Consensus Recommendations for the Diagnostic Approach to Erythrocytosis in Pediatric Patients

Holger Cario
on behalf of Working Group 3 on “Congenital Erythrocytosis” of the MPN&MPNr-EuroNet (COST action BM0902)
Classification

Absolute erythrocytosis

Primary erythrocytosis

Congenital
- Familial Erythrocytosis Type 1; 
  EPOR (syn. Primary familial 
  congenital polycythemia, PFCP)

Secondary erythrocytosis

Congenital
- Hyperaffine hemoglobin variants; 
  HBA, HBB
- 2,3-bisphosphoglycerate deficiency; 
  BPGM, PKLR
- Defective O₂-Sensing
  1. Familial Erythrocytosis Type 2; 
    VHL (e.g. Cherubism polycythemia)
  2. Familial Erythrocytosis Type 3; 
    EGLN1 (PHD2)
  3. Familial Erythrocytosis Type 4; 
    EPAS1 (HIF2a)

Acquired
- Polycythemia vera

Acquired
- Physiological EPO elevation due to 
  - pulmonary
  - cardiac
  - renal
  - hepatic diseases
- Autonomous EPO synthesis
  - Kidney: nephroblastoma, RCC
  - Liver: hepatoma, HCC
  - CNS: e.g. hemangioblastoma
  - Endocrine tumor (e.g. pheoc.)
Current Recommendations for Adult Patients

Stage 1
1. History and examination
2. Full blood count/film
3. JAK2 mutation
4. Serum ferritin
5. Renal and liver function tests

Stage 2 investigations
If the initial screening tests are negative for a JAK2 mutation and there is no obvious secondary cause then further investigations are indicated. A red cell mass is required first and if an absolute erythrocytosis is confirmed then the following tests are appropriate.
1. Red cell mass
2. Arterial oxygen saturation
3. Abdominal ultrasound
4. Serum erythropoietin level
5. Bone marrow aspirate and trephine
6. Cytogenetic analysis
7. Erythroid burst-forming unit (BFU-E) culture

Stage 3
For those patients who do not fulfil either set of criteria and who have erythrocytosis there are a number of specialised tests that may need to be considered. Some of these are listed below.
1. Arterial oxygen dissociation
2. Sleep study
3. Lung function studies
4. Gene mutations EPOR, VHL, EGLN1 (also known as PHD2)


Current Recommendations for Adult Patients

1. these recommendations are widely accepted for the diagnosis of erythrocytosis in adult patients

2. focus on the primary exclusion of PV based on JAK2 analysis as the first step in the diagnostic evaluation of a patient with erythrocytosis

3. subsequent analysis of JAK2-mutation-negative patients includes bone marrow examination.

Is this approach appropriate with regard to children and adolescents affected by erythrocytosis?
Methods

- WG 3: Consensus finding process initiated to answer this question
- A panel of four central questions addressed within the consensus process
- Systematic selective literature search by each author
- Possible answers to the four panel questions and a draft of a specific diagnostic algorithm circulated
- Discussed at the 6th MPN&MPNr EuroNet meeting (Billund, Denmark, 24th-26th October 2012) among 13 WG 3 participants from 8 countries
Questions

1. Do different forms of erythrocytosis in children and adolescent occur with a similar prevalence as in adults?

2. Are the clinical, biochemical, and molecular characteristics of these disorders independent of the age of patients?

3. Do the diagnostic procedures have the same consequences for patients independent of their age?

4. In conclusion from answers 1-3: Is a specific diagnostic algorithm for pediatric patients useful?
1. Do different forms of erythrocytosis in children and adolescent occur with a similar prevalence as in adults?

I. Congenital erythrocytosis (CE):
   • Prevalence independent of age

II. Polycythemia vera (PV):
   • Annual incidence ~ 20 per 1 Mio.
   • Median age at presentation 60 years
   • Incidence estimations:
     • Osgood 1965: 0.1 % of pts. at age < 20 years
     • McNally 1997 (UK): incidence for pts. < 20 years: 0-0.2/10^6 pt.-yrs.
   • Only ~ 50 pediatric patients reported (small series & cases)

→ In pediatric patients, PV is as rare as CE
2. Are the clinical, biochemical, and molecular characteristics of these disorders independent of the age of patients?

Congenital erythrocytosis:

• Sparse data
• Clinical presentation depends on the underlying genetic change and its intrinsic phenotypic variability
• Age dependent differences not suspected apart from the physiologic age-related increase of the risk for vascular complications
2. Are the clinical, biochemical, and molecular characteristics of these disorders independent of the age of patients?

Polycythemia vera: Clinical and hematological data

Table 1: Clinical complications and PV-related symptoms in pediatric patients

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Before/at diagnosis of PV</th>
<th>During follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Budd-Chiari syndrome</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Gangrene</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Stroke (thrombotic)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Stroke (hemorrhagic)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Pulmonary embolism (suspected)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal hemorrhage</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Post-dental extraction bleeding</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>

Symptoms

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>11</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2</td>
</tr>
<tr>
<td>Nausea</td>
<td>3</td>
</tr>
<tr>
<td>Syncope</td>
<td>3</td>
</tr>
<tr>
<td>Lassitude</td>
<td>3</td>
</tr>
<tr>
<td>Dizziness</td>
<td>2</td>
</tr>
<tr>
<td>Pruritus</td>
<td>3</td>
</tr>
<tr>
<td>Impaired vision</td>
<td>2</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>1</td>
</tr>
<tr>
<td>Tinnitus</td>
<td>1</td>
</tr>
</tbody>
</table>

Table 2: Hematological data of pediatric patients at diagnosis of PV (n=number of informative patients)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Median</th>
<th>Range</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin (g/dl)</td>
<td>18.9</td>
<td>15.5-26.7</td>
<td>30</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>61</td>
<td>41-80</td>
<td>31</td>
</tr>
<tr>
<td>Erythrocytes (×10^12/L)</td>
<td>7.6</td>
<td>5.2-11.2</td>
<td>27</td>
</tr>
<tr>
<td>MCV (fl)</td>
<td>76</td>
<td>62-95</td>
<td>14</td>
</tr>
<tr>
<td>MCH (pg)</td>
<td>24</td>
<td>18-35</td>
<td>9</td>
</tr>
<tr>
<td>Reticulocytes (%)</td>
<td>12</td>
<td>5-24</td>
<td>13</td>
</tr>
<tr>
<td>Leukocytes (×10^7/L)</td>
<td>13.2</td>
<td>3.3-22.2</td>
<td>32</td>
</tr>
<tr>
<td>Platelets (×10^9/L)</td>
<td>600</td>
<td>83-2020</td>
<td>32</td>
</tr>
</tbody>
</table>

Table 3: Bone marrow histology data of 31 informative pediatric PV patients (number of patients with reported changes)

<table>
<thead>
<tr>
<th>Changes</th>
<th>Cellularity</th>
<th>Erythropoiesis</th>
<th>Myelopoiesis</th>
<th>Relation of Erytheto Myelopoiesis</th>
<th>Megakaryopoiesis</th>
</tr>
</thead>
<tbody>
<tr>
<td>++</td>
<td>10</td>
<td>7</td>
<td>2</td>
<td></td>
<td>6</td>
</tr>
<tr>
<td>+</td>
<td>17</td>
<td>13</td>
<td>11</td>
<td>10</td>
<td>11</td>
</tr>
<tr>
<td>(*)</td>
<td>3</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>nl.</td>
<td>3</td>
<td>5</td>
<td>5</td>
<td></td>
<td>6</td>
</tr>
</tbody>
</table>

Cario, H et al. Ann Hematol 2009
2. Are the clinical, biochemical, and molecular characteristics of these disorders independent of the age of patients?

Polycythemia vera: JAK2 mutations and EECs

Cohort 1: 8 sporadic, 5 familial PV cases (Teofili et al. Blood 2007)
  • 3x JAK2 V617F+, 1x JAK2 exon 12+; 4x EEC+

Cohort 2: 8 sporadic, 1 familial PV cases (Cario et al. BJH 2008)
  • 7x JAK2 V617F+, 2x JAK2 exon 12+; 7/7 EEC+
3. Do the diagnostic procedures have the same consequences for patients independent of their age?

1. Blood sampling:
   • may be difficult in children
   • frequent painful blood sampling refused by patient and parents

2. Bone marrow aspiration and trephine biopsy:
   • Deep analgesic sedation or general anesthesia needed
   • technical problems particularly in small children
   • small sample size can lead to diagnostic uncertainties

3. MRI (to search for causes of acquired secondary erythrocytosis):
   • sedation or even general anesthesia in young children up to the age of 8 years needed

→ Interventions are more difficult in pediatric patients with regard to technical aspects, impact on the patient, and reliability of results
4. In conclusion from answers 1-3: Is a specific diagnostic algorithm for pediatric patients useful?

A specific diagnostic algorithm for the diagnosis of erythrocytosis in children and adolescents is regarded as useful because of the different prevalence of PV in addition to the specific requirements for diagnostic procedures in children and adolescents.
Diagnostic algorithm

1. Epo may be in the lower normal range in PV. In the case of any typical PV symptom diagnostic procedures should focus on PV exclusion first.

2. In the case of suspected PV but negativity for typical JAK2 mutation additional EPOR analysis should be considered particularly in cases with only mild PV-like symptoms (e.g. mild splenomegaly). If diagnosis of PV is probable, attempts to confirm this diagnosis can be made by analyzing the formation of endogenous erythroid colonies and/or bone marrow biopsy including cytogenetics.

3. In the case of affected relatives the order of analyses will depend on the presumed inheritance pattern (VHL – recessive, EGLN1, EPAS1 – dominant).
3. Do the diagnostic procedures have the same consequences for patients independent of their age?

1. Blood sampling:
   - may be difficult in children
   - frequent painful blood sampling refused by patient and parents

→ if any of a pediatric patient’s relatives is also affected by presumable CE this relative should be examined first
→ careful physical examination and non-invasive procedures, abdominal ultrasound, pulse oximetry, and pulmonary function tests should be performed before or in parallel to the first blood analysis
→ initial blood tests should include a blood gas analysis (to calculate p50), liver and renal parameters (to exclude severe disorders associated with erythrocytosis), iron storage parameters, and serum Epo
→ storage of material for genetic analysis possible
3. Do the diagnostic procedures have the same consequences for patients independent of their age?

1. Blood sampling:
   - may be difficult in children
   - frequent painful blood sampling refused by patient and parents
3. Do the diagnostic procedures have the same consequences for patients independent of their age?

2. Bone marrow aspiration and trephine biopsy:
   - Deep analgesic sedation or general anesthesia needed
   - Technical problems particularly in small children
   - Small sample size can lead to diagnostic uncertainties

→ Bone marrow histology will be useful in only few patients
→ BM biopsy in pediatric patients strictly limited to individual patients with suspected PV but JAK2 negativity and other obvious explanation for his erythrocytosis
   - BM changes affecting non-erythroid cell lines may be present even without corresponding changes in the peripheral blood. Cytogenetic abnormalities substantiate the presence of clonal hematopoiesis

→ Alternatively, EEC formation can be analysed. The presence of EEC formation would strongly support the diagnosis of PV.
   - The EEC test is not standardized and should be performed only in the rare experienced and specialized laboratories.
3. Do the diagnostic procedures have the same consequences for patients independent of their age?

2. Bone marrow aspiration and trephine biopsy:
   - Deep analgesic sedation or general anesthesia needed
   - Technical problems particularly in small children
   - Small sample size can lead to diagnostic uncertainties
3. Do the diagnostic procedures have the same consequences for patients independent of their age?

3. MRI (to search for causes of acquired secondary erythrocytosis):
   - sedation or even general anesthesia in young children up to the age of 8 years needed
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Conclusion

• The proposed diagnostic approach considers the different prevalence of underlying disorders as well as the particularities in the performance of diagnostic procedures in pediatric patients with erythrocytosis.

• Currently, it is expected that the diagnosis of the underlying cause of erythrocytosis is possible in about thirty percent of the patients.

• Future findings on additional genetic causes of inherited erythrocytosis must be integrated into the proposed algorithm.
Acknowledgement

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