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Normoblastemia in Neonates and Infants

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ABSTRACT

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Normoblastemia in neonates or infants is defined as the presence of higher than the normally expected number of nRBC's in the blood or the presence of any nRBC beyond the age of approximately 1 week after full term normal birth. The significance of normoblastemia should be considered in the context of the clinical setting in which it is discovered. Interpretation of normoblastemia should be made with factors including age of the patient, number and the spectrum of maturity of the nucleated red cells, presence or absence of reticulocytes, other red cell abnormalities, circulating immature granulocytes or bizarre platelets, hyposplenism or asplenism. The presence of normoblastemia indicates intravascular haemopoiesis or disruption of marrow structure or the inability of the bone marrow's screening mechanism to prevent their passage into the circulation. Correction of WBC count with even 1 nRBC/100 WBC's should be done, thus alerting the clinicians of the significance of unexplained normoblastemia.

Keywords: Normoblastemia, Causes in neonates and infants

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INTRODUCTION

Normoblasts are nucleated red cells **(Figure 1)** which are less deformable and rarely enter circulation unlike mature bone marrow cells which are not and can squeeze through small "portholes" in the endothelium. Presence of normoblasts in peripheral blood means that the bone marrow barrier has been disrupted or extramedullary haematopoiesis has been activated.[1,2] Recognizing nRBC's is important not only because their presence affects the WBC count but also because even a few nRBC's can have ominous implications in some patients. In critically ill patients the appearance of nRBC's (nucleated red blood cells) in blood is associated with a variety of severe diseases. In such cases the prognosis is generally poor.[1,2,4] This article discusses the conditions which are associated with nRBC's in the peripheral blood and its importance.

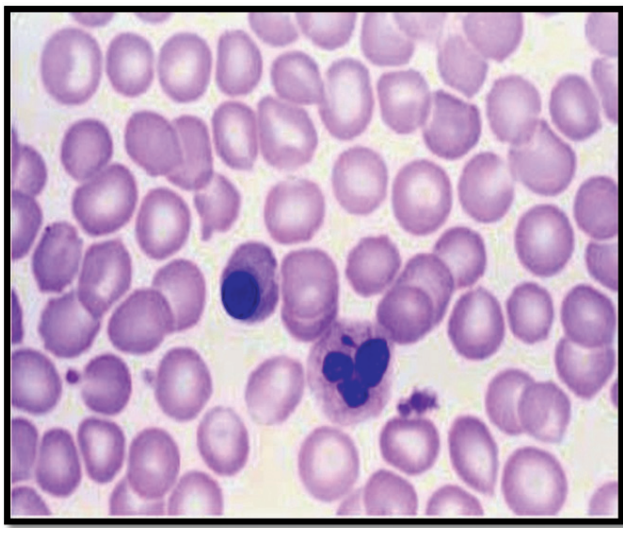

Figure 1. **Normoblast in peripheral smear**

Corrected WBC count

Normoblastemia or erythroblastemia is conventionally quantified by counting number of nRBC's per 100 leukocytes in peripheral smear.[2,3] WBC counts with even 1 nRBC/100 WBC's is to be corrected and reported.[2] In the older haematology analyzers nRBC will be counted along with the WBC's to get the total WBC count as a routine part of automated complete blood count(CBC).[1] To obtain the true or corrected WBC count, the number of nucleated red cells per 100 WBC's should be determined by differential count and the following formula is used.[3]

$$\text{Corrected WBC count} = \frac{\text{Reported WBC count} \times 100}{\text{Nucleated red cells/100WBC's} + 100}$$

Clinically it is better to express nRBC's as an absolute number of cells per unit volume, either "nRBC's / mm^3" or "nRBC's/l".[4] So the modern haematology analyzers like SYSMEX XE-2100 uses nDNA fluores-

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Table 1. Causes of increased nucleated red blood cells in the fetus and newborn
1. Physiological
Labour – Vaginal births Pre term and post-term newborns Hyposplenism/Asplenism
2. Pathological
A. Acute stress
Acute hypoxia Subacute hypoxia Chorioamnionitis
B. Chronic hypoxia
Maternal preeclampsia Maternal diabetes Maternal smoking
C. Postnatal hypoxia
Cyanotic heart disease
D. Anaemia
Blood loss Haemolysis-ABO or Rh isoimmunisation, other
E. Others
Sepsis Leukaemia Downs syndrome TORCH infections
F. IDIOPATHIC

cent dye (polymethine) to stain cells and fluorescence and light scatter measurements to detect and enumerate nRBC's in a specific channel that is different from those used for CBC, DLC and reticulocyte count. Cell membranes of mature red cells and nRBC's are lysed and those of WBC's are slightly perforated to allow influx of dye. The naked nuclei of nRBC's and the nuclei and cell membranes of the intact but perforated nRBC's are then stained with fluorescent dye and subject to flowcytometric measurements of side fluorescent intensity and forward scatter. The difference in size is measured by side fluorescence that allows discrimination of nRBC's from RBC's.[4] Normoblastemia can be classified as physiologic and pathologic based on the mechanism **(Table 1).**

Physiologic Normoblastemia

0-10 nRBC's/100WBC's are usually seen in the peripheral blood in normal infants upto the fifth day of life. Values above 10-20 nRBC's/WBC are elevated, although these values are highly dependent on the total leukocyte count. The mean value of nRBC's in the first few hours of life in healthy term newborns is about 500 nRBC's/mm^3 and a value above 1000 nRBC's/mm^3 is considered elevated. By 12 hours of age, counts may fall by about 50% and by 48 hours only 20-30 nRBC's are found. In term newborns no nRBC's are found after the third or fourth day.[4] Hyposplenism/Asplenism in neonates and infants due to developmental immaturity of the reticuloendothelial system is the reported cause of physiologic normoblastemia. Howell-Jolly bodies (RBC inclusions) in the peripheral blood film is a more sensitive indicator of splenic function.[2]

Pathologic Conditions Associated with Neonatal Normoblastemia

Common causes of normoblastemia are prematurity, hypoxia, anemia, maternal diabetes, acute stress and idiopathic.[1,2,3,4]

Prematurity

In preterm neonates normally 10,000 nRBC's/mm^3 may be seen. However the nRBC's may persist in small numbers upto a week.[4]

Hypoxia

Chronic hypoxia

Hypoxia in tissues causes raise in levels of erythropoietin, which in turn leads to stimulation of erythropoiesis. Intrauterine growth restriction is the most common cause followed by maternal hypertension, maternal smoking, pre-eclampsia, Rh isoimmunisation and maternal diabetes.[2,3,4] Hanlon-Lundberg et al found 14.6 (12.2) nRBC's/100 WBC's in infants of diabetic mothers, compared with 8.3(10.1) nRBC's/100 WBC's in controls.[5,6] Increased erythropoiesis in maternal diabetes is due to increase in erythropoietin levels and direct haematopoietic effect of hyperinsulinemia.[1] Dollberg and colleagues found out that infants whose mothers were exposed to passive smoking had increased numbers of nRBC's in their blood.[5]

Acute and subacute hypoxia

Naeye and Localio found in their study that all of the infants with cerebral palsy caused by developmental events unrelated to birth had less than 2000 nRBC's/cumm and nRBC's were increased to 2000/cumm or more in 15 out of 16 infants injured from acute ischemia and hypoxemia.[7] The precise time required to observe increase in circulating nRBC's in newborns is not known. MC Hermanson in his review article concluded that normoblasts could enter the blood stream within 60 minutes of severe acute hypoxic injury perhaps as short as 20-30 minutes.[4] Magnitude of the increase in nRBC following acute asphyxia is a function of both severity and duration. However there is a large overlap between nRBC values found

after acute, subacute and chronic asphyxia so also with APGAR score. Hanlon- Lundberg and Kirby evaluated the relation between severity of asphyxia and increased nRBC's by comparing cord nRBC's with cord pH and Apgar score. The nRBC counts increased with progressive increases in cord acidosis and with progressive decreases in the APGAR scores. But not all infants with low APGAR scores had increased nRBC's. In some infants with very low APGAR scores almost no nRBC's were detected and other infants with normal APGAR scores had as many as 2250 nRBC's.[1,8] Precise mechanism causing rapid release of nRBC's following acute asphyxia is not known. Increase in levels of erythropoietin can be detected within one hour of acute asphyxia. It is likely that increase in circulating nRBC's represents erythropoietin induced release of normoblasts from their marrow stores. High titres of erythropoietin have been shown to accelerate mitotic division of the normoblasts, increase blood flow through the marrow and increase the porous infrastructure of the marrow allowing escape of rigid and relatively large normoblasts.[1,4]

Postnatal hypoxia

Infants with severe pulmonary disease and cyanotic heart disease have elevated erythropoietin levels during the first week of life.[4] Naeye and Localio reported on infants with severe hypoxemia resulting from pneumonia or cyanotic congenital heart disease who had nRBC count in excess of 2000/mm.[3,7]

Acute chorioamnionitis

Acute chorioamnionitis has been associated with increased levels of erythropoietin and increased newborn nRBC's.[4] Maier et al found significantly elevated erythropoietin levels in neonates whose placentas showed signs of chorioamnionitis.[9] Salafia et al speculated that increase in nRBC may be a fetal response to an inflammed environment and not due to fetal hypoxia.[10]

Anemia

In all types of severe anemia- hemolytic, nutritional or blood loss- reduced oxygen carrying capacity of the anemic blood causes tissue hypoxia, causing kidneys to produce erythropoietin resulting in intense marrow erythropoietic activity.[2]

ABO isoimmunisation is the most common. Hemolytic anemia in neonates characterised. by microspherocytosis, reticulocytosis in the peripheral smear and positive direct Coomb's test in cases of autoimmune hemolytic anemia. Rare causes of anemia due to hemolysis are congenital toxoplasmosis and congenital rubella.[1] Acute haemorrhage during foetal life present with clinical features of acute anemia. Unlike patients with hemolytic disorders these infants do not typically develop hyperbilirubinemia.[1,3] Normoblastemia with anemia should raise suspicion of haemorrhage in the newborn. Atshtuler and Hyder found that nRBC's increased to 2000/ cumm within two hours of acute blood loss in previously healthy term foetuses.[4]

Idiopathic

Normal newborns (1-2%) can have idiopathic increases in nRBC. Green and Mimouni found that 5% of 102 normal control infants had absolute nRBC counts greater than 1700/mm.[3,4]

Septicaemia

Normoblastemia along with a leukoeythroblastic picture is seen in cases of septicemia.[2]

Others

Leukaemia, Down's syndrome and TORCH infections are the other causes. Cytomegalovirus and parvovirus have been associated with increased nRBC's.[2]

CONCLUSION

Appearance of normoblasts in the blood does not in itself provide a diagnosis of the disease but can give invaluable clue to the presence of a serious underlying condition. A recent technological breakthrough is the advent of new haematology analyzers to identify nRBC's separately from WBC's, although grossly abnormal results should be reviewed manually. The different pathological causes of normoblastemia have to be considered in the context of the total clinical picture and treated accordingly.

END NOTE

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