Mannose Binding Lectin Levels in Spondyloarthropathies

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ABSTRACT. ***Objective.*** Mannose binding lectin (MBL), a member of the collectin family proteins, is a major molecule of the innate immune system; MBL deficiency is associated with increased susceptibility to infections. As gastrointestinal and genitourinary infections are suggested to be among the etiological factors of spondyloarthropathies (SpA), we investigated MBL deficiency in ankylosing spondylitis (AS) and undifferentiated SpA (uSpA).

Methods. One hundred seven patients with AS, 43 patients with uSpA, and 74 healthy controls were studied. Disease activity, radiological scores, and demographic features were recorded. MBL levels were measured with standard ELISA kits.

Results. Median MBL levels in AS, uSpA, and controls were 2705 (range 0–5861) ng/ml, 2897 (36–7586) ng/ml, and 3468 (0–7950) ng/ml, respectively. No significant differences were observed in median MBL levels and the prevalence of MBL deficiency between the groups. Bath AS Radiological Index scores were not affected by MBL levels. However, although statistically not significant, radiographic damage quantified by modified Stoke AS Spine Score (mSASSS) was 3 times higher in AS patients with MBL deficiency. Disease activity, clinical picture, and therapies were not associated with MBL levels.

Conclusion. In AS patients with MBL deficiency, there was a tendency towards a more severe radiographic progression detected by mSASSS. (First Release Sept 15 2007; J Rheumatol 2007;34:2075–7)

Key Indexing Terms:
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Several bacterial species are known to induce reactive arthritis (ReA) and the susceptibility to some of these rheumatic disorders is influenced by HLA-B27 positivity. It is well known that about 10% of HLA-B27-positive patients with ReA develop full-blown ankylosing spondylitis (AS) when followed for more than 10 years[1]. In 2 recent studies antibody titers against *Klebsiella* and *Campylobacter* were found to be higher in patients with AS compared to controls[2,3].

Mannose binding lectin (MBL) is a major component of the innate immune system. As a member of the collectin family, MBL functions as a recognition molecule of the complement system. It binds to the carbohydrate structure of a broad range of microorganisms and activates the complement system via the lectin pathway[4,5].

Plasma MBL levels are determined by the allelic dimorphisms in both structural MBL gene and its promoter region[6]. Low MBL levels are associated with recurrent infections in both pediatric and adult patients[7,8].

Recent studies have shown that specific MBL polymorphisms leading to MBL deficiency were found more frequently in patients with rheumatoid arthritis (RA), and this was associated with a more severe radiographic joint destruction[9–11]. Similarly, MBL gene polymorphisms were found to be a risk factor for a susceptibility to systemic lupus erythematosus (SLE) and arterial thrombosis[12,13]. Our group also demonstrated that low MBL levels were associated with Behçet's disease[14].

In our study, serum MBL levels were studied in spondyloarthropathies (SpA) to investigate any association with disease susceptibility and severity.

MATERIALS AND METHODS

One hundred seven patients with AS fulfilling the modified New York criteria[15], 43 patients with undifferentiated SpA (uSpA) according to the European Spondylarthropathy Study Group criteria[16], and 74 healthy controls were studied. All patients gave data by questionnaire for demographic features and Bath AS Disease Activity Index (BASDAI) and Functional Index (BASFI) scores. Bath AS Radiological Index (BASRI) and modified Stoke AS Spine Score (mSASSS) scores of 44 patients with AS were available. Serum MBL levels were measured by MBL oligomer ELISA (Antibody Shop, Copenhagen, Denmark). The study was approved by the Ethical Committee of Marmara University Medical School and informed consent was obtained from all patients and controls.

Mann-Whitney U-test was used to compare MBL levels between the groups. Both groups were subdivided into 2 groups as low (< 500 ng/ml) and very low (< 100 ng/ml) MBL levels and parametric comparisons were performed by chi-square test. Linear regression analysis was used for the determination of contributing factors. In this analysis, age, disease duration, BAS-

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DAI and BASFI scores, and erythrocyte sedimentation rate (ESR) were selected as independent variables for MBL levels. Statistical analysis was performed with the SPSS 11.0 statistical package (SPSS, Chicago, IL, USA).

RESULTS

The characteristics of patients are shown in Table 1. Patients with AS had a longer disease duration, higher ESR levels, and more frequent HLA-B27 positivity. Median MBL levels [AS: 2705 ng/ml (range 0–5861), uSpA: 2897 ng/ml (36–7586), and controls: 3468 ng/ml (0–7950); p = 0.4] and the ratio of low and very low MBL levels were comparable in each group (Table 2).

There was a weak but significant inverse relation between MBL levels and age in the AS group ($R^2 = 0.079$, p = 0.045). The median levels of MBL below and over the median age in AS were 3995 versus 1365 ng/ml (p = 0.005). However, no significant differences according to age were present in patients with uSpA and controls [uSpA: 3144 (36–5820) vs 1883 (37–7586) ng/ml (p = 0.5); controls: 3415 (4–7950) vs 3725 (4–7659) ng/ml (p = 0.5); median levels of MBL below vs those over the median age for each group]. BASDAI/BASFI scores and ESR were not related to MBL levels. BASRI scores were not affected by MBL levels [MBL < 500 ng/ml, BASRI: 4.5 (2–12) (n = 10) vs MBL ≥ 500 ng/ml, BASRI: 5 (2–11) (n = 34); p = 0.91)]. However, although not statistically significant, mSASSS scores were 3 times higher in AS patients with MBL deficiency (MBL < 500 ng/ml, mSASSS: 6.5 (0–72) vs MBL ≥ 500 ng/ml, mSASSS: 2 (0–46); p = 0.3).

Table 1. Characteristics of the study group.

	AS	uSpA	Controls	p*
N	107	43	74	
Female, %	47	70	61	0.017
Age, yrs (range)	40 (17–69)	38 (20–58)	39 (30–58)	0.52
Disease duration, yrs (range)	12 (2–37)	4 (1–22)		< 0.001
HLA B27 positive, %	72	30		< 0.001
Salazopyrin therapy, %	86	69		0.03
Methotrexate therapy, %	55	30		0.021
Anti-TNF-α therapy, %	18	3		0.049
Uveitis, %	41	31		0.6
BASDAI (range)	19 (0–58)			
BASFI (range)	15 (0–85)			
Periferic arthritis, %	65.5	59.4		0.65
ESR, mm/h (range)	28 (5–69)	20 (2–88)		0.049
Modified Schober's, cm (range)	4 (0–7)	5 (3–8)		0.019
Chest expansion, cm (range)	3.2 (1–9)	4 (2–6)		0.47
BASRI (range)	5 (2–12)			
mSASSS (range)	2 (0–72)			

* p values reflect Kruskal-Wallis test comparing 3 groups where applicable. AS: ankylosing spondylitis; uSpA: undifferentiated spondyloarthropathy; TNF: tumor necrosis factor; BASDAI: Bath AS Disease Activity Index; BASRI: Bath AS Functional Index; ESR: erythrocyte sedimentation rate; BASRI: Bath AS Radiological Index; mSASSS: modified Stoke Ankylosing Spondylitis Spine Score

Table 2. MBL levels and ratio of MBL deficiency.

	AS	uSpA	Controls	p*
Median MBL (range)	2705 (0–5861)	2897 (36–7586)	3468 (0–7950)	0.4
< 500 ng/ml, %	21	18	16	0.78
< 100 ng/ml, %	14	9	11	0.7

* Kruskal-Wallis test comparing 3 groups.

Disease duration, sex, and HLA-B27 positivity were not related to MBL deficiency. Therapies and clinical picture including uveitis and axial and peripheral involvement were similar in both MBL groups.

DISCUSSION

MBL deficiency in AS has not been reported in the literature. Although infections are considered as a risk factor for the disease onset and activity in SpA, our study failed to show that MBL deficiency is a contributing factor to infections in AS. Disease activity, acute-phase reactants, and functional status were also not associated with MBL levels in AS in our study. In the only similar study reported, incidence and outcome of ReA caused by *Salmonella, Yersinia,* and *Campylobacter* were not associated with MBL levels[17]. These results suggest that, in contrast to other studies in susceptible populations such as neutropenic or cancer patients, arthritis triggered by bacteria is possibly not related to MBL deficiency in SpA[7,8].

We found an inverse relation between MBL levels and age in AS. Similarly, a previous population-based study investigating the effects of age and sex on MBL reported lower mean MBL levels in older groups, and this relationship was not influenced by gender[18]. Whether low MBL levels contribute to the infection susceptibility of the elderly requires further investigation.

In patients with MBL deficiency, there was a tendency toward a more severe radiographic progression detected by mSASSS, but not by BASRI. Recently, a study by Salaffi, *et al* suggested that mSASSS was superior to BASRI in detecting radiographic damage over time[19]. Although our low patient numbers preclude us from a definite conclusion, chronic damage in AS shown by radiographic progression might be influenced by MBL deficiency. A larger study focusing on radiographic damage in patients with different levels of MBL could be of interest.

One weakness of our study is the cross-sectional analysis of serum MBL levels. Although there was no correlation between disease activity and MBL levels, as mild changes associated with inflammation are reported in serum MBL levels, MBL measurements should be performed at different times to completely exclude the effect of disease activity. Serum MBL levels are shown also to be associated with the

gene and promoter region polymorphism of MBL, which is lacking in our study. However, as we found no association of SpA with low MBL levels, genetic analysis possibly would not contribute much to our results.

In conclusion, similarly to ReA, MBL deficiency does not seem to be an important contributing factor to disease susceptibility in AS. Whether any other genetic defect leading to a susceptibility to infections is associated with SpA necessiates further investigations.

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