

Poster

SYNAPTIC AND EXTRACELLULAR MATRIX REMODELLING IN DYSTONIA: EVIDENCE FROM DYT1/DYT11 MICE AND CERVICAL DYSTONIA PATIENTS

A. Patroni Griffi[1], F.E. Bellomi[1], F. Leo[2], G. Anzini[2], S. Toro[2], G. Andreucci[1|2], E. Patricolo[1|2], C. Caturano[1], M. Marano[2|3], G. Vivacqua[1]

[1]Department of Medicine and Surgery, Laboratory of Microscopic and Ultrastructural Anatomy, Campus Bio-Medico University of Roma, Italy; [2]Parkinson's Disease and Movement Disorders Service, Operative Research Unit of Neurology, Fondazione Policlinico Universitario Campus Bio-Medico, Roma, Italy; [3]Unit of Neurology, Neurophysiology, Neurobiology and Psychiatry, Department of Medicine, Campus Bio-Medico University of Roma, Italy

Introduction. Dystonia is a hyperkinetic movement disorder characterized by sustained or intermittent muscle contractions causing abnormal, often repetitive postures. Cervical dystonia is the most common form of isolated focal dystonia. Available treatments are symptomatic, and the molecular mechanisms underlying the disease remain poorly understood. Moreover, no easily accessible biomarkers are currently available to support diagnosis and molecular follow-up. Recent evidence suggests that cross-talk between the extracellular matrix (ECM), glia and synaptic plasticity contributes to impaired motor control.

Aims. We investigated synaptic protein expression and ECM composition in the brain of DYT1 and DYT11 mice and tested whether the molecular changes identified could be validated in saliva and plasma of patients with cervical dystonia.

Methods. Brains from DYT1 and DYT11 mouse models (3 mutant mice and 3 matched wild-type littermates per model) were cut into 30 µm sagittal sections. Free-floating immunohistochemistry (TOR1a, VAMP2, Synaptophysin, CamKIIβ and SNAP25) and immunofluorescence (SNAP25, CamKIIβ, collagen types I, III and IV) were performed on whole-brain sections. The striatum, cerebellum and brainstem were then selected for analysis, and the percentage of positively stained area was quantified using ImageJ. In parallel, saliva and plasma were collected from 26 patients with cervical dystonia and 14 age- and sex-matched healthy controls, and analysed by ELISA for CamKIIβ, SNAP25, TOR1a, α-synuclein, TNFα, VAMP1, synaptophysin and TGFβ. Group comparisons used Student's t-test or the Mann-Whitney U test depending on data distribution.

Results. In DYT1 mice, CamKIIβ was significantly reduced in the striatum, while SNAP25 was unchanged in the cerebellum and TOR1a showed non-significant regional trends. ECM remodelling was also observed: collagen III increased in the cerebellar granular layer and collagen IV significantly increased in the striatum. Trends in VAMP2 and synaptophysin did not reach statistical significance. DYT1 and DYT11 mice showed broadly similar immunostaining patterns, potentially indicating partially shared molecular alterations. In patients, saliva proved more informative than plasma, as TOR1a and CamKIIβ were detectable only in saliva. Salivary CamKIIβ and α-synuclein were reduced and TNFα increased, with decreasing trends in SNAP25 and VAMP1; TGFβ did not differ. Synaptophysin showed a bimodal distribution in both groups, with no significant salivary difference, while plasma levels were higher in patients. The reduction of CamKIIβ was consistent between the DYT1 model and patients' biofluids.

Conclusions. Our data support an association between altered synaptic protein expression and ECM remodelling in dystonia, in both the DYT1/DYT11 models and cervical dystonia patients, and suggest saliva as a promising source of easily accessible biomarkers for future patient stratification and therapeutic monitoring.