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CASE REPORTS

# Characteristics of Mannose-Binding Lectin Deficiency in Pediatric Septic Patients – Case Presentation

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**ABSTRACT**

*Mannose binding lectin (MBL) is a plasma protein of the innate immune system with the ability to initiate antimicrobial and inflammatory actions. The importance of MBL in defence against infections and especially sepsis is still debated. This article discusses recent developments in MBL research and explores how MBL may be operating in the setting of sepsis.*

*We present the case of a nine-year-old child diagnosed with septic shock but no apparent risk factors, who was found to have low serum levels of mannose-binding lectin on immunological assay.*

*This case suggests that young children with a genetically determined low MBL production are at a higher risk of developing septic shock.*

**Keywords**: mannose binding-lectin, sepsis, septic shock.

## INTRODUCTION

It is well established that sepsis implies a severe clinical and biological disturbance. While the initial insult is of bacterial origin, sepsis develops into a self-sustaining pathological process by means of multiple endogenous mediators that become activated in a complex immunological cascade. It is this uncontrolled mediator synthesis and activation that leads to disturbances in various leukocyte subsets, the complement system and the coagulation and fibrinolysis cascade. The end points are microvascular dysfunction, tissue ischemia and organ dysfunction (1).

A key point to maximize therapeutic benefit in sepsis is risk stratification – identifying various patient subgroups who may show benefit from certain variations in the classical treatment algorithm.

A deficit of mannose-binding lectin – an instrumental component of the innate immunity – is associated with reduced opsonization and consequently, an increased predisposition to treatment-resistant infections (2).

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The following case is that of a female with near total mannose-binding lectin deficiency that rapidly progressed to septic shock.

## CASE PRESENTATION

R. I. is a nine-year-old female patient presenting with the following chief complaints: high fever, wet cough and diarrheal stools with a 48-hour onset. She exhibits a petechial rash on her upper and lower limbs and her general appearance rapidly deteriorates. She was initially admitted to another hospital, where physical exam and preliminary laboratory findings lead to a suspected diagnosis of sepsis; therefore, antimicrobial therapy with Ceftriaxone and Vancomycin was initiated. During her stay, she started exhibiting myalgia and obtundation, prompting subsequent transfer to our clinic.

The patient was severely unwell upon admission with intense pallor, petechial rash along the thorax, abdomen, lower and upper limbs, dry lips, wet cough, displaying tachypnea (45 breaths per minute) with hyperpnea, bilaterally audible vesicular breath sounds with disseminated rales, $SpO_2$ 86% in room air, rhythmic heart sounds with a low-grade systolic murmur best heard in the mitral area, heart rate of 170 bpm, blood pressure of 70/50 mm Hg, distended abdomen, loose stools, no discernable hepatosplenomegaly, oliguria; neurologically, the patient was obtunded but with negative meningeal signs, and had normal reflexes, good sphincter tone, normal sensation, and lower limb myalgia.

Lab results show leukocytosis with neutrophilia (leukocytes 30 100/mm$^3$, neutrophils 21 350/mm$^3$), anemia (Hb 9.9 g/dL), thrombocytopenia (30 000/mm$^3$), highly elevated inflammatory markers (CRP 473 mg/L; procalcitonin >10 ng/mL), elevated creatinine (2.5 mg/dL), elevated transaminases (AST 183 U/L/ALT 700 U/L), hypoalbuminemia (2 g/L), dyslipidemia with hypertriglyceridemia, elevated ferritin (600 ng/mL), altered coagulation tests (prothrombin activity of 55%, Quick time of 16 seconds, aPTT of 30 seconds), D-dimers 50 µg/mL, fibrinogen 180 mg/dL, elevated muscle enzymes (CK 20 000 U/L, CK-MB 400 U/L), total bilirubin > 4 mg/dL, lactic acid > 3 mmol/L.

Chest x-ray reveals increased interstitial opacity with a reticular pattern bilaterally. Abdominal echography shows normal spleen, liver, pancreas, kidney, bladder appearance and echogenicity and no free liquid in the peritoneum. Hemoculture is negative.

The patient is diagnosed with septic shock. IV fluids, plasma, thrombocytes, broad spectrum antibiotics (Meropenem, Linezolide), vasopressors and anti-inflammatory drugs are quickly initiated. Initial response is favorable with steady improvement of general appearance and coagulation markers and lowering levels of inflammatory response markers, hepatic and muscular enzymes and creatinine.

Because of the severity of presenting symptoms and presence of anemia, thrombocytopenia and low fibrinogen associated with elevated ferritin and triglycerides, a diagnosis of macrophage activation syndrome was initially suspected, but bone marrow aspiration negated this diagnosis.

The rapid progression to septic shock also raised the question of an underlying immune deficiency. The patient's immunoglobulin levels are within normal range for her age.

Since the patient's history, physical exam and the host of tests performed ruled out any defects in T- or B-cell lymphocytes, phagocytes or complement system (C3 and C4 – normal values), the decision was made to evaluate mannose-binding lectin values. ELISA was performed on a fasting venous sample, revealing a value below 50 mg/dL, which was consistent with a near-total deficiency.

During hospitalization, the patient started exhibiting high fever with chills, swelling and loss of function in the left knee. Joint echography raised the suspicion of septic arthritis and joint puncture was ordered. On drainage, the fluid was xanthochromic, with a cellularity of 98 096 elements/mm$^3$ (90% granulocytes, 10% mononuclear cells), but joint fluid culture was negative. Broad spectrum antibiotic therapy was continued. It was likely that the joint fluid culture was negative because of the antibiotic therapy that had already been initiated since admission. After the procedure, the course was favorable.

On follow-up at three months and six months after discharge, the patient is well, with no other important infectious episodes and no joint sequelae on MRI scan.

## DISCUSSIONS

According to the 2014 definition by the European Society of Intensive Care Medicine

(ESICM), sepsis is a potentially fatal disease characterized by an uncontrolled, disproportionate inflammatory reaction versus an infectious agent.

These changes in expression and activity of the immune, coagulation and various intermediate pathways concur with severe consequences at the organ level (3, 4).

Diagnosis, monitoring and treatment of septic patients is mainly based on evaluating organ dysfunction. Besides the various routinely used clinical scores (APACHE, SOFA, MODS, PIRO), a multitude of cellular or soluble biochemical markers have been proposed as markers for sepsis diagnosis, severity and short- and long-term prognosis based on their pathophysiological role in this disease (5, 6).

Current literature data pleads for risk stratification primarily for identifying those patient subgroups with possible immune deficiencies rendering them susceptible to severe infections (7).

An important role in sepsis pathophysiology is attributed to the lectin complement activation pathway in which mannose-binding lectin (MBL) plays a pivotal role (8).

Mannose-binding lectin is a polymorphic glycoprotein of the collectin family (10). After calcium-dependent specific binding of mannose and N-acetyl glucosamine, it activates the complement cascade. It is synthesized in the liver and is structurally similar to the C1q fraction. It is made up of oligomers of subunits that are associated with a serine-protease (MASP). There are two MBL-binding serine-proteases that are similar in structure to C1r and C1s (9).

After interacting with the carbohydrate ligand, MBL undergoes a conformational change that leads to activation of the two serine-proteases (MASP-1 and MASP-2) (11). Following activation, MASP-2 cleaves C4 to generate the same C3-convertase (C4b2a) as the classic pathway. MASP-1 can cleave C3 directly, suggesting it could activate the alternate pathway independently. After C3-convertase assembly, the complement cascade continues identically as in the classical pathway with the possibility to alternate pathway activation as well (10).

The result of MBL binding to pathogens and consecutive complement activation leads to microorganism lysis and quick elimination by means of phagocytosis (11). An interaction between membrane-bound MBL and a specific phagocyte receptor has been described, and it seems it facilitates pathogen removal (opsonization) (11).

Genetic studies have confirmed that low serum MBL is genetically programmed. A third of the European population is heterozygote for this characteristic. About 0.3% of the European population is homozygote for low MBL, of which they have an almost complete lack, thus can be associated with a higher risk of infection (9).

Only low levels of MBL are associated with an immune deficiency. High levels indicate an active infection (12).

In this case, the progression towards septic shock was swift, raising the question whether the immune system itself played a role in the patient's fulminant evolution. Laboratory findings revealed an almost total MBL deficit, and knowing its role in the innate immune system, it could offer a possible explanation for the quick deterioration observed by us.

The innate immune system acts as the first line of defense against disease until the adaptive immune system can mount an appropriate response. Since the latter is known to vary with age, younger children mainly rely on the innate response to fight infections.

Low MBL levels have been ascertained 20 years ago and, although they have been associated with susceptibility to infection, the importance of MBL against infection is still under debate (Super *et al.*, 1999).

One of the hallmarks of severe immune deficiencies is an association between the host's defense failure and specific pathogens – for example, a profound decrease in immunoglobulin levels tends to be highly susceptible to encapsulated bacteria. This type of link has yet to be established in the case of MBL and various microorganisms, leading to arguments for MBL being of low clinical importance (13).

A Danish study on a cohort of adult patients failed to prove MBL deficiency increased morbidity or mortality (Dahl *et al.*) (13).

Nevertheless, numerous other studies have shown that MBL can indeed increase the infectious risk, especially in little children with a propensity towards respiratory tract infections (14, 15).

Out of the multitude of bacteria that have been evaluated, it seems that *Streptococcus pneumoniae* is most strongly linked to MBL deficit, with a high incidence of sepsis in selected patients (16).

Another bacterium that is associated with MBL deficit is *Escherichia coli*. Interestingly, neither *Neisseria meningitidis* nor *Staphylococcus aureus* have been definitively linked to low levels of MBL (17). Of note, results in animal models have proven difficult to extrapolate to humans, either adults or children.

Studies carried out at Great Ormond Street Hospital London throughout several years have assembled a cohort of patients whose clinical picture can be explained, or at least is indicative of, low levels of MBL. The typical history paints a child with frequent infections – usually, respiratory infections of the upper or lower airways – that, despite these repeating episodes, grow normally and rarely require admission, but usually end up receiving antibiotics. Although the etiology remains unknown, prophylactic antibiotic administration has beneficial effects (18).

This pattern of frequent infections continues until about seven years, with progressively less infections throughout the year, marking this childhood period as a "vulnerability window" of MBL defect, and shows the importance of the innate immune system until the adaptive immune system is sufficiently mature (18).

Another important aspect in homozygotes for MBL deficit is the immunomodulating effect of this protein during the initial inflammatory cascade of sepsis. A study using homozygotic patients has shown their susceptibility towards severe pneumococcal infection. In pediatric patients with organ failure, MBL deficit has been associated with SIRS or sepsis development (17).

## CONCLUSION

Mannose-binding lectin deficiency has been initially described as the primary cause of opsonization defect but following this, it has been shown that the most important role for MBL is actually in limiting infection and the quick host response to inflammatory or infectious injury (18). In this case, it had a prognostic value.

More studies are necessary to evaluate other possible uses for MBL, especially in patients with multiple comorbidities, because out of all mediators of the innate immune system, MBL has the highest potential for the treatment and prevention of infectious diseases (19). ❑

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