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Decrease of Patients with Brain Infarction through Evaluation of Relative Risk Value of Brain Infarction by Measurement of Protein-Conjugated Acrolein, IL-6 and CRP in Plasma Together with Age

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Abstract

Background: The Relative Risk Value of Brain Infarction (RRVBI) estimated by measuring protein-conjugated acrolein (PC-Acro), interleukin-6 (IL-6) and C-reactive protein (CRP) in plasma together with age finds silent (small) brain infarction (SBI) with 84% sensitivity and specificity. The purpose of this study is to evaluate the effect of RRVBI estimation on the disease onset probability of brain infarction.

Methods: The number of patients with brain infarction was evaluated among the workers belonging to a union of the similar business health insurance.

Results: The number of disease onset patients with brain infarction gradually decreased after the adoption of RRVBI during 7 years evaluation. Finally, the number of disease onset patients with brain infarction decreased to less than 35% compared with the number before the adoption of RRVBI.

Conclusion: Our results suggest that RRVBI contributes to maintenance of quality of life (QOL) for the elderly.

Keywords: Acrolein; C-reactive protein; Interleukin-6; Silent brain infarction

Abbreviations: CRP: C-Reactive Protein; CT: Computed Tomography; IL-6: Interleukin-6; MRI: Magnetic Resonance Imaging; PC-Acro: Protein-Conjugated Acrolein; QOL: Quality of Life; ROS: Reactive Oxygen Species; RRVBI: Relative Risk Value of Brain Infarction; SBI: Silent (Small) Brain Infarction

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Introduction

Brain stroke is a sudden serious illness caused by a burst or blockade of blood vessels in the brain and one of the major causes of disability among the elderly. More than 15 million people suffer stroke each year, 5 million die and another 5 million are disabled permanently, according to the World Health Organization. As the world's population is aging, it is important to prevent diseases such as brain stroke that can severely reduce the Quality of Life (QOL) of the elderly. For the prevention of brain stroke, it is important to know the risk of disease onset.

It is thought that reactive oxygen species (ROS), such as superoxide anion (O_2^-), hydrogen peroxide (H_2O_2) and hydroxyl radical ($\bullet OH$), are prominently involved in cell damage such as brain infarction

[1,2]. However, we found that acrolein ($CH_2=CH-CHO$), mainly produced from spermine [$NH_2(CH_2)_3NH(CH_2)_4NH(CH_2)_3NH_2$], an important factor of cell growth and viability [3-5], is more strongly involved in cell damage during brain infarction through its conjugation with proteins [6,7]. The size of brain infarction was nearly parallel with the multiplied value of PC-Acro (protein-conjugated acrolein) and acrolein-producing enzymes, i.e. spermine oxidase and acetylpolymine oxidase in plasma [8]. Consequently, we could identify silent brain infarction, i.e. small brain infarction, with 84% sensitivity and specificity by measuring PC-Acro, IL-6 and CRP in plasma together with age and by calculating the RRVBI with artificial neural networks [9] using NEUROSIM/L software (Fujitsu) (**Figure 1**) [10-12].

The relative risk value (RRV) is shown from 1.00 (highest) to 0 (none). Acrolein stimulated production of IL-6 in neuroblastoma cells, macrophage and vein endothelial cells, and IL-6 in turn stimulated the production of CRP in hepatoma cells [13]. Acrolein inactivated proteins such as tubulins [14] which are important for cell functions, and IL-6 and CRP were protective proteins for acrolein damage [13]. Thus, the combined measurements of three biomarkers in plasma together with age were well correlated with the size of brain infarction [10,11]. In this study, we assessed the effect of measuring RRVBI on the disease onset probability of stroke.

Materials and Methods

Estimation of the relative risk values of brain infarction (RRVBI)

RRVBI was estimated by measuring protein-conjugated acrolein (PC-Acro), interleukin-6 (IL-6) and C-reactive protein (CRP) in plasma together with age. PC-Acro, IL-6 and CRP were measured using acrolein-lysine adduct competitive EIA kit (Nichiya, Japan), IL-6 ELISA kit (R&D Systems, USA), and CRP N-assay reagents (Nittobo, Japan) according to their manufacturer's protocols. RRVBI was calculated using NEUROSIM/L software (Fujitsu, Japan). The subjects were apparently healthy and did not show any brain infarction associated symptoms at the time of RRVBI estimation. The number of brain infarction patients among the workers belonging to a union of the similar business health insurance was evaluated by medical doctors every year.

Results

Decrease in patients with brain infarction through the evaluation of RRVBI

The median value of relative risk value (RRV, 0–1.00) for control subjects and patients with silent brain infarction was 0.14 and 0.80, respectively (Figure 1) [11]. We then determined whether or not the number of patients with brain infarction decreased by measuring their relative risk values and paying attention to their lifestyles. In 2012, which was the first year of the measurements of RRVBI, the number of subjects with high, medium and low risk values was 240, 365 and 766, respectively (Figure 2), and

the number of patients with brain infarction judged by MRI (magnetic resonance imaging) or by CT (computed tomography) was 23 (Figure 3). In 2013, the number of subjects with high risk values decreased from 17.5% to 6.0% (Figure 2), and that of patients with brain infarction slightly decreased from 23 to 19 (Figure 3). In 2016, which was the fifth year of the measurement of RRVBI, the number of subjects with high, medium and low risk values was 5.2, 23.1 and 71.8%, respectively (Figure 2), and the number of patients with brain infarction was 9 (Figure 3). Similar results were obtained in the estimation at 2017 and 2018; i.e. the number of subjects with high risk values at 2017 and 2018 was 5.6%, and that of the disease onset patients with brain infarction was 6 and 8, respectively.

Year	Total Number of Subjects	Average age (years)	Number of Subjects		
			Low RRV (0.0-0.43)	Medium RRV (0.44-0.79)	High RRV (0.8-1.0)
2012	1,371	58.4	766	365	240
2013	1,493	59.5	844	559	90
2016	1,084	58.1	778	250	56
2017	1,139	58.1	835	240	64
2018	1,233	57.9	888	276	69

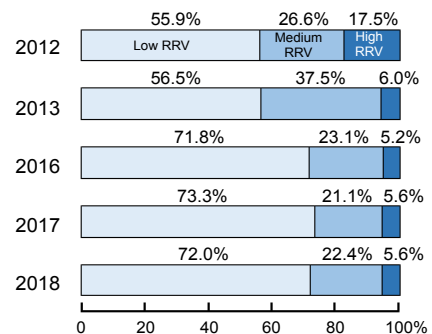


Figure 2 Comparison of subjects with low, medium and high risk values in 2012, 2013, 2016, 2017 and 2018. (RRV was calculated as described in the legend of Figure 1).

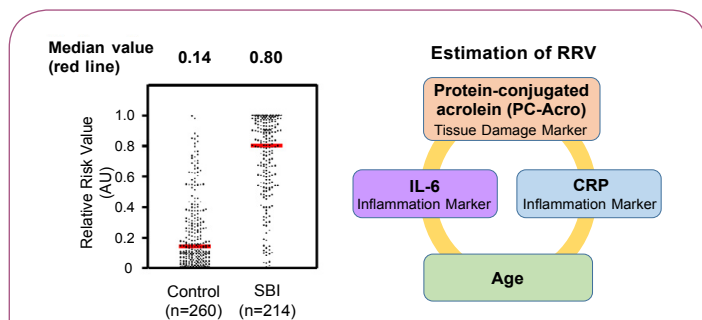


Figure 1 Comparison of RRVBI of Control Subjects and SBI Patients. Median values are shown in vertical red lines. RRV was estimated by measuring PC-Acro, IL-6 and CRP in plasma together with age [11].

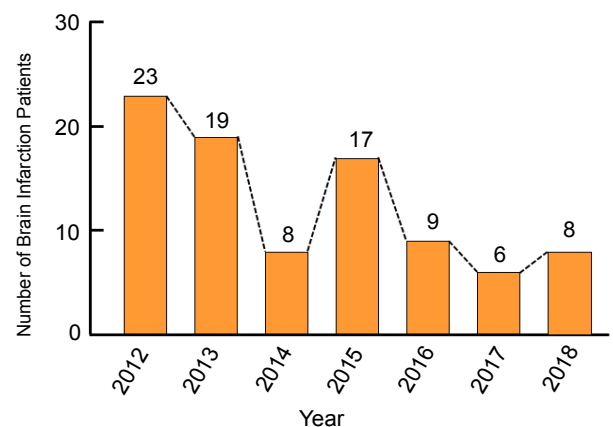


Figure 3 Decrease in the number of patients with brain infarction from 2012 to 2018. Focal infarcts were estimated as described previously [8] by either MRI (Magnetic Resonance Imaging) or CT (Computed Tomography).

Table 1 Recommendations of the lifestyle for the elderly.

1.	Do exercise appropriately
2.	Be careful of a rise in blood pressure
3.	Eat garlic and onion, including acrolein scavenger
4.	Recommend to drink coffee less than 3 times daily
5.	Have an evaluation for relative risk value for brain stroke every year

Discussion and Conclusion

Our results clearly indicate that the number of brain infarction patients decreased by estimating RRVBI. The results suggest that they take care of themselves based on the RRVBI and controlled the risk of brain infarction. Recommendations how they should change their lifestyles are shown in (Table 1). Among the world's population ages, the importance of self-medication and controlling the risk of diseases before the onset is widely recognized. For this purpose, knowing the disease risk of individuals is important. The results presented in this study clearly indicate that estimation of relative risk value of brain infarction (RRVBI) is useful to maintain QOL (quality of life) for the elderly. In summary, the number of brain infarction patients was decreased by estimating RRVBI once a year. Our results clearly indicate that RRVBI estimation contributes to maintenance of quality of life (QOL) for the elderly.

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Ethics Approval and Consent to Participate

The study was approved by the Ethics Committees of the Graduate School of Pharmaceutical Sciences, Chiba University. Responsible persons in the Health Union of the Machine & Metal Related Companies in Chiba Prefecture who are in charge of the physical examinations agreed to publish. The consent from participants is not applicable, since no personal information is provided in the manuscript.

Availability of Data and Materials

All the datasets used during the current cases are presented within the manuscript and available from the corresponding author on reasonable requests.

Author Contributions

All authors of this manuscript have actively participated in the data acquisition, and they all commented and approved the final version of the manuscript. TU, TK, KIs and KK analyzed the data and drafted the initial manuscript. Klg designed the study and revised the manuscript. All authors approved the final version of the manuscript.

Competing Interests

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.