CXCL-13, CXCL-9 and Il-12b cerebrospinal fluid levels predict higher disease activity and are associated with intrathecal IgM synthesis in multiple sclerosis

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Introduction

Intrathecal IgM synthesis predicts higher disease activity in multiple sclerosis (MS). The cytokines CXCL-13, CXCL-9 and IL-12b are involved in MS pathophysiology, mainly by regulation and activation of B- and T-lymphocytes.

Objectives/Aims

We aimed to investigate if cerebrospinal (CSF) levels of these cytokines are associated with intrathecal IgM synthesis and also predict MS disease activity.

Methods

CSF cytokine levels were measured by Octave custom assay panel of 249 clinically isolated syndrome (CIS) or MS patients (CIS: n=121; relapsing-remitting: n=91; secondary-progressive: n=23 and primary-progressive: n=14). 92 CIS patients were longitudinally followed in the Swiss MS cohort study. CIS/MS patients were categorized based on the presence of oligoclonal IgG bands (OCGB), intrathecal IgG (IF=IntrathecalFraction) and IgMIF, as follows: 1) OCGB-/IgGIF-/IgMIF-, 2) OCGB+/IgGIF-/IgMIF-, 3) OCGB+/IgGIF+/IgMIF-, 4) OCGB+/IgGIF+/IgMIF+. We used separate linear regression models with (log2) levels of CXCL-13, CXCL-9 and IL-12b as dependent variables; and CSF category (2-4 vs 1) as independent variables, respectively, adjusted for age, sex and albumin-ratio. To predict the time to second clinical event we used separate Cox regression models with the (log2) cytokine levels as independent variables adjusted for age, sex and albumin-ratio.

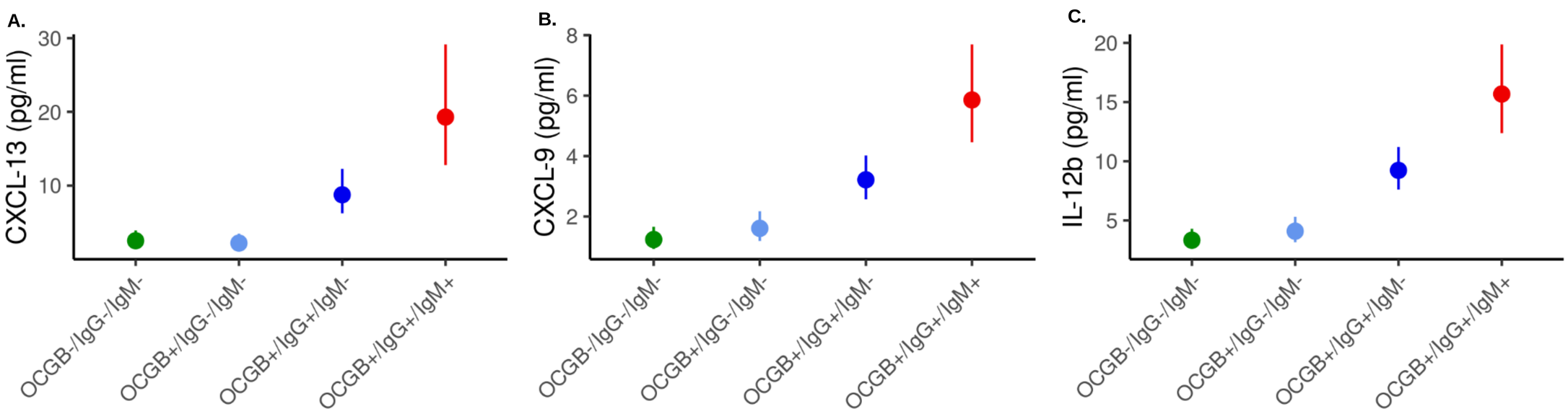

Figure 1. Adjusted CSF levels of A) CXCL-13; B) CXCL-9 and C) IL-12b depending on CSF profiles in patients with CIS/MS

$OCGB^-/IgG_{IF}^-/IgM_{IF}^-$ (n=48); **$OCGB^+/IgG_{IF}^-/IgM_{IF}^-$** (n=52); **$OCGB^+/IgG_{IF}^+/IgM_{IF}^-$** (n=83); **$OCGB^+/IgG_{IF}^+/IgM_{IF}^+$** (n=57).

Patients with an intrathecal IgM-synthesis $OCGB^+/IgG_{IF}^+/IgM_{IF}^+$ had highest CSF levels for all three cytokines (red).

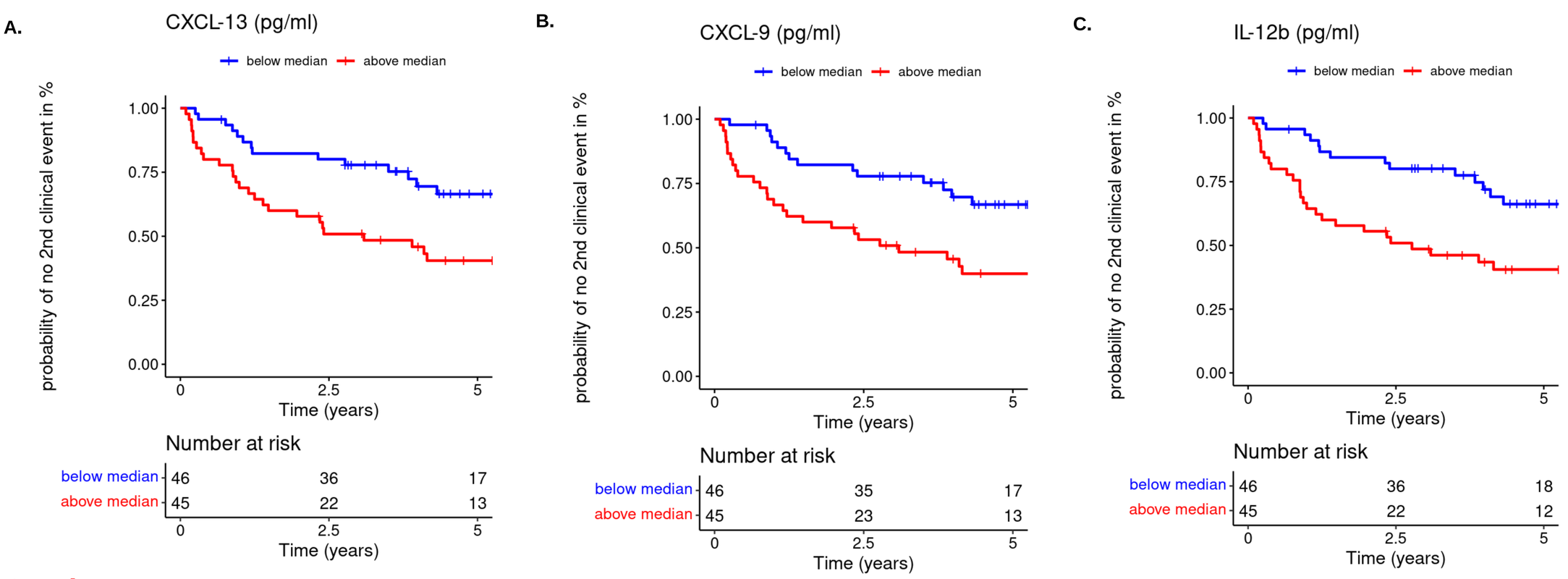

Figure 2. Kaplan-Meier-curves for the time to the second clinical event depending on CSF levels below/ above median for

A) CXCL-13,
B) CXCL-9 and
C) IL-12b.

Higher levels (above median; red) were associated with an increased Hazard Ratio for all three cytokines.

Results

- CXCL-13 levels were increased 3.4-fold (95%-confidence interval 2.0-5.5) in OCGB+/IgGIF+/IgMIF- and 7.9-fold (4.5-13.8) in OCGB+/IgGIF+/IgMIF+ patients compared to OCGB-/IgGIF-/IgMIF- (all p<0.01) (**Fig. 1A**).
- CXCL-9 levels were 2.5-fold (1.8-3.5) higher in OCGB+/IgGIF+/IgMIF- patients (n=83) and 4.4-fold (3.0-6.4) in OCGB+/IgGIF+/IgMIF+ (n=57) versus OCGB-/IgGIF-/IgMIF- (n=48) (all p<0.01) (**Fig. 1B**).
- IL-12b levels in OCGB+/IgGIF+/IgMIF- patients were 2.6-fold (2.0-3.4) increased and in OCGB+/IgGIF+/IgMIF+ patients 4.4-fold (3.2-6.1) compared to OCGB-/IgGIF-/IgMIF- (all p<0.01) (**Fig. 1C**).
- Per doubling of cytokine levels the hazard for time to second clinical event in CIS was 20% higher for CXCL-13 (HR 1.20;1.0-1.4; p=0.019), 27% higher for CXCL-9 (1.0-1.5; p=0.019) and 33% higher for IL-12b (1.1-1.6; p<0.01) (**Fig. 2**)

Conclusions

CSF levels of CXCL-13, CXCL-9 and IL-12b are increased in patients with intrathecal IgG and especially in those with additional intrathecal IgM synthesis. Higher cytokine levels predict increased disease activity. Our results support the concept that in MS, IgM, CXCL-13, CXCL-9 and IL-12b are part of an interconnected pathophysiological process and are all associated with higher disease activity.

Disclosures

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