OBSTRUCTIVE SLEEP APNEAS ARE HIGHLY PREVALENT IN A MOUSE MODEL OF CDKL5 DEFICIENCY DISORDER

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Background: Cyclin-dependent kinase-like 5 (CDKL5) deficiency disorder (CDD) is a rare X-linked neurodevelopmental disease caused by mutations in the CDKL5 gene. Despite its broad spectrum of clinical features, the characterization of sleep disordered breathing in patients with CDD is still lacking, due to limited investigations. However, recent studies have confirmed the presence of sleep apneas in Cdkl5-knockout (Cdkl5-KO) mice, an animal model of CDD (*PMID: 28230307; 34094641*). This study aims to discriminate, for the first time, central (CSA) and obstructive (OSA) sleep apneas in Cdkl5-KO mice and investigate their distribution in comparison to wild-type (WT) mice.
Methods: Male Cdkl5-KO (n = 10) and WT (n = 13) mice were implanted at 49 weeks of age with electrodes for electroencephalographic, neck electromyographic, and diaphragmatic activity (DIA) recording. Five days later, mice were placed in a whole-body-plethysmography (WBP) chamber for 8 hours during the light period to simultaneously record sleep and breathing activity. Sleep states were manually assessed on 4-seconds epochs, while respiratory analysis was restricted to Rapid-Eye-Movements sleep (REMS) and non-REMS (NREMS) episodes lasting ≥12-seconds. CSA and OSA were discriminated based on WBP and DIA signals. Since apneas with an obstructive component are primarily present in REMS (*PMID: 34509609*), apnea categorization was limited to this sleep state. Data were analyzed using two-way ANOVAs with mouse groups and sleep states (NREMS vs REMS) or apnea subtypes (CSA vs OSA) as factors, with significance set at $p<0.05$.
Results: Cdkl5-KO mice exhibited a higher apnea occurrence rate during REMS (P=0.0009), but not during NREMS (P=0.9711), compared to WT. OSA were observed during REMS in both Cdkl5-KO and WT mice, with a significantly greater occurrence rate in Cdkl5-KO mice (P=0.0064). No significant differences in CSA occurrence rate were found between groups.
Conclusions: Our results suggest that sleep apneas in Cdk5-KO mice are mainly associated to airway obstruction during REMS. Cdkl5-KO mice represent a novel mouse model of OSA that may be useful to accelerate the development of new pharmacological therapies for these obstructive events.