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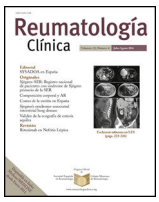

Original Article

Serum immunoglobulin levels, complement components 3 and 4, HLA-B27 allele and spondyloarthropathy in patients with non-infectious anterior uveites☆

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ABSTRACT

Objective: To identify the relationship between serum immunoglobulin levels, complement components 3 and 4, the presence of the HLA-B27 allele and diagnosis of spondyloarthropathies in patients with non-infectious anterior uveitis.
Materials and methods: The participants were 197 patients with a non-infectious anterior uveitis. The concentrations of serum immunoglobulins, C3 and C4 proteins of the complement were determined by turbidimetry. The personal history of suspected immunodeficiency, ophthalmological complications, arthralgia, family history of spondyloarthropathies and the presence of the HLA-B27 allele were collected.
Results: A family history of spondyloarthropathy, axial arthralgias, and ophthalmological complications were more frequent in HLA-B27 positive patients ($P = .0005$, $P \leq .0001$, $P \leq .0001$ respectively) and in patients with spondyloarthropathy diagnoses ($P \leq .0001$, $P \leq .0001$, $P \leq .0001$ respectively). A personal history of recurrent sepsis, and gastrointestinal abnormalities was associated with the presence of the HLA-B27 allele ($P \leq .0001$, $P = .0240$ respectively) and with the diagnosis of spondyloarthropathy ($P = .0492$, $P = .0017$ respectively). IgG decrease was observed ($\chi^2 = 18.5$, OR = 5.03, 95% CI = 2.32–10.89, $P = .0001$) and M (OR = 7.13, 95% CI = 1.40–36.4; $P = .0128$) in patients positive for the HLA-B27 allele and in patients with a diagnosis of SpA ($P = .0364$ and $P = .0028$ respectively). The decrease of C3 proteins (OR = 4.82; CI 95% = 1.35–17.11; $P = .0328$) and C4 (OR = 9.09; CI 95% = 2.13–38.88; $P = .0074$) were associated with a spondyloarthropathies diagnosis.
Conclusions: Patients with non-infectious anterior uveitis, positive for the HLA-B27 allele and diagnosed with spondyloarthropathies have alterations in serum immunoglobulin levels and complement components 3 and 4, which could contribute to the perpetuation and worse clinical course of this disease.

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Niveles séricos de inmunoglobulinas, componentes 3 y 4 del complemento, alelo HLA-B27 y espondiloartropatía en pacientes con uveítis anterior no infecciosa

Palabras clave:
Uveítis anterior no infecciosa
HLA-B27
Inmunoglobulinas
Complemento sérico
Inmunodeficiencia

RESUMEN

Objetivo: Identificar la relación entre los niveles séricos de inmunoglobulinas, los componentes 3 y 4 del complemento, la presencia del alelo HLA-B27 y el diagnóstico de espondiloartropatía en pacientes con uveítis anterior no infecciosa.

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Materiales y métodos: Se incluyeron 197 pacientes con diagnóstico de uveítis anterior no infecciosa. Se determinaron las concentraciones de inmunoglobulinas séricas y proteínas C3 y C4 del complemento mediante turbidimetría. Se recogieron los antecedentes personales de sospecha de inmunodeficiencia, complicaciones oftalmológicas, de artralgias, antecedentes familiares de espondiloartropatías y la presencia del alelo HLA-B27.
Resultados: Los antecedentes familiares de espondiloartropatías, de artralgias axiales y complicaciones oftalmológicas fueron más frecuentes en los pacientes positivos de HLA-B27 ($p = 0{,}0005$, $p \leq 0{,}0001$, $p \leq 0{,}0001$ respectivamente) y en los pacientes con diagnósticos de espondiloartropatías ($p \leq 0{,}0001$, $p \leq 0{,}0001$, $p \leq 0{,}0001$ respectivamente). Los antecedentes personales de sospecha de inmunodeficiencia, sepsis recurrentes y alteraciones gastrointestinales, se asociaron a la presencia del alelo HLA-B27 ($p \leq 0{,}0001$, y $p = 0{,}0240$ respectivamente) y al diagnóstico de espondiloartropatía ($p = 0{,}0492$ y $p = 0{,}0017$ respectivamente). Se observó disminución de las IgG ($\chi^2 = 18{,}5$; OR = 5,03; IC 95% = 2,32−10,89; $p = 0{,}0001$) y M (OR = 7,13; IC 95% = 1,40−36,4; $p = 0{,}0128$) en pacientes positivos del alelo HLA-B27 y en los pacientes con diagnóstico de EspA ($p = 0{,}0364$ y $p = 0{,}0028$ respectivamente). La disminución de las proteínas C3 (OR = 4,82; IC = 1,35−17,11; $p = 0{,}0328$) y C4 (OR = 9,09; IC = 2,13–38,88; $p = 0{,}0074$) se asociaron al diagnóstico de espondiloartropatías.
Conclusiones: Los pacientes con uveítis anterior no infecciosa, positivos del alelo HLA-B27 y con diagnóstico de espondiloartropatías tienen alteraciones de los niveles séricos de inmunoglobulinas, los componentes 3 y 4 del complemento, las cuales pudieran contribuir a la perpetuación y peor curso clínico de esta enfermedad.

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Introduction

Anterior uveitis is a group of heterogonous inflammatory eye diseases with complex phenotypes which essentially affect the uveal tract and it is the fifth cause of blindness worldwide.[1,2] In Cuba, this disease is considered to be among the primary causes of demand for care in ophthalmologic clinics.[3]

Spondyloarthropathies (SpA) are chronic inflammatory rheumatic conditions which share many clinical characteristics. These include ankyilosing spondylitis (AS), inflammatory bowel disease, psoriatic arthritis, reactive arthritis, juvenile SpA and juvenile undifferentiated SpA.[1,2]

SpA are associated with the genes of the major histocompatibility complex, and in particular, with the presence of the human leukocyte antigen-B27 (HLA-B27) allele.[3–5] Uveitis is considered to be the most common extra-articular manifestation of SpA and some authors consider that non-infectious anterior uveitis (NIAU) is associated with the HLA-B27 allele within the SpA group.[5]

Numerous hypotheses have been offered relating infectious processes and other changes to immune response with the triggering and perpetuation of autoimmune and autoinflammatory diseases, which include NIAU and SpA, especially when positivity for the HLA-B27 allele coexists.[1,2,4,6]

The aim of this study was to identify the relationship between Serum Immunoglobulin Levels, complement Components 3 (C3) and 4 (C4), the presence of HLA-B27 Allele and the diagnosis of SpA in patients with NIAU.

Materials and methods

An analytical, observational, cross-sectional study was conducted in the period between January 2013 and March 2018.

Patients

Patients who had been diagnosed with NIAU (197) coming from the Cutan Institute of Ophthalmology were included. They were of both sexes, aged 18 years of above and were not receiving immunosuppressant therapy at the time of study inclusion. The patients were assessed by physicians specialising in ophthalmology and immunology. The diagnosis of SpA was obtained from the medical records of the patients and undertaken by a rheumatologist in accordance with the criteria of the Assessment of Spondyloarthritis International Society group, which included AS, psoriatic arthritis, SpA–associated inflammatory bowel disease, reactive arthritis and undifferentiated SpA.[7,8] This research study was approved by the ethics committee of the National Centre of Medical Genetics in Cuba. All participants in the research signed an informed consent form. They took into account the ethical principles from the Declaration of Helsinki of the World Medical Associations, for medical research studies on humans.

Variables

Demographic variables were analysed including sex and age. Any background of axial arthralgia (cervical, dorsal spine and sacroiliac joint) and peripheral arthralgia (lower members and hands)[9] was recorded, together with familial history of SpA[7] and the presence of HLA-B27 allele. Ophthalmologic complications were obtained from the ophthalmologic medical records and included posterior synechias, vasculitis, glaucoma, macular oedema, ocular hypertension, cataracts, retinal detachment, keratitis, hypopion, sclerouveites and decreased visual acuity.[1,10] Visual acuity with correction through the LogMAR[3] chart. This was defined according to that established by the Standardization of Uveitis Nomenclature-SUN Working Group Standardization of Uveitis Nomenclature for Reporting Clinical Data.[11,12]

Personal histories were recorded where there was suspicion of immunodeficiency[13–15] (Appendix B material supplement, Appendix 1). Serum levels were determined for IgG, IgA and IgM and quantification of components C3 and C4 of the serum complement using a turbidmetry in a chemical analyser (ELIMAT, Italy).

The extraction of deoxyribonucleic acid was made using the saline precipitation technique from 10 ml of human blood and the molecular genotype of the HLA-B27 allele using the polymerase chain reaction technique (PTC-200; MJ Research).

Statistical analysis

Qualitative variables were expressed as frequencies and percentages. The normality of variables was confirmed by the Kolmogorov-Smirnov test. Variables with non-normal distribution were expressed as median and interquartile ranges. The association between study variables with the allele HLA-B27 allele and

Table 1
Demographic variables, clinical, serum levels of immunoglobulins and the complement components 3 and 4 according to the presence of the HLA-B27 allele and diagnosis of spondyloarthropathies in patients with non-infectious anterior uveites.

Variables	Uveitis (n = 197)	Uveites HLA-B27 + (n = 62)		SpA (n = 31)	
	n (%)	n (%)	OR (95R CI); p1	n (%)	OR (95R CI); p1
Male	81 (41.1)	29 (46.8)	1.4 (.8–2,6); .2741	19 (61.3)	4.5 (2,1–10,1); .0001*
Age (years), median (IQR); p2	46 (34–54)		45 (34–52); .9324		48 (37–54); .2731
FH of SpA[a]	15 (7.6)	10 (16.1)	6.9 (2.0–19.1); .0005*	8 (25.8)	7.9 (2.6–23.8); <.0001*
Complications[b]	62 (31.5)	55 (88.7)	16.2 (6.8–38.6); <.0001*	25 (80.6)	2.4 (8.4-60.0); .0000*
Axial arthralgia	55 (27.9)	38 (69.1)	11.0 (5.3–22.6); <.0001*	14 (82.3)	45.6 (5.3–174.6); <.0001*
Peripheral arthralgia	32 (12.2)	27 (84.4)	20.1 (7.2–55.9); <.0001*	2 (11.8)	.7 (.1–3.2); 1.0000
Recurrent Sepsis	71 (36.0)	38 (61.2)	4.9 (2.6–9.3); <.0001*	16 (51.6)	2.1 (1.0–4.7); .0492*
GI changes	61 (31.0)	26 (41.9)	2.1 (1.1–3.9); .0240*	17 (54.8)	3.4 (1.5–7.3); .0017*
Allergies	54 (27.4)	22 (35.4)	1.8 (.9–3.4); .0852	8 (25.8)	.9 (.4–2.3); .8273
IgG reduction	37 (18.8)	22 (35.5)	5.0 (2.2–10.9); .0010*	10 (27.0)	2.4 (1.0–5.8); .0364*
IgG increase	5 (2.5)	0	NC	1 (32.2)	1.3 (.1–12.5); .5793
Decreased IgA	2 (1.0)	1 (1.6)	2.2 (.1–35.7); .5315	1 (50.0)	5.5 (.3–90.3); .2906
Increased IgA	12 (6.1)	3 (4.8)	.7 (.19–2.73); .7562	1 (8.3)	.5 (.1-3.8); .7507
Decreased IgM	8 (4.1)	6 (9.6)	7.1 (1.40–36.4); .0128*	5 (17.2)	10.4 (2.3–46.4); .0028*
Increased IgM	5 (2.5)	1 (1.6)	.5 (.06–4.90); 1.0000	0	NC
Decreased C3	7 (3.5)	4 (6.45)	3.0 (.66–13.99); .2094	4 (14.1)	4.82 (1.3–17.1); .0328*
Increased C3	78 (39.6)	25 (40.3)	3.0 (.7–134.0); .2094	10 (32.3)	2.20 (.9–5.1); .0595
Decreased C4	5 (2.5)	3 (4.8)	3.4 (.55–20.8); .1804	4 (14.1)	9.1 (2.1–38.9); .0074*
Increased C4	34 (17.3)	11 (17.8)	1.0 (.4–2.2); 1.000	6 (19.3)	1.9 (.6–5.6); .2524

C: Complement serum protein; 95% CI: 95% Confidence Interval; FH: Family History; GI: Gastrointestinal; HLA-B27: Human Leukocyte Antigen B27; Ig: Immunoglobulin; IQR: Interquartile Range; NC: Not calculated by frequency equal to zero; OR: Odds Ratio; p1: Probability of association by χ^2; p2: Statistical significance between groups using Mann-Whitney analysis; SpA: Spondyloarthropathis.

[a] A family member with a diagnosis of SpA[10]: ankylosing spondylitis, psoriatic arthritis, SpA-associated inflammatory bowel disease, reactive arthritis and undifferentiated SpA.

[b] Posterior synechias, vasculitis, glaucoma, macular oedema, ocular hypertension, cataracts, retinal detachment, keratitis, hypopion and sclerouveitis and reduction in visual acuity.

* Significant differences for p < .05.

diagnosis of SpA was identified using the Chi-squared test, odds ratio (OR) as a measurement of association and a 95% confidence interval. The comparison of quantitative variables between groups was measured with the Mann-Whitney U test. Statistical analysis of results was performed with the statistical programme lan 7.0 (Statistica Inc., New York, the United States) and EPIDAT version 3.1 (OPS, Spain). A statistical significance level of .05 was used.

Results

Demographic and clinical variables

Out of the total of patients with NIAU, 31.5% were HLA-B27 positive, and of these, only 30.6% were diagnosed with SpA. The SpA diagnosis was found in 15.7% of all patients with NIAU (Table 1). The SpA present in patients with NIAU were AS (58.1%), psoriatic arthritis (16,1%), inflammatory bowel disease, (12.9%) and Reiter syndrome (12.9%). 61.3% of patients with SpA tested positive to the HLA-B27 allele. The diagnosis of SpA was associated with the presence of the HLA-B27 allele (OR 4.53; 95% CI 2.0–10.1; $P = .0001$).

Although there was a predominance of the female sex in patients with uveitis (53.2%), the male sex predominated in those with SpA and this was associated with the SpA diagnosis ($P = .0001$) (Table 1).

A family history of SpA was associated with the presence of the HLA-B27 allele ($P = .0005$) in patients with NIAU and with the diagnosis of SpA ($P < .0001$) (Table 1).

In patients with NIAU axial arthralgias predominated, which were associated with the presence of HLA-B27 ($P < .0001$), and the diagnosis of SpA ($P < .0001$) (Table 1).

Ophthalmologic complications were associated with the presence of the HLA-B27 allele ($P < .0001$) and the diagnosis of SpA ($P < .0001$) (Table 1). The complications found included: posterior synechias, vasculitis, glaucoma,macular oedema, ocular hypertension, cataracts, retinal detachment, keratitis, hypopion and sclerouveitis.

Personal history of a suspicion of immunodeficiency

Recurrent sepsis (36.0%) was the most common suspected personal history of immunodeficiency which was observed in patients with NIAU. Recurrent respiratory infections (73,2%) and diarrhoeas of infectious aetiology (14.1%) were those most frequent in this group. Recurrent sepsis was associated with the presence of the HLA-B27 allele ($P < .0001$) and the SpA (p = .0492) (Table 1).

In patients with NIAU, gastrointestinal (GI) alterations were chronic gastritis (73.8%), duodenal or gastric peptic ulcer (27.9%), chronic recurrent diarrhoeas of imprecise aetiology (16.4%) and inflammatory bowel disease (4.9%). These changes were associated with the presence of the HLA-B27 ($P = .0240$) allele and the SpA ($P = .0017$) (Table 1).

Allergies were represented by bronchial asthma (75.9%), allergic rhinitis (38.9%) and atopic dermatitis (10%). The allergies were not associated with the presence of the HLA-B27 allele ($P = .0852$) or with the diagnosis of SpA ($P = .8273$) (Table 1).

Changes to the humoral immune response

The reduction of IgG (18.8%) was the most common change of those relating to immunoglobulins in patients with NIAU and was associated with the presence of the HLA-B27 allele ($P = .0010$), with the diagnosis of SpA ($P = .0364$) (Table 1), with ophthalmic complications ($P = .0002$), with recurrent sepsis ($P = .0001$) and with GI changes ($P < .0001$) (Table 2).

In patients with positive NIAU HLA-B27 lower serum values of IgG (U = 1.979,5; $P = .0005$) were observed, with a median of 8.4 g/l (7.4–11.5), whilst in patients with negative NIAU HLA-B27 the median was 11.2 g/l (9.0–12.2) (Fig. 1).

The reduction of IgM was associated with the presence of the HLA-B27 allele ($P = .0028$), with the diagnosis of SpA ($P < .0001$) and the presence of arthralgias ($P = .0037$) (Table 1).

The reduction of at least one of the immunoglobulins studied was presented in 42 patients (21.3%) (Table 3).

Table 2
Association of the decrease of IgG e IgM with sex, ophthalmic complications, arthalgias and personal histories of a suspicion of immunodeficiencies in patients with non-infectious anterior uveites.

	Decrease IgG (n = 37)			Decrease IgM (n = 8)	
	n (%)	OR (95R CI); p1	Median (IQR); p2	n (%)	OR (95R CI); p1
Male	16 (43.2)	1.1 (.5–2.3); .7705	–	5 (62.5)	2.5 (.6–10.7); .2772
Age (years) median (IQR); p2	45.6 (36–54); .3894			37.5 (31.5–54); .6099	
Complications[a]	21 (56.8)	3.8 (1.8–8.0); .0002*	–	5 (62.5)	3.9 (.9–16.7); .1116
Arthralgias	23 (62.2)	1.9 (.9–3.9); .0937	–	5 (62.5)	1.7 (.4–7.4); .0037*
Recurrent sepsis	17 (64.9)	4.4 (2.1–10.0); .0001*	–	7 (87.5)	2.3 (.6–9.6); .2562
GI alterations	31 (83.8)	22.4 (8.6–58.5); <.0001*	–	4 (50.0)	2.3 (.6-9.6); .2562
Allergies	13 (35.1)	1.6 (.7–3.4); .2425	–	3 (37.5)	1.9 (.4–8.1); .4140

95R CI: 95% Confidence Interval; GI: Gastrointestinal; Ig: Inmunoglobulin; IQR: Interquartile Range; OR: Odds Ratio; p1: Statistical significance for the association through χ^2; p2: Statistical significance between groups using Mann-Whitney analysis.
[a] Posterior synechias, vasculitis, glaucoma, macular oedema, ocular hypertension, cataracts, retinal detachment, keratitis, hypopion, sclerouveitis and reduction in visual acuity.
* Significant differences for p < .05.

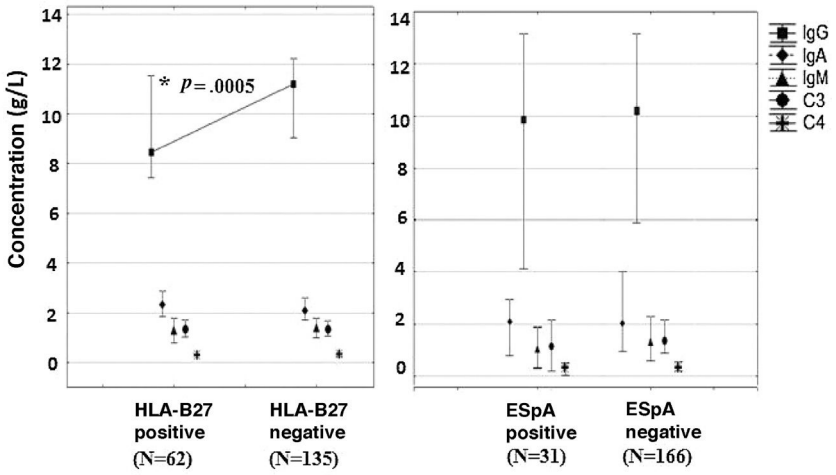

Figure 1. Serum concentration of immunoglobulins and proteins of the complement according to the presence of the HLA-B27 allele and diagnosis of spondyloarthropathy. C: complement; SpA: spondyloarthropathy; HLA-B27: human leukocyte antigen B27; Ig: immunoglobulin.
* Significant differences using the Mann-Whitney U test among HLA-B27 positive and negative patients ($P < .05$).

Table 3
Immunoglobulin alterations in patients with diagnosis of non-infectious anterior uveitis.

	Decrease							Increase						
	IgG	IgM	IgA	IgG IgM	IgG IgA	IgA IgM	Total	IgG	IgM	IgA	IgG IgM	IgG IgA	IgA IgM	Total
No. of patients	33	5	–	3	1	–	42	3	1	10	2	–	2	18
Percentage	16.8	2.5	–	1.5	.5	–	21.3	1.5	.5	5.1	1.0	–	1.0	9.1

Ig: Immunoglobulins.

Of the changes to complement in patients with NIAU an increase in C3 (39.6%) predominated. However, there was an association of the decrease of C3 (OR 4.82; 95% CI 1.35–17.11; $P = .0328$) and a decrease of C4 (OR 9.09; 95% CI 2.13–38.88; $P = .0074$) with the diagnosis of SpA. No association of the increase of C3 and C4 was observed with the variables analysed in the study (Tables 1 and 4).

Discussion

Anterior uveitis is a health problem because it is one of the most common causes of blindness worldwide.[4–6]

HLA-B27 allele in patients with NIAU and SpA

The percentage of patients positive for HLA-B27 with NIAU are within the range described by other authors, which may vary from 12% to 88%, depending on the geographical area of the study population.[1,2,13]

The expression of the HLA-B27 allele is insufficient in itself for presenting NIAU or SpA.[4] However, several approaches try to explain the relationship between the allele studied and NIAU. The molecular mimicry and the arthritogenic peptide hypothesis considers that these diseases are autoimmune. The hypothesis of incorrect folding of molecules HLA-B27 and the deposit of β2 macroglobulin chains on synovial tissues include them within the spectrum of autoinflammatory diseases.[4,16]

The hypothesis of an abnormal HLA-B27 molecule folding is based on the ability of the heavy chains of these molecules to form stable homodimers. These are retained and accumulated in the endoplasmic reticulum which constitutes a response to stress and chronic inflammation.[4,16]

Table 4
Association of drop in C3 and C4 with sex, ophthalmologic complications, arthralgias and personal backgorund of suspicion of immunodeficiency in patients with non-infectious anterior uveitis.

	Decrease C3		Increase C3		Decrease C4		Increase C4	
	n (%)	OR (IC); p1	n (%)	OR (IC); p1	n (%)	OR (IC); p1	n (%)	OR (IC); p1
Male	2 (28.6)	.6 (.1–3.0); .7022	40 (51.3)	2.0 (1.1–3.6); .0189*	4 (80.0)	6.0 (.6–54.5); .1613	13 (38.2)	.9 (.4–1.8); .7074
Age (years). median (IQR); p2	51 (32–62); .4873			44 (34–53); .2844		56 (51–62); .1224		48 (34–52); .5166
Complications[a]	4 (57.1)	3.1 (.7–14.2); .2073	25 (32.0)	1.1 (.6–2.08); .8266	2 (40)	1.5 (.2–9.2); .6464	14 (41.2)	1.7 (.8–3.6); .1659
Arthralgias	3 (42.9)	.7 (.2-3.4); 1.0000	39 (50.0)	1.0 (.6-1.8); .9540	3 (60.0)	1.5 (.2–9.3); .6827	17 (50.0)	1.0 (.5–2.1); .9740
Recurrent sepsis	2 (28.6)	.7 (.1–3.7); 1.0000	30 (38.5)	1.2 (.7–2.1); .5667	3 (60.0)	2.7 (.4–16.8); .3532	14 (41.2)	1.3 (.6–2.8); .4929
GI changes	3 (42.9)	1.7 (.4–7.9); .6789	22 (28.2)	.9 (.4–1.5); .4977	2 (40.0)	1.5 (.2–9.1); .6489	8 (23.5)	.6 (.3–1.5); .3026
Allergies	2 (28.6)	1.2 (.2–6.4); 1.0000	20 (25.5)	1.1 (.6–2.0); .8469	3 (60.0)	4.76 (.8–29.3); .0987	11 (32.3)	1.6 (.7–3.4); .2845

C: Complement serum protein; 95R CI: 95% Confidence Interval; GI: Gastrointestinal; IQR: interquartile range; OR: Odds Ratio; p1: Statistical significance for the association through χ^2; p2: Statistical significance between groups using Mann-Whitney analysis.

[a] Posterior synechias, vasculitis, glaucoma, macular oedema, ocular hypertension, cataracts, retinal detachment, keratitis, hypopion and sclerouveitis and reduction in visual acuity.

* Significant differences for $P < .05$.

In Cuba the diagnosis of SpA in patients with NIAU was described in a range from 10% to 38%, similar to that observed in other studies.[4,5]

The percentage of patients with a diagnosis of SpA and the presence of the allele studied was compared with those found in other studies, which were between 40% and 90%. NIAU may be present on diagnosis of SpA, may be a complication in the course of this disease or precede clinical manifestations of SpA,[5] which could explain the low prevalence of SpA in patients with positive NIAU for HLA-B27 in this study. Other authors have reported that the SpA is not the most prevalent of aetiologies in patients with NIAU.[17,18]

Furthermore, many patients with positive NIAU for HLA-B27 who fulfil the clincial and radiological criteria of SpA are not diganosed.[5,19]

NIAU associated with the presence of this allele is a requisite for suspecting the existence of undiagnosed SpA during long periods of time, which has a poorer prognosis.[5,20]

The greater number of patients with a diagnosis of SpA were HLA-B27 positive. The prevalence of SpA in patients with NIAU HLA-B27 positive is higher than 50% in most of the studies.[1,2,4,6]

The presence of the HLA-B27 allele has been associated with a greater frequency of AS, as occurred in this research.[1,4,5]

Demographic and clinical characteristics

Previous studies record a preponderance of the female sex in patients with NIAU.[1]

Other authors also reported a preponderance of the male sex in patients with SpA.[2,5] The most common extra-articular manifestation in male patients with SpA is NIAU, whilst in female patients it is psoriasis and inflammatory bowel disease. It has been suggested that in many cases this leads to a delayed diagnosis of SpA in women and a preponderance of males in this disease, which also explains why men have more severe radiologic conditions. Furthermore, it is known that differences exist between both sexes regarding immunological, hormonal and genetic responses.[21]

Previous studies report on medians of similar age to those of this research (6). NIAU occurs in people who are professionally active.[2,3]

Both a family history of SpA and a personal background of arthralgias constitute diagnostic SpA criteria,[7,8] which fits in with the association of these histories both with the diagnosis of SpA and with the presence of the HLA-B27 allele in this study.

Other authors found there was predominance in the reduction of visual acuity in patients with NIAU and HLA-B27 positives, as occurred in this research.[10,22]

Personal history of a suspicion of immunodeficiency

One of the most important findings from this research was the relationship between personal histories of a suspicion of immunodeficiency of recurrent sepsis and GI alterations with the presence of the HLA-B27 allele and the SpA diagnosis.

A previous history of infection or pore oral hygiene has been associated with the development of NIAU, a fact which has led to the support for the systemic infection model as a potential trigger of this disease in humans.[1,23]

An analysis study of key genes and pathways of inflammatory uptake found that in patients with NIAU and positive HLA-B27, changes existed in the metabolic signal pathways, of chemokines, and in the cytosine interaction of the receptors and processes involved in response to infections.[2,6]

The hypothesis of molecular mimicry and arthrithogenic peptide, however, suggests that the division of peptide from the HLA-B27 molecule may present microbial peptides similar to certain antigens, which allows the immune response of the positive lymphocytes T CD8 (Cluster of differentiation), restricted by the molecules HLA-B27 against microbial antigens to react with arthrogenic peptides and trigger chronic inflammation which is characteristic of this disease. These T CD8 s+ activated cells induce inflammation as a result of cross-over reactivity between exogenous antigens and peptides located in the eye.[1,7]

It has been suggested that inflammatory stimuli such as infectious processes are able to provoke the rupture of the retinal-blood supply barrier and aid migration of T-cells, which recognise their own antigens (retinal antigens) as foreign or react to them through molecular mimicry and trigger uveitis.[2,4] Several authors consider the role of chronic infection by *Helicobacter pylori*e to be major in ocular diseases such as glaucoma, mucous tissue-associated lymphoma, blepharitis, central serous chorioretinopathy and anterior uveitis.[24]

The raised frequency of chronic gastritis and peptic ulcer (duodenal or gastric) found in the study, could be associated with infection by *Helicobacter pylori* and giardiasis. Patients with impaired antibody response are more likely to suffer from autoimmune or autoinflammatory diseases such as uveitis.[15] Other resarchers observed infection by *Helicobacter pylori* in patients with anterior uveitis and ocular hypertension.[6,8]

Chronic diarrhoeas of unspecified aetiology and recurrent sores may form part of the clinical symptoms of an inflammatory bowel disease which was undiagnosed or the onset of which began at the time of study.[5] A small group of patients also presented with a diagnosis of inflammatory bowel disease. These elements may contribute to the association of GI changes with the presence of the allele studied and the SpA diagnosis.

Although allergies were not associated with changes to the humoral immune response, they predispose the body to recurrent infections due to propitiating in an inflamed tissue the invasion of infectious agents. Immune deficiencies also determine hypersensitive or allergic processes, due to changes in immune responses.[13,14]

Changes in the humoral immune response

Other important findings from this research were the association between the reduction of IgG and IgM and the presence of HLA-B27, and also between the reduction of IgG and IgM and the diagnosis of SpA.

Several authors have published that one of the causes of anterior uveitis is the presence of common variable immunodeficiency, which is mostly determined by the reduction of IgG.[6,14] However, the patients with changes in immune response by immunodeficiency have a greater predisposition to developing autoimmune and autoinflammatory processes.[3,14,25,26]

Notwithstanding it was found that other authors observed hypergammglobulinaemia and an increase in circulating immunocomplexes in patients with uveitis, with no evidence of their relationship with the clinical evolution or pathogenesis of the disease. An increase in some immunoglobulins was also been found in the study, such as that of IgA, which could correspond to a response to recurrent infections in some patients. The association of reduction of IgG with positive NIAU HLA-B27, SpA, complications, recurrent sepsis and GI changes may be explained from the reduction of immunoglobulins being predisposed to infectious processes, which in turn perpetuate and aggravate the inflammatory processes and also predispose them to other autoimmune and autoinflammatory diseases.[4,13,15,16]

As SpA are autoinflammatory or autoimmune diseases, they may require treatments with immunosuppressants, which lead to a reduction of immunoglobulins.[14,15]

In this research it was not possible to establish a definitive diagnosis of primary immunodeficiency due to the fact that assessment of antibody response to vaccine antigens is necessary, together with assessment of number and function of T cells and molecular (9) biology studies. This was one of the study limits. One element to consider for diagnosis of primary immunodeficiency was to rule out the presence of secondary immunodeficiencies, such as those from immunosuppressant treatments, which are needed on occasions in SpA, and in several patients with NIAU.[15]

Although the association found between the reduction of complement serum proteins C3 and C4 and the diagnosis of SpA was of note, their role in NIAU remains controversial.

In one genetic analysis study of the complement protein C3 no risk of susceptibility to uveitis was found.[1,4] However, it was published that with SpA patients who presented with a reduction in complement proteins and antibodies suffered from greater complications and a severe disease course which may be explained by the effects of the recurrent infections in these patients. The patients with defects of these proteins exhibit the two-directional interaction complex between immunodeficiencies and autoimmune diseases.[26]

Conclusions

Patients with NIAU, positive for the HLA-B27 allele and with a diagnosis of SpA have changes to serum levels of immunoglobulins and to components C3 and C4 of the complement, which may contribute to the perpetuation and poorer medical course of this disease.

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Conflict of interests

The authors have no conflict of interests to declare.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.reumae.2020.07.006.

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