Original Article

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Spectrum of Diseases with Nucleated RBCs

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ABSTRACT

Background: Nucleated RBCs (nRBCs) are the precursors of RBCs which are normally found in peripheral smear only in neonatal period. Their presence detected by either peripheral smear examination or automated analyzer beyond neonatal period indicates diverse pathological processes. This study was conducted to evaluate nRBC in the peripheral blood and to determine their significance in spectrum of diseases.

Methods: A retrospective study was conducted over a period of 3 months from February 2018 to April 2018 in a tertiary care centre. Data were collected, subsequently tabulated and analyzed.

Result: A total of 200 cases having nRBCs were found among which 42 were neonatal (more than expected for age) and 158 were adult cases. Out of 200 cases, 30 cases with increased nRBCs were due to non hematological cause. It was found that nRBCs were detected in 35 critically ill patients (admitted in MICU/PICU) and in 12 patients who succumbed to death. The most common age group excluding neonates in which nRBCs were detected was >50years.

Conclusion: Detection of nRBCs in peripheral blood maybe physiological or pathological and there are a wide variety of causes for its release. It's worthwhile to remember that it's not only hematological disorders that would result in release of nRBCs into peripheral blood but also other critical conditions can lead to it.

Keywords: *Nucleated RBCs, Critically Ill Patients, Spectrum Of Diseases, Automated Analyzer.*

Introduction:

Nucleated red blood cells are immediate precursors of mature erythrocytes and are less deformable to pass through fenestrations in endothelial lining of bone marrow. Therefore, its presence in circulation i.e. normoblastemia after the neonatal period is considered abnormal and needs further evaluation. [1, 2, 4]

Materials and Methods

This retrospective study was conducted in a tertiary care centre. The study period was 3months, i.e. from February 2018 to April 2018. The presence of nRBCs in the peripheral blood was detected with the help of automated analyzer (Sysmex XN 1000) and by laboratory data retrieving. Peripheral smear correlation was done. It was followed by tabulation and analysis of results.

Result

A total of 200 cases were detected with normoblastemia in which 42 cases were in neonates (more than expected for age) and 158 cases were in adults. Chart 1 depicts the age wise distribution of the cases which shows that maximum number of cases (n=65) were seen in age group of >50years. Male to female ratio was 1.06:1 with total number of males being 103 and total number of females being 97.

The nRBC count ranged from 0.1-145/100 WBC. Highest number of nRBCs detected were as follows – 145 nRBCs in neonatal period in a case of Meconium aspiration syndrome; 42 nRBCs in 10yr old female who was a case of thalassemia; 4 nRBCs in 57yr old male who had macrocytic anemia with neutrophilia. Elevated nRBCs among neonates more than the normal expected for age were seen in neonatal sepsis (n=19), meconium aspiration syndrome (n=4), Rh incompatibility (n=4), preterm/birth asphyxia (n=4), eosinophilia (n=4), leucopenia (n=3), anemia (n=2), thrombocytopenia (n=1) and oligohydramnios (n=1) [Chart 2].

The causes for the presence of nRBCs in peripheral blood in children of age group (1-15years) are as follows- microcytic hypochromic anemia (MHA) (n=9), normocytic normochromic anemia (NNA) (n=4), thalassemia (n=3), eosinophilia (n=3), hemolytic uremic syndrome (n=1) and congenital heart disease (CHD) with respiratory infection (n=1) [Chart 3]. The highest number of nRBCs detected in this age group was 42 and the lowest was 0.1/100WBC. It was found that nRBCs were seen in 5 PICU cases and 1 NICU case.

Among the patients of age (15-25years), the causes were microcytic hypochromic anemia ± neutrophilia (n=10), thrombocytopenia (n=1), eosinophilia (n=1) and pancytopenia (n=1). The count ranged from 0.1-1.5 nRBCs/100WBC.

In patients of >25years of age, a total of (n=40) cases were microcytic hypochromic anemia, (n=24) were normocytic

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normochromic anemia, (n=14) were dimorphic anemia, (n=7) were eosinophilia, (n=6) were macrocytic anemia, (n=4) were pancytopenia, (n=3) were malaria and (n=1) was dengue. [Chart 4]. NRBCs were found in (n=26) critically ill patients admitted in MICU [Chart 5]

We found that 30 cases with increased nRBCs were due to non hematological cause. It was also noted that nRBCs were detected in 12 patients who had hospital mortality.

On correlating with peripheral smear findings, only 25 cases had detectable nRBCs in peripheral smear. 34 cases were found with presence of polychromatophils in peripheral smear. Reticulocyte count was done in 34 cases. The count ranged from 2.9% to 14.9% in neonatal period and 0.6% to 8.7% in adults. The average reticulocyte count in neonatal age group was 7.09 % and that in adults was 3.14%

An unusual finding encountered in our study was detection of nRBCs by automated analyzer in 15 cases with eosinophilia.

Discussion

In this study we found that the causes of normoblastemia are heterogeneous. We can broadly categorize them as hematological and non-hematological causes. In neonates, nRBCs are normally present upto 5th day of life and their range being 3-10/100WBCs. Healthy bone marrow acts as a barrier for the passage of immature erythrocyte and

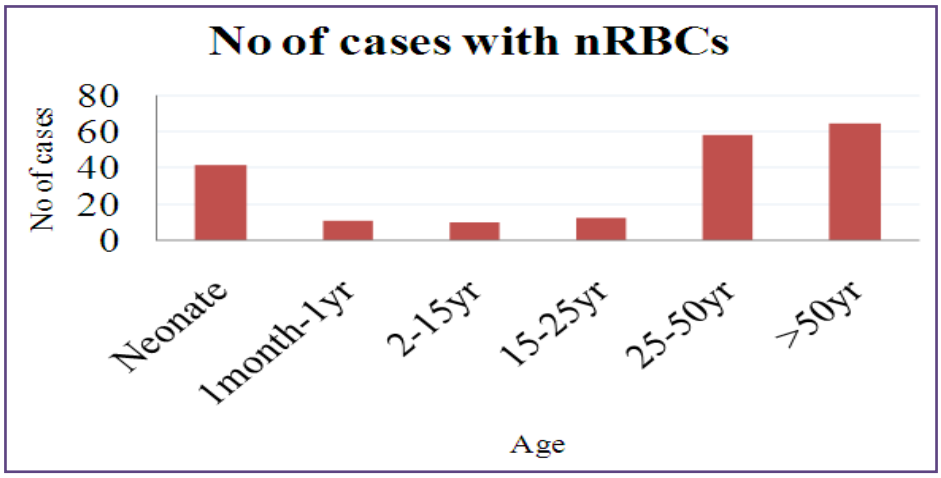
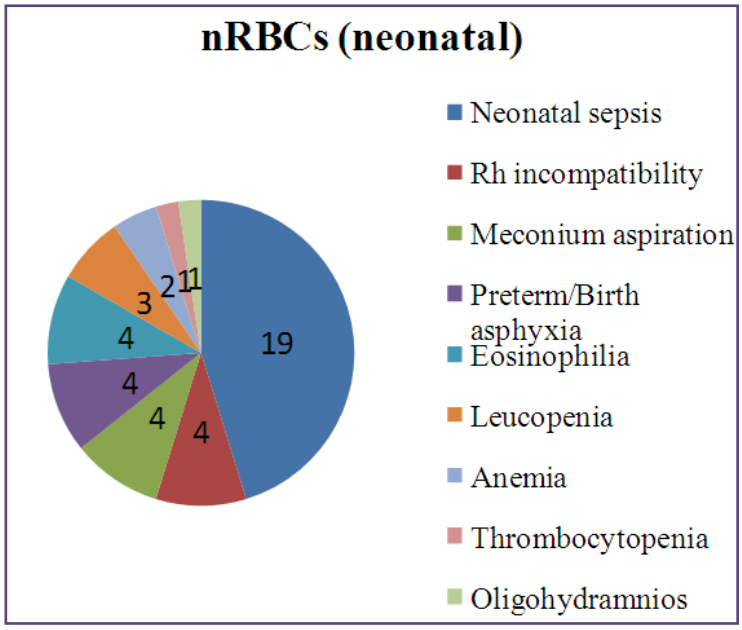


Chart:1



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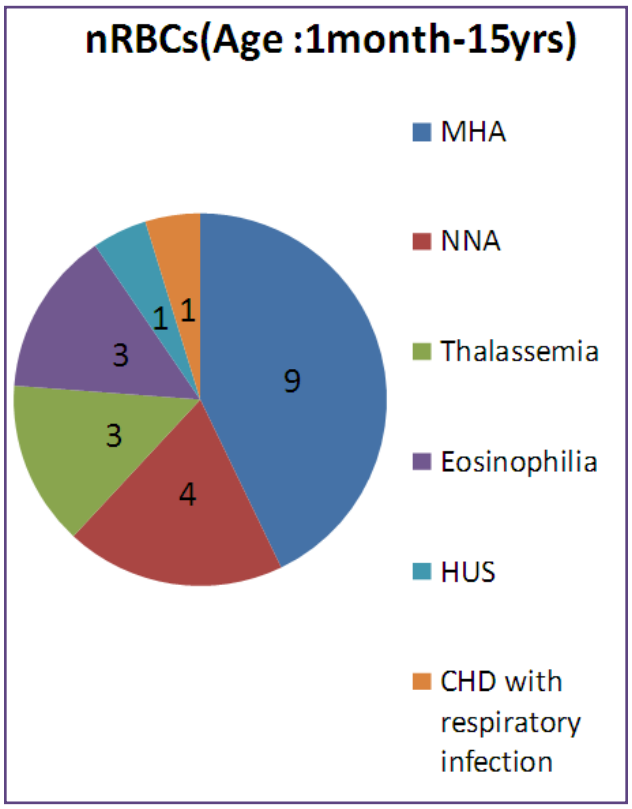

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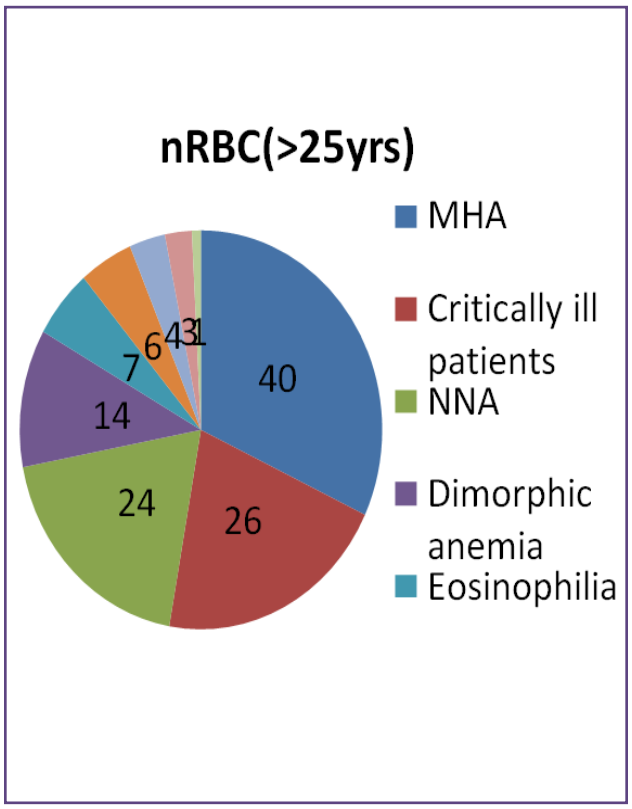

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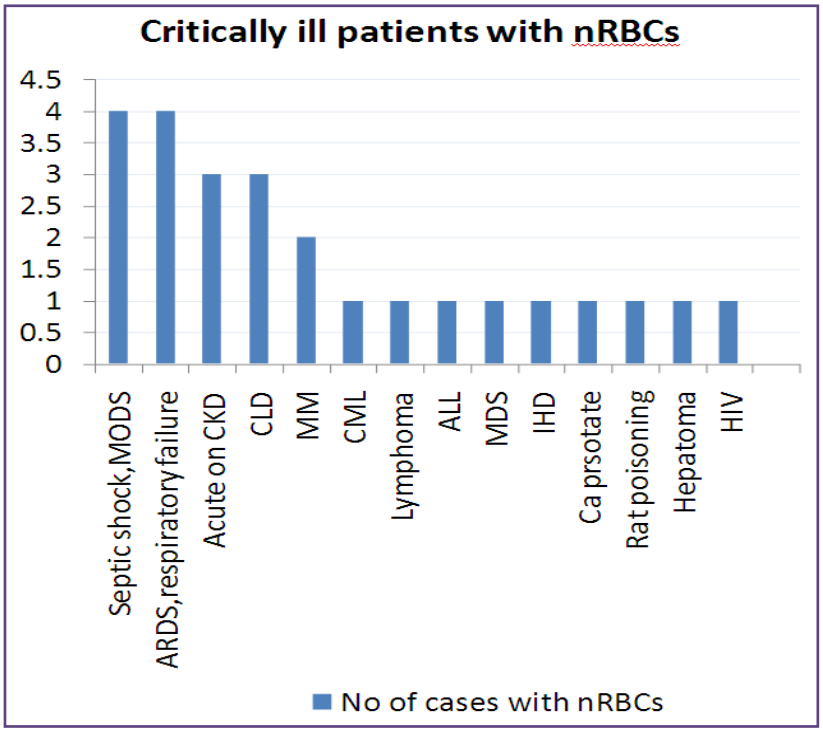

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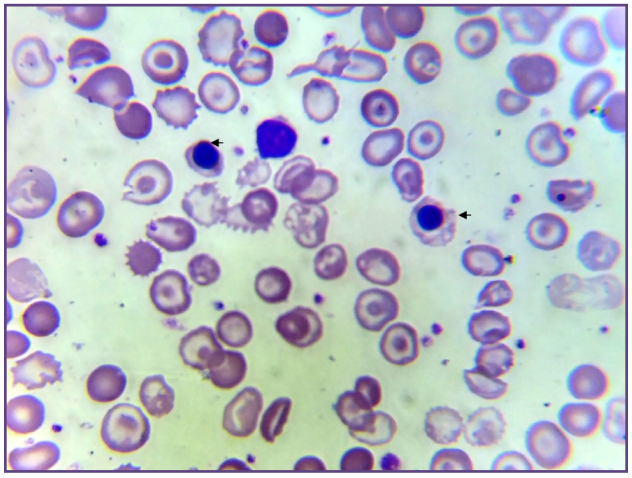
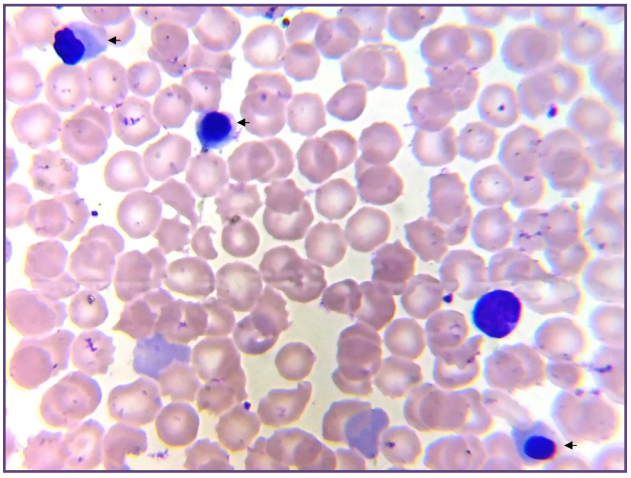


A case of Thalassemia with microcytic hypochromic RBCs, target cells and nRBCs(arrow). 100x. Leishman stain



NRBCs(arrow) and polychromatophils in a neonatal case of Rh incompatibility.100x.Leishman stain

granulocyte precursors as these are less deformable when compared to the mature cells that can easily pass through endothelial fenestrations. Physiological normoblastemia is due to immaturity of reticuloendothelial system at birth, mainly spleen which has a major role in clearing the immature precursors from circulation. [1, 2, 3]

Apart from physiological normoblastemia, the differentials for normoblastemia in neonates are- increased erythropoiesis due to chronic hypoxia, anemia due to blood loss or Rh/ABO incompatibility, maternal diabetes, Down's syndrome, TORCH infection, acute stress release, cyanotic heart disease etc. [2, 3] In this study we found 4 cases with Rh incompatibility where nRBC count ranged from 20-70/100WBCs.

Sepsis is the response of the body to infection that maybe hazardous to its own tissue ultimately subjecting the body to stressful environment. Sepsis evokes inflammatory response by stimulating the production of inflammatory mediators like interleukin, the major one being interleukin-6. [1, 2, 3, 4] Many studies have shown positive correlation between normoblastemia and hike in interleukin-6 level. In our study, the total number of sepsis cases were 24 out of which 19 cases were found in neonatal period in which neutrophilia and thrombocytopenia were seen in peripheral blood. The nRBC count ranged from 0.8-20/100WBCs.

Anemia of any type results in hypoxia that in turn stimulates kidney to produce erythropoietin which increases erythropoiesis in the bone marrow, termed as compensatory erythropoiesis. Underlying anemia maybe hemolytic anemia, megaloblastic anemia, iron deficiency anemia, microangiopathic hemolytic anemia, thalassemia major etc. [1, 4] We found a total of 121 cases with anemia in which the most common cause was microcytic hypochromic anemia (n=65) including 4 cases of thalassemia, followed by normocytic normochromic anemia (n=34), dimorphic anemia (n=14), macrocytic anemia (n=7) and microangiopathic hemolytic anemia [hemolytic uremic syndrome(n=1)].

Cardiopulmonary insufficiency resulting in hypoxia is another mechanism of normoblastemia. [1, 5, 6] The hemoglobin level is either increased or normal along with mild to moderate polychromasia. In our study it was noted that a total of 10 cases were due to cardiopulmonary causes. We found 2 cases of Patent ductus arteriosus, a case of congenital heart disease, 2 cases with cardiogenic shock, 3 cases with acute respiratory distress syndrome leading to respiratory failure, a case of left sided pleural effusion and a case of ischemic heart disease with congestive cardiac failure.

Bone marrow replacement or invasion results in destruction of normal barrier, ultimately ending in release of immature cells into the circulation. Primary hematological disorders like leukemia, lymphoma, myeloma, myeloproliferative disorders, myelodysplastic syndrome, myelofibrosis and secondary causes like tumor invasion, sarcoidosis, fungal infection, tuberculosis, collagen vascular disease, gauchers disease and other storage disorders are important conditions leading to bone marrow replacement. [1, 4] Primary hematological disorders found in our study were plasma cell myeloma (n=2), B- Acute lymphoblastic leukemia (n=1), Chronic Myeloid leukemia (n=1), suspected myelodysplastic syndrome (n=1) and a case of dimorphic anemia with lymphoma spillover.

Extramedullary hematopoiesis happens when bone marrow fails to meet the demand in long standing anemia. This results in hyperplasia of spleen and liver causing splenomegaly and hepatomegaly respectively. Myelophthisic anemia, leukemia, polycythemia vera, chronic hemolytic anemia are the few causes. [1, 4]

Non hematological causes for normoblastemia include uremia, liver disease, diabetic ketoacidosis, thermal injury and chemotherapy. [1, 4] In our study we found 3 cases of chronic kidney disease with patients on dialysis, a case of chronic liver disease and a case of hepatoma with inferior vena cava obstruction.

Increase in nRBCs in critically ill patients is thought to be due to release of inflammatory mediators like interleukin 3, 6 and 12. Steven et al conducted a cohort study in which they assessed nRBCs in critical illness survivors and concluded that presence of nRBCs is a predictor of post discharge mortality and hospital readmission. Similar cohort study was done by Jose et al where they found strong association between increasing mortality in cardiac intensive care patients and rising level of nRBCs in the peripheral blood. [5, 6, 7, 8]

The cause for nRBC release in eosinophilia is not clearly understood and is yet to be discovered. However, the release of inflammatory mediators like interleukin 3 and extramedullary hematopoiesis (pulmonary) in chronic allergic conditions maybe proposed as possible mechanisms. [1, 9]

Conclusion

Presence of nucleated red blood cells in the peripheral blood after neonatal period describes a diseased state of the body. Careful examination of peripheral smear, documenting the presence of nRBCs and alerting the clinician would help in better stratification of its cause as either hematological or non-hematological. Assessing its level carries a prognostic value in critically ill patients.

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