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ORIGINAL ARTICLE

Serum Level and Genetic Polymorphism of Angiotensin Converting Enzyme in Neonatal Sepsis Patients

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ABSTRACT

Background: *Neonatal sepsis (NS) is an important worldwide health problem predominantly in developing regions, Susceptibility to sepsis varies according to various neonatal factors such as innate immune response and pathogens exist in the local environment.* ***Objective****: determination of serum level and genetic Polymorphism of angiotensin converting enzyme (ACE) in NS.* ***Methodology:*** *this case-control study included 116 subjects, 58 in each group. The diagnosis of NS has been based on: thorough history taking, clinical signs and symptoms of NS and laboratory investigations. Blood samples were collected for inoculation on blood culture bottles followed by isolation and identification of the causative bacteria. Detection of polymorphism in ACE gene using Polymerase chain reaction (PCR) and Measurement of serum level of ACE by Enzyme linked immunsorbent assay (ELISA) were done.* ***Results****: Klebseilla was found to be the most common encountered organism.There is a significant increase in serum ACE level in NS cases as compared to healthy controls (p=0.0002). DD genotype was dominant in NS patients, while II genotype was dominant in healthy controls (p=0.00001). The highest level of ACE was detected in DD genotypes in comparison to other genotypes with a statistically significant differences (p= 0.00005).* ***Conclusion****: ACE may play a role as a biomarker for neonatal sepsis pathogenesis.*

INTRODUCTION

Neonatal sepsis is a syndrome that involves clinical signs of infection, shock, and failure in several systems in the body. It has been divided into early onset neonatal sepsis (EONS) occurring during the first 72 hours of life while late onset neonatal sepsis (LONS) takes place beyond this time up to 28 days [1].

Globally, Neonatal sepsis affects approximately four to twenty two newborns per 1000 live births, with the frequency differing inversely with gestational age at birth. In high- income regions, incidence ranges from one to four cases per 1000 live births. However, it is higher in low- and middle-income ones (49–170 cases) [2].

Premature neonatal immune responses (either innate or adaptive) characterized by immature function of neutrophil and reduced immunoglobulin's concentration are possible to make preterm infants more prone to sepsis [3-5].

Unrestrained inflammation will lead to a sepsis cascade that will result in a storm of cytokine which is represented by massive secretion of pro-inflammatory mediators such as IL-6, tumor necrosis factor and interferons. This can trigger activation of fibrinolysis, coagulation and complement pathways. Subsequently septic shock occurs [6-7].

ACE is a dipeptidase enzyme, capable for degradation of angiotensin I to angiotensin II. ACE and its substrates affect many physiologic processes and also contribute to many pathological events such as sepsis [8]. Ang II acts on angiotensin 1 receptors (AT1R) leading to abnormal inflammatory reactions and endothelial dysfunction. Blockade of the AT1R increases the formation of Ang-(1-7) which plays the contrary effects to Ang II allowing vasodilatation in addition to antiproliferation [9-12] .

The importance of ACE lies in its dual functionality. Beyond its role in converting angiotensin I to angiotensin II, ACE modulates the balance between vasoconstriction and vasodilation, influencing vascular integrity and permeability. These factors are critically affected during sepsis, particularly in neonates, who are highly vulnerable to systemic inflammatory responses and endothelial dysfunction. During sepsis, dysregulation of Renin angiotensin system (RAS) can result in altered ACE levels, making it a candidate for diagnostic and prognostic biomarker studies [13-14].

Gene of ACE is found on the 17th chromosome. There were several polymorphisms in ACE gene that may reach 160 polymorphisms. Insertion/Deletion (I/D) polymorphism in ACE gene has been accompanied to ACE serum level and action, high levels were found to be linked with the DD genotype because the D allele

form a higher quantity of mRNA than the I allele in white blood cells [15].

As controlling of neonatal sepsis is constantly a challenge because its symptoms and signs are nonspecific. NS patient observation and monitoring, knowing how to take into account clinical signs and risk factors are essential for diagnosis.

This study aimed to estimate the role of ACE polymorphism and its serum level as risk factors for neonatal sepsis.

METHODOLOGY

Study design and participants:

This study is a case-control study conducted at the Departments of Medical Microbiology and Immunology and Pediatrics, Faculty of Medicine, Zagazig University after review and approval by the Institutional Review Board (IRB#:10347-7-2-2023) committee. A written informed consent was taken from parents of each study participant.

It included 116 subjects; 58 in case group and 58 in control group.

Inclusion criteria: infants with neonatal sepsis, diagnosis of NS will be based on thorough history taking, the presence of clinical signs of NS and lab investigations that include WBCS count, immature to total neutrophil (IT) ratio and C-reactive protein level. Age and sex matched apparently healthy volunteers will be enrolled in the study as a control group.

Exclusion criteria:

Refusal of parents, older patients, newborn infants with low weight less than 11,00 g and those with dangerous congenital abnormalities.

Two and half mL of peripheral blood were obtained from each neonate in the study and divided into 1ml in blood culture bottle, 0.5 ml in EDTA containing tube for genetic study and 1 ml in a tube for serum collection for ACE level measurement by ELISA.

Identification of isolates:

Conventional blood culture method has been used to isolate pathogens from the neonates. Subculture of blood culture bottles was done aerobically at 37 °C for 24 hours on blood and MacConkey agar. Identification of isolates was carried out using conventional biochemical methods like catalase, coagulase, oxidase, citrate, urease and TSI.

Quantitation of Serum ACE concentration (ELISA):

Serum ACE concentration was measured by ELISA according to manufacturer's instructions: **(ELISA KIT, INOVA No. 18, Keyuan Road, Daxing Industry Zone, Beijing, China)**: Known concentrations of human ACE standard and its corresponding OD are plotted on the log scale (x-axis) and the log scale (y-axis), respectively. The original concentration was calculated by multiplying with the dilution factor.

ACE I/D polymorphism was determined by polymerase chain reaction:

DNA extraction was performed using (Gene aid gSYNC DNA extraction kit) following instructions of manufacturer. Thermal cycler amplification of extracted DNA using the following primers (SYN BIOTECH, CHINA); Forward primer: (5`-CTG GAG ACC ACT CCC ATC CTT TCT-3`) and Reverse primer: (5`-GAT GTG GCC ATC ACA TTC GTC AGA T-3`) [16, 17]**.** For a total reaction volume of 20µL; master mix 10 µL, 10 pmol of each primer, 4 µL of template DNA and 4 µL sterile distilled water have been added to each tube. Thermal cycler was programmed to perform initial denaturation step at 95°C for 10min, followed by 35 cycles of denaturation at 94°C for 30 sec, annealing at 67 °C for 40 sec, extension at 72°C for 45 sec, then final extension at 72°C for 10 sec [18].

Amplified products have been visualized on 1.5% agarose gel under UV light. A 100 bp DNA ladder (Tiangen Biotech, Beijing, China) has been used as a molecular size marker. Interpretation of amplified PCR as follow: DD genotype gives band at 190 bp, II genotype gives band at 490 bp and DI genotype gives at both 190, 490 bp.

Statistical analysis:

IBM SPSS Statistics 25 has been used to analyze data , quantitative variables were presented as means and SD. Kruskall Wallis test was performed in comparing more than two groups of non-normally distributed variables. Categorical data were presented by their absolute frequencies and chi square test was applied in comparing the proportion of categorical data . OR was used to describe how strongly an event is associated with exposure. P value < 0.05 means statistically significant (S) results.

RESULTS

This case control study included 116 neonates, 58 neonates with sepsis (case group) and 58 neonates as a healthy control group. There was a statistically significant difference between case and control groups regarding weight (p=0.003). Also, there was a statistically significant difference between both groups regarding history of premature rupture of membranes (PROM) being more frequent with NS. Regarding gestational age all controls were full term babies as shown in **Table 1,2**.

Type of isolated organisms:

According to the result of blood culture, the most common isolated organism was *Klebsiella* (43%) followed by *Coagulase-negative staphylococci (CONS)* (19%) and *E. coli* (15.5%), while *Citrobacter was* the Least common isolated organisms (1.7%), **Table 3**.

Table 1: **Demographic data and weight of studied groups:**

Variable	Studied group		χ 2	P
	Case	Control		
Age per day				
Mean ±SD	5.7 ± 3.7	8 ± 5.8		
Range	(1-17)	(1-21)	**19.8**	**0.406**
Sex N (%)			**0.315**	**0.575**
Male	27 (46.6%)	24 (41.4%)		
Female	31 (53.4%)	34 (58.6%)		
Ratio	0.9	0.7		
Weight per kg				
Mean ±SD	2.2 ± 0.52	2.6 ± 0.42	**40.3**	**0.003**
Range	1.5 - 3.5	2.0 - 3.5		

χ 2: chi square test SD: standard deviation

Table 2: Comparison between studied groups regarding obstetric history:

Variable	Case N (%) 58 (50)	Control N (%) 58 (50)	OR (95%CI)	χ 2	P
Mode of delivery					
NVD	27 (46.5)	28 (48.3)	1.07	0.035	
CS	31 (53.4)	30 (51.7)	(0.517-2.2)		0.852
PROM					
Yes	31 (53.4)	17 (29.3)	2.8	6.96	0.008
No	27 (46.5)	41 (70.6)	(1.3-6)		
Term pregnancy					
Preterm	33 (56.8)	0 (0)	0.3	62.53	0.000
Term	25 (43.1)	58 (100)	(0.2-0.04)		
	Mean ± SD	**Mean ± SD**	**t test**	**P**	
Gestational age (weeks)	34.57 ± 4.0	39.16 ± 1.21	- 8.35	0.000	

OR: odds ratio χ 2: chi square PROM: Premature Rupture of Membranes. CS: Cesarean Section.
NVD: Normal Vaginal Delivery test

Table 3: Isolated organisms from NS patients:

Type of isolated organism	N (%)
Klebsiella	25 (43.1)
CONS	11 (19)
E. coli	9 (15.5)
Staphylococcus aureus	6 (10.3)
Streptococci	2 (3.4)
Acinetobacter	2 (3.4)
Citrobacter	1(1.7)
Pseudomonas	2 (3.4)

Serum ACE level and gene polymorphism in NS patients and control groups:

Serum ACE level in NS patients ranged between 400-5000 pg/ml with mean ± SD (2830.2 ± 1312.4) while serum ACE level in control group ranged between 200-2000 with mean ± SD (461.2 ± 460.8) with a statistically significant difference among both groups (p=0.0002). (**Fig: 1**)

There was a high statistically significant difference regarding genotypes distribution in both groups (p=0.00001). As 58.6 % of NS patients have genotype DD, while 51.7 % of healthy controls have genotype II. Carriers of D allele have a higher risk for acquiring sepsis than non D allele carriers. **(Table 4)**

There was a very highly statistically significant difference between ACE genotypes and its level in NS patients with highest concentration was for DD genotype with a level in NS patients ranged between 1600- 5000 with mean ± SD (3184.6 ± 1040.6) which is the highest level among the three genotypes (p= 0.00005). **(Table 5)**

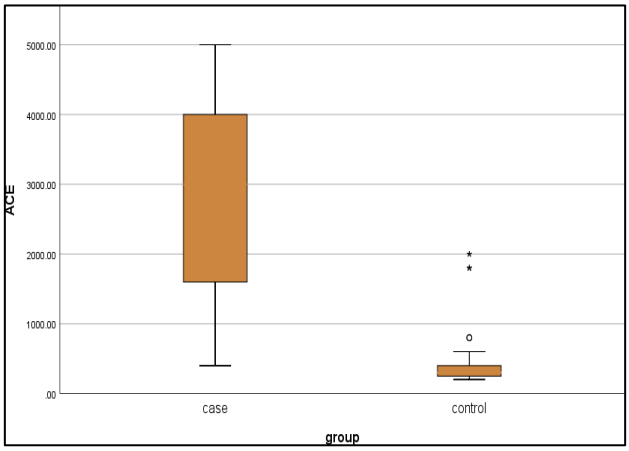

Fig. 1: Box plot of serum ACE level in NS patients and control groups.

Table 4: ACE genotypes distribution among NS patients and healthy controls:

ACE Genotype	Studied groups		χ 2	P	OR (95% CI)
	NS N(%)	control N(%)			
DD	34 (58.6)	10 (17.2)	22.7	0.00001	16.4(6.4-42.1)
II	11 (19)	30 (51.7)			
DI	13 (22.4)	18 (31.03)			

χ 2:Chi square OR: odds ratio

Table 5: Serum ACE levels in NS patients in relation to ACE genetic polymorphism:

Variable	NS patients			P
	DD	II	DI	
ACE (Pg/mL) Mean ± SD Median (min-max)	 3184.6 ± 1040.6 3500 (1600- 5000)	 1050 ± 475.09 800 (400-1600)	 1554.5 ± 524.1 1600 (800-2500)	**0.00005**

KW= Kruskal wallis

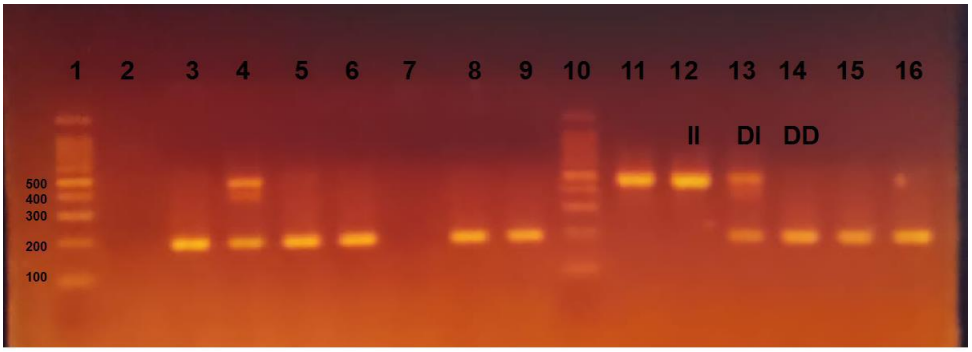

Figure 2: Ultraviolet light transilluminator showing products of ACE gene amplifications:
Lane (1), (10): DNA ladder.
Lane (2): negative control.
Lane (3), (5), (6), (8), (9), (14), (15), (16): DD genotype (one band at190 bp).
Lane (11), (12): II genotype (one band at 490 bp)
Lane (4), (13): DI genotype (two bands at 190 and 490 bp)

DISCUSSION

Neonatal sepsis is a serious medical condition caused by improper host response to infection. It is considered one of the main leading causes to morbidity and mortality all over the world, affecting newborns with the highest incidence and mortality rates [19].

In this research, we investigated the role of polymorphism in ACE gene and ACE serum level as risk factors for neonatal sepsis.

In the present study, no statistically significant difference was detected between both groups regarding sex (P= 0.575) which agreed with Woldu et al. [20]. Meanwhile, El-Behedy et al. [21] stated that male gender was more susceptible to neonatal sepsis.

Our study showed that there was a statistically significant difference between case and control groups regarding the weight of neonates, this result is in accordance with G/eyesus et al, [22] who reported that low birth weight especially premature babies are prone to hospital acquired infections because of their innate vulnerability to infection and the multiple invasive techniques to which they have been exposed.

Regarding obstetric history of the studied groups, premature infants had more susceptibility to develop sepsis. This result agreed with El-Behedy et al, [21] who found more occurrence of sepsis in preterm infants. This may be related to immature immune system and the more need for admission to NICU and various instrumentations [23].

Regarding history of Premature rupture of membranes (PROM) , in our study 53.4 % of NS patients and 29.3% of control neonates had a history of PROM with a high significant difference (P=0.008). This result matched with Zakariya et al, [24] who found that PROM was recognized to be among the risk factor for acquiring sepsis (P=0.048) . On the other side Turhan et al, [25] stated that there is no difference between studied groups regarding PROM.

We found that no statistically significant difference was detected between both groups concerning mode of delivery as NVD accounted for 46.5%, 48.3% and C.S accounted for 53.4, 51.7 in case and control groups respectively, which agreed with El-Behedy et al, [21]. On the other side Utomo et al, [26] and Adatara et al, [27] reported that neonates of cesarean section delivery were more prone to develop sepsis due to delayed breast feeding and prolonged hospital stay. However Hamid al, [28] found that higher incidence of sepsis among neonates of normal labor this may be due to exposure to fecal and vaginal bacteria.

Regarding the isolated microorganisms, the most predominant isolated pathogen in our study was *Klebsiella* (43.1%). Aamir et al, [29] and Chiabi et al, [30] also reported the same findings, This may be due to the adaptation of *Klebsiella* to the hospital environment and surviving longer on hands and surfaces, facilitating infection within hospitals. In contrast, Acheampong et al, [31] stated that prevalence of Gram-positive bacteria (72.0%) were higher than Gram-negative ones.

In our study, high ACE serum level was found among NS group. In agreement with our results Orfanos et al, [32] and Doerschug et al, [33] who reported that serum ACE activity increased in sepsis. In contrast Zhang et al, [34] found that there is a low expression of angiotensin system level (ACE and AngII) in patients suffering from severe sepsis and septic shock.

The quantity of ACE concentration is often correlated with an insertion or deletion (I/D) in ACE's intron 16. The plasma ACE level is highest in those with the DD genotype, intermediate in those with the ID genotype, and lowest in those with the II genotype [35].

In our study DD Genotype was more frequent in neonatal sepsis group (58.6%) than genotype II (19%) and genotype DI (22.4) %. Also Celik et al, [36] and Deng et al, [37] reported that Genotype DD carriers had increasing affinity for sepsis related acute respiratory distress syndrome**.**

In contrast Cogulu et al, [38] found that I allele's carriers were at risk for developing sepsis in comparison to controls. Also John Baier et al, [16] found that ACE I/D polymorphism had no discernible influence on the incidence of neonatal sepsis.

Moreover, we found that ACE serum level was higher in DD genotype than other genotypes. Our findings agreed with Morimoto et al, [39].

Additionally it was reported that DD genotype had higher serum and tissue levels of ACE and also associated with meningococcal infection in children [40].

Sepsis pathophysiology is recognized to be influenced by a wide range of elements, most notably the pathogen's virulence and the host immune response. Therefore, the ACE genotype cannot be the primary determinant in the progression of sepsis since the etiology and outcome of sepsis are determined by the interplay between the pathogens and the polymorphisms in the inflammatory and anti-inflammatory responses. The frequency of ACE gene polymorphisms may show differences between different ethnics and geographic areas [41].

CONCLUSION

ACE I/D polymorphism might play an important role in the pathogenesis of neonatal sepsis. DD genotype is associated with higher levels of ACE in NS patients.

Declarations

Consent for publication: Not applicable

Availability of data and material: Data are available upon request.

Competing interests: The author(s) declare no potential conflicts of interest with respect to the research, authorship and/or publication of this article.
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