Correlations of *MCP-1* –2518A>G Polymorphism and Serum Levels with Cerebral Infarction Risk: A Meta-Analysis

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This meta-analysis was performed to evaluate the relationships between the monocyte chemoattractant protein-1 (*MCP-1*) –2518A>G (rs1024611 A>G) polymorphism and its serum levels, and the risk of cerebral infarction. The PubMed, CISCOR, CINAHL, Web of Science, Google Scholar, EBSCO, Cochrane Library, and CBM databases were searched for relevant articles published before October 1st, 2013 without language restrictions. Meta-analysis was conducted using the STATA 12.0 software. Crude odds ratios (ORs) or standardized mean difference (SMD) with their 95% confidence intervals (95% CIs) were calculated. Twelve case-control studies that met all the inclusion criteria were included in this meta-analysis. A total of 1272 patients with cerebral infarction and 1210 healthy control subjects were involved in this meta-analysis. Our meta-analysis results reveal that the *MCP-1* –2518A>G polymorphism might increase the risk of cerebral infarction (A allele vs. G allele: OR=1.37, 95% CI: 1.18–1.60, $p<0.001$; GA+AA vs. GG: OR=1.33, 95% CI: 1.09–1.62, $p=0.005$; respectively). Furthermore, cerebral infarction patients had higher levels of serum MCP-1 than did healthy control subjects (SMD=2.96, 95% CI: 2.00–3.92, $p<0.001$). Statistical analysis revealed no evidence of publication bias in this meta-analysis (all $p>0.05$). Our findings indicate that the *MCP-1* –2518A>G polymorphism and serum MCP-1 levels may contribute to the development of cerebral infarction. Thus, the *MCP-1* –2518A>G polymorphism and serum MCP-1 levels could be potential biomarkers for the early detection of cerebral infarction.

Introduction

CEREBRAL INFARCTION IS GENERALLY defined as an ischemic stroke resulting from an atherothrombotic or embolic blockage of the blood vessels supplying blood to the brain (O'Donnell *et al.*, 2010). As an atherosclerosis-associated complication, cerebral infarction is widely accepted as a leading cause of mortality and disability and a serious public health concern (Towfighi and Saver, 2011; Sen *et al.*, 2012). Generally, cerebral infarction is known to be a multifactorial disease induced by complex interactions between environmental and genetic factors (Shimizu *et al.*, 2013). Many intrinsic and extrinsic risk factors for cerebral infarction have been established, such as diabetes, tobacco smoking, hypercholesterolemia, high blood pressure, and obesity (O'Donnell *et al.*, 2010). Although the exact cellular and molecular mechanisms leading to cerebral infarction remain unclear, recent studies have indicated that cerebral ischemia may result from the increased expression of several cytokines and chemokines, including the monocyte chemoattractant protein-1 (*MCP-1*) that induces the infiltration of leukocytes into the ischemic lesion (Denes *et al.*, 2010; Bose and Cho, 2013).

As a member of the CC chemokine family, MCP-1 has been demonstrated to play a significant role in the inflammatory response in acute and chronic inflammatory conditions (Deshmane *et al.*, 2009). The human *MCP-1* gene is located on chromosome 17q11.2–q12 and consists of three exons and two introns (Opdenakker *et al.*, 1994). In general, MCP-1 is a chemokine strongly implicated in the recruitment and activation of monocytes or macrophages in the initiation, progression, and development of complications in coronary atherosclerosis, which is a key risk factor in occlusive vascular disease (Piemonti *et al.*, 2009; Jaipersad *et al.*, 2013). It has been widely considered that the inflammatory immune response is one pathogenesis of cerebral infarction and that chemokines play an important role in this process (Jin *et al.*, 2010). Thus, an alteration in chemokine expression or function might lead to the persistence of an inflammatory reaction well beyond its original purpose, thereby potentiating the development of chronic inflammation (Yadav *et al.*, 2010). It has been hypothesized that several single-nucleotide polymorphisms (SNPs) in the *MCP-1* gene and changes in serum MCP-1 levels might be associated with the development and progression of cerebral

infarction (Giannakopoulou *et al.*, 2013). Among these polymorphisms, the most frequent functional polymorphism is a transition from guanine (G) to adenine (A) at position -2518 within the promoter region of the *MCP-1* gene (-2518A>G, rs1024611 A>G), which is associated with serum levels of MCP-1 (Jeon *et al.*, 2013). Currently, a number of studies have documented that the *MCP-1* gene polymorphism and serum MCP-1 levels may be involved in the development of cerebral infarction (Yuasa *et al.*, 2009; Buraczynska *et al.*, 2010; Matos *et al.*, 2011), but the results of other studies have been inconsistent (Kim *et al.*, 2011; Uchida *et al.*, 2012). Therefore, this meta-analysis was performed to evaluate the relationships between the *MCP-1* -2518A>G polymorphism and serum MCP-1 levels, and the risk of cerebral infarction.

Materials and Methods

Literature search

We searched the PubMed, Web of Science, Google Scholar, Cochrane Library, CISCOR, CINAHL, EBSCO, and CBM databases for relevant articles published before August 1st, 2013 without any language restrictions. The following keywords and MeSH terms were used: ["SNP" or "mutation" or "genetic polymorphism" or "variation" or "polymorphism" or "single nucleotide polymorphism" or "variant"] and ["brain infarction" or "cerebral infarction" or "ischemic stroke"] and ["monocyte chemoattractant protein-1" or "chemokine CCL2" or "MCP-1" or "CCR2

receptors"]. We also performed a manual search of the reference lists of relevant articles to find other potential studies.

Selection criteria

Included studies had to meet all five of the following criteria: (1) the study design must be clinical cohort or case-control; (2) the study must relate to the relationship between the *MCP-1* -2518A>G polymorphism or serum MCP-1 levels, and the risk of cerebral infarction; (3) all patients must conform to the diagnostic criteria for cerebral infarction; (4) the study must provide sufficient data on the frequencies of SNP or serum MCP-1 levels; and (5) the genotype distribution of healthy control subjects must conform to the Hardy-Weinberg equilibrium (HWE). Any study that did not meet the above inclusion criteria was excluded. If the authors published several studies using the same subjects, the most recent publication or the publication with the largest sample size was included.

Diagnostic criteria of cerebral infarction

Cerebral thrombosis and infarction due to atherosclerosis were diagnosed according the following criteria: (1) the occurrence of cerebral infarction always in a quiet state; (2) no headache or vomiting in most cases; (3) cerebral infarction is one chronic phase disease, which is associated with the development of cerebral atherosclerosis, and is often common in arteritis and blood disease; (4) patients usually have none or mild impairment 1 or 2 days after the onset of cerebral

FIG. 1. Flowchart of literature search and study selection. Twelve case-control studies were included in this meta-analysis.

infarction; (5) there are internal carotid and vertebrobasilar artery system symptoms and signs; (6) cerebrospinal fluid without blood in the cerebral infarction; and (7) conducted CT examination when differential diagnosis is difficult.

Data extraction

Relevant data were systematically extracted from all the included studies by two independent researchers using a standardized form. The following data were recorded: language of publication, publication year, the first author's surname, geographical location, design of study, sample size, source of subjects, allele frequencies, source of samples, genotyping method of SNP, evidence of HWE in healthy control subjects, serum MCP-1 levels, etc.

Quality assessment

Methodological quality was independently assessed by two independent researchers according to the Newcastle-Ottawa Scale (NOS) criteria (Stang, 2010). The NOS criteria scores quality according to three aspects: (1) subject selection: 0–4 scores; (2) comparability of subject: 0–2 scores; (3) clinical outcome: 0–3 scores. NOS scores range from 0 to 9 with a score ≥ 7 indicating good quality.

Statistical analysis

The STATA version 12.0 (Stata Corp., College Station, TX) software was used for meta-analysis. We calculated crude odds ratios (ORs) or standardized mean difference (SMD) with their 95% confidence intervals (95% CIs) to evaluate relationships. The Z test was used to estimate the statistical significance of pooled statistics. The Cochran's Q -statistic and I^2 test were used to evaluate potential heterogeneity between studies (Zintzaras and Ioannidis, 2005). If the Q -test showed a $p < 0.05$ or the I^2 test had a score $> 50\%$, indicating significant heterogeneity, the random-effects model was conducted; otherwise, the fixed-effects model was used. We also performed a subgroup analysis to investigate potential sources of heterogeneity. To evaluate the influence of single studies on the overall estimate, a sensitivity analysis was performed. We conducted Begger's funnel plots and Egger's linear regression test to investigate publication bias (Peters *et al.*, 2006).

FIG. 2. The distribution of the number of topic-related literature in electronic databases over the last decade.

TABLE 1. BASELINE CHARACTERISTICS AND METHODOLOGICAL QUALITY OF ALL INCLUDED STUDIES

First author	Year	Country	Ethnicity	Sample size		Gender (M/F)		Age (years)		Detection method	Main findings	NOS score
				Case	Control	Case	Control	Case	Control			
Xu	2011	China	Asians	112	49	69/43	24/25	63.4 ± 9.6	59.4 ± 8.1	ELISA		8
Liang	2011	China	Asians	100	100	58/42	63/37	65.3 ± 11.6	62.8 ± 12.5	PCR-RFLP/ELISA		8
Huang	2011	China	Asians	72	38	—	—	70.2	—	ELISA		6
Buraczynska	2010	Poland	Caucasians	164	320	75/119	60/104	69.9 ± 12.5	49.2 ± 9.8	PCR-RFLP		8
Wang	2009	China	Asians	96	90	60/36	56/34	60.3 ± 8.8	65.2 ± 13.5	ELISA		7
Wang	2009	China	Asians	79	30	50/29	22/8	—	66.4 ± 11.0	ELISA		7
Guo	2008	China	Asians	56	30	32/24	17/13	55.8	54.8	ELISA		7
Chen	2007	China	Asians	162	150	99/63	91/59	62.3 ± 11.8	61.1 ± 8.9	PCR-RFLP/ELISA		8
Dai	2006	China	Asians	113	98	55/58	50/48	62.4 ± 7.3	62.5 ± 7.9	PCR-RFLP/ELISA		8
Dai	2006	China	Asians	39	38	—	—	—	—	ELISA		6
Zaremba	2006	Poland	Caucasians	27	20	11/16	—	65.5 ± 6.9	—	ELISA		6
Sanchez-Moreno	2004	America	Caucasians	15	24	—	—	67.0 ± 12.0	61.0 ± 10.0	ELISA		6
Flex	2004	Italy	Caucasians	237	223	132/105	107/116	76.2 ± 9.4	76.1 ± 6.8	PCR-RFLP		7

M, male; F, female; MCP-1, monocyte chemoattractant protein-1; PCR, polymerase chain reaction; RFLP, restriction fragment length polymorphism; NOS, Newcastle-Ottawa Scale; ①, serum level of MCP-1 is associated with the development of cerebral infarction; ②, serum level of MCP-1 is associated with disease severity of cerebral infarction; ③, MCP-1 -2518A>G polymorphism is associated with serum level of MCP-1; ④, MCP-1 -2518A>G polymorphism is associated with the development of cerebral infarction; ⑤, MCP-1 -2518A>G polymorphism is not correlated with the development of cerebral infarction; ⑥, serum level of MCP-1 is not correlated with the development of cerebral infarction.

Results

Characteristics of included studies

Initially, the searched keywords identified 254 articles. We reviewed the titles and abstracts of all articles and excluded 139 articles. After full texts and data integrity were reviewed, another 102 articles were excluded. Finally, 12 case-control studies were found to meet the inclusion criteria and were included in this meta-analysis (Flex *et al.*, 2004; Sanchez-Moreno *et al.*, 2004; Dai *et al.*, 2006; Zar-emba *et al.*, 2006; Chen *et al.*, 2007; Guo *et al.*, 2008; Wang *et al.*, 2009; Wang and Cheng, 2009; Buraczynska *et al.*, 2010; Huang *et al.*, 2011; Liang *et al.*, 2011; Xu *et al.*, 2011). The publication years of eligible studies ranged from 2004 to 2011. Figure 1 shows the selection process of eligible articles. The distribution of the number of topic-related literature in electronic databases over the last decade is shown in Figure 2. A total of 2482 subjects were assessed in this meta-analysis, including 1272 patients with cerebral infarction and 1210 healthy control subjects. Overall, eight studies were conducted in Asian populations and four studies in Caucasian populations. The genotype frequencies of control subjects were all in HWE (all $p > 0.05$). The NOS scores of all included studies were ≥ 6 (moderate-high quality). We summarized the study characteristics and methodological quality in Table 1.

Quantitative data synthesis

Five studies focused on the relationship between the *MCP-1* -2518A>G polymorphism and susceptibility to cerebral infarction. The random-effects model was conducted due to the existence of significant heterogeneity between studies. Our meta-analysis results showed that the *MCP-1* -2518A>G polymorphism might increase the risk of cerebral infarction (A allele vs. G allele: OR = 1.37, 95% CI: 1.18–1.60, $p < 0.001$; GA + AA vs. GG: OR = 1.33, 95% CI: 1.09–1.62, $p = 0.005$; respectively). Subgroup analysis by ethnicity suggested that there were significant associations between the *MCP-1* -2518A>G polymorphism and increased risks of cerebral infarction among Caucasian populations (A allele vs. G allele: OR = 1.56, 95% CI: 1.26–1.92, $p < 0.001$; GA + AA vs. GG: OR = 1.41, 95% CI: 1.08–1.84, $p = 0.011$), but not among Asian populations (all $p > 0.05$) (Fig. 3). Further stratification analysis by source of controls indicated that the *MCP-1* -2518A>G polymorphism might be strongly linked to susceptibility to cerebral infarction in the population-based (PB) subgroup (A allele vs. G allele: OR = 1.56, 95% CI: 1.26–1.92, $p < 0.001$; GA + AA vs. GG: OR = 1.41, 95% CI: 1.08–1.84, $p = 0.011$), but not in the hospital-based (HB) subgroup (all $p > 0.05$) (Fig. 3).

Ten studies reported differences in serum MCP-1 levels between cerebral infarction patients and healthy control

FIG. 3. Subgroup analyses of the relationships between the monocyte chemoattractant protein-1 (*MCP-1*) -2518A>G polymorphism and cerebral infarction risk under the allele and dominant models.

subjects. Since obvious heterogeneity was discovered in the assessment, the random-effects model was used. Our results demonstrated that cerebral infarction patients had higher levels of serum MCP-1 than those of healthy control subjects (SMD=2.96, 95% CI: 2.00–3.92, $p<0.001$). We observed a significant difference in serum MCP-1 levels between cerebral infarction patients and healthy control subjects among Asian populations in both PB and HB subgroups (all $p<0.05$) (Fig. 4). However, no similar result was found among Caucasian populations (SMD=2.61, 95% CI: -1.56–6.78, $p=0.220$).

The results of a sensitivity analysis suggested that no single study significantly influenced the overall pooled estimates (Fig. 5). We found no evidence of obvious asymmetry in the Begger's funnel plots (Fig. 6). The Egger's test also did not display a strong statistical evidence of publi-

cation bias (allele model: $t=-2.22$, $p=0.113$; dominant model: $t=1.31$, $p=0.226$).

Discussion

MCP-1 is capable of recruiting monocytes, dendritic cells, and memory T cells to the sites of inflammation produced by either tissue injury or infection (Panee, 2012; Bose and Cho, 2013). Previous studies have demonstrated that MCP-1 might be a potential factor responsible for the injury-initiated neural progenitor migration, as well as the chemoattractant for neural progenitor migration after ischemia and other neuroinflammatory diseases (Yan *et al.*, 2007; Leker, 2009). Recent studies have suggested that elevated levels of serum MCP-1 is a common feature of both cerebral and myocardial infarction (Parissis *et al.*, 2002;

FIG. 4. Subgroup analyses of the relationships between serum MCP-1 levels and cerebral infarction risk.

FIG. 5. Sensitivity analysis of the summary of odds ratio (OR) coefficients on the relationships between the *MCP-1* – 2518A>G polymorphism and serum MCP-1 levels, and the risk of cerebral infarction. Results were computed by omitting each study in turn. Meta-analysis random-effects estimates (exponential form) were used. The two ends of the dotted lines represent the 95% confidence interval.

Arakelyan *et al.*, 2005). Moreover, genetic variations in the *MCP-1* gene may alter its corresponding biologic and physiologic responses, thus affecting an individual's susceptibility to cerebral infarction (McColl *et al.*, 2009; Mao *et al.*, 2013).

In the present meta-analysis, we evaluated the relationship between the *MCP-1* – 2518A>G polymorphism and serum MCP-1 levels, and susceptibility to cerebral infarction. Finally, 12 independent case-control studies were included with a total of 1272 patients with cerebral infarction and 1210 healthy control subjects. Our meta-analysis results showed that the *MCP-1* – 2518A>G polymorphism was associated with an increased risk of cerebral infarction, suggesting that the *MCP-1* – 2518A>G polymorphism may

be significantly involved in the development of cerebral infarction. Although the exact function of *MCP-1* in the development of cerebral infarction is not yet fully understood, a potential explanation might be that mutations in the *MCP-1* gene attract monocytes into the ischemic brain, thereby leading to cerebral infarction. A previous study has also demonstrated that the *MCP-1* – 2518A>G polymorphism may result in increased expression of MCP-1, as well as significantly increased MCP-1 serum levels that initiate the infiltration of leukocytes into the ischemic lesion, which also contribute to tissue injury in cerebral infarction (Losy and Zaremba, 2001). A subgroup analysis by ethnicity suggested that there were significant associations between the *MCP-1* – 2518A>G polymorphism and an increased

FIG. 6. Begger's funnel plot of publication biases on the relationships of *MCP-1* –2518A>G polymorphism and serum MCP-1 levels with the risk of cerebral infarction. Each point represents a separate study for the indicated association. Log [OR], natural logarithm of OR. Horizontal line, mean magnitude of the effect.

risk of cerebral infarction among Caucasian populations, but not among Asian populations, revealing that ethnic differences may be a source of heterogeneity. Further analysis found that a significant difference in the levels of serum MCP-1 was observed between cerebral infarction patients and healthy control subjects among Asian populations, but not among Caucasian populations, suggesting that serum MCP-1 might be closely related in the inflammatory process of this disease. However, these findings do not mean that there is a contradiction in the association of the *MCP-1* –2518A>G polymorphism and serum MCP-1 levels with the risk of cerebral infarction due to the lack sufficient statistical power resulting from relatively small sample sizes. Additionally, a reasonable explanation may be that mutations in the *MCP-1* gene may alter the stability of a large number of related cytokines, which may consequently be secreted into the serum in cerebral infarction patients; this in turn would increase the levels of serum MCP-1. Our findings are partially consistent with previous studies that suggested that the *MCP-1* –2518A>G polymorphism, as well as serum MCP-1 levels might contribute significantly to an individual's susceptibility to cerebral infarction and thus may be potentially useful

biomarkers in the clinical management and detection of cerebral infarction.

Although this is the first meta-analysis focusing on the associations between the *MCP-1* –2518A>G polymorphism and serum MCP-1 levels, and the risk of cerebral infarction, our study has some limitations. First, our results lacked sufficient statistical power to assess the correlations between the *MCP-1* –2518A>G polymorphism and serum levels of MCP-1 with their susceptibility to cerebral infarction due to relatively small sample sizes. Second, meta-analysis is a retrospective study that may lead to subject selection bias, thereby affecting the reliability of our results. Third, our meta-analysis failed to obtain the original data from the assessed studies, which limited further evaluation of the potential roles of the *MCP-1* –2518A>G polymorphism and serum MCP-1 levels in the development of cerebral infarction. Importantly, the inclusion criteria of cases and controls were not well defined in the included studies, which might also have influenced our results.

In conclusion, our meta-analysis suggests that the *MCP-1* –2518A>G polymorphism and serum MCP-1 levels may contribute to the risk of cerebral infarction. Thus, the *MCP-1* –2518A>G polymorphism and serum MCP-1 levels could be potential biomarkers in the early detection of cerebral infarction. However, due to the limitations mentioned above, further detailed studies are still required to confirm our findings.

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Disclosure Statement

No competing financial interests exist.

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