Review Article

Genetic polymorphisms associated with sepsis incidence, severity, and outcomes among neonates: A mini-review

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Abstract

Genetic variation remains a topic of great interest due to its potential as a risk factor for various diseases. Interactions between genes contribute to diverse phenotypes in response to factors such as infection. The impact of genetic background on susceptibility and clinical outcomes, particularly in neonatal sepsis, has gained recognition. The variability in sepsis susceptibility and outcomes can be attributed to the genetic diversity in coding regions and regulatory elements of genes related to innate immune response. Recent advances in genomics and technology have shed light on genetic polymorphisms among humans, often represented by single-nucleotide polymorphisms (SNPs). These SNPs encode proteins crucial for recognizing and responding to pathogenic bacteria, including Toll-like receptor 4, CD14, tumor necrosis factor-alpha, as well as interleukin-1-10. This literature review specifically discusses the involvement of genetic polymorphism during the pathogenesis stage of sepsis, with an emphasis on previous research findings in neonatal sepsis cases, aiming to discuss the implications of polymorphism in sepsis susceptibility and outcomes.

Key words: Cytokines, immunology, neonates, polymorphism, sepsis

INTRODUCTION

Neonatal sepsis, a serious and life-threatening condition, continues to pose significant challenges in the field of neonatology despite remarkable advancements in recent years. In 2019, the incidence of neonatal sepsis reached a staggering 6.31 million cases.[1] Premature infants and those with very low birth weight are particularly vulnerable.[1] Sepsis, characterized by immune dysregulation in response to systemic infection, is associated with substantial morbidity and mortality during the neonatal period. Uncontrolled hyperinflammation and cytokine storm are the causes of any infectious disease fatality.[2,3] Functions and expression of proteins regulating the innate immune reaction are influenced by genetic factors.[4] Understanding the genetic factors underlying sepsis incidence and outcomes has become an area of increasing interest.[5]

Genetic polymorphisms have emerged as significant contributors to the variability, susceptibility, and outcome of sepsis. These polymorphisms are found in genes encoding key biomolecules corresponding to the immune response during the course of bacterial infection. They encompass proteins associated with early bacterial recognition,

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including but not limited to mannose-binding lectin (MBL), Toll-like receptor 4 (TLR4), Fc-γ receptors, as well as intracellular proteins. Polymorphisms are also responsible for the higher or lower excretion of cytokines and heat shock proteins.[5] Thus, genetic variety may contribute to the pathogenesis and clinical outcomes since it causes the alteration of immune response and inflammatory reaction. In a previous study, for example, a significant relationship between the interleukin (IL)-1β rs1143643 gene polymorphism along with the incidence of bacteremia among neonates was reported.[6] A previous study reported that IL-6-174 G/C gene polymorphism may influence the progression as well as outcomes of septicemia.[7] Nevertheless, the evidence from an updated meta-analysis reported an insignificant relationship between IL-6-174 G/C gene variants and the mortality odds of neonatal sepsis.[8] Taken altogether, it is of importance to explore genetic polymorphism that interplays with sepsis pathogenesis in order to develop novel diagnostic tools, personalized treatment strategies, and improved prognosis for neonatal sepsis.

This review article discusses a brief overview of genetic polymorphisms and their association with neonatal sepsis incidences. Further, the association with sepsis susceptibility and its clinical outcomes will also be discussed.

GENETIC POLYMORPHISMS IN SEPSIS

The immune reaction against infections caused by bacteria involves the recognition of bacterial-derived antigens by specific receptors, which triggers an immune response. Genetic polymorphisms associated with this process contribute to variations in the immune response among individuals.[5] Notably, lipopolysaccharide (LPS), a crucial component of the bacterial cell wall, interacts with cell surface receptors, particularly TLR4, which eventually activates the innate immune cascade.[9] Another important component of the LPS receptor complex, CD14, exhibits a polymorphism at position 159 that affects its transcriptional activity and levels.[10,11] Furthermore, genetic variations in leukocyte Fcγ receptors and MBL have been implicated in the susceptibility to bacterial infections.[12,13]

During the development of sepsis, a dysregulated systemic inflammatory response occurs, leading to the release of cell signaling molecules involved in inflammation, such as tumor necrosis factor-alpha (TNF-α), IL-1, and IL-6, and the following release of anti-inflammatory mediators. Variation in the genes encoding the aforementioned cytokines has been reported for having correlation with sepsis susceptibility. Polymorphisms in the TNF-α gene, including −308 G/A, have shown associations with the risk of sepsis and septic shock.[14] Meta-analyses have further supported the influence of TNF-α gene polymorphisms on sepsis risk in specific populations.[15-18] Similarly, IL-6-174 G/C single-nucleotide polymorphism (SNP) has been examined. Although the direct impact on sepsis risk and outcomes remains inconclusive, overexpression of IL-6 has been linked to higher severity of this disease.[7] Meta-analyses have indicated a potential role for IL-6 gene polymorphisms in sepsis risk, particularly in specific ethnic groups.[19]

NEONATAL SEPSIS WITH GENETIC POLYMORPHISM CLINICAL OUTCOME

Neonatal sepsis, an organ- and system-affecting condition indicated by systemic inflammation corresponding to bacterial or viral infection, can be influenced by genetic factors. Studies have shown that genetic variants are correlated with the development along with worsening of preterm neonatal sepsis, along with a higher risk of contracting particular pathogens. The summary of studies reporting the correlation of genetic polymorphisms with the initiation and worsening of sepsis among neonates is presented in Table 1. Esposito *et al*. identified certain genotypes having association with overall higher risk of contracting sepsis, such as TT and CT genotypes of IL-1β (rs1143643) and GG genotype of MMP-16 (rs2664349).[26] In addition, GG genotype of CD14 (rs2569190) along with AT genotype of IL8 (rs4073) was linked to the risk of higher severity of sepsis. These findings highlight the correlation between genetic polymorphisms and the susceptibility as well as progression of neonatal sepsis.[26]

Another study investigated the association of TNF-α (an initiator in the early phase of inflammatory response in sepsis) with neonatal early-onset sepsis (EOS).[29] They analyzed 471 premature infants, categorizing them into an EOS group with culture-confirmed and clinically diagnosed sepsis and a control group of preterm infants without sepsis. The study revealed that polymorphisms in TNF-α were associated with increased production of TNF-α, possibly due to the enhanced transcription associated with the A allele of TNF-α 308 gene. Clinical symptoms observed in neonates with EOS included respiratory difficulties (apnea, dyspnea, and tachypnea), hemodynamic changes (tachycardia, bradycardia, hypotension, and cyanosis), lethargy, hypotonia, irritability, convulsions, poor perfusion, abdominal distension or feeding intolerance, and hepatosplenomegaly, jaundice, or skin lesions.[29] Meanwhile, a study revealed an insignificant association between the outcome of EOS and IL-6-174 G/C polymorphisms, while TNF-α-308 GA along with AA genotypes were suggested to cause greater risk toward EOS occurrence but not lethal outcome.[29]

Genetic polymorphisms play a significant role in modulating cytokines involved in the inflammatory cascade. Gene variants related to early recognition processes, such as TLR4 and CD14, as well as MBL, are associated with sepsis

Table 1: Neonatal sepsis-associated genetic polymorphisms reported by published studies

Author, year[reference]	Gene	SNP code	Findings
Hedberg *et al*., 2004[20]	TNF-α	−308	Three times mortality in AA/AG than in GG genotype
Baier *et al*., 2006[21]	IL-6	−174 G/C	Increased late bacteremia in AA genotype
	IL-10	−1082 G/A	More severe and high mortality in AA genotype
	CD-14	−260 C/T	Increased Gram-negative bacteremia
Schueller *et al*., 2006[22]	TNF-β	Nco I	No association
	TNF-α	−308 G/A	No association
Reiman *et al*., 2008[23]	IL-6	−174 CC	Correlated with septicemia and sepsis incidence
Abu-Maziad *et al*., 2010[24]	TLR2	rs3804099	Associated with sepsis incidence
	TLR5	rs5744105	
	PLA2G2A	rs1891320	
	IL-10	rs1800896	
Härtel *et al*., 2011[25]	TNF-α	−308 G/A	No association
Esposito *et al*., 2014[26]	IL-1b	rs1143643	Associated with increased sepsis incidence
	MMP-16	rs2664349 GG	
	BPI	rs4358188	Associated with lower sepsis incidence
	DEFb1	rs1799946	
	CD14	rs2569190	Associated with sepsis progression
	IL-8	rs4073	
	LTA	rs1800629	Associated with increased Gram-negative sepsis incidence
	BPI	rs1341023	
Allam *et al*., 2015[27]	IL-1β	Not reported	Associated with increased serum IL-1β
	TNF-α	Not reported	Associated with early-onset sepsis
	IFN-ɤ	Not reported	Associated with increased serum IFN-ɤ
Xue *et al*., 2017[28]	MBL2	−221 Y/X	Associated with increased sepsis incidence
Varljen *et al*., 2019[29]	TNF-α	−308 G/A	Associated with increased sepsis incidence
Mustarim *et al*., 2019[6]	IL-1β	rs1143643 G/A	Associated with increased sepsis incidence
Ma *et al*., 2023[30]	MBL	rs1800450	Associated with increased sepsis incidence
Panigrahi *et al*., 2023[31]	MTHFR	C677T and A1298C	Polymorphism in mothers affecting the sepsis incidence of their neonates

TNF-α: Tumor necrosis factor-alpha, MBL: Mannose-binding lectin, SNP: Single-nucleotide polymorphism, TLR: Toll-like receptor, IL: Interleukin

susceptibility. Specifically, polymorphisms in TLR4 are linked to Gram-negative sepsis as well as septic shock, leading to increased mortality in systemic inflammatory responses. Similarly, an increased level of CD14 has been found to be associated with its gene variants at nucleotide 159 and its homozygous-158 allelic model.[26] Another key cytokine in the inflammatory process is TNF-α, particularly its involvement in the pathogenesis and acute-phase inflammatory response. Children with heterozygous TNF-α-308 GA genotype exhibit a higher risk of severe infection, particularly meningococcal infection.[29]

As witnessed by many studies, proinflammatory cytokines, particularly IL-6, have a significant role in the inflammatory response during sepsis. Serum IL-6 levels are associated with the disease severity and outcomes. However, studies have produced varying results regarding the relationship between IL-6 promoter region polymorphisms along with sepsis in infants. Polymorphisms in the IL-6 promoter region, including the G to C substitution at nucleotide 174, have been found to regulate cytokine production in neonates. Premature neonates with the G allele have shown an association between lower serum IL-6 levels and the incidence of sepsis.[23,27]

Furthermore, the production of anti-inflammatory cytokines is crucial when it comes to suppressing the systemic inflammatory response and maintaining homeostasis. IL-10, an anti-inflammatory cytokine, is a significant contributor in reducing the production of inflammatory promoters such as TNF-α, IL-1α and IL-1β, IL-6, as well as IL-8. Nevertheless, the overwhelming production of IL-10 may lead to immunosuppression, increasing mortality along with impairing bacterial elimination in sepsis. Polymorphisms in IL-10 gene at positions −1082 G to A, −819 C to T, and −592 C to A were reported to be associated with altered IL-10 expression.[5,24]

The susceptibility of neonates to sepsis is influenced by their immature humoral and cellular immune responses, particularly in B-cells and T-cells.[32] Deficiencies in myelopoiesis and defects in the complement cascade activation further contribute to the impaired innate immune system function in neonates. Nevertheless, genetic factors are recognized to play a pivotal role during the course of innate immune reaction and sepsis development.[33,34] Evaluation of the systemic inflammatory response through cytokine markers is commonly employed to identify neonates with infections.

CONCLUSIONS

The genetic variability of individuals significantly contributes to the inflammatory response along with immune regulation during infection. Numerous studies have identified the association between polymorphic genes and sepsis incidences, severity of the disease, risk of specific pathogens, and clinical outcomes. SNPs are involved in early recognition of sepsis, such as TLRs, CD14, and MBL. Evidence suggests that TLR4 gene polymorphism is linked to higher risk of contracting sepsis as well as septic shock where Gram-negative bacteria were the causative agents, consequently contributing to higher mortality rates. Similarly, certain polymorphisms in CD14 have been linked to increased levels of CD14 and an increased risk of contracting sepsis. Furthermore, polymorphisms in crucial proinflammatory cytokines, including IL-6, TNF-α, as well as IL-10, are found having association with altered cytokine production, impacting the immune response, and influencing disease severity. Based on the findings reported up to this day regarding the role of genetic polymorphism in sepsis among neonates, it is recommended to establish early detection and timely intervention and incorporating genetic profiling for personalized management.

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Conflicts of interest
There are no conflicts of interest.

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