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Elevated Serum Levels of NSE and S-100 β Correlate with Increased Risk of Acute Cerebral Infarction in Asian Populations

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Background: We investigated the clinical value of serum levels of neuron-specific enolase (NSE) and human soluble protein-100 β (S-100 β) in acute cerebral infarction (ACI) patients.

Material/Methods: A literature search of electronic databases identified relevant case-control studies that examined the correlations between NSE and S-100 β serum levels, and ACI. The retrieved studies were screened based on our strict inclusion and exclusion criteria, and high-quality studies were subsequently selected for meta-analysis. STATA software (Version 12.0, Stata Corporation, College Station, TX, USA) was utilized for statistical analysis.

Results: A total of 13 case-control studies, containing 911 ACI patients and 686 healthy controls, were enrolled in this meta-analysis. The results of the meta-analysis showed that serum levels of NSE and S-100 β in ACI patients were significantly higher than the control group. Subgroup analysis based on ethnicity revealed that the serum levels of NSE and S-100 β in ACI patients were significantly higher than the control group in Asian population. In Caucasian population, the serum levels of NSE in case group was significantly higher than the control group, but no significant differences in serum levels of S-100 β were observed between ACI patients and the control group.

Conclusions: Based on our results, we conclude that serum levels of NSE and S-100 β strongly correlate with ACI in Asian population, and may be important clinical markers for diagnosis and treatment of ACI.

MeSH Keywords: **Brain Abscess • Diagnosis • Infarction, Anterior Cerebral Artery • Meta-Analysis • Phosphopyruvate Hydratase • Technetium Tc 99m Aggregated Albumin**

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Background

Stroke is the second leading cause of death in people over 60 years of age, and the fifth leading cause of death among the 15–59 age group [1]. Stroke is also the leading cause of morbidity and mortality in industrialized nations, and the leading cause of disability worldwide [2]. Stroke is the second most common cause of death in China, and patients with acute cerebral infarction (ACI), also known as acute ischemic stroke, account for 60–80% of all the stroke patients [3–5]. Most ACIs are caused by an embolic or thrombotic occlusion of an intracranial artery [6]. Dietary factors elevate ACI risk through their influence on blood pressure, thrombosis, insulin resistance, platelet function, oxidation and systemic inflammation [7]. Arterial revascularization to restore antegrade perfusion to the ischemic territory remains the principal therapeutic approach in ACI [8]. However, prevention and early intervention is critical for improved clinical outcomes, and in this context, the discovery of biomarkers useful in predicting ACI severity and clinical prognosis has received special attention in recent years [9].

Neuron specific enolase (NSE) is one such biomarker. It is a dimeric isoenzyme of the glycolytic enzyme enolase and is mainly found in the neurons [10]. Ectopic expression of NSE is used as an auxiliary test in diagnosis of small cell carcinoma of lung, neuroendocrine tumors and Alzheimer's disease [11–13]. Human soluble protein-100 β (S-100 β) is a low molecular weight calcium-binding protein and is found in glial cells of the central and peripheral nervous system [14,15]. S-100 β is mainly expressed in astrocytes but is also present in oligodendrocytes, microglia, neurons, and extracerebral tissues [16], and elevated serum S-100 β level is observed in cerebral infarction, traumatic brain injury, cerebral infarction or subarachnoid hemorrhage [17,18]. The serum levels of NSE and S-100 β are elevated after various types of brain damage, such as focal and global ischemia, head injury and hemorrhagic brain damage [19]. Several previous studies showed that NSE and S-100 β protein levels predict the clinical outcome of ACI, and NSE positively correlates with infarct volume in ACI patients [10,20,21]. However, other studies failed to confirm the relationship between NSE and ACI severity [22]. In order to address this issue with a larger dataset, we used meta-analysis approach to further investigate the clinical value of serum NSE and S-100 β levels in ACI.

Material and Methods

Literature search strategy

We searched PubMed, EBSCO, Ovid, SpringerLink, Web of Science, Embase, Wanfang, China National Knowledge

Infrastructure (CNKI) and VIP Information databases for relevant studies published prior to September, 2014. We used combinations of terms to achieve optimal search sensitivity and specificity. Our search strategy was as follows: (“stroke” or “brain infarction” or “cerebral infarction” or “cerebral ischemic stroke” or “cerebral stroke” or “ischemic stroke” or “acute cerebral infarction”), (“phosphopyruvate hydratase” or “2-phospho-D-glycerate hydrolase” or “enolase” or “NSE” or “neuron-specific enolase” or “muscle specific enolase” or “nervous system specific enolase”) and (“S100B protein, human” or “S100 beta protein, human”).

Study selection

Our study inclusion criteria were: (1) studies that investigated the correlation of ACI with serum levels of NSE and S-100 β ; (2) case-control studies; (3) study subjects are patients with ACI in case group and healthy controls in control group; (4) studies providing complete information related to country, ethnicity, publication year, age, gender, detection method and sample size, and the outcome indicators were serum NSE and S-100 β levels. The exclusion criteria were: (1) the diagnostic basis was undefined; (2) incomplete data was provided; (3) studies that were published repeatedly. In case of duplicate reports, we used data from the study that included the largest number of patients or individual patient data from each study when available. We contacted authors for clarification on the study sample or missing data.

Data extraction

Two investigators independently collected data using a standardized data abstraction form. We abstracted information associated to first author, publication year, country, language, ethnicity, age, gender, detection method, serum levels of NSE and S-100 β . Any disagreements in data extraction were resolved through discussion with multiple investigators.

Statistical analysis

All statistical analyses were performed using STATA software (Version 12.0, Stata Corporation, College Station, TX, USA). The correlation between serum levels of NSE and S-100 β and ACI was measured by the standard mean difference (SMD) and 95% confidence interval (95%CI) with a random or fixed effects model. The overall effect size was detected by Z test [23]. Heterogeneity among studies was evaluated by the Cochran's Q-statistic (if $P < 0.05$ heterogeneity existed) and I^2 test, which is an appraisal of the percentage of total variation across studies ranging from 0 to 100% [24,25]. A random effects model was applied if there was significant heterogeneity ($P < 0.05$ or $I^2 > 50\%$), otherwise, a fixed effects model was utilized [26]. Univariate and multiple meta-regression analyses were used

Table 1. Baseline characteristics of all included studies.

First author	Year	Country	Sample size	Gender (M/F)		Age (years)		Method
				Case	Control	Case	Control	
Yu WH	2014	China	Large	72/46	70/48	48~79	46~75	ELISA
Singh HV	2013	India	Large	70/30	67/34	59.71 $\pm$ 12.6	61.31 $\pm$ 12.37	ELISA
An SA	2013	Korea	Large	101/87	37/53	66 $\pm$ 11	61 $\pm$ 9	ELISA
Lv LZ	2012	China	Large	45/33	26/19	36~73	55.9	ELISA
Gonzalez Garcia S	2012	Cuba	Large	23/38	46/33	32~88	30~98	ELISA
Wang QF	2010	China	Small	–	25/15	–	44~73	ELISA
Brouns R	2010	Belgium	Large	50/39	18/17	71.1 $\pm$ 13.2	68.1 $\pm$ 12.5	ECLIA
Su XH	2009	China	Large	24/21	16/15	48~69	45~68	ELISA
Zhang XN	2008	China	Small	–	15/10	–	45~78	ECLIA
Ma XN	2007	China	Small	–	22/18	–	59.85 $\pm$ 8.24	CLIA
Li Z	2007	China	Small	34/23	12/8	60.2 $\pm$ 8.7	48.4 $\pm$ 12.3	ECLIA
Cao GB	2006	China	Small	27/31	–	46~68	26~65	ELISA
Gao D	2002	China	Small	28/17	19/13	64.2 $\pm$ 9.5	62.8 $\pm$ 7.8	ELISA

M – male; F – female; ELISA – enzyme linked immunosorbent assay; ECLI – electro-chemiluminescence immunoassay.

to estimate the source of heterogeneity, and Monte Carlo simulation (MCS) was performed to verify the results [27,28]. Sensitivity analysis was employed by deleting one included study at a time to evaluate the influence of one single study on the overall results. The publication bias that assesses the reliability of the result was evaluated by funnel plot and the Egger test [29].

Results

Study selection and study characteristics

Our search strategy retrieved 117 citations after removal of duplicates. Forty three papers were remaining after excluding 2 duplicates, 22 animal studies, 8 letters, reviews, or meta-analyses and 44 studies unrelated to the research topic. We further excluded 4 cohort studies, 12 studies not relevant to NSE and S-100 β , 11 studies unrelated to ACI, and 3 studies that had insufficient information. Finally, 13 case-control studies published between 2002 and April 2014 [2,30–41], containing 911 ACI patients in case group and 686 healthy controls in control group, were finally selected for this meta-analysis. Among these 13 studies, study subjects in 11 trials were Asians, 2 trials were performed in Caucasians. A total of 9 studies were from China and 1 each from India, Korea, Cuba, Belgium. Sample sizes ranged from 58 to 236. Serum levels of NSE and S-100 β were detected by enzyme linked

immunosorbent assay (ELISA) or electro-chemiluminescence immunoassay (ECLI). The baseline characteristics all included case-control studies are shown in Table 1.

Correlation between ACI and serum levels of NSE

A total of 13 studies reported serum levels of NSE in ACI patients. Heterogeneity test suggested that heterogeneity existed across studies ($I^2=95.3\%$, $P<0.001$), thus a random effects model was applied. The result of this meta-analysis revealed that serum levels of NSE were significantly higher in ACI patients compared to control group, and the difference was statistically significant (SMD=1.96, 95%CI=1.83~2.09, $P<0.001$) (Figure 1). Additionally, subgroup analysis based on ethnicity indicated that serum levels of NSE were markedly higher in ACI patients, compared to the control group, in both Asians and Caucasians (Asian: SMD=2.11, 95%CI=1.96~2.25, $P<0.001$; Caucasian: SMD=1.32, 95%CI=1.02~1.61, $P<0.001$). A subgroup analysis based on sample size showed that serum levels of NSE in ACI patients of both large sample size ($n\geq 100$) and small sample size ($n<100$) were notably higher than the control group (large sample size: SMD=2.01, 95%CI=1.86~2.17, $P<0.001$; small sample size: SMD=1.80, 95%CI=1.55~2.05, $P<0.001$) (Figure 2). Univariate meta-regression analysis suggested that publication year, country, ethnicity and sample size were not the main sources of heterogeneity or the critical factors in influencing the overall effect size ($P>0.05$) (Figure 3A). Multiple meta-regression analysis also indicated that year of

Figure 1. Forest plots of the differences in serum levels of NSE and S-100β between acute cerebral infarction patients and the healthy controls.

publication, country, ethnicity, and sample size were not the sources of heterogeneity (Table 2).

Correlation between ACI and serum levels of S-100β

Twelve studies investigated the serum levels of S-100β in ACI patients. There was no heterogeneity among these studies ($I^2=98.5\%$, $P<0.001$), thus a fixed-effects model was performed. Results of the meta-analysis suggested that the serum levels of S-100β in ACI patients were higher than in healthy controls (SMD=2.69, 95%CI=2.51~2.86, $P<0.001$) (Figure 1). Additionally, subgroup analysis by ethnicity indicated that serum levels of S-100β in ACI patients was markedly higher than the control group in Asians (SMD=2.84, 95%CI=2.66~3.02, $P<0.001$), while no significant differences in S-100β levels were observed in a Caucasian population between ACI patients and the control group (SMD=-0.56, 95%CI=-1.37~0.24, $P=0.172$). Subgroup analysis by sample size showed that the serum levels of

S-100β in ACI patients in both large sample size ($n\geq100$) and small sample size ($n<100$) were notably higher than in the control group (large sample size: SMD=2.90, 95%CI=2.69~3.12, $P<0.001$; small sample size: SMD=2.33, 95%CI=2.05~2.61, $P<0.001$) (Figure 2). Univariate meta-regression analysis suggested that publication year, country, ethnicity and sample size were not the main sources of heterogeneity or the critical factors in affecting the overall effect size ($P>0.05$) (Figure 3B). Multiple meta-regression analysis also indicated that publication year, country, ethnicity, and sample size were not the sources of heterogeneity (Table 3).

Sensitivity analysis and publication bias

Sensitivity analysis suggested that no single study affected the statistical significance of overall results (Figure 4). $P<0.05$ suggested there was publication bias among studies. Both the summary of funnel plot and Egger test showed no evident

Figure 2. Forest plots of subgroup analyses by ethnicity and sample size on the differences in serum levels of NSE and S-100 β between acute cerebral infarction patients and the healthy controls.

publication bias in NSE and S-100 β levels between ACI patients and control group (NSE: $P=0.459$; S-100 β : $P=0.314$) (Figure 5).

Discussion

In this meta-analysis, we investigated the clinical value of NSE and S-100 β in ACI patients, based on the data extracted from previous studies. We found that serum levels of NSE and S-100 β in ACI patients were significantly higher than in the control group, suggesting that NSE and S-100 β might be reliable markers for ACI. S-100 β is a dimeric calcium-binding protein with α and β subunits. The β subunit is highly specific to the brain and is synthesized in glial cells throughout the central nervous system [42]. Depending on its concentrations in the extracellular space, S-100 β may either be beneficial for

recovery after brain injury, or become neurotoxic [43]. At normal concentrations, in the nanomolar range, S-100 β stimulates neurite outgrowth, glial cell proliferation, and regeneration of injured nerves. Its neuroprotective function also includes enhancing neuronal cell maintenance, preventing motor neuron degeneration, and enhancing the survival of neurons [44]. However, in the micromolar range, the excessive levels of S-100 β result in production of reactive oxidative species, cytochrome C release, and activation of the caspase cell death cascade, leading to induction of apoptosis [44,45]. S-100 β protein can be detected in very low amounts in blood in normal healthy individuals. In acute and chronic brain damage, glial cells respond to the injury by increasing S-100 β production; consequently, higher levels of this protein are seen in the serum and cerebrospinal fluid (CSF) under such conditions [35]. The intracellular S-100 β may enter the blood circulation either

Figure 3. (A) Meta-regression analysis on the correlation between serum level of NSE and acute cerebral infarction patients. (B) Meta-regression analysis on the correlation between serum level of S-100β and acute cerebral infarction patients.

Table 2. Meta-regression analyses of potential source of heterogeneity (NSE).

Heterogeneity factors	Coefficient	SE	t	P	95% CI	
				(Adjusted)	LL	UL
Year	0.0960	0.246	0.39	0.937	-0.472	0.664
Country	-0.687	1.254	-0.55	0.863	-3.578	2.204
Ethnicity	0.971	4.310	0.23	0.987	-8.967	10.909
Sample	-0.000	0.014	-0.01	1.000	-0.034	0.034

NSE – neuron specific enolase; SE – standard error; CI – confidence interval; LL – lower limit; UL – upper limit.

Table 3. Meta-regression analyses of potential source of heterogeneity (S-100 β).

Heterogeneity factors	Coefficient	SE	t	P	95% CI	
				(Adjusted)	LL	UL
Year	0.244	0.576	0.42	0.925	-1.117	1.605
Country	-8.371	4.550	-1.84	0.264	-19.128	2.387
Ethnicity	17.266	11.465	1.51	0.366	-9.843	44.376
Sample	0.018	0.031	0.57	0.867	-0.056	0.091

S-100 β – human soluble protein-100 β ; SE – standard error; CI – confidence interval; LL – lower limit; UL – upper limit.

Figure 4. Sensitivity analysis on the differences in serum levels of NSE and S-100 β between acute cerebral infarction patients and the healthy controls.

directly through the disrupted blood-brain barrier or first into CSF and subsequently into the blood through the arachnoid villi [46]. In contrast to astrocyte-derived S-100 β protein, NSE originates predominantly from neurons [47]. NSE concentration strongly correlates with the volume of infarcted brain

areas, and is an indicator of the severity of clinical features, such as disability. Neuronal injury results in the release of intracellular NSE from injured neurons into CSF and blood circulation [30]. Our results suggest that serum NSE levels are tightly associated with ACI, consistent with a previous study

Figure 5. Publication bias of the differences in serum levels of NSE and S-100 β between acute cerebral infarction patients and the healthy controls.

which reported that NSE concentrations in was serum correlated with clinical outcomes in stroke and neurotrauma patients [48]. Additionally, we also predicted that the serum levels of NSE and S100B also could be good predictive indicators in the treatment of ACI, as a previous study reported by García S et al. that suggested serum concentrations of NSE and S100B after acute stroke might be clinically relevant for predicting the outcome of neurological function and post-stroke depression [21]. Furthermore, the results of another study by Kaca-Oryńska M et al. demonstrated that significant differences in NSE and S100B levels existed between stroke patients and the control group, but only the S100B protein level was associated with stroke volume, neurological status at admission, and the functional outcome compared with NSE [49].

Subgroup analysis by ethnicity revealed that the serum levels of NSE in Asian and Caucasian ACI patients were significantly higher than in healthy controls. A second subgroup analysis indicated that in Asian populations, the serum level of S-100 β in ACI patients was markedly higher than in healthy

controls, while this difference was not statistically significant in Caucasian populations. Different regions, life-styles, and ethnicities may have underlying variations that could have contributed to this result. Subgroup analysis by sample size suggested that in both large and small sample sizes, the serum levels of NSE and S-100 β were markedly higher in ACI patients compared to healthy controls, further confirming the main result of the present meta-analysis.

When interpreting our results, several limitations should be considered. First, 11 of the total 13 trials were in Asian populations, and this might bias the overall results to some extent. However, there was also statistical evidence for the clinical value in diagnosis of ACI in Asian populations. Second, the different detection methods may vary in specificity and sensitivity of S-100 β and NSE measurement, and thus may bias the comparisons and results. Third, we could not perform sensitivity analyses related to age, sex, life-style variables, or family history, due to the varied data presentations or absence of the data in the included studies. Finally, other neurological

diseases and risky behavior also influence serum S-100 β protein concentrations [50,51].

Conclusions

Serum levels of NSE and S-100 β were significantly higher in ACI patients in Asian populations compared to their healthy counterparts, suggesting that the 2 proteins strongly correlate with ACI and could be used as important biological indicators in diagnosis and treatment of ACI in Asians.

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Conflict of interest statement

The authors have no conflict of interest.

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