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Serum S100B levels may be associated with cerebral infarction: a meta-analysis

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ABSTRACT

Objective: The aim of this paper is to explore the potential association of serum human soluble protein-100B protein (S100B) levels with the diagnosis and prognosis of cerebral infarction (CI).
Methods: Potential relevant studies were searched for in PubMed, Springerlink, Wiley, EBSCO, Ovid, Web of Science, Wanfang databases, China National Knowledge Infrastructure (CNKI) databases and VIP databases. Two investigators extracted data and assessed studies independently. Statistical analyses were carried out with the version 12.0 STATA statistical software.
Results: A total of 10 case–control studies that assessed the correlation of S100B serum level with CI, including 1211 subjects (patients = 773, healthy controls = 438) were included. The results showed that S100B serum levels in CI victims were significantly higher compared with those of the control group. According to the subgroup analysis by ethnicity, S100B serum level in CI victims was statistically significant in Asians and the control group, but no statistical significance was found in Caucasians. An additional subgroup analysis was carried out based on sample size, revealing that the S100B serum levels in CI victims in small samples were of statistical significance; however, no statistical significance was discovered in large samples.
Conclusions: Elevator S100B serum levels might be negatively correlated with CI, suggesting that higher serum levels of S100B could lead to more serious condition and worse prognoses for CI patients. Therefore, S100B serum levels could be regarded as a biomarker for CI, and furthermore, S100B could aide in the diagnosis and prognosis of CI.

1. Introduction

Cerebral infarction (CI), also known as cerebral ischemic stroke (IS), is caused by a blood circulatory disorder which induces ischemia, hypoxia and necrosis in the lesion position of the brain. IC is reported to be the leading cause of disability and the second leading cause of death worldwide [1,2]. Additionally, CI can lead to secondary degeneration of the thalamus as well as delay recovery of full functionality [3]. Numerous studies have demonstrated that multiple physiopathologic processes such as inflammation, oxidative stress, necrosis, hypercoagulable state, apoptosis and vascular dysfunction could be used to assess the pathogenesis of CI [4–7]. They have revealed that advanced age, a decreased level of consciousness and low cerebrospinal fluid (CSF) white blood cell count are well-known general risk factors for CI [4,8]. Owing to the complicacy of CI, it is difficult to seek an effective and simple therapeutic method to prevent and cure the disease. More recent reports have declared that the changing serum levels of certain proteins could be significantly related to the physiopathologic process of CI [9,10]. Moreover, the S100B protein has been receiving increasing attention and is regarded to be a predictive and reliable biomarker since its serum concentrations are up-regulated in the development of CI [11].

S100B protein, discovered to have a biological half-life of only 2 h, has been reported to be a part of the multigenic S100 family that is of low molecular weight (9–13 kD) [12,13]. S100B is detected in varying amounts in glial cells of the central nervous system such as astrocytes, pituicytes, neuronal progenitor cells, ependymocytes, maturing oligodendrocytes and certain neural populations [14]. Furthermore, it has been well documented that S100B is closely associated with Ca 2+ dependent regulation of both extracellular and intracellular activities such as astrocyte shape, proliferation, migration, differentiation, protein phosphorylation, cytoskeletal dynamics, enzymatic activity, inflammation, intracellular Ca 2+ homeostasis, structural organization of membranes, transcription as well as protection against oxidative stress [12,15–17]. Furthermore, serum S100B was found in both blood serum and CSF, and considered to be a biomarker of pathological conditions of several brain diseases such as brain tumors, neuroinflammatory/neurodegenerative disorders, perinatal brain distress, psychiatric disorders,

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cerebral infections, subarachnoid hemorrhage, acute brain injury and cerebral infarction [18,19]. Previous research has concluded that patients with CI revealed higher S100B serum levels compared to healthy subjects, supporting the hypothesis that S100B serum level could be an effective and dependable biomarker in the prediction and prognosis of CI (Xun C. Detection and significance of hs-CRP level in acute cerebral infarction patients [J]. China Tropical Medicine, 2011, 8: 050) [14,20]. However, there are inconsistencies between the above mentioned findings and other studies [21]. For this reason, the following meta-analysis was carried out in an effort to further explore the potential association between S100B serum levels and the diagnosis and prognosis of CI.

2. Materials and methods

2.1. Data sources and keywords

For the purpose of determining all relevant articles that assessed the correlation between S100B and CI, we comprehensively searched PubMed, Springerlink, Wiley, EBSCO, Ovid, Web of Science, Wanfang databases, China National Knowledge Infrastructure (CNKI) and VIP databases (last updated search in October 30st, 2014), utilizing common keywords concerning S100B and CI, namely ("serum S100B" or "serum S100β" or "S100 calcium-binding protein β subunit" or "S100 calcium binding protein beta subunit") and ("cerebral infarction" or "ischemia stroke" or "stroke" or "intracranial embolism" or "CI").

2.2. Selection criteria

We searched all human-associated case–control studies estimating the correlation of S100B serum level with CI, and bulletined the befitting standardized mean differences (SMDs) and 95% confidence intervals (CI). We only extracted articles that supplied sufficient information about S100B serum levels and sample numbers, and eliminated those articles with incomplete, unavailable or ill-suited clinicopathologic data, or those regarding CI not confirmed by histopathologic examinations. Furthermore, only those articles with at least 20 cases were selected. In addition, when the extracted articles were based on subjects who overlapped with another study or other studies by more than 50%, we selected the one with the most comprehensive population. Moreover, after careful reexamination, only the newest or complete study was enrolled when the extracted articles were published by the same authors or groups.

2.3. Data extraction and quality assessment

In order to decrease bias and strengthen credibility, information was extracted from the retrieved studies on the basis of the selection criteria by two investigators independently, and they arrived at unanimity on all items via discussion and reexamination. The following relevant information was extracted from eligible studies: surname of first author, year of publication, country of origin, ethnicity, language, disease, age, sex, intervention, case load, the number of control group and detection method of S100B protein serum level. The studies approved by all investigators were enrolled. For assessing the quality of the study, the two investigators separately applied a range of predefined criteria based on the two authors used a set of predefined criteria based on the PEDro (Physiotherapy Evidence Database) scale criteria (available from: http://www.pedro.org.au) [22]. This scale provides the citation details, abstract as well as a link for each guideline, trail or review to the full text. The PEDro scale, ranging from 0 to 10 points, is scored based on whether the study includes internal validity as well as adequate statistical information to allow the outcomes to be interpreted. According to the PEDro scale score, the included studies were classified into two levels: low quality (0–3), and high quality (4–10), respectively.

2.4. Statistical analysis

To count the effect size for each study, the summary SMDs with 95%CI were applied for evaluating case versus control categories of S100B serum levels using the Z test. In order to provide quantitative evidence all selected studies as well as reduce the variance of the summary SMDs with 95%CI, this meta-analysis was conducted utilizing a random-effects model or a fixed-effects model of individual study outcomes when data from independent studies might be combined. A random-effect model was used when there was heterogeneity among studies, and when no statistical heterogeneity existed, a fixed-effects model was applied. In order to explore potential effect modification, subgroup meta-analyses were also conducted by ethnicity and sample size. Then, heterogeneity of the incorporated studies was assessed using Cochran's Q-statistic (statistically significant was considered when $P < 0.05$). Owing to the low statistical power of Cochran's Q-statistic, the I^2 test was also used to estimate the potential of heterogeneity among studies (100%, maximal heterogeneity; 0%, no heterogeneity) [23]. The possible source of heterogeneity was analyzed applying meta-regression [24] to compare single factor and multifactorial interventions, and Monte Carlo simulation (Binder K, Heermann D. Monte Carlo simulation in statistical physics: an introduction[M]. Springer, 2010.) was used to conduct multiple calibration. A funnel plot was made to evaluate publication bias which might influence the validity of the estimates. Egger's linear regression test [25] was then applied to assess the symmetry of the funnel plot. To ensure credibility an accuracy of the results, all information was input separately by two investigators in the STATA software, version 12.0 (Stata Corp, College Station, TX, USA) and an agreement was arrived at.

3. Results

3.1. Included studies

The years of the studies that were enrolled ranged from 2004 to 2014. The study selecting steps are shown in Fig. 1. A total of 667 documents were retrieved initially via electronic database search and manual search, and 42 papers were retained after the removal of duplicates ($n = 69$), letters, reviews or meta-analyses ($n = 2$), non-human studies ($n = 12$) as well as studies unrelated to the research topics ($n = 542$). Moreover, an additional 24 studies were excluded because they were not case–control or cohort studies ($n = 6$), not relevant to CI ($n = 8$) or not relevant to S100B ($n = 10$). In the final step of selection, 8 out of the remaining 18 studies were rejected because they did not supply enough information [11,26–34]. Our selection criteria ultimately left us with 10 case–control studies in full text including 773 patients with CI and 438 normal, healthy people. Baseline characteristics and NOS of the enrolled studies are presented in Table 1 and Fig. 2. Eight studies were conducted on populations of Asian descent, and two studies were on populations of Caucasians.

3.2. S100B serum level in CI

Based on the outcome of current meta-analysis, heterogeneity was discovered, suggesting that the random effects model should be applied. Fig. 3 shows that the S100B serum levels in CI victims were significantly higher compared to those in control group (SMD = 1.59, 95% CI = 0.71–2.47, $P < 0.001$). According to the results of subgroup analysis based on ethnicity as shown in Fig. 4A, serum S100B levels in CI patients were higher than they were in healthy controls among Asians (SMD = 1.71, 95%CI = 0.62–2.79, $P = 0.002$), while no statistical significance was found between CI patients and healthy controls among Caucasians (SMD = 1.12, 95%CI = −0.08–2.33, $P = 0.068$). A further subgroup analysis was carried out based on sample size. The outcome, shown in Fig. 4B, reveals that the S100B serum level in CI victims is statistical significance in small samples (SMD = 1.91, 95%CI = 1.13–2.69, $P < 0.001$),