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A Case of an Atypical Form of Blackfan-Diamond Anemia (BDA)

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Abstract: Blackfan-Diamond Anemia (BDA) is the only recognized form of congenital erythroblastopenia, its mechanisms of occurrence are still obscure. The unexpected discovery of a ribosomal protein "ribosomal protein *S19 (rps19)"* has made this pathology a star of ribosomopathies. This mutation is only found in 25% of patients. It presents a great clinical variability (typical and atypical form), but especially poses a real problem related to the complications and the therapeutic accessibility of which the allograft of the marrow remains the only curative means. We report an atypical case of BDA revealed by an anemic syndrome in an infant at the Hassan II University Hospital Center of Fez, Morocco.

Keywords: Blackfan-Diamond Anemia, CHU Hassan II Fez, Morocco

INTRODUCTION

Blackfan-Diamond Anemia (BDA) is a constitutional erythroblastopenia, defined by the presence of less than 5% of erythroid precursors, in a normocellular marrow without quantitative and qualitative abnormalities of the other lines, associated with anemia Hemogram [1]. This condition is characterized by its great phenotypic and genetic heterogeneity, enamelled by numerous complications and poses a therapeutic problem [2]. It is a rare disease with an evolutive risk towards a solid tumor or a malignant hemopathy. We report the observation of a children in whom anemia led to the diagnosis of BDA.

NOTE

It is a female child of 9 months of age, of normal phenotype, 4th of a sibling of 5, whose elder brother died at the age of 14 months in a table of anemia, requiring several blood transfusions, without precise diagnosis. It is the result of a non-consanguineous marriage, born at the end of a pregnancy of normal course, birth by birth, with a birth weight of 3kg 100 and a good adaptation to the ectopic life and operated for a dislocation congenital hip, addressed to the pediatric department at the CHU Hassan II of Fez for a argenerative anemia requiring several transfusions of globular pellets. On admission, there was a slightly marked delay in weight-bearing, with an anemic syndrome, without haemorrhagic or infectious syndrome or tumor syndrome. The rest of the somatic examination is unusual. The biological balance revealed an anemia (Hb: 6.4 g/dl), microcytic (GMV: 66 fl), normochrome (HCM: 34 g/dl) and argegeative (reticulocytes: 17280/Ml). Leukocytes at 11600/mm^3 (neutrophils: 4617/ul, lymphocytes: 5348/ul,) and platelets at 817000/mm^3, and ferritin levels at 434 mg/L. The electrophoresis of hemoglobin (HbA1: 55.8%, HbA2: 25% and HbF: 17.5%). Sedimentation rate and hemolysis were normal.

Given the persistence of argenerative anemia, a myelogram was performed, showing severe erythroblastopenia with 04% elements of the erythroblastic lineage, granular and megakaryocytic lines were normal. The molecular biology performed did not show a mutation of the ribosomal proteins (notably RPS19). Given the clinical and biological data the diagnosis of atypical Blackfan-Diamond Anemia was retained. The patient was initially placed under transfusions by globular pellets with chelation of iron. At the age of 16 months, corticosteroid therapy was started at a dose of 2 mg/kg/day, combined with calcium and potassium supplements. Clinical improvement, stability of the staturo-weight curve, hemoglobin at around 9 g/dL and decreased transfusion requirements (6-8 weeks) after one year of full-dose corticosteroid therapy were observed.

Table 1: Genes encoding ribosomal proteins involved in Blackfan-Diamond Anemia

Gene	Sub-Unit	Frequency	Year of publication
RSP19	40S	25	1999
RSP24	40S	2,5	2006
RSP17	40S	5	2007
RPL35A	60S	3	2008
RPL5	60S	7	2008
RPL11	60S	5,5	2008
RPS7	40S	1	2010
RPS10	40S	3	2010
RPS26	40S	6,5	2010
RPL26	60S	1	2012
RPL15	60S	1	2013
RPS29	40S	2 family	2014
RPS28	40S	2family	2014
RPL31	60S	1	2014

Table 2: Diagnostic Criteria for Blackfan-Diamond Anemia

Diagnostic Criteria Diagnostic ✓ age less than 1 year ✓ isolated macrocytic anemia: no significant abnormalities of other lines ✓ Reticulocytopenia (<20,000/mm^3) ✓ Wealth marrow with presence of erythroblastopenia (<5%)
Criteria supporting diagnosis ✓ Major: • Mutation of an RP gene already reported in a patient with a classical form • BDA family history ✓ Minors • Increased activity of erythrocyte adenosine deaminase • Congenital malformation already reported in patients with conventional BDA • Elevation of Hb F * • Exclusion of Other Forms of Constitutional Impairment of Marrow
BDA Classic Form All diagnostic criteria are present
Probable form of BDA ✓ 3 diagnostic criteria present + one family ATCD ** ✓ 2 diagnostic criteria present + 3 criteria supporting the diagnosis ✓ Family ATCD + 3 criteria supporting diagnosis
Form of BDA called "non-conventional" ✓ The subject of a mutation identified in his / her family, but without clinical problem ✓ A patient with a mutation in a PR gene, but in whom the diagnostic criteria are insufficient.
BDA: Black-man Diamond Anemia. * Hemoglobin fetal.

DISCUSSION

Blackfan-Diamond Anemia (BDA) is a rare pathology secondary to a blockade of erythroid differentiation at a stage that is still discussed. This blockage is directly responsible for erythroblastopenia. The involvement of ribosomal protein genes has made this pathology the leader of ribosomopathies. Diagnosis of DBA was carried out in 95% of cases before the age of two (2) years, with a sex ratio close to 1 [1]. Our infant was 9 months old and female. Classically, erythropoiesis remains in utero, but foeto-placental anasarca can be linked to a BDA, so the diagnosis of this condition must be systematically mentioned in front of any anasarca chart, particularly in the absence of pathology of the red blood cell identified in the parents [3]. In our reported case, pregnancy was normal and uncomplicated. The disease is most often characterized by anemic syndrome (pallor, difficulty in suckling, loss of acquisitions, or systolic breath) [2], associated in 40% of patients with more or less severe malformations in the face, the extremities of the limbs, the urogenital sphere and the heart [4, 5]. However, none of these malformations is specific to BDA and some are observed in other hematologic syndromes. Hypotrophy or stunting is present in 20-30% of cases [6]. Our patient was pale and she was operated on for a congenital dislocation of the hip, with a delayed staturo-weighting can mark. At the NFS there was microcytic,

normochromic and argenative anemia. According to the literature, anemia is usually macrocytic, sometimes normocytic [7-9]. This microcytic found in our patient can be explained by the multiple transfusions received before arriving in our center. Platelet and white blood cell counts are often normal for diagnosis. In addition to argenerative anemia and erythroblastopenia, other biological elements may be present such as the persistence beyond the first months of life of a fetal erythropoiesis; this was the case of our child. The elevation of erythrocyte adenosine deaminase (eADA), the key enzyme in the purine pathway, is elevated in 90% of non-transfused patients (6). At present, it is recognized that BDA is the first genetic disease associated with the mutation of genes encoding ribosomal proteins, the gene encoding the *rps19* ribosomal protein [10], is the first gene identified, found only in 25% of patients, since other genes encoding ribosomal proteins have been identified or are being identified (Table 1). Apart from point mutations, large deletions were described, which significantly increased the number of patients with an anomaly identified to 70% [11, 12]. The cytogenetic study of our child consisted in the research of the mutation *rsp19*, but this one was not found. The diagnosis of BDA is based on a range of clinical and biological arguments. Diagnostic criteria were the subject of an international consensus conference (Table 2). However, these criteria can be criticized and remarks can be made at various points [1]. Our findings are based on three diagnostic criteria (age less than 1 year, reticulocytes below 20 000/mm^3 and erythroblastopenia at 04%) and three diagnostic criteria (familial ATCD, congenital malformation and elevated HbF) Allowing the diagnosis of ABD in its atypical form: the probable form of the BDA. Initial management relies on transfusion support. Most patients require transfusion every 4 weeks. Optimal chelation is of course of major importance in order to avoid iron overload, the target of the desired ferritin levels of 500 to 1000 ng/Ml [1]. Corticosteroids are to be avoided in the first year of life on the one hand because of their toxicity at this age, on the other hand to ensure that the erythroblastopenia is very chronic. The patient had initially received transfusions by globular pellets every 3 weeks and an iron chelator with ferritin levels around 445 mg/L. Corticosteroids were started only after 16 months of life at a dose of 2 mg/kg/day with a decrease in the frequency of transfusions every 6 to 8 weeks. The only curative treatment of BDA remains allogeneic bone marrow transplantation. The evolution of BDA is unpredictable. Evolutionary complications are often of iatrogenic origin (martial overload, transfusional contamination, side effects of corticosteroids), or related to the disease itself the occurrence of complete bone marrow aplasia [2]. The risk of malignant evolution is estimated according to a french study at 3.7% [2]. For the time being is our in good clinical and biological remission with a rate of Hb: 9g/dl and the erythroblastic line to 14% under corticotherapy and a spacing of the transfusion frequency.

CONCLUSION

Blackfan-Diamond Anemia is the first disease of the described ribosome. This discovery has prompted several studies on erythropoiesis. It poses a real diagnostic problem especially in its atypical but also therapeutic form, even if under certain heavens it remains a diagnosis of elimination.

REFERENCES

1. Leblanc, T., & da Costa, L. (2014). Diamond-Blackfan Anemia: News. Review of oncology pediatric hematology.
2. Costa, L. D., Crétien, A., Marie, I., Tchernia, G., & Leblanc, T. (2005). Diamond-Blackfan anemia since the ribosomal protein *S19 (rps19) gene*. *Revue Hématologie*, *11*(6), 385-97.
3. Da Costa, L., Chanoz-Poulard, G., Simansour, M., French, M., Bou-vier, R., & Prieur, F. (2013). First de novo mutation in *RPS19* gene asthe cause of hydrops fetalis in Diamond-Blackfan anemia. *AmJ Hematol*, *88*, 340-1.
4. Chen, S., Warszawski, J., & Bader-Meunier, B. (2005). Diamond-blackfan anemia and growth status: the French registry. *J Pediatr*, *147*, 669-73.
5. Willig, T. N., Gazda, H., & Sieff, C. A. (2000). Diamond-Blackfan anemia. *Curr Opin Hematol*, *7*, 85-94.
6. Willig, T. N., Niemeyer, C., Leblanc, T., Tiemann, C., Robert, A., Budde, J., ... & Girot, R. (1999). Diamond Blackfan anemia: clinical and epidemiological studies with identification of new long-term prognosis factors from the analysis of a registry of 234 patients. *Pediatr Res*, *46*, 553-561.
7. Tchernia G, Croisille L, Willig TN. Anémie de Blackfan-Diamond: données récentes. Hématologie. 2000 Jun 20;6(2):143-9.
8. Halperin, D. S., & Freedman, M. H. (1989). Diamond-Blacfan Anemia: Etilogy,Pathophysiology, and Treatment. *Am. J. Ped. Hematol. Oncol*, *11*, 380-94.
9. Da Costa L, Proust A, Moniz H, Hurtaud C, Marie I, Tchernia G, Leblanc T. L'anémie de Blackfan-Diamond: un modèle de maladie ribosomique. Hématologie. 2009 Jan 1;15(1):20-34.
10. Draptchinskaia N, Gustavsson P, Andersson B, Pettersson M, Willig TN, Dianzani I, Ball S, Tchernia G, Klar J, Matsson H, Tentler D. The gene encoding ribosomal protein S19 is mutated in Diamond-Blackfan anaemia. Nature genetics. 1999 Feb 1;21(2):ng0299_169.
11. Farrar JE, Vlachos A, Atsidaftos E, Carlson-Donohoe H, Markello TC, Arceci RJ, Ellis SR, Lipton JM, Bodine DM. Ribosomal protein gene

deletions in Diamond-Blackfan anemia. Blood. 2011 Dec 22;118(26):6943-51.

12. Quarello P, Garelli E, Brusco A, Carando A, Mancini C, Pappi P, Vinti L, Svahn J, Dianzani I, Ramenghi U. High frequency of ribosomal protein gene deletions in Italian Diamond-Blackfan anemia patients detected by multiplex ligation-dependent probe amplification assay. haematologica. 2012 Dec 1;97(12):1813-7.