Coagulation/complement activation and cerebral hypoperfusion in relapsing-remitting multiple sclerosis

35

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Background

Multiple sclerosis (MS) is an inflammatory disease of the central nervous system. It has been demonstrated that not only adaptive immunity but also innate immune system plays a relevant role in MS pathogenesis (Gandhi 2010; Mayo 2012). There are several studies confirming platelet (Horstman 2010; Nurden 2011; Behari 2013) and complement (Horstman 2011; Veerhuis 2011; Ingram 2012) involvement in MS, having an important role in the innate immune response by linking inflammation and coagulation. Moreover, decreased cerebral blood volume (CBV) and flow (CBF) , as well as its prolonged mean transit time (MTT), have been demonstrated in all forms of MS, both in white and grey matter, by dynamic susceptibility contrast-enhanced MRI (Adhya 2006, Inglese 2007, Varga 2009).

The aim of our study is to evaluate the serum/plasma levels of coagulation/complement factors in relapsing MS patients (REL) compared to remitting ones (REM) and to healthy controls (CTR), and to assess the presence of brain hemodynamic changes of patients in order to correlate their coagulation status with MRI perfusion data.

Preliminary Data:

We identified by proteomics analysis differently expressed serum proteins: ceruloplasmin, clusterin, apolipoprotein E and in particular anti-thrombin (AT) and complement C3 in 18 MS patients compared to 7 CTR. Moreover, AT has been found oxidatively modified in relapse (REL) compared to remission (REM) reinforcing the importance of the coagulation system in MS (Fiorini, Koudriavtseva et al. PLoS One. 2013). We also tested sera from 58 REM, 26 REL, 16 patients with secondary progressive (SP)MS and 60 CTR for a large spectrum of antiphospholipid antibodies (aPL) using enzyme immunoassays. The overall rate of positivity for at least one aPL was significantly higher in MS pts compared to CTR (32% vs 7% respectively, $p<0.0001$), and in REL compared to REM and SPMS (53.8, 20.7 and 37.5% respectively, $p=0.002$). In the single aPL analysis, the rate of positivity was significantly higher in MS patients compared to CTR for anti-prothrombin IgM (7% vs 0, $p=0.05$), and in REL compared to REM and SPMS for antiß2glycoproteinI IgM (26.9, 1.7, 6.3% respectively, $p<0.0001$), anti-prothrombin IgM (15.4, 3.4, 6.3% respectively, $p=0.05$) and IgG (19.2, 5.2, 0% respectively, $p=0.05$). These data suggest that aPL occurrence in MS could be an expression of inflammatory thrombotic processes during the relapse (Koudriavtseva et al. Neurol Sci 2014). In the same patients antiannexin V IgG were associated with high total and low density cholesterol levels supporting the relevance of thrombogenic mechanisms in MS (Mandoj et al, submitted to J Neuroimmunol). Previously, hypoperfusion and especially decreased CBF has been demonstrated in all forms of MS and even in clinically isolated syndrome, both in normal-appearing white and grey matter and in lesions, by dynamic susceptibility contrast-enhanced MRI (Adhya 2006, Inglese 2007, Varga 2009).

Materials and Methods

Informed and consenting MS patients (1° group: REL; 2° group: REM) and age- and sex-matched CTR (3° group) will be enrolled in the study. Patients' level of disability will be evaluated using the EDSS score and MSFC score. All patients and CTR will be tested for complement/coagulation and soluble markers of endothelial damage assays, all patients will undergo dynamic susceptibility contrast-enhanced MRI using a 3.0-T scanner to evaluate CBF, CBV and MTT, lesion number and volume. **Sample size calculation**: Overall 90 subjects (30 for each group) will be enrolled in order to compare the level of complement C4a (Ingram 2012). By using the ANOVA test, this sample size will allow to detect effect size values [delta=(miA–miB)/sigma] equal to at least 0.71, with a statistical power of 80%, to a level of significance of 5%.

Impact and Translational Implications Identifying a link between activation of coagulation/complement system and cerebral hypoperfusion in MS patients could lead to the development of new effective therapeutic strategies for MS patients. Even if the activation of coagulation system, linked to innate immunity, is a mandatory process following different types of tissue damage and it is not the primary cause of the formation of demyelinating plaque, interfering with coagulation system could represent a new therapeutic target in MS and likely in other inflammatory and neoplastic diseases.

Fig. 1 Fibrinogen as a mediator of inflammation. Fibrinogen acts on different cells through integrin and non-integrin receptors to induce specific inflammatory effects.