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Clinical trial

The predictive value of CSF multiple assay in multiple sclerosis: A single center experience

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ABSTRACT

Background: Multiple sclerosis (MS) is a chronic, immune-mediated, inflammatory, neurodegenerative disorder. Many studies are investigating the potential role of body fluid biomarkers as prognostic factors for early identification of patients presenting with clinical isolated syndrome (CIS) at high risk for conversion to MS or to recognize RRMS patients at high risk for progression.
Objectives: To evaluate the correlation between levels of BAFF, chitinase 3-like 1 (CHI3L1), sCD163, Osteopontin (OPN), both on serum and cerebral spinal fluid (CSF), and the disease activity and progression. We also want to explore a possible relationship between serological and CSF biomarker's levels.
Patients and methods: We enrolled 82 patients between June 2014 and June 2016. Seventy-one received a diagnosis of demyelinating disease of CNS (46 RRMS and 25 CIS), while 11 were affected by other neurological diseases. All patients underwent a neural axis MRI, lumbar puncture and blood samples. Levels of BAFF, CHI3L1, sCD163, OPN on serum and CSF were analyzed by Luminex xMAP system, with a kit 11-plex ad hoc.
Results: The CSF CHI3L1, sCD163 and OPN levels were significantly higher in MS patients than in controls. We did not find significant differences in serum CHI3L1, sCD163 and OPN levels, nor CSF or serum BAFF levels between patient and control groups.

We found significantly higher CSF level of sCD163 and CHI3L1 in all patients' subgroups compared with controls, while OPN was higher in CIS and RR subgroups. We did not find significant differences for serum and CSF levels of all the markers between patients with or without clinical or radiological disease activity.

CSF sCD163 and CHI3L1 levels was significant higher in CIS patients who converted to MS ($p < 0.05$).

Using ROC curve analysis, CSF sCD163 resulted the best predictive factor. CSF CHI3L1 and OPN levels resulted useful independent predictors too. Combined ROCs of those three analytes demonstrated a better predictive value, with sCD163 and CHI3L1 resulting as the best combination.
Conclusions: CSF sCD163 CHI3L1 and OPN levels were higher in MS patients whereas serum CHI3L1, sCD163 and OPN levels did not show differences compared with controls. This finding confirms the high CSF specificity with regards to the analysis of processes, inflammatory and non-inflammatory, that occur within the CNS.

1. Introduction

Multiple sclerosis (MS) is a chronic, immune-mediated, inflammatory and degenerative disorder of the central nervous system (CNS).

MS is the leading non-traumatic cause of disability in young adults in Western countries (Leray et al., 2016).

The etiology of MS is still unknown, although several genetic and environmental risk factors have been identified or are considered. This complex and multifactorial pathogenesis probably accounts for MS clinical heterogeneity, varying from "benign" or even subclinical types to highly disabling forms, and makes it challenging to predict the clinical course at the individual patient level (Gajofatto et al., 2013).

Although there are currently no therapies to reverse the neurodegenerative process of MS, significant progress has been made over the last two decades in the treatment of relapsing remitting forms of MS

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(RRMS) with the introduction of disease-modifying therapies (DMTs) that decrease the frequency of relapses and slow the development of disability.

It becomes very important to find prognostic biomarkers for early identification of patients presenting with clinical isolated syndrome (CIS) at high risk for conversion to MS or to recognize RRMS patients at high risk for progression or with high-disease activity.

Many studies are currently investigating the potential role of body fluid biomarkers as prognostic factors (Agah et al., 2018; Hinsinger et al., 2015; Comabella et al., 2010; Canto et al., 2015; Martínez et al., 2015; Modvig et al., 2015; Puthenparampil et al., 2016; Stilund et al., 2014, 2015; Rittling and Singh, 2015; Kivisakk et al., 2014).

In our study, we aimed to evaluate the serum and cerebral spinal fluid (CSF) levels of B-cell activating factor of the TNF family (BAFF), chitinase 3-like 1 (CHI3L1), sCD163, Osteopontin (OPN), in MS patients using Luminex technology and to correlate those data with disease activity. We also evaluated a possible relationship between serological and CSF biomarker's levels. Luminex technology has emerged in the past 15 years and offers the benefits of the enzyme-linked immunosorbent assay (ELISA), but also enables the added value of higher throughput, increased flexibility, reduced sample volume (essential when the sample is poor as for CSF), and low cost with the same workflow as ELISA. Moreover, the possibility to analyze multiple factors, such as cytokines, in the same time allow to correlate and to adopt different combination of biomarkers to investigate the disease in a more specific way.

2. Patients and methods

2.1. Ethics statement

The study was conducted in accordance with the Ethical Declaration of Helsinki and all patients gave written, informed consent. The study and the material for informed consent were approved by Ethics Committee of our Hospital.

2.2. Patient cohort

We recruited patients admitted for further diagnostic investigations to the MS center of our Hospital, during a 24 months-period (from June 2014 to June 2016) who underwent a lumbar puncture (LBP) and blood samples. All patients performed a brain and spine MRI within 30 days from CSF sampling and at least every 12 months according to standardized clinical procedures. At baseline we collected medical and disease history, and each patient was clinically evaluated with extended disability status scale (EDSS) (Kurtzke, 1983) performed by certified neurologists (www.neurostatus.net). During follow-up, clinical visits were scheduled at least every six months.

We excluded patients with a known MS diagnosis or with a progressive course of disease or with previous use of DMTs or immunosuppressants.

MS was diagnosed according to the 2010 revised McDonald criteria (Polman et al., 2011).

CSF and serum samples were collected within 1 h from sampling and stored at −80 °C until used.

2.3. Luminex assay

A Luminex xMAP system (Bio-Plex 200 System, Bio-Rad Laboratories, Hercules, CA) which is a multiplex biometric ELISA-based immunoassay, containing dyed microspheres conjugated with a monoclonal antibody specific for a target protein, was used according to the manufacturer's instructions. We used the Luminex assay (R&D Systems, Minneapolis, USA) which allows the simultaneous detection of the following circulating analytes: BAFF, CHI3L1, sCD163, OPN. Concentrated human recombinant analytes and a broad range of standards was used to establish standard curves to maximize the sensitivity and dynamic range of the assay. Results were analyzed using a dedicated Bio-Plex Manager software and are expressed in picograms or nanograms per milliliter as appropriate.

2.4. Statistical analysis

Patients characteristics collected at baseline were the following: sex, age, time since first symptom, EDSS score, relapses and absence/presence of gadolinium enhanced (Gd)+ lesions within 30 days from sampling.

Differences in CSF and serum concentrations between different groups were evaluated by non-parametric methods (Mann–Whitney *U* test and Kruskal–Wallis test) according to sample size and distribution. Receiver operating characteristic (ROC) were fitted to estimate the diagnostic performance of CSF concentrations of sCD163, CHI3L1 and OPN.

All two-tailed *p*-values <0.05 were considered as significant, without correction for multiple comparisons considering the exploratory study design.

Data were analysed by using the Statistical Package for Social Sciences, version 22.0 (IBM SPSS, Inc., Chicago, Ill., USA).

3. Results

We enrolled 82 consecutive patients between June 2014 and June 2016. Forty-six patients received a diagnosis of RRMS and 25 were diagnosed as CIS, according to the revised McDonald criteria (Polman et al., 2011). The last eleven patients were affected by other neurological diseases and represented our control group. Patients were age and sex-matched with control group. Demographic characteristics of patients are shown in Table 1.

As presented in Table 1, at the LBP time the mean EDSS score was 1.26 ± 0.79 for CIS, 1.95 ± 1.29 for RRMS. IgG oligoclonal bands (OCB) were positive in 56% of CIS and 84.8% of RRMS. The mean disease duration was 17.6 ± 37.6 months for CIS, 17.1 ± 35.1 months for RRMS. Mean clinical follow-up time was 19.6 ± 9.1 months for CIS group and 16.6 ± 10.3 months for RRMS patients. At the evaluation time, 24% of patients presented a clinical relapse in the CIS group and 58.7% in the RRMS group, while brain and spine MRI documented Gd+ lesions in 8% of CIS and 60.9% of RRMS. RRMS and CIS patients presented significant differences regarding clinical, laboratory and radiological features, as expected according to diagnostic criteria.

3.1. Biomarkers levels

The CSF CHI3L1 and sCD163 concentrations showed significant

Table 1
Patients characteristics.

	Controls $n = 11$	CIS $n = 25$	RRMS $n = 46$	*p*
Female sex, (%)	27.3	28.0	32.6	0.897
Age, years	38.8 (10.7)	37.4 (12.2)	34.0 (9.2)	0.244
Disease duration, months	Na	17.6 (37.6)	17.1 (35.1)	0.955
EDSS score	Na	1.26 (0.79)	1.95 (1.29)	**0.007**
Relapsing patients (%)	Na	24	58.7	**0.004**
Patients with Gd+ lesions (%)	Na	8.0	60.9	**<0.001**
Oligoclonal bands (%)	9.1	56	84.8	**0.016**
Follow-up in months	Na	19.6 (9.1)	16.6 (10.3)	0,239

Patients characteristics. CIS: Clinical isolated syndrome; RRMS: relapsing remitting multiple sclerosis. All values are reported as mean (standard deviation) unless indicated otherwise. In bold are reported significant difference at a two-sided α level <0.05.

Table 2
Biomarker levels.

		Controls $n = 11$	CIS $n = 25$	RRMS $n = 46$	p
BAFF (pg/ml)	CSF	57.0 (27.3)	67.0 (53.4)	53.7 (35.1)	0.274
	Serum	510.3 (170.6)	507.9 (295.7)	446.7 (168.4)	0.464
Chitinase 3-like1 (ng/ml)	CSF	67.8 (29.5)	130.3 (93.5)	148.0 (91.1)	**0.004**
	Serum	16.4 (10.8)	16.6 (13.7)	14.9 (8.9)	0.965
sCD163 (ng/ml)	CSF	8.3 (2.8)	14.7 (6.5)	16.1 (10.0)	**< 0.001**
	Serum	468.3 (263.3)	430.2 (314.1)	470.0 (464.2)	0.667
Osteopontin (ng/ml)	CSF	12.5 (7.4)	32.2 (34.8)	25.0 (19.9)	0.056
	Serum	7.7 (5.8)	9.1 (7.8)	9.7 (6.9)	0.492

Biomarker levels. CIS: Clinical isolated syndrome; RRMS: relapsing remitting multiple sclerosis; CSF: cerebrospinal fluid. All values are expressed as mean (standard deviation). In bold are reported significant difference at a two-sided α level < 0.05.

differences between patients and controls groups (Table 2 and Fig. 1A–B). We found the highest levels of these biomarkers in RRMS CSF and we also found higher levels in CIS patients compared with controls. Although not reaching statistical significance, OPN levels were higher in both patients groups ($p = 0.054$).

We did not find significant differences in serum CHI3L1, sCD163 and OPN levels, nor CSF or serum BAFF levels between patients and controls (Table 2).

We did not find significant differences for serum and CSF levels of all the markers between patients with or without clinical or radiological disease activity, defined as clinical relapse and/or gadolinium-enhanced lesion on MRI within 30 days from sample collection (data not shown).

3.1.1. Conversion risk in CIS patients

At 12 months follow-up, we evaluated CIS patients who converted to definite MS according to 2010 revised McDonald's criteria (Polman et al., 2011). We next divided CIS group in converters and non-

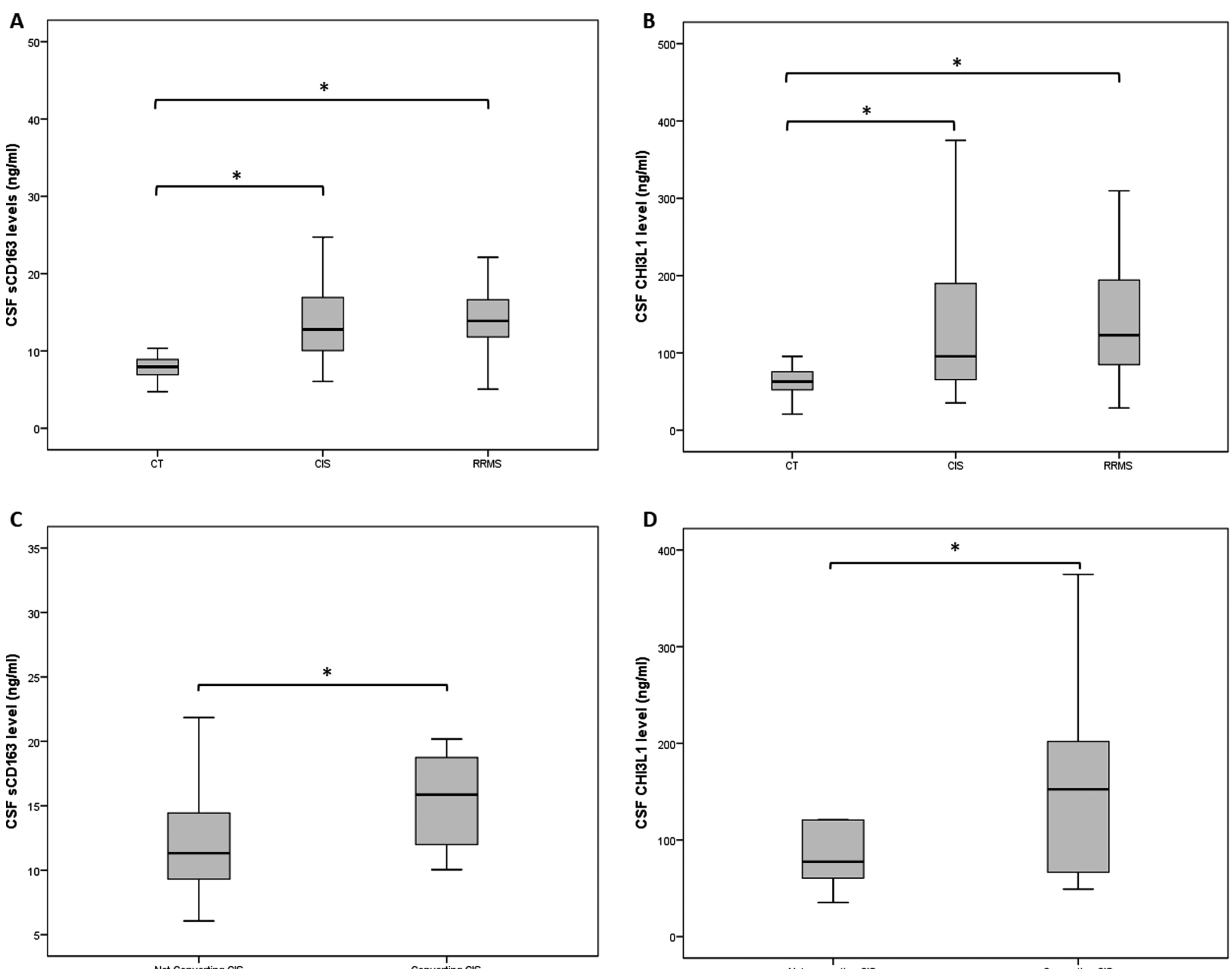

Fig. 1. CSF levels of sCD163 and CHI3L1. CSF levels of sCD163 (A) and CHI3L1 (B) in CIS and RRMS patients. Concentrations of CSF sCD163 (C) and CHI3L1 (D) baseline level in CIS patients according to conversion to MS.
CHI3L1: chitinase 3 like 1; CIS: clinical isolated syndrome; RRMS: relapsing remitting multiple sclerosis; CT: controls.
CSF levels of all biomarkers are expressed in ng/ml.
*represents p-value < 0.05.

Table 3
CIS patients' biomarker levels.

		CIS $n = 24$	Not converting CIS $n = 14$	Converting CIS $n = 10$	P
BAFF	CSF	64.6 (53.2)	67.0 (66.9)	61.3 (27.2)	0.725
(pg/ml)	Serum	511.4 (301.8)	506.5 (335.1)	519.0 (260.7)	0.753
Chitinase 3-like1	CSF	126.6 (93.4)	103.9 (80.2)	158.4 (105.2)	**0.031**
(ng/ml)	Serum	17.0 (13.8)	17.7 (16.3)	16.0 (9.5)	0.900
sCD163	CSF	14.3 (6.3)	12.5 (5.4)	16.9 (6.9)	**0.038**
(ng/ml)	Serum	424.2 (293.4)	424.2 (293.4)	444.5 (378.4)	0.900
Osteopontin	CSF	32.5 (35.6)	30.2 (41.0)	35.6 (28.0)	0.320
(ng/ml)	Serum	9.2 (7.9)	10.5 (9.2)	7.3 (5.3)	0.413

CIS patients' biomarker levels. CIS: Clinical isolated syndrome; CSF: cerebrospinal fluid. All values are expressed as mean (standard deviation). In bold are reported significant difference at a two-sided α level < 0.05.

Table 4
Biomarker levels stratified by the presence/absence of OCBs.

		OCB− $n = 18$	OCB+ $n = 53$	p
BAFF	CSF	81.2 (42.1)	50.7 (40.2)	**0.008**
(pg/ml)	Serum	487.6 (116.1)	462.1 (244.4)	0.689
Chitinase 3-like1	CSF	165.4 (142.6)	175.0 (147.0)	0.668
(ng/ml)	Serum	14.2 (9.8)	17.2 (11.7)	0.248
sCD163	CSF	15.2 (6.6)	17.1 (12.9)	0.933
(ng/ml)	Serum	425.2 (410.2)	469.7 (399.5)	0.360
Osteopontin	CSF	24.1 (19.1)	28.4 (29.2)	0.644
(ng/ml)	Serum	9.5 (7.1)	10.1 (8.0)	0.810

Biomarker levels stratified by the presence/absence of OCBs. OCBs: oligoclonal bands; CSF: cerebrospinal fluid. All values are expressed as mean (standard deviation). In bold are reported significant difference at a two-sided α level < 0.05.

converters, and we found significantly higher concentrations of CSF sCD163 and CHI3L1 baseline level in CIS patients who converted to MS (Table 3 and Fig. 1C–D).

3.1.2. Oligoclonal bands and BAFF levels

By separating patients according to the presence of CSF OCBs, we found significantly lower CSF BAFF levels in OCB+ patients (Table 4 and Fig. 2D).

3.1.3. ROC curves

Receiver operating characteristic (ROC) curve analysis was used to estimate the best independent predictors of disease. CSF sCD163 resulted the best predictive factor (area under the ROC curve (AUC) 0.87; range 0.76–0.98 $p < 0.001$), followed by CSF CHI3L1 levels (AUC 0.79; range 0.67–0.90 $p = 0.002$) and OPN (AUC 0.72; range 0.58–0.87, $p = 0.018$) (Fig. 2A–C).

4. Discussion

MS is a complex disease characterized by acute and chronic CNS inflammation leading to neurodegeneration. At the moment, electrophoresis with isoelectric focusing and immunoblotting or immunofixation for IgG is the only CSF test useful for MS diagnosis, as stressed by the last revision of McDonald criteria (Thompson et al., 2018). The demonstration of two or more CSF-specific oligoclonal bands more reliably indicates intrathecal antibody synthesis.

The possibility of exploring the differential concentration between MS patients and controls of several biomarkers in CSF can be useful to explain some of the complex pathophysiological mechanisms underlying MS pathology.

In our study we demonstrate that CSF CHI3L1 and sCD163 concentrations are significantly higher in RRMS and CIS patients compared with controls. We also show that in CIS patients higher baseline CSF CHI3L1 and sCD163 levels are associated with conversion to definite MS.

CHI3L1 is a glycoprotein secreted by various cell-types including macrophages and elevated CSF concentration of this protein was found in different CNS pathology such as amyotrophic lateral sclerosis and neurodegenerative dementias (Llorens et al., 2017). Several studies (Martínez et al., 2015; Modvig et al., 2015) documented that CSF CHI3L1 levels are higher in RRMS patients than in controls, and in CIS converters compared with not-converters (Hinsinger et al., 2015; Comabella et al., 2010; Canto et al., 2015). Pathological studies on MS patients' biopsy demonstrated that, within the white matter plaques, CHI3L1 is expressed by astrocytes, microglial cells and macrophages (Hinsinger et al., 2015). CHI3L1 role in CNS inflammation seems clear but is not fully elucidated. Nevertheless, a recent paper demonstrated, in the animal model of experimental autoimmune encephalomyelitis, that CHI3L1 promotes oligodendrogenesis through MAPK signaling and EGFR activation (Starossom et al., 2019).

CD163 is a membrane glycoprotein almost exclusively expressed in monocytes and macrophages. Several inflammatory stimuli guide CD163 cleavage through ADAM17/TACE enzymatic activity with the formation of its soluble fraction (sCD163). High plasmatic sCD163 levels were found in many systemic inflammatory diseases such as sepsis, chronic liver injury, diabetes and metabolic syndrome (Møller, 2012). Furthermore, CSF sCD163 levels are higher in early phase of disease, according to macrophage activation in MS plaques (Stilund et al., 2014, 2015). In CNS, CD163 is a marker of microglial M2 polarization being strongly expressed in MS active lesion and in perivascular macrophages (Vogel et al., 2013).

In our cohort, although not reaching statistical significance, OPN levels were higher in both patients groups ($p = 0.054$). Several studies explored the predictive value of CSF OPN in MS with conflicting results (Agah et al., 2018; Stilund et al., 2015; Kivisakk et al., 2014). Since OPN is upregulated in many pathologic conditions, a lack of specificity may limit the use of OPN as a biomarker in MS and other diseases (Rittling and Singh, 2015).

Serum CHI3L1, sCD163 and OPN levels have not showed differences compared with controls.

A correlation between CSF and serum levels could be useful, allowing a more accessible tool for monitoring disease progression over time and a potential tool for assessing the response to treatment. However, this finding confirms the high CSF specificity with regards to the analysis of pathological processes, either inflammatory or non-inflammatory, occurring within the CNS.

Interestingly, we detected significantly lower CSF BAFF levels in patients with OCBs. Only few studies evaluated this biomarker with regard to the presence of oligoclonal bands. Our data are in line with two previous papers analysing two independent cohorts (Ragheb et al., 2011; Puthenparampil et al., 2016). Puthenparampil et al. found the OCB+ MS patients had BAFF CSF levels lower than OCB− MS and controls. Moreover, Ragheb et al. found significantly lower CSF BAFF levels in MS patients compared with other neurological inflammatory

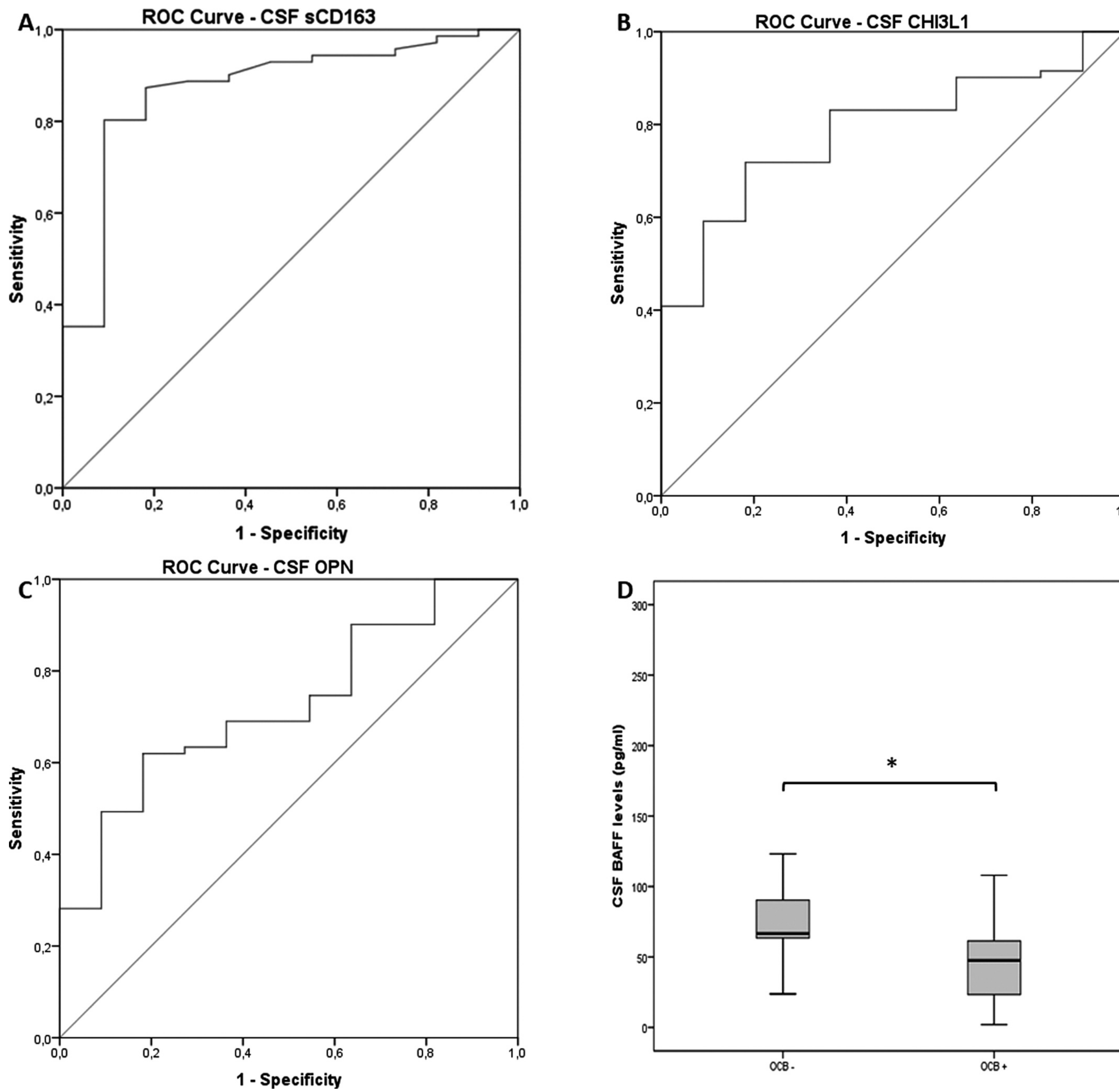

Fig. 2. ROC curve analysis of CSF levels of sCD163 (A), CHI3L1 (B) and OPN (C).
CSF BAFF levels respect to the presence of OCBs (D).
ROC: Receiver operating characteristic; CHI3L1: chitinase 3 like 1; OPN: osteopontin; AUC: area under the ROC curve; OCB: oligoclonal bands. CSF levels are expressed in pg/ml.
*represents *p*-value <0.05.

and degenerative disorders. With regard to MS patients, they found higher BAFF levels in progressive MS. On the other hand Franciotta et al. found higher levels of BAFF levels in patients with more than 6 oligoclonal bands compared with patients with less than 6 OCB+ (Franciotta et al., 2011). BAFF promotes antibody-producing plasma cells and B cells survival and is constitutively produced by astrocytes in the CNS. Higher CSF levels of CXCL13, a chemokine responsible for the recruitment of naïve B cells levels, were found in MS patients. More interestingly, OCB+ MS patients have higher CSF levels of CXCL13 than OCB− patients (Ragheb et al., 2011; Puthenparampil et al., 2017). Higher CXCL13 and lower BAFF concentrations in OCB+ MS patients may indicate an upregulated recruitment of naïve B cells within the CNS and a concomitant higher rate of BAFF consumption by B cells as they mature into antibody-secreting plasma cells. Further studies are warranted to confirm our finding and ultimately clarify its meaning.

5. Conclusions

CSF sampling is important in the diagnostic work up of MS, as emphasized also by the last revision of McDonald diagnostic criteria (Thompson et al., 2018). CSF sCD163 and CHI3L1 levels were significantly higher in MS patients compared to controls. Furthermore, higher CSF sCD163 and CHI3L1 levels in CIS patients, seemed to be independent prognostic factors for conversion to defined MS.

Testing selected CSF biomarkers can be helpful to better characterize MS pathological changes occurring in clinical and MRI well-characterized patients cohorts. This approach may be useful to gain additional information possibly helping, in the next future, to shape a better clinical-pathological patient profile at individual level. Our results confirm the usefulness of a multiplex assay approach allowing fast and accurate analysis of selected multiple biomarker using a small CSF sample amount.

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Declaration of Competing Interest

We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

References

Agah, E., Zardoui, A., Saghazadeh, A., Ahmadi, M., Tafakhori, A., Rezaei, N., 2018. Osteopontin (OPN) as a CSF and blood biomarker for multiple sclerosis: a systematic review and meta-analysis. PLoS One 13 (1), e0190252.
Canto, E., Tintoré, M., Villar, L.M., et al., 2015. Chitinase 3-like 1: prognostic biomarker in clinically isolated syndromes. Brain 138, 918–931.
Comabella, M., Fernández, M., Martin, R., et al., 2010. Cerebrospinal fluid chitinase 3-like 1 levels are associated with conversion to multiple sclerosis. Brain 133, 1082–1093.
Franciotta, D., Di Stefano, A.L., Jarius, S., Zardini, E., Tavazzi, E., Ballerini, C., Marchioni, E., Bergamaschi, R., Ceroni, M., 2011 Jan. Cerebrospinal BAFF and Epstein-Barr virus-specific oligoclonal bands in multiple sclerosis and other inflammatory demyelinating neurological diseases. J. Neuroimmunol. 230 (Jan (1-2)), 160–163.
Gajofatto, A., Calabrese, M., Benedetti, M.D., Monaco, S., 2013. Clinical, MRI, and CSF markers of disability progression in multiple sclerosis. Dis. Markers 35 (6), 687–699.
Hinsinger, G., Galéotti, N., Nabholz, N., et al., 2015. Chitinase 3-like proteins as diagnostic and prognostic biomarkers of multiple sclerosis. Mult. Scler. 21, 1251–1261.
Kivisakk, P., Healy, B.C., Francois, K., et al., 2014. Evaluation of circulating osteopontin levels in an unselected cohort of patients with multiple sclerosis: relevance for biomarker development. Mult. Scler. 20 (4), 438–444.
Kurtzke, J.F., 1983. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). Neurology 33 (11), 1444–1452.
Leray, E., Moreau, T., Fromont, A., Edan, G., 2016. Epidemiology of multiple sclerosis. Rev. Neurol. 172 (1), 3–13.
Llorens, F., Thüne, K., Tahir, W., et al., 2017. YKL-40 in the brain and cerebrospinal fluid of neurodegenerative dementias. Mol. Neurodegener. 12 (Nov (1)), 83.
Martínez, M.A., Olsson, B., Bau, L., et al., 2015. Glial and neuronal markers in cerebrospinal fluid predict progression in multiple sclerosis. Mult. Scler. 21, 550–561.
Modvig, S., Degn, M., Roed, H., et al., 2015. Cerebrospinal fluid levels of chitinase 3-like 1 and neurofilament light chain predict multiple sclerosis development and disability after optic neuritis. Mult. Scler. 21, 1761–1770.
Møller, H.J., 2012. Soluble CD163. Scand. J. Clin. Lab. Invest. 72 (Feb (1)), 1–13.
Polman, C.H., Reingold, S.C., Banwell, B., et al., 2011. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. Ann. Neurol. 69 (2), 292–302.
Puthenparampil, M., Federle, L., Miante, S., et al., 2017. BAFF Index and CXCL13 levels in the cerebrospinal fluid associate respectively with intrathecal IgG synthesis and cortical atrophy in multiple sclerosis at clinical onset. J. Neuroinflamm. 14 (Jan (1)), 11.
Puthenparampil, M., Miante, S., Federle, L., et al., 2016. BAFF is decreased in the cerebrospinal fluid of multiple sclerosis at clinical onset. J. Neuroimmunol. 297, 63–67.
Ragheb, S., Li, Y., Simon, K., et al., 2011 Jul. Multiple sclerosis: BAFF and CXCL13 in cerebrospinal fluid. Mult. Scler. 17 (Jul (7)), 819–829.
Rittling, S.R., Singh, R., 2015. Osteopontin in Immune-mediated Diseases. J. Dent. Res. 94 (12), 1638–1645.
Starossom, S.C., Campo Garcia, J., Woelfle, T., et al., 2019. Chi3l3 induces oligodendrogenesis in an experimental model of autoimmune neuroinflammation. Nat. Commun. 10 (Jan (1)), 217.
Stilund, M., Gjelstrup, M.C., Petersen, T., et al., 2015. Biomarkers of inflammation and axonal degeneration/damage in patients with newly diagnosed multiple sclerosis: contributions of the soluble CD163 CSF/serum ratio to a biomarker panel. PLoS One 10 (4), e0119681.
Stilund, M., Reuschlein, A.K., Christensen, T., et al., 2014. Soluble CD163 as a marker of macrophage activity in newly diagnosed patients with multiple sclerosis. PloS One 9 (6), e98588.
Thompson, A.J., Banwell, B.L., Barkhof, F., et al., 2018. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. Lancet Neurol. 17 (2), 162–173.
Vogel, D.Y., Vereyken, E.J., Glim, J.E., et al., 2013. Macrophages in inflammatory multiple sclerosis lesions have an intermediate activation status. J. Neuroinflamm. 10 (Mar), 35.