neuro-psychiatric deficit	1											
		8	NPH			1									
		1581 (77-3533)	Others	3	3									1	C11: follow-up
		2482	PNP	1											
		1191 (81-2300)	Pseudotumor cerebri	2											
		779	Restless legs Syndrome	1											
		471 (24-1541)	Seizure disorder	4											C1: another non-convulsivus status epilepticus

CIDP chronic inflammatory demyelinating polyneuropathy, *CIS* clinically isolated syndrome, *GBS* Guillain–Barré syndrome, *MS* multiple sclerosis, *MSA* multisystem atrophy, *NMO* neuromyelitis optica device, *NPH* normal pressure hydrocephalus, *PML* progressive multifocal leukoencephalopathy, *PNP* polyneuropathy, *SSP* subacute sclerosing panencephalitis

[1] Under immunosuppressive therapy

[1a] Start immunosuppressive therapy between first and second CSF analysis

[1b] Steroid therapy

[1c] Steroid therapy between first and second CSF analysis

[2] Immunomodulating therapy (IVIG) between first and second CSF analysis

[2a] Immunomodulating therapy (IVIG) before first CSF analysis

[3] Autoimmune disease and immunosuppressive therapy

[4] Under immunomodulating therapy (disease modifying therapy)

[4a] Start immunomodulating therapy (disease modifying therapy) between first and second CSF analysis

[5] Under immunomodulating therapy (disease modifying therapy) and immunosuppressive therapy

[6] Antiviral therapy/antibiotic therapy

[7] Plasmapheresis between first and second CSF analysis

individuals ranged from 18 to 80 years (median, 44 years), and at the second one from 18 to 81 years (median, 47 years). The LP were done between April 1999 and July 2010. The time span between the LP ranged from 1 to 3,533 days (median, 241 days). *Unchanged OCB neg* appeared in 65 patients with mainly neurodegenerative and neurovascular diseases or other widespread diagnosis like headache or epilepsy and particularly without autoimmune or infectious CNS disease (Table 1, column 1). An intrathecal only OCB synthesis (*unchanged OCB pos*) was repeatedly found in 41 individuals with mostly autoimmune or infectious CNS diseases including MS/clinically isolated syndrome (CIS), myelitis, neurosarcoidosis, vasculitis, HIV, meningitis/meningoencephalitis, and neurolues (Table 1, column 2). A systemic OCB synthesis was repeatedly observed in three patients; each one with hemorrhage, motor neuron disease, and normal pressure hydrocephalus (*unchanged OCB pos/pos*).

The group of patients with newly appearing or with disappearing OCB included 21 women and 14 men (Table 1, orange and blue columns). At the date of the first LP the age ranged from 16 to 72 years (median, 51 years) and at the second one from 21 to 75 years (median, 52 years). The LP were performed between July 1999 and July 2010. The time span between the LP ranged from 6 to 2,942 days (median, 339 days); in the subgroup with newly emerging OCB from 6 to 2,942 days (median, 329 days), and in the group with disappearing OCB from 53 to 1,049 (median, 347 days).

The shift *OCB neg → OCB pos* appeared in autoimmune, infectious, and neurooncological diseases including MS/CIS, NMO, chronic inflammatory demyelinating polyneuropathy (CIDP), myelitis, progressive multifocal leukoencephalopathy (PML), neuroborreliosis, meningitis/meningoencephalitis, primary CNS lymphoma. Noteworthy, in the patient with CIDP, the additional diagnosis of possible MS was made between the two LP. The shift *OCB neg → OCB pos+/pos* appeared in one MS patient. The change *OCB neg → OCB pos/pos* occurred in autoimmune and neurodegenerative diseases (Table 1, column 6). In the patient with dementia, the diagnosis of an autoimmune disease (Basedow's disease) was made in addition at the time of the second LP. The shift *OCB pos → OCB pos+/pos* appeared in autoimmune diseases including MS and smoldering lymphoma with paraneoplastic polyradiculoneuropathy. The shift *OCB pos → OCB pos/pos* was only seen in one patient with dementia. Finally, the shift *OCB pos/pos → OCB pos+/pos* was only seen in multiple myeloma with emerging paraneoplastic polyneuropathy.

In the group of patients with a loss of OCB, the shift *OCB pos+/pos → OCB pos* was seen in one patient with autoimmune disease (collagenosis, M. Sjögren with CNS involvement). An immunosuppressive therapy with azathioprine had been established before the second LP. The shift *OCB pos → OCB neg* occurred in autoimmune and infectious diseases including collagenosis with CNS involvement, MS, neurosarcoidosis, breast cancer with paraneoplastic sensory polyneuropathy and leukoencephalopathy of unknown specification, myeloradiculitis, and PML.

In the patient with myeloradiculitis steroid therapy and in the patient with collagenosis cyclophosphamide, hydroxychloroquine and steroids had been started between LP. Moreover, in the MS patients, immunosuppressive therapy had been started between LP because of the additional diagnosis of CIDP and oligoarthritis with positive lupus serologic testing, respectively. Both patients with neurosarcoidosis had been treated with steroids between the LP, one with methotrexate in addition. The patient with PML suffered from chronic lymphocytic leukemia and had been treated with several chemotherapies and allogenic bone marrow transplantation between the two LP.

In all of the 24 MS patients included in our analysis, OCB were found positive at least once (Table 1, column 2, 4–7 and 11). Of the 24 MS patients, 19 had the diagnosis relapsing remitting MS (RRMS). In three of these RRMS patients, OCB were initially negative in the early phase of disease, but were detected in a subsequent analysis (Table 2, column 3–5). Eight patients had the diagnosis of CIS. Each three of them showed and did not show OCB in both LP (time span, 11–482 and 46–333 days, respectively), two had newly emerging OCB in the second LP (time span, 329–1,407 days).

Table 2 Overview of the change of OCBs in MS patients

Diagnosis	*N*	Time between CSF analysis (days), mean (range)	Column 1 *Unchanged OCB neg*	Column 2 *Unchanged OCB pos*	Column 3 *OCB neg → pos*	Column 4 *OCB neg → pos+/pos*	Column 5 *OCB neg → pos/pos*	Column 6 *OCB pos → pos+/pos*	Column 7 *OCB pos → neg*
RRMS	19	953 (64–3,256)		14	1	1	1	2	
PPMS	1	331		1					
SPMS	4	852 (26–2,942)		1				1	2
CIS	8	345 (11–1,407)	3	3	2				

RRMS relapsing-remitting multiple sclerosis, *PPMS* primary progressive multiple sclerosis, *SPMS* secondary progressive multiple sclerosis, *CIS* clinically isolated syndrome

Discussion

Differential diagnoses of diseases associated with CSF IgG OCB include infections, systemic and CNS inflammatory disorders, peripheral neuropathies, and others [10, 13, 16, 19–21].

In clinical practice, OCB are often investigated in the diagnostic work-up of inflammatory CNS disorders, in particular MS. In our study, OCB were not only observed in MS patients but also in patients with several other autoimmune and with infectious CNS diseases, as expected. However, it is noteworthy that OCB were found positive at least once in all of 24 MS patients. Time spans between an initially negative and the second, positive result ranged from 6.6 to 60 months (mean, 25 months). Thus, although presence of OCB in the CSF are no longer criteria for the diagnosis of RRMS and are only a facultative criteria for the diagnosis of primary progressive MS [11], our data suggest that it might be reasonable to do a second LP if OCB are negative at first in cases of suspected MS. If patients continue to have no intrathecal OCB production, it may become necessary to reconfirm an MS diagnosis.

In one-quarter of patients with repeated OCB analyses, the OCB result changed over time. A change to a positive result was often observed in infectious diseases. For example, in four patients with meningitis or meningoencephalitis, OCB where initially negative, but positive in the second LP 6–1,471 days (mean, 17 days) later, presumably corresponding to a post-infectious immunological CNS response.

Changes from a positive towards a negative OCB results were less frequent, observed in autoimmune disorders including MS, neurosarcoidosis, and collagenosis as well as in PML. Interestingly, an immunosuppressive therapy had been established before the second LP in the patients with MS and collagenosis and in one of the patients with neurosarcoidosis (Table 1). These immunosuppressive therapies may be assumed as the reason for the disappearance of OCB, which is unusual in MS patients [16, 22]. In addition to immunosuppression, the treatment with natalizumab can also lead to the disappearance of OCB from the CSF of MS patients [17, 23]. In accordance, Harrer and colleagues [23] showed that CSF IgG production is reduced by natalizumab therapy in MS. Fingolimod treatment also influences the number of lymphocytes in the CNS in neuroinflammatory diseases. Kowarik and colleagues [24] observed that treatment with fingolimod reduces the CSF leukocyte count in MS patients, but the B cell levels were more or less unchanged. Consequently, CSF IgG levels and occurrence of OCB were not influenced. Our data suggest that immunosuppression reduces B cell activity in the CNS in MS patients. It is tempting to speculate that a loss of OCB may be associated with response to immunosuppressive therapy of autoimmune diseases affecting the CNS. This is in line with other studies showing that the degree of humoral CNS immune response may be linked to the prognosis, i.e., the absence (or disappearance) of OCBs in MS patients may be associated with a better prognosis [22].

In five of 19 RRMS patients of our study population, OCB were initially negative or restricted to the CSF, but became positive or also detectable in the serum in the second investigation (Table 2, column 3–6). In one of these five patients, MS was diagnosed at the time of the second LP, and in another patient, the MS diagnosis was made later on. Further, one RRMS patient had initially positive OCB, became negative during natalizumab treatment, but positive again at PML onset (already published by Harrer 2013 [23]). This is in line with the observation of a switch from negative to positive OCB in another patient at PML onset (Table 1, column 4) as well as stable positive OCB in a patient with known PML suffering from HIV (Table 1, column 2). In the same context, Mazzarello et al. [25] found positive OCB in patients with PML.

In conclusion, the analysis of CSF OCB still plays an important role in the diagnostic process of autoimmune diseases affecting the CNS, particularly MS. OCB results may change over time, which can be explained by clinical conditions. Such variability must be taken into account for the interpretation of OCB results.

Limitations of our study are the retrospective analysis of data and the small number of cases per diagnosis. Furthermore, the second or further lumbar punctures were usually done for new clinical situations or for verification of uncertain diagnoses, which leads to selection bias favoring a higher amount of patients with changes in the OCB status.

Conflicts of interest The authors declare that they have no conflicts of interest.

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