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Case Report

Meningitis Caused by Herpes Virus Type 6 in a Pregnant Patient with MBL Deficiency. Report of a Case and Bibliographic Review

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Abstract

Objetive: We present a case of meningitis caused by herpes virus type 6 in a pregnant patient with mbl deficiency.

Case Report: We reprot a case of pregnant woman at 20 + 5 weeks of gestation with meningitis due to Herpes virus type 6 infection disease. The first clinical suspicion was meningitis caused by listeria monocytogenes due to the epidemiological context. At 23 + 5 weeks gestation, she presented a bacterial pneumonia that required hospital admission. The episode of meningitis due to a rare causative microorganism accompanied by community-acquired pneumonia, all during pregnancy, suggested a primary immunodeficiency. During the immunodeficiency study, a MBL deficiency was detected.

Conclusion: Thereby, in the present clinical case, the difficulty to perform a differential diagnosis between meningitis caused by listeria monocytogenes and other etiological agents is presented. In addition, in this work we show the importance to assess the role of a rare primary immunodeficiency such as MBL deficiency in pregnancy.

Keywords: Human Herpesvirus-6; Mannose-Binding Lectin Deficiency; Pregnancy; Meningitis

Abbreviations

HSV-6: Herpes Virus Type 6; MBL: Mannose-Binding Lectin; PCR: Polymerase Chain Reaction; CRP: C-Reactive Protein; IFNAR2: Interferon Alpha and Beta Receptor Subunit 2; ANA: Anti-nuclear Antibodies; ANCAs: Anti-neutrophil Cytoplasmic Antibodies; HSV: Herpes Simplex Virus; HIV: Human Immunodeficiency Virus; IAV: Influenza A Virus

Introduction

The group of herpesviruses is made up of seven viruses, all of which can affect the central nervous system to a greater or lesser degree, being the primary infection unusual in an immunocompetent host and being even more infrequent if it is the Herpes Virus Type 6 (HSV-6) causal agent of sudden rash. Interestingly, from 1998 there were only 17 published cases of meningitis and encephalitis caused by HSV-6 infection, in immunocompetent adult patients [1,2].

HSV-6 can usually cause a sudden rash and occasionally mononucleosis, pneumonia, meningitis and encephalitis [3].

Reviewing the literature, no clinical implications have been identified in pregnant women despite the virus having been identified in peripheral blood and at the maternal genital tract. Furthermore, long-term consequences of congenital infection are still undefined [4].

Given the exceptional nature of meningitis caused by HSV-6, it is necessary to perform immunological studies in order to evaluate immunodeficiencies. In the present case, through these studies, MBL deficiency was detected.

Mannose-binding lectin (MBL) is a pattern-recognition protein of the innate immune system that mediates the killing of a wide range of microorganisms through complement activation. A substantial proportion of all human populations studied to date are MBL deficient due to MBL2 polymorphisms, potentially increasing susceptibility to infectious diseases. MBL binds to numerous respiratory pathogens, but some pathogens can evade the MBL activity, an example is the Streptococcus pneumonia, this microorganism has a capsule that abrogate the efficient MBL binding with microorganism molecules [5], thereby, this immune evasion mechanism would explain the pneumonia presented by our patient.

Case Presentation

21-year-old primigravida woman, 20 + 5 weeks gestation, who was attended in the emergency department due to fever and history of ingestion of a product potentially contaminated by listeria (packaged shredded meat) in the context of an outbreak of this cause consisting in last ingestion in the previous month. Normal pregnancy checks up to the time of consultation. Analytical studies without alterations. Normal obstetric examination and ultrasound.

The pregnant woman was admitted with listeriosis suspected diagnostic and was treated according to the protocol with ampicillin and gentamicin. At 72 hours of admission, she began with an intense headache and doubtful signs of meningism, which is why a lumbar puncture was performed. The PCR (polymerase chain reaction) study detects DNA from HSV-6. No DNA from *Listeria monocytogenes* was detected.

Symptoms gradually subsided, for which acyclovir treatment was not started due to the eventuality of side effects and good evolution. Upon discharge, she was diagnosed with meningitis caused by HSV-6.

At 23 + 5 weeks of gestation, the pregnant woman came to the emergency room again with fever associated with rib pain. The obstetric examination and ultrasound did not show pathological findings. CRP (C-reactive protein) 58 mg/L and chest X-ray evidenced infiltrate at the left upper lobe. She was treated with intravenous ceftriaxone in the hospital and oral cefixime at discharge.

Upon discharge, the continuous follow-up was performed by the Infectious Department and High-Risk Obstetric Consultation. Given the two successive infection diseases in a short period of time, one of them with a very low incidence, in a previously immunocompetent and pregnant patient, it was carried out a study of IFNAR2 (Interferon Alpha and Beta Receptor Subunit 2) immunodeficiency and an screening of predisposition to bacterial infections. Additionally, it was performed ANA (Anti-nuclear antibodies) and ANCAs (Anti-neutrophil cytoplasmic antibodies) studies, extended serology and urine antigen detection against legionella and Streptococcus pneumonie.

Immunological study results: Correct immunity against Haemophilus B and Pneumococcus. Complement levels and activity in the normal range (41 to 90 hemolytic units). MBL levels were decreased to 44.05 ng/ml comparing with normal range (>1000) (Table 1).

Protein section			
Inmunoglobulin G	923	mg/dl	[700-1600]
Inmunoglobulin A	202.00	mg/dl	[70-400]
Inmunoglobulin M	193.70	mg/dl	[40-230]
Inmunoglobulin G1	505.8	mg/dl	[490-1140]
Inmunoglobulin G2	284	mg/dl	[150-660]
Inmunoglobulin G3	*133	mg/dl	[20-110]
Inmunoglobulin G4	37.14	mg/dl	[8-140]
Complement C 3	170.98	mg/dl	[90-180]
Complement C 4	30.31	mg/dl	[10-40]
Complement C1q	32.30	mg/dL	[17-43]
Albumin	3.53	g/dL	[3.5-5.2]
Molecular biology inmunology			
IgE TOTAL 62.60 KU/L [0-100]			
Inmunodeficiences ac. especifics against			
Pneumococcus capsular polysac. (IgG2)	20.87 mg/L RANGE IN MOST ADULTS: 11-90		
Haemophilus B (IgG)	7.32 mg/L MINIMUM PROTECTIVE LEVEL: 0.15. OPTIMAL PROTECTIVE LEVEL: 1.0 (Postimmunization)		
Study of lymphocyte subpopulation			
LYMPHOCYTE COUNT(Cells/ul) 1916	1916 (1000-4800)		
% CD3+ T- cells	79.9 (53-83)		
% CD4+ T- cells	49.33 (24-56)		
% CD8+ T- cells	27.04 (17-41)		
% CD19+ B-cells	9.54 (7-27)		
% NK-cells	9.81 (10-30)		
INMUNOLOGY MBL quantification	44.05 ng/ml (normal range>1000)		

Table 1: Immunodeficiency study (First study).

At 41 weeks' gestation, pregnancy induction was indicated in the process of prolongation. A living woman was born through an instrumented delivery of 4380 grams without current pathologies, under follow-up by her pediatrician.

A new determination was made one month after delivery with the following results: MBL levels 24.56 ng/ml, severe deficit (0-100). In addition, an immunological study was completed (Table 2).

The patient has had a favourable evolution after delivery, without presenting new episodes of infections in relation to the MBL deficiency.

Proteinogram	
Albumin (percentage)	* 58.4% (58.6 -66.1)
Alpha-1-Globulins (percentage)	3.9% (2.9 -4.9)
Alpha-2-Globulins (percentage)	10.3% (7.1 -11.8)
beta-Globulins (percentage)	11.9% (8.4 -13.1)
gamma-Globulins (percentage)	15.5% (11.1 -18.1)
Albumin/globulin ratio (EF)	1.40 ratio (1.30 -2.20)
Proteinogram (interpretation)	
Albumin (EF)	* 4.16 g/dL (43588.00 -43529.00)
Alpha-1-Globulins (EF)	0.28 g/dL (0.10 -0.30)
Alpha-2-Globulins (EF)	0.73 g/dl (0.40 -0.80)
beta-Globulins (EF)	0.85 g/dL (0.50 -1.00)
gamma-Globulins (EF)	1.10 g/dL (0.80 -43617.00)
M-component 0.00	
Component M (quantification)	0.0 g/dL
C-reactive protein	2.3 mg/L (0.0 -5.0)
General IMMUNOLOGY	
Immunoglobulin A	233 mg/dL (40 -350)
Immunoglobulin G	1056 mg/dL (700 -1600)
Immunoglobulin G1	538 mg/dL
Immunoglobulin G2	358 mg/Dl
Immunoglobulin G3	* 116 mg/dL (20 -110)
Immunoglobulin G4	41 mg/dL (8 -140)
Immunoglobulin M	189 mg/dL (50 -300)
Mannose-binding lectin	24.56 ng/ml Severe deficiency (0-100) Low responder (101-500) Normal (>1000)

Table 2: Second immunodeficiency analysis (One month after delivery, 5 months after first determination).

The newborn has presented an adequate development, highlighting only grade III ankyloglossia that required surgical correction.

Discussion

In the present clinical case, the difficulty of differential diagnosis between meningitis caused by listeria and other etiologies was presented. The diagnosis of herpesvirus 6 meningitis and the episode of community-acquired pneumonia raised the suspicion of primary immunodeficiency. During the immunodeficiency study, a deficiency in MBL (mannose-binding lectin) was detected.

MBL deficiency has been related to susceptibility to a large number of diseases, although there is the hypothesis or assumption that this is clinically relevant only when it coexists with another state of immunodeficiency [5]. In the present case, this state of immunodeficiency is assumed to be the state of physiological immunodeficiency produced by the adaptive mechanisms that occur during pregnancy.

MBL levels during pregnancy and the influence on the evolution of pregnancy have been studied in numerous studies. The working group of Van de Geijn et al. has shown that during pregnancy, MBL concentration increases to 140% [interquartile range (IQR) 116-181%, P <0.0001]. This increase was present at 12 weeks of pregnancy and was more pronounced in the high-producing AA genotype. Immediately postpartum MBL concentrations fell to 57% from baseline (IQR 44-66%, P <0.0001). Variations in MBL levels were reflected, in similar changes, in the following complement activation steps, r> 0.93 (P < 0.01). Ficolin-2 levels and classical complement pathway activity were not similarly influenced by pregnancy [6].

Along the same lines, David C. Kilpatrick et al. studied the concentration of MBL during pregnancy. They concluded that the mean MBL concentration (± SD) during pregnancies (5.31 ± 0.52) was significantly higher than the mean of the samples without pregnancy (3.84 ± 0.46) [7].

Based on the foregoing, we confirm that pregnancy and the postpartum period profoundly influence the serum concentration of MBL and the activity of the complement pathway MBL.

This leads us to suppose that the state of gestation produces an increase in MLB levels as an adaptive mechanism against its physiological immunodeficiency state.

In the case of our patient, this physiological increase was not possible due to her MBL deficiency, so she showed the clinical manifestations of her primary immunodeficiency debut during her pregnancy.

Recently, Jia Zhou research group has discovered the role of MBL as a regulator of Natural Killer cell activation, which would explain herpes virus type 6 meningitis [5].

Clearly, MBL deficiency is not a classic primary immunodeficiency, according to the Mendelian concept, given its extremely low clinical penetrance. However, it can have a substantial impact on protective immunity, such as susceptibility to most common diseases and infections under complex genetic control. Several studies have evidence that MBL deficiency is more common in patients with infectious diseases [8,9].

The Mannose-binding lectin (MBL) recognizes several viruses, for example, HSV (Herpes Simplex Virus), HIV (Human Immunodeficiency Virus), and IAV (Influenza A Virus). The interaction between MBL and virus-infected cells is mediated by MBL recognition of carbohydrate patterns containing terminal non-reducing mannose or N-acetyl glucosamine. The binding of MBL to viral envelope proteins triggers complement activation, independently of C1q or antibodies, through the MBL pathway [10].

MBL has been shown to provide a pathway for complement activation by other viruses such as HIV, HSV-1 GC null viruses, and influenza viruses. Previous studies have shown that human MBL binds to HSV-2 through carbohydrate recognition domains. The binding triggered complement activation and increased virus neutralization [11].

Serum levels of MBL are variable and range from 0 to 5 mcg/ml in healthy individuals. However, MBL deficiency is common, being found from 5% to 8% of the population. This deficiency is due to alterations in its gene regulation 41 with flaws in the structural gene or its promoter. Structural mutations have been identified in exon 1 at the level of codons 52, 54 and 57 [12].

In the prospective study by Çalkavur Ş, the polymorphism of codon 54 of the MBL gene was studied. The frequency of the B allele of the MBL variant was closely related with low levels of MBL, associated with recurrent spontaneous abortion, infertility, preeclampsia, gestational diabetes mellitus, premature rupture of membranes lasting more than 72 hours, tocolysis, histological chorioamnionitis, urinary tract infection and vaginitis [13].

The prospective Koucký study evaluated a cohort of 60 patients who found that serum MBL concentrations were significantly reduced in patients with threatened preterm birth (Group A), compared to control group B [14].

This same line is currently underway in a clinical trial NCT04017754 [15].

In the present clinical case, the difficulty of differential diagnosis between meningitis caused by a rare causative agent such as herpes virus type 6 and other more frequent agents is presented, also taking into account the epidemiological context of listeriosis epidemic. Here, we also present the challenge of assessing the role of a rare primary immunodeficiency such as MBL deficiency may have in pregnancy. There is the hypothesis or assumption that this is clinically relevant only when it coexists with another state of immunodeficiency. In our patient, this added immunodeficiency state was pregnancy. Since during it, there should have been a physiological increase in MBL levels, which, far from increasing, remained below what is considered normal outside of pregnancy. So this condition generated the clinical manifestations of her primary immunodeficiency during pregnancy debut.

Ethics Approval and Consent to Participate

The ethical guidelines have been reviewed in accordance with the CARE (2013).

Consent for Publication

The ethical guidelines have been reviewed in accordance with the CARE (2013) protocol and have been sent to the publisher.

Availability of Data and Material

Data sets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Competing Interests

The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

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Authors' Contributions

All authors contributed equally to the manuscript and read and approved the final version of the manuscript.

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