• Clinical Research •

Association between islet autoantibodies and the prevalence of autoimmune uveitis

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Abstract

● **AIM:** To evaluate the predictive value of islet autoantibodies for the diagnosis of autoimmune uveitis (AU), as well as to characterize the association bet ween islet autoantibodies and AU.

● **METHODS:** Totally 97 patients with AU and 100 healthy persons without any autoimmune diseases as the control group were recruited. Multiple serum islet autoantibodies were measured using commercial enzyme-linked immunosorbent assay kits (ELISA). A supplementary questionnaire was used to complement the subject's demographics and clinical features. The level of glucose concentrations and white blood cells were measured. Conditional logistic regression was performed to estimate odds ratios (ORs), and 95% confidence intervals (CIs) of AU according to islet autoantibodies and to evaluate the predictive value of islet autoantibodies for AU diagnosis. Autoantibodies subgroups and other variables were included into analysis.

● **RESULTS:** In AU patients, the prevalence of detecting at least one of the autoantibodies was 31.9% (31/97). The most frequent autoantibody was ZnT8A (30.9%), followed by GADA (11.3%), IA-2A (4.1%), ICA (2.1%) and IAA (2.1%). Islet autoantibodies were found to be correlated positively with AU diagnosis [OR (95%CI): 13.86 (3.28, 58.50), *P*<0.001]. Moreover, Zn-T8A was remarkably correlated with AU diagnosis [OR (95%CI): 6.13 (1.96, 19.17), *P*<0.001], In contrast, neither GADA nor other islet antibodies (IA-2A, ICA and IAA) showed any association with AU risk under an additive model.

● **CONCLUSION:** The prevalence of islet antibodies, especially ZnT8A, in patients with AU is higher. Islet antibodies as well as novel biomarkers should be included in routine evaluation at AU and is a valuable biological marker to classify newly-diagnosed uveitis.

● **KEYWORDS:** autoimmune uveitis; islet autoantibody; ZnT8A; epidemiology

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INTRODUCTION

Uveitis is a diverse group of intraocular inflammatory disease and a significant cause of visual loss worldwide. As the potentially sight-threatening disorders which affect all age groups, uveitis has been estimated to be responsible for approximately 10% of blindness in the United States and various western countries[1]. Uveitis may be caused by infection, injury, autoimmune and sometimes by an unknown etiology. Compared with infection uveitis, autoimmune uveitis (AU) is a specific organ immune-mediated disease and shows strong associations with various systemic immune-mediated diseases. Studies have identified various endogenous immune factors, genetic predisposition and environmental trigger that are involved in the pathogenesis of AU[2].

AU had a close association with diabetes mellitus (DM)[3-4]. With worldwide increasing incidence of DM, this association received more and more attention. The common pathophysiology of inflammation and some degree of autoimmunity was the basis of this association. Both AU and DM manifest with organ-specific immune-mediated disease, moreover, organ-specific autoantibodies as the markers of an on-going autoimmune process could be detected in serums prior to clinical presentation. As the marker for immune destruction of islet beta cells, the islet autoantibodies' predictive value is thoroughly studied and at present well recognized in all type of diabetes. The correlation between islet autoantibodies and other autoimmune diseases (autoimmune thyroid diseases, autoimmune hepatitis) had been explored by several authors[5-11].

According to previous report[4,12-13], AU associated with poorly controlled or undiagnosed DM, but few studies have addressed the relation between islet autoantibodies and AU due to controversial extrapolation reported in previous literature. Current study was designed to investigate serum autoantibodies to islet autoantibodies in a cohort of AU patients and to evaluate the association between islet autoantibodies and AU.

SUBJECTS AND METHODS

Ethical Approval This study was approved by the Ethics Committee of the Fourth Hospital of Xi'an, College of Medicine, Xi'an Jiaotong University, and conducted according to the latest Declaration of Helsinki. Individuals enrolled in these studies had previously consented to participate in the study and then agreed to have their information and clinical samples stored for future studies.

Study Design and Case Definition All patients with AU were referred from the center of Ophthalmology Diseases Research in the Fourth Hospital of Xi'an. Because of no defined diagnosis criteria for uveitis, the diagnoses were made both on the features of clinical epidemiology and laboratory inspection and on the consensus of AU published in the American Journal of Ophthalmology by American Uveitis Society[14-16]. The diagnosis of uveitis and the dilated fundus examination was carried out by an ophthalmologist. The main clinical features include conjunctival injection, ciliary flash in the perilimbal area, cells and flare in the anterior chamber or vitreous opacity, and keratic precipitates on cornea. The full ophthalmic examination included slit-lamp exam, electroretinogram (ERG), intraocular pressure (IOP), and best-corrected visual acuity (BCVA). The laboratory tests for diagnosis included autoimmune serology and genetic tests (*i.e.* rheumatoid factor, anti-neutrophil cytoplasm antibodies, HLA class I typing) and screening for infectious agents such as Toxoplasmosis, Herpes viruses, and syphilis. The classification of uveitis type must include location and onset, duration, and clinical course of uveitis, as it was stated by the Standardization of Uveitis Nomenclature (SUN)[14]. All cases in study were screened by these guidelines. Subjects were excluded if the uveitis was secondary to infection and injury, or if the record lacked of information on fundus examination. Cases were limited to the ones that had full information on ophthalmologic and laboratory examination with cell count, visual acuity, tonometer, and blood glucose.

Matched control subjects were defined as no obvious eye diseases, with neither abnormal visual function. Cases matched for age and sex were enrolled from a random population obtained from the health examinations of the Fourth Hospital of Xi'an.

Measurement of Islet Autoantibodies Plasma samples were stored at -80°C until the analysis of islet autoantibodies. The analysis was performed in the Clinical Laboratory Department of the Fourth Hospital. Islet autoantibodies were qualitatively determined by an enzyme-linked immune-sorbent assay (ELISA; Shenzhen blot GmbH; China). The cut-off for positivity was chosen according to the manufacturer's recommendations, which was based off of ELISA (GADA: 5 AU/mL; IA-2A: 7 AU/mL; IAA: 10AU/mL; ICA: 15 AU/mL; ZnT8A: 15 AU/mL). In the 2017 Islet Autoantibody Standardization Program (IASP) Workshop, sensitivities and specificities were 52% and 100% respectively for IAA, 82% and 99% respectively for GADA, 72% and 100% respectively for IA-2A, 86% and 98% respectively for ICA, and 70% and 97% respectively for ZnT8A. If one or more isotypes was existed in serum it was considered positive.

Covariates Basic information of the participants was collected by a trained study team composed of ophthalmologists, interviewers, and medical coordinator. Attendant completed a structured questionnaire and clinical examination. Demographics and economic characteristics such as age, gender, current and past jobs and literacy were obtained. Family history was regarded as whether the study subject had autoimmunity or diabetes in first-degree relatives (mother, father, sisters, brothers and children). Education level was defined based on the highest education achieved (none/primary school, secondary/high school, college degree or above). Other biochemical markers were measured with fasting blood samples. Fasting blood glucose (FBG) was measured by glucose oxidase method (Auto-analyzer, Hitachi, Japan). The white blood cell (WBC) was determined using a CBC Auto-analyzer (Mindray, China).

Statistical Analysis Statistical analysis of the date was performed using SPSS statistical software (version 18.0, SPSS). Data were presented as number of cases, mean±standard deviation (SD), or median with interquartile range. Comparison of the two groups was made in the initial stage. Differences in categorical characteristics were assessed using the χ^2 test or the Fischer exact test. In the second stage patients were divided into subgroups according to positive islet autoantibodies. Positive islet autoantibodies were defined as the presence of any or multiple confirmed isotype autoantibody. For proportions, Pearson χ^2 or Fisher exact tests were used. A two-tailed P value<0.05 was considered statistically significant.

For assessing correlations between islet autoantibodies and AU, conditional Logistic regression was performed. The odds ratios (ORs) and 95% confidence intervals (CIs) were calculated in univariate and in binary logistic regression models. We evaluated the following factors: gender, age at diagnosis, education level, the presence of islet autoantibodies, white blood cell, glucose concentrations, family history,

and present condition with autoimmunity or diabetes. The statistical tests were two-sided and significance was considered at $P<0.05$.

RESULTS

Characteristics of AU Patients and Controls The general characteristics of the AU patients and the control subjects are presented in Table 1. There were no statistically significant differences between the two groups based on age and gender ($P>0.05$). Secondary or high school was more common among the AU patients than among control subjects, 50.5% and 44.0% respectively.

Associations between Islet Autoantibodies and other AU Risk Factors Subjects were divided into two groups according to the positivity of the islet autoantibodies, as indicated in Table 2. The positive group presented with higher levels of glucose (6.91±2.79 mmol/L) compared to the negative ones (5.30±0.74 mmol/L; $P=0.001$). There also were 12 (33.3%) subjects in positive group and 3 (1.9%) subjects in negative group with FBG levels greater than 7 mmol/L ($P<0.001$). The comparison between the positive and negative groups revealed statistically significant differences with respect to autoimmune illness. Autoimmune disorder accounted for 30.6% in the positive group and 14.9% in the negative group ($P=0.026$). No significant differences were detected in terms of gender, age, education level, family history and WBC.

Associations between Islet Autoantibodies and Autoimmune Uveitis In an unadjusted binary logistic regression analysis, there was a positive correlation between the presence of islet autoantibodies and AU (OR: 8.92, 95%CI: 3.29-24.14, $P<0.001$). As further adjustment for other AU risk factors (education level and WBC) was performed (Table 3), there is an increase of risk with OR of 13.86 (95%CI: 3.28-58.50, $P<0.001$).

A multiple conditional logistic regression analysis was used to investigate the association between subtype islet antibodies and AU. In Table 4, after adjustment for education level and WBC, the presence of Zn-T8Ab was significantly correlated with AU (OR: 6.13, 95%CI: 1.96-19.17, $P<0.001$). However, there were no significant correlations between other islet antibody isotypes (GADA, IA-2A, ICA and IAA).

Table 1 Characteristics of subjects in the uveitis and case-control group *n* (%)

Parameters	Uveitis (*n*=97)	Control (*n*=100)	χ^2	*P*
Gender			3.658	0.056
Male	51 (52.6)	39 (39.0)		
Female	46 (47.4)	61 (61.0)		
Age			1.275	0.259
0-30y	24 (24.7)	32 (32.0)		
≥30y	73 (75.3)	68 (68.0)		
Education level			8.722	0.013
None or primary school only	16 (16.5)	6 (6.0)		
Secondary or high school	49 (50.5)	44 (44.0)		
College degree or above	32 (33.0)	50 (50.0)		
Family history			3.141	0.117
No	94 (96.9)	100 (100.0)		
Yes	3 (3.1)	0		
Systemic autoimmune disease			43.878	<0.001
No	62 (63.9)	100 (100.0)		
Yes	35 (36.1)	0		
Fasting blood glucose			13.224	0.001
<6.1 mmol/L	78 (80.4)	90 (90.0)		
6.1-7.0 mmol/L	5 (5.2)	9 (9.0)		
≥7.0 mmol/L	14 (14.4)	1 (1.0)		
White blood cell			22.948	<0.001
4-10×10^9	77 (79.4)	100 (100.0)		
≥10×10^9	20 (20.6)	0		
Islet autoantibodies			23.961	<0.001
Positive	31 (32.0)	5 (5.0)		
Negative	66 (68.0)	95 (95.0)		
Zn-T8Ab			22.656	<0.001
Positive	30 (30.9)	5 (5.0)		
Negative	67 (69.1)	95 (95.0)		
GADA			9.203	0.02
Positive	11 (11.3)	1 (1.0)		
Negative	86 (88.7)	99 (99.0)		
ICA			4.209	0.04
Positive	4 (4.1)	0		
Negative	93 (95.9)	100 (100.0)		
IA-2A			2.083	0.149
Positive	2 (2.1)	0		
Negative	95 (97.9)	100 (100.0)		
IAA			2.083	0.149
Positive	2 (2.1)	0		
Negative	95 (97.9)	100 (100.0)		

DISCUSSION

In this case-control study, we found the prevalence of islet autoantibodies was significantly different between the AU patients and the controls, with the highest prevalence of ZnT8A. The presence of islet autoantibodies, especially ZnT8A, was positively associated with AU. Moreover, positive ZnT8A in AU indicates an elevated risk of additional autoimmune conditions. Autoantibodies to beta cell antigens, comprising of ZnT8A, could be included in routine screening panels in AU.

In recent years, the strong association between DM and uveitis has raised great concern among researchers. Several case reports have highlighted a possible link between AU and DM[17-20]. In addition, a few authors have defined a DM-related uveitis, which was defined by fibrinous anterior uveitis in the presence of poorly controlled DM and in the absence of any

Table 2 The correlation between islet autoantibodies and other AU risk factors *n* (%)

Exposures	Positive	Negative	χ^2	*P*
Gender			0.893	0.345
Male	19 (52.8)	71 (44.1)		
Female	17 (47.2)	90 (55.9)		
Age			0.098	0.754
0-30y	11 (30.6)	45 (28.0)		
≥30y	25 (69.4)	116 (72.0)		
Education level			1.479	0.477
None or primary school only	6 (16.7)	16 (9.9)		
Secondary or high school	15 (41.7)	78 (48.4)		
College degree or above	15 (41.7)	67 (41.6)		
Family history			4.777	0.087
No	34 (94.4)	161 (99.4)		
Yes	2 (5.6)	1 (0.6)		
Systemic autoimmune disease			4.931	0.026
No	25 (69.4)	137 (85.1)		
Yes	11 (30.6)	24 (14.9)		
Fasting plasma glucose			43.019	<0.001
≤6.1 mmol/L	17 (47.2)	151(93.8)		
6.1-7.0 mmol/L	7 (19.4)	7 (4.3)		
≥7.0 mmol/L	12 (33.3)	3 (1.9)		
White blood cell			3.042	0.138
4-10×10^9	29 (80.6)	146 (90.7)		
≥10×10^9	7 (19.4)	15 (9.3)		

Table 3 The Logistic model of the adjusted risk of islet autoantibodies on AU

Variable	*β*	SE	Wald χ^2	*P*	OR (95%CI)
Islet autoantibodies					
Negative					1.00
Positive	2.63	0.73	12.80	0.00	13.86 (3.28, 58.50)
White blood cell					
4-10×10^9					1.00
≥10×10^9	2.68	0.80	11.04	0.00	14.46 (2.99, 69.93)
Education level					
College degree or above					1.00
Secondary or high school	1.48	0.59	6.17	0.01	4.41 (1.36, 14.23)
None or primary school only	0.84	0.36	5.45	0.00	2.32 (1.15, 4.72)
Constant	0.33	1.19	0.08	0.78	1.39

Adjusting for education, white blood cell, and islet antibodies.

other underlying cause[18,20]. In 1999, Yawata *et al*[21] assessed glucose intolerance in Vogt-Koyanagi-Harada (VKH) patients might be related to the autoimmune inflammatory. Recently, a retrospective cohort study proposed that glycemic control was an important modifiable risk factor for uveitis in patients with diabetes, especially at highest risk with those who had type 1 disease with poor glycaemic control[19]. These reports of patients with uveitis and DM, however, do not establish an association between uveitis and islet autoantibodies, whereas its associated risk factors have not been clarified. The predict vale of islet autoantibodies for uveitis diagnosis is unknown. Although the

Table 4 The Logistic regression of the adjusted risk of isotypes of islet antibody on AU

Variable	*β*	SE	Wald χ^2	*P*	OR (95%CI)
Zn-T8Ab					
Negative					1.00
Positive	1.81	0.58	9.72	0.00	6.13 (1.96, 19.17)
GADA					
Negative					1.00
Positive	0.33	1.27	0.07	0.79	1.38 (0.11, 16.84)
ICA					
Negative					1.00
Positive	18.78	19073	0.00	0.99	146015433 (0.00, -)
IA-2A					
Negative					1.00
Positive	18.48	25629	0.00	0.99	106527305 (0.00, -)
IAA					
Negative					1.00
Positive	20.36	28362	0.00	0.99	697458055 (0.00, -)
Education level					
College degree or above					1.00
Secondary or high school	1.55	0.58	7.09	0.08	4.72 (1.51, 14.76)
None or primary school only	0.81	0.36	5.00	0.03	2.24 (1.11, 4.53)
White blood cell					
4-10×10^9					1.00
≥10×10^9	2.66	0.78	11.44	0.00	14.24 (3.06, 66.34)
Constant	-1.13	0.29	15.54	0.00	0.324

Adjusting for education level, white blood cell, Zn-T8Ab, GADA, ICA, IA-2A, and IAA.

predictive value of insulin antibodies is thoroughly studied and well recognized in diabetes, but few studies investigated the risk associated with the presence of insulin antibodies in AU.

AU is one of the autoimmune disorders characterized by a deviant response to the immune system, with the tissues of the individual failed to distinguish from non-self-molecules in these conditions, ultimately leading to the impairment of target organs on the account of cross-reaction on self-proteins. Some researches deem that although immune privilege prevents large molecules from going into and out of the normal eyes, this separation from the immune system also impedes efficient induction of peripheral tolerance to these privileged-eye antigens. Because of the breakdown of immune privilege as well as ocular cross-antigens such as ZnT8, the T and B lymphocytes in circulation, which were not tolerance to eye antigens, can attack ocular tissues. Therefore, the body's immune defense system was activated. AU inflammatory has been developed by implicating of numerous immune cells and molecules such as inflammatory macrophages, T and B lymphocytes, cytokines, proteases and chemokines. Some of these cells or molecules may serve as biomarkers of the mechanisms and could be detected in serums prior to clinical presentation. These ZnT8A appears to be restricted

by the presence of the corresponding polymorphism in the genome of the patients. The presence of ZnT8A at the protein level is confirmed not only in pancreatic islets, but possibly in retina cells[22-23]. The existence of ZnT8A might therefore represent a state of autonomic retina inflammation. In addition, clarification of the ZnT8 function in cells other than beta cells might facilitate understanding of the association between diverse autoimmune disorders. Positivity for ZnT8A at diagnosis seems to reflect a more aggressive pathophysiology. This theory may explain the association between AU and DM, and autoantibodies to beta cell antigens might be the associated risk factor for AU.

Consistent with previous studies, the presence of islet autoantibodies, especially ZnT8A, is positively associated with AU. Islet autoantibodies might not uniquely represent risk of autoimmune type 1 diabetes mellitus (T1D), but may instead be an unspecific sign of autoimmune disease. Several reports have surveyed the prevalence of islet autoantibodies in associated autoimmune diseases. One recent study had found that positive GADA (8.7%) and ZnT8A (7.6%) in patients with Graves' disease is high and might indicate wide range endocrine autoimmunity, as well as risk for non-autoimmune diabetes rather than exclusively beta cell autoimmunity and T1D[24]. In 2016, Fichna *et al*[9] found that positive serologic markers of beta cell autoimmunity were found in 21 (17.9%) autoimmune Addison's disease (AAD) individuals with no previous history of diabetes, ZnT8A were detectable in 8.5%, GADA in 20.0%, IA-2A in 5.7%, IAA in 1.6% of AAD individuals. ZnT8A are associated with coexisting T1D and predictive of T1D in non-diabetic subjects[10]. Not only ZnT8A was shown to be an improved indicator of autoimmune atrophic body gastritis[8], it was also found to be related to thyroid autoimmunity in children and adolescents as well in healthy children who were followed for their increased risk for the diseases[7]. ZnT8A has also been implicated in celiac disease, autoimmune hypoadrenalism and cystic fibrosis[6,9,25]. This association can be explained, in part, by a shared genetic background and is mainly linked to the HLA system[26] and the CTLA-4, PD-1 genes[27]. Both AU and associated-autoimmune diseases have strong genetic background, immunologic cellular and molecular inflammatory response, and environmental factors.

GADA has been described in several severe autoimmune pathologies of the central nervous system as the autoantigen that is attached to synaptic vesicles in neurons[28]. GADA auto antigen exerts not only in pancreas beta cells but also in ocular lens with signaling functions. The link between GADA and uveitis had been supported by an immunological basis. In this study, no correlation was found between GADA and AU, nor in other isotypes (IA-2A, ICA or IAA).

This study is the comprehensive description of islet autoantibodies in AU, however it does have some limitations. First, sample size is moderate due to low AU incidence. However, its strength relies on very well-documented individual data from each patient, excluding risk of any misclassification in the studies. Second, given the cross-sectional character of our analysis that was conducted in individuals of variable disease duration, some antibodies such as ZnT8A might have vanished by the time of the study in certain proportion of the patients. Systematic evaluation of a wide array of autoantibodies at AU onset and subsequently at fixed intervals might shed more light on dynamics of the autoimmune process. Third would be the technical limitations of the ZnT8A assay. The measurement method was ELISA kit, which qualitatively assesses islet autoantibodies.

In conclusion, our study shows the high prevalence of islet autoantibodies in AU patients, especially ZnT8A. Islet autoantibodies are associated with coexisting T1D, and implicate in the risk of glycemic disorders in non-diabetic AU subjects. Moreover, positive islet autoantibodies among AU show a higher risk for additional autoimmune conditions.

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