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CHRONIC CYCLODEXTRIN ADMINISTRATION AMELIORATES CLINICAL SYMPTOMS AND STORAGE ACCUMULATION IN NIEMANN-PICK TYPE C1 MICE

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Niemann-Pick Type C1 (NPC1) disease is an autosomal-recessive neurodegenerative disorder characterized by accumulation of unesterified cholesterol and glycosphingolipids in the endosomal/lysosomal system. While there is currently no cure, several treatment studies in the mouse model of NPC1 have resulted in delay of onset of clinical symptoms and increased lifespan. During a combination treatment therapy using miglustat (OGT-918) and allopregnanolone, we noted that the lifespan of $NPC1^{-/-}$ control mice receiving only 2-hydroxypropyl-beta-cyclodextrin (HPBCD; vehicle for allopregnanolone) was increased. Cyclodextrins, which are known to complex with cholesterol, are commonly used for *in vitro* manipulations as well as a vehicle to increase drug solubility *in vivo*. The increased lifespan of HPBCD-treated $NPC1^{-/-}$ mice suggested to us that administration of HPBCD alone, but with greater frequency than single weekly injections, might provide additional benefit. $NPC1^{-/-}$ and WT mice were injected SC or IP every other day starting at postnatal day 7 with 20% HPBCD (dose of 4000 mg/kg). $NPC1^{-/-}$ mice treated for two weeks and sacrificed at three weeks of age showed a substantial reduction in intraneuronal accumulation of both cholesterol and gangliosides. At the ultrastructural level, many neurons of treated $NPC1^{-/-}$ mice appeared normal and exhibited few or no storage bodies. Treated $NPC1^{-/-}$ mice allowed to reach end-stage disease showed ~3-week delay in onset of clinical symptoms and survived an average of 27.3 weeks, more than double that of untreated $NPC1^{-/-}$ mice. Although intraneuronal accumulation of cholesterol and gangliosides was present in end-stage treated $NPC1^{-/-}$ mice, the number and complexity of storage vacuoles was reduced compared to that seen in end-stage untreated $NPC1^{-/-}$ mice. Understanding the mechanism(s) by which HPBCD leads to a reduction in cholesterol and ganglioside accumulation may provide important new opportunities for treatment of NPC disease.