Micro RNA as a Potential Biomarker for the Diagnosis of Neonatal Sepsis – A Review

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ABSTRACT

Neonatal sepsis (NS) represents a significant threat around the globe. It is mostly a bacterial infection that occurs within 28 days of age. It is a serious condition which is induced by an infection and accompanied by characteristic inflammatory response. Unfortunately, detection of sepsis is challenging at its initial stages as signs and symptoms are non-specific, and the outcomes of gold standard blood culture are usually delayed with decreased sensitivity. The high mortality rate is intrinsically linked with time-consuming and non-reliable diagnostic techniques with low-sensitivity and specificity. This requires novel diagnostic biomarkers to overcome the limitations. Huge efforts have been made to identify new biomarkers of sepsis. Current scientific investigations have shown the role of latest sepsis biomarkers including circulating micro RNAs (miRNA). miRNAs are single stranded non-coding RNA molecules. They can regulate gene expression and can govern up to 60% of all protein coding genes. As a regulator, microRNAs can play a significant role in various biological mechanisms. During different pathological conditions, the distribution of circulating miRNAs can be altered. Research has demonstrated that the dysregulated miRNAs expression is associated with the pathogenesis of neonatal sepsis and may be critical for host immunity against infections. Some of the miRNAs were closely linked with the stage of the disease, and its prognosis. MicroRNAs are characterized by very high stability, specificity, and selectiveness. A wide range of miRNAs in the blood may be studied by using molecular techniques. Their diagnostic and prognostic values are high. They can be valuable biomarkers for diagnosis and may be useful in clinical decision-making. In this review, we summarize existing studies highlighting the role of circulating miRNAs in neonatal sepsis diagnosis. Mechanism of various micro RNAs like miRNA-181a, miRNA-146a, miRNA187, miRNA101 are described and its association with severity of neonatal sepsis will help in understanding the disease progression. miRNA dysregulation during gram-positive and gram-negative sepsis provides knowledge about pathogenesis. The regulation of immune response genes shows the association of miRNA with different immunological components. Forest plot analysis and comparison of various studies based on their regulation, sensitivity, specificity, p-value and AUC might be useful in critically analysing the different miRNA as a prognostic and diagnostic marker. There may be variations in diagnostic outcomes of miRNA which must be standardised before including it in routine laboratory testing. Combination of micro-RNA along with other biomarkers can be more promising in the diagnosis and prognosis of neonatal sepsis.

KEY WORDS

Neonatal Sepsis, Biomarkers, Circulating Micro RNA, Diagnosis

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BACKGROUND

Neonatal sepsis (NS), mostly a bacterial infection occurs within 28 days of age. Every year about 1 million infants worldwide die from NS, which poses a public health burden.¹ It is a serious condition which is induced by an infection and accompanied by characteristic inflammatory response. Mostly among preterm infants it has significant morbidity and mortality, which can be related to inadequate potential diagnostic methods and delayed antibiotic treatment.² Unfortunately, detection of sepsis is challenging at its initial stages as signs and symptoms are non-specific, and the outcomes of gold standard blood culture are usually delayed with decreased sensitivity.³

The National Institutes of Health defines a biomarker as a “characteristic that can be objectively measured and evaluated as an indicator of normal biological processes, pathological processes, or pharmacological responses to a therapeutic intervention”. Biomarkers such as PCT (procalcitonin) and CRP (C-Reactive Protein) are commonly used in sepsis diagnosis but are of limited sensitivity and specificity.⁴ This requires novel diagnostic biomarkers to overcome the limitations. Huge efforts have been made to identify new biomarkers of sepsis such as circulating micro RNAs.⁵

MICRO RNA AS BIOMARKERS

Micro RNAs (miRNAs) are single-stranded non coding RNA molecules. They are endogenous and small with length of 18-24 nucleotides. They can regulate a gene expression by attaching to the target messenger RNAs (mRNAs) at their 3' untranslated region (3'UTR). It is done by direct degradation of messenger RNA (mRNA) or translation inhibition. It can also inhibit protein synthesis at the post-transcriptional level.⁶

In humans over 1800 miRNAs have been characterized. These miRNA genes are estimated to represent about 1 % of the human genome, but can govern up to 60 % of all protein coding genes. Thus, one miRNA can affect numerous transcriptions. As a regulator, microRNAs can play a significant component in biological mechanisms, like cell proliferation and cell cycle. They are also progressing as modern immune response regulators which includes immune cell differentiation, function and development.⁷

Under various pathological and physiological conditions, the circulating microRNAs are expressed differently. Similarly, further research has demonstrated the dysregulated miRNAs expression is associated with the pathogenesis of neonatal sepsis and may be critical for host immunity against infections. Some of the miRNAs were closely linked with the stage of the disease, and its prognosis.⁸

Micro RNAs are characterized by very high stability (increased or decreased temperature, changes in pH, and repetitive cycles of freezing and thawing), specificity, and selectiveness.⁶ A wide range of miRNAs in the blood may be studied by using molecular techniques (array and single polymerase chain reaction-based methods). Their diagnostic and prognostic values are high. They can be valuable biomarkers for diagnosis and may be useful in clinical decision-making.⁷

Role of Various Micro RNA in Neonatal Sepsis

Mi R-181a

The serum expression of miR181a in NS patients is downregulated. Over-expression of miR181a in monocytes has been able to enhance the inflammatory reaction induced by Lipo-Poly-Saccharide (LPS) by targeting Toll Like Receptor (TLR) 4, which may further uncover the pathological mechanisms in the development of NS. TLR 4 binds to LPS of Gram-negative bacteria as a mechanism of innate immunity. Stimulation of LPS in monocytes also led to reduced miR181a expression. TLR4 has been demonstrated to be a specific target gene of miR181a. The upregulated levels of Tumour Necrosis Factor-TNF α and Inter-Leukin 8 (IL 8) induced by LPS-induced inflammation have been shown to be reduced by miR181a overexpression. TNF- α is a principal mediator of inflammatory response and IL 8 induces chemotaxis in target cells. MiR181a overexpression inhibits the inflammatory response induced by LPS, by targeting TLR4 at least partially.⁷

Mi RNA-146-a

In sepsis group, levels of serum miRNA-146-a were significantly reduced. It is associated with severity of neonatal sepsis. Lowest level was seen in paediatric septic shock group. miRNA-146-a level below 0.4 is correlated with increased rate of mortality. Procalcitonin, CRP, TNF- α and IL6 which induces acute phase response were negatively correlated with serum miRNA-146-a expression.⁸ Toll-like receptor 4 (TLR4) was found to be negatively regulated by miRNA-146 family (miR-146a / b). In neonatal monocytes, the increased level of miR-146a expression following LPS stimulation may be a negative regulator of TLR4 activation.⁹

Mi R-187 and mi R-101

Expression of miR-187 and miR-101 were higher in neonatal sepsis in comparison with control group. miR-101 could serve as an optimistic biomarker for diagnosis of neonatal sepsis because it had statistical significance.¹⁰

Mi R-21

MiR-21 values were considerably increased in non-survivors when compared to survivors' group. Survival analysis showed higher levels of miR-21 expression were correlated with low rates of survival. In addition, miR-21 became a reliable predictor of sepsis prognosis particularly in combination with Score for Neonatal Acute Physiology (SNAP) II.¹⁰

Mi R-223 and mi R-132

In early onset sepsis, levels of miR-223 and miR-132 were decreased. It is related with higher levels of immunological genes involved in TLR signalling and may cause inflammatory changes.⁶

Mi R - 25

Mi R-25 expression in septic neonates was considerably upregulated and target gene of miR-25 was CD69. CD69 activates of T lymphocytes and natural killer cells. In sepsis patients, CD69 position ratio and CD69 protein level along with messenger RNA was higher. The possibility of sepsis in new-borns is related with miR-25-single-nucleotide polymorphism (SNP; rs41274221).¹¹

Mi R-300

Mi R-300 levels were overexpressed in septic neonate mouse model. It was related to inflammatory response such as increased autophagy, increased cell cycle and decreased apoptosis in endothelial cells. Thus, it denotes that miR-300 triggers sepsis and can act as therapeutic target.¹²

Mi R-23b

Mi R-23b levels in new-borns who died from both early and late onset of sepsis was decreased significantly. The decrease in levels of miR-23b may be a key element which favours sepsis progression.¹³

mi R-142a-5p

In a model of zebra fish, infection with *Staphylococcus epidermidis* induces extreme down-regulation of dre-miR-142a-5p, allowing for up-regulation of the IL-6 signalling pathways.¹⁴

Mi R-125b

Higher levels of TNF- α are synthesised by neonatal monocytes. miR-125b significantly decreased following LPS stimulation in correlation with higher TNF- α expression. Precursor miR-125b transfection into neonatal monocytes substantially reduced the expression of TNF- α . This indicates miR-125b regulates TNF- α expression negatively. Proinflammatory reactions can be controlled by miR-125b modulation.¹⁵

Mi RNA-26a

The expression of miRNA-26a was decreased in neonatal sepsis while the levels of mRNA and IL-6 were significantly increased. Direct target of miRNA-26a was found to be IL-6. Pathogenesis, disease progression and immune responses can be modulated by miRNA-26a¹⁶

Mi R-15a and mi R-16

In neonatal sepsis, the levels of miRNAs 15a and 16 are upregulated. The primary target of miR-15a / 16, was TLR 4, IRAK1 (Interleukin 1 Receptor-Associated Kinase 1 is responsible for adaptive immune response and inflammation). It suppresses the expression of TLR4 and IRAK1.¹⁷

Mi Rs-182 and 185

Mi Rs-182 and 185 levels was found to be downregulated in neonatal sepsis. It was correlated with upregulation of apoptosis or programmed cell death inducing FAS-associated protein with death domain (FADD) gene expression.¹⁸

Mi RNA 16 and miRNA 34a

In the blood culture positive neonatal sepsis patients, levels of miRNA 16 was significantly increased when compared with negative blood culture and control groups. Mi RNA 34a levels were significantly decreased in blood culture positive group. We can propose that the levels of miRNA 16 are higher and the levels of miRNA34a are lower during neonatal infection.¹⁹

Mi R-142-3p and let-7g

The lower levels of miR-142-3p and let-7 g expression after LPS stimulation in neonatal Poly Morpho Nuclear (PMN) cells leads to increased synthesis of IL-6. PMN acts as phagocytes of innate immunity.²⁰

Mi R-181a and mi R-184

In neonatal CD4 + T cells, improved calcium signalling is induced by elevated amounts of miR-181a. Elevated levels of miR-184 and miR-181a led to reduced Nuclear Factor of Activated T cells1 (NFAT1) protein and decreased T Helper cells 1 (Th1) response which influences cell-mediated response and the production of various cytokines. This modified immune response is related to both miR-181a and miR-184.²¹

MiR-155 and MiR-146a

Upon TLR stimulation, neonatal Plasmacytoid Dendritic Cell (pDC) releases decreased amounts of Interferon- α (IFN- α has antiviral activity). In neonatal pDCs, increased amount of miR-155 and miR-146a are found. They modulate the TLR-dependent inflammatory responses by negative regulation and decrease the IFN- α synthesis.²²

MiR-181b

Altered class-switch recombination of Immunoglobulin-IgM to IgG / IgA in neonatal B cells was linked to the higher levels of miR-181 b. Such results highlighted the role of miRNAs in neonatal humoral immunity programming.²³

MiR-29

Neonatal CD8 + T cells have reduced miR-29 (miR-29a-3p, miR-29 b-3p, and miR-29c-3p) expression until stimulation. Transcription factors like Eomes and Tbx21 are the direct target of miR-29. This indicates the effective activation of neonatal naïve CD8 + T cells which produces effector cytokines.²⁴

Let-7

Over-expression of Let-7 has been found to reduces the synthesis of cytokines and interleukins (IL-10 and IL-13). Decreased levels of let-7c and let-7b-5p are expressed by Neonatal monocytes and CD4 + T cells. Neonatal monocyte participates in antigen presentation and phagocytosis. Neonatal CD 4 + T cells produces effector cytokines. It is associated with increased production of IL-10 and IL-13. Decreased production of TNF- α and LPS-induced interleukin IL-6 were seen. It is associated with immune response against infection.

Other miRNAs

In neonatal monocytes, increased levels of miR-34a-3p, miR-424 and miR-582-5p, are found. These miRNAs may be involved in developing the neonatal immune response but not demonstrated in neonatal immune cells and require further study. Significantly decreased levels of miR-96, miR-141 and mi R-1184 are found in neonatal sepsis when compared with uninfected neonates. In neonatal monocytes, after LPS stimulation considerable variations in the levels of various micro-RNA such as miR-454-3p, miR-130a, miR-103 and miR-542-3p were demonstrated.^{15,20,25}

Sl. No	Bacteria	Upregulated	Downregulated
1	Gram positive sepsis	miR-122, miR-135a, miR-185, miR-548a-3p, miR-549, miR-551b, miR-611, miR-620, miR-637, miR-761, miR-1299	miR-96, miR-182, miR-210, miR-222, miR-296-5p, miR-365, miR-373, miR-582-5p, miR-631, miR-874, miR-886-3p, miR-886-5p, miR-940,
2	Gram negative sepsis	miR-208a, miR-450a, miR-486-3p, miR-489, miR-491-3p, miR-375, miR-509-3-5p, miR-618, miR-644, miR-720, miR-886-3p, miR-1184.	miR-15a, miR-30a, miR-16, let-7g miR-17, miR-20a, miR-20b, miR-30a, miR-22, miR-26a, miR-28-5p, miR-29a, miR-30e, miR-33a, miR-93, miR-101, miR-106a, miR-126, miR-130a, miR-141, miR-142-5p, miR-143, miR-144, miR-146a, miR-146b-5p, miR-151-3p, miR-151-5p, miR-181a, miR-193a-3p, miR-199a-3p, miR-320a, miR-320b, miR-320c, miR-330-5p, miR-411, miR-425, miR-558, miR-599, miR-604, miR-636, miR-652, miR-768-5p, miR-937, miR-1246, miR-1248, miR-1284, miR-548l, miR-19a.

Table 1. Regulation of Micro RNA in Neonatal Sepsis

Sl. no	Micro RNA	Immune response genes Up regulated	Immune response genes Down regulated	Other immune associated target genes
1	miR - 29a	TBX21, CCR5	TNFRSF1A	TRAF3, TRAF4, TRAF5, IL17, TNFAIP1
2	miR - 96	IL16	PTGS2	TNFRSF13B, IF130, IL17B, CCR8, CD4, CD96
3	miR - 101	IL16, IL13	PTGS2	TLR2, CD86, CD163, CXCL6
4	miR - 122	CD40LG	TNFRSF1B	IL3, IL18, IL22, CD96, CCL13, CCL21
5	miR - 141	IL12B, TBX21	IL1A	CD80, IRF6, CXCL12, IL6R
6	miR - 143	CTLA4	PTGS2	IL36G, BTLA, TLR2
7	miR - 181a	IL2	IL1A, PTGS2, TLR4	IL1B, IL25, FAS, IRF5, CD69, CD4,
8	miR - 182	IL13, IL8, FADD	PTGS2	CCL2, CCL13, CCR9, CD69, IL1F9
9	miR - 185	CCR5, GNLY, FADD		CD84, BTLA, IL18R1, TNFAIP1
10	miR - 1184	IL16		TNF, IL4R, IL21, CCR6, TNFRSF11A

Table 2. Micro RNA in the Regulation of Immune Response Genes

Sl. no	Author /year	Cases and Controls n = Samples	Micro RNA	Regulation	Sensitivity	Specificity	P- value	AUC
1.	Liu et al. 2019	102 with NS, 50 without sepsis	miR - 181a	Down regulated	83.3 %	84 %	(P < 0.01)	0.893
2.	Karam et al. 2019	55 paediatric sepsis patients and 60 control	miR - 146a	Down regulated	86.6 %	56.6 %	P = 0.0001	0.803
3.	Salim et al. 2020	50 with NS, 30with SIRS and 20 healthy neonates	miR - 187 miR - 101 miR - 21	Up regulated Up regulated Up regulated	72 % 84 % 64 %	76 % 84 % 66 %	P = 0.001 P = 0.001 P = 0.001	0.789 0.908 0.711
4.	Dhas et al. 2018	25 with EOS and 25 without sepsis	miR - 132 miR - 146a miR - 155 miR - 223	Down regulated Down regulated Down regulated Down regulated	Nil Nil Nil Nil	Nil Nil Nil Nil	P < 0.01 Nil Nil P < 0.05	Nil Nil Nil Nil
5.	Fatmi et al.	54 new-borns suspected of sepsis	miR - 23b	Up regulated in EOS Down regulated in LOS	Nil Nil	Nil Nil	EOS: preterm - P < 0.001 full-term - P < 0.005 LOS: P<0.005	Nil Nil
6.	Chen et al. 2014	48 neonates	miR-101 / 122 / 185 miR-96 / 182 / 141 / 143 / 181a / 29a / 1184	Up regulated Down regulated	Nil Nil	Nil Nil	Nil Nil	Nil Nil
7.	Yu et al. 2016	5 neonates and adults for isolation of leukocyte subpopulations 31 neonates and 19 adults for isolation of pDC	miR - let-7b - 5p	Down regulated	Nil	Nil	Nil	Nil
8.	Cheng et al. 2018	28 cases of neonatal sepsis	miR - 26a	Down regulated	Nil	Nil	P<0.05	Nil
9.	Rateb, et al. 2018	80 cases and 20 control	miR - 16 miR - 34a	Up regulated Down regulated	82.5 % 100 %	70 % 78.3 %	(P < 0.001) P < 0.001)	0.802 0.857
10.	Ahmed et al., 2017	24 neonates suggestive of NS, 22 high risk neonates 17 healthy neonates as controls	miR - 146a	Up regulated	91.7%	100%	0.037	0.99

Table 3. Micro RNA as Diagnostic Markers

CONCLUSIONS

Difficulty in early diagnosis of neonatal sepsis may be countered by using microRNA as a potential marker. However, there may be variations in the outcomes which must be standardised before including it in routine laboratory testing. Combination of micro RNA along with other biomarkers can be more promising in the diagnosis and prognosis of neonatal sepsis.

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