Mood regulation in Machado-Joseph Disease: a step forward to more comprehensive care

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**ABSTRACT:**

Machado-Joseph disease (MJD) is a rare inherited neurodegenerative disease caused by a CAG repeat expansion in the *ATXN3* gene. While loss of motor function is a key feature in MJD, anxiety and depressive symptoms are frequently reported by these patients. Additionally, recent studies reflect on the presence of executive dysfunction in MJD, as part of the so called – Cerebellar cognitive affective syndrome. Previous studies from our lab revealed a decrease in the glucocorticoid receptor (GR) expression in the brainstem and an elevation of corticosterone (CORT) in the blood of MJD animals at late stages of the disease which could also be mood-related. To address the intricate etiology of these mood alterations, animal models could be of great value, as they lack awareness of their progressive disease condition. Thus, we further investigate the presence of non-motor symptoms in MJD by performing longitudinal behavior analyses using our in-lab generated CMVMJD135 mouse model, that closely mimics MJD both phenotypical and pathologically. Our results showed that MJD mice are not cognitively affected but there is a progressive anxious phenotype, assessed in the elevated plus maze. Moreover, given the importance of GR in the corticoid-dependent feedback loops of the hypothalamus-pituitary-adrenal (HPA)-axis we aimed to study the effects of stressful events in CORT variations and on motor function in the MJD mouse. Importantly, the late-stage elevation of CORT was not determinant for a functional HPA-axis activity while responding to acute stressors as well as recovering from a suppression test using dexamethasone. Also, chronic stress exposure did not have a major impact on MJD motor phenotype. Nevertheless, our findings indicate that beyond its well-known effects on the motor systems, MJD appears to influence emotion regulation processes. The multidimensional symptoms of MJD mirror its complexity, reinforcing the need for integrated care approaches to address its broad spectrum of manifestations.