Journal of the Neurological Sciences 378 (2017) 38–44

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

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

Brain iron concentrations in regions of interest and relation with serum iron levels in Parkinson disease

Paola Costa-Mallen [a,*], Christopher Gatenby [b], Sally Friend [b], Kenneth R. Maravilla [b], Shu-Ching Hu [c], Kevin C. Cain [d], Pinky Agarwal [e], Yoshimi Anzai [f]

[a] Bastyr University Research Institute, Kenmore, WA 98028, United States
[b] University of Washington, Department of Radiology, Seattle, WA 98195, United States
[c] University of Washington, Department of Neurology, Seattle, WA 98104, United States
[d] University of Washington, Department of Biostatistics, Seattle, WA 98195, United States
[e] Booth Gardner Parkinson's Care Center, Evergreen Health, Kirkland, WA 98034, United States
[f] University of Utah School of Medicine, Clinical Radiology, Salt Lake City, UT 84132, United States

ARTICLE INFO

Article history:
Received 28 October 2016
Received in revised form 27 March 2017
Accepted 21 April 2017
Available online 23 April 2017

Keywords:
Brain iron
Magnetic resonance imaging
Parkinson's disease
Serum iron
Serum ferritin

ABSTRACT

Brain iron has been previously found elevated in the substantia nigra pars compacta (SNpc), but not in other brain regions, of Parkinson's disease (PD) patients. However, iron in circulation has been recently observed to be lower than normal in PD patients. The regional selectivity of iron deposition in brain as well as the relationship between SNpc brain iron and serum iron within PD patients has not been completely elucidated. In this pilot study we measured brain iron in six regions of interest (ROIs) as well as serum iron and serum ferritin, in 24 PD patients and 27 age- gender-matched controls. Brain iron was measured on magnetic resonance imaging (MRI) with a T2 prime (T2′) method. Difference in brain iron deposition between PD cases and controls for the six ROIs were calculated. SNpc/white matter brain iron ratios and SNpc/serum iron ratios were calculated for each study participant, and differences between PD patients and controls were tested. PD patients overall had higher brain iron than controls in the SNpc. PD patients had significantly higher SNpc/white matter brain iron ratios than controls, and significantly higher brain SNpc iron/serum iron ratios than controls. These results indicate that PD patients' iron metabolism is disrupted toward a higher partitioning of iron to the brain SNpc at the expenses of iron in the circulation.

© 2017 Elsevier B.V. All rights reserved.

1. Introduction

Parkinson's disease (PD) is a movement disorder characterized by the loss of dopaminergic neurons in the substantia nigra (SN) of the brain, which regulate voluntary movements [1]. Abnormally elevated iron accumulation in the SN of the brain has been demonstrated in post-mortem PD patients [2,3]. In-vivo measurements of brain iron by magnetic resonance imaging (MRI) confirmed the presence of increased iron deposition in the SN [4,5,6] and especially in the substantia nigra pars compacta (SNpc) [7] in PD patients. MRIs measures using multiple gradient echo sequences to map proton transverse relaxation rates ($R2^*$) were reported to correlate well with brain iron concentration from post-mortem measurements [5,7].

Iron can produce reactive oxygen species such as hydroxyl radicals by reacting with hydrogen peroxide via the Fenton reaction. In dopaminergic neurons and glia hydrogen peroxide is generated by the action of monoamine oxidases that catabolize dopamine [8]. The oxidative stress resulting from iron and hydroxyl radical formation is believed to contribute to the neuronal degeneration that occurs in PD [9,10]. A support in the role of iron in neuronal degeneration was observed in the rat model of PD induced by intra-nigral iron injection [11]. Iron chelators on the other hand, have been proven to protect from the neurotoxic effect of 6-hydroxydopamine in the rat model of PD [12]. Recent clinical trials with the iron chelator deferiprone showed that it was possible to achieve a decrease in SN iron in PD patients, which was correlated with a reduction in the Unified Parkinson's Disease Rating Scale motor symptoms of PD progression, further supporting the crucial role of brain iron in PD [13].

Normally, most of the iron in the brain SN is bound to brain ferritin [14], which has a higher ratio of Heavy chain/Light chain ferritin than liver ferritin [15]. In PD patients there is a decrease of brain Light chain-ferritin as compared to controls [16]. The Light-chains of ferritin are involved in the storage of iron within the iron shell of the protein [17], therefore in PD patients there could be an easier efflux of iron from ferritin, which could trigger the Fenton reaction [18]. In normal subjects, about 20% of the iron in the SN is bound to neuromelanin,

* Corresponding author at: Bastyr University Research Institute, 14500 Juanita Drive NE, Kenmore, WA 98028, United States.
E-mail address: pcostamallen@bastyr.edu (P. Costa-Mallen).

http://dx.doi.org/10.1016/j.jns.2017.04.035
0022-510X/© 2017 Elsevier B.V. All rights reserved.

and a small amount bound to hemosiderin [19]. There is evidence that a release of iron occurs also from neuromelanin in PD patients [20].

A higher concentration of non-ferritin, labile iron in PD patients' SN was observed by Wypijewska et al., [21]. Overall, PD patients' SN generally shows a loss of pigmented dopaminergic neurons, decrease in neuromelanin, an increase in ferritin, and an increase in iron, including free iron [22,23]. Ceruloplasmin is a ferroxidase enzyme involved in brain iron levels regulation that facilitates cellular iron export; hereditary aceruloplasminemia causes iron accumulation in the astrocytes, and degeneration with motor symptoms similar to parkinsonism [24]. Interestingly, even allelic variants of the ceruloplasmin gene that don't cause complete absence of ceruloplasmin, but that alter ceruloplasmin activity [25] are associated with elevated SN brain iron content in PD patients [26], suggesting that the low ferroxidase activity that results from these variants contributes to brain iron accumulation. In this respect, peripheral infusion of ceruloplasmin was shown to attenuate neurodegeneration in a mouse model of PD [27], which suggests a therapeutic potential.

The increase in brain iron in the SNpc continues over time in PD patients, as demonstrated by Ulla et al. [28], with a study of follow up of PD patients over three years. On the other hand, the same authors reported that the levels of iron in the brain white matter decreased, over the three-year period in PD patients. Yu et al. [29], observed a significant decrease of iron levels in the temporal cortex of PD patients in the post-mortem study, which was also associated with a decreased expression of divalent metal transporter 1, transferrin receptor, and ferropontin.

In spite of higher levels of brain iron in the SNpc, many studies indicate that PD patients have lower than normal levels of serum iron [30,31]. In the study of Logroscino et al. [30] not only serum iron, but also ferritin, transferrin, total iron binding capacity, and transferrin saturation were lower among PD patients than controls; since transferrin levels were also reduced, this result suggests that in PD patients there is a defect in the systems that regulate the synthesis of major proteins in the liver, implying a systemic defect in iron metabolism [30]. Moreover, a history of recent multiple blood donations, which is a marker of systemic iron stores, was associated with PD among men, in a large longitudinal study [32]. Savica et al. [33], reported that anemia over the lifetime is positively associated with PD risk; anemia is defined as low hemoglobin levels, and iron deficiency is one of the most common causes of anemia.

Conversely, gene variants that are known to increase blood iron levels were found to be associated with a lower risk of developing PD [34].

Lower levels of total serum iron in PD patients than controls were confirmed in our previous study [31], where the drop in serum iron levels was especially pronounced among male PD patients with the haptoglobin Hp 2-1 phenotype [31]. In our previous results, however, ferritin levels were found to be higher in PD patients than controls, in contrast to what previously observed [30].

Some other contradictory results are present in the literature, where serum iron in PD patients were found to be not different from controls [35,36].

However, the regional distribution of brain iron deposition in PD, or selective vulnerability of SN as compared to other regions of the brain, and relative changes in brain iron versus blood iron in PD patients have not been completely elucidated.

In this study we directly tested whether SNpc/white matter brain iron ratios, SNpc brain iron/serum iron ratios, and SNpc brain iron/serum ferritin ratios were different between PD patients and controls. Since these ratios are within-person measures, taking these ratios reduces the across-person variability that would be present by measuring correlations, therefore the ratios are more sensitive than correlations in detecting differences between PD patients and controls. Because PD patients have been shown to have higher levels of iron in the SNpc region of the brain, but not in other brain areas, in several studies [4,5,6,28], we expect that PD patients will have higher SNpc/white matter brain iron ratios than controls.

And since lower blood iron has been shown to be present in PD patients than controls in some studies [30,31], our hypothesis is that SNpc brain iron/serum iron ratios will be higher in PD patients than controls.

2. Methods

2.1. Study participants

All study participants provided written consent. All study procedures were approved by Institutional Review Boards of Bastyr University and the University of Washington. Study participants were recruited in the Puget Sound area of Washington State between March 2013 and July 2015. Recruitment sources for the PD patients were the Washington Parkinson's Disease Registry (WPDR), the Michael J. Fox Foundation Fox Trial Finder, Bastyr University campus, the Bastyr Center for Natural Health (BCNH), Senior Centers, and referral from collaborating neurologists in the Seattle area. Control participants were recruited from the Bastyr University campus, the BCNH, Senior Centers, and advertisement over local websites.

All PD patients recruited met the “UK Parkinson's Disease Society Brain Bank clinical diagnostic criteria” (UKBB) for PD [37]. Only patients meeting UKBB clinical criteria of diagnosis were included in the study.

For all PD cases, medical records were obtained from each patient's neurologist and were reviewed by a second neurologist (S-C Hu) to determine whether each patient met UKBB criteria. Since this study was targeted toward idiopathic PD, patients with more than one relative with PD were excluded, as determined from a screening telephone interview before the study visit and from medical records review.

Control participants were subjects free of PD or other neurodegenerative diseases as determined from chart reviews and subject interviews.

Exclusion criteria for all participants, PD patients and controls, included: the presence of current active cancer under treatment, chronic hepatitis, HIV sero-positivity, blood donation or other reason for severe blood loss within the previous 6 months, as determined from participants' interviews and charts reviews. Participants willing to participate in the study were carefully screened for safety for magnetic resonance imaging by administering an MRI safety screening form. Those individuals who had or were suspected to have any ferro-magnetic metal objects in their body were excluded from the study because of the risks for MRI. Presence of claustrophobia also constituted exclusion criteria for MRI.

The control group was frequency matched to cases by age in 10 year categories. Demographics and smoking status information from study participants was also collected by in-person administration of a questionnaire to study participants.

2.2. Data collection

Blood samples were collected by venipuncture from each study participant in the morning after fasting. All blood draws were performed in the morning in order to avoid possible confounding effects of diurnal variation of blood iron levels [38]. Serum was separated, split in different aliquots and frozen at −70 °C. One aliquot was submitted to the LabCorp Clinical laboratory for tests of total serum iron levels and serum ferritin levels.

MRI imaging was performed for quantification of brain iron. Even if changes in brain iron with respect to the diurnal cycles have not been demonstrated [39], all participants had brain MRI in the morning, for consistency with the blood draws that were done in the morning. The MRI method used for brain iron measurements was a T2 prime (T2′) method similar to the one published by Wallis et al. [5], with some modifications. Iron deposits have been shown to shorten T2′ relaxation times as measured by MRI.

Download English Version:

https://daneshyari.com/en/article/5502822

Download Persian Version:

https://daneshyari.com/article/5502822

Daneshyari.com