Archives of Gerontology and Geriatrics 59 (2014) 439–449

Contents lists available at ScienceDirect

Archives of Gerontology and Geriatrics

journal homepage: www.elsevier.com/locate/archger

Age-related iron deposition in the basal ganglia of controls and Alzheimer disease patients quantified using susceptibility weighted imaging

Dan Wang [a], Yan-Ying Li [b], Jian-Hua Luo [c], Yue-Hua Li [a,*]

[a] Institute of Diagnostic and Interventional Radiology, The Sixth Affiliated People's Hospital, Shanghai Jiao Tong University, No. 600, Yi Shan Road, Shanghai 200233, China
[b] The Second Affiliated Hospital of Harbin Medical University, Radiology Department, China
[c] College of Life Science and Technology, Shanghai Jiaotong University, China

ARTICLE INFO

Article history:
Received 26 January 2014
Accepted 6 April 2014
Available online 18 April 2014

Keywords:
Magnetic resonance imaging
Susceptibility weighted imaging
Iron deposition
Aging
Alzheimer disease

ABSTRACT

This study aimed to investigate age-related iron deposition changes in healthy subjects and Alzheimer disease patients using susceptibility weighted imaging. The study recruited 182 people, including 143 healthy volunteers and 39 Alzheimer disease patients. All underwent conventional magnetic resonance imaging and susceptibility weighted imaging sequences. The groups were divided according to age. Phase images were used to investigate iron deposition in the bilateral head of the caudate nucleus, globus pallidus and putamen, and the angle radian value was calculated. We hypothesized that age-related iron deposition changes may be different between Alzheimer disease patients and controls of the same age, and that susceptibility weighted imaging would be a more sensitive method of iron deposition quantification. The results revealed that iron deposition in the globus pallidus increased with age, up to 40 years. In the head of the caudate nucleus, iron deposition peaked at 60 years. There was a general increasing trend with age in the putamen, up to 50–70 years old. There was significant difference between the control and Alzheimer disease groups in the bilateral globus pallidus in both the 60–70 and 70–80 year old group comparisons. In conclusion, iron deposition increased with age in the globus pallidus, the head of the caudate nucleus and putamen, reaching a plateau at different ages. Furthermore, comparisons between the control and Alzheimer disease group revealed that iron deposition changes were more easily detected in the globus pallidus.

1. Introduction

Excessive deposition of iron in the brain may be a risk factor for degenerative disease (Aquino et al., 2009; Brooks, Luthert, Gadian, & Marsden, 1989; Qin et al., 2011), so the knowledge of the normal range of iron accumulation is essential (Haacke, Ayaz, et al., 2007; Hallgren and Sourander, 1958). In particular, the basal ganglia may exhibit susceptibility to mineralization as a result of its high metabolic rate (Akhlaghpoor et al., 2011). Excessive mineral deposition may, in turn, restrict blood flow and cause neural tissue injury that leads to further mineralization (Castelnau et al., 1998; Cho et al., 2000; Haacke, Ayaz, et al., 2007; Siegelman, Mitchell, & Semelka, 1996). Understanding the quantity of iron deposition in the aging brain is an important step to interpreting imaging studies of the diseased brain.

Alzheimer disease (AD) is a common type of dementia, which seriously affects the quality of life of aging people. Due to a lack of biological markers, the diagnosis can only be confirmed by brain biopsy or post-mortem examination. Therefore, it is important to improve the accuracy of the clinical diagnosis of AD, and the sensitivity of early diagnosis of AD in the initial stages. Although some clinical studies have focused on AD diagnosis, the AD patients included in these studies are often at a relatively late stage of the disease process. It is therefore hard to determine the development or dynamic processes of AD. Currently, imaging studies of AD patients are mainly concerned with the morphology of hippocampal and functional magnetic resonance (MR) imaging (Pfefferbaum, Adalsteinsson, Rohlfing, & Sullivan, 2009). However, there are large individual differences, and hippocampal atrophy is not the main pathological change of AD patients.

Abbreviations: AD, Alzheimer disease; MR, magnetic resonance; ROI, region of interest; SWI, susceptibility weighted imaging.

* Corresponding author. Tel.: +86 21 64844183; fax: +86 21 64844183.
E-mail address: liyuehuaxp@gmail.com (Y.-H. Li).

http://dx.doi.org/10.1016/j.archger.2014.04.002

It has been reported that patients with AD have excessive iron deposition, but its mechanism is as yet not clear (Cho et al., 2000; Kim et al., 2009). These reports have provided a clue to the detection of AD. Some studies have found that iron deposition within the deep brain nuclei increases with increasing age, especially basal ganglia (Hallgren & Sourander, 1958). Iron deposition changes have been correlated with age (Akhlaghpoor et al., 2011), but it is unknown whether physiological iron deposition is related to excessive iron deposition observed in AD. Physiological iron deposition needs to be differentiated from pathological deposition.

Susceptibility-weighted imaging (SWI) provides a method for enhancing contrast in MR imaging (Siegelman et al., 1996). The phase and magnitude images can be combined to create susceptibility weighted images (SWI). In addition, phase images can be used to quantify iron accumulation (de Rochefort et al., 2010; Haacke, Ayaz, et al., 2007; Zivadinov et al., 2010). In this study, the head of the caudate nucleus, globus pallidus and putamen were selected as the regions of interest (ROIs). We were interested in examining the changes in iron deposition associated with age. The main aims of this study were to: quantify levels of iron deposition in the basal ganglia of normal volunteers, and to compare the iron deposition changes between AD patients and normal volunteers from the same age groups.

2. Materials and methods

2.1. Subjects

From June 2011 to June 2012, we recruited 182 people, including 143 healthy volunteers (normal controls, NC group) and 39 AD patients (Fig. 1).

The healthy volunteers ranged in age from 12 to 87 years (mean age, 48.8 years; SD, 18.8 years). Exclusion criteria included arterial hypertension, and structural and other abnormalities that may lead to dementia, such as cortical infarction, tumors, subdural hematoma, brain trauma, epilepsy, alcoholism, psychiatric illness, or other systemic diseases which may affect brain function. All volunteers were right-handed. They were divided into eight groups according to age: group 1 (10–19 years), group 2 (20–29), group 3 (30–39), group 4 (40–49), group 5 (50–59), group 6 (60–69), group 7 (70–79), and group 8 (80–89).

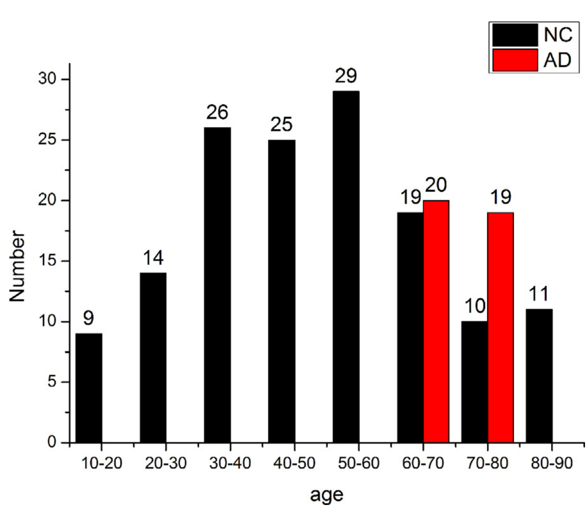

Fig. 1. The number of normal controls (eight age groups) and AD patients (two groups). NC, normal controls.

The 39 selected AD patients (with an age range of 62–80 years) had a clinical diagnosis of probable AD according to the diagnostic criteria recommended by the National Institute of Neurologic and Communicative Disorders and Stroke, and the Alzheimer's Disease and Related Disorders Association (Agosta et al., 2011; McKhann et al., 1984). Arterial hypertension (AH) was included in the exclusion criteria. These AD patients were divided into two groups according to age: 60–70 years old or 70–80 years old. The MR examinations included conventional MR imaging (sagittal T1, axial T2, and axial fluid-attenuated inversion recovery sequences), and the acquisition of a normal SWI sequence.

We obtained written informed consent for the use of data both from volunteers/AD patients themselves and their guardians prior to MR imaging. This study was reviewed and approved by the Ethics Review Board of the Shanghai 6th People's Hospital Affiliated with Shanghai Jiao Tong University.

2.2. MR examination and measurement

A Siemens Verio 3T MR (MAGENTOM, Verio, Siemens Healthcare, Erlangen, Germany) with a 32-channel head coil was used. The imaging sequences included conventional MR sequences (T1W, T2W), diffusion weighted imaging and SWI (Figs. 2a–e and 3a–e). The scanning parameters were as follows: T2 W: TR/TE 6000 ms/95 ms, FA 150°, matrix 384 × 384, slice thickness 6 mm, dist factor 30%, average 1, FOV 250 mm; T1 W fluid-attenuated inversion recovery: axial and sagittal scanning TR/TE 2000 ms/9 ms, FA 150°, matrix 320 × 320, slice thickness 6 mm, dist factor 30%, average 1, FOV 250 mm; and SWI: axial scanning TR/TE 28 ms/20 ms, FA 15°, matrix 320 × 320, slice thickness 1.2 mm, average 1, FOV 230 mm. A group of magnitude, phase, maximum intensity projection (MIP) and SWI images were automatically reconstructed online (Figs. 2c–e and 3c–e) (Haacke, Ayaz, et al., 2007).

2.3. Image analysis

We utilized the phase images to quantify iron deposition. Using the Siemens Workstation (MAGNETOM, VB17 software), two neuroradiologists (with 5-years and 8-years experience, respectively) manually outlined the globus pallidus, putamen and the head of the caudate nucleus as the ROIs, according to the T1 images of anatomical structure. We obtained the mean radian angle values for these ROIs. The mean values were then calculated for statistical analysis. As the measured value (X) has a range of (-4096 to 4095) which maps to the phase value Y (Pi to $-$Pi), the formula used for conversion was as follows:

$$Y = \frac{-X \times \pi}{4096}$$

where X is the direct measured value on the phase image and Y is the corresponding angle radian value (phase value of the radius). The measurement method can be seen in Fig. 3d. The ANOVA model was used to compare values for the head of the caudate nucleus, globus pallidus and putamen between the different age groups with the Fish-LSD test (a two sample t-test comparison). Polynomial fitting was carried out between iron deposition and age. A two sample t-test and the Mann–Whitney test were performed to compare both the differences between the controls and AD patients in the same age groups (i.e., a 60–70 years old group or an older than 70 years old group), and any differences between 60–70 year olds and the older than 70 years old AD patients. Pearson's correlation was performed to analyze the relationship between iron deposition in all the ROIs and the MMSE scores of 60–80-year-old patients with AD.