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Cytokines and chemokines involved in HLA-B27-positive ankylosing spondylitis-associated acute anterior uveitis

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Purpose: Acute anterior uveitis (AAU) is the most common extra-articular symptom of ankylosing spondylitis (AS). This study aims to reveal the cytokines and chemokines involved in the immunopathogenesis of human leucocyte antigen (HLA)-B27$^+$ AS-associated AAU.

Methods: Twenty-one HLA-B27$^+$ AS-associated AAU patients and 21 healthy controls (HCs) were recruited for this study. Serum cytokine concentrations in all 42 subjects were determined by the Meso Scale Discovery (MSD) electrochemiluminescence method. In each sample, 34 cytokines, 10 chemokines, eight angiogenesis mediators, and four vascular injury mediators were measured. The differences in cytokine and chemokine concentrations were compared between the two groups.

Results: Concentrations of serum IL-3, TNF-α, IL-6, IL-17D, IL-22, IP10/CXCL10, MIP-3α/CCL20, sFlt-1/VEGFR-1, CRP, and MCP-4/CCL13 were significantly higher in patients with HL-B27$^+$ AS-associated AAU than in HCs ($p < 0.05$). In contrast, concentrations of serum IL-4, IL-8, MIP-1α/CCL3, Eotaxin-3/CCL26, PlGF, VEGF-C, and VEGF-D were significantly lower in patients with HL-B27$^+$ AS-associated AAU than in HCs ($p < 0.05$).

Conclusions: Significant differences were detected in the levels of several cytokines and chemokines in the serum of HLA-B27$^+$ AS-associated AAU compared with HCs. Some novel differential cytokines and chemokines that have not been reported in other kinds of uveitis were also identified. These results reveal the underlying pathogenesis of HLA-B27$^+$ AS-associated AAU and could potentially aid in clinical diagnosis.

Uveitis is a group of vision-threatening intraocular inflammatory entities with distinct etiologies and pathogenic mechanisms [1]. Related systemic diseases include rheumatic diseases, autoimmune diseases, masque syndromes, or systemic infections that are causally associated with uveitis, such as Vogt-Koyanagi Harada (VKH), juvenile idiopathic arthritis (JIA), Behcet's disease (BD), and syphilis [2].

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Acute anterior uveitis (AAU) is the most common form of uveitis worldwide. AAU was initially identified in 1973 as associated with the major histocompatibility complex type I allele, human leucocyte antigen (HLA)-B27 [3]. Approximately 30%–50% of AAU cases are associated with positive HLA-B27(HLA-B27$^+$) [4,5]. HLA-B27$^+$AAU is more frequent in HLA-B27$^+$ subjects in Western countries than in Africa or Japan [6]. Several studies have proven the significant frequency of systemic disease in AAU patients, most commonly seronegative spondyloarthropathies (SpA), such as ankylosing spondylitis (AS) and reactive arthritis [7-9]. AS is considered the major systemic disease presentation in HL-B27$^+$ AAU, and AS can be diagnosed in about 55%–90% of HL-B27$^+$ AAU cases [10,11].

Despite the high occurrence of AS in AAU, the specific pathogenesis of HL-B27$^+$ AS-associated AAU remains unknown. HL-B27$^+$ AS-associated AAU is recognized as a chronic inflammatory disease. It is well known that cytokines and chemokines are essential for the coordination and maintenance of inflammatory processes. Moreover, previous studies have shown that the levels of certain cytokines and chemokines change in the serum, aqueous, and vitreous humors of the eyes with various types of general uveitis, particularly those associated with VKH and BD. However, to the best of our knowledge, only one previous study has reported the levels of Vit D, LL-37, and IL-8 in the serum of patients with AS-associated AAU. The results showed significantly increased levels of IL-8 and decreased levels of Vit D in patients with AS-associated AAU [12].

An improved understanding of the cytokines and chemokine profiles may provide new insights into the immunopathogenesis and effective treatment of HL-B27$^+$ AS-associated AAU. Therefore, this study aimed to expand the cytokine and chemokine profiles in HL-B27$^+$ AS-associated AAU and better understand which cytokines and chemokines are involved in the pathogenesis of HL-B27$^+$ AS-associated AAU.

METHODS

Study population: The present study was approved by the Institutional Review Boards of the Sichuan Provincial People's Hospital. Twenty-one patients with HL-B27$^+$ AS-associated AAU and 21 healthy controls (HCs) observed from April 2018 to July 2022 were included in this study. All participants had written informed consent in accordance with the Helsinki Declaration of ethical conduct before the analysis. None of the HL-B27$^+$ AS-associated AAU patients had been receiving systemic immunosuppressive medication, biologics, or hormones for at least a week before the blood draws. Patients who had malignancies or other autoimmune diseases were not included in this study. Meanwhile, the exclusion criteria for the HCs were patients with HL-B27$^+$ AS-associated AAU and a history of any other autoimmune disease. Clinical and demographic characteristics, including age, gender, HLA-B27 positivity, disease duration, leukocytes, neutrophils, lymphocytes, monocytes, eosinophils, and basophils, were recorded.

Sample collection and measurement: The patients with HL-B27$^+$ AS-associated AAU and HCs had venous blood drawn from them and collected in ethylene diamine tetraacetic acid (EDTA)tubes. After storing at room temperature for 2 h and centrifuging for 10 min at 1728 ×g, the serum was separated. According to the manufacturer's recommendations, cytokine and chemokine secretion was measured using a V-PLEX Human Cytokine 30-Plex Kit with measurements in a Meso QuickPlex SQ120 (Meso Scale Discovery [MSD], Rockville, MD). Briefly, 250 uL of plasma (10–50 ul for each of the five plates) was diluted in a buffer according to instructions, and 25 ul was then added to the base of duplicate wells. After two hours of incubation and three rounds of washing, the plates underwent another two hours of incubation with a solution containing detecting antibodies. Prior to applying the read buffer and reading the plate in the MSD instrument, the plate was cleaned three more times. To give a quantitative measurement of the analytes in the sample, the equipment monitors the intensity of the emitted light. Overall, 54 indicators were simultaneously quantitatively assessed. This made it possible to accurately and precisely identify cytokines and chemokines simultaneously.

The samples were analyzed using proinflammatory panel 1 (human) kits (Interferon-gamma [IFN-γ], interleukin-1β [IL-1β], IL-2, IL-4, IL-6, IL-8, IL-10, IL-12p70, IL-13, and tumor necrosis factor-alpha [TNF-α]), Cytokine 1 (human) kits (colony-stimulating factor [GM-CSF], IL-1α, IL-5, IL-7, IL-12/IL-23p40, IL-15, IL-16, IL-17A, TNF-β, and VEGF-A), Cytokine 2 panel (human) kits (IL-17A/F, IL-17B, IL-17C, IL-17D, IL-1RA, IL-3, IL-9, and thymic stromal lymphopoietin [TSLP]), Th17 panel 1 (human) kits (IL-17AGen.B, IL-21, IL-22, IL-23, IL-27, and IL-31), Chemokine panel 1 (human) kits (macrophage inflammatory protein-3alpha [MIP-3α]/ chemokine [C-C motif] ligand 20 [CCL20], Eotaxin/CCL11, MIP-1β/CCL4, Eotaxin-3/CCL26, thymus and activation-regulated chemokine [TARC]/CCL17, interferon [IFN]-gamma-induced protein 10 [IP-10]/chemokine [C-X-C motif] ligand [CXCL]10, MIP-1α/CCL3, monocyte chemotactic protein-1 [MCP-1]/CCL2, macrophage-derived chemokine [MDC]/CCL22, and MCP-4/CCL13), angiogenesis panel (human) 1 kits (vascular endothelial growth factor-A [VEGF-A], VEGF, VEGF-C, VEGF-D, tyrosine-protein kinase receptor [Tie-2], soluble fms-like tyrosine kinase-1 [sFlt-1]/VEGFR-1, placental growth factor [PlGF], and basic fibroblast growth factor [bFGF]), and Vascular injury panel 2 (human) kits (Serum amyloid A [SAA], C-reactive protein [CRP], vascular cellular adhesion molecule-1 [VCAM-1], intercellular adhesion molecule-1 [ICAM-1]) following each manufacturer's instructions. The level is given as the average of the duplicate tests performed on each sample. Both the sensitivity and coefficient of variation were within the expected range.

Statistical analysis: Statistical analysis was performed with Prism 8 (GraphPad Software, San Diego, CA) and IBM SPSS Statistics 20 statistical software (IBM Corp, Armonk, NY). After deleting outliers, an unpaired *t* test and Mann–Whitney

U test were used for nonparametric comparison of the concentrations in the two groups. In the Mann–Whitney U tests, Bonferroni correction was used to compensate for multiple comparisons. Correlations were determined via Spearman's *q* test. The values for age, gender, HLA-B27 positivity, disease duration, leukocytes, neutrophils, lymphocytes, monocytes, eosinophils, and basophils were presented as mean ± standard deviation. $p < 0.05$ was considered to be statistically significant.

RESULTS

Basic characteristics of the study population: Twenty-one patients with HL-B27$^+$ AS-associated AAU and 21 HCs agreed to participate in our study. All participants fulfilled the requirements for inclusion. Table 1 summarizes the basic clinical information of the patients with HL-B27$^+$ AS-associated AAU and HCs. The age and gender of the HCs closely matched those of the patient group. Male participants accounted for 67% of the HL-B27$^+$ AS-associated AAU group and 52% of the HC group. The mean ages were 35.9 ± 10.0 years for the patient group versus 38.0 ± 9.5 years for the HC group. The mean disease duration of the patients was 1.21 years. The leukocytes, neutrophil, and monocyte numbers were significantly higher in the HL-B27$^+$ AS-associated AAU group than in the HC group (all $p < 0.05$). The numbers of leukocytes, eosinophils, and basophils were similar in both groups (all $p > 0.05$).

Inflammatory mediator concentrations in the HL-B27$^+$ AS-associated AAU patients and HC groups: To better understand ocular inflammation in patients with HL-B27$^+$ AS-associated AAU, concentrations of 54 molecules were determined in serum samples from patients and HCs. Of the 54 molecules measured, 50 were detected in more than 75% of the serum samples in the patient and control groups. Four assayed molecules, namely IL-1β, IL-23, IL-31, and IL-1α, had percentages of detection within the 0%–50% range. Therefore, for further comparisons, only the concentrations of 50 molecules were employed.

The concentrations of IL-6, TNF-α, Flt-1, IL-17D, IP-10, IL-22, MIP-3α, CRP, IL-3, and MCP-4 were statistically significantly higher in serum samples from patients than from HCs ($p < 0.05$, Appendix 1, Figure 1). CRP showed a 30.97-fold change between the patients and HCs ($p = 0.0008$), IP-10 showed a 5.23-fold change between the patients and HCs ($p < 0.0001$), and MIP-3α had a 3.48-fold change between the patients and HCs ($p < 0.0001$). The remaining seven cytokines had changes ranging between 1.38-fold and 2.59-fold between the patients and HCs. The serum concentrations of IL-4, IL-8, PlGF, VEGF-C, VEGF-D, Eotaxin-3, and MIP-1α were lower in patients than in HCs ($p < 0.05$, Appendix 1, Figure 2). IL-8 had a 0.15-fold change between the patients and HCs ($p < 0.0001$), and MIP-1α had a 0.40-fold change between the patients and HCs ($p < 0.0001$). The remaining five cytokines had changes ranging from 0.53-fold to 0.83-fold between the patients and HCs. After Bonferroni correction, the eight cytokines, including IL-8, Flt-1, VEGF-C, VEGF-D, IP-10, MIP-1α, MIP-3α, and CRP, still had significant differences between HL-B27$^+$ AS-associated AAU patients and HCs ($p < 0.05$). However, no significant differences were detected between the patients and HCs for the remaining 37 molecules ($p > 0.05$, Appendix 1). Subsequently, to identify cytokines with similar profiles, we calculated the correlation matrix of 17 differential cytokines between HL-B27$^+$ AS-associated AAU patients and HCs. IL-6, IL-22, VEGF-C, and MIP-1α highly correlated with each other ($p < 0.05$).

Table 1. General clinical data in the HL-B27$^+$ AS-associated AAU and HCs groups.

Clinical characteristics	HL-B27$^+$ AS-associated AAU group (n=21)	HCs group (n=21)	Reference range	P value
Age (years)	35.9±10.0	38.0±9.5	NA	>0.05
Sex (male/female)	14/21	11/21	NA	>0.05
disease duration	1.21	NA	NA	NA
HLA-B27 positive	21/21	NA	NA	NA
Leukocytes (×10^9/L)	7.63±2.24	5.88±1.27	4.0–10.0	<0.05
Neutrophils (×10^9/L)	5.18±1.89	3.20±1.04	2.5–7.5	<0.05
Lymphocytes(×10^9/L)	1.98±0.78	2.10±0.49	0.8–4.0	>0.05
Monocytes (×10^9/l)	0.53±0.15	0.41±0.11	0.1–0.6	<0.05
Eosinophils(×10^9/l)	0.15±0.11	0.13±0.07	0.05–0.5	>0.05
Basophils(×10^9/l)	0.03±0.02	0.04±0.02	0–0.1	>0.05

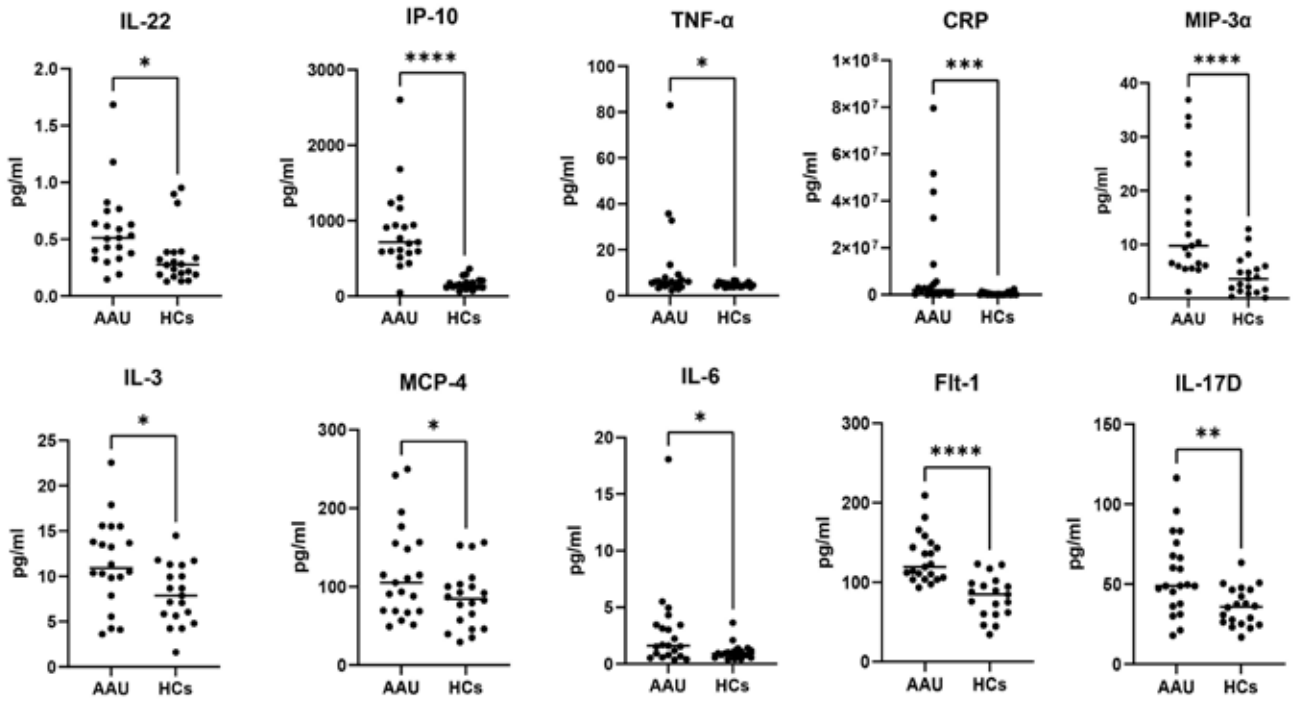

Figure 1. Cytokine/chemokine expressed at higher levels in serum from patients with HLA-B27$^+$ AS-associated AAU compared to HCs. Mann–Whitney U test and Student's *t* test were performed to check for statistical significance between groups when required (****p < 0.001, **p < 0.01, *p < 0.05).

DISCUSSION

In this study, we described the differences in serum concentration profiles for 54 cytokines and chemokines between patients with HL-B27$^+$ AS-associated AAU and HCs. We found increased levels of IL-3, TNF-α, IL-6, IL-17D, IL-22, IP10, MIP-3, Flt-1 CRP, and MCP-4, as well as decreased levels of IL-4, IL-8, MIP-1α, Eotaxin-3, PlGF, VEGF-C, and VEGF-D in the serum of patients with HL-B27$^+$ AS-associated AAU. These findings suggested a potential involvement of T helper (Th) cells immune processes and angiogenesis in the pathogenesis of uveitis.

Antigens activate Th cell progenitors, which differentiate into Th0 cells before further differentiation into Th1, Th2, Th17, and T regulatory (Treg) cells in diverse microenvironments [13]. Th1 cell activation induces considerable protective immunity, producing the hallmark IL-8 and TNF-α cytokines involved in the cell-mediated pro-inflammatory response. Conversely, Th2 cells produce IL-4 and IL-6, which decrease Th1 cytokine production and hence orchestrate the anti-inflammatory humoral response and immunological suppression [14]. Th17 cells are defined as IL-17-secreting CD4$^+$ T cells and secrete IL-22 and CCL20/MIP3α [15]. It is well known that the pathogenesis of uveitis is influenced by an imbalance of Tregs and the Th subsets (Th1/Th2/Th17).

In the present study, the levels of these Th subset-related cytokines, including IL-8 and IL-4, were significantly decreased in patients compared to HCs, whereas the levels of TNF-α, IL22, CCL20/MIP3α, and IL-6 were significantly elevated. In contrast, a previous study reported an upregulation of IL-8 concentrations in the serum of patients with AS-associated AAU [12]. These inconsistencies might be attributable to various reasons, including patients with various phases of continuing inflammation, the use of topical corticosteroids, and distinct immune cell phenotypic infiltration. Our study also revealed significantly increased levels of IL-3, which is mainly produced by activated T lymphocytes and can synergize with IL-4 to enhance Th2 cell differentiation [16]. A previous study also found significantly elevated levels of IL-3 in supernatants from splenocytes in an animal model of experimental autoimmune uveitis, in agreement with our findings [17]. Overall, the results suggest that an imbalance of Th1/Th2/Th17 may be involved in the pathogenesis of HL-B27$^+$ AS-associated AAU.

Notably, the levels of IL-17D, a member of the IL-17 family, were elevated in the serum of patients in our study.

IL-17 family members have been linked to autoimmune diseases, including psoriasis and rheumatoid arthritis [18]. IL-17D has been detected in rheumatoid nodules, and the mRNA expression of *IL17D* was decreased in psoriatic skin [19,20]. These results indicate that IL-17D plays vital roles in autoimmune disease, and our study is the first to report elevated serum IL-17D in uveitis. Further research studies are needed to clarify its role in uveitis.

The vascular endothelial cell growth factor (VEGF) family, the master switch for angiogenesis, is composed of five ligands—VEGF-A, PlGF, VEGF-B, VEGF-C, and VEGF-D—and three tyrosine kinase receptors—VEGFR-1 (Flt-1), VEGFR-2 (Flk-1), and VEGFR-3 (Flt-4) [21]. Previous studies have shown that high VEGF levels have been linked to loss of vision and are a risk factor for the development of ocular disease [22,23]. Our study revealed significantly decreased levels of VEGF-C and VEGF-D in the serum of patients with HL-B27$^+$ AS-associated AAU. However, this finding contradicts the previous reports. For example, in a rabbit lipopolysaccharide-induced model of uveitis, Decker et al. discovered significantly elevated levels of VEGF, VEGF-C, and VEGF-D in aqueous humor samples and described this discovery as suggestive of an inflammatory response. Our findings regarding VEGF-C and VEGF-D, in consideration of prior studies, warrant further investigation. Notably, the levels of VEGFR-1 and its specific ligand, PlGF, were increased in the present study. PlGF has been reported to play various roles in inflammatory diseases, including atherosclerosis, through Flt-1 signaling [24]. Uveitis is well known as a chronic inflammatory disease. A previous study also reported that angiogenesis-related factors could play a role in long-standing complicated JIAU, which is a type of uveitis [25]. Therefore, we can infer that the PlGF/ Flt-1 pathway may be active in HL-B27$^+$ AS-associated AAU and that angiogenesis plays a vital role in the development of this disease.

Chemokines are multifunctional mediators that control leukocyte recruitment into inflamed tissues, induce inflammation, boost immunological responses, and support stem cell survival, development, and homeostasis [26]. In the present

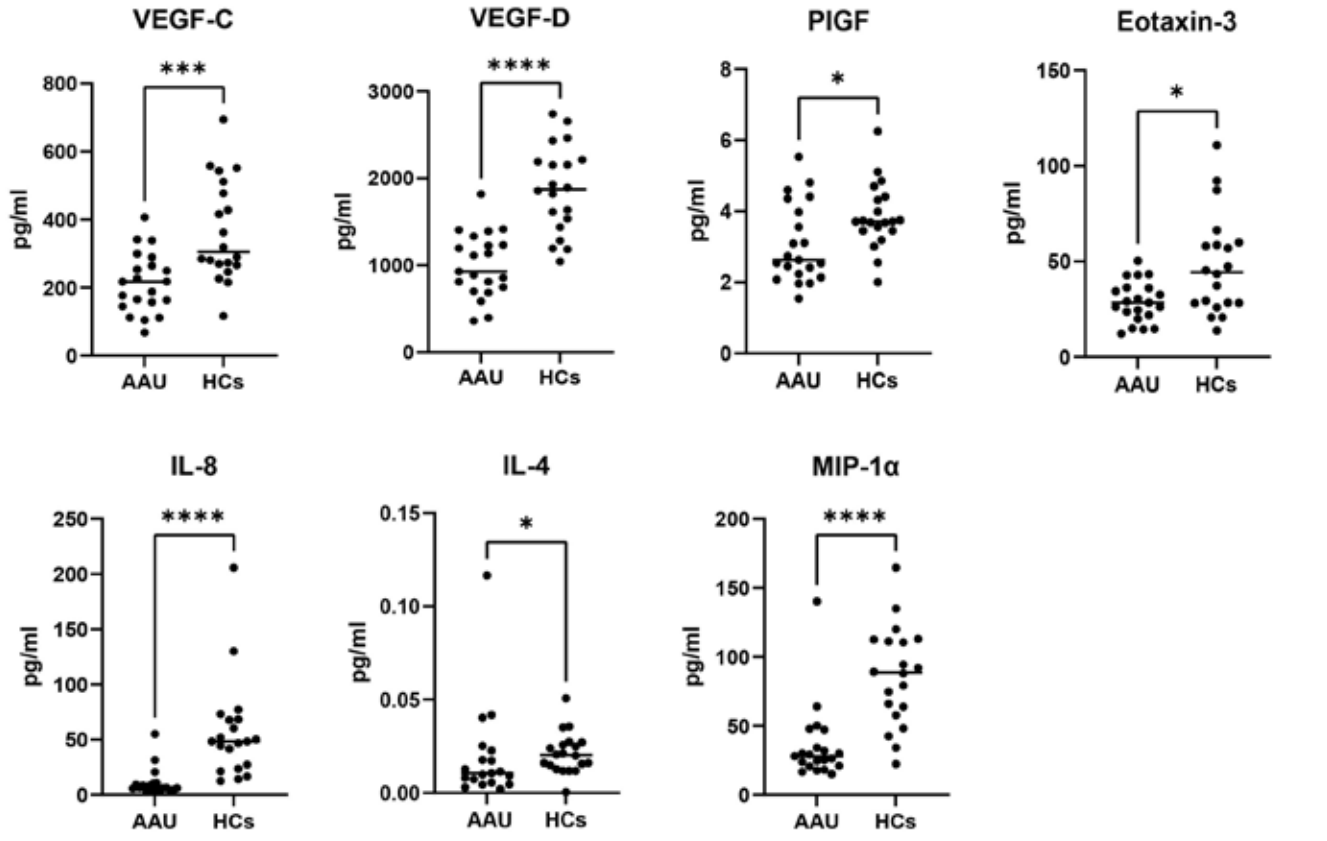

Figure 2. Cytokine/chemokine expressed at lower levels in serum from patients with HLA-B27$^+$ AS-associated AAU compared to HCs. Mann–Whitney U test and Student's *t* test were performed to check for statistical significance between groups when required (****$p < 0.001$, **$p < 0.01$, *$p < 0.05$).

study, the levels of several chemokines, including CCL13, CCL20, and CXCL10/IP10, were significantly elevated, whereas the levels of CCL3 and CCL26 were significantly decreased. No significant difference in CCL26 has been reported in other kinds of uveitis. Consistent with our study, IP-10/CXCL10 was elevated in the aqueous humor of patients with VKH and BD in several previous studies [27,28]. IP-10/CXCL10 is a chemoattractant for initiating T-cell activation and can be induced by the interaction of monocyte-epithelial cells [29]. IP-10/CXCL10 and its receptor, CXCR3, appear to play a role in the development of various autoimmune diseases, including organ-specific and systemic diseases [30]. Furthermore, IP-10 is also the most effective CXCR3 chemokine ligand because of its capacity to steer continuing immune response toward the Th1-type response linked to severe inflammatory diseases [31]. These findings suggest that the Th1 immune response is potent in patients with HL-B27$^+$ AS-associated AAU.

This study has some limitations. The sample size of this study was relatively small, which may lead to lower statistical power. Therefore, to increase the likelihood of identifying a minimum impact with statistical significance, our findings must be validated in a larger cohort. Furthermore, the distinction between active and inactive phases of the disease is unclear due to the incompleteness of the data, and this could represent another limitation of our study. Finally, the specific mechanisms of these differential cytokines and chemokines in HL-B27$^+$ AS-associated AAU must be studied and explored in future studies.

In conclusion, our study showed that cytokines and chemokines play vital roles in the pathogenesis of HL-B27$^+$ AS-associated AAU. We also identified some novel differential cytokines and chemokines that have not been reported in other kinds of uveitis. Further studies are required to validate and interpret their roles in uveitis. A thorough analysis of cytokine expression discrepancies can aid in developing future uveitis diagnostic tests while also increasing the understanding of the pathophysiology of this complex disease.

APPENDIX 1. CONCENTRATIONS OF CYTOKINES IN SERUM FROM HL-B27$^+$ AS-ASSOCIATED AAU PATIENTS AND HCS.

To access the data, click or select the words "Appendix 1." p-values are shown after the unpaired t test and Mann-Whitney U test. q-values are shown after the Bonferroni correction.

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