Gene Polymorphisms Increasing the Risk of Intracranial Aneurysms: Interleukin-6 -174G>C and -572G>C (Part II)

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Abstract. Introduction: The interleukin-6 (IL-6), a proinflammatory cytokine, supports the adaptive immune response and regulates inflammatory processes. The -174 G>C and -572 G>C promoter polymorphisms of the IL-6 gene take part in the pathogenesis of intracranial aneurysms (IAs) and influence the clinical presentation of subarachnoid hemorrhage. This meta-analysis purposes to evaluate whether and which IL-6 allelic variations are related to a risk of IAs formation. Methods: A PRISMA-based literature search was performed on the PubMed/Medline and Web of Science databases. The keywords used were “interleukin-6,” “IL-6,” “polymorphism,” “interleukin-6 genotype,” combined with “intracranial aneurysms” and “subarachnoid hemorrhage.” Only human case-control studies, with a study (IAs) and a control group, written in English, and published in the last 15 years were selected. A meta-analysis was performed, estimating odds ratios and 95% confidence intervals in fixed- or random-effects models, as applicable. Statistical analysis was conducted with RevMan 5.0 software. Results: 9 studies were eligible. No associations were found between -174 G>C polymorphisms and IAs susceptibility. Notable results were reported by the analysis of -572G>C polymorphisms. -572GG/GC/CC genotypes were strongly related to IAs occurrence with a statistical significance of $p=0.03$, $p=0.0009$, and $p=0.00001$, respectively. Conclusion: A higher incidence of -572G>C promoter polymorphisms were demonstrated in the IAs group, highlighting the pivotal role of inflammatory genes in the natural history of brain aneurysms. Additional studies are required considering the racial heterogeneity and the need to widen the population sample. (www.actabiomedica.it)

Key words: Allele Variations; Gene Polymorphisms; IL-6; Inflammatory Cytokines; Interleukin-6; Intracranial Aneurysm; Subarachnoid Hemorrhage.

Introduction

In their saccular type, intracranial aneurysms (IAs) turn out as focal bulges of the arterial wall. They have an overall incidence and prevalence of 4% and 2–5%, respectively (1-3). IAs are typified by specific histological features, including the loss of internal elastic lamina and destruction of tunica media (4). The sudden rupture of the thinned aneurysm layers causes subarachnoid hemorrhage (SAH), a life threatening cerebrovascular disease accounting for 30% of strokes and resulting in high morbidity and mortality (5-12).
Despite the precise mechanisms underlying the natural history of IAs being still unclear, the inflammatory cascade proved to be critical in the genesis, growth, and rupture of IAs (13-15). The local recruitment of inflammatory mediators, macrophages, cytokines, along with endothelial dysfunction and phenotypic switching of smooth muscle cells, leads to the weakening of the arterial wall (16-18).

Amid the pro-inflammatory cytokines recruited, the interleukin-6 (IL-6) has an active role in the boosting of the immune pathways, immunoregulation, and maintenance of inflammatory processes (19, 20). The human IL-6 gene was mapped in the short arm of chromosome 7 (21). It displays two biallelic polymorphisms at positions -174G/C and -572G/C in its promoter region, both due to the replacement of a sole nucleotide (GG/GC/CC) (22-24). IL-6 promoter polymorphisms were revealed to be potential risk factors for many vascular diseases, mostly abdominal aortic, coronary, and brain aneurysms (20, 25-42).

Given the limited pieces of evidence reported in the literature, the present meta-analysis sought to clarify the associations between IL-6 gene promoter polymorphisms, with single nucleotide substitutions, and the incidence of IAs.

Methods

Literature Search Strategy

A comprehensive online literature review was conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines.

The PubMed/Medline (https://pubmed.ncbi.nlm.nih.gov) and Web of Science (https://www.webofscience.com) electronic databases were used with the following keywords: “interleukin-6,” “IL-6,” “interleukin-6 polymorphism,” “IL-6 polymorphism,” “interleukin-6 genotype,” “IL-6 genotype”. The aforementioned terms were merged with further keywords as follows: “intracranial aneurysm,” “cerebral aneurysm”, and “subarachnoid hemorrhage.” Only articles written in English or translated, published in the last 15 years, were chosen and filtered according to the best match and relevance. Inclusion criteria were human case-control studies, available data on GG/GC/CC allele frequencies. Reviews, editorials, comments, case reports, letters to editor, and animal studies, were excluded. The Newcastle-Ottawa quality assessment scale (NOS) was employed to assess the quality of the selected articles (NOS ≥6 high quality).

Statistical Analysis

The meta-analysis was performed with the RevMan 5.0 software (Cochrane Informatics & Knowledge Management Department). Pooled odds ratios (ORs) and corresponding 95% confidence intervals (CIs) were assessed using the Mantel-Haenszel method for fixed effects and the Der Simonian-Laird method for the random ones. The heterogeneity rate was estimated by the Cochrane’s Q test and the consequent p and I2 (% of effect due to heterogeneity) values. p <0.05 and I2 >50% identify a high heterogeneity of the study samples. Fixed-effects models were applied if the results of the Q test were not significant. Otherwise, studies with significant heterogeneity were further analyzed through the random-effect model. Z-test for overall effect was performed in all cases and the p-value was set at < 0.05. ORs and CIs of each endpoint were showed as a Forest plot. The risk of publication bias was estimated by Begg’s rank correlation method and Egger’s regression asymmetry, and reported as a Funnel plot if needed.

Results

Literature Volume

The literature search returned a total of 141 articles. After duplicate removal, screening, and implementation of the exclusion criteria, a total of 37 studies were assessed for eligibility. Further refinements limited the search to 9 studies. Among them, articles on the association between IL-6 -174G>C and IL-6 -572G>C polymorphisms and IAs risk were 8 and 6, respectively. Figure 1 reports the PRISMA flow chart of the study (Figure 1).

All studies reported the genotypes of IL-6 polymorphisms, -174G>C and -572G>C, differentiating
the frequency of alleles in GG/CG/CC. The study design was prospective for 6 articles, and retrospective for the remaining. 4 studies took place in China, 1 in the United Kingdom, 1 in Italy, 1 in Poland, and 1 in Turkey. The NOS score was higher than 6 for all the samples.

Demographic and Genetic Data

A total of 6765 patients belonging to 9 studies were involved in the meta-analysis. The IAs groups consisted of 1912 cerebral aneurysms, whereas the control ones accounted for 4853 healthy patients. The average patients’ age was 45.5 and 48.3 years for the IAs and control groups, respectively. The mean percentage of the male was 43% and 51% in the study and control groups, respectively. Details of patients’ demographics, genetic data, and studies’ features are shown in Table 1.

Quantitative Synthesis and Heterogeneity Analysis

The associations between IL-6 -174G>C polymorphisms and risk of IAs were investigated
### Table 1. Overview of Data reported in the Literature about IL-6 Gene Polymorphisms and IAs

| Author, Year | Study Type | Country | Timeframe | N° of patients | IAs Group | Control Group | IAs Group (average y-o) | Control Group (average y-o) | IAs Group [N° of male (%)] | Control Group [N° of male (%)] | Polymorphism | Allele | IAs Group (N° of patients) | Control Group (N° of patients) | NOS |
|--------------|------------|---------|-----------|----------------|------------|---------------|-------------------------|-----------------------------|-------------------------------|-------------------------------|--------------|--------|--------------------------|-----------------------------|-----|
| Sun et al, 2008 (28) | ROS | China | 2005-2007 | 240 | 240 | 45.2 | 41.8 | 104 (43) | 116 (48) | -572G>C | GG | 59 | 9 |
| Zhang et al, 2011 (29) | POS | China | 2006-2008 | 182 | 182 | 36 | 33 | 103 (57) | 95 (52) | -572G>C | GG | 145 | 165 |
| Pera et al, 2012 (30) | POS | Poland | 2002-2009 | 276 | 581 | 50.5 | 56 | 120 (43) | 274 (47) | -174G>C | GG | 82 | 186 |
| Liu et al, 2012 (31) | ROS | China | 2012 | 220 | 220 | 47.4 | 45.6 | 95 (43) | 103 (47) | -572G>C | GG | 33 | 11 |
| Sathyan et al, 2015 (32) | ROS | India | 2014 | 220 | 250 | 51.2 | NA | 123 (56) | NA | -174G>C | GG | 144 | 153 |
| Bayri et al, 2015 (33) | POS | Turkey | 2015 | 120 | 120 | NA | NA | NA | NA | -174G>C | GG | 72 | 66 |
| Xu et al, 2021 (18) | POS | China | 2016-2020 | 384 | 384 | 57.1 | 66.5 | 117 (30) | 117 (30) | -572G>C | GG | 17 | 18 |

C: Cytosine; G: Guanine; IAs: Intracranial Aneurysms; N: Number; NA: Not Available; NOS: Newcastle-Ottawa quality assessment Scale; POS: Prospective Observational Study; ROS: Retrospective Observational Study
in 6 studies. Results of the analysis on -174GG, -174GC, and 174CC genotypes were OR = 1.13, 95% CI [0.95-1.35], p = 0.17; OR = 0.96, 95% CI [0.81-1.14], p = 0.65; OR = 0.77, 95% CI [0.59-1.00], p = 0.05; respectively. Albeit revealing a clear correlation, the pooled results of each -174 genotype’s examinations did not show differences. Regarding the heterogeneity, the I^2 value was less then 50% and p >0.05 for all the -174G>C analyses (Figures 2-4).

IL-6 -572G>C polymorphisms and their rela-

| Study or Subgroup | IAs Events | Total | Control Events | Total | Weight | M-H, Fixed, 95% CI | Odds ratio M-H, Fixed, 95% CI |
|-------------------|-----------|-------|----------------|-------|--------|-------------------|----------------------------|
| Morgan 2006       | 40        | 91    | 867            | 2720  | 13.6%  | 1.68 [1.10, 2.56] |
| Fontanella 2008   | 78        | 179   | 66             | 156   | 17.2%  | 1.05 [0.68, 1.63] |
| Pera 2012         | 82        | 276   | 186            | 581   | 36.4%  | 0.90 [0.66, 1.23] |
| Bayri 2015        | 72        | 120   | 66             | 120   | 11.4%  | 1.23 [0.74, 2.05] |
| Sathyen 2015      | 144       | 220   | 153            | 250   | 21.4%  | 1.20 [0.82, 1.75] |
| **Total (95% CI)**| **886**   |       | **3827**       |       | **100.0%** | **1.13 [0.95, 1.35]** |
| Total events:     | 416       |       | 1338           |       |        |                   |
| Heterogeneity:    | Chi^2 = 5.76, df = 4 (P = 0.22); I^2 = 31% |
| Test for overall effect: Z = 1.39 (P = 0.17) |

Figure 2. Forest plot for -174GG polymorphism

| Study or Subgroup | IAs Events | Total | Control Events | Total | Weight | M-H, Fixed, 95% CI | Odds ratio M-H, Fixed, 95% CI |
|-------------------|-----------|-------|----------------|-------|--------|-------------------|----------------------------|
| Morgan 2006       | 40        | 91    | 1358           | 2720  | 18.9%  | 0.79 [0.52, 1.20] |
| Fontanella 2008   | 86        | 179   | 71             | 156   | 15.2%  | 1.11 [0.72, 1.70] |
| Pera 2012         | 138       | 276   | 275            | 581   | 34.0%  | 1.11 [0.84, 1.48] |
| Bayri 2015        | 36        | 120   | 42             | 120   | 11.3%  | 0.80 [0.46, 1.37] |
| Sathyen 2015      | 63        | 220   | 80             | 250   | 20.5%  | 0.85 [0.57, 1.27] |
| **Total (95% CI)**| **886**   |       | **3827**       |       | **100.0%** | **0.96 [0.81, 1.14]** |
| Total events:     | 363       |       | 1826           |       |        |                   |
| Heterogeneity:    | Chi^2 = 3.11, df = 4 (P = 0.54); I^2 = 0% |
| Test for overall effect: Z = 0.45 (P = 0.65) |

Figure 3. Forest plot for -174GC polymorphism

| Study or Subgroup | Experimental Events | Total | Control Events | Total | Weight | M-H, Fixed, 95% CI | Odds ratio M-H, Fixed, 95% CI |
|-------------------|---------------------|-------|----------------|-------|--------|-------------------|----------------------------|
| Morgan 2006       | 6                   | 91    | 495            | 2720  | 22.9%  | 0.32 [0.14, 0.73] |
| Fontanella 2008   | 15                  | 179   | 19             | 156   | 14.2%  | 0.66 [0.32, 1.35] |
| Pera 2012         | 56                  | 276   | 120            | 581   | 47.1%  | 0.98 [0.69, 1.40] |
| Bayri 2015        | 12                  | 120   | 12             | 120   | 8.3%   | 1.00 [0.43, 2.32] |
| Sathyen 2015      | 8                   | 220   | 11             | 250   | 7.6%   | 0.82 [0.32, 2.08] |
| **Total (95% CI)**| **886**             |       | **3827**       |       | **100.0%** | **0.77 [0.59, 1.00]** |
| Total events:     | 97                  |       | 657            |       |        |                   |
| Heterogeneity:    | Chi^2 = 6.64, df = 4 (P = 0.16); I^2 = 40% |
| Test for overall effect: Z = 1.94 (P = 0.05) |

Figure 4. Forest plot for -174CC polymorphism
tion to IAs was investigated in 8 case-control studies. About the -572GG genotype, the OR was 1.25, 95% CI [1.03 -1.51], and p=0.03. The analyses of -572GC and -572CC polymorphisms showed significant differences. Results were as follows: -572GC: OR=1.30, 95% CI [1.11-1.51], p= 0.0009; OR= 0.67, 95% CI [0.57-0.80], p= 0.00001 (Figures 5-7).

In the quantitative synthesis of the -572G>C genotype, the I² was found greater than 50% and the pq was <0.05. Consequently, the random-effect model was also applied, and the results were as follows: -572GG: OR= 1.33, 95% CI [0.73-2.42], p=0.34; -572GC: OR= 1.36, 95% CI [0.89-2.06], p= 0.15; -572CC: OR= 1.06, 95% CI [0.50-2.25], p= 0.88.

**Publication Bias**

Begg’s rank and Egger’s methods revealed no publication bias for the -174G>C genotype analysis (Figure 8).

Instead, increased risks of bias were found for the -572G>C polymorphism (Figure 9).

**Discussion**

This meta-analysis aimed to explore the correlation between genotype variability of IL-6 -174G>C and -572G>C and susceptibility to IAs.

In the era of translational medicine, advances in
molecular biotechnologies and haplotype-based genome-wide linkage analysis gave tremendous advantages in the identification of the inflammatory and genetic mechanisms underlying the pathogenesis of many neurovascular and neuro-oncological diseases (43-64).

The natural history of brain aneurysms is controversial, strongly influenced by individual immunogenetic stimuli. The primum movens was identified in the wall shear stress, which promotes endothelial dysfunction, vascular remodeling, and immune activation (13, 65-67). The recruited inflammatory cytokines and the endothelial oxidative stress progressively damage vessels, resulting in the thinning and bulging of the arterial wall (68-70). Genetic mutations of proinflammatory interleukin and the consequent imbalance in immunological response may affect the onset and progression of IAs (14, 71). IL-6 is secreted by macrophages, endothelial and lymphoid cells, and takes part in the adaptive immunity and tissue repair processes (72, 73).

Current pieces of evidence strongly support the correlation between the IL-6 -174G>C and -572G>C polymorphisms and SAH (74, 75). In 2006, Morgan et al. conducted the first population-based case-control study to test the relation of IL-6 genotypes with the intracranial aneurysmal disease, describing a reasonable association of the -572G>C polymorphism in Caucasian people (28). Studies on the Chinese population all reported a higher risk of IAs for patients harboring -572G>C genotype. The G allele variation was

Figure 6. Forest plot for -572GC polymorphism. (A) Fixed and (B) random model.
the most represented (30, 31, 33). Conversely, conflicting results were found in European populations. Neither Fontanella and colleagues, in 2008, nor Pera et al., in 2012, found any correlation between the IL-6 gene and IAs (29, 32). The most recent study by Xu et al. in 2021 demonstrated a close relation between proinflammatory cytokines polymorphisms and the genetic risk factors of IAs in Chinese people (20).

In accordance with the literature, our meta-analysis failed to find any connection between the -174G>C genotype and IAs. Moreover, we reported a statistical difference for -572GG/GC/CC genotypes distribution in the fixed-effects model (p=0.03, p= 0.0009; p= 0.00001), although limited by the high heterogeneity between the groups (I²= 88%, I²= 83%; I²= 92%). By applying the random- model, the associations were no longer detected.

Our results highlight the importance of ethnic-specific differences in genetic polymorphisms expression and the racial influence, as reported by European vs Chinese studies, in IAs pathogenesis.

The increasing allele frequency of -572G>C raises the serum concentration of IL-6. It upregulates the inflammatory cascade, inhibits collagen production in the endothelial cells, and causes progressive damage fragility of the arterial wall (31). IL-6 modulates lipid metabolism, increases the risk of intracranial arteriosclerosis, and has a direct cytotoxic effect on oligodendrocytes (76-80). Furthermore, it acts as a strong vascular vasoconstrictor (81). The high level of IL-6

Figure 7. Forest plot for -572CC polymorphism. (A) Fixed and (B) random model
increases the incidence of vasospasm after SAH, worse cerebral ischemia, and indirectly affects the patient’s outcome (81, 82).

Limitations of the Study

The present study has some limitations. First, the selection bias cannot be avoided because of the relatively limited sample size and the high heterogeneity across ethnicities. Second, we did not include the acquired risk factors like smoking and hypertension. Third, the retrospective nature of studies included in the meta-analysis was a further limitation to be considered.

Conclusion

Local recruitment of proinflammatory IL-6 at the arterial wall primes the endothelial dysfunction leading to the vessel damage and genesis of IAs.

IL-6 polymorphisms result in the upregulation of inflammatory pathways, thus affecting the natural history of IAs.

The present study reported a direct connection between IL-6 -572 GG/GC/CC polymorphisms and IAs, while no differences in -174 G>C polymorphisms were found.

Further genetic studies across different ethnicities are needed to confirm the association between IL6 gene polymorphisms and the risk of IAs.

Conflict of Interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article

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