Behavioral Characterization of Homozygous 6^{neo} Pompe Mice

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BACKGROUND

Pompe disease, also known as glycogen storage disease type II, is a multisystemic disease with variable rates of progression. Pompe is a rare disease that affects approximately 1 in 2800 people and is caused by mutations in the acid α-glucosidase (GAA) gene. GAA is an enzyme that mediates the breakdown of complex sugars and GAA mutations result in an excessive accumulation of glycogen in different tissues, including the CNS. Pompe disease is manifested with severe muscle weakness.
The aim of this study was to characterize the suitability of 6^{neo} mice as an appropriate animal model of Pompe disease, that can be successfully employed to test novel drug agents and therapeutic treatments.

MATERIAL & METHODS

6^{neo} mice were generated by targeted deletion of exon 6 of the mouse *GAA*. Wild type and homozygous 6^{neo} mice of both sexes were employed to measure the effects of GAA deficiency on muscle weakness, motor coordination and exploratory activity, across different ages. Muscle weakness was assessed in the grip strength and wire suspension test, while deficits in motor coordination were evaluated in the beam walk test and in the RotaRod.

RESULTS

Muscle Strength

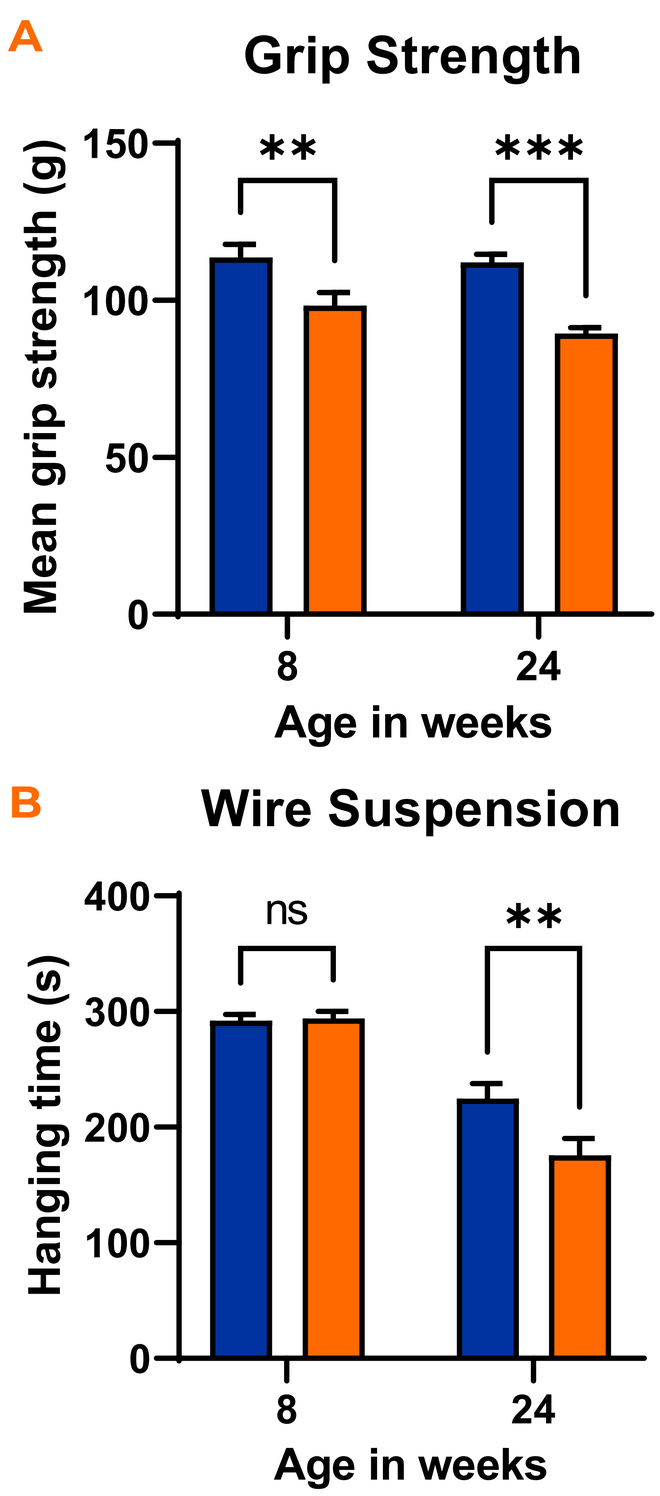

Figure 1: Muscle weakness in 6^{neo} Pompe mice. A) Grip strength test: Mean grip strength in gram. B) Time spent hanging in the wire suspension test in seconds. Two-way ANOVA with genotype and age as main factors, followed by Bonferroni's *post hoc* test. Mean ± SEM. ** p < 0.01, *** p <0.001. N= 24-48/ group. WT: wild type; ns: not significant.

Motor Deficits

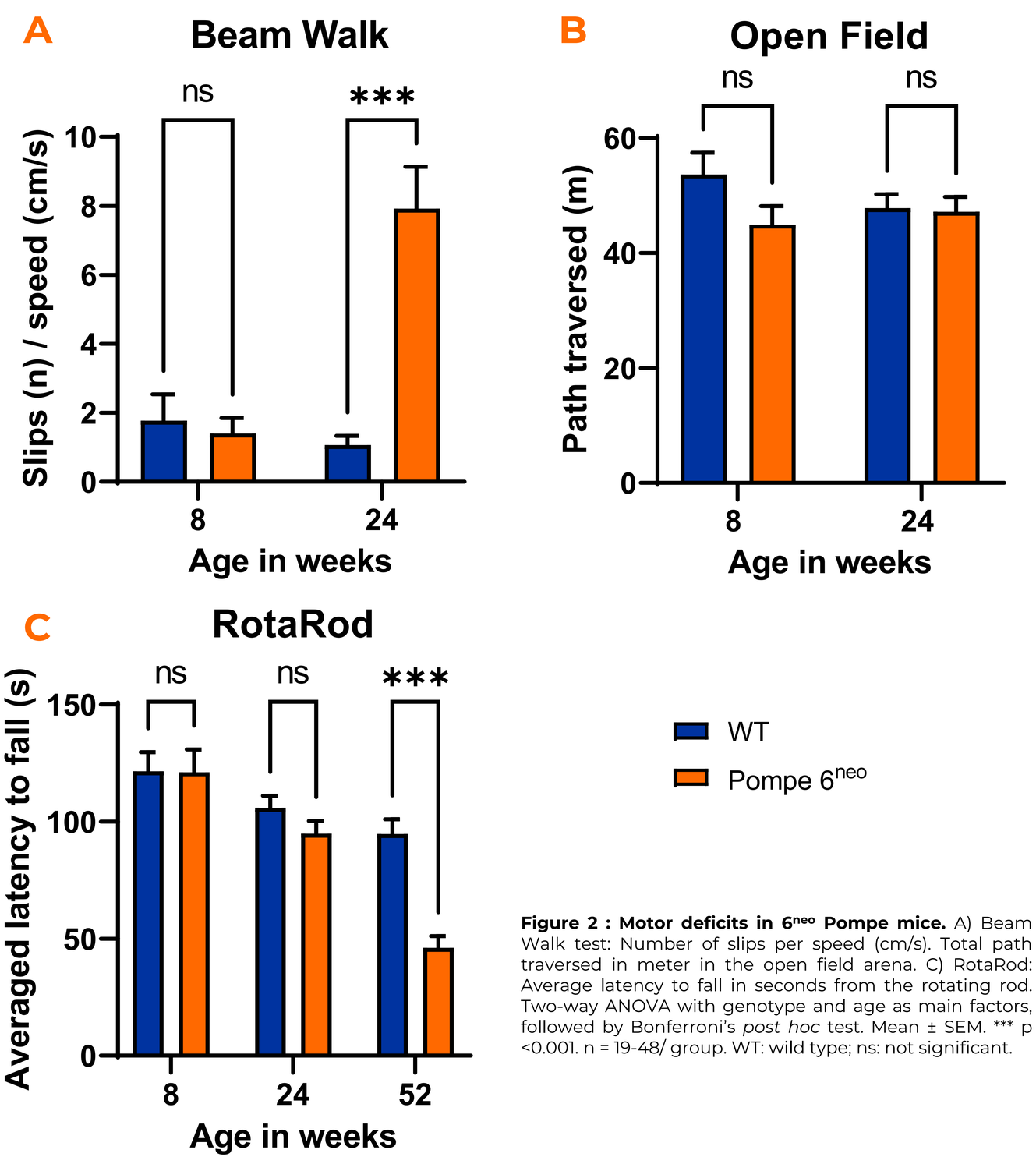

Figure 2 : Motor deficits in 6^{neo} Pompe mice. A) Beam Walk test: Number of slips per speed (cm/s). Total path traversed in meter in the open field arena. C) RotaRod: Average latency to fall in seconds from the rotating rod. Two-way ANOVA with genotype and age as main factors, followed by Bonferroni's *post hoc* test. Mean ± SEM. *** p <0.001. n = 19-48/ group. WT: wild type; ns: not significant.

CONCLUSION

Our behavioral analysis of 6^{neo} mice suggests that GAA deficiency results in severe muscle weakness and motor deficits that can be objectively measured by different behavioral tests. Muscle weakness was evaluated in the grip strength and wire suspension test. In both tests 6^{neo} mice present with strong deficits compared to same-age littermates. In addition, motor coordination of 6^{neo} mice was severely impaired, as measured in the beam walk and RotaRod test. In the open field test, no differences were detected between 6^{neo} mice and their wild type littermates, indicating that GAA deficiency does not impact exploratory activity.
The results of this study, strongly confirm that homozygous 6^{neo} mice phenocopy cardinal symptoms observed in Pompe disease and thus, represent a valuable animal model that can be successfully employed to test novel drug agents and therapies to tackle this devastating disease.

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