Diamond-Blackfan Anemia: Case Series in a Portuguese Tertiary Level Hospital

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Port J Pediatr 2020;51:176-83
DOI: https://doi.org/10.25754/pjp.2020.18600

Abstract

Introduction: Diamond-Blackfan anemia is a rare congenital erythroid aplasia and may be associated with congenital abnormalities. It should be considered when the evolution differs from transient erythroblastopenia of childhood. **Methods:** Retrospective and descriptive study, including the Diamond-Blackfan anemia cases followed in a unit of pediatric hematology in a Portuguese tertiary level hospital, over fourteen years (2006 to 2019).

Results: Nine Diamond-Blackfan anemia cases were identified (56% female, 89% Caucasians, 22% with congenital morphological abnormalities). The median age at diagnosis was 2 months old, and the main symptoms were pallor (89%) and failure to thrive (56%). The median hemoglobin at diagnosis was 3.7 g/dL ([1.4-8.1] g/dL) associated with a severely low reticulocyte count. Bone marrow aspirate and biopsy were performed in in 67% of the cases and in half, there was severe erythroid hypoplasia. Sixty-seven percent had the diagnosis confirmed by genetic testing, and 56% were heterozygotic to a mutation in the *RPS19* gene. The majority of the cases were transfusion-dependent until corticotherapy was initiated (89%). Secondary hemosiderosis was present in one patient. None of them underwent hematopoietic stem cell transplantation. There was remission in 22% and no deaths.

Discussion: Diamond-Blackfan anemia is rare, and high suspicion of the diagnosis in the first year of life is essential. National and international registers, and extensive genetic testing, are crucial for new insights into the pathophysiology and management of Diamond-Blackfan anemia patients.

Keywords: Child; Anemia, Diamond-Blackfan/diagnosis; Anemia, Diamond-Blackfan Anemia/genetics; Diamond-Blackfan/therapy; Genetic Diseases, Inborn; Portugal; Anemia

Introduction

Diamond-Blackfan anemia is a rare, congenital, inherited erythroid aplasia, characterized by red cell failure, presence of congenital anomalies, and cancer predisposition.[1,2] The incidence rate is estimated at 1:500,000 live births and is similar among different ethnicities and genders.[3-5]

In its classic presentation, the diagnosis is suspected when anemia, especially macrocytic, and reticulocytopenia are found with normal neutrophil and platelet counts. Bone marrow aspirate and biopsy reveal normal cellularity with a lack of erythroid precursors.[1,6] In most patients, the diagnosis is then confirmed by genetic testing. More than 98% of patients are diagnosed in the first year of age.[1,2,7]

Approximately 50% of patients have congenital anomalies, mostly craniofacial (50%), musculoskeletal, essentially thumb and upper extremity (39%), genitourinary (38%), cardiac (30%), and ophthalmologic.[1,2,3,8,9] Nonclassic cases may be completely hematologically and physically normal, and the onset may be beyond one year of age.[1]

The most commonly recognized pathophysiology is the existence of ribosomal protein mutations that make erythroid progenitor cells sensitive to apoptosis, leading to the failure of erythropoiesis.[2,4,8]

Diamond-Blackfan anemia is a heterogeneous genetic disease, and mutations can be found in 60%-70% of cases, especially ribosomal gene mutations.[3,8,10,11]

The autosomal dominant inherited cases are the most frequent, estimated in 45%, with variable penetrance and expressivity.[3,8,12,13] To date, multiple mutations in the ribosomal genes, from both the small (*RPS*) and large (*RPL*) ribosomal subunit, were identified.[10] In multiple families, the reported genes were: *RPL5, RPL11, RPL35A, RPS7, RPS10, RPS17, RPS19, RPS24,* and *RPS26*.[14-17] In isolated patients or families, the following genes have also been identified: *RPL3, RPL7, RPL9, RPL14, RPL15,*

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Received: 19/09/2019 | Accepted: 04/02/2020 | Published: 01/07/2020

RPL18, RPL19, RPL23A, RPL26, RPL27, RPL31, RPL35, RPL36, RPS7, RPS8, RPS15, RPS27, RPS27A, RPS28, and *RPS29.*[8,18,19] The most frequent mutated gene is *RPS19*, followed by *RPL5*.[8] Newer research has also noted mutations of non-RP genes: *TSR2, GATA-1*, and EPO.[8,11,18] Despite a significant genetic component to Diamond-Blackfan anemia, about 35% of cases remain genetically indeterminate and, therefore, the diagnosis will depend on the clinical and laboratory evaluation.[2-4,14,17]

When Diamond-Blackfan anemia is suspected, the initial laboratory evaluation should include a complete blood count, reticulocyte count, peripheral blood smear, fetal hemoglobin (HbF) level, erythropoietin levels, and erythrocyte adenosine deaminase (eADA) activity. Diamond-Blackfan anemia is associated with elevated HbF levels, erythropoietin levels, and eADA activity.[2,3,4,11] The latter is high in 80% of the patients, although transfusion within the previous eight to 12 weeks may result in a false normal result.[13,20] Therefore, a normal eADA does not exclude Diamond-Blackfan anemia.[13,20] A bone marrow aspirate and biopsy are also recommended as well as a routine bone marrow blood karyotype and genetic testing. It is additionally mandatory to exclude viral infections that are a common cause of bone marrow failure, particularly parvovirus B19, using serology or polymerase chain reaction.[21] Consider vitamin B12, folate, and thyroid function for the differential diagnosis of macrocytic anemia. Even in the absence of apparent congenital anomalies, echocardiography and renal ultrasound screening should be performed.

The main differential diagnosis of Diamond-Blackfan anemia is transient erythroblastopenia of childhood. This is a self-limiting disorder that presents between three months and four years of age, characterized by reduced erythroid precursors in otherwise normocellular bone marrow, and usually with normal eADA activity.[2,5,22,23] We should also consider acquired conditions with bone marrow failure, for instance, viral infections namely parvovirus B19. The main features to consider in the differential diagnosis of these three disorders are described in Table 1.[5,8]

The differential diagnosis also comprehends other inherited bone marrow failure syndromes (e.g. Fanconi anemia and dyskeratosis congenita) and other viral infections (viral hepatitis, mononucleosis, human T-cell lymphotropic virus type 1, human immunodeficiency virus-associated pure red cell aplasia). Immune-mediated diseases, myelodysplastic syndromes, and drugs are also acquired conditions with bone marrow failure, but these are extremely rare in the first year of life.[5,8,11]

Patient management should include a multidisciplinary approach. Treatment is based on the appropriate use of erythrocyte transfusions and iron chelation, corticosteroids, and hematopoietic stem cell transplantation.[1,2]

Approximately 80% of patients will initially respond to an initial course of glucocorticoid treatment within the first two to four weeks.[1,2,5] The commonly accepted definition of an adequate response is a hemoglobin level greater than 9 g/dL without the need for a transfusion.[1,24] The mode of action of corticosteroids in Diamond-Blackfan anemia is still not widely recognized, although corticosteroids seem to have a non-specific anti-apoptotic effect in erythroid progenitors in bone marrow, especially at the colony-forming unit erythroid/proerythroblast interface. Therefore, glucocorticoid treatment promotes erythropoiesis at the progenitor level.[1,25] Other studies suggest a reciprocal role of the glucocorticoid receptor and p53 in the regulation of erythropoiesis, maintaining the balance between self-renewal and differentiation.[26]

Table 1. Differential diagnosis of anemia and reticulocytopenia in children

Features	Diamond-Blackfan anemia	Transient erythroblastopenia of childhood	Parvovirus B19 infection in immunocompetent hosts
Age at diagnosis	90% under 1 year	80% between 3 months and 4 years	Mainly school-aged children
Etiology	Constitutional	Acquired	Acquired
Antecedent history	None	Viral illness	Viral illness
Congenital anomalies	Up to 50%	Absent	Absent
Laboratory values at diagnosis			
Hemoglobin	2-6 g/dL	3-9 g/dL	Decreases of 1 g/dL
Mean cell volume	30% increased	Normal	Normal
White cell count	Normal	Normal or decreased	Normal or decreased
Platelet	Usually normal	Normal or elevated	Normal or decreased
eADA activity	Elevated or normal	Normal	Normal
Course	Prolonged transfusion support and steroid therapy	Self-limiting: spontaneous recovery within weeks to months	Self-limiting: spontaneous recovery 10 to 14 days after the infection

eADA - erythrocyte adenosine deaminase.

The recommended initial dosing is 2 mg/kg of prednisone, single daily dosing, or the glucocorticoid equivalent. It is then reduced until the minimum dosing required for transfusion independence is determined.[1,2] Some patients, despite initially responsive, may become refractory to this treatment. Furthermore, corticotherapy may have to be discontinued due to unacceptable side effects. Steroid therapy in very early infancy is associated with serious side effects, notably in long-term treatment and even at low doses, such as pathologic fractures, avascular necrosis, cataracts, glaucoma, hypertension, diabetes, growth failure, and infections. Therefore, erythrocyte transfusions are the first choice of treatment during the first year of life.[24,27] Transfusions are essential in order to maintain the hemoglobin level at a minimum of 8-9 g/dL to improve the quality of life and preserve the adequate growth and development.[24]

On the other hand, the major problem with erythrocyte transfusion therapy is iron overload, which can result in cardiac hemosiderosis (leading to toxic cardiomyopathy or fatal arrhythmia), hepatic cirrhosis, diabetes, hypoparathyroidism, hypothyroidism, delayed puberty, and may be fatal.[1]

Allogeneic hematopoietic stem cell transplantation is the only definitive treatment for Diamond-Blackfan anemia, although it is associated with a considerable risk of treatment-related mortality.[28,29] Data from different international registries show that approximately 40% of Diamond-Blackfan anemia patients are transfusion-dependent, 40% are glucocorticoid-dependent, and the other 20% are in remission.[5,13] The latter is defined as an adequate hemoglobin level without any treatment, lasting six months, regardless of prior therapy.[1,9,13]

Recent studies suggest alternative therapies to patients who become refractory to corticotherapy, for instance, cyclosporin A, leucine, erythropoietin, and androgens, without robust success.[1,4,30]

Prognosis is relatively good, but complications related to treatment may alter the patient quality of life.[5] Diamond-Blackfan anemia patients have a high risk of developing myelodysplastic syndromes/acute myeloid leukemia and solid tumors.[5,12,13,31]

Extensive and robust clinical data from patient registries have provided important insights into the characterization, diagnosis, and treatment of Diamond-Blackfan anemia.[1] Molecular studies are crucial to establish a better correlation between Diamond-Blackfan anemia genotype and phenotype, provide genetic counseling to the families, and determine a possible human leukocyte antigen (HLA) compatible hematopoietic stem cell transplantation related donor.[1,2,28]

For that reason, this study aims to characterize the Diamond-Blackfan anemia cases followed in a reference unit of pediatric hematology in a Portuguese tertiary level hospital. We intend to describe the patients concerning the demographic factors, diagnostic and genetic features, and treatment management, so that it is possible to be more aware of the Portuguese reality.

Methods

This is a retrospective and descriptive study. We included all the pediatric patients (aged below 18 years old) with the diagnosis of Diamond-Blackfan anemia, followed over 14 years (from January 2006 until June 2019), in the unit of pediatric hematology of a tertiary level hospital in Portugal.

The diagnosis of Diamond-Blackfan anemia was based on the criteria of prolonged macrocytic anemia due to selective erythroblastopenia in the bone marrow, without other cytopenias, or any alternative etiology.[1]

The data were collected from medical records and organized into a standardized form designed in Microsoft® Office Excel 2010. This form was based on international registries and the available literature and included information on the demographics, patient and family history, clinical and laboratory findings, genetic studies, treatment, and evolution.

Genetic testing was performed using the National Haemoglobinopathy Reference Laboratory
(Oxford University Hospitals) next-generation sequencing (NGS) panel that included the primary established Diamond-Blackfan anemia related ribosomal protein genes *RPS7, RPS10, RPS17, RPS19, RPS24, RPS26, RPS27, RPS29, RPL5, RPL11, RPL26, RPL27, RPL35A, RPL9,* and *GATA-1*. The patients in which the next-generation sequencing panel was negative were not yet tested for other mutations at the time of this study. All parents were also tested using the same next-generation sequencing panel.

Both the data collection and the analysis were performed in an anonymous way, respecting patient privacy and ethical considerations.

Results

The diagnosis of Diamond-Blackfan anemia in the selected period was made for nine children. The summary of the main clinical and genetic characteristics of these patients is shown in Table 2.

Concerning demographic analysis, there were five females (56%) and eight Caucasians (89%). Only one patient 3 was African (Cape Verde).

Table 2. Summary of the main clinical and genetic characteristics of Diamond-Blackfan anemia patients

P	Gender	Current age	Positive FH (anemia)	Age At suspicion	Presenting Hb (g/dL)	Presenting MCV (fL)	eADA	HbF (%) (age)	BM aspirate and biopsy	Genetic testing	Congenital anomalies	Corticotherapy (duration)	Responsive to corticotherapy	Transfusion dependent	Remission
P1	F	3 yrs	No	6 mo	4.3	87.6	-	4.9 (7 mo)	Normocellular, without erythroid hypoplasia	Heterozygous mutation in *RPS19* gene (c.184C»T, exon 4)	Yes, polydactyly	Yes (23 mo)	Yes	No	No
P2	F	14 yrs	No	3 mo	6.1	92.5	-	17.5 (3 mo)	Normocellular, erythroid hypoplasia	No mutation related to DBA identified	No (short stature)	Yes (157 mo)	Yes	No	No
P3	F	4 yrs	No	5 mo	1.9	88.7	Normal	-	Normocellular, erythroid hypoplasia	No mutation related to DBA identified	No	Yes, discontinued (10 mo)	No	Yes (hemosiderosis)	No
P4	M	5 yrs	Yes	1 mo	1.4	109.7	Normal	73.7 (2 mo)	Hypocellular, without erythroid hypoplasia	No mutation related to DBA identified	No	Yes, discontinued (21 mo)	Yes	No	Yes
P5	M	18 mo	No	2 mo	3.1	85.7	-	-	N/A	Heterozygous mutation in *RPS19* gene (NM_001022,3:c,1-1G>C)	No	Yes (7 mo)	Yes	No	No
P6	F	20 mo	Yes	Neonatal	5.1	103.1	Normal	24.6 (1 mo)	N/A	Heterozygous mutation in *RPL5* gene (169_172delAACA (p.Asn57fs))	Yes, cardiopathy	Yes, discontinued (9 mo)	No	Yes	No
P7	M	2 yrs	Yes	Neonatal	8.1	114	Normal	89.6 Neonatal	Hypocellular, erythroid hypoplasia	Heterozygous mutation in *RPS19* gene (c.242del, p.(Gly81fs))	No (short stature)	Yes (20 mo)	Yes	No	No
P8	M	6 yrs	No	23 mo	3.7	70.2	Normal	1.6 (24 mo)	Insufficient	Heterozygous mutation in the *RPS19* gene (c.-173G>A)	No	No	-	No	Yes
P9	F	4 yrs	No	2 mo	3	105.5	-	80.9 (2 mo)	N/A	Heterozygous mutation in *RPS19* gene (c.167G>A(p.R56Q))	No	Yes (44 mo)	Yes	No	No

BM - bone marrow; DBA - Diamond-Blackfan anemia; eADA - erythrocyte adenosine deaminase; F - female; FH - family history; Hb - hemoglobin; HbF - fetal hemoglobin; M - male; MCV - mean corpuscular volume; mo - months; N/A - not applicable; P - patient; yrs - years.

Three cases (33%) had a familiar positive history for a hematologic disorder before the Diamond-Blackfan anemia diagnosis, namely anemia, but none was Diamond-Blackfan anemia. Genetic testing was performed in all of the parents *a posteriori.* In patient 8, after the identification of a genetic Diamond-Blackfan anemia mutation in the child, the same mutation was found in the father. The latter had high eADA, but no clinical signs.

The median age at diagnosis was two months. All of the patients were diagnosed before two years of age and 89% before 12 months (except for patient 8). The main symptoms at presentation were pallor (89%), failure to thrive (56%), cardiac murmur (33%), and lethargy (22%). Concerning clinical manifestations, two patients (22%) displayed congenital anomalies. Patient 1 had polydactyly of both hands, and patient 6 had cardiopathy. Two cases had short stature (patients 2 and 7), which can be both constitutional (Diamond-Blackfan anemia-associated) or the consequence of chronic anemia and corticotherapy. Neither other relevant comorbidities nor toxicity due to medication were reported.

As far as the initial laboratory evaluation was concerned, the median hemoglobin at diagnosis was 3.7 g/dL (range of values between values 1.4-8.1 g/dL) associated with a severely low reticulocyte count (< 20,000 cells/µL in 78%). The mean corpuscular volume was high in 89% (except for patient 8). None had leucopenia/neutropenia nor thrombocytopenia at the diagnosis, and the peripheral blood smear did not have any specific findings. In all of the patients evaluated for HbF levels, these were adequate to their age. Only patients 3 and 5 were not evaluated once they had received erythrocyte transfusions prior to their arrival at our center. The eADA activity was performed in five cases (56%) and it was normal. Erythropoietin levels were not tested.

All of the patients had negative viral serologies as well as a negative direct Coombs test. Bone marrow aspirate and biopsy were performed in six cases (67%), and in half of these, there was severe erythroid hypoplasia (the

erythroid precursor cells count was inferior to 5%).

In six cases (67%), including all three who did not perform bone marrow aspirate and biopsy, the diagnosis was confirmed by genetic testing. All of them were heterozygous for the identified mutation, five patients (56%) in the *RPS19* gene, and one (patient 6) in the *RPL5* gene. In the other three patients (33%), no Diamond-Blackfan anemia-related mutation was found and they were not yet tested for other mutations at the time of this study.

Regarding treatment and response, only one patient (patient 8) did not have glucocorticoids once he did not need any more erythroid transfusions two months after the diagnosis. All of the others were transfusion-dependent before corticotherapy was initiated in order to promote adequate growth and development. Erythroid transfusions were calculated for 15 mL/kg. The median age for initiating corticoids was 11 months of age (minimum 3 months, maximum 16 months), and the preferred corticoid was deflazacort, at an equivalent dose to prednisone of 1-2 mg/kg/day.

At the time of our study, among the eight patients who initiated corticotherapy (patient 8 excluded), one (12.5%, patient 4) was responsive, and corticoids were suspended with sustainable remission, five (62.5%, patients 1, 2, 5, 7, 9) were responsive, and continue on corticoids, two (25%, patients 3 and 6) became refractory to corticotherapy and had the treatment discontinued after nine to ten months. The average duration of corticotherapy was 36 months (minimum 7 months, maximum 157 months).

In three patients, corticotherapy was withdrawn. Patient 4 stopped after 21 months of treatment and was considered on remission. Curiously, genetic testing did not confirm the diagnosis yet. The other two patients, 3 and 6, although initially responding, became refractory and consequently remained transfusion-dependent. They required a monthly erythroid transfusion.

The five patients who continued on corticoids had an equivalent dose of prednisone of 1-2 mg/kg/day. The duration of corticotherapy was between seven to 157 months (approximately 13 years) at the time of our study, as shown in Table 2.

Concerning the treatment's side effects, there was evidence of secondary hemosiderosis only in one patient (patient 3) who was under iron chelation treatment with deferasirox. The maximum ferritin level was 2,521 ng/mL, whereas, at the time of the study, it was 1,225 ng/mL. No iron deposits were documented by magnetic resonance imaging at the time. Patient 6 was also under regular monitoring, although without reported hemosiderosis. As stated previously, two cases had short stature. No other complications associated with transfusional support or corticotherapy were founded, namely ophthalmologic, audiologic, cardiologic, orthopedic, hypertensive, infectious, and other endocrinologic complications.

Diamond-Blackfan anemia patients are candidates for hematopoietic stem cell transplantation, although, in our center, there were no transplants performed to date in these patients. Patients 3 and 6, who became refractory to corticotherapy, were evaluated at another hematopoietic stem cell transplantation center and had an identified HLA-matched unrelated donor. Hematopoietic stem cell transplantation had not yet been performed at the time of our study. Furthermore, alternative therapeutic interventions were not applied.

There was remission in two cases (22%), patients 4 and 8. None of the patients had any neoplastic disease. Our oldest patient was 14 years old, and none of the patients died.

Discussion

The purpose of this study was to characterize the Diamond-Blackfan anemia cases followed in a reference unit of pediatric hematology in a Portuguese tertiary level hospital. There is no extensive Portuguese data published on this subject yet, and therefore, this is the first cohort of Diamond-Blackfan anemia patients of a reference pediatric hematology unit in Portugal.

In our study, we assembled nine patients, which is in accordance with the rarity of the disease. The limited number of cases is insufficient for conducting significant statistical analysis from the data collected. Consequently, the female predominance and the reduced congenital abnormalities described were not in agreement with the data revised.[1,3,4,32,33] The latter might be explained by the reduced number of patients, but also by the possible incidence of specific genetic defects within Portuguese ethnic subgroups. Nonetheless, upper extremity anomaly is one of the most frequent in Diamond-Blackfan anemia as well as cardiopathy.[1,8,9]

Concerning the clinical and laboratory data at diagnosis, the median age, main symptoms, and initial complete blood count were in line with the current literature.[1,6]

Only eADA activity was not increased, once more, probably due to the number of patients. Some studies speculate that this difference might be due to genetic or epigenetic mechanisms involving genes for Diamond-Blackfan anemia or for eADA itself.[34]

As far as genetic testing is concerned, mutations in the *RPS19* gene were the most prevalent as expected.[8] In 33% of the patients, no mutations described as

associated with Diamond-Blackfan anemia were found. On the one hand, this fact could be related to the standardized ribosomal protein gene panel used in Diamond-Blackfan anemia patients. It is described in comprehensive reviews that a similar percentage of the cases remain genetically indeterminate.[3,4]

In one case (patient 8), Diamond-Blackfan anemia diagnosis was made in an asymptomatic adult through genetic parenting screening. Genetic screening of the family is of utmost importance, not only for early diagnosis and monitoring of asymptomatic patients but also for genetic counseling regarding a future child or an HLA-related donor in hematopoietic stem cell transplantation. Furthermore, this contributes to expanding the spectrum of knowledge associated with nonclassic Diamond-Blackfan anemia cases. In addition, as this is a monogenic disease, it offers an opportunity for innovative gene therapy applications.[4]

Concerning the treatment and response, the majority of the patients underwent corticotherapy, which is in agreement with the guidelines, with a generally good response.[1,4,24] Preferably, it was initiated at the end of the first year of age, bearing in mind the severe side effects from both glucocorticoids treatment and regular transfusional support.

The rate of remission (22%) and transfusion-dependent patients (22%) was in agreement with other international studies, despite the limited numbers of patients.[24,32] Our study revealed a reduced incidence of treatment side effects and no malignancies related to Diamond-Blackfan anemia. This is explained not only by the aforementioned limitation but also by the remaining short follow-up time of these patients.

In conclusion, we accomplished our aim to characterize a cohort of Portuguese Diamond-Blackfan anemia patients followed at a reference unit of pediatric hematology. In agreement with previous studies, the Portuguese patients presented a broad spectrum of clinical, laboratory, and genetic characteristics and generally good response to corticotherapy.

As commented previously, the prospective registration of Diamond-Blackfan anemia patients in a national database and multicentric studies are essential for better and more extensive knowledge of the disease, especially the particularities of the Portuguese patients. Advanced and extensive genetic testing is necessary to increase the future comprehension of pathophysiology and the correlation between genotype and phenotype. Moreover, efforts should be made to provide the best care to Diamond-Blackfan anemia patients and diminish the burden of the disease, for instance through multidisciplinary and specialized health teams,[1] involving not only physicians such as hematologists, geneticists, and endocrinologists, but also specialty-trained nurses, nutritionists, psychologists, and educational and social workers. Moreover, resources should be provided for offering hematopoietic stem cell transplantation as a treatment, especially as in our case, with 22% of Diamond-Blackfan anemia patients corticosteroid resistant and 56% dependent on corticoids. Hematopoietic stem cell transplantation is crucial mainly in early corticosteroid resistant patients and is highly dependent on transfusional support despite the significant risks in early age.[29] Taking all of this into account, Diamond-Blackfan anemia patients must be followed at a reference center in a tertiary level hospital. Finally, Diamond-Blackfan anemia is a rare disease that carries significant morbidity and mortality if not diagnosed early and treated appropriately. National and international registries, along with more detailed genetic testing, are essential for new insights into the pathophysiology and management of Diamond-Blackfan anemia patients.

WHAT THIS STUDY ADDS

- This study presented the first cohort of Diamond-Blackfan anemia patients of a reference unit of pediatric hematology in Portugal.
- Diamond-Blackfan anemia is a rare congenital disease, and high suspicion is essential for diagnosis in the presence of isolated and severe aregenerative anemia, especially within the first year of life.
- In agreement with current extensive reviews, the Portuguese patients presented a broad spectrum of clinical, laboratory, and genetic characteristics and generally good response to corticotherapy.
- Genetic testing should be offered not only to suspected Diamond-Blackfan anemia patients but also to first-degree relatives, even if asymptomatic, regarding the early diagnosis and adequate management of the disease.
- Prospective registration of Diamond-Blackfan anemia patient national database and multicenter studies are essential to increase knowledge of the disease.

Conflicts of Interest

The authors declare that there were no conflicts of interest in conducting this work.

Funding Sources

There were no external funding sources for the realization of this paper.

Protection of human and animal subjects

The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Confidentiality of data

The authors declare that they have followed the protocols of their work center on the publication of patient data.

Provenance and peer review

Not commissioned; externally peer reviewed

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Anemia de Diamond-Blackfan: Casuística num Hospital de Nível III Português

Introdução: A anemia de Diamond-Blackfan é uma anemia congénita arregenerativa rara e pode estar associada a malformações congénitas. Deve ser considerada quando a evolução natural da doença não é concordante com eritroblastopénia transitória da infância.
Métodos: Estudo retrospetivo e descritivo, incluindo os casos de anemia de Diamond-Blackfan seguidos numa unidade de hematologia pediátrica de um hospital nível III em Portugal, durante 14 anos (2006 a 2019).
Resultados: Identificaram-se nove casos (56% do sexo feminino, 89% caucasianos, 22% com malformações congénitas). A mediana de idade ao diagnóstico foi de 2 meses e o principal sintoma foi palidez cutânea / mucosas (89%), seguido de má progressão ponderal (56%). A hemoglobina mediana de apresentação foi 3,7 g/dL (mínimo e máximo 1,4-8,1 mg/dL) com reticulocitopénia grave associada. Realizada biópsia osteomedular em 67% e destes, metade com hipoplasia acentuada da série eritroide. Em 67% foi confirmado diagnóstico por estudo genético e 56% eram heterozigóticos para mutação no gene *RPS19*. A maioria dos casos era dependente de suporte transfusional até iniciar corticoterapia (89%). Num caso verificou-se hemossiderose secundária. Nenhum foi submetido a transplante de progenitores hematopoiéticos. Houve remissão em 22% e não ocorreram óbitos.
Discussão: A anemia de Diamond-Blackfan é rara, sendo que a elevada suspeição no primeiro ano de vida é fundamental para o diagnóstico. Os registos nacionais e internacionais, assim como testes genéticos mais abrangentes, são cruciais para novo conhecimento sobre a fisiopatologia e abordagem dos doentes com anemia de Diamond-Blackfan.

Palavras-Chave: Anemia de Diamond-Blackfan/diagnóstico; Anemia de Diamond-Blackfan/genética; Anemia de Diamond-Blackfan/tratamento; Criança; Doenças Genéticas Inatas; Portugal