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Long-term neurologic correction in the Pompe disease mice by intrathecal gene therapy
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Pompe disease is a lysosomal storage disorder caused by acid-α-glucosidase (GAA) deficiency, leading to glycogen storage. The disease manifests as a fatal cardiomyopathy in infantile form. Enzyme replacement therapy (ERT) has recently prolonged the lifespan of these patients, revealing a new natural history. The emergent neurologic phenotype and the poor correction of skeletal muscles in survivors are currently attributed to central nervous system (CNS) glycogen storage, uncorrected by ERT. Hence, we hypothesized that intrathecal delivery of AAV-gaa in Pompe disease mice would correct the neurologic and neuromuscular manifestations of the disease.

GAA-KO mice were injected with ssAAVrh10-gaa into the cisterna magna at one month. Their neurologic and motor skills including auditory function were periodically monitored from three to twelve months by hindlimb clamping reflex, brainstem auditory evoked potentials, wire-hang test, and accelerating rotarod. Grip strength measurement and in situ muscular contractile activity were recorded at end points - 4 and 12 months. Glycogen content, GAA activity, and disease-related pathology were assessed in the CNS and muscles. We also analyzed the treatment related chemical changes in motor neurons and white matter tracts of spinal cord using Fourier transform infrared (FT-IR) microspectroscopy with a synchrotron light source.

We demonstrate a significant functional neurologic correction in treated animals from 4 months onward, a neuromuscular improvement from 9 months onward, and a partial restoration of the muscular strength at end points. The entire CNS, including the regions most affected by the disease such as the brainstem, spinal cord, and spinal ganglia show enzymatic, biochemical and histological correction. Muscle glycogen storage is not cleared by the treatment, thus suggesting that the restoration of muscle functionality is directly related to the CNS correction. This unprecedented widespread CNS cure and its impact on the global neuromuscular function offer new perspectives for the management of patients.