



PROFILE AND SHORT TERM OUTCOME OF HOSPITALIZED NEUTROPENIC CHILDREN

Pediatrics

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ABSTRACT

BACKGROUND AND OBJECTIVES: Neutrophils constitute an essential part of our immune system against invasive microorganisms. Neutropenia is a frequent problem encountered in hospitalized children with myriad implications on duration of hospital stay as well as outcome. This study was conducted to study clinical profile and short term outcome of hospitalized neutropenic children. **METHODS:** This observational study was done at our tertiary care level teaching hospital over two years period from April 2018-March 2020. We included 56 hospitalized children aged <15 years with absolute neutrophil count (ANC) <1500/ cu mm. Necessary investigation were done to identify the cause of neutropenia. Clinical features, admission diagnosis, duration of neutropenia, duration of hospital stay, complications and outcome were studied. Such children were followed up for 4 weeks. **RESULTS:** Mean age was 8.8 years (S.D 2.7 years). Mild neutropenia was seen in 48.2%, moderate neutropenia in 33.9% and severe neutropenia was seen in 17.9% cases. Mean ANC was 1021/cu mm (SD 324) whereas the mean duration of neutropenia was 4.7 days (SD 2.4 days). Infections were the commonest etiology of neutropenia (dengue, malaria & enteric fever were the commonest infections). Thrombocytopenia was seen in 31(55.4%) of such children. Mean duration of thrombocytopenia was 6.24 (SD 2.17) days. Mean & median duration of hospital stay was 8.24(S.D 4.3) days and 7 days respectively. 47 (83.4%) children were discharged and 9 (16.6%) children died. Neutropenia normalized in 48 (85.7%) children by end of first week. No children had persistent neutropenia during the 4 week follow-up period. **CONCLUSION:** Infections are the commonest cause of transient neutropenia in hospitalized children with dengue, typhoid and malaria being the common etiologies. The length of hospital stay as well as the duration of neutropenia increased with the severity of neutropenia and there was an inverse relation of these to the age. Our study also shows that most of the episodes of acute transient neutropenia recover without major complications.

KEYWORDS

Clinical Features, Dengue, Febrile Illness, Neutropenia, Non-malignant

I. INTRODUCTION

Neutrophils constitute an essential part of our immune system against invading microorganisms. Their absolute or relative deficient function leads to impaired immune function, mainly recurrent infections.¹ Such a defect in neutrophil function can be quantitative due to neutropenia or qualitative due to neutrophil dysfunction. Absolute neutrophil count (ANC) is usually considered normal if it is above 1500/cu mm, though it depends upon age, sex and race of individuals. Neutropenia can be primarily a result of marrow hypoplasia due to familial or genetic causes or secondary to cytotoxic agents, aplastic anemia, leukemia, drug induced or infections. Hypersplenism and immune neutropenia are less common causes of neutropenia.² Half-life of circulating neutrophils is approximately 7–12 h, and this further decreases during infection episode due to their migration to extravascular spaces.

Neutropenia severity is graded into mild (ANC 1000-1500/cu mm), moderate (ANC 500-1000/ cu mm), severe (ANC less than 500/cu mm) or very severe (ANC less than 100/ cu mm)^{3,4} Clinical features of children with neutropenia depend on the predisposing condition(s). Common presentations include fever, gingivitis, stomatitis, cervical lymphadenopathy, skin abscess, perirectal abscess, growth retardation etc. However, the duration and severity of neutropenia as well as outcome in such children is quite variable and dependent on the etiology of neutropenia. Acute febrile conditions like dengue, malaria, enteric fever are the commonest causes of transient neutropenia. In these children, neutropenia usually occurs when afebrile phase of the disease begins.⁵ Children with mild neutropenia need not always be admitted but require serial monitoring. However, children with systemic signs irrespective of the severity of neutropenia need hospital admission and parenteral antibiotics. While researchers have focused more on the chronic forms of neutropenia or neutropenia in cancer patients, there is limited research work in Indian children with acute onset neutropenia. Therefore, we undertook this study at our tertiary care level institution in children who were found to be neutropenic during early days of hospitalization. We intended to study etiology, risk of complications and outcome so as to help in planning and implementation of a strategy for early diagnosis and better care in such children.

II. AIM AND OBJECTIVES

Aim: To study the various aspects of neutropenia in hospitalized children.

Objectives

1. To study the clinical and laboratory parameters of neutropenia in hospitalized children.
2. To study short term outcome of such children in terms of duration of hospital stay, duration of neutropenia, association with thrombocytopenia, complications and mortality

III. Materials and Methods

Study setting: Emergency room and I.P.D of department of Pediatrics N.M.C.H Patna.

Study duration: This study was conducted over 2 years, from April 2018 to March 2020.

Study design: cohort observational study.

Inclusion criteria: In the present study, children between 1-14 years age (both age included) who were hospitalized at our tertiary level teaching institute due to some illness were evaluated for neutropenia. Those with ANC (absolute neutrophil count) <1500/mm³ were included in our study and further studied.

Exclusion criteria: Children with pre-existing HIV disease, immunodeficiency, malignancy, aplastic anemia and chronic systemic illness (hepatic, renal, cardiac etc) were excluded as their clinical features and laboratory parameters could mimic or influence the clinical and laboratory picture of neutropenic children. Children who left against medical advice were also excluded from the final analysis.

Data Collection: After obtaining written informed consent, we enrolled participants in our study. Data was collected in structured Performa to document pertinent history and physical examination. We didn't perform any intervention or additional tests other than necessary for this study. As a standard algorithm for neutropenic children is available only for malignant cases, work-up for neutropenic children in our study was done as per standard hospital protocol. Peripheral blood smear examination was done in all neutropenic cases and serological tests for dengue, chikungunya, scrub typhus and Weil Felix test were done as and when warranted. Complete blood count was performed by automated blood analyzer and if neutropenia was found, it was confirmed by a manual TLC and DLC count. Data regarding duration of neutropenia, duration of hospital stay, association with

thrombocytopenia, complications and outcome was analyzed. All such children were followed up for atleast 4 weeks. Complications secondary to neutropenia was defined as any new local or systemic infection presenting >24 hours after hospitalization and diagnosis of neutropenia.

Statistical analysis: The data so collected was entered in Microsoft excel and analyzed using SPSS version 20 software. Variables were presented as mean, median, percentage and standard deviations as appropriate. Chi square test or student's t test was applied for testing significance of difference. P value less than 0.05 was considered significant.

IV. OBSERVATION & RESULTS

Over the 2 year study period, we studied 56 children with neutropenia of which 32 were male and 24 were female (male: female ratio 1.3:1). Mean age was 8.8 years (S.D 2.1 years). Mild neutropenia (ANC 1000-1500/cu mm) was seen in 48.2%, moderate neutropenia (ANC 500-1000/cu mm) in 33.9% and severe neutropenia (ANC <500/cu mm) was seen in 17.9% cases.

Table 1: General characteristics of the study population

Sl No.	Parameter	Number	Percentage/SD
01	Children with neutropenia	56	100%
02	Male sex	32	57.1%
03	Weight on admission in kg	Mean 19.1 kg	5.4 Kg
04	Age in years	Mean 8.8 years	SD 2.7 years
05	Age <1 year	6	10.7%
06	ANC (number)	Mean 1021/ cu mm	SD 324/ cu mm
07	Duration of Neutropenia (in days)	Mean 4.7	SD 2.4

Common clinical features on admission were fever (n= 48, 85.7%), vomiting (n=29, 51.8%), abdominal pain (n=19, 34%), cough (n=13, 23.2%), jaundice (n=9, 16%) and diarrhea (n=7, 12.5%). Among such children, 15(26.8%) had dengue fever, 9(16.1%) had enteric fever, 4(7.1%) had malaria, 1(1.8%) had chikungunya and the definite cause was obscure in rest 14 febrile children. Majority of children with dengue had mild neutropenia (60%). Sepsis was the admission diagnosis in 5 children and blood culture was positive in 4 such children. Megaloblastic anemia (n=4, 7.1%) was the most significant non-infectious cause of neutropenia. Hemophagocytic lymphohistiocytosis wasn't seen in any child. Neutropenia was more severe in infant age group with the majority of infants (83.3%) had moderate or severe neutropenia. Thrombocytopenia was seen in 31 (55.4%) of such children. Mean duration of thrombocytopenia was 6.24 (SD 2.17) days. Table 2 shows variation of ANCs in the 3 most common causes of neutropenia:

Table 2: ANC^{*} in the 3 major infective groups

Disease	ANC at admission	ANC at discharge	Minimum ANC	Duration of neutropenia#
Dengue	1692	2014	534	3.96 (2.12)
Enteric fever	1964	2285	652	3.91 (2.39)
Malaria	2179	2241	796	4.28 (1.95)

*Values expressed as mean; #values expressed as mean (S.D) in days

Acute transient neutropenia was the commonest entity seen. ANC returned to normal in most (85.7%) patients by 7 days. Duration of hospital stay was short in the majority of neutropenic children. Mean and median duration of hospital stay was 8.24 (S.D 4.3) days and 7 days respectively. Only 2 children required hospitalization for more than 2 weeks. Table 3 shows comparison of severity of neutropenia and duration of hospital stay in such children:

Table 3: Comparison of severity of neutropenia with duration of neutropenia & duration of hospital stay:

Severity of neutropenia	Duration ^s of neutropenia	Duration ^s of hospital stay
Mild neutropenia (n=27)	2.95 (1.46)	7.1 (2.9)
Moderate neutropenia (n=19)	5.67 (3.11)	8.9 (4.1)
Severe neutropenia (n= 10)	8.9 (3.78)	11.95 (5.19)

\$ expressed as mean (SD) in days

Influence of age: There was an inverse relationship between age at presentation and duration of hospital stay. The median duration of

hospital stay was almost twice in infants as compared to older children around 10 years of age (Table 4)

Table 4: Relationship between age at presentation and days of hospital stay

Age at presentation in years	Median duration of hospitalization in days
Infants	13
1-5 years	10
5-10 years	7
>10 years	6

Complications and Outcome: 11 neutropenic children suffered from sepsis during their hospital stay with either a positive blood culture (n=5) or CRP >20mg/dl with persistent thrombocytopenia (n=9). Septic shock was seen in 3 children, 4 children required ventilator support and 6 children required inotropic &/or vasopressor support. 2 children had culture positive UTI. Overall, 47 (83.4%) children were discharged and 9 (16.6%) children couldn't survive. Neutropenia normalized in 48 (85.7%) children by end of first week. Only 2 children had persistent neutropenia beyond 2 weeks. However, during the 4 week follow up period since presentation, ANC returned to normal in all patients.

V. DISCUSSION

During the present study, we intended to study the clinical profile of neutropenic children, admission diagnosis as well as short term outcome of such children at our tertiary care level teaching hospital.

Husain et al⁶ in their study on infectious etiologies of transient neutropenia in previously healthy children have described that most cases of pediatric neutropenia are due to viral infections which is similar to our study. In the Indian study of Mahajan et al⁷ at Delhi India, dengue, malaria and typhoid were the commonest infectious causes of acute transient neutropenia in children which is similar to the present study. The comprehensive study of Gaudichon et al⁸ at a French university hospital showed that neutropenia is more common in younger children (median age 22.2 months). However, in our study median age was 8.4 years which could be due to relatively higher incidence of infectious disease (dengue, malaria, typhoid) in school going children as compared to younger children. Mean ANC in the French study was 943/cu mm which is quite comparable to our study (1021/cu mm). Severe neutropenia was seen in around 1/5th patients (17.9%) cases in our study which is quite comparable to the Korean study of Kim et al.⁹ However, the incidence of severe neutropenia was more in younger children (approx 50%). Median duration of neutropenia was 5 days in this study while in a Spanish study the median duration of neutropenia was 6 days.⁹ This reiterates our observation that infections result in transient neutropenia which eventually recovers in most children by end of first week of presentation. However, as we didn't include children with malignancy and neutropenia in our study we couldn't compare the morbidity and organ dysfunction association between neutropenia in malignant vs non-malignant causes.

In our study, no child had persistent neutropenia when followed up till 4 weeks. However, Karavanaki et al¹⁰ in their study found that a substantial percentage of children had persistent neutropenia after bacterial or viral infections. But there was no correlation between this finding and clinical well being of the children studied. Even the study of Thein et al¹¹ concluded that there is no risk of superimposed bacterial disease or complications in severe neutropenia. Whether all such neutropenic children require antibiotic therapy depends on a number of other factors which are beyond the scope of present study. Thrombocytopenia is a common problem in children with dengue and it almost always follows neutropenia. Though thrombocytopenia was seen in almost 2/3rd of dengue patients in the study of Patel et al,¹² we didn't find any correlation between these 2 cell lines.

VI. CONCLUSION

Infections are the commonest cause of transient neutropenia in hospitalized children with dengue, typhoid and malaria being the common infective etiologies. Length of hospital stay as well as duration of neutropenia increased with the severity of neutropenia and there was an inverse relation of these to the age. Our study also shows that most of the episodes of transient infection induced neutropenia recover without major complications.

VII. LIMITATIONS

Children who presented to OPD with neutropenia but were not admitted were not included in our study. We didn't compare outcomes of patients with and without neutropenia. It is likely that the children who presented to the emergency department could have received some medication but we didn't assess relation between drugs administered (both before and during the study) and occurrence of transient neutropenia. As we couldn't do long term follow up of these patients, it is likely that some of these cases could have been a cases of recurrent neutropenia (e.g., cyclical neutropenia).

Conflict Of Interest: None

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Abbreviations: ANC: Absolute neutrophil count; CRP: C-reactive protein; DF: Dengue fever; SD: standard deviation; UTI: urinary tract infection

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