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(CASE REPORT)

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Beta-thalassaemia: Four cases at the mother and child centre of the Chantal Biya Foundation

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Abstract

Beta thalassaemia is one of the most common autosomal recessive diseases in the world. We present the clinical cases of four patients presenting with beta thalassaemia, of which only two cases confirmed. The aim of this case reports is to draw the clinician's attention to the diagnosis of beta thalassaemia and to highlight the importance of a good interpretation of a haemoglobin electrophoresis and to clarify the difficulties in the management of beta thalassaemia in our context.

Keywords: Beta-thalassaemia; Diagnosis; Management; Yaoundé; Cameroun

1. Introduction

Thalassaemia's are a group of inherited diseases with autosomal recessive transmission, characterised by a reduction in the production of normal haemoglobin [1]. Thalassaemia's are cause by localised mutations or deletions in the gene coding for one of the four haemoglobin protein chains: beta-globin on the short arm of chromosome 11 for beta-thalassaemia and alpha-globin on the short arm of chromosome 16 for alpha-thalassaemia. In beta-thalassaemia, Foetal Haemoglobin (HbF), Haemoglobin A2 (HbA2) that are compatible with life [2, 3], compensates for the lack of normal haemoglobin A1. The different combinations of these HbA2, HbF and HbA1 fractions give rise to the different phenotypes of beta-thalassaemia [4].Beta-thalassaemia is widespread throughout the world, with around 80 to 90 million people being healthy carriers and an estimated global incidence of symptomatic forms of the disease of 1/100,000 births per year [5,6]. Although it is one of the most common autosomal recessive diseases in the world [7], clinicians know little about the disease, which leads to delays in diagnosis and management, resulting in high morbidity and mortality. In these medical observations, we report cases of beta-thalassaemia discovered by chance and discuss the clinical and biochemical aspects of this condition.

2. Cases

2.1. Case No 1

The patient was a 26-month-old female infant brought to the clinic by her parents with fever, cough and rhinorrhoea that had been present for 48 hours. Her history included a blood transfusion at the age of 18 months, and a haemoglobin electrophoresis performed 5 weeks after the blood transfusion, which was AA without detailed fractions. The haemoglobin electrophoresis of the parents and brothers was unknown, and there was a notion of consanguinity between the parents. She was the third of three siblings. The first died at the age of four with progressive abdominal distension, anaemia and repeated transfusions (on average once every 4 weeks) from the age of 6 months; the second

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presented with progressive abdominal distension and had received repeated blood transfusions (on average once every 4 to 6 weeks) since the age of 6 months (clinical case No 2).

Clinically, she had severe stunting with a height-for-age ratio of less than -3 Z score, delayed walking and anaemia without jaundice. She also presented with a left pulmonary condensation syndrome, hepatomegaly and Hackett 4 splenomegaly. The diagnosis was left-sided pneumonia with a probable background of haemoglobinopathy.

His biology showed (table No 1): A severe hypochromic microcytic anaemia of 5.2 g/dl, hyperleukocytosis of 23600/mm3 predominantly neutrophilic and normal platelets of 186000/mm3. A haemoglobin electrophoresis profile with HbA reduced to 18.4%, HbF elevated to 77.4% and HbA2 elevated to 4.2%; Ferritinemia was elevated to 502.06 ng/ml; Blood smear showed anisopoikilocytosis and the presence of schizocytes. HIV serology was negative.

The diagnosis of acute community-acquired pneumonia due to beta-thalassaemia intermedia was accepted. Treatment consisted of transfusion of packed red blood cells, administration of antibiotics for 10 days, folic acid supplementation and hydration. The diagnosis was announce and the patient was counselled on the need for follow-up. The patient was discharge and further biological and morphological tests were requested, but unfortunately, she was lost to follow-up.

Table 1 Results of additional examinations Case No 1

Additional examinations	**Results**
Full blood count	Haemoglobin level =5.2 g/dl, mean corpuscular volume (MCV = 59 fl), mean corpuscular haemoglobin content (MCHC) = 23 pg White blood cells = 23600/mm3 (neutrophils 14500/mm3, lymphocytes 6500/mm3, monocytes 2600/mm3) Platelets = 186000/mm3
Electrophoresis of haemoglobin	HbA = 18.4% (for a normal range of 96.8 to 99%) HbF = 77.4% (for a normal of less than 0.5%) HbA2 = 4.2% (for a normal range of 2.2 to 3.2%).
Ferritinemia	502.06 ng/ml (for a normal range of 50 to 180 ng/ml)
Blood smear	Anisopoikilocytosis, polychromatophilia, presence of schizocytes, no platelet or leukocyte abnormalities observed.
HIV serology	Negative

2.2. Case No 2

The patient was a 4-year-old male child. He was brought in with his sister (medical observation No. 1) for severe recurrent anaemia and polytransfusion since the age of 6 months, with an average of one transfusion every 4 to 6 weeks. He also had progressive abdominal distension.

Clinically, he had severe stunting with a height for age of less than -3 Z scores, the typical chipmunk facies with frontal bossing, depression of the bridge of the nose and protruding maxillae. He also had an anaemic syndrome without jaundice, hepatomegaly and splenomegaly Hackett 5.

His biology showed (table No 2): Full blood count: severe anaemia at 5.8g/dl microcytic hypochromia, moderate thrombocytopenia with 72,000 platelets/mm^3 and hyperleukocytosis at 20,200/mm^3 predominantly lymphocytic; blood smear: anisopoikilocytosis and schizocytes. Ferritinemia was very high at 2865.37 ng/ml; transaminases were slightly elevated.

Haemoglobin electrophoresis had not been performed because of a recent blood transfusion.

Based on the family history, clinical presentation and laboratory results, the diagnosis of beta thalassaemia major was accepted. Treatment consisted of a transfusion of packed red blood cells, a prescription for an oral iron chelator and folic acid supplementation. The diagnosis was announced and the parent was counselled on monitoring the disease, but unfortunately, the patient was lost to follow-up.

Table 2 Results of additional examinations case No 2

Additional examinations	Results
Full blood count	Haemoglobin = 5.8g/dl, MCV = 58 fl, MCHC = 19 pg, White blood cells = 20200/mm3 (neutrophils 4600/mm3, lymphocytes 14900/mm3, monocytes 200/mm3) Platelets = 72000/mm3
Blood smear	Anisopoikilocytosis, polychromatophilia, presence of schizocytes, no platelet or leukocyte abnormalities observed.
Ferritinemia	2865.37 ng/ml (for a normal range of 50 to 180 ng/ml)
Aspartate amino transferase	85 IU/L (for a normal range of 8 to 40 IU/L)
Alanine amino transferase	47 IU/L (for a normal range of 5 to 40 IU/L)

2.3. Case No 3

The patient was an 8-year-old male child referred for jaundice and mucocutaneous pallor, which had been present since the age of four. He had a history of 02 hospitalisations for pneumonia, the last of which was 03 weeks ago. He had undergone a blood transfusion 1 year earlier, and his haemoglobin electrophoresis was unknown, as were those of his parents and siblings. Consanguinity was not found between the parents. He was the fourth of seven siblings; the other siblings were in apparently good health.

Clinically, he had severe stunting with a height for age below the third percentile, and had a dysmorphic faces with macro crania and a depressed nasal bridge. He also had an anaemic syndrome with icterus of the sclera, moderate respiratory distress, Hackett 3 splenomegaly and hepatomegaly.

His biology showed (see Table 3): On full blood count severe anaemia at 6.8g/dl, microcytic hypochromic, platelets and white blood cells normal; blood smear showed anisopoikilocytosis, hypochromia and polychromatophilia; Haemoglobin electrophoresis profile with HbA lowered to 40.8%, HbF elevated to 56% and Hb A2 at 3.2% (upper normal value). Ferritinemia was elevated to 341.7 ng/ml.

Given this clinical and Para clinical picture, we diagnosed acute haemolysis of infectious origin in beta-thalassaemia intermedia. He received a transfusion of packed red blood cells, hyper-hydration and folic acid supplementation. He was diagnosed and counselled on the need for follow-up. He was discharged and given a follow-up appointment.

Table 3 Results of additional examinations Case No 3

Additional examinations	Results
Full blood count	Haemoglobin = 6.8g/dl, MCV = 58 fl, MCHC = 23 pg White blood cells = 5400/mm^3 Platelets = 448000/mm^3
Blood smear	Anisopoikilocytosis, hypochromia and polychromatophilia
Haemoglobin electrophoresis	HbA= 40.8% / HbF= 56% / HbA2=3.2%
Ferritinemia	341.7 ng/ml

2.4. Case No 4

The patient was a 7-year-old male child who had been referred to us for recurrent haemolytic anaemia and polytransfusion, i.e. an average of 1 transfusion every 6 to 8 weeks, the last one having been given 03 weeks previously. Progressive abdominal distension since the age of 3 months. His haemoglobin electrophoresis, as well as that of his

parents, and siblings were unknown; consanguinity had not been found between the parents; he was the fourth of six siblings, the other members of which were in apparently good health.

Clinically, he had a dysmorphic faces (see Figure 1) with frontal bossing, protruding zygomatic bones, depressed nasal bridge and maxillary hypertrophy exposing the teeth of the upper jaw. He had an anaemic syndrome with jaundice, Hackett 3 splenomegaly and hepatomegaly.

His biology showed (see Table 4): On full blood count moderate anaemia at 9.4g/dl, microcytic hypochromic, normal platelets and white blood cells; On blood smear anisopoikilocytosis, presence of target red blood cells, no platelet or leucocyte abnormalities observed. Ferritinemia was elevated, blood urea and creatinine were normal. Transaminases were slightly elevated.

Table 4 Results of additional examinations Case No 4

Additional examinations	**Results**
Blood count	Haemoglobin =9.4g/dl, -VGM=52 fl, TCMH=20 pg, White blood cells= 8000/mm3/platelets= 358000/mm3
Blood smear	Anisopoikilocytosis, polychromatophilia target red blood cells, no platelet or leukocyte abnormalities observed
Ferritinemia	6062ng/ml
Blood urea	0.26g/l
Blood creatinine	2.4mg/l
Aspartate amino transferase	130 IU/L
Alanine amino transferase	153 IU/L

Figure 1 Clinical case No 4

3. Discussion

Dr Cooley first described beta-thalassaemia, originally known as Cooley's anaemia, in Detroit in 1925 as an inherited blood disorder [8]. It is an autosomal recessive haemoglobinopathy, characterised by a deficiency in the synthesis of β chains of globin. It is widespread throughout the world, affecting both men and women [1]. Its prevalence varies widely around the world, and is particularly high in countries around the Mediterranean, the West Indies, and the Middle East, South and East Asia and certain regions of Africa [8]. In Cameroon, Nsangou I *et al*. in 2012 showed that the beta-thalassaemia trait was more frequent at 28.05% than that of sickle cell disease, which was 20.73% [4, 9]. However, clinical diagnosis is difficult because of the variability of the clinical presentation due to the diversity of mutations responsible for the haemoglobin abnormalities encountered in beta-thalassaemia. There are more than 300 types of mutation, with point mutations by far the most common [10, 11]. There are three main forms of beta-thalassaemia:

beta-thalassaemia major known as "Cooley anaemia" or "Mediterranean anaemia" which are homozygous or heterozygous composites with the β+/ β+ or β+/β0 or β0/β0 genes ; beta-thalassaemia intermedia which are predominantly heterozygous or homozygous composites with β++/ β+ or β++/ β0 genes, and β-thalassaemia minor also known as "β-thalassaemic trait", "β-thalassaemic carrier" or "heterozygous β-thalassaemia" which are predominantly heterozygous with β++/ βA or β+/ βA or β0/BA genes [6, 7].

3.1. Clinical diagnosis

The diagnosis of beta-thalassaemia is made on clinical grounds or at a pre-symptomatic stage as part of a family assessment or, more often, at birth during the sickle cell screening program [1].

Patients with severe forms of thalassaemia have heterozygous parents who generally come from an ethnic or family group with a high incidence of thalassaemia. Consanguinity therefore plays an important role in the occurrence of familial forms, with variable genotypes, as shown by our clinical cases 1 and 2, where three cases were found, two of them alive and the older brother probably dead from beta-thalassaemia major. Other authors, notably Barouni M *et al,* Maaloul I *et al*, Zahir H *et al*, Souidi H *et al*, have found in their studies a family history of consanguinity in 92.95%, 65.5%, 25% and 17% respectively [12, 13, 14, 15]. Barouni M *et al* also found in their study that 37.1% of thalassaemia patients had at least one brother or sister affected by the same disease [12].

The clinical presentation of beta-thalassaemia varies according to the form. The beta thalassaemia trait has no significant clinical manifestations. Beta-thalassaemia major, which is the most severe form of beta-thalassaemia, is marked by severe anaemia appearing from the 1st year of life, sometimes jaundice, and ineffective erythropoiesis. In the absence of early diagnosis, the body attempts to correct the anaemia and there will be progressive distension of the abdomen due to hepatomegaly and splenomegaly, severe growth retardation of height and weight, skeletal deformities associated with bone marrow expansion, giving a particular faces known as thalassaemic or chipmunk faces with frontal bossing, depression of the nasal bridge, maxillary hypertrophy which tends to expose the teeth of the upper jaw. In this form, survival is generally only possible with regular blood transfusions to correct the anaemia and reduce ineffective erythropoiesis. In the absence of treatment, these children die from the consequences of anaemia [1, 6, 16]. In our study, the clinical manifestations of clinical cases No. 2 and No. 4 began early; they presented with marked deformities and required frequent blood transfusions, which is why we diagnosed them with Cooley's disease.

The clinical manifestations of beta-thalassaemia intermedia occur much later. In the most severe cases, patients may present with failure to thrive and developmental delay between the ages of 2 and 6. In contrast, some patients are asymptomatic and present only mild anaemia in adulthood. In these cases, the anaemia is less severe clinically and may be associated with splenomegaly, hepatomegaly, cardiomegaly and the presence of lumps indicating extramedullary haematopoiesis. Regular transfusions are not necessary for patient survival: this is referred to as non-transfusion-dependent thalassaemia [1, 5, 16]. We noted that our clinical cases 1 and 3 classified as having the intermediate form had a late onset of symptoms and blood transfusions were occasional. In our clinical case No 1, the nutritional deficiencies common in children under 05 years of age in our environment would have favoured the onset of pneumonia and aggravated its clinical presentation. In addition, none of our patients presented with the pain syndrome seen in sickle cell disease, which could have been the cause of the delay in diagnosis observed, since in our context the association of the pain syndrome with recurrent anaemia is the main indication for haemoglobin electrophoresis, which could have revealed these haemoglobin abnormalities earlier. In their 2012 study, Nsangou I et al. in Cameroon also found that all beta-thalassaemia children who did not have the sickle cell trait did not present with sickle cell major pain syndrome [4].

3.2. Biological diagnosis

The full blood count is an important diagnostic test. It is used to assess and characterise the anaemia, the severity of which depends on the form of thalassaemia. In β-thalassaemia minor, the mean haemoglobin level is between 10 and 14 g/dl, associated with a MCHC of between 28 and 32 pg, and a MCV of between 60 and 80 fl. Thalassaemia intermedia is characterised by a haemoglobin level of between 6 and 10 g/dl, a MCV of between 50 and 70 fl and a MCHC of between 22 and 28 pg. Beta-thalassaemia major is characterised by a haemoglobin level of <6 g/dl, a MCV of between 50 and 60 fl and a MCHC of between 16 and 22 pg [16]. This hypochromic microcytic anaemia was found in all our clinical cases to varying degrees.

The blood smear is also an orientation test, showing in patients with minor forms, very moderate polychromatophilia, the presence of target cells, anisocytosis and poikilocytosis are absent. In intermediate forms, anisocytosis, poikilocytosis and polychromatophilia are moderate, and target cells are present. In major forms, anisocytosis, poikilocytosis and polychromatophilia are marked and target cells are present [16]. These abnormalities were found in

all four of our patients, who all had anisopoikilocytosis and polychromatophilia, and clinical case No 4 also had target red blood cells.

Haemoglobin electrophoresis is the golden standard for making the diagnosis of beta-thalassaemia from the age of 2 to 3 months. It analyses the values of the different haemoglobin fractions. In minor beta-thalassaemia, HbA is between 90 and 95%, HbA2 between 4-7% and HbF between 1-5%. In intermediate beta-thalassaemia, HbA is between 30-50%, HbA2 between 0-5% and HbF between 50-70%. In beta-thalassaemia major, HbA is absent, HbA2 between zero and 5% and HbF between 95 and 100% [16]. In our two patients with beta-thalassaemia major, haemoglobin electrophoresis could not be performed because of repeated blood transfusions of less than 3 months. Trawinski E et al in 2017 in France also based their diagnosis of beta-thalassaemia major on the presence of a beta-thalassaemic trait in the parents associated with repeated blood transfusions in the child [17]. Our clinical case No 1 reported a haemoglobin HbAA electrophoresis, which is a frequent finding in our setting, showing a misinterpretation of haemoglobin electrophoresis results because the disease is less known by doctors. Nsangou I *et al* also found in their study that 33.08% of subjects whose haemoglobin electrophoresis results were reported as HbAA were in fact beta-thalassaemic [9]. Correct interpretation of haemoglobin electrophoresis would therefore enable an early diagnosis of beta-thalassaemia and better management.

The vast majority of beta-thalassaemia's are due to point mutations, microdeletions or nucleotide insertions that extend throughout the β gene [15]. Point mutations responsible for the majority of haemoglobin variants and β -thalassaemia are classically identified by sequencing of the β globin gene [18]. The most frequent beta-thalassaemic deletions are identified by gap-PCR or reverse dot-blot [19]. Semi-quantitative PCR and MLPA (multiplex ligation probe amplification) are now increasingly used to screen for rare or yet undescribed deletions [19]. Molecular characterisation is useful or even necessary for genetic counselling of couples at risk and to confirm or refute a clinically suspected diagnosis [15]. We were unable to perform this molecular analysis on our four patients because it was not available.

Hyperferritinaemia is common in patients with beta-thalassaemia major and intermediate. It is secondary to the disease because of dyserythropoiesis, with destruction of red blood cells and accumulation of iron. It is more marked in patients with beta-thalassaemia major who are dependent on regular blood transfusions, which increase the risk of martial overload. Iron overload and its complications represent the main complication of the disease. The life expectancy of transfusion-dependent thalassaemia patients has improved over the last 20 years thanks to management that combines blood transfusions, monitoring of iron overload and the introduction of iron chelators [1, 5, 6]. All four of our patients had elevated ferritinemia, and two of them had ferritin values above 1000 ng/ml, indicating the need for iron chelation therapy, but this treatment was not available.

4. Conclusion

These cases illustrate the under-diagnosis of beta-thalassaemia in our context. Diagnosis is based on history taking, clinical and biological data. Molecular biology in the neonatal period, which confirms the diagnosis by showing abnormalities in the affected chromosomes, is not always available. Proper interpretation of haemoglobin electrophoresis from the age of 2 to 3 months before the first blood transfusion is necessary for early diagnosis.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

Statement of informed consent

The authors certify that they have obtained all appropriate informed consent forms from the patients parents'. In the form, the parents have given their consent for clinical information and imaged to be reported in the journal. Efforts have been made to conceal their children's identity, but anonymity cannot be guaranteed.

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