



Research Paper

## JAK2 V617F POSITIVE POLYCYTHEMIA VERA IN CHILDHOOD

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Polycythemia Vera (PV) is a rare disorder in children and adolescents. Data on clinical and biological features as well as on treatment modalities are sparse. The V617F mutation of *JAK2* has been described recently and is found in almost 90% of adult patients with PV. This mutation allows now a reliable and early diagnosis. Therapeutic management is based on phlebotomy and cytoreductive therapy. In young adults and children, interferon alpha is theoretically superior as it is effective and there is no risk of inducing leukemia. We studied the *JAK2* (V617F) mutation in a sample of 200 MPD patients. Only one case of pediatric polycythemia Vera has been detected in a 17-year-old girl with the V617F *JAK2* mutation.

**Keywords:** *Polycythemia vera, Moroccan child, V617F mutation, Jak2 gene*

### INTRODUCTION

Polycythemia vera is a chronic clonal myeloproliferative disorder which is characterized by an increasing total erythrocyte mass and hemoglobin, without erythropoietin stimulation (Adamson J W et al., 1976). It has an incidence of 3-5 per 100,000 inhabitants and primarily affects adults over 50 years (Levine R L et al., 2005 and Ania B J et al., 1994).

In March 2005 (Baxter E J et al., 2005; Levine R L et al., 2005; James C et al., 2005; and Zhao R et al., 2005), a single mutation in *JAK2* gene involved in transduction signal of protein kinase

activity was found in 65 to 97 % of patients affected by Polycythemia vera. This mutation (V617F) induces an activation of *JAK2* signal and contributes to the myeloproliferative state.

The incidence of polycythemia vera (PV) in children and adolescents is extremely low. Only 1% of patients present PV before 25 years old, and only 0.1% are younger than 20 years (Adamson J W et al., 1976).

Thus, very few pediatric PV patients have been reported to date (Straczek H et al., 2005 and Vodoff et al. 1997). Several cases of polycythemia in children are in fact familial diseases that are

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caused by hereditary defects consisting of specific mutations of the erythropoietin receptor, thrombopoietin or MPL genes.

In this work, we report a case of polycythemia Vera with positive JAK2 V617F mutation diagnosed in a Moroccan young girl (17 years).

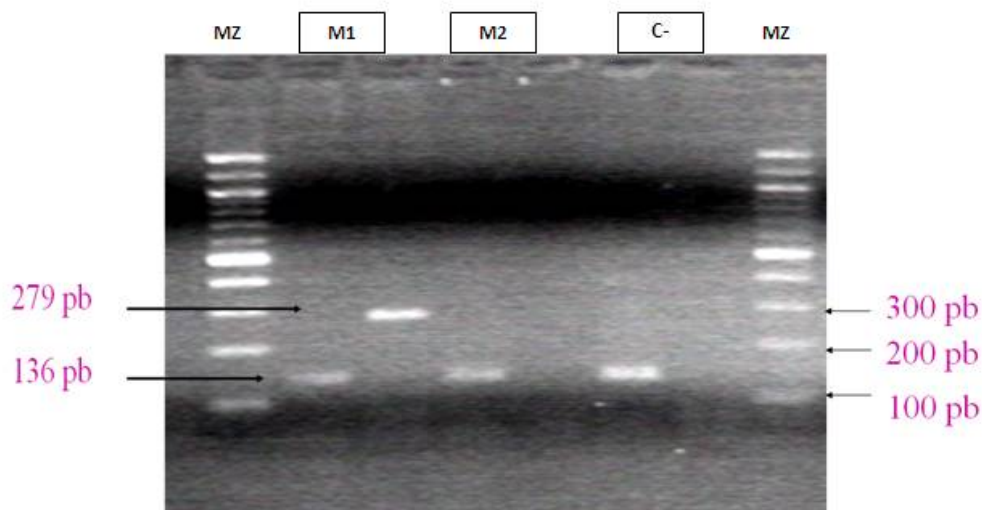
### MATERIALS AND METHODS

In order to confirm the diagnosis, peripheral blood sample was taken after obtaining informed consent from patient. A molecular study of the JAK2 gene was carried out using the ARMS-PCR method to search the V617F mutation that was positive (Figure 1).

### RESULTS AND DISCUSSION

Since 2006, we studied the JAK2 (V617F) mutation in a sample of 200 MPD patients (Benmoussa et al., 2009). Only one case of pediatric polycythemia vera has been detected. A 17 years old girl has been admitted to the Internal Medicine center of Avicenne University hospital in Rabat. The studied case doesn't have any particular personal or familial history. The onset of illness began seven months ago with progressive abdominal mass in the upper left quadrant associated to headache, tinnitus, vertigo and facial erythrose. All these signs occur in a context of apyrexia, and weight loss. At the

**Figure 1: PCR Products for the JAK2 V617F (agarose gel at 2%)**



Note: M1 – Positive patient (V617F) JAK2, M2 – Negative patient, C – Negative Control.

**Table 1: Hematological Data of the Patient**

Hematological Parameters	Values
Hemoglobin (g/dl)	19.9
Hematocrit (%)	61
Platelets (×10 <sup>9</sup> /L)	684 000
Leucocytes (×10 <sup>9</sup> /L)	16 700
Lymphocytes (×10 <sup>9</sup> /L)	2839
PNN	13 193
Erythropoietin (EPO) level mU/ ml	2.4

**Table 2: Comparison of Patient's Hematological Data**

Hematological Parameters	Values	Control values
Hemoglobin (g/dl)	19.9	16.5
Hematocrit (%)	61	51.4
Platelets (×10 <sup>9</sup> /L)	684 000	1 018 000
Leucocytes (×10 <sup>9</sup> /L)	16 700	14 300

physical examination the patient was in good general condition; only cutaneous observation showed a facial erythroze and in the abdominal exam, there was a splenomegaly. Full blood values were summarized in the Table 1.

High levels of hemoglobin (19.9 g/dl), hematocrit (61%) and platelets (684,000 elemnts/l). was found. In contrast, erythropoietin level were normal (2.4 mU / ml). An Abdominal ultrasonography showed homogeneous splenomegaly (16 cm).

The myelogram was most likely to an essential polycythemia. Required bone-marrow biopsy (BMO), showed a suggestive appearance of myeloproliferative disorder particularly polycythemia vera.

Our results confirmed the genetic basis of polycythemia. Thus, the patient was initially treated with phlebotomy at three times and acetylsalicylic acid (KARDEGIC) (160mg/d). After eight months, the full blood count showed the results summarized in Table 2. We noted a decrease in hemoglobin, hematocrit and red blood cells levels. In contrast, platelet count increased to 1 018 000 elmts/mm<sup>3</sup>. According to this result, it was decided to start a treatment with hydroxyurea (HYDREA) at a dose of 20 mg / kg / day.

Myeloproliferative disorders are a heterogeneous group of malignancies characterized by chronic acquired clonal production of myeloid cells (granulocyte precursor cell lines, erythroid and megakaryocytic) with conservation of the ability to differentiate (Spivak J L et al., 2002).

In this group of diseases, four syndromes are defined: chronic myeloid leukemia, essential thrombocythemia (ET), primary myelofibrosis and polycythemia vera (J C Chomel et al., 2009) which is a rare disease in childhood. Very few

pediatric cases have been reported in PV patients aged less than 20 years, the annual incidence is estimated at 2 cases/1 million (McNally R J et al., 1997). This low frequency could be explained by the late onset of complications that will be reason for consultation. In our study, the incidence of polycythemia vera in children was 1.7%. This finding is in harmony with literature (McNally R J et al., 1997, Osgood E E et al., 1965).

Although unusual in childhood, PV can lead to serious complications involving the prognosis such as progressing into Acute Leukemia (AL) or myelofibrosis with myeloid metaplasia (Leone G et al., 2001 and Passamonti Francesco et al., 2003).

Unfortunately, the clinical and laboratory data in pediatric cases of PV are still insufficient. Therefore, it seemed appropriate to report our observation in order to enrich the knowledge about this disease. To the best of our knowledge, there is no information about another Moroccan case of pediatric PV with (V617F) JAK2 mutation.

In this case, the patient has presented progressive heaviness in the left upper quadrant associated with headache, tinnitus, vertigo and facial erythroze. The same signs have been described in our adult patients. In general, clinical and hematological features are similar between children, adolescents and adult (Cario H et al., 2005 and Spivak J L et al., 2002).

In addition, PV can lead to complications like Acute Leukemia (AL) or myelofibrosis which increase because of the long-term of disease evolution and the long exposure to myelo-suppressive agents (Passamonti Francesco et al., 2003). In deed, these complications reduced the life expectancy of children; after 20 years, the risk of AL and MMM reach 15% and 10%,

respectively. Also, a predisposition to develop Budd-Chiari has been reported in children especially females with PV syndrome (Cario, H et al., 2009). Actually, the case studied hasn't presented any complication. This may be due to the short evolution of the disease.

To confirm the diagnosis of polycythemia vera, we used the diagnostic criteria established by WHO (Tefferi A et al., 2007) after the discovery of the (V617F) JAK2 mutation. Found in 65 to 97% of patients with PV (Marlow AA et al., 1960), this mutation was considered as a biological marker of the disease cited.

In a previous study (Teofili L et al., 2007), 38 children with PV and ET were diagnosed in accordance with the WHO criteria. The first important observation in this study was the high frequency of hereditary forms.

In addition, this study showed that the incidence of JAK-2V617F mutation in children with PV was significantly lower than in adult control group patients (92% vs. 37%). It also concludes that in a child investigated for PV or ET, a careful screening for familial thrombocytosis and erythrocytosis is required, since familial MPDs observed at this age are most likely due to inherited, although often unknown, defects.

In our case, the JAK-2V617F mutation was positive at the age of 17 years old, so it could be speculated that children showing a wild type JAK2 may become JAK2V617F positive at a later age. However, the presence of EEC growth and of PRV-1 RNA over-expression in patients who proved negative for the JAK2V617F mutation suggests that, in pediatric MPDs, other molecular defects, functionally similar to the JAK2V617F mutation, could affect the JAK2 dependent signalling pathway (Teofili L et al., 2008 and Thiele J et al., 2009).

Therefore, the data that have emerged from these studies indicate that the new criteria, including the JAK2 mutation as a major element of the diagnosis were not appropriate for the diagnosis of pediatric essential polycythemia (Tefferi A et al., 2007 and Teofili L et al., 2008).

Importantly, the identification of specific hereditary defects could help these young patients to avoid more invasive diagnostic approaches, such as a bone marrow biopsy. As therapeutics, our patient was initially treated by phlebotomy and acetyl-salicylic acid; we have noticed an improvement in the hemoglobin, hematocrit and red blood cells levels. In contrast, there was an increasing in platelet count which could be caused by phlebotomy.

Similarly, a study by the "polycythemia vera study group (PVSG-01) (Berk P D et al., 1995) showed the existence of a higher risk of thrombocytosis during the first three years of treatment with phlebotomy, when the hematocrit was 50%. Actually, our patient is treated with hydroxyurea (Hydrea) and presents a good evolution.

## CONCLUSION

Polycythemia vera is a heterogeneous disease that can reach both adults and children. It may be presented as familial or sporadic form. The rarity of pediatric PV has determined for many years, data on the clinical presentation and biologic features have been sparse (Marlow AA et al. 1960). Furthermore, all biological information usually obtained from studies on adult series is applied to pediatric patients as well.

Recently, several studies (Teofili L, et al., 2007; Teofili L et al., 2008 and Thiele J et al., 2009) have investigated PV in children. A low incidence of

(V617F) JAK2 mutation was demonstrated and it was speculated that different genetic basis were implicated. Thus, we concluded that new criteria of WHO are not appropriate in children PV. Also, a careful screening for familial erythrocytosis is required in the children investigated for PV, since familial MPDs observed at this age are most likely due to inherited, although often unknown, defects. Importantly, further researches and close collaborations between clinicians and biologists are needed to demystify the genetic basis and find other diagnostic criteria of PV in children.

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