



T follicular helper/regulatory lymphocyte ratio (TFH/TFR) correlates with intrathecal IgG synthesis in multiple sclerosis patients at clinical onset



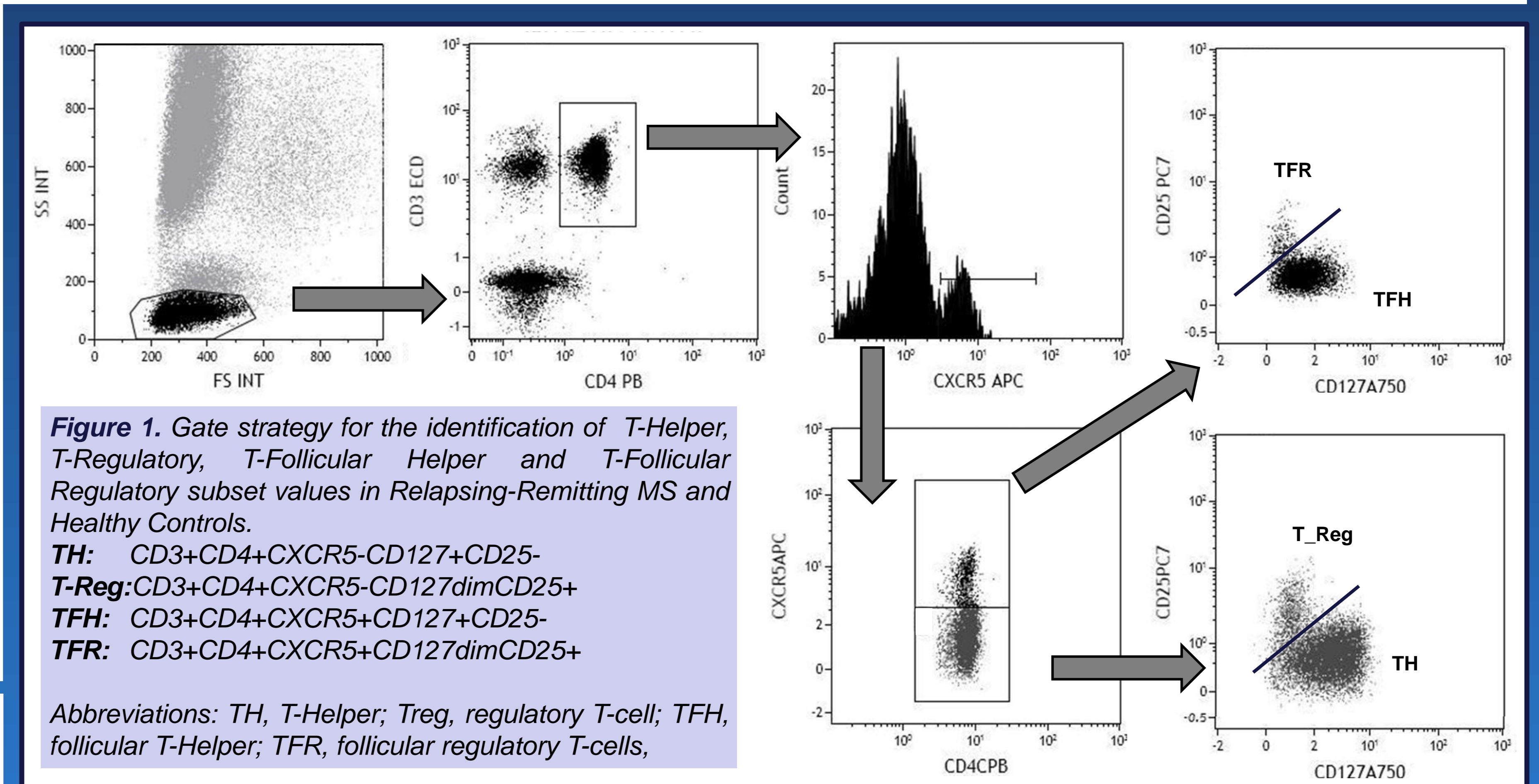
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Introduction. An imbalanced stimulation/regulation of B cell activity is believed to play a central role in the pathogenesis of autoimmune diseases.

Aims. To investigate number and percentage of T Follicular Helper (TFH) and T Follicular Regulatory (TFR) lymphocytes, and their ratio, in multiple sclerosis (MS) at clinical onset.

Materials and Methods. Paired cerebrospinal fluid (CSF) and peripheral blood specimens were collected from 27 relapse-onset MS (RMS) patients. Peripheral blood was also obtained from 12 gender- and age-matched healthy controls (HC). The absolute numbers and percentages of conventional T-Helper (TH), T-Regulatory (T-Reg), T-Follicular Helper (TFH) and Regulatory (TFR) lymphocytes were analyzed in peripheral blood of RMS and HC.

CSF analysis included quantitative measurement of intrathecal IgG synthesis by means of IgG Index and IgG Hyperbolic Function (IgLoc and IgGIF) as well as the detection of IgG Oligoclonal Bands (IgGOB) by isoelectric focusing.



Results.

CD4+ lymphocyte count was slightly increased in RRMS (896.1±291.0/μL) compared to HC (574.5±211.1/μL, p=0.05). However, the absolute counts of each CD4+ subsets were not significantly higher in MS compared to HC. On the other hand, a lower percentage of TFR on CD4+ T was observed in RRMS (0.7±0.5%) compared to HC (1.1±0.5%, p<0.01). Moreover, the TFH/TFR ratio was significantly higher in MS patients than in HC (18.7±12.5 vs 9.3±5.2, p<0.001) (Figure 2). No difference was observed between RRMS and HC for TH and T-Reg percentage on CD4+ T-cells.

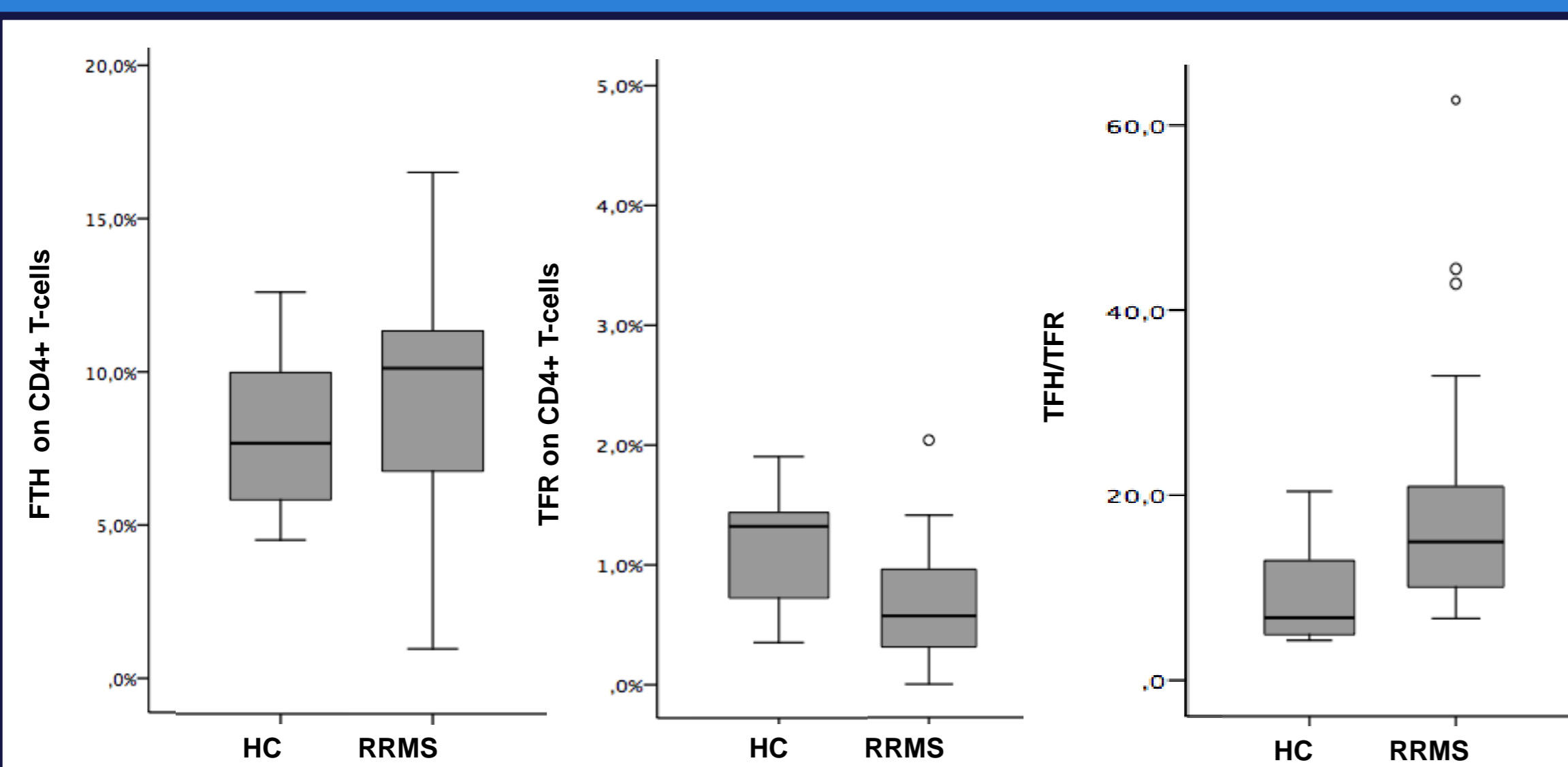


Figure 2. TFH, TFR and their ratio in HC and RRMS. A decreased TFR count on CD4+ T-cells and an increased of TFH/TFR ratio was observed in RRMS.

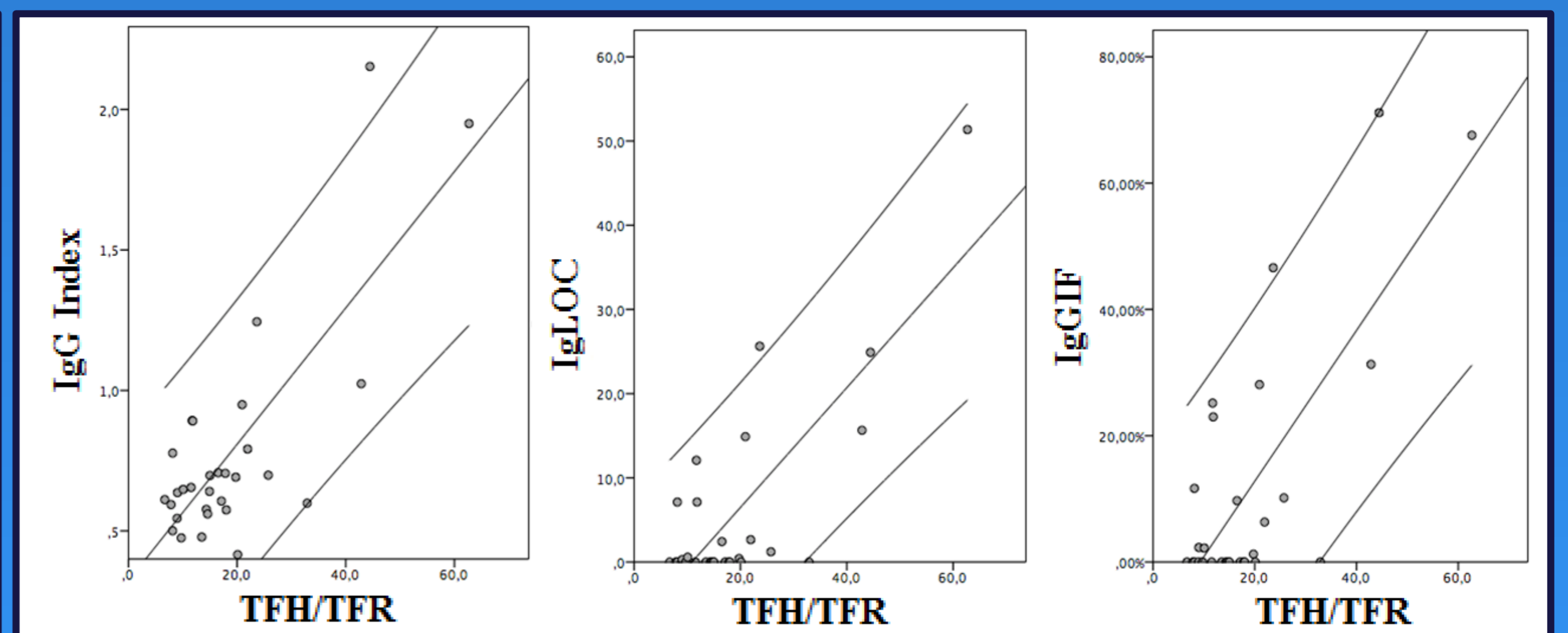


Figure 3. Intrathecal IgG synthesis correlates to TFH/TFR. In RRMS all quantitative indexes of intrathecal IgG synthesis correlate to the imbalance between T-Follicular Helper (TFH) and Follicular Regulatory T-cells (TFR).

Intrathecal synthesis of IgGOB was detected in 81.5% of RMS patients, while increased IgG Hyperbolic Function (>0 mg/L) or IgG Index (>0.7) were found in 40.7% and 33.3% of RMS patients, respectively. Interestingly, TFH/TFR ratio correlated with quantitative intrathecal IgG synthesis parameters (r= 0.4, p<0.05), but not with peripheral B cell count (r= -0.3, p=0.11) or percentage (r=-0.2, p=0.37).

Conclusions. The increased TFH/TFR ratio observed in RMS compared to HC indicates an imbalanced follicular reaction that may contribute to support the intrathecal IgG synthesis. Our findings suggest a possible role of follicular T-cell subsets in favoring the development of self-reactive central nervous system-targeting B-cells in MS patients since clinical onset.

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