Tauopathy in Niemann-Pick type C disease carriers: analysis in a mouse model

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Niemann-Pick type C disease (NPC) is a rare, fatal lipid storage disorder characterized primarily by progressive neruodegeneration of Purkinje neurons in the cerebellum and neuroinflammation (activation of microglia and astrocytes). NPC is caused by dysfunction of cholesterol transport proteins NPC1 and/or NPC2, which leads to accumulation of free cholesterol and other lipids within late endosomes and lysosomes. Assuming that heterozygous mutations in *NPC1* and/or *NPC2* genes do not cause any symptoms, the carriers of NPC disease are considered healthy. Our goal is to characterize the brains of *NPC1* heterozygous mice for pathological features of NPC (including neurodegeneration, neuroinflammation, endolysosomal disfunction and tau hyperphosphorylation) and to identify the earliest changes upon loss of single *NPC1* allele. We used the BALB/cNctr-*Npc1*$^{N/+}$ mouse model (NPC1$^{+/-}$, Jackson Laboratory, Bar Harbor, Maine, USA) and analyzed the brains of 60- and 100-weeks old NPC1$^{+/-}$ and NPC1$^{+/+}$ (wt, control) mice by western blotting and immunohistochemistry. Here, we demonstrate that 60-weeks old NPC1$^{+/-}$ mice show increased tau hyperphosphorylation in contrast to age-matched control mice. The differences in neuroinflammation level, as well as endolysosomal dysfunction between the two groups of mice were not observed. These preliminary findings suggest that hyperphosphorylation of tau may be the earliest pathological feature that occurs in *NPC1* heterozygous mice. We, thus, conclude that the aged murine carriers of NPC disease may not be considered healthy and that human *NPC1* heterozygous mutation may be a risk factor for neurodegenerative disorders (such as tauopathy) in the aged population.