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Novel Cases of Diamond Blackfan Anaemia in Two Nigerian Toddlers: Roadmap for Care in Resource-Limited Nations

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ABSTRACT

Diamond Blackfan anaemia (DBA) is a rare cause of anaemia in children. To the best of our knowledge, these are the first cases reported in Nigeria. Two toddlers with a history of recurrent anaemia, which started within the first three months of life. Investigations conducted in both cases yielded macrocytic anaemia, reticulocytopenia, and bone marrow biopsy, indicating reduced erythroid precursors. Erythrocyte adenosine deaminase was elevated in a subject while the other had abnormal genitalia. Only one subject achieved remission following two months of therapy with steroids. A high index of suspicion for DBA should be drawn in children with a history of recurrent non-haemolytic anaemia from infancy refractory to available basic therapy.

1. Introduction

Anaemias resulting from pure red cell aplasia is generally rare in childhood. Congenital causes of pure red cell aplasia such as Diamond Blackfan anaemia (DBA) should be suspected in any infant with severe macrocytic anaemia during the first year of life reticulocytopenia preserved bone marrow cellularity of all cell lines except for erythroid precursors. Other supportive criteria include detecting gene mutations linked with DBA, a positive family history, elevated erythrocyte adenosine deaminase activity, congenital anomalies associated with DBA, raised haemoglobin F levels, and no evidence of another inherited bone marrow failure. The most common pathology in DBA is a genetic aberration in ribosome protein 19, either of familial or sporadic origin, which leads to impaired erythropoiesis.[1, 2] Most individuals with this disorder present with a unique history of recurrent severe anaemia from infancy managed with multiple blood transfusions. This recurrent anaemia also occurs on a three-monthly timeline, corresponding to the average half-life of a red blood cell and impaired marrow function.[3] Other clinical findings may include congenital anomalies, characteristic facies, endocrine defects, and malignancies. Laboratory features in DBA include macrocytic anaemia, reticulocytopenia, high haemoglobin F and erythrocyte adenosine deaminase activity, and normal marrow cellularity with a paucity of red cell precursors.[3–5]

This disease among Africans is generally unknown due to the lack of existing national registries and a dearth of skilled specialists. In the United Kingdom, a retrospective study on 80 cases reported an estimated incidence of five DBA cases per one million live births.[6] There is no known gender predilection. This rare red blood cell disease management includes chronic blood transfusions, prednisolone, and hematopoietic cell transplant.[7] The response rate to the steroids-the least invasive form of management- ranges from 50 to 75%.[8, 9] Children who are refractory to steroids stand the risk of being exposed to a myriad of complications associated with chronic blood transfusions.[10] In resource-poor nations, the added risk is even more profound due to the scarcity of needed blood products, failure to meet healthcare management's financial demands, and limited infrastructure and investigative modalities for safe blood transfusions.[10] To the best of our knowledge, we are reporting for the first time two cases of Diamond Blackfan anaemia in Nigerian toddlers with a chronic history of recurrent severe anaemia since birth. This report highlights the clinical features and challenges observed during management.

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2. Case Presentation

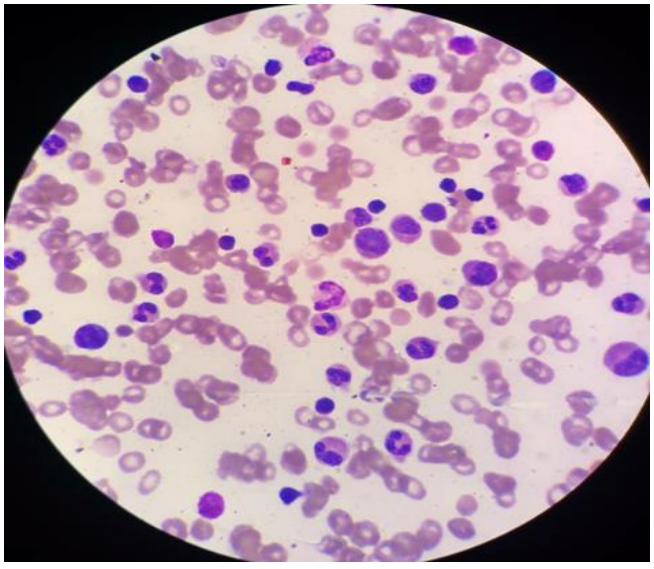
Case one

A 15-month old female infant was referred to our facility with a history of anaemia, fast breathing, and fever. Past medical history revealed that since birth, the child has had recurrent severe anaemia requiring blood transfusion every two to three months. A day before the presentation, a unit of blood was transfused to a nearby health care facility. There was no known family history of a similar illness in a sibling or other relatives. On clinical examination, the child was found to be pale, anicteric, acyanosed, and in mild respiratory distress. The temperature was 37.8C, pulse rate 160 beats per minute, full volume, and regular. The respiratory rate was 56 cycles per minute. All systemic examinations conducted were essentially normal.

A full blood cell count demonstrated a total white blood cell count of 9.5 x 109cells/L, predominantly neutrophils (49.9%) and lymphocytes (33.9%). Red blood cell indices of 1.8 x 1012 cells/L with the mean cell volume of 108fL. Haemoglobin concentration was 6.1g/dl with a packed cell volume of 0.12% with a platelet count of 230 x 109cells/L. Peripheral blood film indicated toxic granulocytosis with macrocytic red blood cells. Genotype was AA, blood group O+ve, reticulocyte count 0.5% (reference range of 1-2% in children), and erythrocyte sedimentation rate 20mm/hr. Direct and indirect Coombs tests were both negative. The child was transfused with 150 milliliters of sedimented blood in our facility, and intravenous antibiotics commenced. A clinical improvement was observed with constituted therapy, and the child was subsequently discharged. Three weeks later, a bone marrow aspiration biopsy revealed a hypocellular marrow with suppressed erythropoietic cell series. All other cell line precursors were found to be normal. Following these findings, a substantive diagnosis of Diamond Blackfan anaemia was made. A daily regimen of 10mg of prednisolone (1mg/kg) was commenced with a favorable response recorded, evidenced by a rise in packed cell volume from 0.25L/L to 0.35L/L in 6 weeks. Following remission, prednisolone was slowly tapered over three months with a persistent good response. An erythrocyte adenosine deaminase test done in South Africa reported an elevated value of 9.9nmol/min/ml (reference range of 1.0-3.0nmol/min/ml). The child continues to be in remission at the time of this write-up.

Case two

A two-year-old female was referred to our facility with a history of recurrent anaemia since three months of age. At the time of presentation, the patient was relatively stable. She was reported to have received an average of at least one blood transfusion every two to three months since the onset of illness. There was no history of jaundice or coke coloured urine during these anaemic episodes. Before presentation in our facility, the child was transfused to another health care centre with a full blood count done before transfusion indicating a haemoglobin concentration of 4.1g/dl and a haematocrit count of 0.12%; total white blood cell count of 10.4 x 109cells/L and platelet count of 615 x 109cells/L. On general examination, the patient was relatively stable and playful. She had frontal bossing, was moderately pale, anicteric, acyanosed with no signs of peripheral lymphadenopathy, digital clubbing, or pedal oedema. Hepatomegaly of 6cm was derived, and an abnormal female external genitalia was observed. Investigations conducted in our facility revealed a total white blood cell count of 12 x 109cells/L consisting mainly of neutrophils (22.8%) and lymphocytes (71.3%). Red blood cell concentration was 1.04 x 1012 cells/L with a mean cell volume of 71.2fL. Haemoglobin concentration was 2.5g/dl, haematocrit 7.4%, and a platelet count of 361 x 109cells/L. Peripheral blood film demonstrated features suggestive of poikilocytosis (+), hypochromia (+++), microcytosis (+), and macrocytosis (++). Reticulocyte count was 0.54% (reference range 1-2%). Haemoglobin electrophoresis demonstrated haemoglobin A2 of 3.3%, with no detection of haemoglobin F. Owing to financial constraints, the mother could not do a bone marrow biopsy to confirm a suspected case of Diamond Blackfan anaemia. 10 mg of prednisolone at 1mg/kg was started, but no remission was attained after two months of therapy, leading to the subsequent tapering of the steroids. Four months into care, bone marrow biopsy was finally conducted with findings indicative of reduced erythroid precursors with normal granulocyte and megakaryocytic cell counts. A definitive diagnosis of Diamond Blackfan was made, and the mother counselled on the need for periodic blood transfusions pending when resources for hematopoietic stem transplants are made available.



Figs. 1. Photomicrograph of bone marrow in case report two showing markedly reduced red cell precursors with normal granulocyte and megakaryocytic cell counts. The second image demonstrates an abnormal female external genitalia in case report two.

3. Discussion

Globally, a dearth of data exists on the prevalence of DBA among children of African descent. Out of the three cases reported in Africa, two had occurred in the 1960s from Zimbabwe and South Africa.[11, 12] In those two reports, the chronic nature of the disease characteristic of DBA was not well established, alluding to the possibility of transient erythroblastopenia of childhood, the most common cause of pure red cell aplasia in children.[13] More recently, the third case of DBA was discovered and confirmed in a 6-week old Caucasian female with recurrent anaemia in South Africa.[14] The lack of data in African literature is not surprising due to the paucity of national blood-related registries, scarcity of skilled specialists in haematology, and poorly equipped infrastructures to appropriately detect and manage the disease, leading perhaps to an appreciable degree of missed diagnosis. Notwithstanding the rarity of this disease worldwide, we were able to identify two cases of DBA in two female toddlers who surprisingly had both presented within six months in our facility, thus pointing to the notion that this disease may not be that uncommon.

Identifying children with DBA in resource-poor settings can be challenging. Nevertheless, a high index of suspicion can be reasonably made with a careful history and necessary blood investigations. In our case report, both children presented with a history of recurrent anaemia observed during infancy and requiring the need for repeated blood transfusion at two to three monthly intervals, an intermission in tandem with the average half-life of a red blood cell. Both cases also presented with a haemoglobin concentration below the threshold expected for common infectious diseases like malaria and indicated an adaptive response to chronic anaemia. The absence of jaundice and coke-coloured urine points to a non-haemolytic pathology, a useful indicator that eliminates sickle cell anaemia and glucose-6-phosphate dehydrogenase deficiency prevalent among Africans. Finally, reticulocytopenia demonstrates a profound bone marrow failure of the red cell line series. Combined with normal counts of total white blood cell and platelet counts, it suggests pure red cell aplasia precluding other conditions like Fanconi Anaemia, Shwachman-Diamond syndrome, and dyskeratosis. Highly specialised tests like bone marrow biopsy, erythrocyte adenosine deaminase activity, and DNA sequencing are largely unattainable due to high financial costs and lack of skilled manpower.

Although earlier reports have consistently demonstrated no gender preference in DBA, we found it interesting that both of our cases were females. The only other confirmed case of DBA in Africa was also a female.[14] However, more cases are needed to comprehensively conclude a possible female preponderance among subjects from this continent. Management of DBA in resource-limited centres, particularly among individuals refractory to steroids, can be very demanding. Chronic blood transfusion increases the risk of haemolytic transfusion reactions and blood-borne infections. Furthermore, it promotes the onset of alloimmunization characterised by the development of antibodies against specific red blood cell antigens. In a study done in a tertiary facility located in South-East Nigeria, the observed prevalence of RBC sensitisation varied between 3.4% and 18.7%.[10] Iron overload from multiple blood transfusions can damage vital organs such as the thyroid, adrenal, liver, and heart. Finally, the high financial demands of this modality of treatment, iron chelation therapy, and hematopoietic stem cell transplant make compliance to care quite difficult in affected subjects. To address these challenges in regions with limited resources, we advocate for comprehensive national blood bank policies to promote affordable and available blood products, appropriate blood screening tests, and safety practices to avoid transfusion reactions; leuko-reduced antigen matched blood products to prevent allosensitization and iron chelation therapy to address iron overload. National registries and robust research are crucial to tracking this disease trend and developing novel treatment modalities, notably during the foetal period.

4. Conclusion

DBA, though rare, may not be uncommon within our population. A high index of suspicion and prompt referrals can significantly mitigate the complications associated with this disease and its therapy.

Conflict of Interest

The authors declared that there is no conflict of interest.

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