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Endothelin-1 as a candidate cerebrovascular biomarker in Multiple Sclerosis

Author(s): C Criscuolo[1], R Lanzillo[1], A Cianflone[1], R Liuzzi[2], M Mancini[2], E Tedeschi[3], E Postiglione[1], G Vacca[1], V Vacchiano[1], M Moccia[1], M Vastola[1], G Puorro[1], A Marsili[1], M Incoronato[4], M Salvatore[3], V Brescia Morra[1]
Institution(s): Federico II University, Neurosciences, Reproductive and Odontostomatological Sciences, Napoli, Italy (1); Institute of Biostructure and Bioimaging - National Research Council, Napoli, Italy (2); Federico II University, Advanced Biomedical Sciences, Napoli, Italy (3); IRCSS SDN Foundation, Napoli, Italy (4)

Background: Clinical and experimental evidence suggests that endothelin-1 (ET-1) plays a role in cardiac and vascular disease and inhibit remyelination. Patients with multiple sclerosis (MS) show global cerebral hypoperfusion. The widespread decrease in perfusion in normal-appearing white matter and grey matter in MS seems to be secondary to increased blood concentrations of ET-1.
Objectives: To evaluate ET-1 in MS patients vs healthy subjects (HS) in the context of a larger study on the association among MS, amyotrophic lateral sclerosis (ALS), and vascular changes at molecular, genetic, anatomic and functional level.
Methods: ET-1 levels will be measured in 300 MS patients, 50 ALS patients and 300 HS recruited over 3 years. Serum ET-1 levels were coded and assayed with a commercially available ELISA kit in blinded fashion by a laboratory assistant (detection range 0.39–25 pg/mL; R&D Systems).
Results: ET-1 levels were performed in 312 MS patients (190 females, 122 males), 311 HS (184 females, 127 males) and in 57 ALS (23 females, 34 males). ET-1 mean were significantly higher in MS compared to HS (1.74 vs 1.49 pg/mL, $p<0.0001$) and in ALS compared to HS (2.06 vs 1.49 pg/mL, $p<0.0001$) at student t-test. ET-1 levels were significantly lower in MS vs ALS (1.74 vs 2.06 pg/mL, $p=0.001$).

When stratified for gender, mean ET-1 levels were significantly higher in females MS vs HS (1.71 vs 1.44 pg/mL, $p=0.0001$). In MS women ET-1 levels positively correlated with age and disease duration (DD; Pearson correlation coefficient= 0.193, p= 0.014; Pearson correlation coefficient= 0.181, p= 0.024). No significant relationship was found between age and ET-1 in HS woman ($p<504$). The mean values for age and DD in MS women vs men were nonsignificant.

Conclusions: We confirm that serum ET-1 levels are significantly increased in MS patients, **especially in women.** Furthermore, ET-1 levels positively correlate with DD, but not with EDSS and MSSS in women. These findings suggest a role for ET-1 in MS as an index of disease and not of progression, possibly associated to the inflammatory status. In men a protective factor could act, directly or indirectly, reducing ET-1 levels.

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Key words: multiple sclerosis, endothelial factors, ET-1