Prolonged survival of Diamond-Blackfan anemia and RPS19 mutation: an observation in Togo.

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Abstract

Objective

Drawing up a balance sheet of 16 years follow-up of the sole case of Diamond-Blackfan anemia diagnosed in Togo with arguments of molecular biology.

Observation

T.S a boy, born on 5th september 2006 has been followed up since he was three months, for Diamond-Blackfan anemia (DBA) in whom there has been found the mutation of ribosomial protein RPS19 in july 2010. It was the first observation in Subsaharian Africa. The treatment by transfusions from december 2006 to december 2022 has been associated with iron chelation through deferoxamin and promptly with corticotherapy at the dosage of 2mg/kg/day. The corticotherapy has been reduced as a consequence of corticoresistance from the fourth week, then definitely interrupted after four months. The evolution is marked by a clinical improvement with a staturo-balanced curve, and during the last control of 28th december 2022, the child was 53 kg heavy and 160 cm tall. The monthly physical tests did not reveal any signs of eventual overloading and the echocardiography of 26th december 2022 was normal. On the biological plan, the rate of the haemoglobin had been stable around 50g/l as a resultant of a transfusion each 4 to 6 weeks of red blood cell pellet. The chelation of iron had been done through deferoxamin with a monthly control of serum ferritin. That serum ferritin was 738,39ng/mg at diagnosis before the beginning of transfusions and during the follow-up, we noticed an average of 2977,3ng/ml (range 1817,1ng/ml and 4448,5ng/ml)

Conclusion

Thanks to the regular transfusions derived from the survey of the parameters of iron and the use of deferoxamin, we have succeded in keeping alive during sixteen years a patient who caught a disease whose evolution is unpredictable.

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Introduction

The Diamond-Blackfan anemia (DBA) is the only congenital erythroblastosis known [1,2]. It is a severe erythroblastonis with less than 5% precursors of erythroids in the normocellular marrow [3]. The DBA manifests very early, often at the age of 2, by a decompensated anemic syndrom, often associated to lateness of growth and isolated congenital malformations or associated between them [4]. In Europe, its incidence is estimated between 5 to 7 cases/1000000 of living births [5,6]. The diagnosis of DBA is based on diagnosed criteria or help the diagnosis established at a consensus conference [6,7].

On the therapeutic plan, allogenic bone marrow transplant is the only healing treatment. However, the transfusional mediums with chelation of iron associated with corticotherapy can improve the pronosis. A first case of DBA diagnosed with arguments of molecular biology had been reported in Togo. It was the first observation in Sub-Saharan Africa [8]. The aim of this work is to draw up a balance sheet after 13 years follow up of this sole case.

Observation

T.S a thirteen years old boy (born on 5th september 2006) is observed from the age of 3 months for anaemia of Diamond-Blackfan anemia with the presence of ribosomial protein RPS19 mutation at molecular biology diagnosed in 2010. The child had been admitted to consultation in january 2007 for a non generative anemia of 20 grammes per liter (g/l).The parents of this child were not blood relatives. The mother has not had miscarriages or repeated abortions. The birth took place through the vagina without any bleeding or other complications in a public hospital. The pregnancy had no problem and developed into maturity. At birth the baby was 3375 grammes(g) and 50 centimeters (cm) tall. There were neither respiratory nor neonatal jaundice problems. He was the second born and nourished exclusively with breast milk. He underwent a surgical operation for polydactyl with supernumerary right thumb at the age of one month. One could note a deformation in swan neck of the right thumb after removal of one supernumerary thumb. There was also a depressed anemic syndrom without any cyanosis, jaundice, peripheral adenopathy or bleeding syndrom. The blood cell count, born marrow count and molecular biology realised in France had permitted to make the diagnosis with certainty.

On the therapeutical plan, the treatment consisted first of all in providing a transfusional device with chelation of iron by deferoxamin from 2007 to today. Furthermore it had been associated with corticotherapy at the initial dosage of 2mg/kg/day. The corticotherapy had been reduced progressively owing to the realisation of corticoresistance from the fourth week and therefore stopped definetely at the end of four months. The child receive in average one transfusion of red blood cell pellet every 4 to 6 weeks. The evolution is characterized by a clinical improvement with a staturo-balance curve and at the last control of 28th decmber 2022, the child was 53 kg heavy and 160 cm tall. The monthly, physical examinations did not reveal any skin lumps or organomegaly in relation with any eventual overdosage of iron. On the biological plan, the evolution is characterized by a rate of haemoglobin, stable around 50g/l for a monthly transfusion of about 250 mililiters (ml) of red blood cell pellet every 4 to 6 weeks. The last transfusion had been done on 28th december 2022. The chelation of iron had been done by deferoxamin with a monthly control of ferritnemy. That ferritnemy was of 738,39 nanogrammes per milliliter (ng/ml) during the diagnosis before the beginning of the transfusions and during the follow-up, we noticed an everage ferritnemy of 2977,3 ng/ml(ange 1817,1 ng/ml to 4448,5ng/ml) and that of 26th november 2022 at 3883ng/ml. During all the duration of the follow-up the serologies of HIV, of hepatitis B and C, of syphilis were negative. The abdominal scans, Doppler radars revealed no irregularity. The Echocardiography of 26th december is normal and doesn't show any sign of overdosage of iron.

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Discussion

Diamond Blackfan anemia (DBA) is an autosomal dominant ribosomopathy caused predominantly by pathogenic germline variants in ribosomal protein genes. Despite a better understanding of the genotype of DBA, the biological mechanism resulting in the clinical phenotype remains poorly understood, and wide heterogeneity can be seen even within a single family [9]. There exist essentially three types of classical treatments. Corticotherapy, periodical blood transfusions and the transplant of the marrow which remains the main option of healing [5,10]. Other teams have obtained the remission of patients by using either cyclosporin [11] or metoclopramid [12]. In the contest of lack of appropriate technical convenience (unavailability of immunosuppressors) and the social security cover (no security cover or universal health insurance), the latter had been taken care of thanks to red cell transfusions every 4 to 6 weeks. This helped him to have a normal staturo-ponderal growth. Jahan D et al had the same therapeutic attitude in the absence of financial means for performing a hematopoietic stem cell transplant [13]. This therapeutic option that is recommanded by international option consensus permits a normal growth during the first year of life and thus allowing to limit the delay of growth of patients [5].

We have been able to keep our patient alive for 16 years thanks to this transfusional program alone, accompanied by iron chelation. With this therapeutic option, we fear the arrival of transmissible infection through transfusion. This is not the case because during the last control of 26th december 2022, the serologies of hepatitis virus B and C and the serology of HIV were negative, the echocardiography of the same date were normal and contained no overdose of iron. The only complication observed with our patient is post transfusional hemochromatosis despite the regular recurse to iron chelation. In fact, during the transfusions, our patient received directly in his blood red corpuscles filled with haemoglobin which liberate the iron when the corpuscles will be degraded. The iron was not eliminated and was accumulated in his organism. El-Beshlawi A[11] and Da-Costa L [14] have also observed the appearance of hemochromatosis with some patients whom they submitted to repeated red blood cell transfusions.

After the confirmation of the diagnosis of DBA with our patient we tried a corticotherapy in order to maintain an efficace erythropoiesis at the level of the latter in order to reduce his transfusional needs. Globally, about half of the patients responded efficacely to this treatment, leading too much often to its interruption to avoid unwilling side effects of corticotherapy for long. We have also realised a corticoresistance which led us to stop it progressively. Other, researchers also noted a corticoresistance with certain patients [11,15]. We can discuss the place of an intermittent corticotherapy and the allogenic transplant which is unfortunately unavailable in Togo.

Conclusion

Like almost all the scarce diseases, the availability of means of covering varies in relation to the level of development of the country. Thanks to the regular transfusion coming from the survey of the parameters of iron metabolism and the use of deferoxamin, we have succeeded in keeping in life a patient who contracted a disease whose evolution is unpredictable, for sixteen years.

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