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ORIGINAL PAPER

The Prognostic Value of Mannose-Binding Lectin in Community-Acquired Pneumonia

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ABSTRACT

Introduction: *Community-acquired pneumonia is among the most widespread health issues in the pediatric population, affecting children around the world. Mannose-binding lectin is a component of the innate immune system that binds to carbohydrate fragments expressed by various microorganisms, thus aiding in their recognition and eventually activating the complement system through a specific pathway called "the lectin pathway".*

Materials and methods: *204 pediatric patients whose mannose-binding lectin levels were evaluated at the beginning of infection were included in the study.*

Results: *Mannose-binding lectin deficit was observed in 18% of subjects and 83.78% of these developed complications.*

Conclusion: *This study makes use of the relevant literature and tackles somewhat controversial aspects, as mannose-binding lectin deficit is classified as a fairly common disturbance of the immune system. For a comprehensive understanding of mannose-binding lectin role in infectious diseases, it is necessary to take into account even contextual factors.*

Keywords: community-acquired pneumonia, prognostic, mannose-binding lectin.

INTRODUCTION

Community-acquired pneumonia (CAP) along with other inferior respiratory tract infections represented, according to data released by the World Health Organization, the leading cause of death in children in 2018 (1). The severity of CAP can vary from nearly asymptomatic to septic shock and multiple organ failure. A possible explanation for this variation may be the large genetic variability of the host response, variability that increases the chance of an unfavorable evolution of the disease process.

Throughout the years, researchers have developed numerous systems and scores that evaluate disease risk, severity and prognosis; also, concomitantly with increasing technological advancements, different biomarkers that may aid

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the clinician in making critical decisions regarding pneumonia patients are being proposed. Mannose-binding lectin (MBL) is synthesized in the liver and is a polymorphous glycoprotein of the collectin family, proteins that are characterized by having both collagenic and lectin domains in the same subunit (2). It was the first protein considered to have a major role in complement activation. The lectin pathway and classic pathway are very similar, the difference being the trigger – presence of microorganisms with multiple mannose fragments (3). These repetitive carbohydrate structures are recognized by a lectin (MBL), which is a soluble pattern recognition receptor, and is structurally similar to the C1q fraction involved in the classic pathway, serving as a recognizance molecule (3). Mannose-binding lectin also binds serin proteases (mannose associated serum protease or MASP) that have similar roles to C1r and C1s, in that a molecular MBL-MASP complex forms (in a similar fashion to the C1qC1sC1r complex) upon which fraction C4 binds. After this moment, both pathways follow the same course (3). ❑

MATERIALS AND METHODS

The study included 204 patients aged between six months and 18 years, who were admitted to "Maria Sklodowska Curie" Emergency Children's Hospital Bucharest with a positive diagnosis of community-acquired pneumonia in the period from 1 January 2017 to 1 May 2019. Approval from the local medical Ethics Committee was sought and received. All included patients had their mannose-binding lectin levels evaluated at the beginning of the study through ELISA, samples being drawn from venous blood. A value below 450 ng/mL was considered low (4).

Statistical analysis was performed using SPSS 25 (IBM SPSS, Chicago, IL) and Analyse IT 5.4 (Microsoft Office Excel add-on, Leeds, UK). Data with uniform distribution are presented as a mean and standard deviation (SD). Data with non-uniform distribution are presented as medians and quartile intervals. The difference between quantitative parameters was tested using the T test for normally distributed data and non-parametric tests for non-normally distributed data. The difference between semi-quantitative variables was evaluated through the Mann-Whitney U test. Qualitative data were compared using the Chi-square or Fisher exact tests. The multivariate regression results are expressed as 95% confidence intervals (CIs). If the p-value of the predictor in the univariate analysis was below 0.05, this predictor was included in the multivariate regression model.

Cohort characteristics regarding MBL were as follows: Group I – low MBL < 450 ng/mL *versus* Group II – normal MBL > 450 ng/mL). ❑

Parameter	Low MBL (37 patients)	Normal MBL (167 patients)	P value
Male sex	16 (43.24%)	85 (50.89%)	0,39
Age in months	42 [18.7; 70,3]	42 [24; 74.7]	0,6
Vaccination status	34 (91.89%)	162 (97%)	0,14
Anti-pneumococcal vaccine status	3 (8.1%)	5 (2.99%)	0,14
Comorbidities	14 (37.83%)	36 (21.55%)	<0,01
-Malnutrition	7 (18.91%)	17 (10.17%)	0,13
-Prematurity	3 (8.1%)	15 (8.98%)	0,86
-Cardiac malformations	4 (10.81%)	4 (2.39%)	0,01
-Lung malformations	3 (8.1%)	4 (2.39%)	0,08
Immunodeficiency status	3 (8.1%)	1 (0.59%)	<0,01
Past upper respiratory tract infections (*per* year)	6 [4.7; 7]	4 [3; 4]	<0,01
Past lower respiratory tract infections (*per* year)	2 [2; 2]	0 [0; 1]	<0,01

TABLE 1. Demographics and relevant history

Parameter	Low MBL (37 patients)	Normal MBL (167 patients)	P value
Mannose-binding lectine	250 [76; 292]	2300 [1245; 3250]	<0.01
Leukocytes	21000 [16086; 28453]	17000 [11833; 22783]	0,011
Neutrophils (percentage)	82 [75,7; 85]	75 [64; 80]	<0,01
Lymphocytes (percentage)	9 [6.67; 14,33]	15 [9; 24]	<0,01
Platelets	326 [265; 417]	337 [270; 416]	0,69
C-reactive protein	155 [107; 333]	90 [50; 153]	<0,01
Procalcitonin			<0,01
> 10	17 (45.94%)	17 (10.17%)	
2-10	9 (24.32%)	20 (11.97%)	
0.5-2	6 (16.21%)	32 (19.16%)	
<0.5	5 (13.51%)	98 (58.68%)	
IgA			0,44
-Low for age	0 (0%)	3 (8.1%)	
-Elevated for age	3 (8.1%)	7 (4.19%)	
IgG			0,01
-Elevated for age	3 (8.1%)	2 (1.19%)	
IgM			0,16
-Low for age	0 (0%)	1 (0.59%)	
-Elevated for age	4 (10.81%)	6 (3.59%)	
IgE	15 [11; 21]	17 [12; 27]	0,66
C3 mg/dL (n=49)	147 [129; 164]	147 [134; 162]	0,65
C4 mg/dL (n=49)	27.5 [21; 35]	23 [17; 28,3]	0,15

TABLE 2. Laboratory findings

RESULTS

A total of 204 patients (101 males and 103 females) were studied. All had a positive diagnosis of community-acquired pneumonia and a mean age of 42 months; 18% of subjects had a low value of mannose-binding lectin (< 450 ng/mL) and 82% normal values.

The cohort's characteristics were analysed in relationship to the MBL level interval, thus forming two groups: the first group with low MBL lectin levels and the second one with normal MBL levels.

Table 1 shows demographic and patient history data. Various comorbidities (malnutrition, heart or lung malformations, prematurity, immunodeficiency) occur more frequently in the low MBL group (37.83% *versus* 21.55%).

Table 2 summarises laboratory data, showing that the low MBL level group has a higher number of total white cells and neutrophils, and levels of C-reactive protein and procalcitonin than the normal MBL group. Total immunoglobulin levels were evaluated for a possible link between an immunoglobulin and MBL deficit. The theory was refuted because immunoglobulin levels were normal in all patients in the low MBL group. In order to more closely correlate disease severity with low MBL levels, C3 and C4 complement fractions were evaluated in some low MBL patients, but values were normal, suggesting that the lack of MBL is an independent severity factor in these patients. Because C3 and C4 levels were obtained in only 49 subjects, it is not possible to perform a regression type analysis.

In Table 3, clinical data reveal that in the first group, 56.75% had a severe form of pneumonia (5), compared to 13.17% of patients in the second group. The low MBL group has also shown a 54.05% presence of acute respiratory failure compared to only 13.17% in the normal MBL group. Local complications developed in 48.64% of children with MBL deficit and in 23.25% of children with normal levels.

Parameter	Low MBL (37 patients)	Normal MBL (167 patients)	P value
Chest X-ray and echography			<0.01
-Single lobe consolidation	18 (48.64%)	128 (76.64%)	
-Abscess	4 (10.81%)	0 (0%)	
- Serofibrinous pleurisy	5 (13.51%)	22 (13.17%)	
-Empiema	6 (16.21%)	3 (8.1%)	
-Multiple lobe consolidation	4 (10.81%)	14 (8.38%)	
SpO_2 (%)	85 [76; 90]	96 [94; 98]	<0.01
Severe CAP (BTS criteria)	21 (56.75%)	22 (13.17%)	<0,01
Acute respiratory failure	20 (54.05%)	22 (13.17%)	<0.01
Local complications	18 (48.64%)	39 (23.35%)	<0.01
-Serofibrinous pleurisy	6 (16.21%)	26 (15.56%)	
-Empyema	4 (10.81%)	4 (2.39%)	
-Abscess	5 (13.51%)	2 (1.19%)	
-Pyopneumothorax	1 (2.7%)	1 (0.59%)	
-Lung fissure inflammation	1 (2.7%)	1 (0.59%)	
-Necrotizing pneumonia	0 (0%)	1 (0.59%)	
Systemic complications	31 (83.78%)	65 (38.92%)	<0.01
-SIRS	5 (13.51%)	30 (17.96%)	
-Sepsis	19 (51.35%)	30 (17.96%)	
-Severe sepsis	4 (10.81%)	4 (2.39%)	
-Septic shock	2 (5.4%)	0 (0%)	
-MSOF	1 (2.7%)	1 (0.59%)	
CURB			<0.01
0	7 (18.91%)	99 (59.28%)	
1	25 (67.56%)	64 (38.32%)	
2	5 (13.51%)	3 (1.76%)	
3	0 (0%)	0 (0%)	
4	0 (0%)	1 (0.59%)	
PIRO	3 [2; 4]	1 [0; 2]	<0.01

TABLE 3.
Clinical data

Serofibrinous pleurisy developed in both the low MBL and normal MBL groups in 16.21% and 15.56% of patients, respectively. Empyema developed in 10.81% of low MBL patients and in 2.39% of patients whose MBL levels were above 450 ng/mL. Lung abscess developed in 13.51% in MBL deficient patients compared to 1.19% of those without MBL deficiency.

Regarding systemic complications (SIRS, sepsis, septic shock, MSOF), the low and normal MBL group also show differences with 83.78% and 38.92% of patients presenting with at least one of those complications, respectively. Two severity scores, both used mainly in adult patients, CURB and PIRO were used in order to simplify and broaden the evaluation. Applying these quantification systems, a relationship between an unfavorable prognosis as specified by these scores and MBL deficit.

On average treatment duration was 14 days for MBL deficient patients and seven days for the other group. Pleural drainage, thoracotomy with pleural decortication or surgical resection were necessary in 24.32% of patients with low MBL levels compared to 4.19% in the normal level group. Sequelae (evaluated prior to six months)

Parameter	Low MBL (37 patients)	Normal MBL (167 patients)	P value
Antibiotic treatment (days)	14 [10; 21]	7 [5.2; 10]	<0.01
Surgical intervention	9 (24.32%)	7 (4.19%)	<0.01
-Pleural drainage	3 (8.1%)	4 (4.19%)	
-Resection	4 (10.81%)	1 (0.59%)	
-Thoracotomy	2 (5.4%)	2 (1.19%)	
Intubation and ventilation	8 (21.62%)	4 (2.39%)	<0.01
Days spent in hospital	14 [10; 21]	7 [5.2; 10]	<0.01
Sequelae < 6 months	10 (27.02%)	10 (5.98%)	<0.01
-Pleural thickening	5 (13.51%)	9 (5.38%)	
-Lobectomy	1 (2.7%)	1 (0.59%)	
-Segmentectomy	2 (5.4%)	0 (0%)	
-Atelectasis	1 (2.7%)	0 (0%)	
-Pneumothorax	1 (2.7%)	0 (0%)	

TABLE 4. Treatment and outcome

Variables in the equation						
		B	Sig.	Exp(B)	95% CI for Exp (B)	
					Lower	Upper
Final step	MBL (cat)	2.073	0.011	7.948	1.594	39.620
a. Variable(s) entered on step 1: DG POZ, SpO_2, MBL (cat)						

TABLE 5. Risk of ICU admission

such as pleural thickening, lobectomy, segmentectomy, atelectasis, pneumothorax were present in 27.02% and 5.98% of subjects in the low and normal MBL groups, respectively.

Using a multivariate regression model, the necessity for ICU admission as evaluated by oxygen saturation levels and diagnosis of severe community-acquired pneumonia was linked to MBL levels. Low levels of MBL increased the odds of ICU admission with an OR of 7.98 (CI 95% 1.594–39.620) (Table 5). ❑

DISCUSSIONS

Susceptibility to community-acquired pneumonia has been linked to age, children being the most frequent population affected by this disease (6). The role of the immune system in dealing with infections is intensely studied to this day. The innate immune response is the organism's first line of defense, which is initiated and reacts quickly, within minutes, through neutrophils, the complement system and a selective group of cells that possess cytotoxic properties (7). It is essential in stopping the passage of microorganisms that colonize the nasophaynx towards the lower portions of the respiratory tract (8).

The interest towards the role of mannose-binding lectin in CAP pathophysiology was increased by acknowledging that patients homozygote for the MBL2 gene had an increased risk of infection with invasive serotypes of *Streptococcus pneumoniae* (9). Although a number of studies failed to confirm this result (10-12), a meta-analysis of these studies showed a significant association between MBL2-gene deficient patients and susceptibility towards pneumococcal disease (10). Garcia-Laorden *et al* (13) revealed that MBL deficit predisposes CAP patients to a severe disease form with more frequent complications and a worse prognosis, but this hypothesis was not confirmed by the work of Endeman *et al* (14).

In our study, a correlation between low MBL levels and a history of frequent upper and lower respiratory tract infections is seen in CAP patients. This relationship has been also evaluated by N. J. Klein, who helped in identifying a cohort whose clinical manifestations are probably caused by a deficit of MBL (15). He shows the typical clinical picture of a child with an important history regarding repeated upper and lower respiratory tract infections until satisfactory adaptive immune response is achieved. This pattern

of repeated infections usually diminishes or disappears along with age and serves to point out the importance of the innate immune system in protecting children until the adaptive immune response is mature enough (15).

Our research revealed important differences in leukocyte and neutrophil counts, C-reactive protein and procalcitonin values between groups, with MBL deficient patients showing markedly higher values in all parameters, thus suggesting a possible correlation between low MBL levels and markers for severe bacterial infections.

Data shows that 54.05% of patients have acute respiratory failure and 56.75% develop severe forms of CAP in the low MBL group. The same phenomenon is observed when analyzing local and systemic complications; 48.64% of them developed local complications such as serofibrinous pleurisy, empyema, lung abscess or necrotizing pneumonia, and 83.78% developed systemic complications, with sepsis being the most frequent (51.35%).

The importance of MBL deficit in pneumococcal infection was established in studies using mouse models (16). Koch *et al* reported an association between MBL deficit and increased acute respiratory tract infection risk in children between six and 17 months (17). Low MBL deficit has been linked to other various pediatric infectious diseases, studies reporting an association between MBL2 deficient genotypes and an increased risk of pneumococcal meningitis (18).

The link between Gram-negative bacterial infections and MBL has also been explored, the association with *Pseudomonas aeruginosa* being well documented (19), but proposal of a crucial role in MBL deficit in pneumococcal infection susceptibility has been still contested by a number of functional and evolutionary studies. The lack of association between MBL and CAP should not be surprising, because no in vitro link between mannose-binding lectin and/or MBL-mediated opsonophagocytosis and *Streptococcus pneumoniae* has been established (20, 21). If MBL plays a role in granting protection against *S. pneumoniae*, then one would expect a selective reduction of MBL2 deficient alleles, but these alleles are frequent in many populations throughout the world, and recent studies showed that the pattern of MBL2 gene variance world-wide was compatible with a neutral evolution (22, 23).

Based on our statistical results, we report that MBL patients had a slowly favorable outcome, with more frequent complications, greater odds of being admitted to ICU and requiring surgical treatment. These patients needed on average 14 days of treatment and required antibiotic association, as opposed to those with normal MBL levels. Of all MBL deficient subjects, 21.62% were admitted in ICU, compared to 2.39% of patients from the other group. Besides complement mediated opsonophagocytosis, other mechanisms might explain the above clinical correlations such as the immune modulating effect of mannose-binding lectin or the direct action of phagocytic cells in phagocytosis promotion (24, 25).

There are limitations to our study, the main impossibility of patient genotyping. Although the study sample allowed for statistically relevant results, a broader analysis on a larger population is required. Secondly, etiologic diagnosis was not possible for the entire study population, so the percentage of patients infected with *Streptococcus pneumoniae* or other bacteria such as *Staphylococcus aureus* or *Haemophilus influenzae* could not be established. ❑

CONCLUSIONS

Our study suggests a correlation between mannose-binding lectin deficit and clinical picture, development of complications and longer treatment in children diagnosed with community acquired pneumonia. Host factors are better predictors of morbidity compared with microorganism virulence factors, so whether an opportunist serotype will cause disease or determine a disease progression with frequent complications is more strongly linked to an improper immune response (26). Another confirmation of the link between MBL deficit and CAP can provide a path towards practicing personalised medicine where pediatric professionals will evaluate the risk of pneumonia complications not only through epidemiological, clinical or microbiological characteristics but also through predictive factors derived from the hosts' immune characteristics. Future research in this domain may include: clarifying the complement activation model, determining the degree of importance and other relationships between the three complement activation pathways as well as pos-

sible deleterious effects that may appear. Patients with low MBL plasma levels appear to have a higher risk for severe respiratory tract infection. As such, evaluating MBL could be used to identify those predisposed to recurrent or sever infections.

In the near future, substitution with plasma purified or recombinant MBL could protect patients with severe forms of pneumonia and low MBL levels. However, a large well-conceived prospective multicenter study should confirm the association between low levels of plasma MBL and severe respiratory disease. This study should include measures of mannose-binding lectin both at the start and throughout the infection and needs to perform MBL2 genotyping in order to validate these measurements. ❑

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