LETTER TO THE EDITOR

A Case–Control Study: Infectious Burden Increased the Occurrence of Vascular Cognitive Impairment No Dementia

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Vascular cognitive impairment (VCI) refers to the cognitive decline due to cerebrovascular disorders, which would ultimately progress to fully developed dementia [1]. No drugs so far can halt or reverse the development of dementia. Therefore, the early detection and management of VCI patients are of great clinical importance. In this case–control study, we investigated the correlation between patients’ infectious burden and their likelihood of developing vascular cognitive impairment no dementia (VCIND), the primitive stage of VCI.

The study was approved by the Research Ethic Committee at Beijing Tiantan Hospital. Written consent forms were obtained from each participant. The enrollment period was between June 2006 and October 2007.

A patient from the 101,510 employees of Kailuan Group Company Limited in Tangshan, China would be included in the VCIND cohort if he met all of the following criteria: (1) he had no cerebrovascular disorders or heart diseases before the enrollment, (2) he was aged between 50 and 65 years at the time of enrollment, and had a caregiver at least 4 days in a week, (3) he was diagnosed of a cognitive impairment between January 2008 and December 2014, (4) a blood test was completed within 1 week of diagnosis and a brain magnetic resonance imaging (MRI) scanning within 1 month of diagnosis, (5) the level of his cognitive impairment was between normal and dementia based on Criteria of the Diagnostic and Statistical Manual of Mental Disorders, (6) the Clinical Dementia Rating test yielded a score >0.5 in any of the subareas and a composite score <0.5, (7) the Mini-Mental State Exam (MMSE) yielded a score >20 for patients with elementary education or 24 for patients with secondary or higher education, (8) MRI showed more than three infarctions with diameter between 3 and 20 mm; or a Fazekas score of 2 or above; or one or more infarction in caudate nucleus, (9) MRI showed no cortex infarction, cerebral hemorrhage, or hydrocephalus.

Patients were excluded from the VCIND cohort if he met one of the following criteria: (1) he was unable to complete the cognitive tests, (2) he had neurological disorders that impaired his cognitive ability, (3) Hamilton Rating Scale for Depression (HRSD) yielded a score of 17 or more.

Table 1

| Variables                  | Control (N = 147) | VCIND (N = 130) | P-value |
|----------------------------|-------------------|-----------------|---------|
| Age                        | 65.1 ± 9.99       | 64.70 ± 9.48    | 0.78    |
| Male                       | 78 (53.1%)        | 81 (62.3%)      | 0.70    |
| Smoking                    | 40 (27.2%)        | 26 (20.0%)      | 0.05    |
| Education†                 | 80 (54.4%)        | 84 (64.6%)      | 0.61    |
| Diabetes                   | 28 (19.0%)        | 34 (26.2%)      | 0.38    |
| Hypertension               | 46 (31.3%)        | 25 (19.2%)      | 0.003   |
| Coronary heart disease     | 19 (12.9%)        | 20 (15.4%)      | 0.86    |
| Mini-Mental State Exam     | 27.9 ± 1.19       | 19.70 ± 5.78    | <0.001  |
| Hs-CRP (pg/mL)             | 1.98 ± 1.21       | 3.21 ± 1.31     | <0.001  |
| TNF-α (pg/mL)              | 16.6 ± 6.80       | 29.10 ± 13.24   | <0.001  |
| IL-6 (pg/mL)               | 4.79 ± 2.32       | 6.05 ± 2.56     | 0.002   |
| HSV-1                      | 98 (66.7%)        | 93 (71.5%)      | 0.48    |
| HSV-2                      | 10 (6.8%)         | 31 (23.8%)      | <0.001  |
| H. pylori                  | 35 (23.8%)        | 58 (44.6%)      | 0.003   |
| CMV                        | 89 (60.5%)        | 100 (76.9%)     | 0.13    |
| Cpn                        | 89 (60.5%)        | 83 (63.8%)      | 0.43    |

*Education: secondary or higher education.
The impact of infectious burden on the likelihood of VCIND occurrence and onset time point

| Number of pathogens | Likelihood of occurrence | Onset time point |
|---------------------|--------------------------|-----------------|
|                     | P-value | HR     | 95% CI | P-value | HR     | 95% CI |
| 0-2²               | 0.02 | 1.33 | 1.06–1.68 | <0.001 | 2.06 | 1.57–2.70 |
| 3                   | <0.001 | 3.79 | 2.10–6.84 | 0.005 | 1.93 | 1.22–3.06 |
| 4-5                 | <0.001 | 4.41 | 2.19–8.90 | <0.001 | 4.25 | 2.49–7.26 |
| 0-1³               | 0.004 | 1.61 | 1.16–2.23 | <0.001 | 1.77 | 1.39–2.25 |
| 2-3                 | <0.001 | 2.84 | 1.67–4.85 | <0.001 | 2.08 | 1.39–3.11 |
| Number of bacterial pathogens | 0-1⁴ | 0.11 | 1.33 | 0.04–1.90 | 0.001 | 1.49 | 1.17–1.90 |
| 2                   | 0.06 | 1.74 | 0.98–3.10 | 0.007 | 1.72 | 1.16–2.54 |

¹Adjusted for age, sex, smoking, education, diabetes, hypertension, and coronary heart disease.
²Category of patients with 0, 1, or 2 pathogens. This category was also used as control for the inter-category analyses of all pathogens.
³Category of patients with 0 or 1 viral pathogens. This category was also used as control for the inter-category analyses of viral pathogens.
⁴Category of patients with 0 or 1 viral pathogens. This category was also used as control for the inter-category analyses of bacterial pathogens.

score above 17; or he had been diagnosed of schizophrenia, (4) he had gastrointestinal, nephrological, or respiratory disorders, (5) he had cancer, (6) he was on medication that might cause cognitive impairment, (7) he was taking antidepressant, sedative, or cholinergic agonists.

Employees of Kailuan Group Company Limited admitted to the 11 local hospitals in Tangshan were included into the control cohort if he met all of the following criteria: (1) he was admitted between 2006 and 2014, (2) he was aged between 50 and 65 when he was admitted, (3) he had no cerebrovascular disorders, heart diseases, or cognitive impairment, (4) he completed a blood test after being admitted.

Medical information, including age, sex, smoking, education, diabetes, hypertension and coronary heart diseases, and a blood sample were collected from each patient. Herpes simplex virus 1 (HSV-1), herpes simplex virus 2 (HSV-2), cytomegalovirus (CMV), Helicobacter pylori (H. pylori), Chlamyphila pneumoniae (Cpn), tumor necrosis factor-a (TNF-a), interleukin (IL-6), and C-reactive protein (CRP) was measured.

Student t-test was used to analyze patients’ age, TNF-a, IL-6, and CRP concentrations. Chi-square test was used to analyze patients’ sex, smoking, diabetes, hypertension, coronary heart diseases, and pathogens. Linear regression analysis was used to determine the correlation between MMSE and CRP, TNF-a, IL-6, HSV-2, H. pylori. COX regression analysis was used to analyze the correlation between different infectious burden categories and the onset of VCIND occurrence. Log rank test was used to analyze the survival period of different infectious burden categories. The significance level was set at 0.05 for all tests. All analyses were performed using SPSS.

No difference of patients’ age, sex, smoking, education, diabetes, or coronary heart disease was observed between the VCIND and control cohorts. Hypertension was more commonly associated with the control cohort. However, HSV-2 and H. pylori were more commonly associated with the VCIND cohort, probably because chronic infections of HSV-2 and H. pylori would lead to dementia [2-6]. An increased level of TNF-a, IL-6, and CRP were more commonly associated with the VCIND cohort (Table 1). CRP, TNF-a, and IL-6 was shown to be risk factors for cognitive decline and dementia [7,8]. The correlation coefficient between MMSE scores and CRP, TNF-a, IL-6, HSV-2, and H. pylori were 0.67, 0.24, 0.38, 0.66, and 0.71, respectively.

To investigate the correlation between the infectious burden and VCIND, patients were grouped into categories based on the number of pathogens (Table 2). In terms of total pathogens, patients were grouped into three categories, that is, patients with 0, 1, or 2 pathogens, patients with three pathogens, and patients with four or five pathogens. The category of patients with 0, 1, or 2 pathogens was used as control for inter-category analyses. Similarly, patients were grouped into categories based on his number of viral or bacterial pathogens.

The statistical analysis showed that the increase of VCIND occurrence was associated with the increase of total pathogens as well as viral pathogens but not bacterial pathogens. But both viral and bacterial could advance the onset time point of VCIND. The median survival length was 58 months in VCIND patients with 0, 1, or 2 pathogens, 35 months in those with three pathogens, and 19 months in those with four or five pathogens, respectively.

Our study showed that CRP, TNF-a, IL-6, HSV-2, and H. pylori were more commonly associated with the VCIND cohort. Moreover, the increase in the overall infectious burden could advance the onset of VCIND occurrence and reduce the survival period, but only the increase of viral pathogens led to an increased likelihood of VCIND occurrence.

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Conflict of Interest

The authors declare no conflict of interest.
Infectious Burden is a Risk Factor of VCIND

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