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J Hematol. 2021;10(3):106-113

Essential Thrombocythemia in Children: A Retrospective Study

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Abstract

Background: Essential thrombocythemia (ET) is one of the "classic" Philadelphia chromosome negative (Ph-) myeloproliferative neoplasms characterized by sustained thrombocytosis, increased megakaryopoiesis and high risk of vascular complications. ET is very rare in childhood. The annual incidence is approximately 1 per 10,000,000 in children less than 14 years, and about 60 times lower than adults. The genetic landscape and clonal features in childhood ET has not been well defined. There is no evidence-based guidance on the diagnosis of childhood ET.

Methods: Medical records of 28 pediatric patients (age ≤ 14 years at diagnosis) with ET were reviewed and evaluated to characterize the different mutation profiles and to evaluate the treatment modalities used and the potential long-term outcome.

Results: More than half of the patients were found to have positive history of parental consanguinity (57.1%) whereas positive family history was documented for more than a quarter of our patients (28.6%). Janus kinase 2 gene (*JAK2*) V617F mutation was positive in two of 26 patients (7.7%). Myeloproliferative leukemia virus oncogene (*MPL*) exon 10 and calreticulin (*CALR*) mutations were tested in eight patients, which were negative for all of them. Treatment included low-dose aspirin (LDA) in seven patients (50%), combination of LDA with hydroxyurea in three patients (21.4%), hydroxyurea in two patients (14.3%), combination of platelets apheresis with LDA and anagrelide in one patient each (7.1%). During the treatment, two patients experienced stroke (7.1%), one patient developed Budd-Chiari syndrome (3.6%) and one patient developed azoospermia (3.6%).

Conclusions: The incidence of ET in children is extremely low in Saudi Arabia. Most of the children with ET were asymptomatic, and thrombocytosis was often discovered incidentally. *JAK2* V617F mutation has no known impact on the prognosis or on the outcome of the disease in the pediatric age group that is in contrast to the adult ET. Children less than 1 year are at high risk for complications particularly during acute precipitating infectious episode. The potential complications and clinical course of pediatric ET are unpredictable.

Keywords: Essential thrombocythemia; Pediatric ET; *JAK2* mutation

Introduction

Essential thrombocythemia (ET) is one of the subtypes of breakpoint cluster region protein/Abelson murine leukemia viral oncogene homolog 1 (*BCR*/*ABL1*)-negative myeloproliferative neoplasms (MPNs). It is a clonal hematopoietic stem cell disorder that is characterized by isolated thrombocytosis and is associated with complications such as thrombosis, hemorrhage, and progression to myelofibrosis or acute myeloid leukemia. ET is a disorder occurring predominantly in middle-age adults. The disorder is very rare in childhood and adolescence [1-3]. The annual incidence of ET is approximately 1 per 10,000,000 in children less than 14 years and about 60 times lower than that of adults [4-6].

The past decade and a half has enabled us to understand ET better due to the developments made in the field of molecular pathogenesis. Discovery of Janus kinase 2 gene (*JAK2*) V617F in 2005, followed by myeloproliferative leukemia virus oncogene (*MPL*) mutations in 2006 and calreticulin (*CALR*) mutations in 2013 has contributed to a more subtle understanding of disease pathology, diversity of clinical presentation and diagnostic possibilities [7-11]. The most frequent driver mutation seen is *JAK2* V617F, which is found in about 99% of patients with polycythemia vera (PV), 55% ET, and 65% in primary myelofibrosis (PMF) [12]. The genetic landscape and clonal features in childhood ET has not been well defined.

For a diagnosis of ET to be consistent with the World Health Organization (WHO) criteria it has to have a platelet count of $\geq 450 \times 10^9$/L, presence of one of the three above mentioned driver mutations or in their absence the exclusion of other causes of thrombocytosis (reactive and clonal), and bone marrow morphologic assessment, especially for distinguishing ET from prefibrotic PMF and "masked" PV [13, 14]. In addition to clonal thrombocytosis, some patients with ET can have clinical signs of mild splenomegaly, leukocytosis, microvascular symptoms, thrombotic and bleeding complications

Manuscript submitted March 28, 2021, accepted April 17, 2021
Published online June 16, 2021

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doi: https://doi.org/10.14740/jh822

while running the risk of leukemic transformation or fibrotic progression as time goes on.

Herein we present our retrospective analysis of 28 patients treated at our institution. Our aim was to evaluate and characterize the different mutation profiles associated with ET in our indigenous population and assess the treatment modalities used along with their potential long-term outcome.

Materials and Methods

A retrospective case study was conducted at the King Faisal Specialist Hospital and Research Center (KFSHRC), Saudi Arabia. Medical records of 28 pediatric patients (age ≤ 14 years at diagnosis) with ET from January 1987 to December 2017 were reviewed and evaluated. Data on demographics, diagnosis, hematological parameters and outcome were obtained from clinical databases and through medical charts review. After quality assurance checks, the dataset was then transferred to IBM-SPSS for Windows Version 20.0 for final analysis. Furthermore, a literature review of similar studies was conducted, and a comparison was drawn between the findings of our study and the previous literature.

Statistical considerations

All continuous data are presented as median with minimum and maximum points, while discrete data are provided as number (%). Independent-samples Mann-Whitney U test was utilized to test for significance of difference between genders for continuous data.

Ethical consideration

This study was submitted to the Institutional Review Board of KFSHRC, Riyadh, Saudi Arabia, and was approved by the Research Advisory Committee through established procedures with approval number 2181192.

This study was conducted following international guidelines and policies on conducting research on human subjects. Data of interest collected from the patients' medical records were secured and governed by the institutional policies on patient confidentiality and privacy. All patient identifiers were masked at the time of data collection.

Results

This study showed a female to male ratio of 2.1:1, a female preponderance was observed. The median age at diagnosis was 8.8 years (range, at birth - 13.8 years). More than half of the patients were found to have positive history of parental consanguinity (n = 16, 57.1%). The patient's characteristics and primary disease-related parameters are presented in Table 1.

With a median follow-up time of 71.6 months, all our patients were alive at the last follow-up. Patient's hematological parameters at presentation are provided in Table 2. The median platelet count at presentation was found to be 846.5 × 10^9/L with a range of 529 × 10^9/L to 2,003 × 10^9/L (Fig. 1). We did not observe statistically significant difference between the genders for all recorded hematological values, neither any measure of correlation was found to be statistically significant except for hemoglobin (Hb) and red blood cell (RBC) (Spearman's rho = 0.755, P < 0.001, Fig. 2). Peripheral blood film confirmed thrombocytosis in all patients. Their workup included serum ferritin level, iron profile, prothrombin time (PT), activated partial thrombin time (PTT), von Willebrand level and function. PT and PTT were prolonged in 12 (52.2%) and five (21.7%) patients, respectively. Platelet function assay (PFA-100) was normal in all three patients, for whom it was performed. Bone marrow findings confirmed a hyperplastic megakaryocytic marrow, large and mature morphology with hyperlobated nuclei and abundant cytoplasm without myelofibrosis in all patients. Standard cytogenetic analysis for *BCR/ABL* rearrangement showed no detectable abnormalities. *JAK2* V617F mutation was positive in two of 26 (7.7%) patients (Table 3). Clinical and laboratory features of these patients are provided in Table 4. Median platelet counts were significantly lower in *JAK2* positive cases. Other than *JAK2* V617F mutation, we checked for *MPL* exon 10 and *CALR* mutations in eight patients that was negative for all of them. Evaluation for von Willebrand (antigen and activity) was performed in all patients, and the level was normal in all patients (Table 2).

With regards to treatment, half of the patients (n = 14) were offered treatment while the other half was kept under observation. Treatment included low-dose aspirin (LDA) in seven patients (50.0%), combination of LDA with hydroxyurea in three patients (21.4%), hydroxyurea alone in two patients (14.3%), combination of platelets apheresis with LDA and anagrelide in one patient each (7.1%). During the treatment and follow-up period, two of our patients experienced stroke (7.1%), one patient developed Budd-Chiari syndrome (3.6%) and one patient developed azoospermia (3.6%). The two patients who had stroke were on LDA, the patient who developed Budd-Chiari syndrome was on combination of platelets apheresis with LDA, while the patient who developed azoospermia was receiving hydroxyurea.

Discussion

The therapeutic goal in general for ET patients is to avoid the occurrence of major vascular events while minimizing the side effects induced by medication. Consensus regarding the management of adult ET follows a risk-adapted strategy. Currently, there is insufficient evidence to guide the management of childhood ET and usually a conservative approach is adopted. At our institution we treated our pediatric ET patients with LDA, if microcirculatory symptoms were present or the platelet counts were more than 1 million. Hydroxyurea or anagrelide was added, if the existing symptoms or the increased platelet counts did not improve. Otherwise, all other patients

Table 1. Demographics and Clinical Characteristics (N = 28)

Variables of interest	Female	Male	Overall
Patients, n (%)	19 (67.9)	9 (32.1)	28 (100.0)
Age at diagnosis (years)	10.0 (0.14, 13.8)	6.0 (at birth, 12.1)	8.8 (at birth, 13.8)
Height (cm)	127.0 (61.0, 163.0)	132.0 (70.0, 151.0)	130.0 (61.0, 163.0)
Weight (kg)	40.1 (6.7, 62.0)	28.7 (9.1, 41.0)	35.0 (6.7, 62.0)
Parental consanguinity, n (%)			
Negative			12 (42.9)
Positive			16 (57.1)
Symptoms[a], n (%)			
Headache			4 (14.3)
Bleeding			2 (7.1)
Vomiting			2 (7.1)
Abdominal pain			1 (3.6)
Nausea			1 (3.6)
Fatigue			1 (3.6)
Palpitation			1 (3.6)
Myopathy			1 (3.6)
Blood group[b], n (%)			
A+			5 (27.8)
B+			1 (5.6)
O+			10 (55.6)
AB+			2 (11.1)

[a]Twenty patients (71.4%) were asymptomatic. [b]N = 18. Values are number (%) or median (minimum, maximum).

were managed conservatively with regular follow-up visits and complete blood count (CBC) every 3 - 6 months.

We studied a total of 28 patients diagnosed with ET. In our cohort of pediatric patients, the diagnosis of ET was

Table 2. Hematological Profile at Presentation

Parameters	Female (n = 19)	Male (n = 9)	Overall (n = 28)	P value
Platelets ($\times 10^9$/L)	826.0 (529.0, 2,003.0)	848.0 (625.0, 1,556.0)	846.5 (529.0, 2,003.0)	0.562
WBC ($\times 10^9$)	8.8 (4.1, 16.5)	9.6 (7.8, 15.9)	9.2 (4.1, 16.5)	0.172
Hb (g/L)	123.0 (101.0, 156.0)	126.0 (119.0, 152.0)	125.5 (101.0, 156.0)	0.383
RBC ($\times 10^{12}$/L)	4.4 (3.4, 5.6)	4.8 (4.5, 5.4)	4.6 (3.4, 5.6)	0.142
Reticulocyte count (%)	1.3 (0.9, 2.0)	1.1 (0.7, 1.7)	1.3 (0.7, 2.0)	0.267
Reticulocyte count ($\times 10^9$/L)	60.7 (35.0, 93.0)	55.9 (15.0, 99.0)	55.9 (15.0, 99.0)	0.764
RDW	14.0 (12.1, 18.0)	13.0 (8.0, 15.0)	13.8 (8.0, 18.0)	0.085
MCV	81.8 (70.0, 95.0)	80.2 (75, 88.4)	80.9 (70.0, 95.0)	0.322
MPV	9.1 (8.4, 10.5)	8.8 (5.5, 10.0)	9.0 (5.5, 10.5)	0.129
Serum ferritin	40.0 (18.0, 237.0)	34.4 (23.0, 101.0)	40.0 (18.0, 237.0)	0.809
TIBC	57.6 (49.9, 80.8)	59.0 (53.8, 67.0)	58.1 (49.9, 80.8)	0.945
ESR	13.0 (5.0, 222.0)	16.0 (10.0, 113.0)	14.5 (5.0, 222.0)	0.443
vWF antigen	1.51 (0.5, 60.0)	39.5 (0.8, 94.0)	1.51 (0.5, 94.0)	0.556
vWF assay	0.6 (0.4, 50.0)	20.5 (0.6, 49.0)	0.93 (0.42, 50.0)	0.556

Values are median (minimum, maximum). WBC: white blood cell; Hb: hemoglobin; RBC: red blood cell; RDW: red cell distribution width; MCV: mean corpuscular volume; MPV: mean platelet volume; TIBC: total iron binding capacity; ESR: erythrocyte sedimentation rate; vWF: von Willebrand factor.

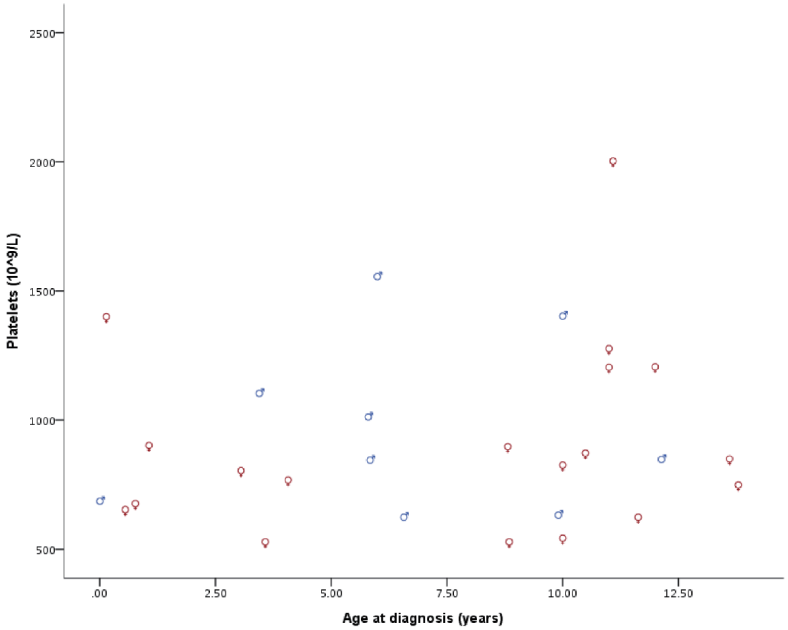

Figure 1. Platelet count at diagnosis by gender and age.

made according to the 2016 WHO criteria in the absence of other known causes of reactive (secondary) thrombocytosis. Most of our patients (n = 20, 71.4%) were asymptomatic with high platelet counts with just a few of them (n = 8, 28.6%) experiencing symptoms. Our results on thrombocytosis in the absence of symptoms are comparable to others. Randi et al reported that majority (60%) of their patients were asymptomatic as well with other studies showing similar results [13]. Our results are also in line with published literature that has shown a low incidence of *JAK2* V617F mutation in childhood ET [14-16].

During the follow-up period, four patients developed

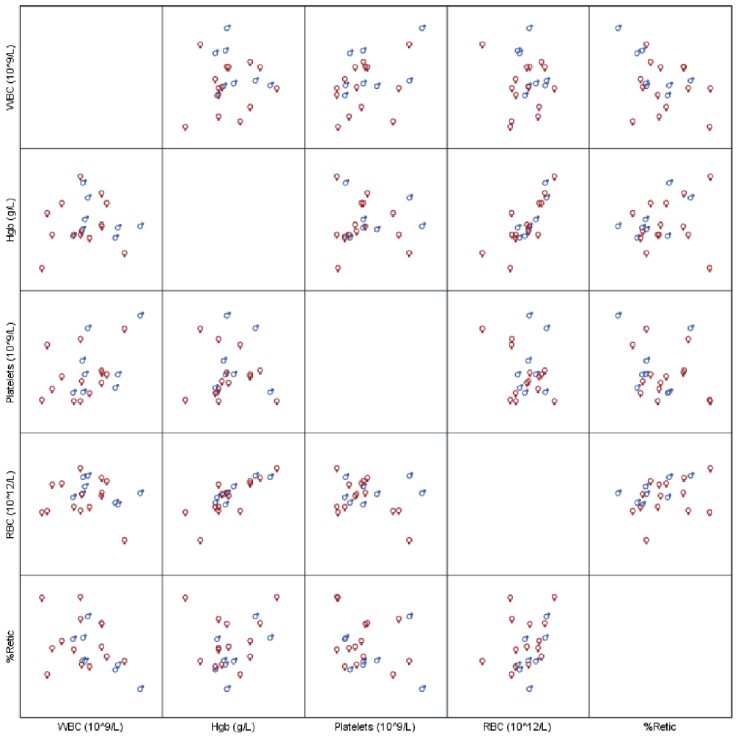

Figure 2. Scatterplot of hematological parameters of interest.

Table 3. Patient's Profile at Presentation, Treatment Regimen and Follow-Up

Patient	Gender	Age at diagnosis (years)	Symptoms at presentation	Platelets ($\times 10^9$/L)	WBC ($\times 10^9$/L)	*JAK2*	*CALR*	*MPL*	Treatment regimen	Symptoms during follow-up	Duration of follow-up (months)
1	Male	6.6	None	625	7.8	Negative	Not done	Not done	None	None	54.9
2	Male	9.9	None	633	9.0	Negative	Not done	Not done	LDA	None	228.6
3	Male	1.2	None	686	12.9	Negative	Negative	Negative	None	None	72.2
4	Male	5.8	None	845	13.2	Negative	Not done	Not done	Anagrelide	None	192.0
5	Male	12.1	None	848	9.2	Negative	Not done	Not done	None	None	41.5
6	Male	5.8	None	1,012	8.9	Negative	Not done	Not done	None	None	41.9
7	Male	3.5	None	1,104	12.8	Negative	Negative	Negative	None	None	12.5
8	Male	10.0	None	1,403	9.6	Negative	Not done	Not done	Hydroxyurea	Azoospermia	87.0
9	Male	6.0	None	1,556	15.9	Not done	Not done	Not done	LDA	None	148.6
10	Female	3.6	None	529	7.9	Negative	Not done	Not done	None	None	178.7
11	Female	8.9	Weakness, fatigue, myopathy	529	8.7	Positive	Not done	Not done	LDA + hydroxyurea	None	218.2
12	Female	10.0	None	543	4.1	Positive	Not done	Not done	Platelets + LDA	Budd-Chiari syndrome	208.4
13	Female	11.6	None	625	9.8	Negative	Negative	Negative	LDA	Stroke	219.5
14	Female	1.6	None	654	16.5	Negative	Not done	Not done	None	None	20.0
15	Female	1.8	Headache, abdominal pain, nausea, vomiting	677	5.3	Negative	Negative	Negative	None	None	113.8
16	Female	13.8	Headache	750	11.3	Not done	Not done	Not done	LDA	None	101.9
17	Female	4.1	Palpitation	769	8.8	Negative	Negative	Negative	None	None	17.6
18	Female	3.1	Bleeding (spontaneous)	805	7.0	Negative	Not done	Not done	None	None	78.7
19	Female	10.0	None	826	6.5	Negative	Not done	Not done	None	None	65.6
20	Female	13.6	None	850	11.9	Negative	Not done	Not done	None	None	21
21	Female	8.8	None	898	11.3	Negative	Not done	Not done	None	None	71.0
22	Female	1.1	None	903	14.2	Negative	Not done	Not done	None	None	32.6
23	Female	11.0	None	1,205	6.5	Negative	Not done	Not done	LDA + hydroxyurea	None	74.5
24	Female	12.0	None	1,207	4.7	Negative	Not done	Not done	LDA	None	227.5
25	Female	11.0	Headache, vomiting	1,277	8.7	Negative	Not done	Not done	LDA + hydroxyurea	None	55.4
26	Female	1.0	Bleeding	1,401	14.0	Negative	Negative	Negative	LDA	Stroke	26.0
27	Female	11.1	None	2,003	9.2	Negative	Negative	Negative	LDA	None	12.1
28	Female	10.5	Headache	873	11.3	Negative	Negative	Negative	Hydroxyurea	None	32.9

WBC: white blood cell; *JAK2*: Janus kinase 2 gene; *CALR*: calreticulin; *MPL*: myeloproliferative leukemia virus oncogene; LDA: low-dose aspirin.

Table 4. Clinical and Laboratory Features[a] by *JAK2* Mutation Positivity (N = 26)

	JAK2+ (n = 2)	*JAK2*- (n = 24)	P value
Age at diagnosis (years)	9.4 (8.9, 10.0)	7.7 (at birth, 13.6)	0.745
Platelets (× 10^9/L)	536.0 (529.0, 543.0)	849.0 (529.0, 2,003.0)	0.012
WBC (× 10^9)	6.4 (4.1, 8.7)	9.2 (4.7, 16.5)	0.123
Hb (g/L)	128.5 (101.0, 156.0)	124.5 (110.0, 152.0)	1.000
Reticulocyte count (× 10^9/L)	89.5 (86.0, 93.0)	55.9 (35.0, 99.0)	0.042
Follow-up time (months)[b]	213.0 (208.4, 218.2)	60.5 (one visit, 228.6)	0.098
Symptoms (at presentations), n (%)			0.474
Asymptomatic	1 (50.0%)	18 (75.0%)	
Symptomatic	1 (50.0%)	6 (25.0%)	
Weakness	1 (33.3%)	None	
Fatigue	1 (33.3%)	None	
Myopathy	1 (33.3%)	None	
Headache	None	3 (30.0%)	
Vomiting	None	2 (20.0%)	
Abdominal pain	None	1 (10.0%)	
Nausea	None	1 (10.0%)	
Palpitation	None	1 (10.0%)	
Bleeding (spontaneous)	None	1 (10.0%)	
Bleeding (NOS)	None	1 (10.0%)	
Complications (during follow-up), n (%)			0.289
None experienced	1 (50.0%)	21 (87.5%)	
With issues	1 (50.0%)	3 (12.5%)	
Budd-Chiari syndrome	1 (100%)	None	
Stroke	2 (66.6%)	None	
Azoospermia	1 (33.3%)	None	

[a]Values are median (minimum, maximum) unless otherwise specified. [b]Overall follow-up time, median (minimum, maximum): 71.6 months (one visit, 228.6). *JAK2*: Janus kinase 2 gene mutation; WBC: white blood cell; Hb: hemoglobin; NOS: not otherwise specified.

complications. Two patients experienced stroke, one was an infant who presented with viral infection with diarrhea at 3 months of age, while the second patient did so in adulthood following the diagnosis of ET. One of our patients developed Budd-Chiari syndrome around 15 years after diagnosis of ET. The last patient developed azoospermia that was probably secondary to the use of hydroxyurea. In our experience none of our patients had major complications with regards to leukemic or myelofibrotic transformation, which is in accordance with outcomes seen in the younger population [14, 17, 18]. High platelet count can lead to qualitative deficiency of von Willebrand factor (vWF) [19]. Acquired vWF disease can lead to bleeding in patients with ET. Bleeding was not a complication seen in any of our patients.

A limitation of our study is that it is a single institution data with retrospective analysis. Given the rarity of classical Philadelphia chromosome-negative myeloproliferative neoplasms (Ph- MPNs) disorders in children we believe that there should be both national and international collaborative efforts to study clinical and biologic parameters prospectively in these children. Knowing that majority of our studies patients did not carry the driver mutations we recommend a conservative approach for our indigenous population if there are no clinical concerns for pharmacologic intervention.

Conclusions

In conclusion, our experience shows that most of our children with ET were asymptomatic, and thrombocytosis was often discovered incidentally. In our practice pediatric patients are considered prone to complication particularly during acute infectious episodes that might place them at risk for dehydration and subsequent thrombosis. The potential complications and clinical course of pediatric ET can still be unpredictable.

Acknowledgments

None to declare.

Financial Disclosure

This work was not funded by any funding agency.

Conflict of Interest

The authors declare no conflict of interest.

Informed Consent

No informed consents were obtained since this was a retrospective review; all data items collected were already documented in medical charts as part of the patient care and disease management documentation.

Author Contributions

Muhammed Ameen conducted the study, data collection through chart reviews, data entry, review of the results and manuscript preparation. Saadiya Khan: review of results and manuscript preparation and final approval of the manuscript. Khawar Siddiqui: study design, data management, processing and cleaning, primary data analysis, result presentation and reporting, and preparation of the manuscript. Mahasen Saleh: review of results, manuscript preparation and final approval of the manuscript. Abdullah Al-Jefri: review of results, manuscript preparation and final approval of the manuscript. Abdulrahman Al-Musa: conceptualization, study design, overall supervision of the project, review of the results, manuscript preparation and review as corresponding author with final approval of the manuscript, and as principal investigator of the study.

Data Availability

Any inquiries regarding supporting data availability of this study should be directed to the corresponding author.

Abbreviations

JAK2: Janus kinase 2 gene; *CALR*: calreticulin; *MPL*: myeloproliferative leukemia virus oncogene; *BCR/ABL*: breakpoint cluster region protein/Abelson murine leukemia viral oncogene; PT: prothrombin time; PTT: activated partial thrombin time; PFA-100: platelet function assay

References

1. Cervantes F. Management of essential thrombocythemia. Hematology Am Soc Hematol Educ Program. 2011;2011:215-221.
2. Hasle H. Incidence of essential thrombocythaemia in children. Br J Haematol. 2000;110(3):751.
3. Barbui T. How to manage children and young adults with myeloproliferative neoplasms. Leukemia. 2012; 26(7):1452-1457.
4. Teofili L, Giona F, Martini M, Cenci T, Guidi F, Torti L, Palumbo G, et al. Markers of myeloproliferative diseases in childhood polycythemia vera and essential thrombocythemia. J Clin Oncol. 2007;25(9):1048-1053.
5. Baxter EJ, Scott LM, Campbell PJ, East C, Fourouclas N, Swanton S, Vassiliou GS, et al. Acquired mutation of the tyrosine kinase JAK2 in human myeloproliferative disorders. Lancet. 2005;365(9464):1054-1061.
6. Ismael O, Shimada A, Hama A, Sakaguchi H, Doisaki S, Muramatsu H, Yoshida N, et al. Mutations profile of polycythemia vera and essential thrombocythemia among Japanese children. Pediatr Blood Cancer. 2012;59(3):530-535.
7. James C, Ugo V, Le Couedic JP, Staerk J, Delhommeau F, Lacout C, Garcon L, et al. A unique clonal JAK2 mutation leading to constitutive signalling causes polycythaemia vera. Nature. 2005;434(7037):1144-1148.
8. Pardanani AD, Levine RL, Lasho T, Pikman Y, Mesa RA, Wadleigh M, Steensma DP, et al. MPL515 mutations in myeloproliferative and other myeloid disorders: a study of 1182 patients. Blood. 2006;108(10):3472-3476.
9. Pikman Y, Lee BH, Mercher T, McDowell E, Ebert BL, Gozo M, Cuker A, et al. MPLW515L is a novel somatic activating mutation in myelofibrosis with myeloid metaplasia. PLoS Med. 2006;3(7):e270.
10. Klampfl T, Gisslinger H, Harutyunyan AS, Nivarthi H, Rumi E, Milosevic JD, Them NC, et al. Somatic mutations of calreticulin in myeloproliferative neoplasms. N Engl J Med. 2013;369(25):2379-2390.
11. Tefferi A, Pardanani A. Myeloproliferative Neoplasms: A Contemporary Review. JAMA Oncol. 2015;1(1):97-105.
12. Barbui T, Thiele J, Gisslinger H, Finazzi G, Vannucchi AM, Tefferi A. The 2016 revision of WHO classification of myeloproliferative neoplasms: Clinical and molecular advances. Blood Rev. 2016;30(6):453-459.
13. Kvasnicka HM, Orazi A, Thiele J, Barosi G, Bueso-Ramos CE, Vannucchi AM, Hasserjian RP, et al. European LeukemiaNet study on the reproducibility of bone marrow features in masked polycythemia vera and differentiation from essential thrombocythemia. Am J Hematol. 2017;92(10):1062-1067.
14. Randi ML, Putti MC, Scapin M, Pacquola E, Tucci F, Micalizzi C, Zanesco L, et al. Pediatric patients with essential thrombocythemia are mostly polyclonal and V617F-JAK2 negative. Blood. 2006;108(10):3600-3602.
15. Giona F, Teofili L, Moleti ML, Martini M, Palumbo G, Amendola A, Mazzucconi MG, et al. Thrombocythemia and polycythemia in patients younger than 20 years at diagnosis: clinical and biologic features, treatment, and long-term outcome. Blood. 2012;119(10):2219-2227.
16. Nakatani T, Imamura T, Ishida H, Wakaizumi K, Yamamoto T, Otabe O, Ishigami T, et al. Frequency and clinical features of the JAK2 V617F mutation in pediatric patients with sporadic essential thrombocythemia. Pediatr

Blood Cancer. 2008;51(6):802-805.
17. Alvarez-Larran A, Cervantes F, Bellosillo B, Giralt M, Julia A, Hernandez-Boluda JC, Bosch A, et al. Essential thrombocythemia in young individuals: frequency and risk factors for vascular events and evolution to myelofibrosis in 126 patients. Leukemia. 2007;21(6):1218-1223.
18. Boddu P, Masarova L, Verstovsek S, Strati P, Kantarjian H, Cortes J, Estrov Z, et al. Patient characteristics and outcomes in adolescents and young adults with classical Philadelphia chromosome-negative myeloproliferative neoplasms. Ann Hematol. 2018;97(1):109-121.
19. Awada H, Voso MT, Guglielmelli P, Gurnari C. Essential thrombocythemia and acquired von Willebrand Syndrome: the shadowlands between thrombosis and bleeding. Cancers (Basel). 2020;12(7):1746. Published 2020 Jun 30.