Title: Altered CSF cytokine network in Amyotrophic Lateral Sclerosis patients: A pathway-based statistical analysis

Additional authors (in order): César E. Escamilla-Ocañas\textsuperscript{a}, Juan Miguel Tenorio-Pedraza\textsuperscript{b}, Maria Teresa Gonzalez \textsuperscript{b} Leticia A. Olguín-Ramírez\textsuperscript{b,c}, Sergio Salazar-Marioni\textsuperscript{a}, Martín Hernández-Torre\textsuperscript{b}

Institution name, city, state, country of additional authors: \textsuperscript{a}Instituto de Neurología y Neurocirugía, Tecnológico de Monterrey. \textsuperscript{b}Terapia Celular, Escuela Nacional de Medicina, Tecnológico de Monterrey. \textsuperscript{c}Servicio de Neurología, Hospital Universitario UANL

Introduction. Increased cytokine expression is a prominent finding in amyotrophic lateral sclerosis (ALS). Due to their interdependence and pleiotropism, interpretation of CSF concentrations of a single cytokine is challenging. We describe a cytokine analysis in ALS patients using a pathway-based statistical method to identify changes in the whole cytokine network.

Methods. We analyzed 19 cytokines in CSF of ALS patients and controls. An equality of concentration matrices was conducted that allowed us to evaluate disturbances in the relationship of cytokines between controls and ALS patients with less and more than 12 months of disease length. MANOVA assessed differences in cytokines and interdependence was compared by partial correlations among specific pairs of cytokines.

Results. Seventy-seven ALS patients and 13 control subjects were included. Significant differences were identified in the cytokine pathway between controls and ALS patients with less (p <0.0001) and more than 12 months of disease length (p <0.0001), and between ALS patients with less than 12 months and those with more than 12 months (p=0.0058). In ALS patients with a shorter disease length, IL4 and IL6 were negatively correlated (-0.3571), whereas in ALS > 12 months, a positive correlation was detected (0.4080).

Conclusions. The pathway-based statistical method revealed remarkable variations in the whole cytokine pathway in ALS patients and controls. Cytokine-network changes and the positive correlation between IL4 and IL6 were related to disease length; these variations might explain the deleterious immunological effects on motor neurons. A further analysis using this method is needed to confirm the exact interaction among cytokines in ALS.