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Thrombocytosis in Children and Adolescents: does this need Separate Approach? – A Review

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In childhood inflammation and infection, secondary thrombocytosis is frequent finding. Primary thrombocytosis is often hereditary and may occur due to germline mutations in genes which encode key thrombopoiesis regulators such as receptor's effector kinase Januskinase2 (JAK2), thrombopoietin (THPO) or receptor c-MPL. Additionally, somatic mutations within MPL, JAK2 and calreticulin (CARL) may act as driver mutations in Philadelphia – negative myeloproliferative neoplasms including polycythemia vera, essential thrombocythemia and primary myelofibrosis. Enhanced and detailed knowledge on clinical complications and molecular mechanisms are such disease are echoed by recommendations of European LeukemiaNet (ELN) and World Health Organization diagnostic criteria on adult myeloproliferative neoplasms. Although data on thrombocytosis in children is rare and does not contain any guidelines for thrombocytosis in pediatric age group. Additionally, complications according to age and specificity of pharmacology advise that recommendations personalized to children population is essential in routine practice. In this review, we recapitulated literature related to classification, diagnostic modalities, and management of thrombocytosis in children.

Keywords: Children, thrombocytosis, hereditary, myeloproliferative neoplasms, adolescents

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Introduction

Current research has permitted to delineate the pathogenesis and characteristics of thrombocytosis, which allow for considerable changes of classification, stratification of risk and therapeutic approaches. Although, current recommendations have been centered on population limited to adults, and very limited data and guidelines are available in regard with children and adolescent thrombocytosis. Substantial differences are described in clinical presentation and epidemiology of childhood thrombocytosis in comparison to adult thrombocytosis. In inflammatory and infectious processes in children, transient thrombocytosis is common entity. Kucine et al demonstrated this as caused by higher infections incidence, frequent deficiency of iron in children or immune response immaturity.[1] Although, primary acquired thrombocytosis is less common in children as compared to adult population.[2-3] A recent review that explored incidence of essential thrombocythemia annually, one of Philadelphia–negative MPNs, ranged between 0.004-0.11 per 100,000 children in ages between 0–16 years, although adult meta–analysis showed pooled rate of incidence annually of 1.03 per 100,000.[4] Apart from essential thrombocythemia (ET), polycythemia vera (PV) and primary myelofibrosis (PMF) are also included in Philadelphia–negative MPNs, and all are characterized by excessive hematopoietic clonal proliferation in one or more lineages. Such patients may be suffered from hemorrhage, thrombotic events, disturbances in microvasculature and transformation into fibrosis or leukemia.[5] Current research has clarified the link between myeloproliferative neoplasms and genes JAK2, CALR and MPL somatic mutations.[6-10] Adult ET with mutations of JAK2 V617F comprises about 55%, followed by mutations in CALR (15-24%) and MPL (4%); although 20% patients do not show any mutation from three genes; known as ''triple–wildtype'' or ''triple–negative''.[11-12] In children with ET, there is lower incidence of these mutations. [12] Randi et al. showed in his study that from 89 children with ET, 75% turned out to be triple–negative and showed non–clonal disease.[12] As there is heterogeneity of childhood and adult ET, diagnostic criteria in children should be specified.[13] Teofili et al. showed reduced risk of thromboembolic events in children with sporadic or familial ET as compared to adult group.[14] Randi et al. explored that 3.4% (3 cases) developed thromboembolic complications.[12] Such findings underline those thromboembolic events may be seen in children, but they need different approach clinically. For adults, the risk – adapted therapy guidelines are available, although no

recommendations are reserved for children.[11] The current review is aimed to describe characteristics of children and adolescent's thrombocytosis in terms of classification, diagnostic modalities, and treatment.

Classification of Thrombocytosis in Children

The proposed classification of thrombocytosis in children is given in Figure 1. As defined in previous classifications, the term thrombocytosis is called when platelet count exceeds 450 x 10^9/L.[1, 15] Additionally, the count of platelets ranges from 450-700 x 10^9/L can be termed as mild, between 700-900 x 10^9/L as moderate and 900-1000 x 10^9/L as severe thrombocytosis and if it is more than 1000 x 10^9/L, it can be termed as extreme thrombocytosis. [2] In a study by Fu et al., it is stated that increased threshold for childhood ET diagnosis may be beneficial to avoid misdiagnosis of MPNs if there is persistent secondary thrombocytosis. [15] Apart from that, changes according to age should also be considered in childhood. Additional sources suggested increased level of platelets for consideration as physiological up to 6 years of age.[16] Maximum limit of 650 x 10^9/L was established at 2 months age with slow decline to reach level of adults at school-going child age. [(17)] One study described age– and sex–dependent platelet count dynamics relying on 32,000 samples, mostly patients with white origin were having similar results as from German population.[16] As there is increase in platelet count during first month, they gradually decrease and by the age of school-going children, 97.5th percentile with standard cutoff value of 450 x 10^9/L is reached. Slight differences were also observed according to gender with females having higher counts than males.[17] While examination of child with thrombocytosis, these factors should not be ignored.

Reactive or Secondary Thrombocotysis in Children

In initial step, the primary and secondary/reactive type of thrombocytosis must be recognized. In patients with secondary thrombocytosis, increased level of platelets occurs due to extrinsic cause e.g., inflammation, causing megakaryocytopoiesis stimulation.[2] Thrombopoietin (THPO) and c-Mpl (its receptor) regulate the process of thrombopoiesis.[18] Interleukin–6 (IL-6) is the key mediator in secondary thrombocytosis. Secondary thrombocytosis is usually a temporary process as it includes scaled–up production of platelets without permanent thrombopoiesis dysregulation.[19] Apart from iron deficiency, bacterial and viral infection, the activators of secondary thrombocytosis comprise autoimmune diseases, hemolytic anemia, tissue damage, asplenia, drug effects and malignancy.[2] Transient platelet count elevation can be seen after bleeding episodes or following recovery of myeloid after chemotherapy. In present classification of erythrocytosis in children, germline mutations causing increased e levels of erythropoietin (EPO) are considered as secondary erythrocytosis.[20] Yet, in current classification of thrombocytosis in children, germline mutations cause increased levels of THPO were categorized among primary thrombocytosis.

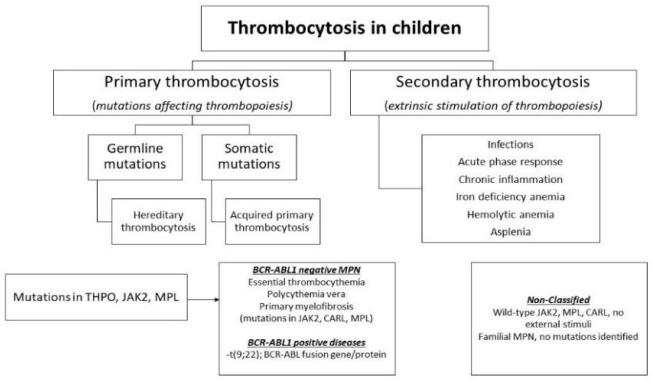

Figure 1. Classification of Thrombosis in Children

Primary Thrombocytosis: Hereditary Thrombocytosis

Primary thrombocytosis depends upon intrinsic defect that involves thrombopoiesis dysregulation. Usually, a gene mutation affiliated with hematopoiesis can be observed. [19] Hereditary types of primary thrombocytosis occur due to germline mutations in genes associated with thrombopoietin, MPL and JAK2 (Table I, figure 2). Mutations of MPL which cause hereditary thrombocytosis mostly include MPL-S505N, MPL-P106L, MPL-W515R and MPL-K39N (MPL Baltimore).[30, 32, 39, 42] Recent study showed germline mutation in MPL-R102P, which was formerly termed as homozygous disease that cause mutation in congenital amegakaryocytic thrombocytopenia (CAMT).[31, 56] In contrast to hereditary thrombocytosis which cause MPL gain-of-function mutation, there is MPL loss-of-function mutation in CAMT. [56] MPL gain-of-function mutation

Table I: Germline mutations in hereditary thrombocytosis

Gene	Nucleotide change	Transmission mode	Phenotypes	Comments
THPO	G516, on 5'-UTR	AD	HT with increased THPO and defects in distal limb	Loss of translational inhibition physiologically [21-22]
	c.13+1 G>C mutation of intron 3	AD	HT with increased THPO and vasomotor, hemorrhagic, and thrombotic symptoms; AML, myelofibrosis, defects of distal limb, multiple myeloma	Loss of translational inhibition physiologically [23-27]
	T>C transition at intron 2	AD	HT with increased THPO	Loss of inhibition of 5'-UTR sequence and skipping of exon 2[28]
	Deletion of guanine at 5'-UTR	AD	HT with increased THPO	Location at position 3252[29]
	Mutation of A-G in intron 3	AD	Increased THPO	-[19]
MPL	K39N	AD with incomplete penetrance	HT (isolated)	MPL Baltimore [30]
	R102P	AD with incomplete penetrance	HT with increased THPO	Cause mild thrombocytosis in heterozygosity [31]
	P106L	AR	HT with increased THPO Hemorrhagic symptoms in homozygosity	A little population of Arabic population are carriers [32-33]
	S505N	AD	HT with thromboembolism, myelofibrosis	Somatic mutation [39-41]
	W515R	-	HT (isolated)	Somatic mutation [42-44]
	R321W	-	ET, sometimes HT	Heterozygosity in ET patient[45]
	V285E	-	PMF, sometimes HT	Heterozygosity in PMF[45]
JAK2	R564Q	AD	HT, sometimes ET	Affects exon 13 pseudokinase domain [46]
	H608N	AD with incomplete penetrance	HT (isolated)	Affects pseudokinase domain [47]
	L611S	-	Sometimes HT	De novo and somatic mutation [48]
	V617I	AD	HT and ET	Somatic mutation, affects pseudokinase domain and exon 14 [37-38]
	V625F	-	HT and ET	Gain-of-function [45]
	R938Q/S755R	-	HT (isolated)	Affects kinase and pseudokinsae domain [49]
	T875N	-	ET, sometimes HT	Family history of HT, involve exon 18 [50]
	R867Q	-	HT, progressing to PV	Affects kinase domain [49, 51]
	R938Q	-	HT (isolated)	Somatic mutation[49, 52]
	46/1 haplotype or GGCC	-	Predisposition to MPN	Combination of SNPs [53-55]
	G335D	-	ET (isolated)	Heterozygosity in ET[45]
	G571S	-	ET (isolated)	Heterozygosity in ET[45]
	F556V	-	HT and ET	Germline mutations possibly[45]
	N1108S	-	HT and ET	Germline mutation[43]

AD = Autosomal dominant; AR = Autosomal recessive; ET = Essential thrombocythemia; HT = Hereditary thrombocytosis; MPN = Myeloproliferative neoplasm; PMF = Primary myelofibrosis; PV = Polycythemia vera; SNP = Single nucleotide polymorphism; UTR = Untranslated region

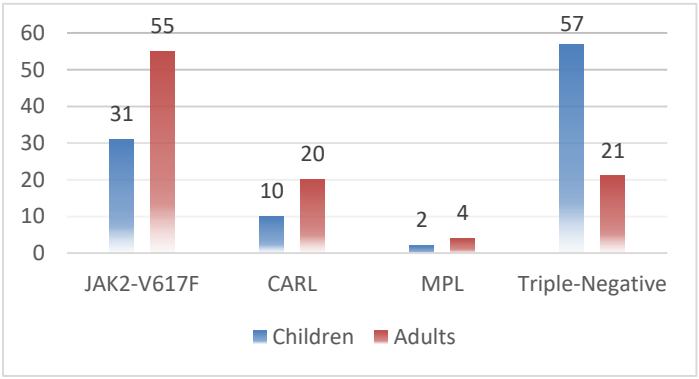

Figure 2. Frequencies of mutations in essential thrombocythemia

P106L was presenting fundamental, activity of receptors independent of cytokines and increased levels of THPO despite dysregulated glycosylation and surface expression of receptor.[33] Although, in cell model, the active receptors having codon 505 and 515 mutations were expressed and glycosylated on surface of cell. [39] These codon mutations may present as somatic mutations which are responsible for launching MPNs. [8, 39-40, 42] Similar trend is portrayed for mutations of JAK2 at 617 codon, although MPL mutations K39N and P106L are not common in this regard. [11, 38]

Clinically, primary hereditary thrombocytosis is regarded as benign disease with polyclonal hematopoiesis with no risk of complications of thromboembolism. Although, Toefili et al. showed high risk of events of thromboembolism and transformation to fibrosis in patients with germline mutations of MPL-S505N. [41] Additionally, three siblings who were affected by MPL-P106L showed bleeding tendency as a complication of extreme thrombocytosis along with von Willebrand disease. [34]

Various mutations have been shown to decrease the inhibition of THPO–mRNA translation physiologically, which leads to increased hormone level and ultimately thrombocytosis consequently.[21,23-24,28-29,57] It was discussed that mutations of THPO loss-of-function may produce aplastic anemia, thrombocytopenia and bone marrow failure which do not respond to bone marrow transplantation. [58-59] Families with germline mutations of THPO are also associated with multiple myeloma, leukemic transformation, fibrotic transformation, and defects in distal limb. [22, 25-26] In two infants, transient MPN was reported who were involved by hereditary thrombocytosis due to intro 3 THPO-mRNA mutation. [7] Likewise, a transient MPN mimicking chronic myeloid leukemia has been reported in infant having inherited mutation of THPO. [60]

Germline mutations at hot-spot 617 codon and at foci which affects its pseudokinase and kinase domains have shown to develop increased platelets levels congenitally. In three family members with JAK2-V617I germline mutation, vascular complications were seen. [38] Additionally, one first – degree relative of patient having chronic thrombocytosis and JAK2-T875N germline mutation experienced cerebral infarction.[50] The association between MPNs and hereditary thrombocytosis is not properly defined. Both JAK2 and MPL mutations have shown to present in somatic forms of hereditary thrombocytosis. Isolated case reports are published, showing progression to MPNs in patients having germline mutations of hereditary thrombocytosis.[50-51] In majority of families having clustered MPNs; called familial MPNs, there is no mutation found yet, therefore risk of MPNs in hereditary thrombocytosis is not defined properly. [61]

Primary Thrombocytosis: Acquired Forms in Children and Adults

Primary acquired thrombocytosis is identified by somatic mutations and occurs in various myeloid malignancies, more common in adults. Thus, majority of recent knowledge on pathogenesis and management are derived from adult studies, including MPNs, MDS and MPN/MDS. [19, 62] The chromosome 9 and 22 translocation causing BCR-ABL1 fusion protein and gene generation, represents Philadelphia (Ph)–positive disease. Hence, BCR-ABL1 screening is important agnostic step in primary thrombocytosis. In group of Philadelphia (Ph)–negative MPNs, increased count of platelets is basic feature of ET. In patients with PV, major abnormality is constituted by erythrocytosis, so increased level of platelets alone is not major criteria for diagnosis of pre–PMF and PMF. [(62)] Ph–negative MPNs are derived through JAK2 mutations, mostly JAK2-V617F in exon 14, CARL mutations in exon 9, and MPL mutations in exon 10, especially at codon 515 (Table II-IV) [(6-10, 44)] Rare mutations in MPL are also recognized in single adult cases of ET or other MPNs. [(45)] MPL-Y252H mutation is described in pediatric ET. [(64)] In PV, rare JAK2 mutations in exons 14 and 12 are also found, but not in adults. [(11)] In addition to Ph–negative MPN, MPL somatic mutations are described in other hematological disease in pediatric population such as MDS, idiopathic acquired aplastic anemia, and acute megakaryoblastic leukemia. [(71-72)] Similarly, JAK2 somatic mutations are described in pediatric diseases including ALL with trisomy and MDS/MPN with thrombocytosis and ring sideroblasts. [(35-36, 73)] In sporadic MPNs, somatic gain-of-function mutations in THPO are very rare. [(27)]

Table II: JAK2 somatic mutations in essential thrombocythemia

Change in protein	Exon	Phenotypes	Remarks
V617F	14	ET, PV, PMF, ALL, AML	Commonest somatic mutation in MPN; 55% cases of adult ET; affects pseudokinase domain [7, 35-36]
V617I	14	ET, MPN	Affects pseudokinase domain; germline mutation [37-38]

ALL = Acute lymphoblastic leukemia; AML = Acute myeloid leukemia; ET = Essential thrombocythemia; MPN = Myeloproliferative neoplasm; PMF = Primary myelofibrosis; PV = Polycythemia vera

Apart from common mutations, MPNs can also be associated with rare variants involving JAK2 regulation, including LNK, TET2, EHZ2, TP53, U2AFI, SF3B1, IKZF1, CBL, ASXLI and IDH1/IDH2. [1, 61, 74-80] Familial MPNs clustering were shown to have 5 to 7 folds higher risk. [81] Nonetheless, the basic element of familial clustering is still poorly understood.

As ET is characterized as clonal disease, this group of evident ET but without clonality may either suggest additional mechanism with specific disease with thrombocytosis in children or certain patients may be exposed by persistent secondary thrombocytosis. In both scenarios, variable clinical approach will be needed including close platelet count and clinical monitoring instead of invasive testing and management. [12] These findings show that there is part of patients having

persistent thrombocytosis in which the classification remains difficult.

Table III: CARL somatic exon 9 mutations in essential thrombocythemia

Mutation type	Change in protein	Phenotypes	Remarks
More than 30 deletions or insertions which cause frameshift, leads to changed C-terminal and premature termination		ET, PMF, MDS, CML, RARS-T, atypical CML	15-24% adult ET cases [9-11]
	p.L367fs*46	ET and PMF	45-53% CARL mutations of MPN (type 1 mutation) [9-10]
	p.K385fs*47	ET and PMF	32-41% CARL mutations of MPN (type 2 mutation) [9-10]

CML = Chronic myeloid leukemia; ET = Essential thrombocythemia; PMF = Primary myelofibrosis; MDS = Myelodysplastic syndrome; RARS-T = Refractory anemia with ring sideroblasts associated with marked thrombocytosis

Table IV: MPL mutations in essential thrombocythemia

Exon	Change in protein	Phenotypes	Remarks
3-9	T119I	ET	Affects exon 3 [45]
	F126fs	ET	Affects extracellular domain[63]
	S204F	ET and PMF	Affects exon 3 [43, 45]
	S204P	ET and PMF	Affects exon 4 [43, 45]
	E230G	ET	Affects exon 5 [45]
	Y252H	ET	Affects extracellular domain [63-64]
10	-	ET	Commonest MPL mutations affect exon 10 [11]
	A497-L498ins4	ET	-[65]
	V501A	ET and PMF	Presents in association with MPL-W515L/R [66]
	S505C	ET	Presents in association with MPL-W515L/R [66]
	S505N	ET, HT and PMF	Germline mutation [39-40]
	W515K	ET and MMM	-[8]
	W515L	ET and MMM	-[8, 67]
	W515A	ET	-[44]
	W515R	ET and PMF	Germline mutation [42-44]
12	Y591N	ET	-[43]
	Y591D	ET and PV	Associated with other mutations [45]
Needs additional diagnostic workup			
	P70L	ET	No gain-of-function [68]
	V501A	MPN (JAK2-negative)	Presents with MPL-S505N [69]
	V507I	MPN (JAK2-negative)	-[69]
	W515G	MPN (JAK2-negative)	Affects exon 10 [69]
	W515S	MPN (JAK2-negative)	Affects exon 10 [69]
	W515R Q516E	ET	Double point mutation[65]
	W515-P518 ins/del KT	MPN (JAK2-negative)	Affects exon 10[69]

ET = Essential thrombocythemia; HT = Hereditary thrombocytosis; MMM = Myelofibrosis with myeloid metaplasia; MPN = Myeloproliferative neoplasm; PMF = Primary myelofibrosis; PV = Polycythemia vera

Diagnostic Evaluation of Thrombocytosis in Children

Due to epidemiological and clinical differences of pediatric thrombocytosis, an approach specifically should be adapted for children age group. Kucine et al. and Harrison et al. portrayed diagnostic framework for childhood thrombocytosis and adult thrombocytosis respectively.[1, 82] As awareness regarding germline mutations is increasing in terms of hereditary thrombocytosis, the significance of hereditary thrombocytosis exclusion before imperiling children to inadequate invasive testing, has been highlighted by Teofili et al. [13] Diagnostic approach for early recognition of hereditary pediatric thrombocytosis has been given in Figure 3.

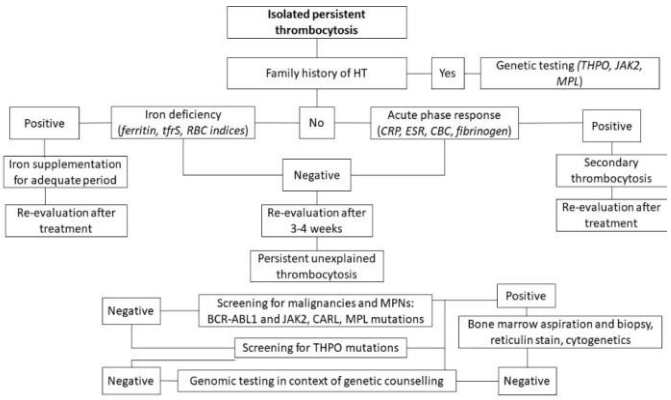

Figure 3: Algorithm for diagnosis of thrombocytosis in children

When persistent and isolated thrombocytosis is present, a complete clinical history and physical examination should be carried out; especially addressing history of family (Figure 1). For the differentiation of sustained and transient thrombocytosis, an interval of 3-4 weeks prior to re-assessment, have been proposed by Kucine et al.[1] If family history indicates hereditary thrombocytosis and when etiology of secondary thrombocytosis is present, direct diagnostic testing by genetic sequencing should be started after genetic counselling (Table I). Likewise, if hereditary thrombocytosis is suspected, the adult relatives affected

can be analyzed initially for minimization of diagnostic interventions in children.[20] In other cases, diagnostics should be initially concentrated for exclusion of secondary thrombocytosis and should include inflammatory markers e.g., complete blood count with white blood cells differentiation, fibrinogen, C-reactive protein, and erythrocyte sedimentation rate along with ruling out of iron deficiency; in case of asymptomatic iron deficiency, iron supplementation should be started. Likewise, if thrombocytosis is secondary to acute phase reaction, then platelet number should be re-evaluated after subsiding the process.

Primary thrombocytosis should be considered once causes of secondary thrombocytosis has been excluded. In case, when there is no isolated persistent thrombocytosis, but associated with additional blood changes, other hematological disorders should be considered. When there is persistent thrombocytosis with increase in red cell mass, polycythemia vera should be excluded.

When primary thrombocytosis is suspected, professional genetic counselling along with genetic testing should be done for myeloid malignancies (Table II-IV). While JAK2-V617F, CARL exon 9 mutations and MPL exon 10 mutations testing usually identify about 75% of ET adult cases, this percentage is comparatively decreased in adolescents and children, and required extensive testing for diagnosis.[11-12] If there is somatic mutation, examination of bone marrow including cytogenetics and reticulin stain will be needed for diagnosis of MPN or myeloid malignancies. Morphology of bone marrow is essential to differentiate between prefibrotic–PMF and ET.[11] If pediatric ET diagnosis is confirmed, then screening of further risk factors for thrombophilia (such as Protein C, protein S, AT deficiency, prothrombin mutation and factor V Leiden), hemorrhagic risk factors (such as vWD) and risk factors for cardiovascular events should be done for appropriate management of patients.[1]

If there are no positive findings in primary genetic testing, screening of mutations in THPO at 5'UTR region is recommended for exclusion of additional causes of hereditary thrombocytosis.[9, 33] Though, measurement of THPO levels is challenging as the investigations is not offered by majority of laboratories. When hereditary thrombocytosis is suspected, non-hematopoietic cells (e.g., fibroblasts) analysis and family studies can be performed to differentiated between germline and somatic mutations, followed by bone marrow examination.

Screening of BCR-ABL1 and genetic panel (e.g., JAK2, CARL, MPL, THPO) can be performed as an alternative approach, along with genetic counselling. Ultimately, if there is no finding on genetic testing and there is persistence of thrombocytosis, examination of bone marrow will be needed for exploration and genetic testing of family may be considered.

Management of Thrombocytosis in Children

In children, only limited data is available in terms of adolescent and children thrombocytosis diagnostics and management.[82] In primary thrombocytosis, the complications related to thromboembolism are more common as compared to secondary.[83-84] Barbui and Tefferi explained the leukemic transformation risk after two decades of thrombocytosis diagnosis for approximately 10% in polycythemia vera and 5% in ET.[11] Malignant transformation was rarely seen in young patients. A recent study showed fibrotic transformation in 2% of adult patients and no transformation into leukemia. [70] In adult ET, the thrombotic risk is between 1.5-2.5% per patient-year. Independent risk factors for development of arterial thrombosis include JAK-V617F mutation, age more than 60 years, cardiovascular risk factors, and thrombosis history.[85] In children, events related to thromboembolic events are less common as these risk factors are age-oriented and are more evident in adults and older patients. In children, there was increase percentage of patients with triple-negative status and difficult diagnosis of MPNs, misinterpretation can be seen in few cases.

In adult ET, guidelines for risk-adapted therapy by European LeukemaNet (ELN) gave recommendation for assessment of thrombotic risk of patients by utilization of International Prognostic Score for Thrombosis in ET (IPSET). Patients are given low-risk, intermediate-risk and high-risk class depending on risk factors. In patients with high risk factors, anti-platelet therapy by acetylsalicylic acid is recommended, provided with no hemorrhagic risk. Acetylsalicylic acid is recommended twice daily, depending on risk factors individually. If there is history of VTE, systemic anticoagulation along with anti-platelet

therapy is recommended.[11] It is suggested that patients having platelet count more than 1000 x 10^9/L may lead to episodes of bleeding due to acquired vWD. It is therefore recommended that vWF antigen and vWF function parameters should be monitored. [11] If acquired vWD is present, acetylsalicylic acid therapy should be withheld in patients with low risk.[11, 62] In patients with age more than 60 years in the presence of either thrombosis history, cardiovascular risk factors or JAK2 mutations, cytoreduction therapy is recommended.[11] In case of major bleeding or if platelet count is more than 1500 x 10^9/L, cytoreduction therapy is indicated. Cytoreduction therapy can be used to control symptoms caused by myeloproliferation or systemic symptoms.

In adults, hydroxyurea was first-line treatment recommended for cytoreduction. Due to leukemogenicity, the use of hydroxyurea remained controversial.[86] Although long-term therapy of hydroxyurea in children with sickle cell anemia does not support this concept.[11] In young patients and pregnancy females, safe second-line treatment includes Interferon-α.[11, 86-88] Anagrelide is non-leukemogenic option for treatment which reduce count of platelet. [(89)] In one analysis, it has been shown that anagrelide is safer alternative in terms of children for decreasing platelet count.[91-92] As compared to hydroxyurea, the efficacy of anagrelide is found similar with decreased risk of VTE.[90, 92-93] Guidelines still recommend hydroxyurea as the use of anagrelide has shown transformation of fibrosis, hemorrhagic and embolism events in adults. Busulfan is limited to elder age group due to its leukemogenicity.[86]

Consideration of Anti – Platelet Treatment in Children

Due to increased complications risk including Reye syndrome in adolescents and children, the use of anti–platelet treatment should be used with caution.[86] Acetylsalicylic acid in low doses may decrease the Reye syndrome risk in children.[82, 86] Giona et al. suggested avoidance of any prophylactic therapy in infants.[94-95] Harrison et al. recommended acetylsalicylic acid 2-3 mg/kg, not exceeding 75 mg/day in children with ET.[82] The American College of Chest Physicians Evidence-Based Clinical Practice Guidelines recommends 1-5 mg/kg/day acetylsalicylic acid in children for anti–platelet therapy.[96] In extreme thrombocytosis, the anti-platelet treatment should only be started if activity of ristocetin cofactor is more than 30%.[97] In abnormal bleeding, screening for acquired vWD should be done including determination of both vWF function parameters and vWF antigen, regardless of platelet number.[98] As JAK2-V617 mutation is taken as independent thromboembolic risk factor in adults, the treatment by acetylsalicylic acid can be offered to asymptomatic pediatric patients with this mutation.

Consideration of Cytoreductive Therapy in Children

In thrombocytosis of children, the cytoreduction therapy is limited due to significant side effects.[82, 86, 97] In high-risk ET children who did not respond to low-risk treatment or thrombosis history, the Kucine et al. suggested cytoreduction therapy. Additionally, there is also recommendation for use of cytoreduction treatment in extreme persistent thrombocytosis.[1] This underlines the problems in adequately deciding the indications for cytoreductive therapy in primary thrombocytosis of children.

The selection of agent is not easy in children. Kucine et al. recommends the use of hydroxyurea as first-line therapy in childhood ET.[1] Although, infertility in males can be caused by use of hydroxyurea, indicating that preventing measures for fertility should be started prior to treatment with hydroxyurea in young patients.[99]

Interferon-α or pegylated interferon-α is proposed in pregnancy women and young adults, they may also be used in children.[11, 86] However, in children, few side effects may be seen including influenza–like symptoms.[88]

Recommendations in Children

Giona et al. recommended for monitoring asymptomatic patients and consider acetylsalicylic acid in case of complications by thromboemboli or if there are microcirculation clinical features, in children having primary hereditary thrombocytosis.[95] The basis of these recommendations was group of 16 children who were affected with primary hereditary thrombocytosis, and of which 15 were having codon 505 MPL mutation.[95] In children, Giona et al. did not recommend cytoreductive treatment; although they may be considered when the disease is resistant to acetylsalicylic acid or if size of spleen is persistently increasing.[95] Similar considerations were given by Tefferi et al. [19]

Discussion

Increased proportion of children having primary acquired thrombocytosis along with status of triple-negative mutations is important while classifying thrombocytosis in children. This was demonstrated in both single studies and review by Ianotto et al.[12, 70] The familial MPNs are still not easy to classify because the underlying pathophysiology is not known. Oclaydu et al. suggested that in these patients, mutations lead to somatic mutations acquisition which may ultimately increase risk of transformation into MPN.[55]

Differentiation between primary and secondary thrombocytosis may be challenging in children. The re-assessment interval of platelet count may be important. Kucine et al. suggested that interval of at least 3-4 weeks should be considered prior to re-assessment of platelet count.[1] Although for rare diseases, the methodology choice for tests of genetics, especially unbiased analysis of genomes should be done rather than selecting single gene. Such analysis should always be conducted along with genetic counselling.

All suggested therapies need validation as they are mostly based on adults. The basic aim of the treatment should be the reduction of thromboembolic complications along with limited side effects in patients. Current suggestions recommend that anti-platelet treatment with low-dose should be initiated in pediatric essential thrombocythemia in presence of symptoms, JAK-2 mutations, or other risk factors. They can also be used in extreme persistent thrombocytosis. These approaches should always include monitoring of acquired vWD. When thromboembolic complications are seen, management of particular risk should be started as acetylsalicylic acid alone is insufficient. Cytoreductive therapy should be reserved and only considered in case of bleeding complications or major thrombosis.[97]

Conclusion

In children, primary thrombocytosis is rare as compared to secondary causes. Secondary thrombocytosis may be caused by inflammation, infection, iron deficiency etc. When there is persistent thrombocytosis in children is seen without any secondary stimulus, primary hereditary thrombocytosis and MPNs can be considered. Diagnostic approach should include evaluation of myeloid neoplasms with their causative mutations. In asymptomatic or mild disease, only monitoring may be sufficient. Children with symptoms or with risk factors e.g., JAK-2 mutations may get acetylsalicylic acid low-dose therapy along with careful monitoring, although risk for treatment should also be considered. Treatment by cytoreductive therapy is not used commonly except in vascular complications. In order, data from large cohort studies are required for validation of suggested treatment recommendations.

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