Screening Mutagenic Mice with Ventricular Mutation: A Longitudinal Study

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Synopsis

To screen mice with ventricular mutation, longitudinal mice ventricular volumes of each compartment were established using high resolution 3D T2 weighted MR images.

Introduction

The phenotype-driven approaches to induce a large scale of mutant mice with randomly damaged DNA by using chemical mutagen N-ethyl-N-nitrosourea (ENU) is a unique animal model uncover the mechanisms of gene mutation [2]. To screen mice with ENU-induced brain disorders, one of the important features among several symptoms induced by phenotype-driven mutagenesis is the ventricular volume variation. The abnormal dilatation of ventricular volume often serve as an assessment for cerebral disorders, such as schizophrenia, Alzheimer's disease, and benign intra-cranial hypertension [3]. Therefore, in this study, longitudinal ventricular volumes of wide mice were acquired by using non-invasive MRI T2WI. 5 mice were longitudinal traced from 3rd to 100th week. Ventricular compartments, 3rd ventricle, 4th ventricle, Aqueduct, and bilateral ventricular volume were measured. Our results showed that volumes of bilateral ventricle and 3rd ventricle were dilated while 4th ventricular volume was shrunk. This study might serve as criteria for ENU-induced brain disorder in the future.

Material & Methods

5 male C57BL/6J mice were recruited in this study from 3 to 100 weeks years old. The MR images were acquired on a 7T Bruker, Pharmascan scanner. Sagittal T2-weighted image was acquired with TR = 2000ms, TE = 88.3ms, FOV = 3 x 3 cm^2 and matrix = 256×128 to determine the location and length of the brain. 3D T2 weighted image was acquired axially with TR = 4000ms, TE = 80ms, voxel size = 2.86 × 10^{-6} cm^3, Matrix = 256×128×64.

To eliminate manual errors, two imaging analysts who are blind to the test subjects were responsible for manual depicting ROIs of ventricle. ROIs of ventricle are delineated carefully into the right lateral ventricle, the left lateral ventricle, the 3rd ventricle, the aqueduct, and the 4th ventricle. The voxels assigned to these individual parts of ventricle were summed and multiplied by the voxel size. To obtain their volumes respectively, the total ventricular volume was sum up from all of these separate parts. All images were processed using manual trace tool and edge editing function provided by ANALYZE (Biomedical Imaging Resource, Mayo Foundation, Rochester, Minn). Volume index and brain length index were introduced to correct individual volume deviation which was calculated from each mouse. The volume index was defined as the ratio between the ventricular volume and the brain volume. The brain length index was defined as the ratio between the ventricular volume and the brain length, where brain length was defined as the length from the boundary between the olfactory bulb and fore-brain to the bottom of the cerebellum in the mid-sagittal view of the brain. The mean and standard deviation of all the measurements are subjected to paired t tests for the relation between each different age level and different ventricular parts. $p<0.05$ was considered as statistical significant.

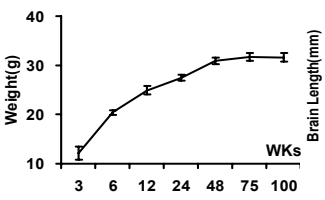

Fig. 1 Mice weight

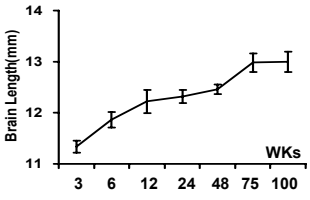

Fig. 2 Brain length

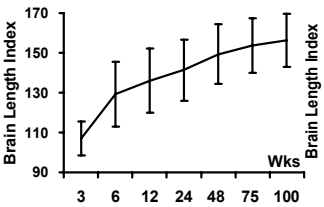

Fig. 3 Total ventricular brain length index

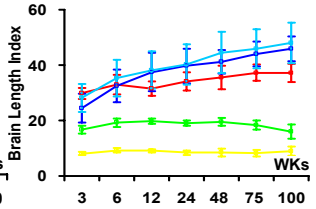

Fig. 4 Individual ventricular brain length index

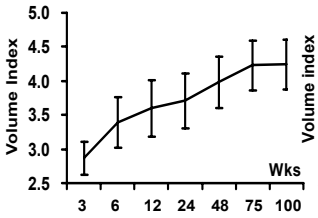

Fig. 5 Total ventricular volume index

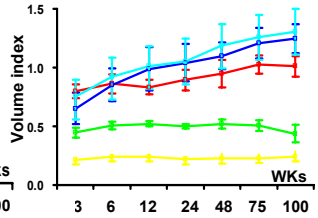

Fig. 6 Individual ventricular volume index

Results

Figure 1-2 show the relationship between mice weight, brain length, and age, respectively. Body weight and brain length were increased from 3rd to 48th week ($p<0.05$) and 3rd week to 75th week ($p<0.05$), respectively. Figure 3-6 show the brain length index and volume index of total ventricle and individual ventricular compartment versus age. Brain length index and volume index of whole ventricle, left lateral, right lateral and 3rd ventricle was apparently dilated following age growth while 4th ventricle and aqueduct differed slightly. Figure 7 shows the selected ROIs by manual depiction (a-c), and the 3D display of each ventricular compartment (d).

Discussion

Ventricular volumes of 5 mice were longitudinal traced from 3rd to 100th week to bypass the individual mice variation. Two indices, brain length index and brain volume, were introduced in this study to correct the individual volume deviation. As shown in Fig. 4 and Fig. 6, two indices were similar in brain ventricular volume calculation. These indices demonstrated that mouse weight and brain length grew from 3rd to 48th week and to 75th week, respectively. Brain total ventricular and bi-lateral ventricular volumes were dilated while that of 4th ventricle and Aqueduct retained following age growth. This might indicate that 4th ventricle and Aqueduct have reached their mature status earlier. By measuring mice ventricular volume longitudinally, this study has set up standard ventricular indices for further brain disorder studies.

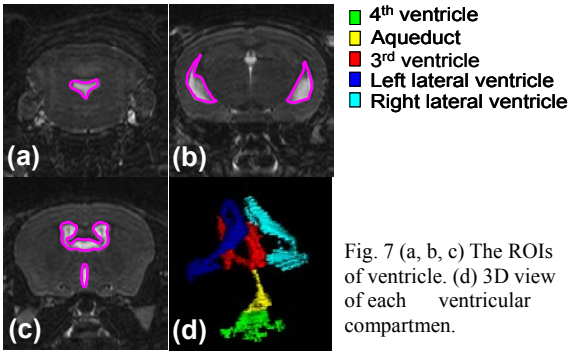

Fig. 7 (a, b, c) The ROIs of ventricle. (d) 3D view of each ventricular compartmen.

References

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