Behavioral characterization of homozygous 6^{neo} mice as model of Pompe disease

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BACKGROUND

Pompe disease is an inherited lysosomal storage disease caused by a deficiency of α-glucosidase, encoded by the *GAA* gene. Lysosomal glycogen accumulates in tissues, including the central nervous system and muscles, most notably skeletal and cardiac muscles. In this study, we evaluated GAA knock out mice - commonly known as Pompe 6^{neo} mice - for their behavioral deficits.

While this model is over 20 years old and well characterized, reports regarding the onset of symptoms are conflicting. We therefore performed an in-depth behavioral characterization of this model. In addition to behavioral analyses, histological and biochemical evaluation of various tissues will be performed soon.

MATERIALS and METHODS

For this study 94 GAA knockout mice (Pompe 6^{neo}) of mixed sex and 94 wild type (WT) littermates at the age of 4, 8 and 24 weeks were included in the cross-sectional experiment. Animals were evaluated in a behavioral test battery including the open field, RotaRod, wire hanging, beam walk, and grip strength test. In addition, half of animals of the 24 weeks age group were kept until the age of 52 weeks and retested in the RotaRod test.

RESULTS

First differences in the mean grip strength of Pompe 6^{neo} mice could already be detected at the age of 8 weeks (Fig. 1A) while first deficits in the wire hanging test were measurable at the age of 24 weeks (Fig. 1B).

Muscle Strength

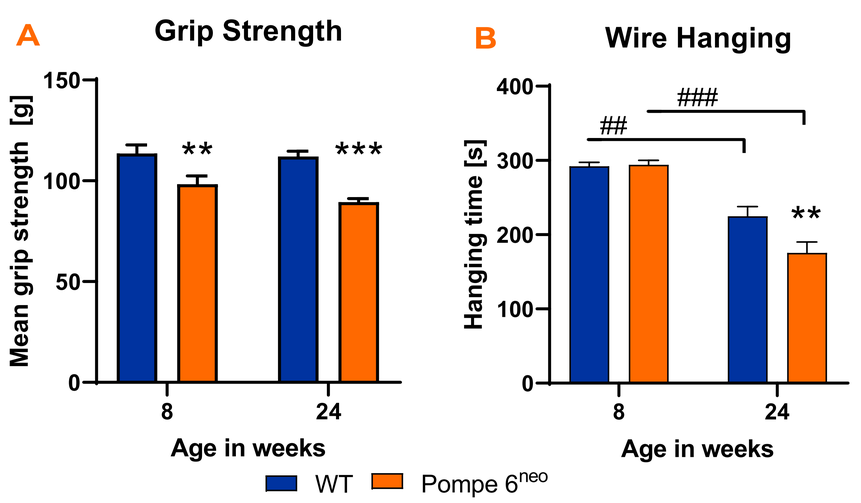

Figure 1. Grip strength test and wire suspension test of Pompe 6^{neo} mice. Mean grip strength of 6^{neo} and WT littermates at the age of 8 and 24 weeks (A). Hanging time of 8 and 24 weeks old 6^{neo} mice compared to WT littermates. 8 weeks: n=24 per group; 24 weeks: n=48 per group. Two-way ANOVA with Bonferroni's *post hoc* test; mean + SEM; **/##p<0.01; ###p<0.001.

RESULTS

Evaluation of Pompe 6^{neo} mice for motor deficits in the RotaRod test resulted in first significant differences compared to WT littermates at the age of 52 weeks (Fig. 2A). Further analysis of Pompe 6^{neo} mice in the beam walk test showed motor deficits already at the age of 24 weeks (Fig. 2B). Differences most likely depend on the higher sensitivity of the beam walk test.

Motor Deficits

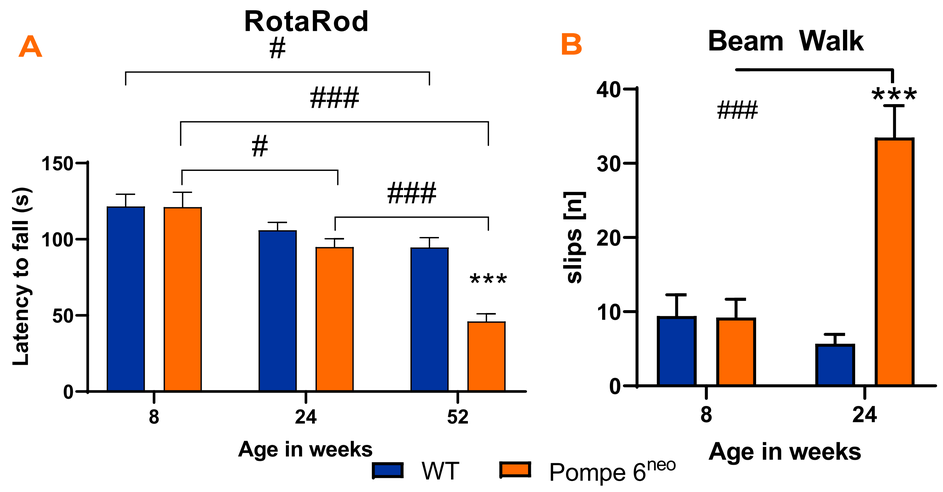

Figure 2. RotaRod and beam walk test of Pompe 6^{neo} mice. Latency to fall off the RotaRod of 6^{neo} and WT littermates at the age of 8 to 52 weeks (A). Number of slips in the beam walk test of 8 and 24 weeks old 6^{neo} mice compared to WT littermates (B). n=10-48 per group. Two-way ANOVA with Bonferroni's *post hoc* test; mean + SEM; #p<0.05; **/##p<0.01; ###p<0.001.

General Health

Analysis of Pompe 6^{neo} mice for general health in the open field test showed no significant changes in activity, hyperactivity and distance moved during a 5-minutes test session (Fig. 3A-C), while the number of rearings decreased in 24 weeks old Pompe 6^{neo} mice compared to WT littermates (Fig. 3D).

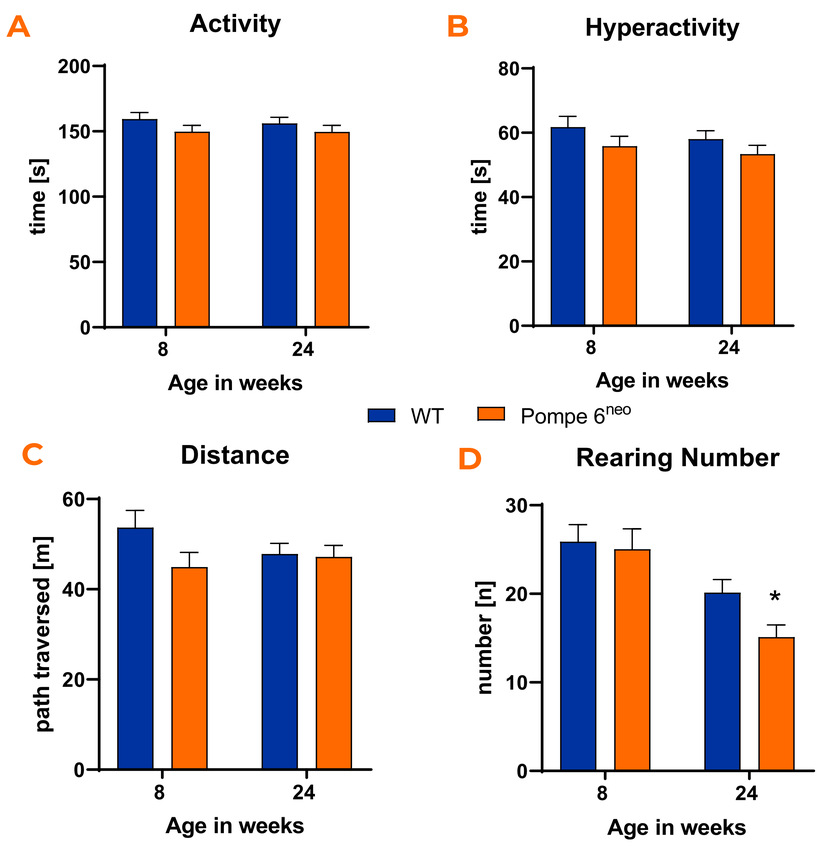

Figure 3. Open field test of Pompe 6^{neo} mice. Activity (A), hyperactivity (B), distance moved (C), and number of rearings (D) of Pompe 6^{neo} mice and WT littermates at the age of 8 and 24 weeks; 8 weeks: n = 24 per group; 24 weeks: n = 48 per group. Two-way ANOVA with Bonferroni's *post hoc* test; mean + SEM; *p<0.05.

SUMMARY and CONCLUSION

Our results show a start of the muscle and motor phenotype already at the age of 8 weeks that progresses with age. The Pompe 6^{neo} mouse model is thus a valuable tool to evaluate new compounds against this devastating lysosomal storage disease.

For more information about the models please visit:

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