Untangling Alzheimer´s Disease Hallmarks in Sensory Systems of Rodent Models

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BACKGROUND

Alzheimer´s disease (AD) is the most common form of neurodegenerative dementia. Major hallmarks of the disease are: (1) extracellular plaque deposits of the β-amyloid peptide (Aβ) and (2) intracellular neurofibrillary tangles of phosphorylated tau. Published research suggests an association between AD and functional impairments of sensory systems. In fact, the occurrence of tau-mediated glaucoma has been reported, as well as AD protein-associated neuropathology in sensory systems.

MATERIALS and METHODS

To explore disease mechanisms and investigate features of AD-related pathological changes, we analyzed retina from the Tau mouse model TMHT and non-transgenic littermates, aged 6 and 12 months in order to address suitable biomarkers for early screening tests of AD. The TMHT mouse model expresses the longest human tau isoform Tau441 (2N2R) with V337M and R406W mutations under control of the Thy1 promoter. For macro-based image analysis Image-Pro 10 software, enabling fast and cost-efficient quantification of large batches of images was used. Importantly, the results are operator-independent and fully reproducible.

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RESULTS

Histological analyses of different neuronal and neuropathological markers showed mostly a signal increase in TMHT mice compared to non-transgenic (ntg) littermates. Those markers include cholinergic neurons (Figure 1A), phosphorylated tau at Thr231 (Figure 1D), astroglia (Figure 1E) and microglia (Figure 1F). Furthermore, tyrosine hydroxylase (TH) signal was significantly reduced in 6 month old TMHT mice compared to ntg littermates (Figure 1C), suggesting impaired chatecholaminergic function. Differences between genotypes did barely change over age. The GABAergic signal did not change in TMHT mice compared to ntg littermates (Figure 1B). Cholinergic cells were mainly found in the inner plexiform layer while TH positive cells were located between inner and outer plexiform layer of TMHT mice (Figure 2B,D). GFAP, to label astroglia, could be found throughout the inner and outer plexiform layer while ptau Thr231 was found in the outer plexiform and nuclear fiber layer of TMHT mice (Figure 3B,D).

SUMMARY and CONCLUSION

Here we could show alterations in the expression of various neurotransmitters and neuropathological markers analyzed in TMHT mice compared to non-transgenic littermates, not only at the age of 6 but also at 12 months. Our results suggest that CHAT, pTau, GFAP and IBA1 in the retina are potential biomarker for tauopathies. Additionally, evaluation of the visual cortex of the same animals has been started in order to receive a detailed characterization of the visual system neuropathology.

RESULTS

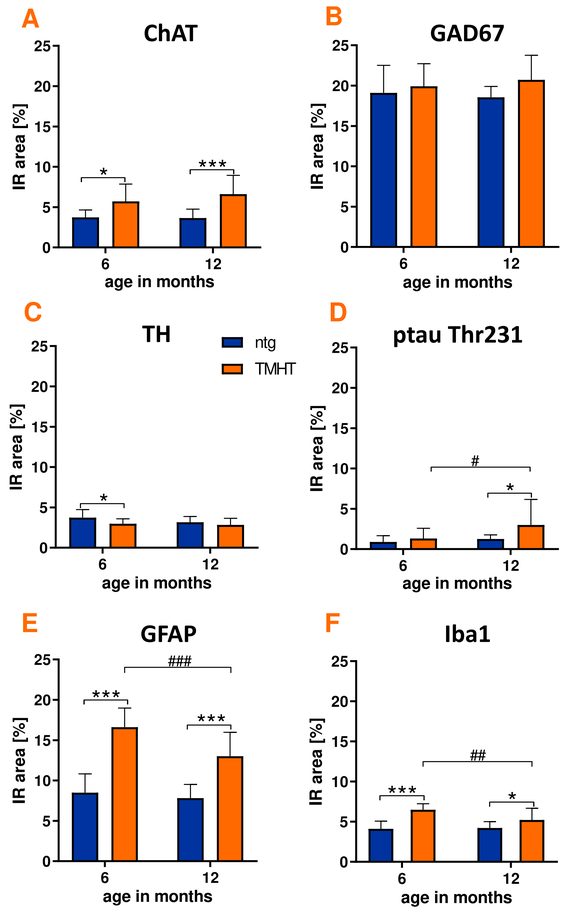

Figure 1: ChAT, GAD67, TH, GFAP, Iba1 and pTau Thr231 expression in the retina of TMHT mice: A: Choline acetyltransferase (ChAT) to label cholinergic cells; B: Glutamic acid decarboxylase 67 (GAD67) to label GABAergic cells; C: Tyrosine hydroxylase (TH) to label chatecholaminergic cells; D: Phosphorylated Tau at Thr231 (pTau Thr231). E: Glial fibrillary acidic protein (GFAP) to label astroglia; F: Ionized calcium-binding adapter molecule 1 (Iba1) to label microglia; n = 12-19 per group; mean + SEM; A-F: Two-way ANOVA followed by Sidak's multiple comparisons *post hoc* test. *p<0.05; **p<0.01; ***p<0.001.

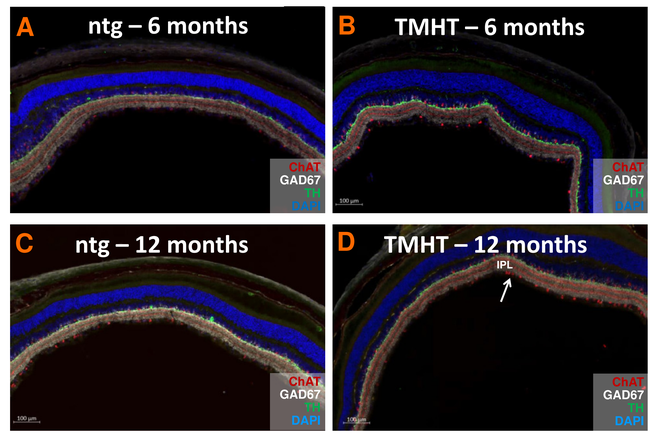

Figure 2: Detection of neurotransmitters in the retina of TMHT mice. Peak expression of ChAT is observed in the inner plexiform layer (IPL) where cholinergic amacrine and ganglion cell dendrites form two distinct synaptic strata (white arrow in D). CAD67 signal is restricted to IPL. TH is in the inner nuclear layer (INL), and mainly at the border to the IPL.

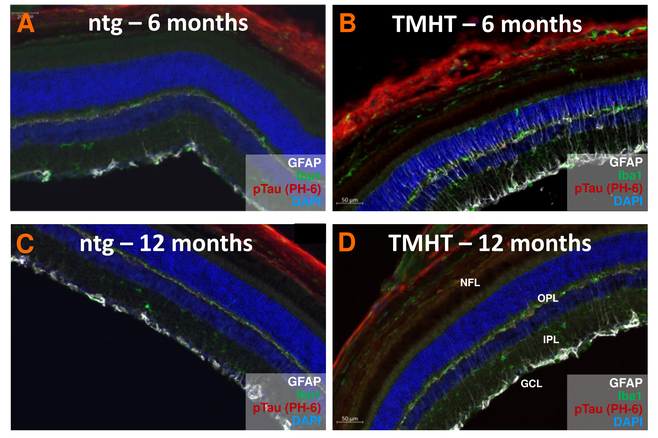

Figure 3: Detection of gliosis and tau in the retina of TMHT mice. GFAP signal is restricted to ganglion cell layer (GCL) showing a significantly increased expression in TMHT mice. Iba1 (green) is expressed in the GCL, nerve fiber layer (NFL), and IPL and outer plexiform layer (OPL). The region labeled by pTau is the NFL.