Advances in Infectious Diseases, 2023, 13, 586-595
https://www.scirp.org/journal/aid
ISSN Online: 2164-2656
ISSN Print: 2164-2648

Neonatal Thrombocytopenia at Dakar Principal Hospital

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How to cite this paper: Wagué, G.M., Khadija, F., Macoura, G., Silman, D.P., Maguette, N., Diop, N.A., Mbacké, D.S.M., Mor, N., Mbène, F., Tagouthie, N., Ndew, S.M. and Bécaye, F. (2023) Neonatal Thrombocytopenia at Dakar Principal Hospital. *Advances in Infectious Diseases*, **13**, 586-595.
https://doi.org/10.4236/aid.2023.134048

Received: September 26, 2023
Accepted: December 1, 2023
Published: December 4, 2023

Abstract

Neonatal thrombocytopenia accounts for 20% of neonates hospitalized in the neonatal intensive care unit (NICU) at DPH. The etiologies are multiple, but bacterial infection is the third leading cause of neonatal mortality worldwide. We therefore set out to assess the frequency of neonatal thrombocytopenia associated or not with bacterial infection in the NICU. We conducted a retrospective and prospective study with the DPH NICU, over 10 months (August 2018 and April 2019). Thrombocytopenia encountered in the NICUs, were the subject of research into bacteriological, inflammatory, and epidemiological parameters using Inlog laboratory data processing software. During this period, 1280 babies were hospitalized, 94 of whom underwent thrombocytopenia, corresponding to 7.34%, with a sex ratio of 0.92. The number of babies presenting with thrombocytopenia during the first week of hospitalization was 72, accounting for 76.6%. The clinical context was usually low birth weight in 30.8% of cases and perinatal asphyxia (25%). Thrombocytopenia ranged from 2000 to 137,000 with an average of 69,520/mm^3. Among these thrombocytopenias, 64 cases (68%) were below 100,000 mm^3 and 44 cases had a CRP >5 mg/l. A total of 30 bacteria were isolated, including 23 Enterobacteria, 2 Streptococci, and 1 Acinetobacter. Among these enterobacteria, 14 were multidrug-resistant (MDR). Thrombocytopenia associated with a multidrug-resistant bacterial infection is a real challenging management.

Keywords

Neonatal Thrombocytopenia, Bacterial Infection, Enterobacteria, Newborns

1. Introduction

Thrombocytopenia is a frequent hematological abnormality during the neonatal period, particularly in neonates hospitalized in neonatal intensive care units (NICUs) and premature infants. It occurs in 30% of neonates hospitalized in intensive care units [1], in 0.8% to 4% of healthy full-term neonates [2], in 22% of premature or sick infants [3], and in around 0.2% to 4.5% of fetuses [4] [5]. It is defined by a drop in the number of blood platelets below 150,000/mm^3 [1]. Its prevalence is still poorly known worldwide, due to its polymorphism in etiology [6]. The causes of thrombocytopenia in the intensive care unit are often multifactorial, both central due to a production defect, and peripheral due to destruction and/or increased sequestration of platelets in the circulating blood. Peripheral etiology appears to be involved in over 50% of cases, while 10% of isolated cases are at least of central origin [7]. It may be secondary to infection, inflammation, or consumption coagulopathy [7] [8]. A study reports that 20% - 50% of severely ill neonates develop thrombocytopenia, with 5% - 10% having a platelet count of less than 50,000/mm^3 [9]. In children with more than 20% body surface burns, 82% of them undergo thrombocytopenia during the first week, and 18% will experience it afterward, the main etiology being sepsis [10]. According to the World Health Organization (WHO), infections are the leading cause of infant mortality worldwide [11]. The vast majority of deaths related to neonatal infection (NCI) occur in low-income countries [12]. In 2017, 2.5 million children worldwide died during their first month of life. This represents around 7000 neonatal deaths per day. More than two-thirds of neonatal deaths occur within the first week of life, and around one million newborns die within the first 24 hours [13]. Premature births, obstetric complications, infections, and congenital malformations are the main causes. The majority of these deaths occur in sub-Saharan Africa [14]. The major complication of thrombocytopenia in neonates is intracranial hemorrhage, leading to death or neurological sequelae in cases of severe thrombocytopenia. The management of thrombocytopenia in neonatology is a real challenge, due to the multiple etiologies involved, including bacterial and immunological. The first-line treatment is an infectious approach due to the frequency of thrombocytopenia and the lack of resources to diagnose other etiologies.

It's against this backdrop that we conduct this work to assess the prevalence of thrombocytopenia, whether or not associated with infection, to make a contribution to the management of thrombocytopenia in neonatology.

2. Materials and Methods

This is a retrospective, prospective study carried out between the federation of laboratories and the neonatology department (nursery) of Dakar Principal Hospital (DPH). The study was carried out over a 10-month period, from August 2018 to May 2019. The selection of our study population was based on the results of the blood count of the newborns admitted to the neonatal department

and presenting with thrombocytopenia on admission or during hospitalization. Non-inclusion criteria were patients with thrombocytopenia who did not undergo inflammatory and infectious markers assay. In neonatology, in regards to thrombocytopenia, an infectious work-up is often undertaken, in particular:

- Gastric swab;
- Blood culture;
- C-reactive protein (CRP);
- Other markers depend on the clinical context.

Every day, thrombocytopenia encountered in neonates using the XN1000 automated blood count system was analyzed for bacteriological, inflammatory, and epidemiological parameters using the laboratory's Inlog® data processing software.

The blood count provides information on the number of platelets, with or without the context of cytopenia or pancytopenia. In bacteriology, the appearance of a pure culture or the presence of a predominant population in the culture medium is suggestive of the presence of a bacterial strain that may be responsible for the infection. This requires an antibiotic susceptibility study (antibiogram) to determine the strain's susceptibility profile, meaning its wild-type phenotype (the bacterium is sensitive to all beta-lactam antibiotics or has no acquired resistance to beta-lactam antibiotics), moderate resistance (resistant to a group of beta-lactam antibiotics) and multi-drug resistance or MDR (resistant to strong molecules). CRP, considered an inflammatory marker, is positive when its value exceeds 5 mg/l (CRP > 5 mg/l). Clinical information and the date of hospital admission were obtained from the attending physician. Data analysis was performed using Epi info software version 7.2.2.6. Statistical results for the parameters analyzed were expressed in terms of proportion and mean.

3. Results

During the study period, 1280 neonates were hospitalized, of whom 94 presented with thrombocytopenia, corresponding to 7.34%. The age of occurrence of neonatal thrombocytopenia (NT) ranged from 1 to 39 days, with an average of 5.44 days. The number of cases recorded was 72 (76.6%) in the first week, 16 in the second week, and 6 (6.4%) after more than fifteen (15) days of hospitalization. Males accounted for 45 cases (47.87%), corresponding to a ratio (45/49) of 0.92. The clinical context was usually dominated by low birth weight in 30.8% of cases, and perinatal asphyxia in 25% of cases. A risk of infection was present in almost half the cases. The clinical picture was sometimes serious, with severe hemorrhage (hematemesis, epistaxis, coma) and sepsis with generalized sclerema. These clinical courses were often interrelated. The mean platelet count was 69,520/mm^3 with extremes of 2000 and 137,000/mm^3. Thrombocytopenia was classified, according to hemorrhagic risk, into three classes as follows:

- Platelets < 50,000/mm^3: 33 cases accounting for 35%;
- Platelets between 50,000 and 100,000/mm^3: 31 patients corresponding to

33%;

- Platelets > 100,000/mm^3: 30 cases representing 32%.

The biochemical aspect was characterized by the detection of C-reactive protein (CRP). Eighty-five (85) patients benefited from this biomarker assay, with an average of 50.64 g/l [0.2 - 292 g/l]. CRP > 05 mg/l was observed in 44 neonates, thus determining the inflammatory context. A bacteriological assay was carried out in 81 neonates representing 86% of cases. These were mainly gastric samples in 73 cases and blood cultures in 67 cases. A total of 30 bacteria were isolated from all pathological products, as shown in Table 1. Antibiograms performed on the isolated strains revealed the following profiles:

- Methicillin-sensitive *Staphylococcus aureus* (Meti-S);
- Imipenem-resistant *Acinetobacter Spp* (ABRI);
- Enterobacteriaceae showed variable susceptibility profiles, including fourteen (14/23) broad-spectrum beta-lactamase (ESBL) producers, 5 cases of low-level penicillinase (LBP), and 4 cases of wild-type phenotype.

Broad-spectrum beta-lactamase bacteria are resistant to third-generation cephalosporins, including cephamycins. Low-level penicillinase bacteria are resistant to penicillins, carboxypenicillins, and ureidopenicillins. Bacteria with a wild-type phenotype have no natural resistance to beta-lactam antibiotics. Mean CRP levels remained significant across all thrombocytopenic classes. The highest value was observed in neonates with thrombocytopenia below 50,000/mm^3, as shown in Table 2. We also noted a negative correlation between thrombocytopenia and CRP values (correlation coefficient = −0.027).

Bacteria isolated from pathological products are represented, according to the degree of thrombocytopenia, in Table 3. Among these bacteria, 50% were multi-resistant. The isolated MRB were distributed as follows: 10 cases in neonates with thrombocytopenia below 50,000/mm^3, 4 cases (27%) with thrombocytopenia between 50,000 and 100,000/mm^3, and 1 case (7%) in neonates with thrombocytopenia above 100,000/mm^3, as shown in Table 3. The severity of thrombocytopenia was inversely proportional to the frequency of MRB. However, this

Table 1. Distribution of isolated bacteria.

Bacteria	Gastric samples	Blood cultures
Escherichia coli	6	0
Klebsiella pneumoniae	0	11
Enterobacter cloacae	0	6
Acinetobacter.spp	0	1
Staphylococcus aureus	1	0
Staphylococcus à coagulase négative	0	2
Streptococcus du groupe b	2	0
Other Streptocoque	0	1
TOTAL	**9**	**21**

Table 2. Thrombocytopenia-CRP correlation.

	Average CRP and standard deviation	Median and Extreme CRP (mg/l)
Platelets < 50000/mm^3	46.52 ± 71.6	13 [0.1 - 292]
Platelets 50,000 - 100,000/mm^3	54.84 ± 78.78	16.96 [0.2 - 237]
Platelets > 100,000/mm^3	52.25 ± 53.74	32.9 [0.8 - 165]

Table 3. Correlation between thrombocytopenia and bacterial infection.

Platelets	Isolated bacteria	Multidrug-resistant bacteria (MDR)
<50,000/mm^3	14	10
50,000 - 100,000/mm^3	9	4
>100,000/mm^3	7	1

the difference was not statistically significant (p = 0.1221). Imipenem-resistant Acinetobacter Spp was found in neonates with thrombocytopenia below 50,000/mm^3. The presence of broad-spectrum beta-lactamase-producing Enterobacteriaceae was mainly associated with severe thrombocytopenia. Non-MRB were mostly classified as moderate thrombocytopenia.

4. Discussion

Platelets express a wide panel of membrane and intracellular receptors enabling them to detect or recognize different types of pathogen, then triggering platelet activation with a dual consequence, hemostatic and inflammatory. In the neonate, the immaturity of platelet function during this period of life, combined with any hemodynamic instability secondary to prematurity or other intercurrent disease only increases the risk of hemorrhage. Neonatal thrombocytopenia is common in neonates hospitalized in intensive care (30% of cases) [1]. In our study, thrombocytopenia was observed in 7.34% standing for 94 cases out of 1280 hospitalized neonates, which is sometimes two-fold of the rate found in the literature, ranging from 0.8% to 4% [11] [12] [13]. Some fifteen Studies carried out in Northern Europe, Kuwait, and the USA have reported annual incidence estimates of between 1.1 and 12.5 per 10^5 inhabitants in children, and between 1.6 and 3.9 per 10^5 inhabitants in adults [15]. The etiologies are diverse. Thrombocytopenia of infectious origin was the leading cause in 66% of cases [16]. According to [M Trifa *et al.*], in Tunisia, thrombocytopenia in children admitted to surgical intensive care was associated with infection (p < 0.001), in particular due to Gram-negative bacilli (GNB) [17]. According to the WHO, neonatal infection is responsible for between 30% and 40% of neonatal mortality in limited-resource settings [18]. Fetal and neonatal alloimmune thrombocytopenia are the most common severe thrombocytopenia [19] [20]. The incidence has been estimated at between one case per 800 and one case per 1000 births [21].

Constitutional thrombocytopenia (CT), often unrecognized or underdiagnosed, is a rare disease that constitutes a very heterogeneous group, particularly in terms of prognosis [22]. The mean age of the population was 5.44 days, with extremes of 1 to 39 days. Male neonates accounted for 45 cases (47.87%) and female neonates 49 cases (52.13%), with a ratio of 0.92. In Morocco, on the other hand, [Maoulainine] and [Abdelkarim] showed a male predominance with 56% and 64.81% respectively [16] [23]. Other studies carried out in children older than the study population has shown a male predominance, with a recrudescence in winter [24]. Thrombocytopenia on blood count was mild in 45%, moderate in 33%, and severe in 13% of cases [16]. In our study, severe thrombocytopenia occurred in 33 cases (35%), moderate in 31 patients, and mild in 32%. Our results are similar to those obtained in a thesis carried out in Rabat involving 54 cases of thrombocytopenia. These included 15 severe cases (platelets < 30,000/mm^3), 25 moderate cases (platelets: 30,000 and 100,000/mm^3), and 14 mild cases (platelets > 100,000/mm^3) [23]. Neonatal infection is one of the main causes of morbidity in pediatric settings. It is a major public health problem because of the high mortality rate attributed to it [25]. Bacterial and viral infections are the major cause of neonatal thrombocytopenia, accounting for around 67.25% of cases [26]. These germs will disrupt thrombopoïesis, promote platelet aggregation at the injured endothelium or the formation of leuko-platelet complexes, trigger platelet apoptosis induced directly by bacteria, and phagocytosis of platelets to Kupffer cells or circulating macrophages to eliminate bacteria [27]. However, several studies have investigated the association between thrombocytopenia and infection in adults [28] [29], which could help guide the choice of probabilistic antibiotic therapy. To our knowledge, few studies have concluded this in children. These include three studies in very-low-birth-weight neonates:

N˚1: Bhat *et al.* [30] investigated an association between the organism responsible for the infection and thrombocytopenia in 415 very-low-birth-weight infants. The frequency and duration of thrombocytopenia were significantly greater in children with Gram-negative bacterial or yeast infections. Thrombocytopenic patients had significantly more persistent bacteremia, greater multivisceral failure, and higher mortality.

N˚2: Guida *et al.* [31] reported in their cohort of 943 very-low-birth-weight infants that sepsis due to Gram-negative bacteria was associated with lower platelet counts and prolonged duration, compared with those due to Gram-positive bacteria.

N˚3: Manzoni *et al.* [32], however, found no correlation between the occurrence of thrombocytopenia and the category of infecting germ in their retrospective study of 514 very-low-birth-weight babies over 9 years.

In another register, Agrawal *et al.* attempted to evaluate platelet count variation and risk factors for thrombocytopenia and mortality in 138 children hospitalized in pediatric intensive care unit. Sepsis was associated with thrombocytopenia [33]. In our study, 30 bacteria were isolated: 24 GNB and 6 Gram-positive Cocci (GPC). GNBs were mainly represented by *Klebsiella pneumoniae* (11 cas-

es), *Escherichia coli* and *Enterobacter cloacae* (each 6 cases), and *Acinetobacter Sp* (1 case). GPCs were mainly represented by Group *B Streptococcus*, coagulase-negative Staphylococcus, and *Staphylococcus aureus*. The bacteria isolated were mainly observed in neonates with thrombocytopenia below 50000/mm3. Among all the bacteria isolated, 50% (15 cases) were multidrug-resistant (MDR). The severity of thrombocytopenia is often inversely proportional to the presence of MRB. However, this difference was not statistically significant ($p = 0.1221$). Early neonatal bacterial infections (first 72 hours of life) are almost exclusively of maternal-fetal origin. The two most frequent germs are Streptococcus agalactiae or Group B Streptococcus (GBS), currently the leading germ in neonatal infections of full-term infants, and *Escherichia coli*, the leading germ in premature infants. Per-partum antibiotic prophylaxis reduces early neonatal GBS infections but has not reduced late neonatal infections [34]. Primary immune thrombocytopenia (IT) in children may be related to an autoimmune disorder. It is characterized by its isolation (platelets < 100,000/mm^3) in the absence of other conditions [35] [36]. It can often be associated with an infectious cause, aggravating the severity of thrombocytopenia and making management complex. A study in Tunisia showed an average platelet count of 25,000/mm^3, with extremes ranging from 1000 to 50,000/mm^3 [37]. The limited diagnostic resources in our laboratories are an obstacle to determining the association of constitutional or autoimmune thrombocytopenia in an inflammatory context.

5. Conclusion

Thrombocytopenia is common in neonates hospitalized in neonatal and intensive care units. The etiologies are multiple. Thrombocytopenia associated with Gram-negative bacterial infection is a major public health problem, given the frequency of multidrug-resistant bacteria, in the context of antimicrobial resistance (AMR) which is a worrying situation worldwide. Collaborative studies with more significant sampling are needed to better understand the place of thrombocytopenia in an infectious context and improve the management of AMR in the neonatal setting.

Acknowledgements

The staff of the federation of laboratories and the pediatrics/neonatology department of the main hospital in Dakar/Senegal contributed to the production of this document.

Declaration of Ties of Interest

The authors declare that they have no ties of interest in this article.

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