HK J Paediatr (new series) 2022;**27**:10-18

Original Article

Monocyte HLA-DR Expression in Children with Acute Bacterial Meningitis and Meningococcemia: A Predictor of Outcome and Prognosis

C ***Aydin***, F ***Genel***, I ***Devrim***, S ***Gozmen***, O ***Olukman***

Abstract

Introduction: Acute bacterial meningitis (ABM) and meningococcemia are among the most serious causes of mortality and morbidity in children. Faster tests with high specificity and sensitivity are required to provide early diagnosis and better prognosis. This study aimed to get serial measurements of monocyte HLA-DR expression rate to evaluate the outcome and prognostic value in children with ABM and meningococcemia. ***Population and Methods:*** This prospective case-control study was carried out on 18 paediatric patients diagnosed as ABM and meningococcemia and 36 healthy controls between 2011-2017 at Dr. Behcet Uz Children's Hospital, Izmir, Turkey. Monocyte HLA-DR expression was determined by flow cytometry on admission and the third day of treatment. ***Results:*** In the study group, HLA-DR expression was significantly low both on admission and on day 3, as well as HLA-DR mean fluorescence intensity ($p<0.001$, $p=0.001$, $p=0.001$, respectively). When compared to the third day of treatment, monocyte HLA-DR expression was significantly lower on admission ($p=0.003$). Five patients suffered neurological complications. On day 3, monocyte HLA-DR expression was found significantly lower in patients with neurological complications than the ones with a normal neurological examination ($p=0.043$). Six patients had used antibiotics before admission. Patients without prior antibiotic usage showed significantly lower monocyte HLA-DR expression ($p=0.007$). ***Conclusions:*** Monocyte HLA-DR expression is down-regulated in patients with ABM and meningococcemia. Higher percentages of monocytes expressing HLA-DR in patients with prior antibiotic treatment supports the importance of early treatment. Low monocyte HLA-DR expression on day 3 also seems to be a valuable predictive marker for neurological complications.

Key words *Acute bacterial meningitis; Meningococcemia; Monocyte HLA-DR expression; Paediatric population*

Department of Pediatrics, Division of Neonatology, İzmir Bakırçay University, Çigli Training and Research Hospital, Izmir, Turkey

C **Aydin** *MD*

O **Olukman** *MD*

Department of Pediatrics, Division of Pediatric Allergy and Immunology, Dr. Behcet Uz Children's Hospital, Izmir, Turkey

F **Genel** *MD*

Department of Pediatrics, Division of Pediatric Infectious Diseases, Dr. Behcet Uz Children's Hospital, Izmir, Turkey

I **Devrim** *MD*

Department of Pediatrics, Division of Pediatric Hematology, Dr. Behcet Uz Children's Hospital, Izmir, Turkey

S **Gozmen** *MD*

Correspondence to: Dr O **Olukman**
Email: drolukman2002@yahoo.com

Received January 27, 2020

Introduction

The morbidity and mortality caused by acute bacterial meningitis (ABM) in children remains significant worldwide, despite advances in vaccines, chemoprophylaxis, antimicrobial therapy and supportive care.[1] The overall annual attack rate for ABM is 2-5 cases for 100,000 population and the mortality rate is 6-16% in the United States.[2] In developing countries incidence is up to 10 folds and the mortality rate is 2-4 folds higher than the United States.[3] Severe neurological sequelae due to ABM have been reported in 10-20% of the patients.[4,5] Meningococcemia is a life-threatening bloodstream infection caused by Neisseria meningitidis. Septic shock due to this organism is unique and requires early aggressive management to improve outcome. It is most common in childhood and mortality rates for meningococcemia ranges from 10% in adolescents and 20% in infants.[6,7]

In children, early diagnosis is very important to improve prognosis both in ABM and meningococcemia. The identification of prognostic factors on admission could alert clinicians and could decrease the occurrence of undesirable events, so faster tests with high specificity and sensitivity are required to predict the outcome and prognosis.

Monocytes are a specific type of leukocytes that have functions in phagocytosis, cytokine production and presentation of antigen to lymphocytes for initiating both cellular and humoral immune responses. Monocytes play an important role in immune regulation and host defence against foreign organisms. HLA-DR molecules are expressed on the majority of monocytes and reflect the activation state of these cells. HLA-DR molecules are important for presenting antigen to the CD4+ cells.[8-10]

In the paediatric population, significant diminished HLA-DR expression on monocytes in preterm and full-term neonates has been reported.[11] Low monocyte HLA-DR expression was also found to be correlated with lower gestational ages in very low birth weight infants.[12] Downregulation of HLA-DR expression on monocytes has been reported in neonatal sepsis, adult sepsis, different groups of surgical patients, pancreatitis and trauma. It has also been associated with septic complications and increased risk of mortality.[13-16] Recent studies suggest that decreased monocyte HLA-DR expression is a reliable marker of excessive anti-inflammatory response and immune paralysis.[17,18] In a study by Shankar-Hari et al, it has been suggested that the optimum biomarker combination associated with subsequent sepsis in emergency department patients with suspected acute infection is the combination of increased neutrophil CD24 and neutrophil CD279 with reduced monocyte HLA-DR expression.[19]

This study aimed to get a serial measurement of monocyte HLA-DR expression rate to predict the outcome and prognosis in children with ABM and meningococcemia.

Population and Methods

Date and Time of Study Conduction / Study Design

This prospective case-control study was carried out between 1st August 2011 and 31st July 2017 at the department of paediatric infectious diseases of Dr. Behcet Uz Children's Hospital which is a 400-bed paediatric training hospital in Izmir, Turkey. In the study period, 18 children hospitalised with the diagnosis of ABM or meningococcemia were enrolled. The control group consisted of 36 healthy age and gender-matched children that applied to the outpatient departments for routine paediatric follow-up. Neonates were excluded from the study.

Hypothesis

Monocyte HLA-DR expression rate can predict the outcome and prognosis in children with ABM and meningococcemia.

Diagnosis of ABM and Meningococcal Disease

Patients were accepted as ABM according to the following criteria: increased cerebrospinal fluid (CSF) protein >100 mg/dL or decreased CSF glucose <40 mg/dL or CSF leukocyte count >100 white blood cell/mm^3 with at least 80% neutrophils, identification of bacterial agents in gram staining, or isolation of bacteria from the CSF samples.[2,13,20]

The clinical diagnosis of meningococcemia or meningococcal septic shock was made (in the absence of bacterial isolation) if the ill child had a fever and a petechial or purpuric rash and/or signs of meningitis as described before.[21]

Determination of Cell Surface Markers by Flow Cytometry

A study designed by Wu et al showed that a single measurement of mHLA-DR within the first week after patient admission had no predictive value regarding mortality. In contrast, results expressed as dynamic parameters (i.e., differences between two-time points)

provided excellent predictive values, especially the difference in mHLA-DR expression between days 0 and 3 or days 0 and 7.[22] Similarly, Zhuang et al found that dynamic monitoring of monocyte HLA-DR expression was more valuable for the diagnosis, prognosis, and prediction of sepsis.[23] In this respect, we also investigated the monocyte HLA-DR expression on admission and the third day of treatment. Measurements were performed via three-colour flow cytometry by one of the authors who knew neither clinical nor laboratory findings of the patients. In the patient group, samples of peripheral blood were collected in EDTA anticoagulant tubes. In the control group, the plasma of the peripheral blood drawn for routine complete blood count was separated and used. Freshly collected blood samples (100 mL) were stained within 15 min after arrival at the laboratory with 10 mL of each conjugated monoclonal antibodies (mAb). The following commercial mAbs were used: phycoerythrin-cyanin 5 (PC5)-labeled CD45 (clone J.33; Beckman Coulter), fluorescein isothiocyanate (FITC)-labeled HLA-DR (clone Immu-357; Beckman Coulter), and phycoerythrin-labelled CD14 (clone RMO52; Beckman Coulter). After completion of the incubation, the erythrocytes were lysed and leucocytes were stabilised and fixed by TQ-Prep (Coulter). The appropriate isotype controls were used. At least 10,000 cells from each sample were analysed on the Cytomics FC500 (Beckman Coulter) flow cytometer, and the data were processed with CXP cytometer software. The cytometer was routinely optimised using the Flow-Check Fluorospheres (Coulter, Fullerton, California, USA). Monocytes were identified by gating on forwarding/side scatter in combination with CD45 and CD14. Results were expressed as the percentage of monocytes expressing HLA-DR and as mean fluorescence intensity (MFI) of monocytes showing expression.

Ethical Considerations

The study was approved by the "Local Research Ethics Committee of Dr. Behcet Uz Children's Hospital, Izmir, Turkey" (Protocol number: 21; Date: 17.04.2013) and adhered to the Declaration of Helsinki for Medical Research involving Human Subjects. The parents of the patients gave their informed consent for participation in the study.

Statistical Analysis

Data were expressed as the mean, allowing for the Standard deviation of the mean (mean±SD). All data were tested for normality using the Kolmogorov-Smirnov test. Quantitative values were assessed through analysis of variance (ANOVA) when normally distributed, and by the Kruskal-Wallis test in other cases. Comparisons between two groups were made using the Mann-Whitney U-test or t-test, as appropriate. Categorical data were analysed with the chi-squared test (χ^2). Statistical analyses were performed with SPSS software, version 15.0 (SPSS Inc., Chicago, IL). Statistical significance was defined as $p<0.05$.

Results

Out of the 18 patients in the study group, 10 were male and 8 were female. The mean age was 55.2 months (4.6 years), ranging from 1 month to 15 years. In the control group, male to female ratio was 1.57 (22/14) and the mean age was 54.1 months (4.5 years) ranging from 1 month to 15 years. Comparison of patients and controls in terms of age and gender did not reveal any statistical significance (p=0.944 and p=0.695, respectively) (Table 1).

Demographical Features, Complications and Outcome of Patients

All of the 18 patients in the study group had fever and meningeal irritations at admission (100%) followed by confusion (n=14, 77.8%), hypotension (n=14, 77.8%), coagulopathy (n=14, 77.8%), vomiting (n=12, 66.7%), headache (n=12, 66.7%) and rash (n=12, 66.7%). Laboratory features of the study group on admission are reviewed in Table 2. Thirteen out of 18 patients had leukocytosis, 1 had leucopenia and 1 had thrombocytopenia. CRP levels of all 18 patients were remarkably high. In 5 patients, the lumbar puncture could not be performed because of haemodynamic instability due to septic shock. Twelve of the patients were diagnosed as meningococcemia with petechial and purpuric skin lesions, confusion, hypotension, prolonged capillary filling time and coagulopathy. CSF analysis of the 13 patients was compatible with ABM. Twelve patients had negative CSF culture and six of these had the history of beforehand

Table 1 Comparison of age and gender between groups

	Patient group (n=18)	Control group (n=36)	p
Age, (months) (mean±SD) (range)	55.2±60.2 (1-180)	54.1±52.1 (1-180)	0.944
Gender			
Female (n)	8	14	
Male (n)	10	22	0.695

administration of empirical antibiotics that can penetrate through the blood-brain barrier (5 intravenous ceftriaxone, 1 gentamicin+ceftriaxone). While CSF culture of one patient yielded isolation of *N. meningitidis*, another one resulted in *S. pneumoniae*.

Among 18 patients, 5 had neurologic sequelae including seizures, papillary stasis and strabismus, left hemiparesis, ptosis in the left eye and central facial palsy. No death occurred and all patients were discharged after medical treatment.

HLA-DR Expression

Mean percentage of monocytes expressing HLA-DR in the study group on admission was significantly lower than the control group (30.1±23.4 vs 93±5.1, p<0.001). In the study group, monocyte HLA-DR mean fluorescence intensity (MFI) on admission was also significantly lower compared to the control group (12±6.1 vs 18±6.1, p=0.001) (Table 3). Representative flow cytometry plots of an ABM patient a healthy control are presented in Figure 1 and Figure 2, respectively. When compared to initial values, the percentage of monocytes expressing HLA-DR significantly increased (49.9±24 versus 30.1±23.4, p=0.003) on the third day of the treatment, but monocyte HLA-DR MFI did not differ significantly (12±6.1 vs 11.3±1.8, p=0.466) (Table 4). On admission, the percentage of monocytes expressing HLA-DR and monocyte HLA-DR MFI were lower in patients with neurological complications compared to patients with normal neurological examination but these differences were not statistically significant (p=0.104 and p=0.217, respectively). The percentage of monocytes expressing HLA-DR was found to be significantly lower in patients with neurological complications on the third day of treatment (p=0.043), however, monocyte HLA-DR MFI values did not differ significantly (p=0.084) (Table 5). Six patients had used empirical antibiotics before admission. On admission when compared to patients who used antibiotics prior to admission, the percentage of monocytes expressing HLA-DR was significantly lower in patients who did not use antibiotics before hospitalisation (19.11±12.8 vs 52.33±25.1, p=0.007), but monocyte HLA-DR MFI values were similar (11.61±6.92 vs 12.86±4.45, p=0.482). Neither the percentage of monocytes expressing HLA-DR nor the monocyte HLA-DR MFI values differed significantly on the third day of treatment between patients with and without antibiotic usage prior to admission (p=0.349, p=0.373 respectively) (Table 6). In neither the patient nor the control groups we observed any additional MHC class 2 expression defects that could be interpreted as a possible genetic variation.

Table 2 Some important laboratory results of the study group on admission (n=18)

Parameters	Mean value (range) (±SD)
Haemoglobin (g/dL)	11.34±1.83 (8.8-15.3)
Thrombocyte count (/mm^3)	268,000±120,696 (76,000-498,000)
Leucocyte count (/mm^3)	18,562±9,673 (3,800-33,500)
Absolute neutrophil count (/mm^3)	14,038±8,034 (900-34,000)
Absolute lymphocyte count (/mm^3)	1,866±1,091 (700-4,200)
Erythrocyte sedimentation rate (mm/h)	47±32.8 (3-104)
C-reactive protein (mg/dL)	14.72±7.2 (3-25)

Table 3 Comparison of percentage of monocytes expressing HLA-DR and monocyte HLA-DR mean fluorescence intensity between the groups on admission

Parameters	Study group (n=18)	Control group (n=36)	p
Percentage of monocytes expressing HLA-DR (%)	30.1±23.4	93±5.1	<0.001
Monocyte HLA-DR MFI	12±6.1	18±6.1	0.001

MFI: mean fluorescence intensity

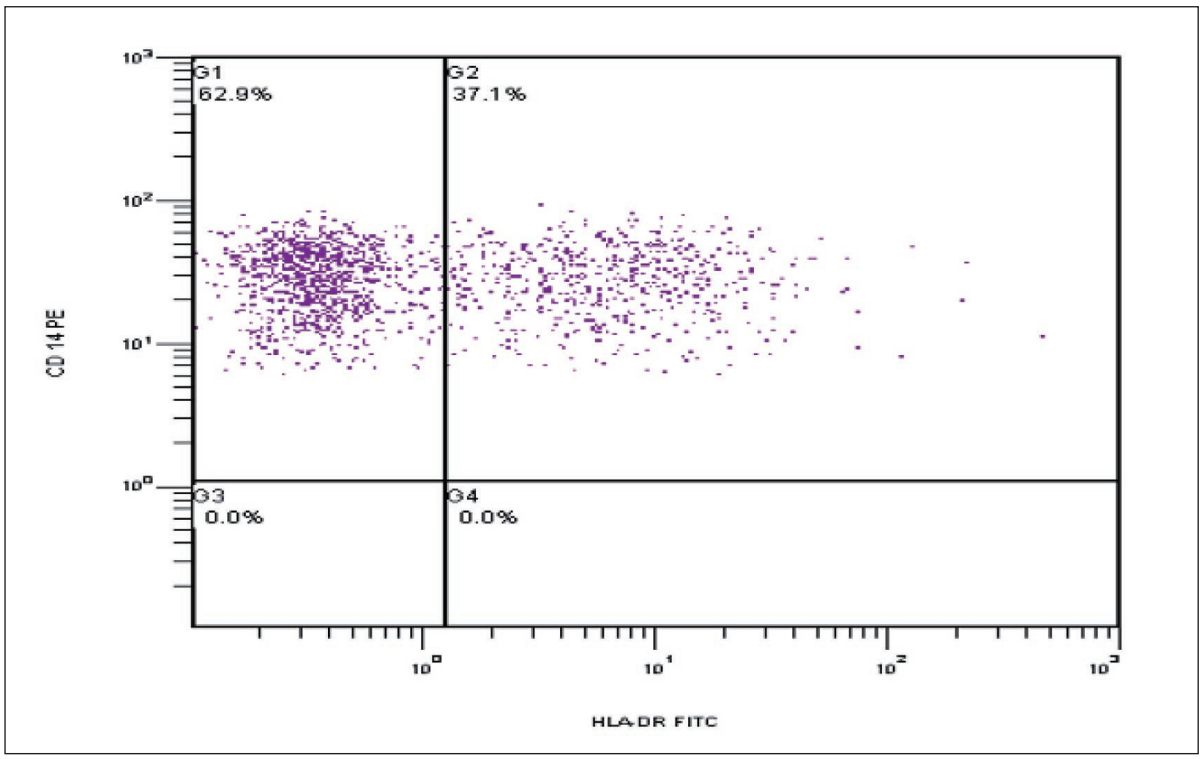

Figure 1 Monocyte HLA-DR expression percentage of an ABM patient on admission (flow cytometry).

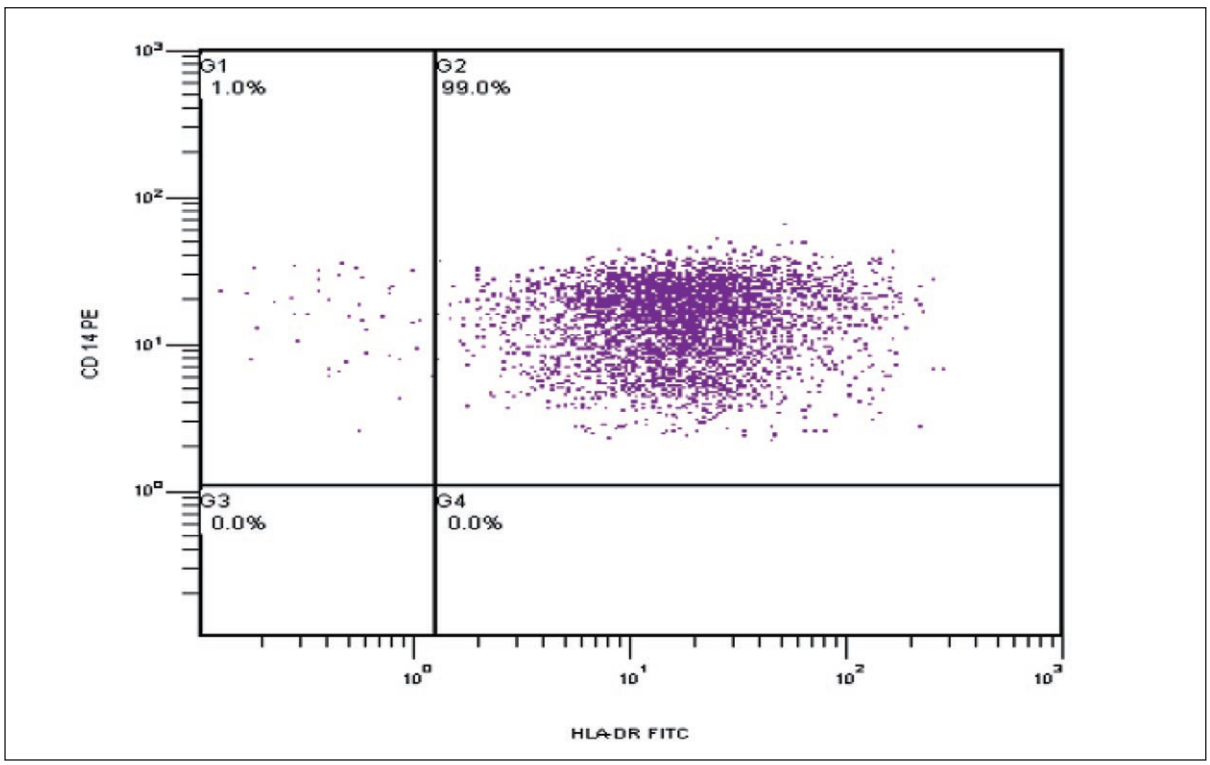

Figure 2 Monocyte HLA-DR expression percentage of a healthy control on admission (flow cytometry).

Discussion

In the pathogenesis of sepsis and serious infectious diseases such as meningitis and meningococcemia, the immune system plays a major role in host defence. In the initial phase of the immune response, increased release of pro-inflammatory cytokines leads to an effective immune response against infection. However, excessive production of these cytokines may be associated with excessive cellular injury, multiple organ failure and death. Following this phase, anti-inflammatory mediators are produced to modulate the inflammatory response. Excessive anti-inflammatory stimulation results with a state termed immune paralysis.[24] The percentage of monocytes expressing HLA-DR is found normal or increased in the inflammatory phase. In the anti-inflammatory phase, damaged monocyte functions and activations, inadequate oxidative burst and antigen presentation result in a decreased percentage of monocytes expressing HLA-DR.[24-26] Decreased monocyte HLA-DR expression is considered as a reliable marker of immune paralysis.[17,18]

In our study, we found the percentage of monocytes expressing HLA-DR and monocyte HLA-DR MFI significantly lower on admission in the study group. On the third day of treatment, the percentage of monocytes expressing HLA-DR was significantly higher than the initial values. Fortunately, no mortality occurred. However, 5 patients developed neurological complications. Patients with neurological complications had a lower percentage of monocytes expressing HLA-DR and lower monocyte HLA-DR MFI on admission, but these differences were not statistically significant. On the other hand on the third day of treatment, the percentage of monocytes expressing HLA-DR was significantly lower in patients with neurological complications while the monocyte HLA-DR MFI values remained similar.

Percentage of monocytes expressing HLA-DR is considered to be one of the best reflectors of immune functions in adults with serious diseases treated in intensive care units.[27,28] A low percentage of HLA-DR expression on monocytes has been reported as a poor prognostic factor in septic adults, different groups of surgical patients, pancreatitis and trauma.[14-16] In adult sepsis, percentage of monocyte HLA-DR expression less than 20% and its persistence on consecutive 5 days are associated with mortality rates as high as 90%.[17] In a study involving adult patients with cryptococcal meningitis, authors defined an immune signature associated with early mortality which was characterised by monocyte deactivation (reduced HLA-DR expression and tumour necrosis factor α response

Table 4 Comparison of percentage of monocytes expressing HLA-DR and monocyte HLA-DR mean fluorescence intensity of the study group on admission and the third day of treatment (n=18)

Parameters	On admission	The third day of treatment	p
Percentage of monocytes expressing HLA-DR (%)	30.1±23.4	49.9±24	**0.003**
Monocyte HLA-DR MFI	11.3±1.8	12±6.1	0.466

MFI: mean fluorescence intensity

Table 5 Comparison of the patients with and without neurological complications in terms of percentage of monocytes expressing HLA-DR and monocyte HLA-DR mean fluorescence intensity on admission and the third day of treatment

Parameters	Patients with neurological complications (n=5)	Patients without neurological complications (n=13)	p
Percentage of monocytes expressing HLA-DR on admission (%)	14.88±6.39	36.07 ±25.14	0.104
Percentage of monocytes expressing HLA-DR on the third day of treatment (%)	25.76±20.11	59.31±29.99	**0.043**
Monocyte HLA-DR MFI on admission	14.75±7.11	10.98±5.62	0.217
Monocyte HLA-DR MFI on the third day of treatment	7.69±2.80	13.38±8.42	0.084

MFI: mean fluorescence intensity

to lipopolysaccharide); increased serum interleukin 6, CXCL10 and interleukin 10 levels; as well as increased neutrophil counts; and decreased T-helper cell type 1 responses.[29] Published reports on the relationship between monocyte HLA-DR expression and outcome in children are limited. A study including children after cardiac bypass surgery reported that decreased HLA-DR in the early postoperative period predicts sepsis/systemic inflammatory response syndrome and prolonged stay in the intensive care unit.[30] Hoffman et al, showed the association between persistent low monocyte HLA-DR expression and the risk of post lung transplant pneumonia in children.[31] Döring et al investigated children and young adults after haematopoietic stem cell transplantation. In this study, prior to and during sepsis or bacterial infection, a significant decrease in human leukocyte antigen DR expression occurred.[32] Wakiguchi et al studied the relationship between T-cell HLA-DR expression and intravenous immunoglobulin (IVIG) treatment response in Kawasaki disease (KD).[33] They found increased T-cell HLA-DR expression associated with IVIG resistance in KD patients, indicating that T-cell activation could be a contributing mechanism underlying this phenomenon. A previous study in our centre demonstrated that the percentage of HLA-DR expressing monocytes was significantly lower in the non-survivor late-onset neonatal sepsis group (16.6%), compared with the survivor group (45.2%), and patients with monocyte HLA-DR expression ≤30% had lower survival rate with a 30-fold higher risk of mortality.[13] These results may indicate monocyte HLA-DR expression as an early predictive marker for prognosis in critically ill children and late-onset neonatal sepsis. In the present study, children with ABM and meningococcemia had down-regulated monocyte HLA-DR expression compared with healthy children reflecting compensatory anti-inflammatory response and immune paralysis. The increase on the third day of antibiotic treatment demonstrated improved immune functions. Our study also showed that the percentage of HLA-DR expressing monocytes on the third day may be a predictive marker for the development of neurological complications. In the present study, we found that a mean monocyte HLA-DR expression ≤50% on admission was strongly associated with the diagnosis of ABM. Moreover, we also demonstrated that the patients with monocyte HLA-DR expression still ≤40% on the third day of treatment were more likely to have poor neurological outcome. HLA-DR MFI did not differ significantly either on the first or the third day of follow up. Similarly, we could not find any significant relation between neurological complications and first or third-day monocyte HLA-DR MFI values. In a previous study, Wu et al reported that in survivors of sepsis monocyte HLA-DR MFI values increased significantly after 6 days.[34] In our study, we did not obtain any values further than the third day of treatment.

In ABM and meningococcemia, it is vital to begin antimicrobial treatment as early as possible. Bacterial load must be reduced immediately in order to prevent the complications of uncontrolled infection. Large studies, especially in adults with meningitis indicate that delay in antimicrobial treatment is a strong and independent risk factor for mortality and morbidity.[35-37] Recent data in children suggest early antibiotics are independently associated with improved outcomes in septic shock.[38,39] In our study, six patients had used empirical blood-brain barrier penetrating antibiotics (ceftriaxone) before admission. The percentage of monocytes expressing HLA-DR was significantly lower in patients without prior antibiotic usage than the patients who used antibiotics before admission, supporting the importance of early treatment. This result also suggests that early antibiotic treatment may have favourable effects on immune response and regulation in serious infections.

The strength of the current study comes from its being the first study in the current literature that introduces decreased monocyte HLA-DR expression as a reliable predictive marker of outcome and prognosis in paediatric patients with ABM and meningococcemia. On the other hand, the main drawback of the study is the small sample size. Larger scaled prospective studies are required to confirm our findings.

Conclusion

According to our findings, monocyte HLA-DR expression is downregulated in paediatric patients with ABM and meningococcemia. Higher percentages of monocytes expressing HLA-DR in patients referred with prior antibiotic treatment supports the importance of early treatment of ABM and meningococcemia. The percentage of monocyte HLA-DR expression on the third day of treatment also seems to be a valuable predictive marker for complications during follow up. Using monocyte HLA-DR expression may help clinicians to save time and effort in the differential diagnosis of critically ill children, lead them in decision making of early antibiotic treatment and prediction of possible complications.

Conflicts of Interest

None of the authors declares any conflict of interest.

Sponsorship

The authors declare that the present work was supported for laboratory test kits by "Beckman Coulter Biomedical Products, Inc., Bornova, Izmir, Turkey" under application number "2013/H298A-2G-SDDI4246".

References

1. Dash N, Panigrahi D, Al Khusalby S, Al Awaidy S, Bawikar S. Acute bacterial meningitis among children <5 years of age in Oman: a retrospective study during 2000-2005. J Infect Dev Ctries 2008; 2:112-5.
2. Thipgen MC, Whitney CG, Messonnier NE, et al. Bacterial meningitis in the United States, 1998-2007. N Engl J Med 2011; 364:2016-25.
3. Sigauque B, Roca A, Sanz S, et al. Acute bacterial meningitis among children, in Manhiça, a rural area in Southern Mozambique. Acta Trop 2008;105:21-7.
4. Kabani A, Jadavji T. Sequelae of acute bacterial meningitis in children. Antibiot Chemother (1971) 1992;45:209-17.
5. Dodge PR. Neurological sequelae of acute bacterial meningitis. Pediatr Ann 1994;23:101-6.
6. Kirsch EA, Barton P, Kitchen L, Giroir BP. Pathophysiology, treatment and outcome of meningococcemia: a review and recent experience. Pediatr Infect Dis 1996;15:967-78.
7. Hazelzet JA. Diagnosing meningococcemia as a cause of sepsis. Pediatr Crit Care Med 2005;6:50-4.
8. Kanakoudi-Tsakalidou F, Debonera F, Drossou-Agakidou V, et al. Flow cytometric measurement of HLA-DR expression on circulating monocytes in healthy and sick neonates using monocyte negative selection. Clin Exp Immunol 2001;123:402-7.
9. Birle A, Nebe CT, Gessler P. Age-related low expression of HLA-DR molecules on monocytes of term and preterm newborns with and without signs of infection. J Perinatol 2003;23:294-9.
10. Lekkou A, Karakantza M, Mouzaki A, Kalfarentos F, Gogos CA. Cytokine production and monocyte HLA-DR expression as predictors of outcome for patients with community-acquired severe infections. Clin Diagn Lab Immunol 2004;11:161-7.
11. Schefold JC, Porz L, Uebe B, et al. Diminished HLA-DR expression on monocyte and dendritic cell subsets indicating impairment of cellular immunity in pre-term neonates: a prospective observational analysis. J Perinat Med 2015;43: 609-18.
12. Palojärvi A, Petäjä J, Siitonen S, Janér C, Andersson S. Low monocyte HLA-DR expression as an indicator of immunodepression in very low birth weight infants. Pediatr Res 2013;73:469-75.
13. Genel F, Atlihan F, Ozsu E, Ozbek E. Monocyte HLA-DR expression as predictor of poor outcome in neonates with late-onset neonatal sepsis. J Infect 2010;60:224-8.
14. Ho YP, Sheen IS, Chiu CT, Wu CS, Lin CY. A strong association between down-regulation of HLA-DR expression and the late mortality in patients with severe acute pancreatitis. Am J Gastroenterol 2006;101:1117-24.
15. Venet F, Tissot S, Debard AL, et al. Decreased monocyte human leukocyte antigen-DR expression after severe burn injury: correlation with severity and secondary septic shock. Crit Care Med 2007;35:1901-17.
16. Haveman JW, van der Berg AP, Verhoeven EL, et al. HLA-DR expression on monocytes and systemic inflammation in patients with ruptured abdominal aortic aneurysms. Crit Care 2006;10: R119.
17. Perry SE, Mostafa SM, Wenstone R, Shenkin A, McLaughlin PJ. Is low monocyte HLA-DR expression helpful to predict outcome in severe sepsis? Intensive Care Med 2003;29:1245-52.
18. Monneret G, Finck ME, Venet F, et al. The anti-inflammatory response dominates after septic shock: association of low monocyte HLA-DR expression and high interleukin-10 concentration. Immunol Lett 2004;95:193-8.
19. Shankar-Hari M, Datta D, Wilson J, et al. Early prediction of sepsis using leukocyte surface biomarkers: the EXPRES-sepsis cohort study. Intensive Care Med 2018;44:1836-48.
20. Zhang L, Ma L, Zhou X, et al. Diagnostic value of procalcitonin for bacterial meningitis in children: A comparison analysis between serum and cerebrospinal fluid procalcitonin levels. Clin Pediatr (Phila) 2019;58:159-65.
21. Carrol ED, Thomson AP, Mobbs KJ, Hart CA. The role of RANTES in meningococcal disease. J Infect Dis 2000;182: 363-6.
22. Wu JF, Ma J, Chen J, et al. Changes of monocyte human leukocyte antigen-DR expression as a reliable predictor of mortality in severe sepsis. Crit Care 2011;15:R220.
23. Zhuang Y, Peng H, Chen Y, Zhou S, Chen Y. Dynamic monitoring of monocyte HLA-DR expression for the diagnosis, prognosis, and prediction of sepsis. Front Biosci (Landmark Ed) 2017;22: 1344-54.
24. Tschaikoxsky K, Hedwig-Geissing M, Schiele A, Bremer F, Schywalsky M, Schuttler J. Coincidence of pro and anti-inflammatory responses in the early phase of sepsis: Longitudinal study of mononuclear histocompatibility leukocyte antigen-DR expression, procalcitonin, C-reactive protein, and changes in T-cell subsets in septic and postoperative patients. Crit Care Med 2002;30:1015-23.
25. Docke WD, Randow F, Syrbe U, et al. Monocyte deactivation in septic patients: restoration by IFN gamma treatment. Nat Med 1997;3:678-81.
26. Muller Kobolt AC, Tulleken JE, Zijlstra JG, et al. Leukocyte activation in sepsis; correlations with disease state and mortality. Intensive Care Med 2000;26:883-92.
27. Venet F, Lepape A, Monneret G. Clinical review: flow cytometry perspectives in the ICU- from diagnosis of infection to monitoring of injury-induced immune dysfunctions. Crit Care 2011;15:231.
28. Moneret G, Venet F, Pachot A, Lepape A. Monitoring immune dysfunctions in the septic patient: a new skin for the old ceremony. Mol Med 2008;14:64-78.
29. Scriven JE, Graham LM, Schutz C, et al. A glucuronoxylomannan-associated immune signature, characterized by monocyte deactivation and an increased interleukin 10 level, is a predictor of death in cryptococcal meningitis. J Infect Dis 2016;213:1725-34.
30. Allen ML, Peters MJ, Goldman A, et al. Early postoperative

monocyte deactivation predicts systemic inflammation and prolonged stay in pediatric cardiac intensive care. Crit Care Med 2002;30:1140-50.
31. Hoffman JA, Weinberg KI, Azen CG, et al. Human leukocyte antigen-DR expression on peripheral blood monocytes and the risk of pneumonia in pediatric lung transplant recipients. Transplant Infect Dis 2004;6:147-55.
32. Döring M, Cabanillas Stanchi KM, Haufe S, et al. Patterns of monocyte subpopulations and their surface expression of HLA-DR during adverse events after hematopoietic stem cell transplantation. Ann Hematol 2015;94:825-36.
33. Wakiguchi H, Hasegawa S, Suzuki Y, Kudo K, Ichiyama T. Relationship between T-cell HLA-DR expression and intravenous immunoglobulin treatment response in Kawasaki disease. Pediatr Res 2015;77:536-40.
34. Wu HP, Shih CC, Lin CY, Hua CC, Chang DY. Serial increase of IL-12 response and human leukocyte antigen-DR expression in severe sepsis survivors. Crit Care 2011;15:R224.
35. Lepur D, Barsic B. Community-acquired bacterial meningitis in adults: antibiotic timing in disease course and outcome. Infection 2007;35:225-31.
36. Proulx N, Fréchette D, Toye B, et al. Delays in the administration of antibiotics are associated with mortality from adult acute bacterial meningitis. QJM 2005;98:291-8.
37. Auburtin M, Wolff M, Charpentier J, et al. Detrimental role of delayed antibiotic administration and penicillin-nonsusceptible strains in adult intensive care unit patients with pneumococcal meningitis: the PNEUMOREA prospective multicenter study. Crit Care Med 2006;34:2758-65.
38. Kumar A. An alternate pathophysiologic paradigm of sepsis and septic shock: implications for optimizing antimicrobial therapy. Virulence 2014;5:80-97.
39. Fletcher M, Hodgkiss H, Zhang S, et al. Prompt administration of antibiotics is associated with improved outcomes in febrile neutropenia in children with cancer. Pediatr Blood Cancer 2013; 60:1299-306.