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Case Study

A Morbid Complex Consisting of Polyglobulia, Congenital Heart Disease, Staturo-ponderal and Puberty Delay: About a Case at the Kipe Medical and Health Counseling Center

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Abstract

The identification of the etiology of polycythemia sometimes poses clinician difficulties leading to a diagnostic and therapeutic delay.

We report a clinical case to illustrate the route that led to the late identification of the etiology of polycythemia. This is a young girl born on 16/11/199 seen in consultation on 16/02/2017 for exertional dyspnoea, palpitations and failure to thrive. She had been seen in consultation 9 years earlier by a pediatrician who had suspected congenital heart disease in view of labial cyanosis and digital clubbing. Examinations made on that date were normal. Due to the strong suspicion of heart disease, two other echocardiograms were performed in 2009, the reports of which were also normal. The patient is lost sight of for many years. She was seen in consultation in 2017, hospitalized for dyspnea and 82% desaturation in ambient air. The blood count revealed polycythemia (Hb = 20 g/dl, Hematocrit at 69%). Again, the echocardiography was normal. It was at this stage that she was consulted by a pediatric hematologist. Her clinical examination revealed a frank digital clubbing, failure to thrive and a harsh systolic pulmonary murmur of 4/6th with a saturation of 75% in ambient air. The hypothesis of polycythemia Vera was raised, but quickly ruled out. Another echocardiography performed in March 2017 concluded to a wide ventricular sepal defect with a free pulmonary pathway. It should be noted that echocardiograms are carried out for the most part by non-cardiologists with very poor quality equipment. It was ultimately the cardiac ultrasound in April 2017 that formally identified the tetralogy of FALLOT which also explains the delay in puberty (puberty at 19 years old) and height and weight: 32.30 kg (- 2.9 DS), Height: 145 cm (- 3 DS), head circumference: 51 cm (- 4 DS). To reduce the risk of complications related to hyper viscosity, bloodletting and hydroxy urea were the only resources available.

Conclusion: If the antenatal diagnosis of tetralogy of FALLOT is currently done in developed countries, the late diagnosis in this patient at the age of 21 shows that the equipment and training of medical personnel is far from optimal in Guinea.

Keywords: Polycythemia; Tetralogy of Fallot; Echocardiography

Observation

OHD young girl, born on 16/11/1996, is followed at the hospital of Kamsar (North-West of Guinea) for polycythemia. She was referred on 02/27/2017 to the Medical and Consulting Center (CEMECO) for a hematological opinion.

History of the disease

The onset of symptoms dates back approximately 9 years. It was progressive marked by helmet headaches, nocturnal and resistant to the usual analgesics; midline chest pain of moderate

intensity, exacerbated by physical exertion, cyanosis of the lips and finger clubbing. In front of this table the parents consulted at the hospital of Kamsar (industrial zone of the region of Boké (Lower Guinea) where an assessment was carried out with the following results: hematocrit 60% (N: 37-48%), leucocytes 10200 (N: 5000 to 10000/mm^3), TE negative, EG negative, blood sugar 5.7 mmol/l (N: 4.2 - 6.1 mmol/l), urea 2.22 mmol/l (N: 1.7 - 8.3), calcium 2.08 mmol/l (N: 2.02 - 2.6 mmol/l), the result of the urine dipstick, chest X-ray and echocardiography considered normal. normal of the first echocardiogram, because of the strong suspicion of heart disease, two other echocardiograms were carried out on 04/11/09 and 24/11/09 with results returned to normal. After a year of diagnostic wandering the patient was lost to follow-up for many years. On 02/16/17, she returned for: NYHA stage II dyspnea on exertion, palpitations, physical asthenia, burning-type osteoarticular pain e predominant in the lower limbs, bilateral hypoacusis and generalized pruritus.

She was then hospitalized and received oxygen therapy without improvement. Hemodynamically, the heart rate was 94 beats/minute with blood pressure at 100/60 mm Hg and saturation at 82% in ambient air. A check-up was carried out with the following results: blood count (Hb = 20g/dl, Hte = 69%), the other lines were normal, chest X-ray: interpreted normal, echocardiography (interpreted normal, abdominal ultrasound (normal.). It was at this stage that she was referred to a pediatric hematologist at the Center Medical et Conceal en in health Kipé (CEMECO) for a hematological opinion and possible treatment.

Background

Personal

Obstetrics

3 prenatal consultations carried out, delivery at the Kamsar hospital at term, adaptation to ectopic life not specified (the birth record lost). The birth weight would be 2500g (according to the mother). She walked around 8-9 months.

She went to school when she was 5 years old. At 21, she attends the eighth grade class because of absenteeism due to illness.

Medical

Hospitalized in 2009, at the age of 12, for suspected heart disease and on 02/16/17 for a hypoxic crisis at Kamsar hospital. No concept of diabetes, arterial hypertension, haemoglobinopathies.

Surgical

Never operated.

Gyneco-Obstetrics: Menarche at 19 years old; with an irregular cycle. The duration of menstruation varies from 5-7 days, and the bleeding is moderate.

- **Lifestyle:** Single, cared for by family. She does not drink alcohol, smoke or take drugs.

Family: No consanguinity between the parents.

- A 42-year-old mother at birth, she made nine gestures, nine parities, four of which died.
- Father died in 1997 following a road accident.

Collaterals: Ninth child of a family of nine children, 5 of whom are living and 4 deceased.

- The first died at the age of 4, following a cardio-respiratory arrest that occurred without prodrome.
- The second died at the age of 2, of a sudden death.
- The third died, at the age of one year, of a sudden death.
- The fourth died, at the age of 2, of a sudden death.

Physical examination

- **General appearance:** Conscious, cooperative, active attitude, purplish red coloring of the conjunctival and oral mucous membranes, cyanosis of the lips, digital clubbing.
- There are no signs of dehydration or edema in the lower limbs.

Anthropometric measurements

- **Weight:** 32.30 kg (- 2.9 DS), Height: 145 cm (- 3 DS), head circumference: 51 cm (- 4 DS): a staturo-weight delay. Temperature was 37°6 C, blood pressure = 100/60 mmHg, heart rate = 96 beats/minute, saturation= 82%, respiratory rate = 26 cycles/minute.
- **Heart:** Stitch shock was visible and palpable at the left fifth intercostal space, medial to the midclavicular line. Heart sounds were regular with a harsh systolic murmur of 3/6th intensity at the pulmonary focus. There was no sign of heart failure.
- **Vessels:** Peripheral pulses are perceived symmetrical and synchronous with heartbeats.

Pleuropulmonary examination

Symmetrical thorax, no deformation, well transmitted vocal vibrations, audible vesicular murmur.

- **Examination of the digestive tract:** Clean purplish tongue, complete dentition, no decayed teeth. The abdomen is symmetrical, flexible, painless, no palpable mass.
- **Examination of the musculoskeletal system:** There are hot and painful swellings, bilateral at the knee, ankle and metatarsophalangeal joints.
- **Lymph node areas:** Free. There was no splenomegaly

Genito-external organ

Female type, normal appearance. Puberty: Tanner stage S4P3 (S4: forward projection of the areola and nipple, which forms a second protuberance above the chest, P3: the hairs are thick, wavy and spread laterally).

Syndromic summary

21-year-old patient who progressively presented with the symptomatology mentioned above. The clinical examination carried out revealed: Cyanosis, finger clubbing, systolic murmur in the pulmonary focus, hyper viscosity syndrome, painful osteo-articular syndrome, failure to thrive, and delayed puberty. Faced with these symptoms and syndromes, we considered the following diagnostic hypotheses:

- A cyanotic congenital heart disease such as tetralogy of Fallot;
- Hemoglobinopathy;

Biological assessments carried out in first intention showed the following results.

Settings	Results	Normal values
03/03/2017		
GR (tera/l)	9,04	4 - 5,20
Hte %	68	38 - 48
Hb (g/dl)	20,5	12 - 15
VGM (fl)	75,22	80 - 99
TCMH (pg)	22,68	26 - 32
CCMH (g/dl)	30,15	32 - 36
GB count (giga/l)	6,8	4 - 10
Platelet count (giga/l)	167	150 - 400
Urea (mmol/l)	5,33	1,7 - 8,3
Creatinine (µmol/l)	64,1	53 - 97
Uric acid (mol/l)	388	150 - 340
Sodium	141,6	135 - 145
Potassium	4,5	3,5 - 5
Chlorine	108.60	135 - 145
Ferritinemia (ng/ml)	< 1,5	12 - 150
Blood sugar (mmol/l)	5,60	3,85 - 6,93
Thyrostimulin (µui/ml)	3,22	0,25 - 5
Thyroxine (pmol/l)	15,22	10,6 - 19,4
Triiodothyronine (pg/ml)	2,53	1,4 - 4,2
Protein (g/l)	74,4	66 - 83

Table 1: Result of the blood test.

Polycythemia, microcytosis, hypochromic and elevation of uric acid.

The diagnosis of polycythemia Vera was retained in the presence of a hematocrit level greater than 60% in the absence of signs of dehydration.

The diagnosis of Hemoglobinopathy was suggested in the face of recurrent osteoarticular pain, predominantly in the lower limbs; ruled out before electrophoresis of hemoglobin which is normal with: Hb A at 97.6% and Hb A2 at 2.4%. We therefore move towards polycythemia secondary to Cyanotic congenital heart disease in the face of the following arguments: Acrocyanosis; finger clubbing; hypoxia with low SPO2 on room air (varying between 75 -82%); a systolic murmur at the pulmonary focus. A cardiology consultation was carried out and assessments were carried out: The frontal chest X-ray performed on 03/02/17 showed no pleurae-parenchymal lesion. At the level of the cardio-mediatisnal silhouette: the apex of the heart is raised, supra-diaphragmatic with an overhang of the lower right arch giving the appearance of a hoofed heart. Cardiothoracic index ICT= 0.47.

The electrocardiogram: regular sinus rhythm with a heart rate of 60 beats/min and a right axis deviation of +180°.

Cardiac Doppler ultrasound performed on 07/03/17 concluded with: Wide interauricular communication, the pulmonary pathway is free, good systolic function of the left ventricle.

This result is not clinically compatible; a second ultrasound was performed on 04/24/17 and objectified a tetralogy of Fallot:

- Inter ventricular communication under aortic 6 mm in diameter;
- Moderately severe valvular pulmonary stenosis: (max V: 3m/s, max gradient: 47 mm Hg);
- Extroposition of the aorta
- Hypertrophy of the right ventricle.

The abdomino-pelvic ultrasound performed on 02/21/17 was normal with a small anteverted uterus measuring 4.03 cm/2.5 cm, an endometrium of 6cm. The left ovary measures 2.28 cm/1.58 cm and the right ovary 2.14 cm/1.50 cm, containing follicles.

The brain scan performed on 03/04/17 was normal.

The diagnosis of polycythemia secondary to tetralogy of Fallot is retained.

We introduced as treatment

- An antiplatelet agent: Aspégic 100 mg/day in a single dose.
- An anti-gout (allopurinol) 10 mg/kg weight, 1 tablet per, a myelofrinator treatment (hydroxyurea) 30mg/kg weight per day divided into two doses from 03/03/17 to 04/13/17 and from 09/22/ 17 to date.
- Four 300cc bleeds were performed on 04/05/17, 04/13/17, 04/21/17, 05/02/17.
- Oxygen therapy with O_2 saturation monitoring on demand.
- Health and dietary advice provided: sufficient oral rehydration, good oral hygiene.

Follow-up

The treatment was effective since there was a drop in hematocrit (from 68% to 53.2%), regression of clinical signs and no thromboembolic accident. Ferritinemia was requested at the start but could not be done until the 4th month of treatment; the rate was less than 1.50 ng/ml (N=12-150). Martial treatment was initiated based on tardyferon 5 mg/kg weight per day in two doses for two months. The patient is reviewed weekly for the first 2 months and monthly until her 6th month of treatment. The biological assessments were satisfactory and there was an improvement in the symptoms of hyperviscosity. After 2 months of non-compliance with treatment, she returned in the 8th month with a picture of blood hyperviscosity with an Hb level of 20.1 g/l, a Hte of 72.30% and uric acid of 550 µmol/l. A 200cc bleeding was done and the same treatment (Aspegic, Allopurinol and Hydroxyurea) was renewed. Hygiene and dietary advice was provided.

Therapeutic education was done and this improved compliance.

Six months later there was an improvement in the symptoms of hyperviscosity and a drop in hematocrit of 72 - 56.5%. Her condition has remained stable and she has not benefited from bloodletting for the past six months. Checks were carried out, the results are shown in the table below.

Date (2017)	**3/3**	**17/3**	**5/4**	**13/4**	**21/4**	**2/5**	**3/6**	**28/8**	**22/9**	**22/1 2**	**03/03**
Settings											
GR (tera/l)	9,04	9,61	9,38	8,31	7,54	8,01	8		9,81	8,63	8,25
Hte %	68	63,8	61,9	55,6	51,1	56,3	53,2	72,3	66,57	61,7	56,5
Hb (g/dl)	20,5	23	21,9	20,1	18,5	18,6	18	20,1	19	23,3	21,9
VGM (fl)	75,22	66,4	66	66,8	67,8	69,1	66,6		68	71 ,5	68,5
TCMH (pg)	22,68	23,9	23,3	24,1	24,5	23,2	22,6		25	26,9	26,5
MCHC (g/dl)	30,15	36	35,3	36,2	36,2	33,6	38,8		37	37	38
GB	6,8	5,3	6,2	4,8	3,2	4	4		4	3 ,4	3 ,2
Inserts	167	372	367	328	233	340	355		167	344	278
Urea (mmol/l)	5,33								2,67	4,11	
Creatinine (µmol/l)	64,1								68,7	74,7	

(Uric acid µmol/l)	388							550	387	384	
Sodium	141,6							143,8			
Potassium	4,5							4,58			
Chlorine	108.60							110			
Ferritinaemia (ng/ml)							< 1,50				

Table 2: Monitoring sheet.

Figure 1

Discussion and Conclusion

Early diagnosis of congenital heart disease has a positive impact on its evolution. Diagnosed late or untreated, they can be complicated by heart failure, infective endocarditis, stroke, brain abscess, or severe polycythemia [1]. Tetralogy of Fallot is the most common cyanotic congenital heart disease. It accounts for nearly 8% of all congenital heart disease. Polycythemia, a form of adaptation to any chronic hypoxia, is constant in tetralogy of Fallot. It develops gradually and its importance makes it possible to estimate the degree of hypoxia [2,3]. The clinical symptomatology of secondary polycythemia is the direct reflection of blood hyperviscosity responsible for headaches, dizziness, tinnitus, visual disturbances, paresthesias and vascular thrombosis [4]. Currently, screening for tetralogy of Fallot is done prenatally or at a young age in developed countries. This screening allows early surgical correction which can lead to a definitive cure. It happens, exceptionally, to make the diagnosis in adulthood of repairable cyanotic congenital heart disease. This usually happens in developing countries [5].

We report the case of a 21-year-old patient with tetralogy of Fallot revealed by severe polycythemia. The late diagnosis of cyanotic congenital heart disease in our patient (at age 21) shows that the level of hospital equipment and the training of nursing staff is not quite optimal in our country. In the absence of antenatal screening, the diagnosis should be considered in the face of any neonatal cyanosis, but it was only at the age of 12 that the parents consulted. The diagnosis was only made 9 years later, during his 6th cardiac ultrasound despite the presence of symptoms suggestive of cyanotic heart disease. This delay could be explained by: the late consultation in a specialized environment, the diagnostic wandering in a context of difficulties of access to care, the lack of personnel and the insufficiency of the technical platform. In developing countries, the supply and accessibility of care raise a thorny problem, particularly for the poor and those living in rural areas.

The diagnosis of polycythemia, which is disconcertingly easy, is possible at all levels of the health pyramid in Guinea. Despite this possibility of diagnosis in all health structures, the diagnosis of polycythemia was itself late. Polycythemia in cyanotic heart disease is a beneficial reaction to improve oxygen transport. IT happens that it decompensates causing major hyperviscosity. The hematocrit threshold value, beyond which treatment should be initiated, is generally 65%. The treatment of polycythemia is classically based on bloodletting which must be 5 to 7 Cm^3/kg. Too much blood depletion can induce microcytosis, which aggravates hyperviscosity and promotes the occurrence of thromboembolic accidents, which is why all children with cyanotic heart disease are put on martial treatment [6]. We performed 4 bleedings. They were effective because we obtained a regression of the Hte from (68 to 53.2%). The collapse of serum ferritin to 1.50 ng/ml in the patient is due to polycythemia itself and, probably, to repeated bleeding.

Bloodletting stimulates erythropoiesis and induces iron deficiency. In addition, iron intake alone induces outbreaks of polycythemia leading to an increase in the number of bleedings. To get out of this vicious circle, some teams have proposed a

myelosuppression treatment based on hydroxyurea (off-label) to slow down the production of red blood cells by the marrow [7,8]. R Boussaada et al had used hydroxyurea in the treatment of polycythemia secondary to incurable cyanotic heart disease and reported obtained a good result since they noted a regression of hematocrit from 72 to 58% and hemoglobin level from 23 g/dl to 17 g/dl [4]. Surgical cure for tetralogy of Fallot is not yet feasible in Guinea. Unfortunately, due to the limited resources of the parents, his transfer abroad is unthinkable unless a philanthropic organization comes to the rescue of the family. Moreover, because of the late diagnosis at the age of 21, she cannot benefit from the support of non-governmental organizations that assist children. This is why we instituted hydroxyurea treatment in this patient. We obtained a satisfactory result. Indeed, the hematocrit went from 72% to 56.5% and we did not note any thromboembolic accident or side effects.

Hydroxyurea tolerance has been relatively well studied. Indeed, at the start of treatment hydroxyurea is usually well tolerated, however side effects can set in five years after the start of treatment with very variable incidences according to the authors. In fact, the main toxicity concerns the skin and mucous membranes and is seen in 35% of cases. These include leg ulcers, mouth ulcers, acne breakouts and dry skin. Acute leukemia or myelodysplasia are late complications with an incidence estimated at 10% in the 13th year. Severe cytopenias, especially of the reversible thrombocytopenia type after discontinuation of treatment, were observed in 3.5% of cases. Other side effects such as severe cytolytic hepatitis, osteitis secondary to drug eruption triggered by taking hydroxyurea and multiple skin and oral carcinomas occurring 13 years after the start of treatment [4]. The etiological diagnosis of polycythemia, the high cost of products and examinations, non-compliance for a period, and the ignorance of this pathology by the parents constituted our main difficulties. Biological monitoring includes blood count and formula every month, blood ionogram, uremia, creatinine and uric acid [9].

Hyper uricemia is common in polycythemia and can lead to gout attacks or even uric lithiasis [6]. In our observation we noted hyper uricemia at 388 µmol/l. This is what justified long-term treatment with allopurinol.

Our patient presented a delay in stature and weight, as is often the case in tetralogy of Fallot. She also had delayed puberty (first period at age 19). The age of menarche in patients with congenital heart disease is slightly increased compared to the reference population. However, these patients are the most likely to present with menstrual cycle disorders. Puberty is most often complete even if it is sometimes late and of slower evolution [10].

Figure 2

Figure 3: 21-year-old female patient with staturo-ponderal retardation. Weight: 32.30 kg (- 2.9 DS), Height: 145 cm (- 3DS).

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