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ORIGINAL ARTICLE

Impact of Factor V Leiden G1691A, MTHFR C677T, and Prothrombin G20210 Amutations on the development of neonatal thrombosis

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ABSTRACT

Background: Neonatal thrombosis is a rare disorder usually develops because of underlying conditions in the neonatal period, such as thrombophilia gene mutations, sepsis, congenital heart disease and surgical interventions or intravascular catheters.
Objective: The goal is to look at the prevalence of neonatal thrombophilia and its risk factors among neonates admitted to the Neonatal Intensive Care Unit (NICU).
Patients and methods: A cohort research that took place in neonatal ICUs in Zagazig University Hospitals from January to December 2021. Forty patients were involved. Patients were given a thorough medical history, clinical, neurological examinations, laboratory routine tests and Screening for thrombophilia gene variants by RT-PCR using the Vienna Lab Diagnostics GmbH's (FVL, PTH and MTHFR Strip Assay) ® A kit (Vienna, Austria).
Results: Concerning factor V gene mutation (G1691A) there was 6 (15%) had mutations, four of them (10%) showed heterozygous and two (5%) showed homozygous s mutations while 34 (85%) were normal. Nine (22.5%) patients had mutation of prothrombin G2010A gene with five (12.5%) of them were heterozygous and four (10%) were homozygous while 31 (77.5%) were normal. As regard MTHR C677T, 10 (25%) were normal, 23 (57.5%) had heterogeneous and 7 (17.5%) showed homozygous mutations. There was statistically significant increase in D-dimer and the presence of the Factor V (G1691A) and prothrombin G20210A while it was non-significant as regard mutations of MTHFR C677T.
Conclusion: Neonatal thrombosis is a critical condition. Its incidence increased with the presence of homozygous thrombophilia gene mutations especially with surgical intervention or venous catheterization.

Key words: Thrombophilia, Neonatal thrombosis, venous thromboembolism (VTE).

INTRODUCTION

The risk of venous thromboembolism (VTE) is about 40 times higher in newborns than in children, while the peak incidence occurs in neonates and infants under the age of one year. [1], [2], [3].

There was a surveillance done by the Egyptian Ministry of Health (2010-2014) to assess the prevalence of sepsis among newborn in Egyptian NICUs, the highest prevalence was found in North Sinai (12.83%) and the lowest prevalence was found in Dakahleya (2.56%) [20].

The cause of lower prevalence of venous thromboembolic disease (VTE) in children than adults is mainly caused by the integrity of the vessels and increase anticoagulant activity of the endothelium, and decrease ability for thrombin generation, thrombin inactivation by a 2-macroglobulin, high antagonist concentrations, antithrombin deficit, protein C and protein S deficiency, tissue factor levels in cord blood are low, and the level of proteoglycans varies with age. [4],[5].

The word 'thrombophilia' refers to coagulation disorders that are either inherited or acquired and have been related to an increased risk of thrombosis. Activated protein-C resistance, which can be caused by the inherited factor-V Leiden (FVL) mutation, protein C, S, or antithrombin III deficiencies, the prothrombin G20210A mutation, or hyper-homo-cysteinemia, which can be caused

by nutritional factors or the 5,10-methylenetetrahydrofolate reductase gene (MTHFR) mutation are examples of inherited causes [6].

During early stages, coagulation proteins were synthesized in the fetus and cannot cross the placental barrier. When compared to adult levels, numerous procoagulant proteins, such as vitamin K dependent coagulation factors and contact factors, are lower in fully term newborns. [7].

Because of neonates' high hematocrit, high viscosity, and small vascular diameter, capillary flow is sluggish, especially when dehydration or hypercoagulability is present due to prematurity or infection. Additionally, arterial, or venous catheters are one of the most common causes of thrombosis in this time. (15 % of NICU babies and at least 50percent of preterm babies weighing less than 1000 gram have umbilical vein catheter) [8].

Antithrombin III, protein C, heparin cofactor II, and protein S are all naturally occurring anticoagulants. also decreased early in neonatal life, although there is significantly increased alpha 2-macroglobulin. The fibrinolytic system also revealed plasminogen concentrations that were about half of what they were in adults. [9]. These characteristics are related to the fetus's age; hence they were more prominent in preterm infants [10]. During the first several weeks and months of life, the fibrinolytic system appears to have changed drastically as the concentrations of many components adjust to typical adult levels. [11].

The effect of inherited prothrombin gene mutations on thrombotic events in the newborn is rarely studied. In neonates with thrombosis, antithrombin III deficiency, protein C, protein S deficiency, and activated protein C resistance have all been identified, including spontaneous occurrences. [12],[13].

Protein C and S deficiencies appear to be very frequent in ill, preterm newborns, and there is some limited evidence to suggest that these individuals have a higher risk of thrombosis [14]. Because of the transplacental transmission of antiphospholipid antibodies, thrombotic events in newborns have been observed sometimes in connection with maternal systemic lupus erythematosus [15].

PATIENTS AND METHODS

The study included forty neonates admitted in neonatal ICU in Zagazig University Hospitals, between January to December 2021. Written informed consent was obtained from all participants, the study was approved by the research ethical committee of Faculty of Medicine, Zagazig University. The study was done according to The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans. Inclusion criteria include the age groups was from birth to 28 days and neonates with symptomatic or asymptomatic venous or arterial system thromboembolism confirmed by imaging technique. Exclusion criteria were any age more than 28 days. **All patients were exposed to,** Detailed medical background (gender, age of mother, maternal antenatal care history, delivery type, gestational age, birth weight, medication of neonate, delayed crying, cyanosis, and seizures). Clinical examination of the newborn including APGAR s coring. Imaging as chest X-ray, echocardiography, or abdominal ultrasound. Laboratory routine investigations, samples were collected as follow: 3ml on two EDTA tubes, 1.5 ml in each, for CBC and PCR detection of gene mutations, 2ml on plain tubes for liver functions, CRP and electrolytes assay, 2ml blood withdrawn under complete aseptic conditions for blood culture on special pediatric yellow BaCT/ALERT tube for blood culture and sensitivity. CBC was performed on automated cell counter (XN330-Sysmex, Japan) with differential count on Leishmania-Giemsa stained peripheral. C-reactive protein (CRP) by turbidimetry on Roche Cobas C 501. Blood culture and sensitivity were done on BaCT/ ALERT 3D 60. Electrolytes Na, K, Ca, CL, Mg done on Sensa core ST200 plus. Liver function tests and blood urea, creatinine and blood sugar were done on Cobas 8000. Finally, D-dimer done on Roche Cobas 6000, Prothrombin time [PT], and partial thromboplastin time [PTT] was performed on Sysmex CS2500. Screening for thrombophilia gene variants, the first step was extraction of DNA and Amplification (PCR), DNA was extracted using components from the Vienna Lab Diagnostics GmbH's (FVL, PTH and MTHFR Strip Assay) ® A kit (Vienna, Austria). Three gene mutations were tested (Figure 1). One hundred microliters of EDTA-blood were used to extract DNA.

To detect various mutations in the three genes, a multiplex PCR amplification reaction mixture was constructed by adding sequence specific biotinylated primers (FVL-PTH and MTHFR). Initial denaturation at 94°C for 2 minutes was followed by 35 cycles of denaturation at 94°C for 15 seconds, annealing at 58°C for 30 seconds, and an extension step at 72°C for 30 seconds during the amplification process.

Gel electrophoresis was used to examine the amplification product (on 3 % agarose gel): 173, 202, and 223 bp fragment lengths. The amplified products were hybridized specifically to the

Vienna lab. Diagnostic GmbH's strip assay, which comprised allele-specific oligonucleotide probes (wild and mutant) immobilized as an array of parallel lines. Streptavidin-alkaline phosphatase and color substrates were used to detect the bound biotinylated sequences. Each amplification product was employed in ten microliters in the typing trays, with one milliliter hybridization buffer applied to a test strip and orbital shaking at 45°C for 30 minutes at 50 rpm, followed by washing at 45°C with shaking. A visible enzymatic color response was used to detect selectively binding mutant and wild type alleles. One milliliter conjugate solution (containing streptavidin-alkaline phosphatase) was applied to each test strip and incubated for 15 minutes at room temperature with shaking in the dark.

Interpretation was as shown in the following table (1):

ANALYTICAL STATISTICS

By using Microsoft Excel software, the collected data were tabulated and analyzed using SPSS version 24 software (SPSS Inc, Chicago, ILL Company). Categorical data were presented as number and percentages. Chi square test (X2) were used to analyze categorical variables. Quantitative data were expressed as mean ± standard deviation, median and range. Student "t" test was done to analyze normally distributed variables among 2 independent groups. Spearman's correlation coefficient was used to detect correlation between nonparametric variables. The accepted level of significance in this study was stated at 0.05 (P <0.05 was considered significant and P value < 0.001 was considered highly significant.

RESULTS

Table (2) shows that females accounted for 65 % of the patients investigated. They were 1 to 28 days old, with a median of 17 days**.**

There was highly statistically significant rise in neonatal thrombosis with Umbilical venous catheter (UVC) and statistically significant with sepsis, patients on total parental nutrition (TPN) and congenital anomalies. **Table (3)**.

Radiological studies revealed that only fourteen patients had Doppler study, 6 of them had limb ischemia. Thirty- one patients had echo studies, 10 of them had Patent foramen ovale (PFO) with pulmonary hypertension while inter-atrial thrombosis occurred in nine patients. MRI was done for twenty- one patients of them, 11 had cerebral thrombosis and 10 had Hypoxic Ischemic Encephalopathy (HIE)**.**

Table (4) reveals that median hemoglobin, TLC, platelet count, PT, PTT, and D- dimer were 18.4g/dl, $13.5x10^3$/µL, $290x10^3$/µL, 12 sec, 31.2 sec and 6 µg/ml respectively. Throughout liver functions, there was elevated bilirubin, AST, ALT 5.2mg/dl, 50u/L, 68u/L respectively. 87.5% of patients had positive CRP and 82.5% had positive blood culture.

By studying thrombophilia genes, **Table (5)** showed that six (15%) patients had mutation of factor V gene mutation (G1691A) in which four (10%) infants showed heterozygous mutations and two (5%) patients showed homozygous mutations while 34 (85%) patients were normal. Nine (22.5%) patients had mutation of prothrombin G2010A gene with five (12.5%) patients of them were heterozygous and four (10%) infants were homozygous while 31 (77.5%) patients were normal. As regard MTHR C677T, 10 (25%) infants were normal, 23 (57.5%) patients had heterogeneous mutation and seven (17.5%) patients showed homozygous gene mutation.

There was statistically significant increase in D-dimer with the presence of the factor V G1691 and prothrombin G20210A while it was non-significant difference between heterozygous and homozygous mutations of MTHFR C677T.

Table 1: Interpretation of test results

	Wild type line	Mutant type line	Genotype
Normal	Positive	Negative	Normal
Heterozygous	Positive	Positive	Heterozygous
Homozygous	Negative	Positive	Homozygous mutant

Table (2): The demographic distribution of the studied patients

	N=40	%
Sex:		
Male	14	35.0
Female	26	65.0
Age (days):		
Median	17	
Range	1 – 28	

Table 3: Relation between risk factors affected neonate in ICU and development of neonatal thrombosis (total no: 40 neonate)

	Congenital anomalies	Sepsis	UVC	TPN	CPAP	Gestational age ≥37w	Neonatal age at admission ≥3	Lower limb edema
Patients with risk factors	10	7	2	5	28	18	5	11
Patients with risk factors and thrombosis	5	28	23	1	4	3	1	5
Patients without risk factors	25	5	15	34	6	19	34	24
X^2	**9.524**	**13.33**	**29.33**	**7.48**	**0.29**	**2.93**	**7.48**	**8.75**
P-value	**0.002***	**0.003***	**0.0001 ****	**0.006***	**1.11**	**0.08**	**0.006***	**0.004***

Table (4): Laboratory data from the patients in the study

	Mean ± SD	Median
Hemoglobin (g/dL)	17.19 ± 5.94	18.4
TLC ($\times 10^9$)	15.98 ± 6.58	13.5
Platelet count ($\times 10^9$)	354 ± 105	290
Total bilirubin (mg/dL)	7.33 ± 1.2	4.9
PT(s)	10.19 ± 2.06	12.0
PTT (s)	35.0 ± 4.42	31.2
D-dimer (ug/ml)	4.77 ± 1.04	5.4
CRP (mg/L)	65.8 ± 17.04	43
Serum total bilirubin (mg/dL)	8.4 ± 1.04	5.2
ALT (U/L)	73 ± 11.04	50
AST(U/L)	87 ± 14.04	68
	No of patients	**%**
Positive blood culture	33	82.5

Table 5: Correlation between gene mutations and D-dimer in the studied patients (total no: 40 patients).

Gene Mutation	No.	%	Mean± SD	t	P-value
Factor V G1691:				5.85	0.004**
Heterozygous:	4	10	1.02 ± 0.4		
Homozygous	2	5	4.19 ± 1.04		
Prothrombin G20210A:					
Heterozygous	5	12.5	0,6 ± 0.81	5.98	0.0008**
Homozygous	4	10	3.9 ± 0.84		
MTHR C677T mutation:					
Heterozygous:	23	57.5	1.07 ± 0.90	2.24	0.3
Homozygous:	7	17.5	1.86 ± 0.40		

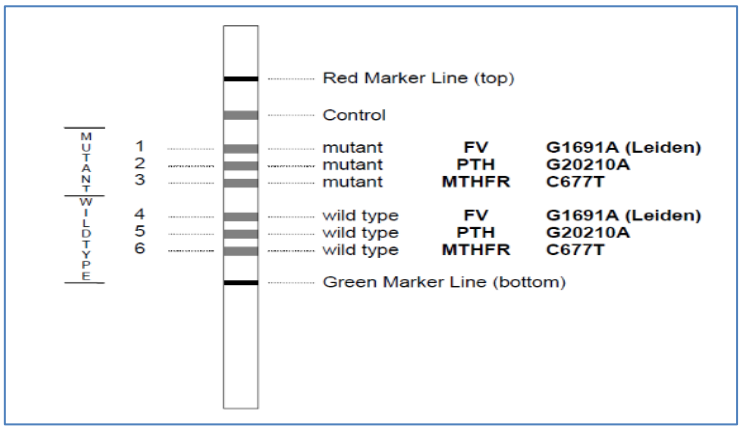

Figure 1: test strip design

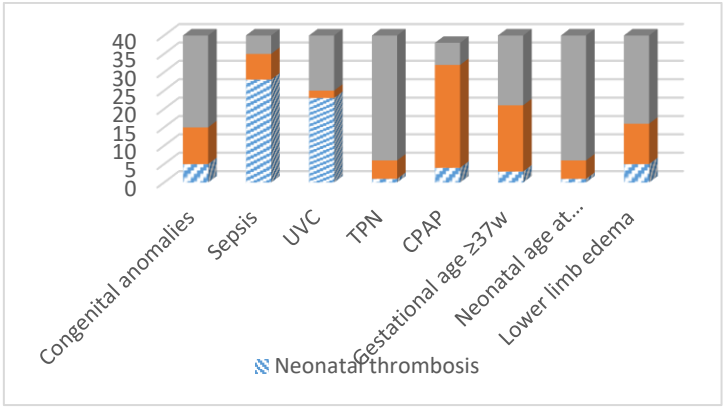

Figure 2: The effect of risk factors on neonatal cases in ICU and the development of neonatal thrombosis

DISCUSSION

Thromboembolic events in newborns are a serious problem. Handicapping or death is possible outcomes. During the first year of life thrombo-embolic events are most common in children. Acute ischemic stroke (AIS), cerebral venous sinus thrombosis (CVST), and deep vein thrombosis are all common in neonatal period [16].

The term 'thrombophilia' refers to coagulation disorders that are either inherited or acquired and have been linked to an increased risk of thrombosis. Activated protein-C resistance, which can be caused by the inherited factor-V Leiden mutation, protein C, S, or antithrombin deficiencies, which can be caused by the prothrombin G20210A (factor II) mutation, or hyper-homo-cysteinemia, which can be caused by nutritional factors or the 5,10-methylenetetrahydrofolate reductase gene (MTHFR) mutation. [6].

The research was carried out in neonatal ICU in Zagazig University Hospitals between January to December 2021 on 40 neonates with complete genetic results, were included in our analysis of the relationship between thrombosis and genetic mutations.

The results of this study revealed that the average gestational age of the neonates studied was 34.3±3.7 weeks, with preterm births accounting for 60% and terms accounting for 40 percent, which matched another study by Ferraresi and Arrais [17] and El-Ganainy et al. [18].

Because our hospital gets high-risk pregnant women and referrals for critically ill preterm neonates, our NICU's preterm admission rate had been increased and the variation of neonatal care and hospital care in the study locations.

The median newborn age at admission to the NICU in this study was 17 days, which was consistent with Farah et al. [19].

In the current study, 82.5% of cases had sepsis which matched with blood culture and CRP level. With our result there was a surveillance done by the Egyptian Ministry of Health (2010-2014) to assess the prevalence of newborn sepsis in Egyptian governorates NICUs. There was also a high prevalence of newborn infections in Ethiopia (77.9%) and Iran (51.8 percent) which was in concordant with our results [21].

Cailes et al. [22], in contrast to our findings, found a low prevalence of newborn infections in the UK, with 6.1/1000 live births and 48.8/1000 neonatal hospitalization.

Differences in infection prevalence in NICUs between studies could be related to differences in methodology, notably in terms of infection definitions, populations, and locality, NICU resource availability, and infection control strategies.

In this work, six patients (15%) had mutations of factor V gene (G1691A), four infants (10%) of them showed heterozygous mutations and two (5%) patients had homozygous mutations. Nine (22.5%) patients had prothrombin G20210A gene mutation with five (12.5%) patients of them were heterozygous and four (10%) infants were homozygous. As regard MTHR C677T mutation, with 23 patients (57.5%) had heterogeneous mutation and seven infants (17.5%) showed homozygous mutation.

The frequency of the three mutations was like that reported for the Italian population, according to this study. Independent risk factors for venous thrombosis include mutations in the factor V gene. [23]. Turebylu et al. [24] found that prothrombotic mutations in either the heterozygous or homozygous state were widespread, with 90 percent of the population having them. FVL was discovered in 8% of the population. Prothrombin 20210G>A was not detected in any of the infants. MTHFR667 was found to be homozygous in five patients (10 percent of the population).

In six of 22 neonates with arterial central nervous system events, Hagstron et al. [26] detected the factor V Leiden mutation, but Zenz et al. [27] reported a substantial increase in the presence of this mutation only in strokes that occurred after the neonatal period.

In the present study, there was statistically significant increase in D-dimer and the presence of the Factor V (G1691A) and prothrombin G20210A while there was non-significant difference between heterozygous and homozygous mutations of MTHFR C677T. This agree with another study by Rosendaal and Reitsma [31] and White [32] who proved the increasing risk of thrombosis with the presence of homozygous mutations of FVL G1691A and prothrombin G20210A and not found as regard mutations of MTHFR C677T.

The increased prevalence of neonatal thrombosis in our study could be attributed to maternal infections during pregnancy with poor evaluation and therapy, as well as a variety of NICU manipulations that could contribute to newborn infections, such as central line insertion, CPAP, and endotracheal intubation. This contradicts previous findings by Manco-Johnson et al. [28], who reported no such relation between catheter-related incidents and neonates in a study of only neonates.

The prevalence of newborn thrombosis was 32.5 percent in our study. Thrombosis rates in several Egyptian NICUs were (20%, 21.4 percent, 28 percent, 30 percent) in Al-Azhar University, Mansoura University, Ain Shams University, and South Sina state hospital, respectively [20, 29,30].

Despite the increased incidence and risk factors for newborn thrombosis, there are no evidence-based preventative strategies. The implementation of a risk-stratification model that can identify neonates who could benefit from prophylactic anticoagulation could be beneficial.

CONCLUSION

Thrombophilia genetic mutations in NICU population, especially when central catheters are present are major risk factors of neonatal thrombosis.

RECOMMENDATIONS

Although some genetic risk factors are well recognized testing for hereditary thrombophilia should be part of routine screening in newborn to assess the risk of thrombosis. Owing to advances in medical care and better survival rates for younger births, collaboration among thrombosis experts is essential.

Conflict of Interests

The authors declare that they have no conflict of interests.

Financial Disclosures:

There were no any financial interests, relationship and affiliations relevant to the subject of the study.

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