Multiparametric MR assays of Spinocerebellar Ataxia 17 Transgenic Mice

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Introduction

Spinocerebellar ataxia (SCA) 17 is a rare neurodegenerative disorder caused by an expanded polyglutamine in the TATA-binding protein (TBP), a general transcription factor that involves the initiation of transcription. SCA 17-related morphological changes in the brain mainly include atrophy in the cerebellum and the basal ganglia. Thus, the major symptoms associated with SCA 17 are prominent cerebellar ataxia, movement disorders, and psychotic disturbances. Besides this, little is known about the underlying neuroanatomical abnormalities caused by the polyglutamine expansion of TBP, and thus treatment for this disease remains difficult. To better understand SCA 17, in this study, multiparametric MR assays were carried out using T2-weighted imaging (T2WI) based volumetric analysis, diffusion tensor imaging (DTI), and magnetic resonance spectroscopy (MRS) in SCA 17 transgenic mice, in which the gene construct contained a human TBP cDNA with 109 repeats of the trinucleotide CAG. Volumetric analysis first identified the size change of brain structures at the macroscopic level, DTI evaluated the structural/functional abnormalities at a microscopic level, and MRS served as an additional functional/metabolic assessment of the abnormalities.

Materials and Methods

On the experiment day, each mouse was anesthetized by 2% isoflurane in O2 at a flow rate of 1 liter/minute. The breathing rate was maintained between 60 and 70 breaths/minute. The anesthetized mouse was fixed in a customized head holder by two ear bars and an incisor fixer. The holder was then horizontally inserted into a 7-T scanner (PharmaScan 70/16, Bruker, Germany) with an active shielding gradient of 300 mT/m in 80 μs. The scanner used a 38-mm volume coil for signal transmission and reception. For volumetric analysis, an axial T2-weighted 3D RARE (rapid acquisition relaxation-enhanced) image was acquired (TR=4000 ms, TEeff=80 ms, FOV=2x2x1.5 cm, matrix=256x128x64 zero-filled to 256x256x64, in-plane resolution=78 umx78 um, number of excitation =2, RARE factor=8). The total scan time was 85 minutes per animal. This scan was repeatedly performed on the mice at ages of 4w, 6w, 8w, 12w, 16w, and 1yr.

DTI was acquired from the 16w, and 1 yr old mice, and MRS was acquired from the 1yr-old mice at a 4.7-T spectrometer (Biospec 47/40, Bruker, Germany). The scanner was equipped with a 72-mm volume coil as the radio frequency (RF) transmitter and a quadrature surface coil placed on the head as the receiver. A spin echo imaging sequence was employed for acquiring the required series of axial diffusion-weighted images (DWIs) with b values of 0 and 1100 mm^2/s applied along six directions: [Gx, Gy, Gz] = [1,1,0], [1,0,1], [0,1,1], [–1,1,0], [0,–1,1], and [1,0,–1] with repetition time = 1.5 s, spin echo time = 31 ms, time between diffusion gradient pulses = 15 ms, duration time of diffusion gradient = 7.5 ms, slice thickness = 1 mm, field of view = 2x2 cm^2, data matrix = 128x128, and four averages. For MRS data acquisition, MRS was acquired by the PRESS sequence with voxel size=2 x 1.3 x 1.3 mm^3, TR=3000ms, TE=136ms, NEX=512, and total scan time= 13 min. The ROI was localized at the cerebellum. MRS data analysis was preformed by Bruker ParaVision software for the integral ratio of each spectrum.

Results

Ventricular expansion is an important indicator of brain atrophy. Figure 1 shows that cerebral aqueduct and the 4th ventricle were enlarged in the transgenic (TG) mice as opposed to the wildtype (WT). This suggests that brain atrophy may occur to areas surrounding these ventricular spaces. The size of the cerebrum was not different between the TG and WT until the age of 1 yr, indicating the cerebrum gradually underwent atrophy. By contrast, the cerebellum of the TG was smaller than the WT throughout the lifetime. As shown in Figure 2, DTI reveals that the cerebellum of the TG mice showed increased diffusivity although the anisotropy of diffusion was not altered. The diffusivity change was explained by increased $\lambda_{\parallel}$ and $\lambda_{\perp}$. Neuronal loss may account for the observation. MRS acquired from 1 yr old mice indicates that the TG had less NAA levels in the cerebellum, which may also suggest a decreased neuronal level. This finding is consistent with the DTI result.

Discussion

Shrunk size, increased diffusivity, and decreased NAA levels of the cerebellum surrounded by enlarged ventricular spaces characterize the TG mice of the SCA 17 human disease. These indications reveal the importance of cerebellar cell loss in SCA17.

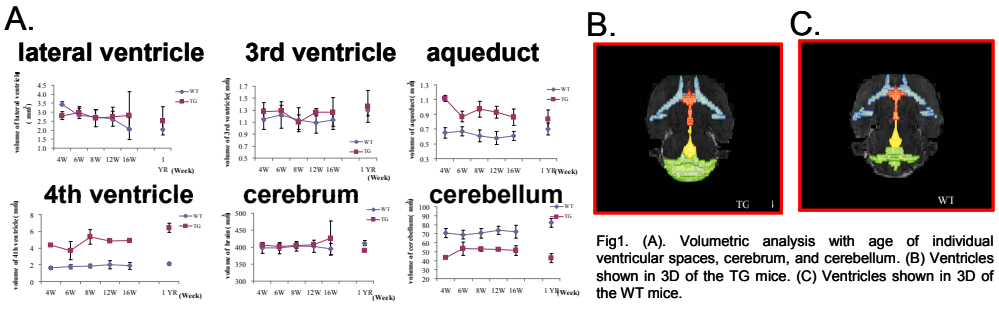

Fig1. (A). Volumetric analysis with age of individual ventricular spaces, cerebrum, and cerebellum. (B) Ventricles shown in 3D of the TG mice. (C) Ventricles shown in 3D of the WT mice.

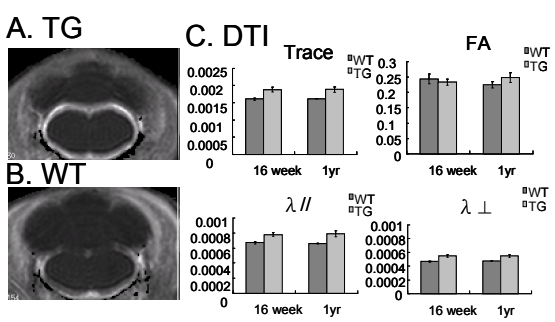

Fig2. (A) The Trace map of the TG. (B) The Trace map of the WT. (C) The Trace, FA (fractional anisotropy), λ//, and λ ⊥ of the TG and WT mice at 16 week and 1 yr old. Trace, λ//, and λ ⊥ were elevated in TG as compared to in WT whereas FA did not differ. There was no age effects in the changes.

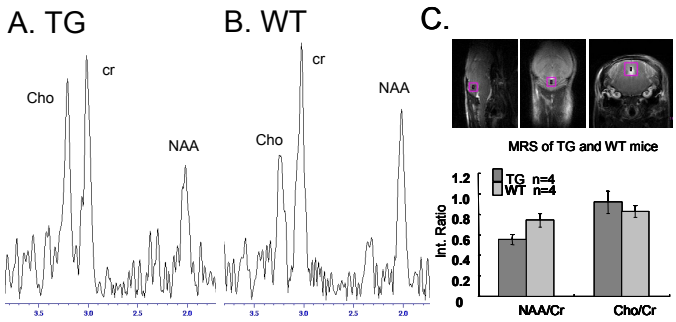

Figure 3. (A) MRS of TG. (B) MRS of WT. (C) Top: The location of the voxel. Bottom: NAA levels in the TG mice were decreased as compared to the WT.