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Quantifying cerebellar atrophy in multiple system atrophy of the cerebellar type (MSA-C) using three-dimensional gyrification index analysis

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ABSTRACT

Multiple system atrophy of the cerebellar type (MSA-C) is a degenerative neurological disease of the central nervous system. This study employed a method named, "surface-based three-dimensional gyrification index" (3D-GI) to quantify morphological changes in normal cerebellum (including brainstem) and atrophied cerebellum, in patients with MSA-C. We assessed whether 3D-GI can exclude gender and age differences to quantify cerebellum and brainstem atrophy more accurately. Sixteen healthy subjects and 16 MSA-C patients participated in this study. We compared 3D-GI values and volumes in the cerebellum, based on T1-weighted MR images. We also compared the images of reconstructed 3D cerebellum gray matter (3D-CBGM) and cerebellum white matter (3D-CBWM) to detect the atrophied cerebellar region in MSA-C patients. The 3D-GI values were in a stable range with small variances, exhibiting no gender effect and no age-related shrinkage. Significantly lower 3D-GI values were exhibited in both CBGM and CBWM of the MSA-C patients compared with healthy subjects, even in the early phases of the disease. Decreases in 3D-GI values indicated the degeneration of the cerebellar folding structure, exactly reflecting the morphological changes in cerebellum. The 3D-GI method based on CBGM resulted in superior discriminative accuracy compared with the CBGM volumetric method. Using the two-dimensional 3D-GI values, the K-means classifier can evidently discriminate the MSA-C patients from healthy subjects.

Introduction

Multiple system atrophy (MSA) is a form of sporadic spinocerebellar degeneration characterized by varying degrees of Parkinsonism, cerebellar ataxia, and autonomic dysfunction (Gilman et al., 2008; Quinn, 1989; Wenning et al., 2004). According to Gilman et al., MSA can be categorized into two main subtypes: MSA-C (cerebellar) and MSA-P (Parkinsonism) (Gilman et al., 2008). In Taiwan, MSA-C is more common than MSA-P, while MSA-P is more common in the United States. Gait ataxia is the most typical early symptom of this disease. Other clinical features include dysarthria, tremor, and parkinsonian or other extrapyramidal symptoms (Berciano, 1982). Many investigators have reported that the main pathological changes of MSA-C are the loss of neurons in the ventral portion of the pons, inferior olives, and cerebellar cortex. Its fundamental lesions occur in the arcuate, pontine, inferior olivary, pontobulbar nuclei, and the cerebellar cortex (Pemde et al., 1995). Atrophy of the brain stem and cerebellum is an important feature on magnetic resonance (MR) images of MSA-C patients (Matsusue et al., 2008); the atrophy is aggravated as the disease progresses, and atrophy rates correlate negatively with disease duration (Miyatake et al., 2010; Paviour et al., 2006). Therefore, the quantification of cerebellar atrophy is important for the diagnosis of MSA-C and relevant studies.

Neuroscientists and psychiatrists have applied several methods to assess the morphological changes of MSA-C in MR images, including voxel-based morphometry (VBM) (Brenneis et al., 2007; Minnerop

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et al., 2007; Specht et al., 2003, 2005), volumetric analysis (VA) (Bürk et al., 2004; Miyatake et al., 2010) and cerebral area analysis (Horimoto et al., 2000). These methods are voxel-based measurement, and can be categorized as the volumetric analysis. Postmortem and in vivo image studies have demonstrated the intrinsic biological variability of sex differences and age-associated shrinkage in cerebellum and brain stem volumetric analysis (Oguro et al., 1998; Raz et al., 1998, 2001; Torvik et al., 1986). The cerebellar volumes (especially the right hemisphere) were larger in men, even after adjusting for height (Raz et al., 2001). The cerebellar volume began to decrease at age 50, with progressive decrease until age 65; thereafter, the decline became slower and the volume stabilized at a "virtual" volume of 90 ml (Luft et al., 1999). Male subjects showed more significant age-related atrophy of the cerebellar hemispheres, especially the right hemisphere (Xu et al., 2000). The brainstem also showed significant sex differences of age-associated shrinkage in different sub-regions (Oguro et al., 1998). The volumetric analysis method has limitations in preserving the topology of cortical surface and cannot describe the complexity and variability of brain structural organization (Zhang et al., 2006). Accordingly, methods that can eliminate these differences and quantify the surface complexity are preferred for assessing cerebellar atrophy.

The gyrification index (GI), proposed by Zilles et al., defined as the ratio of the folded inner contours to its exposed outer contour, and has been commonly used to measure the degree of cortical folding (Bonnici et al., 2007; Harris et al., 2004; Moorhead et al., 2006; Oyegbile et al., 2004; Zilles et al., 1988). Zilles and his colleagues have reported that the cerebral GI values are not significantly affected by age, gender, body weight, body length, or brain volume differences (Zilles et al., 1988). Brain with higher degree of cortical folding yields larger values of GI, and these values increase proportionally to the number and complexity of gyri (Harris et al., 2004; Kesler et al., 2006; White et al., 2010; Zilles et al., 1997). The original GI method required manual tracing of the inner and outer contours which is a subjective measure. The manual tracing procedure can be time-consuming and biased by different operators. Besides, visual inspection may not be sensitive enough to trace the contours with spatially high-frequency changes. Recently, Moorhead and his colleagues have developed an automated GI (A-GI) methodology to alleviate these limitations (Moorhead et al., 2006). Differently from the manual GI, A-GI is an unbiased and objective measure and has low susceptibility to noise (Moorhead et al., 2006). In comparison with manual tracing, A-GI substantially reduces the time costs and improves repeatability (Moorhead et al., 2006). The A-GI permits a rapid determination of GI with unbiased in its application and unlimited in the size of test cohort (Bonnici et al., 2007; Moorhead et al., 2006). They further demonstrated that the GI was sensitive to atrophy and useful for neurodevelopment measurement (Mirakhur et al., 2009). These suggest that GI analysis is an effective method for quantifying atrophy of cortical folding.

Previous GI studies of cortical folding were mainly focused on cerebral and psychiatric disorders (Bonnici et al., 2007; Gaser et al., 2006; Harris et al., 2004; Zhang et al., 2009, 2010), but less in the diseases with atrophied cerebellums. In this study, we aim to characterize and distinguish the cortical folding alteration of cerebellum between healthy and MSA-C patients using the 3D-GI method. In addition, we measure the cerebellar volumes of the participants and investigate whether there are sex difference and age effect in the 3D-GI and volumetric measurements.

Material and methods

Subjects

Sixteen MSA-C patients (8 female (F)/8 male (M); mean age 56 ± 7 years) and 16 healthy subjects (8 F/8 M; 51 ± 10 years) participated in this study. The MRI scans were conducted by the Department of Radiology, Taipei Veterans General Hospital, Taiwan. The study was approved by the ethics committee of the Taipei Veterans General Hospital and complied with the 1964 Declaration of Helsinki. Written informed consent was obtained from each volunteer before the study commenced. Diagnoses of MSA were made according to the established guidelines (Gilman et al., 2008). The severity of ataxia was graded as follows: (I) walking without assistance (II) walking with partial assistance (III) needing assistance walking (IV) needing assistance standing and (V) bedridden (Bang et al., 2003). The severity of Parkinsonism was evaluated according to a modified Hoehn–Yahr staging system (Kim et al., 2003). The duration of illness was according to the patient's memory of the onset of earliest symptoms. This was asked at their first visit to the outpatient clinic (MRI scans were arranged at this time). The mean illness duration for the patient group was 4.3 ± 2.8 years. Demographic features and clinical data for the study groups are summarized in Table 1. No significant age difference ($p = 0.071$, *t*-Test) and gender difference ($p = 1$, Chi^2-Test) were revealed between the control and MSA-C groups. All patients met the second consensus criteria for a clinical diagnosis of probable MSA (Gilman et al., 2008). According to the clinical symptoms, patients were categorized into MSA-C.

Data acquisition and image procedures

Axial magnetic resonance (MR) images of the human brain, covering the entire cerebrum and cerebellum, were acquired using a 1.5-T Vision Siemens scanner (Erlangen, Germany). A circularly polarized head coil was used, based on a T1-weighted MR sequence with the following parameters: number of axial slices = 124; slice thickness = 1.5 mm; echo time = 5.5 ms; repetition time = 14.4 ms; flip angle 20°; field of view 25 cm; matrix size = 256 × 256; and in-plane resolution = 1 mm × 1 mm.

The image procedures are summarized in Fig. 1. First, the cerebellum (CB) image, which included the brainstem, was manually

Table 1
Demographic features and clinical data of the study groups.

Demographic features	Normal(16)	MSA-C(16)	P value
Age[a](years)	51 ± 10	56 ± 7	0.071
Duration[a] (years)	–	4.3 ± 2.8	–
Gender[b](male/female)	8/8	8/8	1
Clinical data			
Severity of ataxia[c]			
I	16(100%)	0	
II	0	16(100%)	
III	0	0	
IV	0	0	
V	0	0	
Modified Hoehn–Yahr stage[c]			
0	16	0	
1	0	0	
2	0	16(100%)	
3	0	0	
4	0	0	
5	0	0	
MRI features[c]			
Normal	16(100%)	0	
Cerebellar atrophy	0	16(100%)	
Hot cross bun sign	0	13(81%)	
Putaminal slits	0	5(31%)	

Age: age at MRI scanning. The severity of ataxia: (I) walking without assistance (II) walking with partial assistance (III) needing assistance walking (IV) needing assistance standing and (V) bedridden. MSA-C: multiple system atrophy of the cerebellar type. Modified Hoehn–Yahr: stage of Parkinsonism.

[a] Continuous data were expressed as mean ± standard deviation (SD) and the age difference was tested by independent *t*-Test.

[b] Gender difference was tested by Chi^2-Test.

[c] Categorical data were expressed as number (%).