Can rats help us when we face the prospect of Alzheimer's dementia?

Case #21

SIGNALMENT: Rat (*Rattus norvegicus*) 17 month, albino female, TgF344-AD on a Fischer 344 background. This is a transgenic rat model of Alzheimer's disease.

HISTORY: The rat was submitted to the diagnostic core facility for necropsy after unexpected death during propofol anesthesia for a brain imaging study.

GROSS FINDINGS: Brain, thorax and abdomen were all normal.

HISTOPATHOLOGIC/CYTOLOGIC FINDINGS: The brain had pale foci with a radiating appearance and eosinophilic bodies which may be swollen axons in the cerebrum and cerebellum. The heart had moderate multifocal myocardial fibrosis. The lungs had hemosiderophages in alveolar spaces and edema plus moderate multifocal aspiration pneumonia.

MORPHOLOGIC/ETIOLOGIC DIAGNOSIS: Brain, neurophil plaques, multifocal with axonal degeneration. Lungs pulmonary edema moderate.

DISCUSSION:

Several transgenic models of Alzheimer's disease (AD) have been developed in mice, but models fail to demonstrate some of the pathological hallmarks of AD without additional human transgenes. An additional concern is the failure of clinical trials in human subjects of compounds that had shown efficacy in mouse models. The need for a model that is genetically, morphologically and physiologically closer to the human disease was addressed with a transgenic rat model. A transgenic rat model was developed by Cohen.[1] This model has mutations in the amyloid precursor protein (APP) and presenilin 1. Both are independent causes of early onset familial AD. The model was reported to show many of the changes seen in humans including amyloid and hyperphosphorylated tau deposition and neuronal loss. These rats also have cognitive decline.

The rat model has advantages for multiple reasons including having a complex social behavior that includes courting, playing and aggression. Rats have sophisticated behaviors that are well characterized and possess fine motor coordination. Moreover, the rat is evolutionary closer to the human. The larger body size enables easier manipulation for medical procedures. Rats can reach the age of 20 months or longer the human equivalent of 60-70 years allowing for natural disease age progression.[2]

The devastating effects of AD, a form of dementia, are well understood. One in 9 humans over the age of 65 have AD costing Medicare $236 billion in 2016 with family members providing 18.1 billion hours of unpaid care. Of the top 10 causes of death, this one has no treatment, no cure, and no therapy to slow progress. The forgetfulness, memory loss, and the inability to lead an independent life requiring full time care makes this illness demoralizing and expensive.[3]

It has been found that amyloid plaques are a natural part of aging yet these take on an unusual pattern in AD patients. Accumulation of amyloid beta is increased by secretase cleavage defects due to secretase enzyme mutations. Normally the amyloid precursor protein (APP), which is part of the cell membrane, is cleaved by alpha secretase and subsequently by gamma secretase producing a protein that can be secreted. The remaining part of the APP embedded in the cell's membrane is beneficial to the cell for neuronal growth and survival. When this pathway goes awry, beta secretase cuts the APP at a different site and the second cut by gamma secretase is at the wrong location. The remaining peptide (oligomers) accumulates in the cytoplasm which eventually clumps. This process continues leading to a large extracellular plaque which is visible by H&E and further highlighted by immunohistochemistry with amyloid beta. [4, 5]

Another damaging pathway of AD is the accumulation of hyperphosphorylated tau or neurofibrillary tangles. Microtubules in neurons assist in transport of large molecules from the cell body along axons. Microtubules are normally stabilized by tau, an associated protein. AD patients have an overproduction of soluble tau that leads to binding with other tau molecules due to hyperphosphorylation. The straight microtubules become tangled interfering with axonal transport. This disruption in transport interferes with intracellular communication, increases inflammation and ultimately leads to neuron death.[6]

In our study of the TgF344-AD rats have age-dependent amyloid accumulation replicating that of humans. Rats were tested for behavioral measures at 6, 12 and 18 months. Our results show an age-dependent decline in all tests performed including the T-maze, the buried food task, and the open field test. We also found that sleep time was diminished in the AD rats. Immunohistochemistry with amyloid beta revealed age-dependent changes in the hippocampus later spreading to the cerebral cortex. Amyloid beta accumulation was sparse in the hippocampus at 6 months in the TgF344-AD rats, with heavy accumulation in the hippocampus and to a lesser degree in the cerebral cortex at 12 and 18 months. These changes were all absent in the WT rats. Rates of brain protein synthesis in the rat model are being explored to see if decreases in protein synthesis accompany degenerative changes. We hypothesize that changes in brain protein synthesis precede plaque accumulation and might serve as a biomarker for disease progression. We have developed techniques to make such measurements in human subjects with positon emission tomography (PET). Measuring and monitoring changes in protein synthesis might serve as a marker of early degenerative changes and an indicator of treatment efficacy.

REFERENCES:

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