The intrathecal synthesis of CXCL13 associates with a decreased cortical thickness in multiple sclerosis at clinical onset

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Objective. To analyse the presence in the cerebrospinal fluid (CSF) of cytokines that may play a role in B-cell development, differentiation and activation, and their association with magnetic resonance imaging (MRI) parameters of white and grey matter damage.

Materials an Methods. 22 patients with clinically isolated syndrome or very early Relapsing Remitting Multiple Sclerosis (CIS/eRRMS) and 11 individuals with no evidence of neurological diseases (normal controls, NC) were enrolled in the study. All subjects underwent 3T MRI examination (including HD 3D-T1, to quantify Global Cortical Thickness, CTh, 3D-FLAIR). Paired CSF and serum samples were analysed for diagnostic purposes (IgG Index and IgGOB) and stored at -80°C until cytokine testing. BAFF, APRIL and CXCL13 were detected by means of commercially available Elisa Kits, and their concentration were expressed as Index ($[cyt]_{CSF}/[cyt]_S$: $[Alb]_{CSF}/[Alb]_S$).

Results.

Serum and CSF CXCL13. Serum concentrations of CXCL13 did not differ between patients and controls (Figure 1a). However, CXCL13 was detectable in 14/22 (63.6%) CSF of CIS/eRRMS and in none of NC. In CXCL13 $^+$ CSF, the mean value of CXCL13 was 38.8±41.1pg/mL (range 1.4 -132.8, Figure 1b), and its ratio was not correlated to albumin ratio (r: 0.27, p=0.4).

Mean CSF lymphocyte count in CXCL13$^+$ and CXCL13 $^-$ was 13.0±16.6/μL and 3.8±3.2/μL, respectively ($p<0.05$ versus NC). The percentage of IgGOB positive CSF in CXCL13$^+$ and CXCL13$^-$ was 100% ($p<0.0001$) and 50% ($p<0.05$), respectively, and the difference was significant ($p<0.05$). No further difference in other CSF standard parameters was disclosed between CXCL13$^+$ and CXCL13$^-$ (Table 1).
Finally, in both CXCL13$^-$ and NC the Alb ratio correlated to IgG ratio (r: 0.9, $p<0.005$), while this correlation was not observed in CXCL13$^+$ (r: 0.3, p=0.4, Figure 1c and 1d).

Serum and CSF BAFF and APRIL.
BAFF and APRIL were detected in all the sera and CSF specimens. No difference in concentration was observed between NC and CIS/eRRMS and between CXCL13+ and CXCL13-. No correlation between standard CSF parameters and APRIL or BAFF concentrations, ratios or Index were disclosed.

MRI parameters: gCTh was significantly thinner in CXCL13$^+$ (2.38±0.08 mm) compared to CXCL13$^-$ (2.53±0.07mm, $p<0.005$, Figure 2).
No difference in WM lesion volume and number was disclosed within the two groups.

	Cellularity (/μL)	IgGOB frequency	LCS [Alb] (g/L)	S [Alb] (g/L)	Alb ratio (g/L*10^3)	LCS [IgG] (g/L)*10^3	S [IgG] (g/L)	IgG Ratio (*10^3)	IgG Index
CXCL13+	13.0 ± 16.6	100%	0.3 ± 0.1	43.6 ± 4.0	5.8 ± 2.9	56.1 ± 41.4	10.9 ± 2.2	5.5 ± 4.8	1.0 ± 0.7
p	0.1	*<0.05*	0.4	0.6	0.5	0.1	0.8	0.2	0.2
CXCL13-	3.8 ± 3.2	50%	0.2 ± 0.1	42.7 ± 3.4	5.0 ± 1.4	32.5 ± 12.1	10.6 ± 2.0	3.2 ± 1.8	0.6 ± 0.2

Table 1. Standard CSF parameters in CXCL13+ and CXCL13-

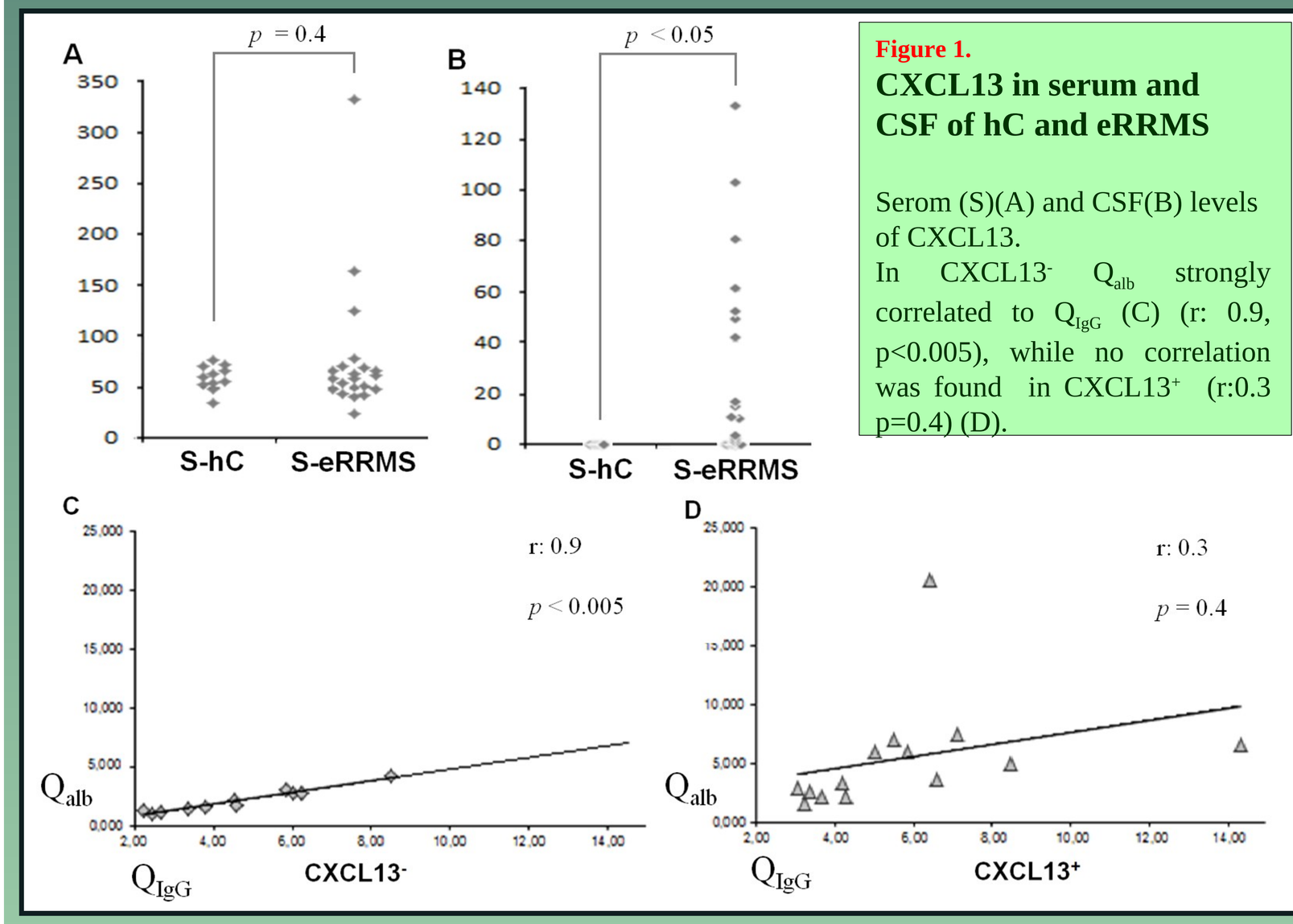

Figure 1.
CXCL13 in serum and CSF of hC and eRRMS

Serom (S)(A) and CSF(B) levels of CXCL13.
In CXCL13$^-$ Q_{alb} strongly correlated to Q_{IgG} (C) (r: 0.9, $p<0.005$), while no correlation was found in CXCL13$^+$ (r:0.3 p=0.4) (D).

Discussion. Meningeal B-cell follicule-like structures have been histologically associated with cortical inflammation and neurodegeneration in Multiple Sclerosis (MS), especially in patients with secondary progressive MS. However, to what extent the development of B-cell follicules is linked to cortical damage in the early disease phases has never been investigated. In this study we found that CXCL13 was associated to CSF markers of intrathecal antibody production (IgG Index and IgGOB) and correlated with a higher diffuse cortical damage, thus supporting the early involvement of B cells in the pathogenesis of cortical atrophy in MS.

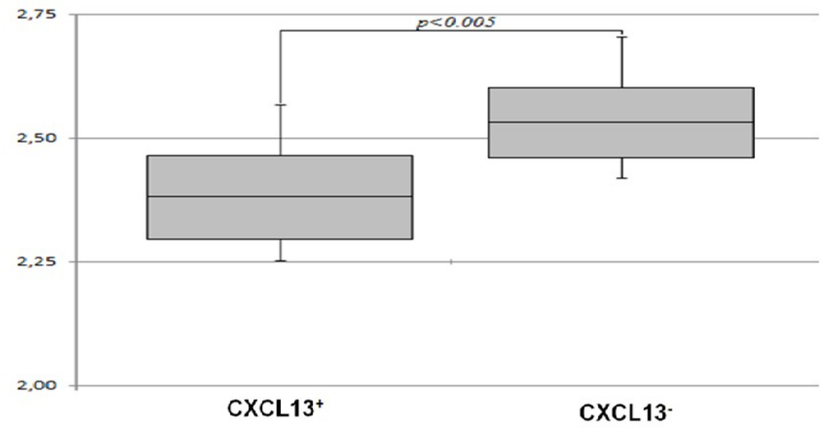

Figure 2.
MRI in CXCL13$^+$ and CXCL13$^-$ patients.

In CXCL13$^+$ patients a significant thinning of gCTh was observed compared to the CXCL3$^-$ and to NC ($p<0.005$ and $p<0.05$, respectively).

Conclusions. The intrathecal synthesis of the CXCL13, but not that of BAFF and APRIL, is associated with a decreased cortical thickness in a subgroup of CIS/eRRMS. This chemokine may play a role in driving B-cell follicle formation in early disease phases. The use of CXCL13 as marker of cortical damage in MS merits further investigation.

Conflicts of Interest: *Puthenparampil Marco* received travel grant from Novartis, Genzyme, Biogen Idec, Teva and Sanofi Aventis; he has been consultant for Genzyme. *Miante Silvia* received travel grant form Biogen Idec, Novartis, Sanofi Aventis and Teva. *Federle Lisa* has received funding for travel from Novartis, Merck Serono, Biogen Idec, Sanofi-Aventis, Bayer Schering Pharma, Almirall, Genzyme, Teva and honoraria from Merk Serono, Teva and Almirall. *Poggiali Davide* received travel grant from Biogen Idec, Novartis, Sanofi Aventis and Teva. *Rinaldi Francesca* serves as an advisory board member of Biogen-Idec and has received funding for travel and speaker honoraria from Merck Serono, Biogen Idec, Sanofi-Aventis, Teva and Bayer Schering Pharma. *Perini Paola* has received funding for travel and speaker honoraria from Merck Serono, Biogen Idec, Sanofi-Aventis, and Bayer Schering Pharma and has been consultant for Merck Serono, Biogen Idec and Teva. *Gallo Paolo* has been a consultant for Bayer Schering, Biogen Idec, Genzyme, Merck Serono and Novartis; has received funding for travel and speaker honoraria from Merck-Serono, Biogen Idec, Sanofi-Aventis, Novartis Pharma and Bayer-Schering Pharma, Teva; has received research support from Bayer, Biogen Idec/Elan, Merk Serono, Genzyme and Teva; and has received research grant from the University of Padova, Veneto Region of Italy, the Italian Association for Multiple Sclerosis, the Italian Ministry of Public Health.