Association between Mannose-Binding Lectin Deficiency and Septic Shock following Acute Pyelonephritis Due to *Escherichia coli*

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Structural and promoter *MBL2* gene polymorphisms responsible for low MBL levels are associated with increased risk of infection. The objective of this study was to assess the possible association between polymorphisms of the *MBL2* gene and the incidence of septic shock and bacteremia in patients with acute pyelonephritis due to *Escherichia coli*. The study included 62 female patients with acute pyelonephritis due to *E. coli* who required hospital admission, as well as 133 healthy control subjects. Six single-nucleotide polymorphisms (−550 G/C, −221 C/G, +4 C/T, codon 52 CGT/TGT, codon 54 GCC/GAC, and codon 57 GGA/GAA) in the *MBL2* gene were genotyped by using a sequence-based typing technique. No significant differences were observed in the frequencies for low-expression *MBL2* genotypes (O/O and LXA/O) between patients with acute pyelonephritis and healthy controls. Patients with acute pyelonephritis and septic shock had a higher incidence of low-expression *MBL2* genotypes than patients with acute pyelonephritis without septic shock (odds ratio = 9.019, 95% confidence interval = 1.23 to 65.93; *P* = 0.03). No association was found between bacteremic acute pyelonephritis and low-expression *MBL2* genotypes. We found that low-expression *MBL2* genotypes predispose to septic shock but not to bacteremia in patients with *E. coli*-induced acute pyelonephritis. Determination of *MBL2* polymorphisms could be useful for assessing the risk of septic shock in women undergoing acute pyelonephritis.

Annually in the United States, at least 250,000 episodes of acute pyelonephritis (AP) in adults occur, with nearly 200,000 hospitalizations and an estimated mortality rate among female patients of 7.3 cases per 1,000 hospital admissions (7, 19). Despite the fact that most cases of AP have a good prognosis, they often require prolonged therapy and, when accompanied by bacteremia, AP has a mortality rate of 10 to 20% (31). Several host conditions, such as immunosuppression (44), age (27), diabetes (29, 32), pregnancy (14), and bedridden status (6), have been associated with more serious forms of AP.

Besides the existence of clinical conditions that predispose to severe AP, the biological substrate of such predisposition is not yet clearly understood. In recent years increasing evidence suggests that different host factors could be involved in the pathogenesis of urinary tract infections (UTIs), particularly in recurrent UTIs (38). Evidence of the importance of these host factors includes the facts that women with recurrent UTIs or with uncomplicated AP are more likely to be nonsecretors of blood group antigens (20, 36) and that specific HLA phenotypes are more prevalent in women with recurrent UTIs (34). Additional evidence includes the demonstration that children prone to recurrent AP have a decreased expression of the interleukin-8 receptor CXCR1 (8), although these data differ from those observed by our study group in which premenopausal women with recurrent UTIs, including women with recurrent AP, showed a decreased expression of CXCR2 (37).

The mannose-binding lectin (MBL) is a circulating C-type plasma lectin, mainly produced by the liver, that plays an important role in innate immunity. MBL is a pattern recognition molecule that binds with high affinity to the terminal mannose, fucose, glucose, and N-acetyl-D-glucosamine moieties present on the surface of various pathogens (26, 35), including *Escherichia coli*, the pathogen most commonly involved in UTIs (42). In addition to acting as an opsonin for phagocytosis for numerous pathogens, MBL activates the complement cascade through the lectin pathway, using MBL-associated serine proteases, namely, MASP-2 (25).

The *MBL2* gene (MBL-1 is a pseudogene) is located on chromosome 10q11.2-q21 (33). Three missense single-nucleotide polymorphisms (SNPs) have been reported at codons 52 (allele D), 54 (allele B), and 57 (allele C) of the exon 1 of the *MBL2* gene, which result in amino acid substitutions interfering with oligomerization of MBL monomers into multimers and reducing serum MBL levels (17, 45). In addition to these structural variant alleles, three SNPs in the promoter region of the *MBL2* gene, at positions −550 (H/L), +4 (P/Q) and, particularly, −221 (Y/X), influence the rate of transcription and are also associated with low concentrations of serum MBL (40). The SNPs at exon 1 are in strong linkage disequilibrium with those at the promoter and give rise to seven common haplotypes (HYPA, LYQA, LYPA, LXPA, LYPB, LYQC, and HYPD), which show considerable variation in their frequencies between ethnic groups (23, 24). The HY haplotype induces high MBL concentrations, whereas exon 1 mutations (O variants) and the LX haplotypes cause reduced MBL con-
centsations (24). Thus, based on previous reports, patients can be classified into high (HYA/HYA, HYA/LYA, HYA/LXA, LYA/LYA, and LYA/LXA), intermediate (LXA/LXA, HYA/O, and LYA/O), and low (LXA/O and O/O) MBL expression groups (40). Although MBL deficiency appears to predispose to serious infections (43), particularly during early childhood (22) and in patients undergoing chemotherapy (30), as well as in adults with comitant diseases (10, 11), the association between MBL deficiency and severe forms of AP has not been established.

The aim of the present study was to investigate whether the existence of low-expression MBL2 genotypes confers an increased risk for septic shock and bacteremia in women with AP due to E. coli.

MATERIALS AND METHODS

Study population. We prospectively collected blood samples from 62 female Caucasian patients with community-acquired AP caused by E. coli who required admission to our tertiary hospital between January 2003 and January 2004. Inclusion criteria for patients were >18 years of age, the presence of clinical symptoms of AP (armpit temperature of >38°C, pyuria, and lumbar tenderness), and a positive uroculture for E. coli. For further comparison, 133 healthy controls (104 Spanish blood donors from the geographic area of Barcelona and 29 female members of the hospital staff without previous urinary tract infections) were included in the study. The present study was conducted with the approval of the hospital Ethics Committee and the informed consent of all participants. The human experimentation guidelines of the U.S. Department of Health and Human Services and those of the authors' institutions were followed in conducting the clinical research.

Urine samples were obtained by use of a clean midstream catch method. Urine samples were spread on MacConkey and cystene lactose electrolyte-deficient agar plates for quantification, followed by incubation for 48 h. Positive urine culture results were defined as pathogen growth of ≥105 CFU/ml. Identification of E. coli was performed by standard methods. Blood cultures were processed by means of an automatic infrared culture system (Bactec 9240; Becton Dickinson) for 5 days.

Septic shock was defined according to the 1992 American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference guidelines (3). In summary, septic shock was diagnosed in cases of AP with an arterial systolic pressure of <90 mm Hg for at least 1 h after fluid resuscitation or required vasopressor therapy (dopamine at 5 μg/kg of body weight or more per min or any dose of epinephrine, norepinephrine, or vasopressin) to maintain a systolic blood pressure of >90 mm Hg.

Age and the following comorbid host conditions were included in the analysis: cirrhosis, heart failure, chronic kidney failure (defined as a creatinine level of >1.5 mg/dl), diabetes mellitus, underlying neoplastic disease, and immunosuppressive or corticosteroid therapy.

DNA samples. Genomic DNA was extracted from EDTA-treated whole blood samples by using the QIAamp DNA blood minikit according to the manufacturer's instructions (QIAGEN GmbH, Hilden, Germany) and then stored at –80°C until used.

Sequence analysis of MBL gene variants. Genotyping of the MBL2 gene was performed by using a sequencing-based typing technique. Specific primers were designed according to the published genomic DNA sequences (GenBank accession number AF360991). A 969-bp fragment encompassing the promoter to the end of exon 1 of the MBL2 gene was obtained by PCR amplification using sense (5′-GGG GAA TTC CTGCCA GAAAGT-3′) and antisense (5′-CAT ATC CCCAGG CAG TTT CCT C-3′) primers and the Expand 20kb Plus PCR system (Roche Diagnostics GmbH, Mannheim, Germany). The cycling conditions used for amplification of the MBL2 gene were 94°C for 8 min, followed by 35 cycles at 94°C for 45 s, 58°C for 30 s, 72°C for 90 s, and 72°C for 10 min. Portions (5 μl) of the resulting PCR product were treated with ExoSAP-IT (USB Corp., Cleveland, OH) and then subjected to direct sequencing with the BigDye Terminator v1.1 cycle sequencing kit (Applied Biosystems, Warrington, United Kingdom) according to the manufacturer's instructions with the sense and antisense gene-specific primers described above.

Statistical analysis. Continuous variables were compared by the Student t test or Mann-Whitney U test when the distribution departed from normality and are given as means (±standard deviations) or medians (range of values), respectively. Categorical data were compared by using the chi-square or Fisher exact test as appropriate. Variables associated to septic shock or bacteremia in the univariate analysis (P < 0.1) were included in a binary logistic regression analysis with septic shock and bacteremia as separate dependent variables. In the logistic models, age was analyzed with the median as a dichotomizing value (the two groups were values less than the median and values greater than or equal to the median). Statistical significance was defined as a two-tailed P value of <0.05. Statistical analysis was carried out by the program SPSS (version 11.0; SPSS, Inc., Chicago, IL).

RESULTS

Clinical data. The study included 62 women with AP due to E. coli. The mean age of the patients included in the study was 43 years (±20.6). Twenty-six (42%) patients had bacteremic AP. A total of 18 (29%) patients had associated comorbidity; 3 (4.8%) had cirrhosis, 5 (8%) had past history of heart failure, 7 (11.3%) had chronic kidney failure, 8 (13%) had diabetes mellitus, 4 (6.4%) had underlying neoplastic diseases, and 5 (8%) were receiving immunosuppressive or corticosteroid therapy. The patients with underlying neoplastic diseases included one patient with a cervix neoplasia, another with a hypernephroma (neither of whom had obstruction of the urinary tract), and two with hematological disorders (one patient with a polycythemia vera and another with a multiple myeloma). Patients under immunosuppressive or corticosteroid therapy included two with systemic lupus erythematosus that were on corticosteroid treatment and three kidney transplant recipients that were on corticosteroid therapy plus immunosuppressive therapy. Among the patients with chronic kidney failure, one received dialysis therapy. Seven patients (11.3%) met the criteria for septic shock; one had nonbacteremic AP and six had bacteremic AP. One patient with septic shock (haplotype LYPB/LYPB) died of a cause unrelated to UTI (stroke).

Analysis of the MBL polymorphisms. The sequence-based typing analysis of the exon 1 and the promoter region of the MBL2 gene allowed the categorization of individuals according to haplotypes and genotypes responsible for high (HYA/HYA, HYA/LYA, HYA/LXA, LYA/LYA, and LYA/LXA), intermediate (HYA/O, LYA/O, LXA/LXA), and low (O/O, LXA/O) MBL serum levels as described previously (40). Table 1 shows the frequency for the MBL2 haplotypes and genotypes found among the healthy controls and the patients with AP. No significant differences in the frequencies for the different haplotypes were found among the healthy control group and the patients with AP. LYPB was the predominant variant type haplotype both in the healthy control group and in the patients with AP. No overall statistical significant differences were observed for the frequencies of high (57.1% versus 51.6% [P = 0.46]), intermediate (30.1% versus 30.6% [P = 0.93]), and low (12.8% versus 17.7% [P = 0.35]) MBL2 genotypes among the healthy controls and the patients with AP, respectively (Table 1). The differences found in the frequencies for high (65.5%), intermediate (31.8%), and low (3.4%) MBL2 genotypes among the 29 members of the personal staff without previous UTI and the patients with AP were not statistically significant (P = 0.21, 0.97, and 0.09, respectively).

In the univariate analysis, low-MBL2-expression genotypes and chronic kidney failure were the only variables associated with septic shock (Table 2). To further assess the independent value of the previous associations, we performed a logistic...
In our study, the MBL2 genotype frequencies observed in the healthy control group closely resembled those previously reported in a Canary Islands (Spain) population (9), which in turn was similar to that observed in other healthy control groups from several European studies performed with Caucasian populations (1, 12, 13). LYPB, as previously reported, was the predominant variant type haplotype both in the healthy control group and in the patients with AP. An interesting regression with septic shock as a dependent variable. In the logistic regression model, heart failure and age were also included (\( P < 0.1 \)). Only low-MBL2-expression genotypes (odds ratio \( \text{OR} = 9.019, 95\% \text{ confidence interval} \ (\text{CI}) = 1.23 \text{ to } 65.93; \ P = 0.03 \)) were independently associated with the development of septic shock. In contrast, chronic kidney failure did not reach statistical significance (Table 2).

Bacteremia was associated in the univariate analysis with old age, neoplasia, chronic kidney failure, and the existence of any comorbidity but not with the presence of low-expression MBL2 genotypes. By logistic regression analysis, old age was the only variable significantly associated with bacteremia (Table 3).

TABLE 1. Frequency of the MBL2 haplotypes and genotypes found among healthy controls and patients with acute pyelonephritis

| Expression typea | Healthy controls | Patients | \( P \) |
|------------------|-----------------|----------|--------|
| **MBL2 haplotypes** |                 |          |        |
| LYOA             | 59 (22.2)       | 19 (15.3) | 0.11   |
| HYPA             | 72 (27)         | 38 (30.6) | 0.46   |
| LYPB             | 23 (8.6)        | 6 (4.8)   | 0.18   |
| LYQB             | 42 (15.8)       | 20 (16.1) | 0.93   |
| LYPD             | 50 (18.8)       | 29 (23.3) | 0.29   |
| LYQC             | 5 (1.8)         | 4 (3.2)   | 0.47   |
| **MBL2 genotypes** |                 |          |        |
| High expression  |                 |          |        |
| HYA/HYA          | 6 (4.5)         | 6 (9.6)   |
| HYA/LYA          | 24 (18)         | 8 (12.9)  |
| HYA/LXA          | 18 (13.5)       | 8 (12.9)  |
| LYA/LYA          | 12 (9)          | 1 (1.6)   |
| LYA/LXA          | 16 (12)         | 9 (14.5)  |
| Intermediate expression |         |          |        |
| LXA/LXA          | 4 (3)           | 3 (4.8)   |
| HYA/O            | 18 (13.5)       | 9 (14.5)  |
| LYO/O            | 18 (13.5)       | 7 (11.3)  |
| Low expression   |                 |          |        |
| LXA/O            | 17 (12.8)       | 11 (17.7) |
| O/O              | 8 (6)           | 6 (9.6)   |
|                  | 9 (6.7)         | 5 (8)     |

\( a \) Y and X indicate base exchanges at codon = 221. A, normal structural allele; O, variant alleles (B, codon 54; C, codon 57; and D, codon 52).

TABLE 2. Univariate and multivariate analyses of the association between different clinical characteristics and the presence of septic shock

| Characteristic                        | No. (\%) of subjects | Presence of septic shock (\( n = 7 \)) | Absence of septic shock (\( n = 55 \)) | \( p^b \) | Multivariate analysisd |
|---------------------------------------|----------------------|---------------------------------------|---------------------------------------|--------|------------------------|
| Cirrhosis                             | 1 (14.3)             | 2 (3.6)                               |                                       | 0.306  | NS                     |
| Heart failure                         | 2 (28.6)             | 3 (5.4)                               |                                       | 0.093  | NS                     |
| Neoplasia                             | 1 (14.3)             | 3 (5.4)                               |                                       | 0.389  | NS                     |
| Immunosuppressive or corticosteroid treatment | 1 (14.3)             | 4 (7.3)                               |                                       | 0.462  | NS                     |
| Chronic kidney failure                | 3 (42.8)             | 4 (7.3)                               |                                       | 0.026  | NS                     |
| Diabetes                              | 1 (14.3)             | 7 (12.7)                              |                                       | 1.00   | NS                     |
| Presence of comorbidity               | 4 (57.1)             | 14 (25.4)                             |                                       | 0.179  | NS                     |
| Low-MBL2-expression genotypes         | 4 (57.1)             | 7 (12.7)                              |                                       | 0.015  | 9.019 (1.23–65.93)     |
| Median age in yr (range)\(^c\)        | 52 (34–75)           | 35 (18–94)                            |                                       | 0.087  | NS                     |

\( a \) Except where otherwise noted, data are the numbers (\%) of subjects with the indicated characteristics, and the results are expressed as proportions of patients with septic shock in the presence or absence of the clinical condition.

\( b \) Determined by univariate analysis of the correlations between the presence of septic shock and each characteristic.

\( c \) In the logistic model, age was dichotomized by means of the median age (35.5 years) of the patients with AP.

\( d \) Clinical variables associated with septic shock (\( P < 0.1 \)) were included in the multivariate analysis. NS, nonsignificant differences.

DISCUSSION

Despite the fact that AP is one of the most common infectious diseases and a potentially life-threatening disorder, little is known about the predictor variables associated with an unfavorable outcome. The presence of septic shock has been described as one of the clinical variables related to death in patients with AP (6). In recent years many studies have stressed the implication of the innate immune response on the pathogenesis of septic shock and particularly of one of its components, the MBL (12, 15). In light of the accumulated evidence, we have evaluated the implication of the MBL2 genotypes associated with MBL deficiency on the incidence of septic shock and secondarily of bacteremia in women with AP due to \( E. coli \).

The MBL is a circulating human collectin (a family of proteins that possess both collagenous regions and lectin domains) with the ability to activate the complement and mediate phagocytosis after binding to specific carbohydrates on the surface of several bacteria, fungi, and viruses. The serum concentration and functional activity of the MBL are mainly determined by SNPs at the promoter and the exon 1 of the MBL2 gene. Genotypes associated with low serum MBL levels have been correlated with an increased risk, severity, and frequency of infections, particularly those mediated by capsulated bacteria (46). Genetically defined MBL deficiency is remarkably common in the general population, with an estimated prevalence of more than 10 to 15% in several Caucasian populations (17, 18). In our study, the MBL2 genotype frequencies observed in the healthy control group closely resembled those previously reported in a Canary Islands (Spain) population (9), which in turn was similar to that observed in other healthy control groups from several European studies performed with Caucasian populations (1, 12, 13). LYPB, as previously reported, was the predominant variant type haplotype both in the healthy control group and in the patients with AP. An interesting
observation of our study was the relatively low frequency of MBL2 genotypes associated with MBL deficiency detected in the staff members without previous UTI. Although these low genotype frequencies were probably related to the small number of individuals with this condition included in the study, the potential implication of the MBL lectin pathway in the pathogenesis of UTI may justify further studies.

To our knowledge, this is the first study on MBL2 genotyping that has focused on patients with AP. Our results suggest that patients with MBL2 genotypes associated with serum MBL deficiency undergoing AP due to E. coli have a higher risk for developing septic shock but not bacteremia. The multivariate analysis has revealed that the presence of MBL2 genotypes associated with low MBL production was the only variable associated with septic shock even though other clinical variables, such as age, immunosuppression, and diabetes mellitus, previously related to AP with an unfavorable outcome (27, 29, 32, 44) were also included in the study. Although one possible limitation of our study is the fact that serum MBL levels were not measured, the relationship between MBL2 genotypes and serum MBL levels has been clearly established in numerous studies (12, 13, 40). Therefore, MBL2 genotyping could be of clinical interest as a molecular marker defining patients with AP at risk for septic shock.

The method by which low serum MBL levels seem to favor the progression of localized infections and the development of septic shock remains unclear. Although activation of the immune system during microbial invasion is generally protective, septic shock may develop as a consequence of an exacerbated inflammatory response (2). MBL is known to activate the complement cascade and, as a result, to induce the release of proinflammatory cytokines, particularly of tumor necrosis factor alpha, from monocytes (4, 39). An excess of complement activation could lead to enhanced inflammation, which could be deleterious for the host. One might hypothesize that low MBL levels could in fact be beneficial since they may reduce inflammation and therefore the development or the severity of septic shock. A novel mechanism by which MBL could influence the development of septic shock is through a direct effect as a modulator of proinflammatory cytokine production. Jack et al. addressed this issue by incubating Neisseria meningitidis with increasing concentrations of MBL before adding MBL-deficient whole blood. Release of tumor necrosis factor alpha, interleukin-6, and interleukin-1β from monocytes was enhanced at low MBL concentrations and suppressed at higher concentrations, which suggests that MBL is not only involved in complement activation but is also a potent regulator of inflammatory pathways (21). Another mechanism by which MBL could interfere in the development of shock is through an increased clearance of endotoxin, one of the most powerful inducers of septic shock. Ono et al. have demonstrated that MBL is able to enhance the uptake of lipid A, the molecular component responsible for the toxic effects of the endotoxin, by increasing the cell surface expression of scavenger receptor A by Kupffer cells (28).

However, the implication of MBL in the pathogenesis of septic shock, in patients with AP, is complex and could depend not only on host (quantity of MBL) but also on bacterial characteristics (the binding capacity of MBL to different types or strains of bacteria). In our study all of the episodes of AP included were due to E. coli, which is responsible for most of the cases of AP. The MBL binding capacity to E. coli has been evaluated by means of flow cytometry (26) and enzyme-linked lectin assay (35), with conflicting results depending on the method used. While in the study by Neth et al. (26) only one isolate of E. coli bound to MBL, in the study by Shang et al. E. coli demonstrated a high binding capacity to MBL (35). In both studies different isolates of E. coli showed different intraspecies binding rates. These results could be related to differences in the sugar array compositions of the membranes of E. coli. The membrane of E. coli is mainly composed of lipopolysaccharide, which is the major acceptor molecule for MBL on gram-negative bacteria (5). It has been demonstrated that several serotypes of E. coli, which possess different lipopolysaccharide

### TABLE 3. Univariate and multivariate analyses of the association between different clinical characteristics and the presence of bacteremia

| Characteristic                             | Presence of bacteremia (n = 26) | Absence of bacteremia (n = 36) | p<sup>b</sup> | Multivariate analysis<sup>d</sup> |
|-------------------------------------------|---------------------------------|---------------------------------|---------------|----------------------------------|
| Cirrhosis                                 | 3 (11.5)                        | 0                               | 0.069         | NS                               |
| Heart failure                             | 4 (15.4)                        | 1 (2.8)                         | 0.152         |                                  |
| Neoplasia                                 | 4 (15.4)                        | 0                               | 0.027         | NS                               |
| Immunosuppressive or corticosteroid treatment | 4 (15.4)                        | 1 (2.8)                         | 0.152         |                                  |
| Chronic kidney failure                    | 7 (26.9)                        | 0                               | 0.001         | NS                               |
| Diabetes                                  | 5 (19.2)                        | 3 (8.3)                         | 0.262         |                                  |
| Presence of any comorbidity               | 13 (50)                         | 5 (13.9)                        | 0.002         | NS                               |
| Low-MBL2-expression genotypes             | 7 (26.9)                        | 4 (11.1)                        | 0.177         |                                  |
| Median age in yr (range)<sup>c</sup>      | 58 (26–94)                      | 26 (18–84)                      | <0.0001       | 8.32 (1.91–36.23) 0.005          |

<sup>a</sup> Except where otherwise noted, data are the numbers (%) of subjects with the indicated characteristics, and results are expressed as proportions of patients with bacteremia in the presence or absence of the clinical condition.

<sup>b</sup> Determined by means of univariate analysis of the correlations between the presence of bacteremia and each characteristic.

<sup>c</sup> In the logistic model, age was dichotomized by means of the median age (35.5 years) of the patients with AP.

<sup>d</sup> Clinical variables associated with bacteremia (P < 0.1) were included in the multivariate analysis. NS, nonsignificant differences.
compositions, show different binding capacities to MBL (47). Unfortunately, the strains of *E. coli* involved in the episodes of AP were not serotyped in our study. In vitro studies have demonstrated that MBL is able to increase the phagocytosis of *E. coli* by Kupffer cells (28). Therefore, one would expect a higher incidence of bacteremia in patients with MBL deficiency, which was not the case in our study, thus suggesting that bacterial factors are important when analyzing the implication of host MBL genotypes in different infectious disease scenarios. To add another degree of complexity, functionally relevant polymorphisms of MASP2 have recently been described, and therefore genotyping of the MBL alone may not be sufficient to evaluate the MBL pathway (16, 41).

In conclusion, the present study suggests that patients with AP due to *E. coli* with MBL2 genotypes associated with MBL deficiency have a higher risk for developing septic shock but not for bacteremia. A rapid determination of the MBL genotypes would be an important tool to identify patients with AP who are at risk for developing septic shock.

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