Prevalence of Subclinical Amyloidosis in Ankylosing Spondylitis

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ABSTRACT. ***Objective.*** To study the prevalence of secondary amyloidosis in Indian patients with ankylosing spondylitis (AS).

Methods. Seventy-two AS patients with disease duration of more than 5 years were included in this study over a period of one and a half years. Abdominal subcutaneous fat pad aspiration (ASFA) was performed with a fine needle, and smears were examined for apple-green birefringence under polarized light after Congo red staining. The amyloid deposits were graded from 1+ to 3+ by visual inspection. Clinical and laboratory features of the patients were correlated with the absence or presence of amyloid deposits.

Results. Five patients (6.9%) with AS were positive for amyloid on ASFA. All the patients had 1+ deposit and were male. None of the patients had clinical amyloidosis. ASFA positive patients had a trend towards older age, longer disease duration, more limitation of the spinal mobility, and significantly lower hemoglobin levels.

Conclusion. We found in our population that subclinical amyloid deposits can be detected in 7% of AS patients with disease duration longer than 5 years. There is a need to follow up patients with positive ASFA tests to check for the development of clinical amyloid. (First Release Jan 15 2007; J Rheumatol 2007;34:371–3)

Key Indexing Terms:
SERUM AMYLOID A PROTEIN OUTCOME SPONDYLOARTHROPATHIES

Ankylosing spondylitis (AS) is a chronic inflammatory rheumatic disease that primarily involves the spine and the entheseal sites. The majority of patients have continued disease activity on long followup[1]. Chronic inflammation is characterized by elevation in levels of acute phase proteins like C-reactive protein (CRP), serum amyloid A protein, and IgA in sera. Among these, serum amyloid A can deposit as insoluble form, i.e., AA amyloid[2]. Amyloidosis has been found to be the direct cause of death in up to 12% of patients with AS on longterm followup[3]. However, clinical amyloidosis is rare, reported in 2 patients among 47 on longterm followup[4] or as case reports[5,6]. Among 203 patients with AS, renal amyloidosis occurred in 3.8% cases[7]. A prospective study from Europe reported the prevalence of subclinical amyloidosis in patients with AS to be 7%[8]. European descent is a risk factor for higher prevalence of amyloidosis in patients with juvenile idiopathic arthritis (JIA) and rheumatoid arthritis (RA)[9].

Amyloidosis is a histological diagnosis, so various tissue biopsies have been used in the past including rectal, gingival, gastroduodenal, and kidney. Abdominal subcutaneous fat pad aspiration (ASFA) is a safe, simple, rapid, repeatable, outpatient based technique and has a good patient acceptability. It causes minimal patient discomfort with little risk of morbid complications. The ASFA has a sensitivity and specificity of 80 and 100%, respectively[10].

The clinical spectrum of AS in India is quite similar to that reported from other parts of the world. However the diagnosis is often delayed in our country[11]. Since the prevalence of amyloidosis varies in different ethnic groups and no data are available on prevalence of amyloidosis in patients with AS from southeast Asia, we studied the prevalence of amyloidosis in patients with AS using ASFA.

MATERIALS AND METHODS

Patients with AS from India seen at our outpatient clinic and fulfilling the 1984 modified New York criteria[12] with more than 5 years of disease duration were included in the study. All subjects gave informed consent. Patients with coexisting chronic disorders that could lead to secondary amyloidosis, e.g., tuberculosis, leprosy, or bronchiectasis, were excluded from the study.

ASFA with a fine needle using standard procedure was performed in these patients. Fat specimens were analyzed under polarized microscope after Congo red staining. Positive ASFA test was defined as presence of apple green birefringence after Congo red staining. Amyloidosis was graded semi-quantitatively on a scale of 1–3[13].

Clinical variables recorded were: age, sex, age at onset, duration of symptoms, axial involvement, peripheral arthritis, uveitis, diarrhea, hip joint involvement, chest expansion, spinal mobility by Schober's test, finger to floor distance, lateral flexion, occiput to wall distance, erythrocyte sedimentation rate by Westergren's method, routine urine examination for proteinuria, and spot protein/creatinine ratio to quantitate proteinuria was done in all patients. Patients with positive ASFA had 24 hour urine protein estimation performed.

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All patients were questioned for presence of pedal edema, bowel disturbances, and symptoms of renal insufficiency. And some patients were examined for pedal edema, hepatosplenomegaly, and signs of nutritional deficiency suggestive of malabsorption. Patients with proteinuria or clinical signs suggestive of malabsorption and positive ASFA test were categorized as having clinical amyloidosis, and patients with only positive ASFA test but no clinical features were categorized as having subclinical amyloidosis. In patients who were ASFA positive, serum electrophoresis was done to exclude AL amyloid.

RESULTS

Between December 2004 and May 2006, 93 consecutive patients with AS of more than 5 years' disease duration were seen in clinic. Of these, 72 agreed to participate in the study. The mean age of these patients was 34.4 ± 10.2 years and mean disease duration was 13.5 ± 6.4 years; 63 of the patients were male.

Amyloid deposits were observed on ASFA in 5 (6.9%) of these patients. All the patients had 1+ (mild) amyloid deposit. None had clinical amyloidosis (Table 1). All the patients with subclinical amyloidosis were male. Patients with subclinical amyloidosis had a trend towards longer disease duration, higher age, and more limitation of spinal mobility as measured by Schober's test as compared to patients without amyloid deposits (Table 2). However, none of these comparisons reached statistical significance due to the small number of patients with subclinical amyloidosis.

DISCUSSION

Our data suggest a low prevalence of subclinical amyloidosis in patients with AS of 5 or more years' duration, and no patient had clinical amyloidosis.

The prevalence of ASFA positivity for amyloidosis in our study is similar to a prevalence of 7% in a previous study. Our study group did not have any patient with clinical amyloidosis in contrast to 2 patients in Gratacos, *et al*'s study; this could be due to shorter mean duration of disease of 13.5 years in our study as compared to 18 years in theirs[8].

Does subclinical amyloidosis lead to clinical amyloidosis? In the followup study by Gratacos, *et al*, 3 of 8 patients with

Table 1. Clinical and laboratory variables in patients with subclinical amyloidosis.

Patient	Duration of Disease (yrs)	Uveitis	Peripheral Arthritis	Creatinine (mg/dl)	Albumin (g/dl)	24 h Urinary Protein (g)
1	15	No	No	0.9	3.5	0.2
2	16	Yes	Yes	1.5	3.0	0.2
3	12	No	Yes	0.9	3.4	0.2
4	19	Yes	Yes	1.0	4.1	0.1
5	14	No	No	1.4	4.8	0.1

Normal reference value for serum creatinine (0.6–1.4 mg/dl), 24 h urinary protein (< 0.3 g/day), serum albumin (3.5–5.5 g/dl).

Table 2. Clinical features of patients with ankylosing spondylitis.

	Total, n = 72	ASFA Positive, n = 5	ASFA Negative, n = 67
Males, no. (%)	63 (87)	5 (100)	58 (86)
Age, yrs, mean ± SD	34.6 ± 10.2	39.2 ± 7.4	34.3 ± 10.4
Disease duration, yrs, mean ± SD	13.5 ± 6.4	15.2 ± 2.5	13.0 ± 6.6
Age at onset, yrs, mean ± SD	21.8 ± 7.8	24.0 ± 6.5	21.6 ± 7.9
Hip pain, no. (%)	46 (70)	5 (100)	41 (61)
Neck pain, no. (%)	57 (79)	5 (100)	52 (77)
Uveitis, no. (%)	29 (40)	2 (40)	27 (40)
Peripheral arthritis, no. (%)	38 (53)	3 (60)	35 (52)
Family history, no. (%)	22 (31)	1 (20)	21 (31)
Chest expansion, cm, mean ± SD	2.7 ± 1.4	2.9 ± 1.7	2.7 ± 1.3
Schober's, cm, mean ± SD	2.1 ± 1.3	1.8 ± 1.8	2.2 ± 1.3
Finger floor distance, cm, mean ± SD	22.6 ± 16.9	26.6 ± 9.3	21.6 ± 17.8
Lateral flexion, cm, mean ± SD	7.4 ± 5.0	4.2 ± 1.6	7.9 ± 5.3
Occiput to wall distance, cm, mean ± SD	5.6 ± 6.9	11.4 ± 7.13	5.2 ± 7.0
Hemoglobin, gm/dl, mean ± SD*	11.3 ± 2.0	8.7 ± 1.5	11.4 ± 2.0
ESR, mm/h, mean ± SD	59.6 ± 37.8	55.0 ± 20.9	58.8 ± 40.4
Creatinine, mg/dl, mean ± SD	1.0 ± 0.28	1.14 ± 0.28	1.0 ± 0.2

* p = 0.007 between patients with positive ASFA vs. those without it. ASFA: Abdominal subcutaneous fat pad aspiration, Normal reference values for erythrocyte sedimentation rate (ESR) (:0–10 for males and 0–20 for females.).

subclinical amyloidosis progressed to clinical amyloidosis after a mean followup of 5.4 years (range 2–10 years)[8]. In rheumatoid arthritis (RA) clinical amyloidosis developed in 10% of patients with ASFA positivity after 10 years of followup[14]. Thus, it seems that only a small number of patients with subclinical amyloidosis progress to clinical amyloidosis and, except for better control of disease activity, no specific intervention is needed.

Despite using the same methodology in a previous study in RA, the prevalence of subclinical amyloidosis in 113 patients with RA from our center was 26%, and 5 patients had clinical amyloidosis[13]. Further, the mean disease duration was only 10 years in patients with RA in contrast to AS, where it is 13 years. Both these observations suggest a lower burden of inflammation in patients with AS compared to RA. Even in autopsy studies the prevalence of amyloidosis is lower (6%) in AS[15] compared to RA, where it is 15–20%[16].

In our patients with AS, the prevalence of amyloid deposits was 7%, and in all AS was subclinical. Our patients with subclinical amyloidosis should be followed to see if they will develop clinical disease in future.

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