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**Acute hemolytic anemia caused by G6PD deficiency in  
children in Mayotte : a frequent and severe complication.**

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# **Acute hemolytic anemia caused by G6PD deficiency in children in Mayotte: a frequent and severe complication**

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## **Key Points:**

**Acute hemolytic anemia due to G6PD deficiency is frequent and severe in children in Mayotte.**

**The African variant of G6PD deficiency is also responsible for severe anemia.**

**Traditional medicine based on local plants is an under-recognized trigger.**

## **Abstract**

Severe hemolytic anemia is a rare complication of Glucose-6 Phosphate dehydrogenase (G6PD) deficiency. It occurs with the Mediterranean (Med) variant corresponding to a class 2 deficiency according to the World Health Organization classification, and it correlates with a severe deficiency in G6PD activity. In Mayotte, the majority of patients have the African (A-) variant as a WHO class 3 deficiency. Yet we have observed numerous cases of severe hemolytic anemia defined by a hemoglobin level of less than 6 g/dL. In this study, we aimed to describe the epidemiological, clinical, and biological features as well as the treatment modalities of children presenting with a severe hemolytic crisis secondary to G6PD deficiency in Mayotte. The secondary objective was to study the disease genotype when this information was available.

Between April 2013 and September 2020, 73 children presented with severe anemia due to G6PD deficiency in Mayotte. The median hemoglobin level during the hemolytic crises was 3.9 g/dl. All of the patients underwent a transfusion and hospitalization. Twenty patients had a disease genotype: eleven had the African mutation and nine had the Mediterranean mutation.

Although they are among the most common triggers of G6PD acute hemolytic anemia, drugs were found to not be present and fava bean ingestion was found in only one child. One of the specific triggers was traditional medicine, including *Acalypha Indica*.

Severe hemolytic crisis in children due to G6PD deficiency is a frequent occurrence in Mayotte. The patients had severe disease symptoms, but the severity did not correlate with the genotype: the African (A-) variant and the Mediterranean variant resulted in the same level of disease severity.

Keywords: G6PD deficiency, severe hemolytic anemia, African and Mediterranean genotypes

## **Introduction**

Glucose-6-phosphate dehydrogenase (G6PD) deficiency is the most common human enzyme deficiency in the world, affecting an estimated 400 million people worldwide (1).

The activity of the G6PD enzyme protects red blood cells against oxidation. G6PD deficiency results in red blood cells that are more sensitive to infection, stress, and certain foods or medications, as well as a reduction in their biological half-life. Most patients remain asymptomatic their entire lives (WHO classes 4 and 5) (2). The symptomatic phenotypes vary from chronic hemolysis (WHO class 1) to episodic hemolytic crises (WHO classes 2 and 3).

The distribution of G6PD deficiency in the world is similar to that of malaria, which has led to the hypothesis that G6PD deficiency may be protective. The prevalence in the African population may be as high as 25% (3).

Mayotte Island is a French territory in the Comoro Archipelago located in the Mozambican Channel. Malaria is still endemic in this region of the world. The current population of Mayotte is the result of early migration from Africa and the Persian Gulf, which are areas with high levels of G6PD deficiency. The prevalence of G6PD deficiency in the Comoro Archipelago is estimated to be 9.5% (4) compared to 0.39% in metropolitan France (5) (PNDS 2017), but this is almost certainly an underestimation.

Among the 200 X-linked G6PD mutations known in the world, only two mutations are found in the Comorian population, with mostly the African mutation (A-) (14 out of 17

patients in the study by Baden et al.), and a lesser incidence of the Mediterranean mutation (Med) (3 out of 17 patients) (4). A- patients belong to the non-severe symptomatic group of the WHO classification (class 3), unlike Med patients, who belong to class 2 and who can suffer from severe hemolytic crises.

For several years, we have observed numerous cases involving severe hemolytic crises related to G6PD deficiency in the pediatric population in Mayotte. These incidences of hemolysis generally lead to hospitalization and red blood transfusion. The patients sometimes require pediatric intensive care, and the condition can also result in death.

The principal objective of this study was to study children with severe hemolytic crises due to G6PD deficiency and to describe anamnestic, clinical, and biological features as well as the treatment modalities. The secondary objective was to study the disease genotype when this information was available.

## **Methods**

### Patients

This observational retrospective study focused on children with severe hemolytic anemia related to G6PD deficiency who had been hospitalized in Mayotte Hospital between the 1<sup>st</sup> of April 2013 and the 16<sup>th</sup> of September 2020. Biological hemolysis was defined by an increase in the levels of lactate dehydrogenase and indirect bilirubin and a reduction in haptoglobin levels. The threshold for defining severe anemia was a hemoglobin level of less than 6 g/dL. The criterion for relating hemolysis to G6PD deficiency was quantitative spectrophotometric evidence of reduced G6PD activity during the hemolysis or later, and/or the presence of bite cells or Heinz bodies on blood smears.

The patients with a known other cause of chronic hemolytic anemia (thalassemia major, congenital spherocytosis, or sickle cell disease) were not included.

The exclusion criteria were an absence of documented of G6PD deficiency, another hemolytic cause of extrinsic hemolytic anemia (autoimmune hemolytic anemia (positive direct antiglobulin test), microangiopathies (schistocytes on peripheral blood smears)) hypersplenism with thrombocytopenia, and an abnormal hemoglobin profile (minor thalassemia or sickle cell disease). Malaria was also excluded by a peripheral blood smear or a rapid diagnostic test.

This study was submitted for approval by the Ethics Committee of Mayotte Hospital. All of the patients were informed of the study and did not oppose the use of their data.

We used the national database codification of French hospitals (*programme de médicalisation des systèmes d'information* (PMSI)) and we selected files corresponding to D55 (anemia due to enzyme abnormalities) and D64 (other anemia) according to the International Classification of Diseases (ICD10). The clinical and biological data were extracted from the computerized medical files.

The collected data comprised age, gender, family or personal history of hemolysis, duration of symptoms before hospitalization, medication or food known to cause hemolysis, documented infection, externalized hemorrhage, time between hospitalization and confirmation of diagnosis, and genetic testing results. The clinical data collected comprised the presence of fever, clinical signs of hemolysis (jaundice or anemic syndrome), the presence of hemoglobinuria, abdominal pain, oxygen dependence, hepatomegaly or splenomegaly, asthenia, discomfort, heart failure, signs of shock (tachycardia, hypotension, or vascular filling), the place of hospitalization, the number of days in hospital, the number of transfusions, need for intubation, amines, dialysis or death, and recurrence of hemolysis. The biological data comprised: biological hemolysis (high free bilirubin and LDH levels, low haptoglobin levels); the

hemoglobin level; the mean corpuscular volume; white blood cells counts as the number of lymphocytes, neutrophils, and platelets; reticulocyte levels; renal failure; the presence of bite cells on blood smears; liver transaminase levels; blood pH; and the levels of methemoglobin, lactate, PCT, and CRP. The level of G6PD activity was analyzed when available, as was the TIBC and serum ferritin level.

Some of the patients had the option of providing a sample for genetic testing during the hemolysis or during a follow-up consultation. As genetic testing is not available at the laboratory in Mayotte, after obtaining patient consent, the samples were sent to the Henry Mondor Hospital in metropolitan France for analysis. The technique used to study the G6PD gene was Polymerase Chain Reaction (PCR) with direct sequencing of the Xq28 locus. The G6PD gene comprises 13 exons, and several exons were studied, including mutations found in the Comorian population: mutation of exon 6 c.466A>G; p. Asn156Asp (N126D; A) associated with Val68Met on exon 5 g.11585G>A; c.292G>A; p. Val98Met (V68M; Matera) are responsible for the African variations (A-/Matera). The Mediterranean variant is the result of a single amino-acid substitution on exon 7: g.13168C>T; p. Ser218Phe (S188F; Med).

### Statistical analysis

A descriptive analysis of the general population was undertaken. The data were collected with EXCEL 2010 and analyzed with SPSS software (IBM SPSS 23.0, IBM Corp. Armonk, NY, USA).



## Results

Ninety-seven patients were included in this study. Six patients were excluded because they were born premature, four patients had an abnormal hemoglobin profile, for 10 patients the G6PD deficiency was not confirmed, two patients had a positive direct antiglobulin test, and for two patients the medical files were not available (Figure 1).

The epidemiological, clinical, and biological characteristics of the 73 included patients are presented in Table 1.

Ten patients (13.7%) were female, and the median age was 26 months [7,5-61]. Sixteen patients (21.9%) had a personal history of hemolysis, two patients had a family history of G6PD deficiency, and 14 patients (19.2%) with severe hemolysis were known to have a G6PD deficiency.

The hospitalization of the patients according to the time of year (the month) is shown in Figure 2. Acute hemolytic crises occurred more often in certain months (March, April, and November) and other months have relatively few cases (May, June, and July). Based on the years 2014 to 2019, for which we had complete data, 38% of the crises occurred during the four months of the rainy season. This repartition varied however according to the year and no statistical link was found.

A trigger was found for 31 patients (42.4%). None had taken medicine known to induce hemolysis in G6PD-deficient patients. Forty-four patients had consumed food or traditional plants that should be avoided in case of G6PD deficiency, while 19 patients confirmed that they had consumed herbal tea based on traditional plants (or it had been ingested by the nursing mothers), which in some cases was *Acalypha Indica* while others were unable to provide the name of the plant. One child reported eating *ambrevades* (local fava) and other fava beans a few days before the onset of symptoms.

An infectious cause was confirmed in 11 patients (15%), and Table 2 summarizes the various pathogens and sites.

The parvovirus status was known for 31 patients, 6 of whom had prior immunity and 25 had a negative serology a few weeks after the hemolysis.

The clinical presentation at the time of the initial assessment was respiratory symptoms for 57.5 percent of the patients, and digestive symptoms for 50.7 percent. Ninety-three percent of the patients had clinical signs of hemolysis. Hepatomegaly was recorded in 21 patients (28.8%) and splenomegaly in 6 patients (8.2%). Ten patients (13.7%) had abdominal pain, while hemoglobinuria occurred in 38 patients (52.1%). Pallor was the most common symptom, occurring in 75.3% of the patients, followed by jaundice, which occurred in 64.4% of the patients. Fifty-eight patients were found to have asthenia, approximately 52.1% had signs of shock at the start of the treatment, and two patients (2.7%) required resuscitation.

Three patients had oxygen dependency without pulmonary distress. Their oxygen levels were not significantly altered by nasal oxygen supply. Only one patient had arterial blood gas analysis during the initial assessment, and although their saturation level was not known without oxygen, it remained less than 90% with a high-concentration oxygen mask with a partial pressure of oxygen at 169 mmHg.

The median hemoglobin level was 3.9 g/dL [3.4-4.9], with an average mean glomerular volume of 85.1 fl. Most of the patients exhibited signs of regeneration, with a median reticulocyte level of 133 g/L. The level of white blood cells was 25.8 G/L [5.4-153], with a predominance of neutrophils of 76.8%. The median platelet level was 402 G/L. The median levels of C-reactive protein and procalcitonin, which reflect blood inflammation, were 26 mg/L [10-53] and 1.76 mg/L [0.79-3.79], respectively. The median level of creatinine was 36  $\mu$ mol/L, and 24 patients (33.3%) had renal failure.

All of the patients had biological signs of hemolysis, with a median lactate dehydrogenase level of 1,601 IU/L [355-27,027]. The median indirect bilirubin level was 45  $\mu$ mol/L [28,5-98]. The level of ASAT was high at 107 IU/L [31-13,460] (N 5-50), with no significant increase in ALAT; there was an associated hepatocellular insufficiency in four patients. Not every patient had their blood gases analyzed, and in most cases they were venous samples (25 out of 34). Six patients with desaturation had arterial blood gas determinations, of whom four had a normal partial oxygen pressure. Methemoglobinemia was measured in 20 patients, and the median value was 8.75% [1-30].

A peripheral blood smear was performed in 59 patients, and 61 percent of them revealed the presence of bite cells or ghosts. The presence of Heinz bodies, which requires additional handling, was not assessed.

All of the patients were hospitalized: 13 patients (17.8%) required intensive care, 51 (69.9%) were hospitalized in the pediatric ward (continuous monitoring unit or standard pediatric unit), 7 (9.5%) were hospitalized in the “short-term hospitalization unit”, and one (1.4%) in another unit. The average length of the hospital stay was 5.6 days [2-56] and 76.2% of the patients had a stay of 5 days or less.

All of the patients underwent red blood cell transfusions. Fifty-seven patients (81.4%) had a single transfusion, while 12 patients (17.1%) underwent two or more. For three patients there was no data regarding the number of transfusions.

Thirty-seven patients (50.7%) received supplementary oxygen at the time of the initial assessment. Six patients had to be intubated, four needed hemodynamic supplementation, and three patients required dialysis.

Fifty patients had an evaluation of the G6PD activity during the hemolysis, with a median value of 8.6 IU/gHb [0.2-64]. The level was associated with the activity of

another erythrocyte enzyme (pyruvate kinase or hexokinase) for only 18 patients. Thus, the deficiency was only confirmed in 16 patients (32% of the 50 patients) during the hemolysis.

G6PD activity was assayed after hemolysis in 50 patients, and 94% of these patients had a confirmation of the deficiency at this time, with a median G6PD activity of 2.3 IU/gHb [0.3-7.6].

The G6PD deficiency was confirmed with the recommended method in 56 patients (76.7%). The level of activity was severely reduced in 7 patients (defined as < 10% normal activity and equating to WHO class 2), and moderate in 49 patients (defined as 10-60% of normal activity and equating to WHO class 3).

G6PD deficiency was mentioned in almost all of the patient files. For 69.9% of the patients, the first sample was taken on the day of hospitalization for severe hemolysis, and for 89.9% of the patients this was done during the first seven days after hospitalization.

The disease genotype was available for 20 patients. Eleven had the A- mutation, nine had the Med mutation. The numbers were too low to make statistical links. The characteristics of the 20 patients are reported in Table 1.

Two patients died during the severe hemolytic crisis: one died of a brain hemorrhage secondary to liver failure related to severe shock, the other did not respond to resuscitation. Another patient died subsequent to their hospitalization, but the cause of death remains unknown. Eight patients (11.1%) had a recurrence, which was severe in some cases, of hemolysis in the ensuing months. Forty-two patients (57.5%) were not reassessed by a clinician and were hence considered lost to follow-up.

## Discussion

This study is the first to focus on clinical, biological, and genotypic analysis in children with severe hemolytic anemia due to G6PD deficiency in Mayotte.

Seventy-three patients had severe hemolytic anemia related to G6PD deficiency in Mayotte during the 78 months of inclusion. Thus, this condition occurs more than once a month on average, with a yearly incidence of 1/13,000 children based on the official census in 2017 in Mayotte. These numbers were determined based on the means of recruitment in this study (retrospective, and coding). Severe hemolytic anemia with transfusion is thought to be a rare complication (6-8). In 2018, Luzzatto and Arese described acute hemolytic anemia induced by fava beans, also called favism, and they found that this complication is only frequent in areas where G6PD deficiency is common and where fava beans are a popular food item, which is not the case in Mayotte (9). They refer to the incidence in two studies: in 1983, Meloni et al. reported a yearly incidence of 1.2 cases per 10,000 individuals in Sardinia, while in a 2013 study by Reading, the yearly incidence was reported to be 1 case per 50,000 children in Gaza (10-11). The 2012 study by Pamba et al. is the only large study to have analyzed drug-induced acute hemolytic anemia in children in Kenya, and severe anemia requiring blood transfusion only occurred in 10.9% of the children with G6PD deficiency (12).

All of the patients had severe anemia, and the median hemoglobin level was 3.9 g/dL [3.4-4.9]. They all had at least one blood transfusion, 12 patients (17.1%) needed two or more transfusions. The median hemoglobin level in our study was much lower than in two other studies, which had average hemoglobin levels of 6.26 g/dL ( $\pm 0.63$ ) (11), and 7.2 g/dL (12). In the study by Pemba et al., all but two of the patients received a transfusion, but the thresholds for transfusion were 7 and 8 g/dL. This difference may be explained by the hemoglobin cut-off threshold of our study including patients with

hemoglobin levels equal to and less than 6 g/dL. This cut-off threshold was chosen because of the atypical frequency of acute hemolytic anemia in Mayotte.

The clinical symptoms before transfusion were severe as more than half of the patients who had hemodynamic failure (52.1%). Of these, 17.8% required intensive care, with six patients being intubated and four receiving hemodynamic support. Although renal failure is a rare complication (7), it occurred in 33.3% of our cohort, and three patients even needed dialysis.

Three patients died, which in two cases was directly related to the hemolytic anemia. The severity in our study stands out compared to what has been reported in the literature (13-14).

We searched for other factors that could explain the severity of the anemia. In Mayotte, 77% of the population was deemed to be living below the poverty line in 2018 (15), and 10 percent of children between 0 and 4 years of age are extremely underweight (16). As the staple food is rice, these children tend to suffer from severe iron deficiency. We did not analyze their nutritional status, however, and the TIBC and serum ferritin levels were not interpretable in case of hemolysis.

Drugs (e.g., for malaria treatment) and fava bean ingestion are common hemolysis triggers in G6PD deficiency (6-7, 9, 17-18). None of the patients in our cohort were taking drugs before the hospitalization that could induce hemolysis, and only one patient revealed that they had ingested fava beans.

Specific triggers reported in our cohort comprised traditional plants and endemic beans. Traditional medicine based on the use of plants is common in Mayotte and often precedes the use of Western medicine (19). When asked, several of the patients revealed that they had consumed traditional plants one or several days before their hospitalization. Some patients had consumed *Acalypha Indica*, which is an exotic plant that grows on Mayotte Island and that is commonly used in tisanes to treat a cough.

This entity is also found in parts of Asia, where it is similarly used for medical purposes (20). There have been a number of case reports in Asia (21-23) and in Mayotte (24) describing hemolysis in G6PD-deficient patients after they had consumed *Acalypha Indica*.

A local fava called ambrevade (*Cajanus Cajan*) had been consumed by one patient, but no study to date has analyzed the effect of this bean on G6PD-deficient patients.

Infection is also a common trigger (6-7), and some infectious agents such as pneumococcus, viral hepatitis and cytomegalovirus (25), *Escherichia coli*, beta-hemolytic *Streptococcus*, and *Rickettsia* (6) are particularly associated with hemolytic anemia.

The clinical condition was improved by transfusion, and the etiological investigations were either not pursued or performed. The etiology of infection was most often investigated for patients with severe disease involving hemodynamic, renal, or hepatic failure.

In our 11 patients with proven infection, two had a CMV infection and one was positive for *Escherichia coli*. Hepatitis A and E viruses are known to cause more severe hemolysis, with hepatic insufficiency, renal failure, and severe jaundice (26-28). Only two patients had hepatitis A in our cohort, despite the fact that this disease is still a frequent occurrence in Mayotte (incidence of 44/100,000 inhabitants) (29).

The standard test to confirm G6PD deficiency, which was used in this study, is quantitative spectrophotometric measurement of G6PD activity (5).

These analyses are not performed in Mayotte's laboratory and the samples have to be sent to a laboratory in metropolitan France. This increases the time for diagnosis by about a week.

This diagnosis method is suitable for hemizygous males with severe deficiency, but it is inadequate for males with moderate G6PD deficiency as well as for females (13). Both the determination and interpretation of G6PD assays are difficult (5). G6PD activity can be normal during hemolysis, and several blood samples are sometimes required when there is no hemolysis. Only 32% of our patients had evidence of deficiency based on the first sample. A high proportion of patients was not told to or did not attend follow-up consultations (57.5% lost to follow-up) and ultimately only 68.5% had a diagnosis confirmation with the standard assay method.

Despite the non-specific clinical aspect of patients with severe hemolytic anemia, for most of the patients, a tentative diagnosis of G6PD deficiency could be made in the first few days of hospitalization. Twenty-six patients (44.8%) had a confirmation of G6PD deficiency in the first month, although the longest delay in diagnosis was 45 months.

Acute hemolytic anemia often can occur in patients with no history of hemolysis. Rapid clinical and biological assessments help with the diagnosis of G6PD deficiency in case of severe hemolytic anemia upon admission to the emergency ward. We encountered patients with few respiratory signs but low oxygen saturation levels. For most of them, the partial oxygen pressure in their arterial blood gas was normal or high. Blood gas analysis was not carried out systematically, and most of them involved capillary or venous blood samples. In practice, arterial blood gas analysis is rarely performed in infants. Venous and capillary acid-base gas analysis are an alternative to arterial gas analysis and a way to avoid the complications of arterial puncture, but measurement of pO<sub>2</sub> is not recommended with venous or capillary blood gases analysis (30). For one patient with desaturation and few symptoms of distress, the level of methemoglobin was measured and found to be elevated at 5.4%. Methemoglobinemia has only been described in a small number of cases of G6PD deficiency (31). Methemoglobin is a form of hemoglobin in which the heme iron is reduced to its ferric state and is unable



to deliver oxygen (32). At equilibrium, methemoglobin is reduced to hemoglobin by NADH. With excessive oxidation, the G6PD-dependent pentose pathway is necessary. In G6PD deficiency, methemoglobin is not reduced and its level increases. Pulse oximetry then provides false readings as both methemoglobin and hemoglobin absorb at the same wavelength (33). Patients have low oxygen levels based on pulse oximetry but they have a normal arterial pressure of oxygen. This dissociation can be seen more clearly with a low hemoglobin level. In our study, the level of methemoglobin was determined in 20 patients and the median value was 8.75%. The patients with a high methemoglobin level (more than 15%) had respiratory distress and oxygen dependence, but the oxygen level was not estimated in the arterial blood gas and hence could not be correlated. Methemoglobinemia is a key clinical indicator of G6PD deficiency.

Other biological indicators that clinicians can use at the initial assessment are the presence of ghosts or hemighosts in peripheral blood smears. This technique can be readily performed by the biologist but is not carried in every patient (approximately 60% in our study).

Typical biological signs in early blood samples are the presence of hemolysis with a low level of haptoglobin, a high LDH level, moderate cytolysis, and indirect hyperbilirubinemia. We noticed a high degree of that leukocytosis, with a median of  $25.8 \times 10^9/L$  and a majority of neutrophils, with moderate C-reactive protein levels. Other case reports or series present data regarding white blood cells (WBCs). In the 2016 study by Reading et al., the WBC count was  $17.68 \times 10^9/L$  ( $\pm 7.03$ ) during hemolysis and  $8.28 \times 10^9/L$  ( $\pm 2.15$ ) four months later. In the study by Pamba et al., the highest value during the study was  $13.9 \times 10^9/L$  ( $\pm 5.9$ ) in G6PD-deficient patients. It stayed below the values of our study, with WBC sometimes so elevated that diagnostic of G6PD deficiency was wandering. The numbers returned to normal a few days after transfusion. Infection-induced leukocytosis was suggested, and some patients received intravenous or oral antibiotics, although there were no further data in this regard.

Leukocytosis has also been described in favism and drug-induced acute hemolytic anemia (12), with a majority of granulocytes, which does not fit with an infectious reaction in our study. Faraji-Goodarzi et al. analyzed the development of leukocytosis in favism after transfusion, antibiotics, or both. They showed that blood transfusion was an effective therapeutic option for treating leukocytosis in favism, rather than treatment with antibiotics. They concluded that this condition may be due to inflammation (34). In our study, we postulate that leukocytosis was also evidence of bone marrow regeneration. The level of reticulocytes could be low at first but with high leukocytosis and moderate CRP levels. The WBC count appears to be proportional to the anemia.

Out of the twenty genotypes studied, 11 had the A- variant (approximately 55%), although Mégarbane in 2008 and Howes et al. in 2013 claimed that the A- mutation did not result in severe symptoms, with the hemolytic crisis not requiring hospitalization or transfusion. In our study, we found that hemolytic crisis in patients with the A- mutation can be severe. The clinical and preventative measures need to be considered for patients with the A- variant as for patients with the Med variant. As severe hemolytic crises and favism have been observed in A- patients, some authors suggest that the A- variant should not be underestimated (9, 11, 12, 31, 35, 36). The hemoglobin level and G6PD activity in these studies were also much lower. The study by Reading et al. of the Palestinian population in Gaza found an average of anemia of 6.26 ( $\pm$  0.63) g/dL and G6PD activity of 3.75 ( $\pm$  1) IU/gHb in 9 patients with the A- mutation. But the crises were described as less severe and requiring less hospitalization than the Cairo and the Med mutations (11). Galiano et al. described two case reports with A- patients after fava bean ingestion. A four-year-old child from Venezuela with a hemoglobin level of 4.1 g/dL and a Jamaican boy aged 6 months with a hemoglobin level of 6.6 g/dL. Calabrò et al reported the case of a child from the Matera region of southern Italy who exhibited several episodes of hemolysis in his life: at 6 months of age after fava

bean ingestion, at 7 years of age after cotrimoxazole treatment, and at 11 years of age in a viral context. Neither the severity nor the G6PD activity were described (35).

The recommended test to confirm G6PD deficiency is evaluation of G6PD activity using qualitative or quantitative tests (2). We have already mentioned the limitations of this diagnosis method in our setting, such as the length of time to obtain results in Mayotte and the difficulty with conditioning and interpretation during hemolysis. The diagnosis method is also not sufficiently sensitive for females and patients with a moderate deficiency. In our cohort, we described severe hemolysis in patients with moderate deficiency. Ten patients were even excluded from the study due to the absence of clear evidence of a deficiency. The severity of the deficiency did not correlate with the genotype as described by the WHO: two of the Med patients in our cohort had a class 3 deficiency. Larue et al. have reported that A- patients can have a class 2 deficiency, which was not the case in our cohort (37).

In light of the frequency and severity of hemolytic crisis in Mayotte, in addition to the difficulties with obtaining a rapid and reliable diagnosis, a test meeting these characteristics would of considerable value. In 2009, Joly et al. developed a rapid genotyping test of the two variants present in Mayotte based on high-resolution melting (HRM) analysis (38). Their protocol confirmed that HRM analysis is a rapid, simple, and cost-effective tool to screen for the A- and Med variants. This method has recently become available in Mayotte and it is likely to help clinicians in this regard.

This study highlighted that severe hemolytic crisis related to G6PD deficiency is a frequent occurrence in Mayotte, with high morbidity and mortality. The African A- mutation and the Mediterranean mutation are responsible for severe hemolytic anemia in children. Cultural and geographic conditions result in exposure to different triggers such as medicinal plants (e.g., *Acalypha Indica*). Making a diagnosis is difficult. In the

event of hemolytic anemia in patients not known to have a G6PD deficiency, clinical elements (false oxygen dependence) and biological elements (increased methemoglobinemia and ghosts or hemighosts in peripheral blood smears) may guide the diagnosis towards a G6PD deficiency. HRM analysis appears to be a promising approach for Mayotte Island.

### **Acknowledgments**

### **Authorship Contribution**

MB, EF, and RB contributed to the conception and design of the study. MB and EF collected the data and conducted the statistics, OM analyzed the statistics. All of the authors contributed to the manuscript and approved the submitted version.

### **Disclosure of Conflicts of Interest**

The authors declare no conflicts of interest.

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## Tables

Table 1: Patient characteristics

	All patients (percentage with available data)	Available data for n patients/total	Genotype	African mutation	Mediterranean mutation
n (%)	73 (100)	Total = 73 (100%)	20 (27.4)	11 (15.1)	9 (12.3)
<b><u>Epidemiology</u></b>					
Age, median (IQR <sup>a</sup> ), month	26 [7.5-61]	73/73	44 (8.25-79.25)	52 (14-74.5)	36 (6-71)
Gender: female, n (%)	10 (13.6)	73/73	2 (10)	1	1
Personal history of hemolysis, n (%)	16 (21.9)	73/73	2 (10)	1	1
Family history of hemolysis, n (%)	2 (2.7)	73/73	1 (5)	0	1
Known G6PD deficiency, n (%)	14 (19.2)	73/73	0 (0)	0	0
Triggering element, n (%)	31 (42.4)	73/73	5 (6.9)	2	3
Medicine known to trigger hemolysis, n (%)	0 (0)	52/73	0 (0)	0	0
Food known to trigger hemolysis, n (%)	4 (5.8)	69/73	0 (0)	0	0
Traditional plants tisane, n (%)	19 (43.2)	44/73	6(30)	2	4
Proven infection, n (%)	11 (17.2)	64/73	0 (0)	0	0
<b><u>Symptoms before hospitalization</u></b>					
Respiratory symptoms, n (%)	25 (34.7)	73/73	16 (80)	-	-
Digestive symptoms, n (%)	10 (13.8)	73/73	8 (40)	-	-
<b><u>Clinical symptoms at initial assessment</u></b>					
Presence of fever, n (%)	41 (56.9)	73/73	8(40)	5	3
Respiratory failure, n (%)	42 (57.5)	73/73	16 (80)	10	6
Oxygen dependence, n (%)	37 (61.6)	60/73	15 (75)	8	7
Digestive symptoms, n (%)	37 (50.7)	73/73	8 (40)	3	5
Pallor, n (%)	55 (80.8)	68/73	16 (80)	10	6
Jaundice, n( %)	47 (67.1)	70/73	14 (70)	7	7
Hemoglobinuria, n (%)	38 (63.3)	60/73	11 (55)	5	6
Abdominal pain, n (%)	10 (14.9)	67/73	2 (10)	1	1
Hepatomegaly, n (%)	21 (30.8)	68/73	3 (15)	1	2
Splenomegaly, n (%)	6 (8.8)	68/73	1 (5)	0	1
Asthenia, n (%)	58 (79.5)	73/73	17 (85)	10	7
Malaise, n (%)	12 (16.4)	73/73	4 (20)	1	3
Signs of shock, n (%)	38 (53.5)	71/73	14 (70)	6	8
Heart failure	2 (2.7)	73/73	1 (5)	0	1
<b><u>Biology</u></b>					
Hemoglobin level, median (IQR <sup>a</sup> ), g/dL	3.9 [3.4-4.9]	73/73	3.7 (3.1-4.55)	3.7 (3.2-3.9)	4.3 (3.2-4.9)
MCV median (IQR <sup>a</sup> ), fl	85.1 [79.75-92.8]	73/73	86.45 (79.4-96.85)	80.5 (75.3-89.45)	86.8 (81.1-97.3)
Leukocytes median (IQR <sup>a</sup> ), G/L	25.8 [19.6-40.05]	73/73	36.3 (16.2-60.025)	41.1 (19.9-60.65)	24.3 (19.1-50)
Lymphocytes median (IQR <sup>a</sup> ), G/L	7.4 [4.1-12.5]	69/73	8.15 (3.275-15.15)	8.95 (3.35-13.75)	9.7 (8.4-9.9)
Neutrophils median (IQR <sup>a</sup> ), G/L	16.3 [11.4-23.8]	69/73	23.2 (10.4-38.3)	30.65 (9.75-39.65)	24.5 (23.8-25.9)
Platelets median (IQR <sup>a</sup> ), G/L	402 [338-513]	73/73	392.5 (337.5-507)	473 (395.25-571.5)	339 (281-374)
Reticulocytes median (IQR <sup>a</sup> ), G/L	133 [82-193.75]	68/73	128 (88.75-189.5)	172 (110-189)	103 (84-147)
Creatinine median (IQR <sup>a</sup> ), μmol/L	36 [25-53.25]	73/73	39.150 (25.25-82)	36 (28-64.15)	54 (25-61)

Renal failure, n(%)	24 (32.9)	73/73	10 (50)	4 (36.36)	6 (66.6)
ASAT <sup>b</sup> median (IQR <sup>a</sup> ), IU/L	107 [57.75-264]	73/73	129 (53-319)	120 (50.25-132.5)	218 (64-419)
ALAT <sup>c</sup> median (IQR <sup>a</sup> ), IU/L	22 [14-35.75]	73/73	19 (14-46)	15.5 (12.5-24.5)	35 (17-84)
PT <sup>d</sup> median (IQR <sup>a</sup> ), %	77 [61.25-87]	56/73	75 (47-84.5)	76 (61-81)	49 (33.5-88)
Hepatic failure, n (%)	4 (7.1)	56/73	3 (15)	1	2
LDH <sup>e</sup> median (IQR <sup>a</sup> ), IU/L	1601.5 [1021.2-2145.2]	62/73	1357 (930-2270)	1214 (939.5-1488)	1649 (1187-4999)
Low haptoglobin, n(%)	70 (100)	70/73	20 (100)	11	9
Indirect bilirubin median (IQR <sup>a</sup> ), µmol/L	45 [28.5-98]	73/73	58.5 (27.75-105.25)	30 (23.5-100)	85 (45-106)
CRP <sup>f</sup> median (IQR <sup>a</sup> ), mg/L	26 [10-53]	73/73	24 (11.75-62.25)	17 (13.5-50.5)	27 (14-63)
PCT <sup>g</sup> median (IQR <sup>a</sup> ), ng/mL	1.76 [0.79-3.79]	32/73	2.69 (0.96-29.12)	1.76 (1.23-48.8)	3.62 (1.21-22.25)
Venous blood gas n (%) / Arterial blood gas, n (%)	25 (34.2)/13 (17.8)	34/73	-	-	-
pH median (IQR <sup>a</sup> ),	7.355 [7.27-7.42]	34/73	7.33 (6.8-7.485)	7.13 (6.95-7.5)	7.36 (7.055-7.41)
Lactates median (IQR <sup>a</sup> ), mmol/L	3.05 [1.8-7.725]	34/73	3.1 (1.8-15)	8.5 (2.8-14.25)	3.1 (1.5-13.9)
Methemoglobin median (IQR <sup>a</sup> ), % Hb	8.750 [4.52-14.47]	20/73	14 (5.5-22.575)	9.1 (7.35-14.6)	18.9 (12.05-24.45)
<u>Hospitalization place, n (%) days</u>		73/73			
Pediatrics, n(%)	51 (69.8)	73/73	11 (55)	6	5
PICU <sup>i</sup>	13 (17.8)	73/73	7 (35)	4	3
<u>Stay, median (IQR<sup>a</sup>), days</u>	4 (3-5)	63/73	4 (3-5.5)	4	4
<u>Blood transfusion, n (%)</u>	73 (100)		18 (16.18-20.5)	18 (16.7-18.2)	20 (18-32)
<u>Quantity, median (IQR<sup>a</sup>), mL/kg</u>	20 [15-20]	69/73			
<b>Number</b>					
1 n(%)	57 (81.4)	70/73	14 (70)	9	5
2 n(%)	10 (14.3)	70/73	4 (20)	2	2
> 2 n(%)	2 (2.8)	70/73	2 (10)	0	2
Intubation, n (%)	6 (8.4)	71/73	3 (15)	0	3
Hemodynamic support, n (%)	4 (5.6)	71/73	2 (10)	0	2
Dialysis, n (%)	3 (4.2)	71/73	2 (10)	0	2
Confirmation deficiency conventional method, n (%)	50 (68.5)	73/73	15 (75)	-	-
Presence of bite cells in blood smear, n (%)	36 (61)	59/73	11 (55)	-	-
G6PD activity during hemolysis median (IQR <sup>a</sup> ), IU/gHb	8.6 [4.25-16.3]	49/73	11.6 (3.35-19.4)	-	-
Number of patients confirmation of deficiency during hemolysis, n (%)	16 (32)	50/73	4 (20) (30.8)	-	-
G6PD activity away from hemolysis median (IQR <sup>a</sup> ), IU/gHb	2.3 [1.05-3.35]	49/73	2 (0.7-3.3)	-	-
Number of patients confirmed lately, n (%)	47 (64.4)	50/73	14 (70) (87.5)	-	-
Erythrocyte enzyme with G6PD activity	18 (28.1)	64/73	9 (45)	-	-
Lost to follow-up, n (%)	42(57.5)	73/73	7 (35)	5	2
Recurrence of hemolysis, n (%)	8 (11.1)	72/73	2 (10)	1	1
Death, n (%)	3 (4.1)	73/73	0 (0)	0	0

<sup>a</sup>: interquartile range 25-75, <sup>b</sup>: aspartate aminotransferase, <sup>c</sup>: alanine aminotransferase, <sup>d</sup>: prothrombin, <sup>e</sup>: lactate dehydrogenase, <sup>f</sup>: C-reactive protein, <sup>g</sup>: procalcitonin, <sup>h</sup>: oxygen partial pressure, <sup>i</sup>: pediatric intensive care unit

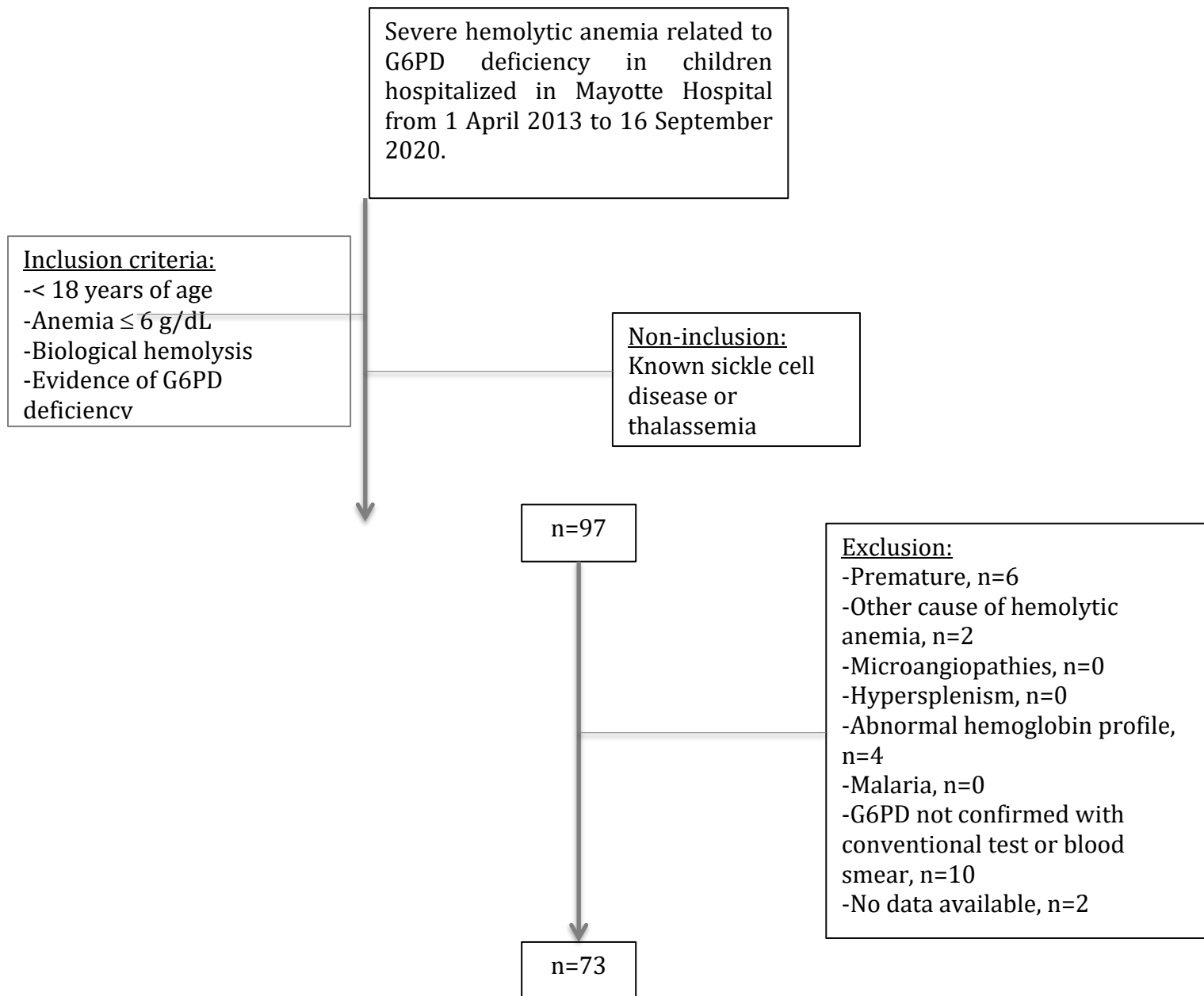


Table 2: Infectious pathogens and site

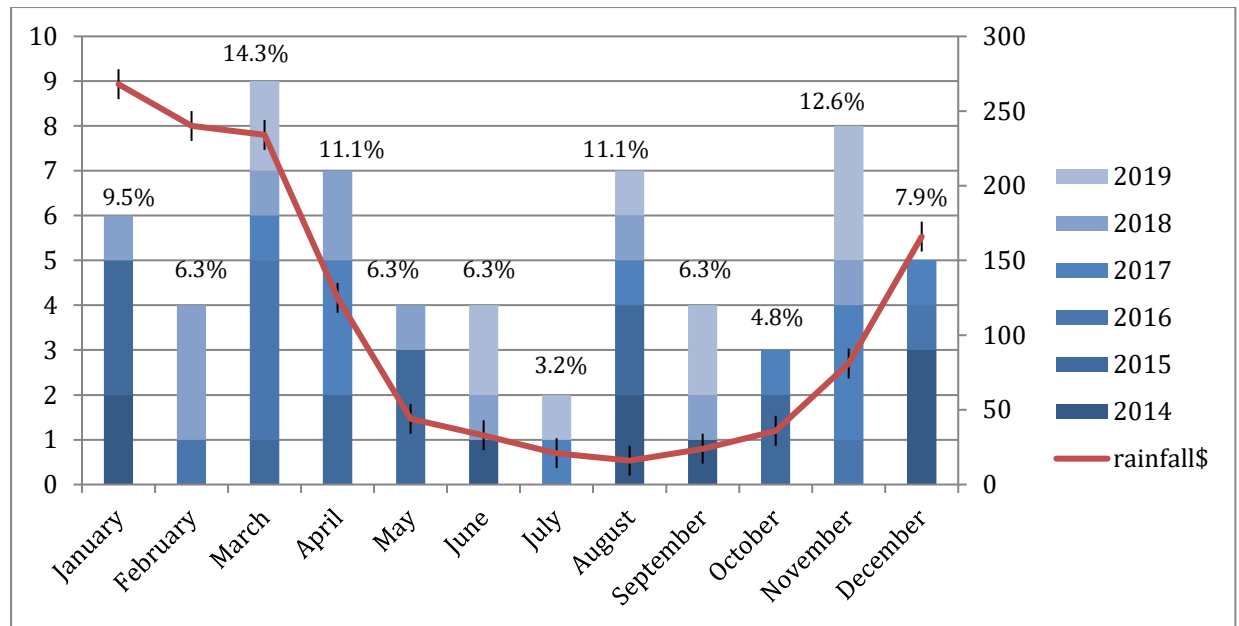
<u>Site</u>	<u>Microorganism</u>	<u>Number of patients/patients tested</u>
<u>Stool</u>	Enteroinvasive <i>E. coli</i>	1
<u>Blood culture</u>	<i>Salmonella Typhi</i>	2
<u>Blood PCR</u>	CMV	1
	Dengue/Leptospirosis	0/20
<u>Blood serology</u>		
	HAV IgM	2/16
	EBV IgG	9/21
	EBV IgM	2/21
	Parvovirus B19 IgG	6/31
	Parvovirus B19 IgM	0/31
<u>Nasopharynx PCR</u>	VRS	1
	Rhinovirus/Enterovirus	1
<u>Cerebrospinal fluid PCR</u>	EBV, CMV, VZV	1

## Figures

**Figure 1** Flowchart



**Figure 2: Patient repartition according to the month of hospitalization\*.**



\*Only whole years are represented. \$: Average precipitation in Mayotte 1978-2017, data source hikersbay.com. Rainy season according to Météo France: December to March. Right axis: rainfall in millimeters. Left axis: number of patients. The percentage of patients according to the month of hospitalization appears at the top of each data bar.

## LE SERMENT D'HIPPOCRATE

Au moment d'être admis(e) à exercer la médecine, je promets et je jure  
d'être fidèle aux lois de l'honneur et de la probité.

Mon premier souci sera de rétablir, de préserver ou de promouvoir la  
santé dans tous ses éléments, physiques et mentaux, individuels et  
sociaux.

Je respecterai toutes les personnes, leur autonomie et leur volonté, sans  
aucune discrimination selon leur état ou leurs convictions. J'interviendrai  
pour les protéger si elles sont affaiblies, vulnérables ou menacées dans  
leur intégrité ou leur dignité. Même sous la contrainte, je ne ferai pas  
usage de mes connaissances contre les lois de l'humanité.

J'informerai les patients des décisions envisagées, de leurs raisons et de  
leurs conséquences.

Je ne tromperai jamais leur confiance et n'exploiterai pas le pouvoir  
hérité des circonstances pour forcer les consciences.

Je donnerai mes soins à l'indigent et à quiconque me les demandera. Je  
ne me laisserai pas influencer par la soif du gain ou la recherche de la  
gloire.

Admis(e) dans l'intimité des personnes, je tairai les secrets qui me seront  
confiés. Reçu(e) à l'intérieur des maisons, je respecterai les secrets des  
foyers et ma conduite ne servira pas à corrompre les mœurs.

Je ferai tout pour soulager les souffrances. Je ne prolongerai pas  
abusivement les agonies. Je ne provoquerai jamais la mort délibérément.

Je préserverai l'indépendance nécessaire à l'accomplissement de ma  
mission. Je n'entreprendrai rien qui dépasse mes compétences. Je les  
entretiendrai et les perfectionnerai pour assurer au mieux les services qui  
me seront demandés.

J'apporterai mon aide à mes confrères ainsi qu'à leurs familles dans  
l'adversité.

Que les hommes et mes confrères m'accordent leur estime si je suis fidèle  
à mes promesses ; que je sois déshonoré(e) et méprisé(e) si j'y manque

## **Anémie hémolytique due au déficit en G6PD chez les enfants à Mayotte : une complication fréquente et sévère.**

### **Résumé**

**Introduction :** L'anémie hémolytique est une complication rare chez les patients atteints de déficit en G6PD. Elle est surtout décrite chez les patients porteurs de la mutation Méditerranéenne qui sont décrits par l'OMS comme ayant une activité G6PD sévèrement altérée. A Mayotte, la majorité des patients sont porteurs du variant Africain connu pour avoir une activité G6PD modérée. Nous observons à Mayotte beaucoup d'anémies hémolytiques sévères avec une hémoglobine inférieure à 6g/dL. Dans cette étude nous avons voulu décrire l'épidémiologie, la clinique, la biologie et la prise en charge des enfants présentant une crise hémolytique sévère secondaire à un déficit en G6PD. Le second objectif était d'analyser leur génotype quand il était disponible.

**Méthode :** Les données de patients ayant présenté une anémie hémolytique sévère entre le 1<sup>er</sup> Avril 2013 et le 16 septembre 2020 ont été recueillies de manière rétrospective.

**Résultats :** 73 enfants ont présenté une anémie hémolytique sévère durant cette période à Mayotte. La médiane de l'hémoglobine était de 3,9g/dL. Tous les patients ont bénéficié d'une transfusion et d'une hospitalisation. Vingt enfants ont eu un génotype : 11 étaient porteurs de la mutation Africaine et 9 de la mutation Méditerranéenne.

**Conclusion :** Des éléments déclenchant habituellement retrouvés, la prise de médicaments ne faisait pas partie des éléments déclenchant de notre cohorte, et l'ingestion de fèves a été retrouvée chez un seul enfant. La médecine traditionnelle est très présente et l'une des plante souvent utilisée *Acalypha Indica* était souvent retrouvée.

Les anémies hémolytiques sévères dues au déficit en G6PD sont fréquentes à Mayotte. L'atteinte clinique est plus sévère et n'est pas corrélée au génotype. Les variants Africain et Méditerranéen ont la même gravité.

**Discipline : pédiatrie, hématologie**

**Mots clés :** Déficit en G6PD, anémie hémolytique sévère, génotype Africain et méditerranéen.

## **Acute hemolytic anemia due to G6PD deficiency in children in Mayotte : a frequent and severe complication.**

### **Abstract**

#### **Background :**

Severe hemolytic anemia is a rare complication of Glucose-6 Phosphate dehydrogenase (G6PD) deficit. It is described in Mediterranean variant corresponding to severe G6PD activity deficit according to the WHO classification. In Mayotte, the majority of patients are African variant with moderate deficit activity. Yet we observe a lot of severe hemolytic anemia defined by a hemoglobin rate lower than 6 g/dL. In this study, we aimed to describe the epidemiological, clinical, biological and treatment of children, presenting severe hemolysis crisis secondary to G6PD deficiency in Mayotte. The secondary objective was to study genotype when it was available.

**Method :** A retrospective collection of children with severe hemolytic anemia related to G6PD deficiency hospitalized in Mayotte hospital from April 1st 2013 to September 16<sup>th</sup> of 2020 have been achieved.

**Results :** 73 children had severe anemia due to G6PD deficit in Mayotte. The median of hemoglobin during hemolysis crisis was 3.9 g/dl. All patients benefited for a transfusion and hospitalization. Twenty patients had a genotype: eleven had African mutation and 9 had a Mediterranean mutation.

**Discussion :** Among the most common triggers of G6PD acute hemolysis anemia, drugs were not present and fava bean ingestion was found in only one child. One of the particular triggers was traditional medicine, including *Acalypha Indica*.

Severe hemolysis crisis of children due to G6PD deficiency is frequent in Mayotte. Patients are more serious, and severity is not correlated with genotype: African (A-) variant and Mediterranean variant have the same gravity.

**Discipline pediatrics, hematology**

**Keywords** G6PD deficiency, severe hemolysis anemia, African and Mediterranean genotype