GM1 gangliosidosis is an autosomal recessive lysosomal storage disorder caused by an enzyme deficiency of β-galactosidase (β-gal) leading to toxic accumulation of GM1 ganglioside in the central nervous system (CNS) and progressive neurodegeneration. Adeno-associated virus (AAV) mediated gene delivery of lysosomal enzymes to the CNS has shown great potential for the treatment of lysosomal storage diseases with neurological involvement. In this work we use MALDI mass spectrometry imaging (MSI) to assess the spatial distribution of gangliosides, ganglioside metabolites and related lipids in a GM1 gangliosidosis mouse brain model following adeno-associated virus (AAV) gene therapy.

Deficiency of β-galactosidase enzyme in a β-gal−/− mouse brain showed an overall 8-fold increase in GM1 relative to the control by MSI analysis, with specific spatial localization based on its ceramide content. Bilateral thalamic injection of AAVrh10-βgal in β-gal−/− mice significantly reduced GM1 levels relative to untreated β-gal−/− mice. The therapeutic efficacy of this approach is through distribution of functional enzyme via axonal transport through the extensive connectivity of the thalamus with most of the brain, with some exceptions such as the temporal cortex. Accordingly MSI showed AAV gene therapy reduced GM1 nearly to the control levels in all regions of the brain except in the temporal cerebral cortex. This correlated with low levels of βgal in this brain region as assessed by histochemical staining of tissue sections. MSI also detected asialo-GM1 and other ganglioside metabolites elevated in untreated β-gal−/− mice, which were also reduced after AAV therapy. Interestingly sulfated galactocerebrosides reduced in the myelin sheath in untreated β-gal−/− mice were restored to normal levels after AAV therapy. Overall, this study demonstrates that MALDI MSI can be used to map specific target analytes and their metabolites while also offering the ability to detect unanticipated effects caused by gene therapy.

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