European Journal of Radiology 84 (2015) 1325–1332

Contents lists available at ScienceDirect

European Journal of Radiology

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

Iron deposition in the gray matter in patients with relapse-remitting multiple sclerosis: A longitudinal study using three-dimensional (3D)-enhanced T2*-weighted angiography (ESWAN)

Silin Du [1], Shambhu K. Sah [1], Chun Zeng [2], Jingjie Wang [2], Yi Liu [2], Hua Xiong [2], Yongmei Li *

Department of Radiology, The First Affiliated Hospital of Chongqing Medical University, No. 1 Youyi Road, Yuzhong District, Chongqing 400016, China

ARTICLE INFO

Article history:
Received 25 December 2014
Received in revised form 5 April 2015
Accepted 12 April 2015

Keywords:
Multiple sclerosis
Iron deposition
Gray matter
Longitudinal
Susceptibility-weighted imaging

ABSTRACT

Purpose: To investigate the relationship between the iron content by magnetic resonance imaging (MRI) and clinic correlation in patients with relapse-remitting multiple sclerosis (RRMS) over a two-year period.
Methods: Thirty RRMS patients and 30 healthy control subjects were examined twice, two years apart, by undergoing brain conventional MRI and three-dimensional (3D)-enhanced T2*-weighted angiography (ESWAN) sequences at 3.0 T. Quantitative differences in iron content in deep gray matter (GM) nuclei and precentral gyrus GM between patients and control subjects with repeated-measures the mean phase values (MPVs) for ESWAN-filtered phase images. Spearman's rank correlation coefficient analysis was used to evaluate correlations of the MPVs, both 2-year-difference and single-time measurements, to disease duration, expanded disability status scale (EDSS) and times of recurrence.
Results: The RRMS patients had higher GM iron concentration than that of the healthy control subjects in both single-time measurements, but only the substantia nigra (SN), and the precentral gyrus GM (PGM) showed a significant statistical difference ($p < 0.05$). Using the paired samples t test, we found that there were significant differences in two-year-difference measurements of the MPVs in the putamen (PUT), the globus pallidus (GP), the head of the caudate nucleus (HCN), the thalamus (THA), SN, the red nucleus (RN), the dentate nucleus (DN) and PGM, especially in SN ($t = 2.92$, $p = 0.007$) in RRMS patients. The MPVs of the PUT, GP, HCN, THA, SN, RN, DN and PGM for the subgroup with RRMS patients in times of recurrence less than twice were similar to the healthy controls. There was no significant difference in all regions of interests (ROIs). However, there were significant differences in all ROIs except THA and GP for the other subgroup with RRMS patients in times of recurrence more than and equal to twice. Spearman's rank correlation coefficient analysis showed there were significant negative correlations between disease duration and the MPVs in the HCN ($r = -0.516$, $p = 0.004$), DN ($r = -0.468$, $p = 0.009$) and PGM ($r = -0.84$, $p = 0$). However, no correlations were found between the EDSS scores and the MPVs.
Conclusions: Iron content in the GM can be measurable using MRI and our results confirmed that iron concentration was increasing in the GM of MS patients during two-year period compared to healthy controls. Furthermore, this study had also shown significant and substantial correlation of iron concentration with disease severity.

* Corresponding author. Tel.: +86 023 68899931; fax: +86 023 6881 1487.
E-mail addresses: 182389558@qq.com (S. Du), mrsks2007@hotmail.com (S.K. Sah), zengchun19840305@163.com (C. Zeng), 345151097@qq.com (J. Wang), 993537544@qq.com (Y. Liu), rjdfxyh@163.com (H. Xiong), lymzhang70@aliyun.com (Y. Li).
[1] Tel.: +86 023 89012654; fax: +86 023 68811487.
[2] Tel.: +86 023 89012655; fax: +86 023 68811487.

http://dx.doi.org/10.1016/j.ejrad.2015.04.013
0720-048X/

1. Introduction

Multiple Sclerosis (MS) has long been considered an autoimmune disease primarily affecting the white matter (WM); components of the pathology include demyelination, inflammation, and neurodegeneration [1]. However, it has become increasingly clear that GM pathology is also an important aspect of the disease. Furthermore, several studies have demonstrated a stronger correlation between GM lesions and fatigue, physical disability, and cognitive deficits than with WM lesion burden, suggesting that GM pathologic changes are of great clinical importance [2]. Moreover, the precentral gyrus is the location of the primary motor cortex. It works together with other motor areas to plan, initiate and execute movements [3].

Iron is indispensable to normal neuronal metabolism and plays a major role in physiological processes, such as oxygen transport, neurotransmitter synthesis, electron transfer, mitochondrial energy generation and myelination [4]. Although iron is essential for normal neurobiological functioning, its increased level can contribute to the formation of free radicals, thereby causing lipid peroxidation and neurotoxicity [5]. Recent reports have documented that the levels of iron content were found to be elevated in numerous neurological disorders, such as multiple sclerosis (MS) [6,7], Parkinson's disease [8] and other diseases. In addition, increased deposition of iron in MS patients in the cross-time study predominantly in the deep gray matter [9], the cerebral cortex [10], within the lesions [11] and the experimental autoimmune encephalomyelitis (EAE) animal models of MS [12], is also related to the pathologic process. However, whether iron deposition is an epiphenomenon in the disease process of MS, or may play a primary role in disease development, remains unclear at present.

The cross-time iron measurements may not be sufficient to determine whether iron content is pathologically changing in individual MS patients. Longitudinal analysis would be more powerful in understanding the iron pathophysiologic processes in MS or may represent a new method of classifying disease severity. Recently a longitudinal study by Walsh AJ et al. [13], it has shown that using different methods R_2^* mapping and phase imaging to evaluate iron content in the deep GM between MS patients and control subjects, iron content significantly increases in the deep gray matter of MS patients during two years.

To our knowledge, no studies have longitudinally investigated abnormal iron concentration in the precentral gyrus GM. The purpose of this study was to longitudinally investigate the changes of iron deposition in the deep GM nuclei and precentral gyrus GM of MS. Furthermore, the correlations between iron content in the deep GM nuclei and the precentral gyrus gray matter and Expanded Disability Status Scale (EDSS), disease duration in MS patients over a 2-year period were evaluated using a 3D-enhanced T2* susceptibility-weighted angiography (ESWAN).

2. Materials and methods

2.1. Subjects

In this study, thirty patients with RRMS and 30 age- and sex-matched control subjects were recruited from November 2009 to May 2013 from the First Affiliated Hospital of Chongqing Medical University (Chongqing, China). Each subject was imaged twice, two years apart. The RRMS group was further divided into two subgroups: one group with patients in times of recurrence less than twice and the other group with patients more than or equal to twice. The diagnosis of RRMS was made according to the 2005 revised McDonald criteria [14]. The patients were treated with glucocorticoid before entering the study and during the follow up period. MS patients were graded according to the EDSS scores. Disease duration is as measured from the date of the original diagnosis to the second scan and the times of recurrence is as measured from the first time symptom appearing to the second scan. Exclusion criteria for all subjects were that they had other neurologic diseases or that they had contraindications to MR imaging. The main demographic and clinical characteristics of the patients are shown in Table 1.

Table 1
Characteristics of RRMS patients and control subjects.

Number of subjects	RRMS (30)	Control (30)
Sex (M/F)	12/18	12/18
Age scale (year)	16–69	16–69
Median age (year)	48.4 ± 13.4	45.5 ± 14.5
EDSS range (the first scan)	1–6	–
Mean EDSS (the first scan)	2.5 ± 1.2	–
EDSS range (the 2nd scan)	0.5–7.5	–
Mean EDSS (the 2nd scan)	2.5 ± 1.5	–
Disease duration range (year)	3.0–10.1	–
Mean disease duration (year)	4.86 ± 1.83	–

RRMS: relapse-remitting multiple sclerosis; EDSS: expanded disability status scale.

This study was supported by the institutional review board of Chongqing Medical University and complied with the Health Insurance Portability and Accountability Act. Written informed consent was obtained from all participants at the beginning of the study.

2.2. MRI data acquisitions

All MR images were performed using a 3.0 Tesla (T) MR scanner (Signa, HD, General Electric [GE] Healthcare, Milwaukee, WI, USA) equipped with an eight-channel phased array head coil. All subjects were subjected to the standard MRI protocols proposed by the international MS group diagnosis center. The parameters of conventional MR imaging are as follows: (1) a conventional axial 2D multi-planar dual fast spin-echo (FSE) proton density (PD) and T_2-weighted images (WI): repetition time [TR] 2900 ms, echo time $[TE]_1/TE_2$ 25 ms/93 ms, echo train length [ETL] 12, matrix size 256 × 192; (2) an axial T1WI:TR 8000 ms, TE 120 ms, inversion time [TI] 2000 ms, ETL 8, matrix size 256 × 160; and (3) fluid attenuated inversion recovery (FLAIR): TR 2050 ms, TE 24 ms, TI 750 ms, matrix size 256 × 256. These routine sequences were acquired with 5-mm-thick contiguous sections, no space and a 24 cm × 24 cm field of view (FOV).

All ESWAN sequences were acquired using a 3D-enhanced T2* susceptibility-weighted angiography contrast flow compensated (i.e., the gradient moment was null in all three orthogonal directions) multi-echo (eight different TE) gradient echo sequence which was performed with the following parameters: TR 60 ms, effective TE 6 ms (TE_i 5.8–54.4 ms, where TE_i is the effective TE range), FOV 22 cm × 22 cm, slice thickness 2 mm, matrix size 488 × 320, bandwidth 31.25 Hz/pixel and flip angle 20°. All scans were oriented parallel to the anterior–posterior commissural (AC–PC) line with 56–64 locations on the middle sagittal plane and covered the entire brain parenchyma. The total acquisition time was between 6 and 8 min, depending on the spatial ratio and the number of sections.

3. Data processing and analysis

3.1. Data processing

Phase images serve as a direct measure of magnetic field variation. Based on the following formulas: ϕ (phase) = $-r\Delta B$TE (where r signifies gyromagnetic, ΔB is the change in the magnetic field between tissues and TE is the echo time); $\Delta B = cV\Delta x B_0$ (where c is the iron content, V is the voxel volume and Δx is the variation