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Title: Plp1 mutation induces altered respiratory response to an airway challenge

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Body: Pelizaeus-Merzbacher disease (PMD) is a disease caused by mutations of the proteolipid protein1 (PLP1) gene that result in defective CNS myelination. Mice with an extra copy of Plp1, called Plp1dup, develop a syndrome that models the duplication form of PMD. Patients with all except the mildest forms have respiratory involvement. Objective: We hypothesized that Plp1dup mice would lack protective airway responsiveness (AR) to an autonomic drug challenge. To address this, we investigated whether respiratory mechanics in these mice would be different at baseline (BL) or during methacholine (MCh) challenge. Methods: Wild type (Wt) n=16, carrier (Car) n=8 & affected (Af) n=17 mice, 3 months (3m) and 6 months old (6m), were anesthetized, mechanically ventilated & challenged with 0.1-6 mg/ml of aerosolized MCh. We calculated resistance (R), dynamic/static compliance (Cdyn/Cstat), asynchrony (PhRTB); lung tissue biomarkers & histological analysis are ongoing. Results: BL differences were found in R, between Wt6 vs.Car6 ($p=<0.05$) dependent on group ($p=<0.001$) & age ($p=<0.0001$), and in Cdyn, among Wt3 vs. Af3 ($p=<0.01$). MCh increased R as a function of dose in Wt6 & Car6, whereas Af6 mice lacked sensitivity to MCh ($p=<0.05$). No differences in body weight, gender (Wt females vs. Wt Males) and Cstat were found. Af6 mice had the highest PhRTB. Conclusions: Wt mice compared with Af mice were lacking of AR to MCh at 6m, but not at 3m. These results indicate an age-associated lack of protective autonomic AR in the Plp1dup mouse model and suggest that respiratory autonomic disequilibrium may contribute to the respiratory involvement in PMD patients. The Plp1dup animal model may be used for testing therapeutic interventions.