Biochemical and Biophysical Research Communications 430 (2013) 907–911

Contents lists available at SciVerse ScienceDirect

Biochemical and Biophysical Research Communications

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

Increase in the IgG avidity index due to herpes simplex virus type 1 reactivation and its relationship with cognitive function in amnestic mild cognitive impairment and Alzheimer's disease

Nobuyuki Kobayashi [a,b,*], Tomoyuki Nagata [b,c], Shunichiro Shinagawa [b], Naomi Oka [a], Kazuya Shimada [a], Akihiro Shimizu [a], Yoshitaka Tatebayashi [d], Hisashi Yamada [c], Kazuhiko Nakayama [b], Kazuhiro Kondo [a]

[a] Department of Virology, The Jikei University School of Medicine, 3-25-8 Nishi-Shimbashi, Minato-ku, Tokyo 105-8461, Japan
[b] Department of Psychiatry, The Jikei University School of Medicine, 3-25-8 Nishi-Shimbashi, Minato-ku, Tokyo 105-8461, Japan
[c] Division of Molecular Genetics, Institute of DNA Medicine, The Jikei University School of Medicine, 3-25-8 Nishi-Shimbashi, Minato-ku, Tokyo 105-8461, Japan
[d] Affective Disorders Research Team, Tokyo Metropolitan Institute of Medical Science, 2-1-6 Kamikitazawa, Setagaya-ku, Tokyo 156-8506, Japan

ARTICLE INFO

Article history:
Received 6 December 2012
Available online 19 December 2012

Keywords:
Herpes simplex virus type 1
Alzheimer's disease
aMCI
Avidity index
Cognitive function
Viral reactivation

ABSTRACT

After infection with herpes simplex virus type 1 (HSV-1), latent infection persists for life in the trigeminal ganglion and reactivation results in an outbreak of cold sores around the mouth. Many previous studies have reported HSV-1 reactivation to be a risk factor for Alzheimer's disease (AD). This study enrolled subjects with AD ($n = 85$), subjects with amnestic mild cognitive impairment (aMCI; a prodromal stage of AD) ($n = 34$), and healthy controls ($n = 28$). The avidity index of anti-HSV-1 IgG antibodies—a known indicator of HSV-1 reactivation—was measured in order to clarify the relationship between HSV-1 reactivation and symptoms of cognitive function in AD.

Cognitive function in AD and aMCI were evaluated using scores from the mini-mental state examination (MMSE) and frontal assessment battery (FAB). The results showed that the subjects with aMCI, for which cerebral function is better preserved than subjects with AD, had a higher anti-HSV-1 IgG antibody avidity index than the AD subjects or healthy controls. Furthermore, the anti-HSV-1 IgG antibody avidity index was even higher in the subjects with high MMSE scores on orientation to time and three-step command subscores. We observed a negative correlation between the anti-HSV-1 IgG antibody avidity index and plasma BDNF concentration, which is an indicator of encephalitis. This suggests that HSV-1 reactivation, as observed through an increase in the anti-HSV-1 IgG avidity index, does not progress to encephalitis. These results suggest that HSV-1 reactivation occurs from the stage of aMCI, which is prodromal to AD, and can affect AD symptoms without an intermediary stage of severe encephalitis. The study demonstrates that the anti-HSV-1 IgG antibody avidity index could be a useful biomarker for the early diagnosis of aMCI as well as AD, and suggests that antiviral medication to treat HSV-1 could play a role in preventing the onset of AD.

© 2012 Elsevier Inc. All rights reserved.

1. Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disease characterized by memory disturbance, visuospatial agnosia, attention deficit, and difficulties with executive functions [1,2]. AD is most powerfully explained by the amyloid cascade hypothesis, whereby beta amyloid (Aβ) is produced through proteolysis of amyloid precursor protein (APP) and aggregates in the brain, resulting in the patient progressing through a stage of mild cognitive impairment (MCI) to AD.

Herpes simplex virus type 1 (HSV-1) is thought to be a risk factor for AD, based on reports that HSV-1 has been detected in senile plaques and brains of AD patients and on the high rates of anti-HSV-1 intrathecal antibodies detected in AD patients [3–6]. HSV-1 infection usually occurs during childhood, after which the virus remains dormant in the trigeminal ganglion. Stress and fatigue can reactivate HSV-1, and cause an outbreak of cold sores around the mouth [7]. HSV-1 infection is particularly widespread in the elderly, with research suggesting that over 70% of individuals aged 50 years and above are infected with HSV-1 [8].

HSV-1 affects APP transport and distribution [9], and research has shown that HSV-1 is related to Aβ plasma concentration [10], suggesting that HSV-1 affects how APP is processed within the brain. However, other research shows that HSV-1 DNA is also detected in the brain of elderly subjects without AD [11], and that

* Corresponding author at: Department of Virology, The Jikei University School of Medicine, 3-25-8 Nishi-Shimbashi, Minato-ku, Tokyo 105-8461, Japan. Fax: +81 3 3434 1629.
E-mail address: kobayashi-n@jikei.ac.jp (N. Kobayashi).

0006-291X/$ - see front matter © 2012 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.bbrc.2012.12.054

IgG antibodies are detected in the brain at the same levels in subjects with AD and healthy individuals [6]. Therefore, researchers have yet to reach a conclusion over the relationship between HSV-1 and AD.

Other research has attempted to clarify the relationship between HSV-1 and AD by measuring anti-HSV antibodies in the peripheral blood. One study reported no difference in serum anti-HSV-IgG antibody titers between AD subjects and healthy individuals [12], whereas another study reported higher anti-HSV-IgG antibody titers in healthy individuals than in AD subjects [13]. Hence, the assessment of serum anti-HSV IgG antibody titer has not resulted in clear conclusions being drawn. We attribute this to the difficulty of using IgG antibody titer measurements to distinguish between initial HSV infection and HSV reactivation. A report on differentiating between initial HSV infection and reactivation through the measurement of both anti-HSV-IgG antibodies and anti-HSV-IgM antibodies suggested that anti-HSV-IgM antibody positivity (i.e., HSV reactivation) was a risk factor for AD onset [14].

The findings above suggest the need to distinguish between initial HSV infection and HSV reactivation when investigating the relationship between AD and HSV by measuring anti-HSV antibody titers in the peripheral blood. Compared with initial HSV infection, HSV reactivation is characterized by an increase in high-avidity anti-HSV IgG antibodies, and an avidity index that uses the ratio of high-avidity anti-HSV IgG antibody titers of wells washed with urea buffer to anti-HSV IgG antibody titers of wells washed with non-urea buffer has been found to be a good indicator of reactivation [15,16]. Therefore, in this study we measured the anti-HSV-1 IgG antibody titer and anti-HSV-1 IgG avidity index as indicators of HSV-1 reactivation in AD patients.

In order to clarify the relationship between HSV-1 and the clinical disease stage of AD, we targeted not only AD but also amnestic mild cognitive impairment (aMCI), which is thought to be a precursor stage to AD. MCI is defined as an intermediate state between normal aging and AD, and a high proportion of the aMCI subgroup (subjects with memory disturbance) progress to AD [17–19]. Our objective was to clarify the detailed relationship between HSV-1 reactivation and cognitive function in AD patients by using scores from the mini-mental state examination (MMSE) and frontal assessment battery (FAB) to evaluate cognitive function in these patients.

HSV-1 is also known to suddenly cause severe encephalitis, although the incidence is very low [7]. Given that research has shown an increase in brain-derived neurotrophic factor (BDNF) with encephalitis [20,21], we also assessed whether severe encephalitis had occurred in the study subjects at the time of testing by measuring plasma BDNF concentrations.

2. Materials and methods

2.1. Participants

The study enrolled 85 subjects diagnosed with AD and 34 subjects with aMCI who were Japanese outpatients being treated at The Jikei University Hospital (Tokyo) or The Jikei University Kashiwa Hospital (Kashiwa city, Chiba prefecture). All subjects were diagnosed with AD or aMCI based on the US National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS–ADRDA) criteria for the diagnosis of AD or the MCI diagnostic criteria defined by Peterson [17,22]. In this study, aMCI included both amnestic MCI-single domain and MCI-multiple domain types subjects. Subjects were excluded from the study if they had dementia with Lewy bodies (DLB), frontotemporal dementia, vascular dementia, normal pressure hydrocephalus (NPH), other CNS disease, head trauma, substance-related disorder, major depressive disorder, psychotic disorder, epilepsy, or delirium. Subjects were also excluded if they had been diagnosed with their condition for over 3 years, because the objective of the study was to evaluate early stage aMCI and AD. Cognitive function was evaluated using scores from MMSE (ranging from 0 to 30) [23] and FAB (ranging from 0 to 18) [24,25]. Whole blood samples were collected on the same day as the cognitive function tests, centrifuged to separate the plasma, and stored at −80 °C until analysis.

The study enrolled 28 healthy individuals aged 60 years or above with no memory deficit and 13 subjects with mood disorders (eight with major depressive disorder, five with bipolar disorder) as controls. Whole-blood samples were centrifuged to separate the plasma and stored at −80 °C until analysis.

This study was approved by the Ethics Committee of The Jikei University School of Medicine and Tokyo Metropolitan Institute of Medical Science. All subjects as well as their caregivers provided written informed consent.

2.2. Anti-HSV-1 antibody titer

We used an HSV-1 IgG ELISA Kit (Phoenix Pharmaceuticals, Inc.). The anti-HSV-1 antibody titer was measured according to the attached protocol. To measure the high avidity anti-HSV-1 antibody titer, we modified the attached protocol through the addition of 6 M urea to the washing solution at the washing step after the plasma reaction. A TriStar LB941-vTi Microplate Reader (Berthold Technologies) was used to measure optical density (450 nm) after the color reaction. Following the attached protocol, the anti-HSV-1 antibody titer was expressed as an HSV-1 IgG index by comparing the patient sample optical density and the cut-off calibrator optical density. A sample was defined as being positive for anti-HSV-1 IgG antibody if the HSV-1 IgG Index was above 1.0.

The anti-HSV-1 IgG avidity index was derived as follows from the anti-HSV-1 IgG antibody positive samples: Avidity index (%) = anti-HSV-1 antibody titer measured with washing including urea/anti-HSV-1 antibody titer measured with washing without urea.

2.3. Plasma BDNF concentration

Plasma BDNF concentrations were measured using the Emax ImmunoAssay System (Promega) according to the attached protocol. The plasma was diluted five-fold with Dulbecco's PBS, and the optical density (450 nm) after the color reaction was measured using a TriStar LB941-vTi Microplate Reader (Berthold Technologies).

2.4. Statistical analysis

ANOVA was used to compare most of the background characteristics of subjects in the aMCI, AD, and healthy control groups. The exceptions were gender and percentage of subjects positive for anti-HSV-1 antibodies, which were compared using the chi-squared test. The unpaired Welch's t test was used to compare age, years of education, duration of disease, MMSE and FAB scores between two groups. The Kruskal–Wallis test was used to compare anti-HSV-1 IgG antibody titers and anti-HSV-1 antibody avidity indices in the aMCI, AD, and healthy control groups. The Mann–Whitney U test was used for comparisons between two groups regarding the anti-HSV-1 IgG antibody titers and anti-HSV-1 antibody avidity indices. Spearman's rank correlation coefficient was used to investigate the correlation between variables. $P < 0.05$ was considered statistically significant. Statistical analyses were performed using SPSS Statistics version 19 (IBM) and Prism 5 (GraphPad).

Download English Version:

https://daneshyari.com/en/article/10759845

Download Persian Version:

https://daneshyari.com/article/10759845

Daneshyari.com