

Diamond–Blackfan anemia

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Abstract

*Diamond-Blackfan anemia (DBA) is characterized by aregenerative anemia with erythroblastopenia. The incidence in France is estimated at 7.3 cases per million live births per year. No ethnic predisposition has been identified and both sexes are equally affected. The anemia is discovered early in life, usually before the age of 2 years. Pallor and dyspnea, especially during feeding or while sucking, are the principal warning signs. Pallor is isolated, without organomegaly, nor signs that might suggest involvement of the other hematopoietic cell lines. DBA is an inherited disease. It was recently demonstrated that, in 25% of the cases, it is linked to a mutation in a gene localized to chromosome 19 at 19q13.3, which codes for a ribosomal protein (RP), RPS19; the role of this protein in erythropoiesis and embryogenesis is not known. The diagnosis can be supported by a notion of a familial history (10-20% of the cases) or associated malformations (more than 40% of the cases). Elevated erythrocyte adenosine deaminase is a frequent but non-specific sign. The two main therapeutic approaches are regular transfusions and long-term administration of corticosteroids, but treatment must be adapted to each case individually. Allogeneic bone-marrow transplantation, the only radical treatment for this disease, is restricted to corticoreistant patients.. *Authors: Prof. G. Tchernia and J. Delaunay (October 2003)*.*

Key words

Diamond–Blackfan anemia, Blackfan–Diamond anemia, erythroblastopenia, inherited anemia, ribosomal protein, corticotherapy, congenital malformations, transfusions, bone-marrow transplant

Name of the disease and synonyms

- Diamond–Blackfan anemia (DBA)
- Inherited erythroblastopenia
- Blackfan–Diamond anemia

Definition/diagnostic criteria

An aregenerative anemia accompanied by erythroblastopenia (less than 5% of nucleated

cells in the bone marrow are erythroblasts); discovery early in life, often before the age of 2 years; a notion of a familial disease: 10–20% of the cases; associated malformations: 40% of

the cases; elevated erythrocyte adenosine deaminase, a frequent but non-specific sign.

Differential diagnosis

A diagnosis of DBA should be accepted conditionally if its onset occurs after the age of 2 years. In this case, the notion of similar cases in the family, elevated erythrocyte adenosine deaminase alone in the patient or apparently healthy family members, potentially associated malformations in the proband should be taken into account as well. The main differential diagnosis is parvovirus B19 erythroblastopenia in its neonatal form, acquired *in utero* during a primary maternal infection. This possibility must be excluded in all cases by a negative polymerase chain reaction (PCR) search for parvovirus B19 DNA in bone-marrow hematopoietic cells.

The diagnosis of Fanconi's anemia can more rarely be considered. It is a congenital medullary aplasia discovered during the first years of life and associated with small stature and a variable setting of malformation(s). Should doubt persist, the search for spontaneous and provoked (by caryolysin or diepoxybutane) *in vitro* chromosome fragility of circulating lymphocytes will allow the distinction to be made. The chromosomal fragility typical of Fanconi's anemia is not found in DBA.

Transitory erythroblastopenia of childhood is an acquired disease, probably of infectious origin, occurring often as limited outbreaks. It occurs later than DBA, most frequently after 2 years of age. It is not associated with malformations; there is no family history of the disease; it resolves spontaneously; no rise of erythrocyte adenosine deaminase is observed.

Autoimmune erythroblastopenia, rare in children, is acquired and most often occurs in a setting of dysimmunity (autoimmune hemolytic anemia, in particular).

Congenital dyserythropoieses are inherited aregenerative anemias. However, analysis of the myelogram detects no quantitative deficit of the erythroid cell line but rather qualitative anomalies of the maturation of this cell line.

Etiology

DBA is an inherited disease. It was recently shown that, in 25% of the cases, it was linked to a mutation in a gene situated on chromosome 19 at 19q13.3 that encodes a ribosomal protein (RP), RPS19. In all affected individuals of a given family, the same mutation is found when it exists in one member. A mutation can also be found in apparently healthy individuals in a family with one afflicted member carrying the mutation: the expression of the mutation can thus be limited to biological signs, such as macrocytosis and/or elevated erythrocyte

adenosine deaminase. Several European and American laboratories are able to identify mutations in the *RPS19* gene by sequencing.

Clinical description and biological methods of diagnosis

The anemia is rarely discovered at birth or the first days of life; it will progressively become evident over several weeks: fewer than 10% of the cases are identified at birth but 90% are by the age of 3 months; thus, fetal erythropoiesis is most often preserved and erythroblastopenia probably does not exist *in utero*. Pallor and dyspnea, most evident during feeding or while sucking, and hypotonia are the main warning signs, frequently escaping recognition because of their insidious onset. The pallor is isolated, without organomegaly or signs suggestive of the involvement of the other hematopoietic cell lines (hemorrhagic signs, infections).

The diagnosis relies on a group of clinical and biological signs. Although it is often supported by the two notions described below, their absence does not allow the diagnosis to be excluded.

A notion of a familial history of DBA

In 20–30% of the cases, one of the two parents is affected. The disease, transmitted by dominant inheritance, can affect one or several members of a kindred. More rarely, the consanguinity of the parents is suggestive of recessive inheritance. In families that appear to have only one affected member, it is sometimes possible to find a member who experienced moderate or transitory anemia during childhood or pregnancy and/or biological abnormalities without clinical repercussions: macrocytosis without an etiological deficiency or toxicity, moderately elevated hemoglobin F, elevated erythrocyte adenosine deaminase.

A notion of associated malformations

Very diverse in their localization and their severity, these malformations are present in more than 40% of the patients. They most often concern the face (palatine cleft, ogival palate, pseudo-Turnerian (webbed) appearance of the neck, microphthalmia), limbs (low-seated thumb, supernumerary digits, bifide cleft, other malformations of the radial axis, syndactyly), the urogenital tract, heart and/or spinal cord. Small size at birth, the first sign of height–weight growth retardation, is part and parcel of the context of malformation. It will often be further aggravated by long-term corticotherapy. Complementary examinations often attest to severe anemia, with a low or even non-existent reticulocyte count. Macrocytosis is usually present as is an elevated amount of hemoglobin F, which should be interpreted as a function of age. The elevated erythrocyte adenosine

deaminase level is a strong argument, which is often lacking at the time of the initial evaluation because of the small number of laboratories able to perform this dosage, the need to make this determination long after a transfusion and the usual emergency of the first transfusion into a severely anemic newborn which cannot be deferred. The myelogram is an essential element of the diagnosis: less than 5% if the nucleated medullary cells are erythroblasts, which can be totally absent on several bone-marrow smears. The erythroblasts present are often large proerythroblasts without maturation beyond this stage (however, DBA patients with erythroblastopenia proven on several successive myelograms can have periods during which the marrow is transiently enriched with erythroblasts, but the dependency on transfusions persists).

Incidence

The incidence of DBA was estimated to be 7.3 cases/million live births per year. No seasonal variation as a function of the date of conception has been observed; the incidence seems to be stable over time. No ethnic predisposition has been identified and both sexes are equally affected. This incidence is close to that found in other European countries (5–10 cases/million live births per year).

Genetic counseling and prenatal diagnosis

In the setting where a single genetic mutation can give rise to phenotypes of widely varying severity, genetic counseling remains far from perfect, even for a known mutation. A DBA patient has about a 10% risk of having an affected child; the risk is much higher if a first child is affected. The patient cannot be assured of his offspring any more than a normal couple that has had an affected child. The prenatal diagnosis can only be offered within the limits of our present knowledge, even for families whose mutation has been identified. On the other hand, should a bone-marrow graft be indicated and if the recipient is a carrier of an *RPS19* mutation, it seems reasonable to exclude an apparently healthy donor with the same mutation.

Management including treatments

The two essential therapeutic arms are transfusions and corticotherapy. It is highly unusual that a child with DBA does not receive one or two transfusions when the anemia is first diagnosed and/or during the first search for its cause. The natural history of the disease then becomes that of a relapsing anemia, rendering the child dependent on regular transfusions. However, 50–60% of the patients respond to corticosteroids and can become transfusion-independent under this long-term therapy.

The destiny of corticosensitive patients will depend on:

- the required dose: it is estimated that, above 0.5 mg/kg/d of prednisone, the treatment should be discontinued in favor of regular transfusions because of the side effects of prolonged corticotherapy;
- the stability of the response to treatment: for many patients, the minimal dose required will decline over the years to reach a very low level (around 5–20 mg/d for an adult), and a complete withdrawal can sometimes be possible. For others, in contrast, the threshold will rise and, sometimes, corticoresistance may develop. Because of the impact of long-term corticotherapy on growth, some teams, when confronted with severe growth retardation, recommend temporarily discontinuing steroids and administering regular transfusions to allow growth to 'catch-up'.

The future of corticoresistant patients will depend on:

- the iatrogenic complications associated with repeated transfusions: iron overload is unavoidable and should be treated with regular chelation with deferoxamine. The transmission via transfusion of infectious agents is always possible. Hepatitis C can aggravate the hepatic consequences of iron overload. All these patients, whether or not they are transfusion dependent, should be vaccinated against hepatitis B.
- the permanence of transfusion dependency: certain patients can secondarily become corticosensitive (or even independent of all treatment). This possibility implies that all major therapeutic decisions, especially bone-marrow transplantation, be preceded by a new attempt to administer corticosteroids.

Initial corticosteroid therapy

Steroids are generally prescribed as soon as the diagnosis is made at a dose of 2 mg/kg/d taken in one or two doses of prednisone. Four types of responses are distinguished:

- reticulocyte response and transfusion independence,
- reticulocyte response and prolonged intervals between transfusions,
- an isolated reticulocyte response with no impact on transfusion requirements,
- no response.

For patients with type 3 or 4 responses, corticotherapy should be rapidly and completely withdrawn, then attempted again every 2–3 years for short periods to assess the development or not of a reticulocyte response within 15 days. For patients with a type 2 response, an equilibrium must be found between the prednisone dose and the interval between transfusions to avoid solutions generating iatrogenic side effects of the two therapies. For patients with a type 1 response, the steroid dose should be lowered to empirically search for the minimal effective dose, by monitoring the hemoglobin level and the number of reticulocytes. Should this dose be higher than or equal to 0.5 mg/kg/d, the patient should be managed like those with type 3 and 4 responses.

Other treatments

The only radical treatment of DBA is allogeneic bone-marrow transplantation. It can only be offered to corticoreistant, regularly transfused subjects. It seems reasonable, in most cases, to consider only haplotype-identical brothers and sisters as donors and to exclude unrelated donors. The age at which such a graft is indicated remains an unresolved problem, in part because of the possibility of spontaneous remission or secondary development of corticosenitivity and, in part, because of the better prognosis of early grafts in children still relatively rarely transfused. However, it is a therapy that carries life-threatening risk for a non-malignant disease, whose prognosis might be modified in the coming decade by advances made in our understanding of its pathophysiology. This decision must be made case-by-case. Certain treatments of DBA tested in clinical trials have given promising results in several patients: interleukin 3 induced long-term treatment independence in approximately 10% of the patients. This drug is not commercially available at present. Very high doses of corticosteroids proposed by two groups rarely seemed to be effective and are surely dangerous. The results obtained with immunomodulating agents, such as cyclosporine, anti-lymphocyte antiserum or intravenous immunoglobulins, are inconsistent and, for many published cases, it is difficult *a posteriori* to know if the treated patients truly had DBA. Finally, metoclopramide would seem to have some efficacy against DBA. A precise evaluation of this possibility will be undertaken in the near future.

Unresolved questions

The role of ribosomal protein S19 in erythropoiesis and embryogenesis is unknown. The factors that render a single mutation able to provoke erythroblastopenia with different

therapeutic responses, associated or not with malformations, or to have only one biological expression are still unelucidated. The patients are all heterozygotes and a modulation of the disease by the degree of haploinsufficiency has been hypothesized. DBA is thought to be a polygenic disease: in patients without mutations in the *RPS19* gene, other genes are probably responsible. Recently, a second genetic locus on chromosome 8 was described. For families with several affected members but with no involvement of the *RPS19* gene, study of the genetic links between the disease and this locus, located on 8p, recently led to the suggestion that a third locus might be involved.

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