Cytokines Interleukin 4 (IL-4) and Interleukin 10 (IL-10) Gene Polymorphisms as Potential Host Susceptibility Factors in Virus-Induced Encephalitis

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Background: This study aimed to analyze and explore the relationship between the cytokines IL-4 and IL-10 in relation to gene polymorphism and their respective effects on the susceptibility to virus-induced encephalitis.

Material/Methods: From January 2012 to June 2013, 112 patients with virus-induced encephalitis (the case group and 109 healthy individuals (the control group) were recruited for the purposes of this study. The functional variations that IL-4 and IL-10 genes exhibit were detected through the use of a function analysis and selection tool for single-nucleotide polymorphisms (FASTSNP). The genotypes of IL-4 were rs2227283 and IL-4 rs2227288, and the genotypes of IL-10 were rs1800871 and IL-10 rs1800872. These genotypes were respectively assessed using direct sequencing.

Results: IL-4 rs2227283 and IL-10 rs1800871 have no correlation in with risk of virus-induced encephalitis (both \[P > 0.05\]). GA and AA genotypes were related to IL-4 rs2227288 and GT, while TT and GT + TT genotypes were related to IL-10 rs1800872. These were highlighted as being risk factors in virus-induced encephalitis (all \[P < 0.05\]). However, the duration of fever, white blood cell (WBC) count, C-reactive protein (CRP), neutrophils, and lymphocytes and monocytes of virus-induced encephalitis patients with IL-4 rs2227288 and IL-10 rs1800872 all displayed significant differences (all \[P < 0.05\]). Frequencies of GAGT and CAGT haplotypes were evaluated and deemed to be of statistical significance and subsequently were highlighted as being risk factors in virus-induced encephalitis (all \[P < 0.05\]).

Conclusions: IL-4 rs2227288 and IL-10 rs1800872 may contribute to an increased risk for virus-induced encephalitis. Through use of direct sequencing, we showed that genotypes of IL-4 rs2227288 and IL-10 rs1800872 may have particular host susceptibility to virus-induced encephalitis.

MeSH Keywords: Encephalitis, Arbovirus • Microbial Sensitivity Tests • Transcription Factor TFIIIA

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Background

Virus-induced encephalitis is a life-threatening disorder characterized by inflammation of brain tissue. The inflammation associated with brain parenchyma is linked to and a consequence of viral infections [1–3]. Virus-induced encephalitis is associated with misdiagnosis and delays in recognition, which may have devastating consequences for patients [4]. Additionally, the efficacy of therapies is highly time-dependent due to high morbidity and mortality rates [5,6]. Enterovirus is the main etiological agents of virus-induced encephalitis, followed by mumps, rubella, and Japanese encephalitis virus. However, the lack of unified guidelines in the assessment and management of the illness is a serious limitation [2,7]. The most common symptoms and neurological signs of virus-induced encephalitis are fever, reduced consciousness, seizures, and focal neurological deficits [8–10]. Patients with virus-induced encephalitis suffer from various degrees of renal damage [11]. Additionally, virus-induced encephalitis may cause serious brain damage and bleeding; therefore, prompt diagnosis and early treatment are crucial to prevent the disease from developing, and delayed treatment often results in poor prognosis [1]. In patients who are able to survive the virus-induced encephalitis, impairments of neurologic defect and cognitive, emotional, and behavioral function impairments are common [12]. However, chronic encephalitis has been reported as being uncommon, possibly owing to its viral origins, which may result in the disease being exhibited in patients that have compromised immunity, as well as in healthy individuals [13]. Thus, difficulties are faced in correctly diagnosing patients and subsequently providing prompt therapies for individuals with virus-induced encephalitis [14]. Consequently, it is important to further explore the details and mechanisms involved. At present, increasing numbers of scientific and clinical studies are being initiated to further understand virus-induced encephalitis.

Interleukin 4 (IL-4) and interleukin 10 (IL-10), are 2 cytokines that have been found to have strong links to encephalitis [15–17]. It has been suggested that IL-4 is crucial to the induction of the naive helper T (Th0) cells differentiating to type 2 helper T (Th2) cells [18,19]. IL-4 is known to have 2 different receptor complexes: the IL-4Rx chain and the γc chain [20]. IL-4 has a role in maintaining physiological balance and repairing tissues [21]. Moreover, IL-4 has exhibited in anti-inflammatory functions. IL-4 derived by activated CD4+ T cells can promote allergic responses [20,22,23]. Additionally, IL-10 is a cytokine produced by T cells, B cells, and macrophages, exhibiting a role in anti-inflammation and immunosuppression [24–26]. Virus-induced encephalitis is reported to respond to IL-10 [27]. IL-4 and IL-10 gene polymorphisms have been widely investigated in inflammatory diseases, such as asthma, chronic polyarthritis, rhinovirus bronchiolitis, and type 2 diabetes mellitus (T2DM) [28–31]. Patients previously diagnosed with virus-induced encephalitis formed the basis of the experimental exploration of this study. The IL-4 and IL-10 gene polymorphisms and their correlation to virus-induced encephalitis susceptibility, through direct sequencing, were analyzed during the study.

Material and Methods

Ethic statement

The Ethics Committee of Taizhou Municipal Hospital approved the study. All subjects were given official consent documents that were subsequently agreed upon and signed by all.

Study subjects

Between January 2012 and June 2013, 112 patients (63 males and 49 females) with a mean age of 39.89±15.98 years ranging from 14 to 78 years, participated in the study. All subjects had been previously diagnosed with virus-induced encephalitis and were evaluated during the study as a case group. The control group consisted of 109 healthy individuals. The inclusion criteria were as follows: (1) Patients previously diagnosed with symptoms such as fever of varying degrees, disorders of consciousness, seizure, meningeal irritation sign, pyramidal sign, and intracranial hypertension detected by computed tomography (CT) head scan, electroencephalogram (EEG), and cerebrospinal fluid (CSF), which corresponded to the seventh edition of the diagnostic criteria regarding virus-induced encephalitis [32]; (2) Positive results were detected using reverse transcription-polymerase chain reaction (RT-PCR) of encephalitis virus nucleic acid in the stool of subjects as well as cerebrospinal fluid (CSF) samples. The exclusion criteria were as follows: (1) patients who had experienced mumps, meningo-encephalitis, epidemic encephalitis B, or herpes simplex encephalitis; and (2) Patients that exhibited abnormalities detected by brain CT or magnetic resonance imaging (MRI)

Blood sampling and DNA extraction

Peripheral venous blood samples (3 ml) were collected from healthy individuals as well as virus-induced encephalitis patients in the acute phase (5-day duration) with empty stomachs. The general conditions, signs, symptoms, and other accessory examinations of virus-induced encephalitis patients were recorded within 13 to 20 days from clinical observation to admission. The blood samples (3 ml) were placed in tubes with ethylenediamine tetraacetic acid (EDTA)-K2 and shaken. DNA was extracted using the improved potassium iodide method.

Single-nucleotide polymorphism (SNP) selection and sequencing

Using HapMap database, the genomic data was downloaded. The following methods were used: (1) literature review; (2) Tag
SNP selection; and (3) functional variations in IL-4 and IL-10 genes detected by function analysis and selection tool for single-nucleotide polymorphisms (FASTSNP). After selection, IL-4 rs2243283/rs2243288 and IL-10 rs1800871/rs1800872 were eligible for further study.

SNPs detection

The PCR primers were designed by Primer Premier 5.0 and synthesized by Shanghai Sangon BioTech Co., Ltd. (Shanghai, China). The forward and reverse primers of IL-4 and IL-10 gene polymorphisms are shown in Table 1 and IL-4 rs2243283/rs2243288 and IL-10 rs1800871/rs1800872 shared a pair of primers. The total volume of PCR reaction system was 50 μl, including 0.5 μl of DNA template, 5 μl of forward primer and reverse primer, respectively, 25 μl of PCR-pfu mix enzyme, and 14.5 μl of water. After DNA was dissolved, 5-μl samples (concentration >0.1 μg/μl) were assessed using an ultraviolet spectrophotometer on the basis of the ratio (260/280) of the range between 1.8 to 2.1. The PCR reaction conditions were as follows: pre-denaturation at 94°C for 45 s, annealing at 60°C for 45 s, extension at 72°C for 45 s, 39 cycles, and extension at 72°C for 5 min by proper adjustment of annealing temperature according to primer synthesis report. A total of 1.5 μl of PCR product was detected with 1.0% agarose gel using electrophoresis. The gel was transferred and photographs were taken with an ultraviolet analyzer for observational purposes. Selected PCR product was sequenced in Beijing ZhongKe Xilin Biotechnology Co., Ltd. to determine the genotypes of IL-4 rs2243283, IL-4 rs2243288, IL-10 rs1800871, and IL-10 rs1800872.

Table 1. Primer sequences for IL-4 rs2243283/rs2243288 and IL-10 rs1800871/rs1800872.

| Gene | SNP   | Primer sequence         |
|------|-------|-------------------------|
| IL-4 | rs2243283 | Forward 5’-GGCTGAAAGGGGAAACGAT-3’ |
|      |        | Reverse 5’-CCCTGCGCGCAGCTTTTCAT-3’ |
|      | rs2243288 | Forward 5’-CAGTCATGCAAGGGGACATGTA-3’ |
|      |        | Reverse 5’-GGCCAGCAGGGTTTGCTATT-3’ |
| IL-10| rs1800871 | Forward 5’-TCACAAGCAGCCTTCCATT-3’ |
|      | rs1800872 | Reverse 5’-CCAATTCTCGAGTGGCAGTG-3’ |

Table 2. Baseline characteristics of subjects between the case and control groups.

|                          | Case group        | Control group       | t/χ²   | P   |
|--------------------------|-------------------|---------------------|--------|-----|
| Age                      | 39.89±15.98       | 40.70±14.52         | 0.059  | 0.953|
| Gender                   |                   |                     |        |     |
| Male                     | 63                | 65                  | 0.259  | 0.611|
| Female                   | 49                | 44                  |        |     |
| WBC count (×10⁹/L)       | 6.95±0.88         | 4.55±0.83           | 20.845 | <0.001|
| CRP (10⁹/L)              | 9.12±0.49         | 5.05±0.21           | 79.870 | <0.001|
| Neutrophils (×10⁹)       | 9.38±2.22         | 3.88±1.97           | 19.462 | <0.001|
| Lymphocyte (×10⁹)        | 5.49±1.04         | 2.37±0.62           | 26.997 | <0.001|
| Monocyte (×10⁹)          | 3.70±0.33         | 0.58±0.15           | 90.064 | <0.001|

WBC – white blood cell; CRP – C-reactive protein.

SNPs detection

SPSS 19.0 software was used for data analysis. The Hardy-Weinberg equilibrium (HWE) detection was performed for genotype distribution analysis. Measurement data are shown as mean ± standard deviation and compared by t test and categorical data are presented as percentage and rate and were examined by the χ² test or Fisher’s exact test. The odds ratio and 95% confidence intervals were estimated using nonconditional logistic regression analysis. Haplotype analysis of IL-4 and IL-10 genes was performed using Shesis software.

Statistical methods

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**Results**

**Baseline characteristics of subjects between the case and control groups**

There was no significant difference in age and sex of subjects between the case and control groups (P > 0.05). However, remarkable differences were found in the number of white blood cells (WBC), C-reactive protein (CRP), neutrophils, lymphocytes, and monocytes between the 2 groups (all P < 0.05, Table 2).

**HWE detection in the case and control groups**

Genotype distributions of IL-4 rs2243283/rs2243288 and IL-10 rs1800871/rs1800872 were tested by HWE method. The observed and expected values of each genotype in the case and control groups were compared and chi-square analysis demonstrated no statistically significant difference (all P > 0.05) in the distribution of observed number and the expected number of each genotype in the 2 groups. This allowed for the achievement of genetic balance with group representation (Table 3).

**Correlation of IL-4 and IL-10 genes with the clinical features of patients in the case group**

The sex and age of virus-induced encephalitis patients with different genotypes in IL-4 rs2227283 and IL-10 rs1800871 gene polymorphisms were not associated with the risk of virus-induced encephalitis (both P > 0.05); however, GA, AA, and GA + AA genotypes in IL-4 rs2227288, and GT, TT, and GT + TT genotypes in IL-10 rs1800872, A allele in IL-4 rs2227288, and T allele in IL-10 rs1800872 were risk factors for virus-induced encephalitis (all P < 0.05).

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Table 3. The observed and expected values of the frequencies of IL-4 rs2243283/rs2243288 and IL-10 rs1800871/rs1800872 in the case and control groups.

| SNP         | Genotype | Case group E | O | χ²  | P  | Control group E | O | χ²  | P  |
|-------------|----------|--------------|---|-----|----|-----------------|---|-----|----|
| IL-4 rs2243283 | GG       | 34           | 31 | 1.613 | 0.204 | 27             | 27 | 0.033 | 0.856 | 2.248 | 0.134 |
|             | CC       | 34           | 31 | 1.613 | 0.204 | 27             | 27 | 0.033 | 0.856 | 2.248 | 0.134 |
|             | GG       | 56           | 62 | 3.033 | 0.082 | 52             | 61 | 0.033 | 0.856 | 2.248 | 0.134 |
| IL-4 rs2243288 | GG       | 27           | 27 | 0.033 | 0.856 | 27             | 27 | 0.033 | 0.856 | 2.248 | 0.134 |
|             | GA       | 56           | 55 | 0.033 | 0.856 | 48             | 41 | 0.033 | 0.856 | 2.248 | 0.134 |
|             | AA       | 29           | 30 | 0.033 | 0.856 | 11             | 15 | 0.033 | 0.856 | 2.248 | 0.134 |
| IL-10 rs1800871 | GG       | 20           | 18 | 0.447 | 0.504 | 24             | 19 | 0.447 | 0.504 | 3.499 | 0.061 |
|             | GA       | 54           | 58 | 0.447 | 0.504 | 54             | 64 | 0.447 | 0.504 | 3.499 | 0.061 |
|             | AA       | 38           | 36 | 0.447 | 0.504 | 31             | 26 | 0.447 | 0.504 | 3.499 | 0.061 |
| IL-10 rs1800872 | GG       | 8            | 7  | 0.557 | 0.456 | 15             | 19 | 2.133 | 1.144 |
|             | GT       | 45           | 48 | 0.557 | 0.456 | 51             | 44 | 2.133 | 1.144 |
|             | TT       | 59           | 57 | 0.557 | 0.456 | 43             | 46 | 2.133 | 1.144 |

SNP – single nucleotide polymorphism; E – expected values; O – observed values.

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Haplotype analysis in the case and control groups

Haplotypes of IL-4 rs2227283/rs2227288 and IL-10 rs1800871/rs1800872 are shown in Table 6, which were analyzed by using the Shesis software (haplotypes with the frequency under 0.05 in these 2 groups were excluded). The results revealed that the frequencies of haplotypes (CAAT, GAGT, GAAT, CAGT, and CGGT) showed statistical significance (all $P < 0.05$) as the risk factors for virus-induced encephalitis, while the frequencies of several other haplotypes (CGAG, CGGG, GGAG, GGGT, CGAT, and CGAG) showed no significant differences between the 2 groups (all $P > 0.05$).

Discussion

During the evaluation of the correlation between encephalitis and other viral infections at similar time points, impairments of the central nervous system and associated inflammation were observed (CNS).

When virus-induced encephalitis was correlated with viral infections, the central nervous system (CNS) also shows associated impairment and inflammation [3,33,34]. Virus-induced encephalitis affected approximately 7.5 people out of every 100 000, with considerable morbidity and mortality rates and displaying an increased risk for development of seizures in approximately 22% of patients [35]. This being said it was of considerable importance that the mechanisms in which

Table 4. Distributions of genotype and allele frequencies of IL-4 rs2243283/rs2243288 and IL-10 rs1800871/rs1800872 in the case and control groups.

| SNP         | Genotype | Case group (n=112) | Control group (n=109) | $\chi^2$ | OR (95%CI) | P   |
|-------------|----------|--------------------|-----------------------|----------|------------|-----|
| IL-4 rs2243283 | CC       | 31 (27.68)         | 35 (32.11)            | Ref.     |            |     |
|             | CG       | 62 (55.36)         | 61 (55.96)            | 0.203    | 1.148 (0.630~2.089) | 0.652 |
|             | GG       | 19 (16.96)         | 13 (11.93)            | 1.327    | 1.650 (0.702~3.882) | 0.249 |
|             | CG + GG  | 81 (72.32)         | 74 (67.89)            | 0.518    | 1.236 (0.693~2.201) | 0.472 |
|             | C        | 124 (55.36)        | 131 (60.09)           | Ref.     |            |     |
|             | G        | 100 (44.64)        | 87 (39.91)            | 1.015    | 1.214 (0.832~1.772) | 0.314 |
| IL-4 rs2243288 | GA       | 55 (49.11)         | 41 (37.62)            | 9.719    | 2.633 (1.423~4.872) | 0.002 |
|             | AA       | 30 (26.79)         | 15 (13.76)            | 12.579   | 3.926 (1.810~8.514) | 0.001 |
|             | GA + AA  | 85 (75.89)         | 56 (51.38)            | 14.376   | 2.980 (1.679~5.286) | < 0.001 |
|             | G        | 109 (48.66)        | 147 (67.43)           | Ref.     |            |     |
|             | A        | 115 (51.34)        | 71 (32.57)            | 15.971   | 2.184 (1.485~3.213) | < 0.001 |
| IL-10 rs1800871 | GG       | 18 (16.07)         | 19 (17.43)            | Ref.     |            |     |
|             | GA       | 58 (51.93)         | 64 (58.72)            | 0.014    | 0.957 (0.458~1.998) | 0.906 |
|             | AA       | 36 (32.61)         | 26 (23.85)            | 0.829    | 1.462 (0.645~3.314) | 0.363 |
|             | GA + AA  | 94 (83.93)         | 90 (82.57)            | 0.073    | 1.103 (0.543~2.235) | 0.787 |
|             | G        | 94 (41.96)         | 102 (46.79)           | Ref.     |            |     |
|             | A        | 130 (58.04)        | 116 (53.21)           | 1.042    | 1.216 (0.835~1.771) | 0.307 |
| IL-10 rs1800872 | GG       | 7 (6.25)           | 19 (17.43)            | Ref.     | 1 (Ref)    |     |
|             | GT       | 48 (42.86)         | 44 (40.37)            | 5.194    | 2.961 (1.135~7.722) | 0.023 |
|             | TT       | 57 (50.89)         | 46 (42.20)            | 6.706    | 3.363 (1.301~8.696) | 0.010 |
|             | GT + TT  | 105 (93.75)        | 90 (82.57)            | 6.788    | 3.202 (1.287~7.969) | 0.010 |
|             | G        | 62 (27.68)         | 82 (37.61)            | Ref.     | 1 (Ref)    |     |
|             | T        | 162 (72.32)        | 136 (62.39)           | 4.966    | 1.575 (1.055~2.353) | 0.026 |

SNP – single nucleotide polymorphism; OR – odd ratio; CI – confidence interval; Ref. – reference.
### Table 5. Comparison of IL-4 and IL-10 genes with the clinical features in the case group.

| SNP – single nucleotide polymorphism; CRP – C-reactive protein; WBC – white blood cell. |
|---|---|---|---|---|---|---|---|---|
| **Gender** | **Age** | **Duration of fever** | **CRP (10^9/L)** | **WBC count (r/10^6·L^{-1})** | **Neutrophils** | **Lymphocyte** | **Monocyte** |
| **IL-4 rs2243283** | | | | | | | |
| CG | 18 | 13 | 41.10±17.09 | 2.57±0.41 | 9.03±0.50 | 6.80±0.93 | 8.95±2.14 | 5.35±1.03 | 3.64±0.32 |
| CC | 33 | 29 | 38.39±15.67 | 2.68±0.43 | 9.18±0.49 | 7.04±0.87 | 9.65±2.29 | 5.59±1.07 | 3.74±0.35 |
| GG | 12 | 7 | 42.84±15.38 | 2.59±0.38 | 9.06±0.46 | 6.87±0.81 | 9.21±2.07 | 5.40±0.97 | 3.67±0.31 |
| **IL-10 rs1800871** | | | | | | | |
| CG | 16 | 13 | 37.37±12.64 | 2.12±0.26 | 8.51±0.25 | 5.91±0.67 | 6.52±1.14 | 4.12±0.58 | 3.29±0.12 |
| GA | 32 | 23 | 41.78±15.94 | 2.61±0.13* | 9.09±0.20* | 6.88±0.23* | 9.28±0.73* | 5.36±0.36* | 3.67±0.3 |
| AA | 17 | 13 | 38.70±18.63 | 3.14±0.26* | 9.71±0.56* | 7.99±1.07* | 12.14±1.07* | 6.69±0.58* | 4.14±0.16* |
| **IL-10 rs1800872** | | | | | | | |
| GG | 9 | 9 | 42.11±16.33 | 2.74±0.33 | 9.24±0.41 | 7.20±0.67 | 10.02±1.91 | 5.72±0.79 | 3.79±0.30 |
| GA | 33 | 27 | 38.21±16.05 | 2.68±0.45 | 9.17±0.52 | 7.05±0.92 | 9.64±2.33 | 5.63±1.09 | 3.75±0.35 |
| AA | 21 | 15 | 41.5±15.84 | 2.51±0.39 | 9.07±0.69 | 6.86±0.78 | 9.17±2.04 | 5.38±0.92 | 3.67±0.29 |
| **IL-10 rs1800872** | | | | | | | |
| GG | 4 | 3 | 38.47±17.24 | 1.75±0.20 | 8.15±0.15 | 4.97±0.62 | 4.97±1.03 | 3.30±0.45 | 3.13±0.07 |
| GT | 32 | 16 | 41.21±15.51 | 2.40±0.15* | 8.80±0.19* | 6.51±0.28* | 8.03±0.96* | 4.87±0.46* | 3.47±0.13* |
| TT | 27 | 30 | 39.09±16.42 | 2.94±0.29* | 9.50±0.30* | 7.56±0.62 | 11.06±1.40* | 6.28±0.61* | 3.97±0.23* |

### Table 6. Haplotype analysis of rs2243283, rs2243288, rs1800871 and rs1800872 in the case and control groups.

| Haplotype | Case group (n=112) | Control group (n=109) | OR | 95% CI |
|---|---|---|---|---|
| CG | 16 (0.149) | 8 (0.071) | 0.031 | 1.997 1.056~3.777 |
| GA | 12 (0.100) | 11 (0.102) | 0.269 | 0.713 0.390~1.302 |
| GG | 6 (0.051) | 1 (0.014) | 0.049 | 3.409 0.933~12.462 |
| GT | 32 (0.283) | 16 (0.143) | <0.001 | 0.115 0.044~0.305 |
| TT | 27 (0.243) | 13 (0.119) | 0.025 | 2.350 0.905~6.469 |

OR – odd ratio; CI – confidence interval.
Conclusions

In conclusion, IL-4 rs22272788 and IL-10 rs1800872 may lead to increased risk in relation to virus-induced encephalitis. This being said, the sample size of this study was relatively small and the range of research should be extended for future research in this particular area. It remains unknown in our study whether IL-4 rs22272788 and IL-10 rs1800872 gene polymorphisms affect the levels of IL-4 and IL-10 and subsequently participate in the pathogenesis of encephalopathy. Further prospective studies should be performed to provide stronger evidence of the underlying mechanisms of IL-4 rs22272788 and IL-10 rs1800872 gene polymorphisms in virus-induced encephalitis.

Conflicts of interest

None.

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