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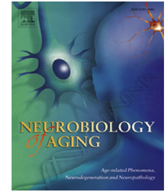

Altered brain development in an early-onset murine model of Alzheimer's disease

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ABSTRACT

Murine models of Alzheimer's disease (AD) have been used to draw associations between atrophy of neural tissue and underlying pathology. In this study, the early-onset TgCRND8 mouse model of AD and littermate controls were scanned longitudinally with in vivo manganese-enhanced MRI (MEMRI) before and after the onset of amyloid plaque deposition at 12 weeks of age. Separate cohorts of mice were scanned at 1 week (ex vivo imaging) and 4 weeks (MEMRI) of age to investigate early life alterations in the brain. Contrary to our expectations, differences in neuroanatomy were found in early post-natal life, preceding plaque deposition by as much as 11 weeks. Many of these differences remained at all imaging time points, suggesting that they were programmed early in life and were unaffected by the onset of pathology. Furthermore, rather than showing atrophy, many regions of the TgCRND8 brain grew at a faster rate compared to controls. These regions contained the greatest density of amyloid plaques and reactive astrocytes. Our findings suggest that pathological processes as well as an alteration in brain development influence the TgCRND8 neuroanatomy throughout the lifespan.

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1. Introduction

Alzheimer's disease (AD) is a neurodegenerative disorder associated with cognitive impairments, dementia, and eventual death. The decline in cognitive function has been attributed to a cascade of neuropathology that alters the cellular and molecular environment in the brain. Early in the disease, toxic soluble amyloid-β (Aβ) oligomers disrupt the structure and function of neuronal synapses (Ferreira and Klein, 2011; Lacor et al., 2007). As the amyloid burden increases, these soluble fragments deposit as insoluble plaques in the parenchyma (Braak and Braak, 1991) and around the vasculature (Zlokovic, 2005), triggering an inflammatory response (Wyss-Coray, 2006). By the late stages, accumulations of intracellular neurofibrillary tangles impair cellular function and contribute to neuronal death (Braak and Braak, 1991).

These pathological events cumulatively change the anatomy of the brain (Lehéricy et al., 2007). In particular, the atrophy of cortical and hippocampal regions has been correlated with cognitive decline and can be used as an early diagnostic tool to differentiate AD progression from mild cognitive impairment (Apostolova and Thompson, 2008; Chételat et al., 2010; Mcevoy et al., 2009). Thus, monitoring the neuroanatomical changes in AD and the relationship to the underlying neuropathology is important for advancing our understanding of disease progression and for developing treatments that target the cellular mechanisms of atrophy.

Mouse models of AD offer the opportunity to directly study the relationship between the pathological processes of the disease and the effects on brain anatomy. Previous cross-sectional and longitudinal magnetic resonance imaging (MRI) studies of murine

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models of AD have demonstrated that regional and whole-brain anatomical changes arise as the pathological burden develops (Badea et al., 2010; Delatour et al., 2006; Grand'maison et al., 2013; Hébert et al., 2012; Maheswaran et al., 2009; Redwine et al., 2003). However, many of these studies have limited their analyses to a few time points before or after the onset of AD plaque deposition, potentially overlooking important spatial and temporal information. To study the relationship between the cellular mechanisms of disease and the corresponding changes in neuroanatomy, multiple imaging sessions must be implemented before and after the onset of AD pathology.

We set out to longitudinally track the MRI-detectable neuroanatomical changes over the time course of pathology using the early-onset TgCRND8 mouse model of AD. In this model, Aβ plaque deposition arises in the cortex and hippocampus by 12 weeks of age, followed by reactive micro- and astrogliosis, dystrophic neuropathy, decreased spine density, and vascular impairments (Chishti et al., 2001; Dorr et al., 2012; Dudal et al., 2004; Steele et al., 2014; Woodhouse et al., 2009). In this study, TgCRND8 and wild-type littermate control mice were imaged with MRI before (9 weeks of age) and on multiple occasions after the reported onset of plaque deposition (12, 16, and 20 weeks of age). These intervals between scanning sessions were chosen to acquire a precise time course of the neuroanatomical changes, as the TgCRND8 quickly becomes affected by pathology around 12 weeks of age (Chishti et al., 2001).

Based on the previously characterized disease progression, we hypothesized that alterations in the TgCRND8 brain would correspond to the timing of plaque deposition, with no apparent differences before this event and substantial volume changes as the pathological burden increased. We further hypothesized that degenerative mechanisms, such as reduced synaptic density, would drive decreases in brain volume, whereas the accumulation of plaques and reactive astrogliosis would displace the surrounding parenchyma, ultimately leading to volume increases.

We initiated the study by longitudinally imaging mice over the time course of amyloid plaque deposition (9, 12, 16 and 20 weeks of age) with the intention of monitoring the relationship between brain atrophy and disease progression. Rather than atrophying, regions of the TgCRND8 brain grew at a faster rate compared to those of controls. However, of particular interest were the unexpected differences in neuroanatomy before the onset of plaque deposition. These findings motivated us to scan separate cohorts of mice at 1 week and 4 weeks of age to determine when the neuroanatomy began to diverge between groups. Interestingly, neuroanatomical differences were apparent at these early post-natal time points and were localized to brain regions similar to those of the older mice in the longitudinal study. These findings led us to conclude that the TgCRND8 is affected by an alteration in brain development that persists into adulthood.

2. Methods

2.1. Animals

The TgCRND8 mouse model of AD encodes a double mutant form of the humanized amyloid precursor protein (hAPP695) with the Swedish (KM670/671NL) and Indiana (V717 F) familial mutations under the control of the Syrian hamster prion promoter (Chishti et al., 2001). Male and female hemizygous TgCRND8 (TG) and nontransgenic littermate controls (wild-type [WT]) on a hybrid 129SvEv/C57BL/6 background were used for all experiments. Mice were housed 2-5 per cage and maintained on a 12-hour light/dark cycle with ab libitum access to food and water. The Toronto Centre for Phenogenomics Animal Care Committee approved all experiments.

2.2. In vivo imaging

Twenty-four hours before each imaging session, mice received a 0.4-mmol/kg intraperitoneal injection of $MnCl_2$ (Manganese (II) chloride tetrahydrate, #M8054, Sigma-Aldrich) in a 0.9% saline vehicle to increase contrast (Silva and Bock, 2008). The anatomical images of the brain were acquired from 7 mice at a time (Bock et al., 2003) using a multi-channel, 7.0 T MRI console (Agilent Technologies) with manganese-enhanced MRI (MEMRI) sequence parameters: T1-weighted gradient echo sequence, TR = 100 ms, TE = 3.6 ms, field of view (FOV) = $3.5 \times 2.1 \times 2.1$ cm^3, matrix = $280 \times 168 \times 168$, 125-μm isotropic resolution, 1 hour 35 minutes scan time (Gazdzinski et al., 2012).

In this study, yoked WT and TG mice underwent a series of longitudinal MEMRI scans at 9, 12, 16, and 20 weeks of age. However, some mice were not scanned at all time points because of the high mortality rate of TG. If a TG mouse died during the study, the yoked WT mouse was also excluded (total of 29 mice (WT = 12, TG = 17) were excluded). A separate cohort of mice was also scanned with MEMRI at 4 weeks of age (all mice were included).

2.3. Sample preparation for ex vivo imaging and immunohistochemistry

In preparation for ex vivo imaging, 1-week-old male pups were separated from their mothers, immediately anesthetized (150 mg/kg of ketamine and 10 mg/kg of xylazine) and perfused through the heart with 10 mL of heparin diluted in phosphate-buffered saline (PBS), followed by 10 mL of 4% paraformaldehyde (PFA) diluted in PBS. After decapitation and removal of the surrounding skin, the skulls containing the brain were post-fixed for 24 hours at 4 °C in a 4% solution of PFA. The skulls were then placed into a solution of 0.01% sodium azide in PBS at 4 °C until the time of scanning.

To determine whether differences in contrast caused by differential manganese uptake were influencing our longitudinal neuroanatomical analyses, an additional cohort of 9-week-old (WT = 4, TG = 4), 12 (WT = 14, TG = 5), 16-week-old (WT = 11, TG = 5), and 20-week-old (WT = 6, TG = 1) mice were sacrificed with a similar perfusion method (Cahill et al., 2012) in preparation for ex vivo imaging. To rule out toxic effects on the neuroanatomy caused by repeated exposures to manganese, 24-week-old mice scanned with MEMRI over the time course of the longitudinal study (WT = 6, TG = 5) and an additional group of mice never exposed to manganese (WT = 9, TG = 3) were prepared with the same perfusion methods. Additional cohorts of mice at 4 and 16 weeks of age (WT = 5, TG = 5) were prepared with the same perfusion method and were used for immunohistochemistry.

2.4. Ex vivo imaging of 1-week-old pups and adults

At 1 week of age, TG pups are small and feeble in comparison to their WT littermates. To avoid any complications that may arise during live imaging, we decided not to scan these mice with in vivo MEMRI. As an alternative, we used an ex vivo diffusion-weighted sequence to acquire high-resolution images with enhanced gray to white matter contrast compared to a typical T2-weighted scan of the postnatal brain (Sussman et al., 2013; Zhang et al., 2006).

Brains of 1-week-old pups were imaged using a 3D diffusion-weighted fast spin echo sequence: TR = 350 ms, echo train length = 6, first TE = 30 ms, subsequent TEs = 6 ms, 1 average, FOV = $2.5 \times 1.4 \times 1.4$ cm^3. A cylindrical acquisition was used to acquire 77% of the k-space data from a matrix of $324 \times 180 \times 180$,

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