**Analysis of serum protein biomarkers in clinical forms of Multiple Sclerosis**

**(Serum protein biomarkers in MS)**

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The combination of membrane proteins and their soluble isoforms is an important source for the search of non-invasive biomarkers in MS. The aim of this study was to identify soluble proteins associated with the different clinical forms of MS, to establish whether a differential expression can provide insight into some of the mechanisms underlying the pathogenesis of the different forms.

Serum samples from 18 untreated patients with MS (7 RRMS, 7 SPMS and 4 PPMS) and seven healthy subjects (HC), matched in aggregate by age and gender, were analyzed by a quantitative proteomic analysis for differences in their patterns of protein expression, using nano-liquid chromatography coupled to tandem mass spectrometry. Validation of the results in an independent cohort of 60 untreated MS patients (20 of each clinical form) and 20 HC was done by ELISAs.

In the proteomic analysis, PPMS patients showed a unique profile, perfectly distinguishable from controls and the other MS clinical forms. There were 7 proteins deregulated in PPMS patients compared to controls, 2 compared to SPMS patients and 3 compared to RRMS patients. Most of the proteins differentially expressed in PPMS patients are involved in "*innate immune system pathways*", as well as in "*regulation of complement cascade*".

Not all the differences discovered in the proteomic study were confirmed by ELISA. However, we found that **APEH** was overexpressed in PPMS compared to RRMS and HC. **MST1** was overexpressed in PPMS and HC compared to RRMS. **CFHR2** was underexpressed in PPMS compared to HC. **BST1** was higher in RRMS patients than in PPMS and HC. **PRDX6** was overexpressed in both progressive forms related to HC, and **PCSK9** was underexpressed in RRMS compared to HC and both progressive forms.

Our results support the use of these -omics techniques as a high throughput method for the identification of serum biomarkers for the diagnosis and prognosis of MS. Yet, these results need to be confirmed in larger groups.

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