Anti-*Saccharomyces cerevisiae* antibodies and its relationship with radiological damage in ankylosing spondylitis

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Received 30 November 2013
Accepted 10 January 2014

Egyptian Rheumatology & Rehabilitation
2014, 41:45–50

Aim

The presence of anti-*Saccharomyces cerevisiae* antibodies (ASCA) is controversial in ankylosing spondylitis (AS). In this study, we aimed to investigate the prevalence of ASCA in AS and its relationship with disease activity and radiological damage in patients attending Sharkia governorate hospitals.

Patients and methods

Thirty AS patients and 30 apparently healthy volunteers were included in the present study. All patients were questioned for Bath Ankylosing Spondylitis Disease Activity Index, Bath Ankylosing Spondylitis metrology Index and Bath Ankylosing Functional Index (BASFI). Total Bath Ankylosing Spondylitis Radiology Index (BASRI-T) and ASCA levels were measured.

Results

ASCA IgA level was significantly higher in AS patients than in healthy controls ($P < 0.001$). The ASCA-positive group, although not significant, tended to have higher BASFI scores. ASCA IgA-positive patients had higher BASRI-T levels ($P = 0.037$). In AS patients, significant positive correlation was found between ASCA IgA level and BASRI-T and BASFI ($r = 0.19$ and 0.31, respectively, $P < 0.05$). Bath Ankylosing Spondylitis Disease Activity Index scores, BASFI and ASCA IgA positivity were significantly associated with increased BASRI-T ($P = 0.01$, 0.03 and 0.04, respectively). The most significant risk factor for increased BASRI-T is ASCA IgA positivity ($P < 0.001$).

Conclusion

ASCA IgA was detected more frequently in AS patients than in healthy controls. ASCA IgA could be considered a marker of severe radiological damage. Further studies are recommended to investigate ASCA level versus radiological damage and intestinal involvement in AS patients.

Keywords:

ankylosing spondylitis, anti-*Saccharomyces cerevisiae* antibodies, functional limitations, outcome, radiological damage, severity

Egypt Rheumatol Rehabil 41:45–50

1110-161X

Introduction

Spondyloarthropathies (SpAs) are a group of diseases characterized by chronic inflammation of the axial and peripheral joints with common clinical, biological and genetic characteristics [1]. They are also characterized by dactylitis and enthesopathy as well as inflammation of the extra-articular sites such as eyes, skin and gut [2]. Experimental and clinical observations indicate an important link between the gastrointestinal tract and the articular system [3]. Approximately, one in five adult patients with classical inflammatory bowel disease (IBD) shows peripheral arthritis, axial involvement or both [4].

Because of the IBD-like mucosal changes that occur in a substantial percentage of ankylosing spondylitis (AS) patients, Palm *et al.* [5] hypothesized that serologic activity normally used to detect loss of tolerance to enteric antigens related to mucosal dysregulation in IBD will be detectable in levels above normal controls in AS patients.

Anti-*Saccharomyces cerevisiae* antibodies (ASCA) have been suggested as a serological marker for the diagnosis of undetermined IBD, although their pathological role is not yet clear [6]. ASCA are directed against the cell wall of *S. cerevisiae*, commonly known as Baker's or Brewer's yeast [7].

Although the cause of AS is still unknown, associated mucosal dysregulation with disease onset of AS would bring us closer to potentially discovering the trigger that initiates the disease phenotype called AS. Further, as in IBD, these serologies may help provide clinical information in AS that could indicate which AS patients are more likely to have intestinal inflammation or even develop overt IBD. They may help determine patients who are more likely to have aggressive disease, different phenotypic patterns of ankylosis or response to biologics [4].

The aim of the study was to investigate the prevalence of ASCA in AS and its relationship with disease

activity and radiological damage in patients attending Sharkia governorate hospitals.

Patients and methods

Study participants and design

This study was an analytical case–control study carried out in the Rheumatology and Rehabilitation, Clinical Pathology and Radiodiagnosis Departments, Faculty of Medicine, Zagazig University, Sharkia governorate, Egypt. The study included all SpAs patients who attended university hospitals, Alahrar hospital as well as insurance hospitals of Zagazig (the main hospitals that offer full assessment and follow-up as well as free treatment to patients in Sharkia governorate) during the period from June 2011 to December 2012. Three of the total 35 AS patients refused to participate in the study. Two other patients had IBD and were diagnosed as enteropathic arthropathy; hence, they were excluded from the study. The remaining 30 AS patients comprised the patient group and their diagnosis was made according to the European Spondyloarthropathy Study Group criteria [8].

Thirty age-matched and sex-matched apparently healthy volunteers were included as a control group; the clinical examination as well as routine laboratory investigations confirmed their healthy state.

Patients were not included, if they had evidence suggesting any of the following: chronic IBD (Crohn's disease, ulcerative colitis), reactive arthritis, clinical history of metabolic or degenerative diseases and/or positive rheumatoid factor, in addition to undifferentiated spondyloarthritis (uSpA) — diagnosis of uSpA was made in patients who had features of SpA but who failed to meet the European Spondyloarthropathy Study Group criteria [9] — or psoriatic arthritis — diagnosis of psoriatic arthritis was made according to criteria described by Taylor *et al.* [10].

The study was approved by the Ethical Committee of Zagazig University and informed consent was obtained from all patients and controls.

Clinical measurements

In all AS patients, we used the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) [11]. BASDAI value of 4 or more is considered to reflect a high disease activity, whereas value less than 4 is considered a low disease activity. The Bath Ankylosing Spondylitis Metrology Index (BASMI) score was also determined [12]. AS patients functional assessment was performed using the Bath Ankylosing Spondylitis Functional Index (BASFI) [13].

Radiological outcome measurements

Sacroiliac joint, anterior and posterior pelvis, anterior–posterior and lateral lumbosacral radiographies and cervical radiography of the patients were taken. All radiographs were collected and radiological evaluation was performed within 1 week. The physician who performed radiological scoring was blinded to clinical assessment results of the patients. Radiological scoring was performed according to the Total Bath Ankylosing Spondylitis Radiology Index (BASRI-T).

The lumbar spine was defined as extending from the lower border of T12 to the upper border of S1, and the cervical spine was defined as extending from the lower border of C1 to the upper border of C7. BASRI-T (total scoring) is calculated by the addition of both the BASRI-s (scoring of the spine) and BASRI-h (scoring of hip joints) [14].

The lumbar and cervical spine were graded separately on a scale of 0–4 (0 = no change; 1 = no definite change; 2 = any number of indications of erosions, squaring or sclerosis, with or without syndesmophytes, on one or two vertebrae; 3 = syndesmophytes on three or more vertebrae, with or without fusion involving two vertebrae and 4 = fusion involving three or more vertebrae). Each sacroiliac joint was scored as: 0 = no disease; 1 = suspicious change; 2 = loss of definition at the edge of the joint, minimal erosions, mild sclerosis and joint space narrowing might be present; 3 = definite sclerosis on both sides, larger erosions with loss of joint space and 4 = complete fusion or ankylosis of the joint (without residual sclerosis).

The BASRI-s score is the sum of the mean scores for the right and left sacroiliac joints in addition to that of the lumbar spine and the cervical spine and has a possible range of 2–12. The hips were graded on a scale of 0–4 (0 = no change, 1 = focal joint space narrowing, 2 = circumferential joint space narrowing >2 mm, 3 = circumferential joint space narrowing ≤2 mm or bone-on-bone apposition of <2 cm and 4 = bone deformity or bone-on-bone apposition of ≥2 cm). The BASRI score of the most severely affected hip was used. The BASRI-T includes radiological change in the spine, sacroiliac and hip joints (range 2–16).

Laboratory procedures

(1) Erythrocyte sedimentation rate (ESR) was performed according to the Westergren method.
(2) Sera of patients and controls were collected by centrifugation of venous blood samples and were stored at –20°C, and the following investigations were performed: ASCA IgA and IgG were detected

using the commercial kit, Bindazyme EIA Kit (Binding Site Ltd, Birmingham, UK). All samples were measured in duplicate and the results were then averaged. The intra-assay coefficients of variation for the ASCA IgA measurement was 6.5% and for ASCA IgG was 6.6%; the interassay coefficients of variation was 6.0% for ASCA IgA and 3.8% for ASCA IgG. The quantitative ASCA IgA and IgG results were obtained in U/ml and were accepted as positive according to the cutoff values by the manufacturer's instructions, greater than 10 U/ml. Results were expressed as negative or equivocal, if values were less than 10 or 10 EU, respectively.

(3) High-sensitivity C-reactive protein (hsCRP) measurements for the quantitative determination of hsCRP in serum was performed by particle-enhanced immunoturbidimetric assay. Results were evaluated automatically by Cobas c 501 (Roche, Los Angeles, CA, USA) and were represented in mg/l. Expected values for healthy individuals are typically lower than 3 mg/l.

(4) HLA-B27 typing was performed using a semiautomated commercially available reverse dot blot method, Inno-LiPA, following the manufacturer's instructions. The reaction patterns were interpreted using Inno-LiPA (Inno-LiPA Innogenetics N.V. GENT, Belgium) software. HLA-B27 subtypes were identified using either single-strand conformational polymorphism after amplification with B27-specific primers or the Inno-LiPA software [15].

Statistical methods

Descriptive statistical methods were used to calculate mean and SD. For comparison between two variables, the *t*-test was used. Comparison of categorical data was performed with the χ^2-test or the Fisher exact test. *P*-value of less than 0.05 was considered statistically significant. Receiver operating characteristic curve was performed to calculate the cutoff value of ASCA (>10 U/ml). Linear regression analysis (univariate analysis) was applied to evaluate the association of the different risk factors with radiological changes (BASRI-T). Analytical results of univariate analysis were presented as the odds ratio (OR) and 95% confidence interval (CI). Multiple logistic regression analysis was performed to assess the weight of detected risk factors. The statistical analysis was carried out using statistical package of social science (SPSS, version 11.0; SPSS Inc., Chicago, Illinois, USA).

Results

Characteristic data of the studied groups

The female to male ratio was 1 : 2 in AS. The sex ratio of the healthy control was matching and the difference between groups was insignificant. In addition, difference between groups was insignificant with respect to age ($P > 0.05$).

ASCA IgA positivity was significantly more frequent in AS (57%) compared with controls (10%) ($P < 0.001$). The level of IgA was significantly higher in AS patients than in healthy controls ($P < 0.001$) (Table 1).

Comparing clinical and laboratory data in ankylosing spondylitis patients with respect to anti-*Saccharomyces cerevisiae* antibodies IgA positivity

BASDAI, BASMI and BASFI scores in AS were comparable in ASCA IgA-positive versus negative patients (mean scores were 6.5 vs. 6 for BASDAI and 5 vs. 6 for BASMI, respectively). Although not significant, chest expansion was more limited in ASCA IgA-positive patients (mean 2.1 vs. 2.6 cm, $P = 0.076$), and ASCA IgA-positive patients tended to have higher BASFI scores [median (range) 38 (0–78) vs. 30 (0–92), $P = 0.23$]. ASCA IgA-positive patients had significantly higher BASRI-T levels [median BASRI-T (range) 12 (2–16) vs. 5 (2–10), $P = 0.037$]. This is shown in Figure 1.

There was no significant difference between ASCA IgG-positive and IgG-negative patients regarding disease duration, age, morning stiffness, HLA-B27 positivity, enthesopathy, detection of peripheral arthritis, uveitis, ESR, hsCRP, Schöber's test/cm, hand-to-ground distance/cm, occiput-to-wall distance/cm, chest expansion/cm, BASFI, BASDAI, BASMI and BASRI-T scores (Figs. 1-3).

Correlation between anti-*Saccharomyces cerevisiae* antibodies IgA level and clinical and laboratory parameters

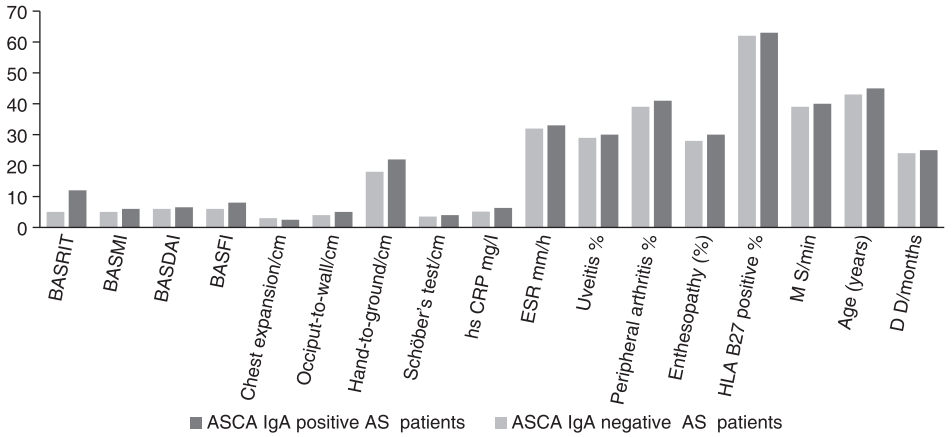
A significant positive correlation was found between ASCA IgA level in AS patients and the following parameters: BASRI-T and BASFI, whereas no correlations were found between it and the remaining parameters (Table 2).

Table 1 Demographic data and frequency of HLA-B27 and anti-*Saccharomyces cerevisiae* antibodies in the studied groups

	Group I (AS) (*n* = 30)	Group II (control group) (*n* = 30)
Age (years)	43.8 ± 10.4	46.5 ± 3.9
Sex (♀ : ♂)	10 : 20	11 : 19
Disease duration (months)	15 (4–48)	–
HLA-B27	21 (70)	Not done
ASCA IgA+	17 (57)*	3 (10)
ASCA IgG+	5 (10)	2 (6)
ASCA IgA level (U/ml)	35 ± 9*	8 ± 2

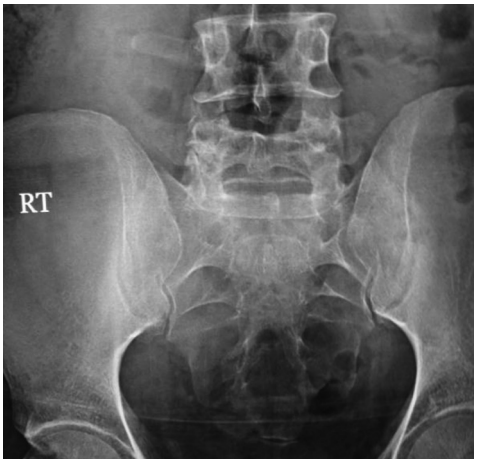
Numerical data are expressed as mean and SD; categorical data are expressed as number (%). AS, ankylosing spondylitis; ASCA, anti-*Saccharomyces cerevisiae* antibodies; *n*, number of patients with available data. *Significant, $P < 0.001$.

Figure 1



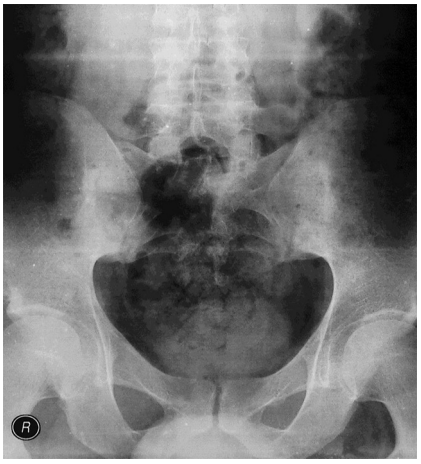
Frontal radiograph showing normal sacroiliac joint in anti-*Saccharomyces cerevisiae* antibodies IgA-negative patient.

Figure 2



Comparing ASCA-positive versus ASCA-negative AS patients regarding different assessment parameters. AS, ankylosing spondylitis; ASCA, anti-*Saccharomyces cerevisiae* antibodies; BASDAI, bath ankylosing spondylitis disease activity index; BASFI, Bath ankylosing spondylitis functional index; BASMI, bath ankylosing spondylitis metrology index; BASRI-T, total bath ankylosing spondylitis radiology index; DD, disease duration; ESR, erythrocyte sedimentation rate; hsCRP, high-sensitivity C-reactive protein; MS, morning stiffness.

Figure 3



Frontal radiograph of sacroiliac joint (SIJs) showing bilateral blurring of joint line with prominent bilateral subchondral sclerosis (grade III) in anti-*Saccharomyces cerevisiae* antibodies IgA-positive patient.

Table 2 Correlation between anti-*Saccharomyces cerevisiae* antibodies IgA level and different assessment parameters including the radiological parameters in ankylosing spondylitis patients

	DD	ESR	hsCRP	BASFI	BASDAI	BASMI	BASRI-T
R	0.13	0.16	0.11	0.31*	0.021	0.19	0.35*
P	>0.05	>0.05	>0.05	0.02	0.6	0.09	<0.05

BASDAI, bath ankylosing spondylitis disease activity index; BASFI*, bath ankylosing spondylitis functional index; BASMI, bath ankylosing spondylitis metrology index; BASRI-T*, total bath ankylosing spondylitis radiology index; DD, disease duration; ESR, erythrocyte sedimentation rate; hsCRP, high-sensitivity C-reactive protein.

Significant indicators of radiological damage

Univariate analysis (linear regression test) showed that BASDAI, BASFI scores and ASCA IgA positivity were significantly associated with increased radiological damage (BASRI-T > 5 in AS patients); OR and 95% CI were 2.1 (1.9–2.1), 2.4 (1.5–2.9) and 2.9 (2.1–3.1), respectively (Table 3).

Multiple logistic regression analysis showed that the most significant risk factor for radiological damage was ASCA IgA positivity. OR and 95% CI were 2.5 (2.85–3.19) (Table 4).

Discussion

Increased gut permeability and inflammation have been observed in AS in multiple previous studies [16]. The authors of the present study investigated the prevalence of ASCA in AS and its relationship with disease activity and radiological damage in patients attending Sharkia governorate hospitals.

Table 3 Relationship between different risk factors and Total Bath Ankylosing Spondylitis Radiology Index in ankylosing spondylitis patients

	BASRI-T > 5 (*n* = 13) [*n* (%)]	OR (95% CI)	*P*
Sex			
Male (20)	8 (40)	2 (0.9–3.2)	0.09
Female (10)	4 (40)		
Peripheral arthritis			
+(13)	6 (46)	4 (0.3–6.2)	0.08
–(17)	7 (41)		
Uveitis			
+(7)	3 (43)	2.3 (0.1–1.9)	0.10
–(23)	10 (43)		
BASDAI			
≥4 (17)	8 (47)	2.1 (1.9–2.1)*	0.01
<4 (13)	5 (38)		
BASMI			
>5 (16)	7 (44)	3.2 (0.1–2.6)	0.12
≤5 (14)	6 (43)		
BASFI			
>5 (18)	9 (50)	2.4 (1.5–2.9)*	0.03
≤5 (12)	4 (33)		
hsCRP			
>3 (14)	6 (43)	2.4 (0.3–2.2)	0.06
≤3 (16)	7 (44)		
HLA-B27			
+(16)	7 (44)	2.7 (0.6–3.3)	0.06
–(14)	6 (43)		
ASCA IgA positive			
+(17)	8 (47)	2.9 (2.1–3.1)*	0.04
–(13)	5 (38)		
ASCA IgG positive			
+(5)	2 (40)	2.9 (0.1–2.1)	0.07
–(25)	11 (44)		

ASCA IgA positive*, anti-*Saccharomyces cerevisiae* antibodies; BASDAI*, bath ankylosing spondylitis disease activity index; BASFI*, bath ankylosing spondylitis functional index (BASFI); BASMI, bath ankylosing spondylitis metrology index; BASRI-T, total bath ankylosing spondylitis radiology index; CI, confidence interval; hsCRP, high-sensitivity C-reactive protein; OR, odds ratio.

Table 4 Multiple logistic regression analysis for risk factors significantly influencing radiological damage in ankylosing spondylitis patients as reflected by Total Bath Ankylosing Spondylitis Radiology Index

	BASRI-T > 5 [OR (95% CI)]	*P*
ASCA IgA	2.5 (2.85–3.19)	<0.001
BASFI>5	2.1 (1.39–1.97)	<0.01
BASDAI≥4	1.9 (1.11–2.8)	<0.05

ASCA, anti-*saccharomyces cerevisiae* antibodies; BASDAI, bath ankylosing spondylitis disease activity index; BASFI, bath ankylosing spondylitis functional index; BASRI-T, total bath ankylosing spondylitis radiology index; CI, confidence interval; OR, odds ratio.

In the present study, ASCA IgA positivity was significantly more frequent in AS patients (57%) compared with controls (10%) ($P < 0.001$). The level of IgA was significantly higher in AS patients than in healthy controls ($P < 0.001$). Similar to this finding, Hoffman *et al.* [17] found that higher ASCA IgA levels, but not IgG levels, were frequently detected in AS and uSpA patients than in controls. In addition, ASCA IgA positivity was more frequent in AS patients in Török *et al.* [18] study.

In contrast, another study failed to show the increased frequency of ASCA positivity in AS arthritis patients [19]. The most reasonable explanation for this controversial result is the methodological difference between the assays. The two studies using the same kit had found similar results in AS patients, supporting the role of assay-related factors [17,18].

ASCA IgA level was significantly higher in AS patients than in healthy controls ($P < 0.001$). These results were in agreement with the study by Hoffman *et al.* [17].

Parameters about disease activity in AS patients, such as ESR, hsCRP and BASDAI scores, were found to be similar in the ASCA-positive and ASCA-negative groups; however, ASCA IgA-positive patients tended to have higher BASFI scores (functional index) ($P = 0.037$) and BASRI-T scores (radiological index). Our results are in agreement with the results of Aydin *et al.* [20] who found a significant association between ASCA positivity and the severity of the disease (BASRI).

Similar to our findings, several studies did not find any association between the BASDAI scores and ASCA positivity [17,21,22].

A significant correlation was found between ASCA IgA level in AS patients and the following parameters: BASRI-T and BASFI ($P < 0.05$ for both), and this was correlated with the results of Aydin *et al.* [20].

The comparison of the modified Stroke Ankylosing Spondylitis Spinal Score of Aydin *et al.*'s [20] study, however, failed to show any significant correlation according to ASCA positivity. They stated that the most reasonable explanation for this result is the wide range of both ASCA IgA and IgG levels. ASCA level seems to be a better marker than ASCA positivity.

In the present study, ASCA-positive patients had more radiological damage as represented by BASRI-T. A possible explanation of this finding is that AS patients with advanced disease may have more intestinal involvement and ASCA positivity may be a marker of ongoing antigenic stimulus. In this hypothesis, ASCA positivity may be a reflection of higher disease activity causing a higher radiological damage [7].

Some authors even suggested that IBD and uSpA could be different phenotypes of the same autoimmune disease that are expressed in different ways because of

genetic influence [23]. Hypothetically, if an increased exposition to microbial antigens from the gut is associated with increased inflammatory reaction in the joints, one could anticipate an increased intestinal permeability associated with uSpA activity [23].

As our study is cross-sectional, whether ASCA presence is the result of or a pathogenic factor for disease severity and radiological damage is unclear. Aydin *et al.* [20] suggested that there might be a relationship between the higher ASCA IgA levels seen in SpA, especially in AS patients, and the subclinical gut inflammation reported in patients with SpA. This hypothesis gained strength because of the fact that ASCA levels are not increased in patients with psoriatic arthropathy, as in this patient group the presence of gut inflammation is lower than in AS or uSpA [24].

Univariate analysis showed that BASDAI, BASFI scores and ASCA IgA positivity were significantly associated with increased BASRI-T greater than 5 in AS patients (P = 0.01, 0.03 and 0.04, respectively), which is in agreement with previous studies [20,25]. Multiple logistic regression analysis showed that the most significant risk factor for the development of radiological damage (BASRI-T) is ASCA IgA positivity (P < 0.001). Increased intestinal permeability (as shown by ASCA positivity) in AS patients may lead to higher antigenic stimulus and radiological damage [20].

In conclusion, ASCA IgA was detected more frequently in AS patients than in healthy controls. ASCA IgA could be considered a marker of severe radiological damage. Further studies are recommended to investigate ASCA level versus radiological damage and intestinal involvement in AS patients.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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