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Clinical Study

Association between plasma homocysteine levels and obstructive sleep apnoea in patients with ischaemic stroke

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ABSTRACT

We aimed to investigate the association between plasma homocysteine and obstructive sleep apnoea (OSA) syndrome in patients with ischaemic stroke. A total of 102 patients with ischaemic stroke were classified into four OSA groups based on their apnoea–hypopnoea index (AHI): absent (AHI < 5/hour); mild (5–14/hour); moderate (15–30/hour); and severe (>30/hour). The mean (±standard deviation) homocysteine levels in the four OSA groups were: absent, 8.98 ± 3.74 μmol/L; mild, 11.46 ± 3.31 μmol/L; moderate, 14.18 ± 4.36 μmol/L; and severe, 18.57 ± 4.56 μmol/L; and these differences were statistically significant ($p < 0.001$). The Pearson correlation analysis revealed a positive correlation between homocysteine levels and the severity of AHI ($r = 0.482$, $p < 0.001$). Multiple linear regression analysis showed that AHI and folate were independent predictors of homocysteine levels ($R^2 = 0.539$, $p < 0.001$, β for AHI = 0.259, β for folate = –0.400). In conclusion, the severity of OSA is significantly associated with elevated homocysteine levels in patients with ischaemic stroke, and this association is independent of other factors that cause elevation in homocysteine.

1. Introduction

Ischemic stroke is a major cause of morbidity and mortality worldwide. The most promising strategy to reduce the disease burden is controlling the risk factors. Previously unrecognized risk factors for stroke may include elevated plasma homocysteine and obstructive apnoea syndrome (OSA). Many studies have demonstrated there is a strong, independent, dose-related association between homocysteine and stroke.[1] But whether homocysteine is a causal risk factor for stoke is still unknown. Several recent prospective studies and meta-analyses failed to reveal a causal relationship,[2,3] thereby suggesting that homocysteine may not be a cause, but a consequence of stroke or a marker that is associated with a particular causal risk factor, such as OSA. OSA may be another potential risk factor for stroke. Many case-control and cohort studies have identified a strong, independent association between OSA and atherosclerotic vascular disease, including stroke.[4–6] Furthermore, treating OSA in patients with stroke can reduce the morbidity and mortality of stroke.[7]

Whether the two important factors associated with stroke, homocysteine elevation and OSA, are correlated, are still unclear. Some studies[8] have indicated that elevated homocysteine levels are related to OSA, and that treating OSA with continuous positive airway pressure (CPAP) can lower homocysteine levels. However, other studies[9] have provided conflicting findings that plasma homocysteine levels are not elevated in patients with OSA and are not affected by treatment with CPAP. In addition, most of the studies on the OSA–homocysteine association have been performed in patients with ischaemic heart disease[8] or OSA alone,[9,10] but very few studies have involved patients with ischaemic stroke.

Therefore, the aim of this study was to investigate the association between plasma homocysteine levels and OSA syndrome in patients with ischaemic stroke.

2. Patients and methods

We conducted a clinical cross-section study, which was approved by the local ethics committee. All participants were required to give informed consent before being enrolled in the study.

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2.1. Patients

The study population included consecutive patients who were admitted to the Department of Neurology of Jinling Hospital, and were registered in the Nanjing Stroke Registry Program (NSRP)[11] between March 2009 and September 2009. The inclusion criteria were as follows: (i) first-ever arteriosclerosis-related ischaemic stroke within 10 days after symptom onset; (ii) ischaemic stroke confirmed by MRI brain scan; (iii) mild and moderate stroke (National Institutes of Health Stroke Scale [NIHSS] score < 15) without altered consciousness[12] (the third criterion was included to promote a homogeneous study population with regard to stroke severity, to reduce the effect of massive subacute cerebral infarction and brain oedema on the respiratory centres, and because patients with severe stroke cannot tolerate polysomnography (PSG); (iv) more than 45 years of age; and (v) agreement to participate and provide informed consent. Patients were excluded if they had: (i) haemorrhagic infarction; (ii) cerebral infarction caused by heart disease, vasculitis, infection, or tumors; (iii) a history of stroke or other neurological disease; (iv) severe heart or lung failure, kidney dysfunction, hypothyroidism, or malignant tumors; (v) true bulbar palsy, pseudo bulbar palsy, or throat muscle paralysis caused by other diseases; (vi) CPAP treatment; (vii) long-term use of sedative drugs; (viii) administration of any medication that could affect plasma homocysteine, including folic acid, vitamin B6 and B12 during the 10 days before the onset of stroke; and (ix) central or mixed apnoea–hypopnoea syndrome.

2.2. Polysomnography

A total of 108 participants were examined with attended PSG (Sandman Elite, Nellcor Puritan Bennett, Kanata, ON, Canada) between 10 days and 14 days after stroke onset. PSG was recorded from 9.00 p.m. to 6.30 a.m. The data such as the apnoea–hypopnoea index (AHI), maximum oxygen saturation, and low oxygen saturation were recorded. Apnoea was defined as a complete cessation of air flow for at least 10 s. Hypopnoea was defined as a 30% or greater decrease in air flow associated with a decrease in oxygen saturation of at least 4% for 10 s or longer. The AHI was defined as the total number of apnoea and hypopnoea events that occurred per hour of electroencephalogram-monitored sleep. OSA was diagnosed based on the International Classification of Sleep Disorders criteria.[13] Because central or mixed apnoea–hypopnoea syndrome was regarded as a possible sequela of stroke, stroke patients with central or mixed apnoea–hypopnoea syndrome were excluded. After excluding the above-mentioned conditions, the remaining patients were classified into four groups based on AHI events: absent (AHI < 5/hour), mild (AHI 5–14/hour), moderate (AHI 15–30/hour) and severe (AHI > 30/hour).[7,14]

2.3. Blood chemical assays

Upon completion of PSG, fasting venous blood was drawn. Blood concentration of high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), triacylglyceride (TG), glucose, creatinine, homocysteine, folate and vitamin B12 were assayed. Total plasma homocysteine was measured by fluorescence polarization immunoassay (AxSYM, Abbott Diagnostics, Chicago, IL, USA), and serum folate and vitamin B12 were analysed using chemiluminescence.

2.4. Statistical analysis

The results were presented as percentages (%) and means ± standard deviation (SD). Categorical data were analysed using the chi-squared (χ^2) with Pearson test. The continuous values were analysed by one-way analysis of variance (ANOVA) followed by the Bonferroni test, or by the Kruskal–Wallis *U*-test for the variables that were not normally distributed. The correlation between homocysteine levels and AHI was determined by the Pearson correlation coefficient (*r*). Stepwise multiple linear regression analysis was used to determine the variables that affected homocysteine levels. Differences were considered significant at $p < 0.05$ (two-tailed). All statistical analyses were performed using the Statistical Package for Social Sciences version 13.0 (SPSS, Chicago, IL, USA).

3. Results

A total of 143 consecutive patients with first-ever mild to moderate ischaemic stroke confirmed by MRI were recruited; of these patients, 11 were excluded due to progressive conditions, eight were excluded due to secondary haemorrhage that occurred before the PSG examination, nine were excluded due to other causes including: vasculitis (three), infection (three) and cardiac disease (four), and seven participants were excluded due to their inability to tolerate the PSG examination. A total of 108 patients were

Table 1
Demographic, clinical and biochemical characteristics of stroke patients from four apnoea–hypopnea index (AHI) groups: absent, mild, moderate and severe obstructive sleep apnoea (OSA)

	Absent OSA (*n* = 27)	Mild OSA (*n* = 20)	Moderate OSA (*n* = 31)	Severe OSA (*n* = 24)	All patients (*n* = 102)	Statistics	*p*
AHI (events/hour)	2.78 ± 1.013	9.95 ± 2.982	20.58 ± 3.557	38.29 ± 6.16			
Age (years)	58.78 ± 10.34	58.65 ± 10.36	63.74 ± 9.72	66.79 ± 8.97	62.15 ± 10.27	$F = 3.943$	0.011*
Male (*n*) (%)	15 (55.6)	11 (55.0)	19 (61.3)	15 (62.5)	60 (58.8)	$\chi^2 = 0.452$	0.929
BMI	22.01 ± 2.30	24.81 ± 1.79	25.85 ± 2.27	26.40 ± 2.96	24.76 ± 2.92	$F = 18.01$	0.000*
Smoking (*n*) (%)	7 (18.9)	9 (24.3)	10 (27.0)	11 (29.7)	37 (36.3)	$\chi^2 = 3.075$	0.380
Hypertension (*n*) (%)	10 (37.0)	6 (30.0)	25 (80.6)	22 (91.7)	63 (61.8)	$\chi^2 = 29.30$	0.000*
Diabetes (*n*) (%)	6 (22.2)	4 (20.0)	4 (12.9)	7 (29.2)	21 (20.6)	$\chi^2 = 2.248$	0.522
Admission NIHSS score	7.70 ± 3.010	7.30 ± 2.993	7.97 ± 2.601	7.79 ± 3.514	7.73 ± 2.982	$F = 0.203$	0.894
Creatinine (μmol/L)	65.52 ± 23.09	67.90 ± 19.40	66.81 ± 30.24	71.67 ± 26.11	67.82 ± 25.31	$F = 0.270$	0.847
Homocysteine (μmol/L)	8.98 ± 3.74	11.46 ± 3.31	14.18 ± 4.36	18.57 ± 4.56	13.30 ± 5.35	$F = 25.29$	0.000*
Folate (ng/L)	11.59 ± 2.90	11.20 ± 350	11.29 ± 3.32	10.75 ± 3.30	11.23 ± 3.21	$F = 0.291$	0.832
Vitamin B_{12} (pg/L)	350.07 ± 63.33	328.05 ± 56.99	338.294 ± 69.56	324.75 ± 81.24	336.21 ± 68.41	$F = 0.692$	0.559
Glucose (mmol/L)	4.97 ± 1.10	5.30 ± 1.23	5.59 ± 2.06	5.59 ± 2.06	5.55 ± 1.34	$F = 0.977$	0.407
HDL–C (mmol/L)	1.15 ± 0.39	1.05 ± 0.26	1.11 ± .177	1.11 ± 0.26	1.11 ± 0.280	$F = 0.426$	0.735
LDL–C (mmol/L)	2.67 ± 0.46	2.67 ± 0.44	2.79 ± 0.80	2.76 ± 0.41	2.73 ± 0.57	$F = 0.342$	0.795
TG (mmol/L)	1.42 ± 0.31	1.57 ± 0.48	1.49 ± 0.69	1.54 ± 0.50	1.50 ± 0.52	$F = 0.395$	0.757

BMI = Body mass index, HDL–C = high-density lipoprotein–cholesterol, LDL–C = low-density lipoprotein cholesterol, NIHSS = National Institutes of Health Stroke Scale, TG = triacylglyceride.
* $p < 0.05$, significant difference. Data are presented as mean ± standard deviation or *n* (%).