Idiopathic erythrocytosis and other non-clonal polycythemias

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Idiopathic erythrocytosis (IE) is characterized by an increase of red blood cell mass without an identified cause. Its diagnosis is based on the exclusion of polycythemia vera (PV), secondary acquired polycythemias and various congenital primary and secondary polycythemias. The frequency of IE has been estimated to be 1.1 per 1000 subjects, which is higher than that observed in PV. Heterogeneous mechanisms underlying IE have been suggested, including ‘early’ PV and unrecognized secondary or congenital polycythemia. However, the transition of a patient initially classified as IE into PV is a rare occurrence, when more sophisticated diagnostic techniques are employed. IE is a stable disease with a low thrombotic risk and a low, if any, tendency to spontaneous progression to acute leukemia or myelofibrosis. Phlebotomy in patients with IE is controversial. Myelosuppressive drugs should be avoided since their use is associated with evolution into acute leukemia in about 10% of patients.

Key words: idiopathic erythrocytosis; polycythemia vera; secondary polycythemia; phlebotomy.
IDIOPATHIC ERYTHROCYTOSIS

Definition

The term ‘idiopathic erythrocytosis’ (IE) applies to a situation when a patient has a measured red cell mass (RCM) above the normal range, i.e. an absolute erythrocytosis, but—following further investigation—no cause of primary or secondary erythrocytosis/polycythemia can be established.\(^1\) The condition has been variably called ‘benign erythrocytosis’ by Modan and Modan\(^2\) and ‘pure erythrocytosis’ by Najean et al.\(^3\) However, although these terms identify two typical features of this condition, i.e. the more benign clinical course as compared with polycythemia vera (PV) and the isolated involvement of the erythroid lineage, the term ‘idiopathic erythrocytosis’ is preferred because it emphasizes that the underlying cause driving erythropoiesis is unknown.

Most patients with an absolute erythrocytosis\(^4,5\) have an identifiable cause and can be classified into primary and secondary types based on the responsiveness of the erythroid progenitors to erythropoietin (Epo) (Table 1). Primary polycythemias are characterized by an autonomous and/or augmented response of the haematopoietic progenitors to Epo due to inherited germline or acquired somatic mutations; this group includes PV. By contrast, secondary polycythemias have normal responsiveness of the erythroid progenitors to Epo and are due to increased levels of circulating factors driving erythropoiesis (most commonly Epo, but also insulin-growth-factor 1, aberrations of angiotensin 2/angiotensin receptor axis, and cobalt).\(^6\) IE constitutes the remaining group of patients in whom no cause for polycythemia has yet been identified.

<table>
<thead>
<tr>
<th>Table 1. Pathophysiological classification of absolute erythrocytosis.</th>
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<tbody>
<tr>
<td><strong>Primary polycythaemia</strong></td>
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<tr>
<td>Congenital:</td>
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<tr>
<td>Primary familial congenital polycythemia (including mutations of the EPO receptor)</td>
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<tr>
<td>Acquired</td>
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<td>Polycythemia vera</td>
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<td><strong>Secondary erythrocytosis</strong></td>
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<tr>
<td>Congenital</td>
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<tr>
<td>Mutant high oxygen-affinity haemoglobins</td>
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<td>Congenital low 2,3-biphosphoglycerate deficiency</td>
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<td>Methaemoglobinemia</td>
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<td>Chuvash polycythemia and other VHL mutations (with some features of primary polycythemia) (autonomous high Epo production)</td>
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<tr>
<td>Acquired</td>
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<tr>
<td>Hypoxaemia (chronic lung disease, high altitude, cyanotic congenital heart disease)</td>
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<td>Renal disease (tumours, cysts, hydronephrosis, renal artery stenosis, renal transplantation)</td>
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<td>Liver disease (hepatoma)</td>
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<td>Endocrine disorders (Cushing’s syndrome)</td>
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<td>Tumours (cerebellar hemangioblastoma, pheochromocytoma, paragaglioma. uterine fibroids,)</td>
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<tr>
<td>Drugs (erythropoietin, androgens)</td>
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<td><strong>Idiopathic erythrocytosis</strong></td>
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Frequency

IE is a frequent disorder. The prevalence has recently been evaluated in a prospective cohort of 10,000 healthy subjects carried out in Italy. The study was preceded by a pilot phase in which the hematocrit at presentation was measured in 100 consecutive patients with definite PV, diagnosed according to the Polycythemia Vera Study Group criteria, which include increased RCM. The hematocrit in all male and female PV patients was >0.51 or >0.48, respectively. These hematocrit values were chosen as the upper limits of normal. Hematocrit was evaluated at presentation in all participants and at a second follow-up in 88 patients with increased baseline values. Thirty-five patients with confirmed high hematocrit were extensively investigated for a diagnosis of PV or secondary polycythemias and all subjects with an increased hematocrit at enrolment were followed for at least 5 years. At the end of the study, 11 patients were diagnosed as having IE that was stable after 5 years. The estimated prevalence was 1.1 cases per 1000 persons. In the same study, the prevalence of PV and secondary polycythemias was 0.3 and 2.2 per 1000 persons, respectively. Thus, IE is about four times more frequent than PV in the general population.

Diagnosis

By definition, the diagnosis of IE requires the exclusion of other causes of primary or secondary polycythemias (Figure 1). This diagnostic work-up has become increasingly frequent because an elevated hematocrit is a relatively common finding, since the introduction of the automated blood cell count. The first and clinically most important step is to rule out the presence of a clonal hematopoietic disorder—chiefly PV or less commonly other myeloproliferative disorders that might present with an elevated hematocrit (essential thrombocythemia, chronic myelocytic leukemia, and idiopathic myelofibrosis). The differentiating features of the myeloproliferative disorders are reviewed in other chapters of this issue.

The next step is to exclude the most frequent causes of secondary polycythemias. Routine screening procedures include measurement of arterial oxygen saturation and especially in smokers, COHb levels, abdominal ultrasound scan and Epo levels. The finding of an arterial oxygen saturation below 92% indicates a diagnosis of secondary hypoxaemic erythrocytosis. However, some patients desaturate markedly during sleep, but have a normal awake oxygen saturation. Thus, it is important to explore the presence of both underlying lung disease and ‘sleep apnea’, both of which might cause transient arterial oxygen desaturation. In one study, 25% of patients who would have otherwise been designated as having IE were found to have nocturnal hypoxaemia despite normal daytime oxygen saturation values. Cigarette smoking per se is an uncommon cause of erythrocytosis. Smoking, with the concomitant rise in COHb, is more commonly additive to other factors, such as lung disease, sleep apnea and obesity. Kidney disease can also cause erythrocytosis as a result of different pathologies including multiple cysts, renal artery stenosis, renal cell carcinoma, and after renal transplantation (‘postrenal transplant erythrocytosis’). In addition, illicit or excessive androgen and Epo administration should always be considered in the evaluation of patients with erythrocytosis.

The final diagnostic step is to consider rare causes of congenital polycythemias. In patients with apparent IE, it is important to take a careful family history, bearing in mind the fact that the recessively inherited erythrocytoses/polycythemias are seen more
Three groups of congenital polycythemia have been described: (1) primary familial and congenital polycythemia (PFCP) characterized by low serum Epo and normal P50 (oxygen pressure at 50% haemoglobin–oxygen saturation); (2) secondary congenital polycythemias characterized by low P50, including high oxygen-affinity haemoglobinopathy, congenital types of methaemoglobino-pathy, and 2,3-biphosphoglycerate mutase deficiency; and (3) polycythemias with an autonomous high or inappropriately normal Epo levels for given hematocrit and a normal P50; these include Chuvash polycythemia, other von Hippel–Lindau mutations, and other polycythemias whose underlying cause is yet to be identified.11

**IS IDIOPATHIC ERYTHROCYTOSIS A SEPARATE CLINICAL ENTITY?**

It is generally believed that a variety of mechanisms may be the underlying cause of IE. Pearson and Messinezy1 listed these possibilities: (1) physiological variant; (2) ‘early’ polycythaemia vera; (3) unrecognized secondary acquired erythrocytosis; (4) unrecognized congenital erythrocytosis/polycythemia; (5) currently undescribed forms. We will discuss these possible mechanisms in the light of recently available clinical data.7,12
Physiological variant

The current criteria for measuring and reporting RCM, i.e. the gold standard for diagnosing an absolute erythrocytosis, were proposed by the Expert Panel on Radionuclides of the International Council for Standardization in Hematology (ICSH). The panel suggested that measured RCM data should be compared with reference ranges related to the individual's surface area, and gave a reference range of ±25% for each surface area value. This range includes 98 and 99% of normal males and females, respectively. It follows that one in 100 normal males and one in 200 normal females will fall above this range and will be included in the IE group. These considerations are supported by the recent finding that IE is a frequent condition in healthy individuals.

Differentiation of IE from PV

‘Early’ PV

Previous longitudinal studies have reported that patients initially presenting with IE might have haematological evolution and clinical features enabling them to be reclassified as PV. In one study, this transition was found in 12 of 30 patients within 6 years of follow-up. We suggest that the rate of 40% of progression to PV is excessive given the current diagnostic techniques for better recognition of early PV. These include serum Epo level, acquired cytogenetic abnormalities, assay for endogenous erythroid in vitro formation, and assay for constitutive JAK2 mutation—JAKV617F. Some also suggest that bone marrow histology increases the sensitivity and specificity of PV diagnosis. Adopting these tests, when indicated, in the initial evaluation of a patient with absolute erythrocytosis facilitates the differential diagnosis of PV and IE. The clinical relevance of the proper differentiation of IE from PV is underscored by clinical prospective study of these patients (see below).

Differentiation of IE from congenital polycytemias

Primary familial and congenital polycythemia

Primary familial and congenital polycythemia (PFCP) is characterized by low serum Epo and normal P50. The cardinal features of PFCP are low Epo levels and typically autosomal dominant inheritance. However, it should be kept in mind that the family history might be misleading, if PFCP derives from a new mutation in a studied individual, if there is non-paternity, or if previous hematological data in these frequently asymptomatic patients and their relatives are not available. If needed, a diagnosis of PFCP could be confirmed by demonstrating in vitro assay hyper-responsiveness of erythroid progenitors to Epo. Some, but not all, of these patients have a truncated Epo receptor (gain of function mutation; reviewed in Ref. [11]).

Secondary congenital polycytemias

Secondary congenital polycytemias characterized by low P50 include high oxygen-affinity haemoglobins, methaemoglobinemia, and 2,3-bisphosphoglycerate mutase deficiency. Patients with any of these secondary polycytemias might have either normal or elevated Epo levels.
High oxygen-affinity haemoglobins result from mutations of alpha, gamma or beta globin genes, each presenting with different phenotype. Polycythemia due to mutations of the alpha globin gene is persistent since birth, whereas that due to gamma globin mutations is present shortly after birth, but generally disappears over 3–6 months of age after transition from haemoglobin F to A; polycythemia due to beta globin mutations develops only after the age of 3 months. It should be noted that haemoglobin electrophoresis fails to detect some of these mutations and the appropriate diagnostic test is the measurement of P50. When available, P50 should be determined by co-oximeter that measures the full haemoglobin oxygen dissociation curve; if not available, P50 can be estimated from venous blood gases.21

Differentiating IE from congenital methaemoglobinemia presents little clinical difficulty because patients with congenital methaemoglobinemia are cyanotic. Acquired methaemoglobinemia is not associated with erythrocytosis. The diagnosis of methaemoglobinemia is readily made by confirmation of elevated methaemoglobinemia levels and, if needed, identification of cytochrome b5 reductase (methaemoglobinemia reductase) deficiency, presence of haemoglobin M (globin mutations), or the extremely rare cytochrome b5 gene mutation.22

Deficiency of 2,3-biphosphoglycerate mutase is an extremely rare cause of erythrocytosis, with only a few families properly studied, and it appears that the polycythemia phenotype could be inherited in either a recessive or autosomal dominant pattern. Its cause is usually identified after globin mutations have been excluded in patients with erythrocytosis and low P50.22

Polycythemias with autonomous high or inappropriately normal Epo

Polycythemias with autonomous high or inappropriately normal Epo levels for a given hematocrit are the most difficult to differentiate from IE. However, in this group several separate entities with defined molecular defects have been identified. The 598G > T mutation of the von Hippel–Lindau (VHL) gene constitute that Chuvash polycythemia that is endemic in the Chuvash Republic of the former Soviet Union23 and presents sporadically in other racial and ethnic groups worldwide.24 Other germline VHL mutations, typically present in both VHL alleles in conjunction with or without Chuvash VHL mutation, can also account for this polycythemic syndrome. The results of in vitro assay of erythroid colonies are heterogeneous, demonstrating Epo hypersensitivity (feature of primary polycythemia) in Chuvash polycythemia25, but may be normal or hypersensitive in other VHL mutations.26,27 Rare patients with apparent congenital polycythemia and mutation of only one VHL allele have been described.24 However, whereas VHL mutations are—in our experience—the most common identified cause of congenital polycythemia, the molecular basis of the majority of patients with congenital polycythemia and high or inappropriately normal Epo levels remains obscure. We (JTP) have now studied four patients with congenital polycythemia and high Epo level without germline VHL mutations who developed pheochromocytoma/paraganglioma.

Other mechanisms

The stability of IE during long-term follow-up observed in recent clinical studies7,12,28 makes it unlikely that most cases are actually due to unrecognized acquired secondary causes. It is possible that a very small pathological lesion will not be recognized at initial investigation, but will subsequently become manifest during follow-up of IE patients. Nevertheless, in the authors’ experience (GF and TB), reclassification of IE patients into
secondary acquired erythrocytosis is a rare occurrence. Another problem of failing to identify the cause of the erythrocytosis, and thereby removing a patient from the IE subgroup, is the failure to obtain information and perform critical investigations to establish a congenital disorder. These conditions are rare, and some of us believe (GF and TB), are not representative of the vast majority of IE patients.

**CLINICAL PRESENTATION AND COURSE**

The diagnostic criteria used to identify PV (and therefore exclude IE) have changed significantly over the years and we have distinguished more recent from older clinical studies.

**Early studies**

Three studies specifically designed to evaluate the clinical course of IE patients were published between 1968 and 1981. An abstract updating the observations of one of these studies was reported later. Like PV, the median age at presentation was between 54 and 65 years, but there was a greater male predominance than seen in PV—ranging from 2.2 to 5.5:1. Patients were frequently diagnosed after vascular complications (63% of 30 patients in one series) or other symptoms, including headaches, gout, and pruritus. Only 20% of patients were detected based on an abnormal routine blood count.

Evolution into PV during follow-up was reported in 10–40% of cases. Other patients were found to have a secondary erythrocytosis, notably hypoxemia. In the majority, however, neither features of PV nor a cause of secondary erythrocytosis emerged. The incidence of vascular occlusions was high in all three formal reviews of these patients. In the first published series, the vascular occlusive incidence was similar to that observed in PV. Examination of the cause of death in two studies showed that a cerebrovascular accident or cerebral thrombosis was the cause in half of 21 patients. A reduction in cerebral blood flow was observed in IE, as in PV, and a limited study of treatment of IE demonstrated that the risk of vascular occlusion was six times greater in patients with hematocrit values above 0.50 than in those with values below this level. A reduction of hematocrit was proposed from these observations but the heterogeneity and retrospective design of those series make it difficult to formulate a specific management strategy for all IE patients.

**Recent case series**

In the current era, asymptomatic IE patients are often discovered on routine blood counts, mandating the need to update the natural history of IE. In a prospective cohort study, we (GF and TB) evaluated the clinical course of 74 patients (66 males, 8 females; median age 56 years, range 14–82) diagnosed as having IE in two Italian institutions. Twelve patients (16%) presented with a history of thrombosis (seven ischemic cardiac disease, four cerebral ischemic events, one deep vein thrombosis), whereas the great majority were investigated because of an incidentally found increased hematocrit. At presentation, median hematocrit value was 0.54 (range 0.48–0.68) and, by definition, RCM was increased by 25% or more above the mean normal predicted value. Normal leukocyte and platelet counts, spleen volume, Epo levels, and bone marrow histology
argued against PV. Expression of the polycythemia rubra vera-1 (PRV-1) gene, recently found to be increased in most PV patients, but in only a few normal controls or secondary erythrocytosis, was normal in all examined patients (n = 23). Normal arterial oxygen saturation and other routine screening procedures excluded a secondary polycythemia. In selected cases, congenital polycythemia was excluded by appropriate investigations, including P50 measurement. All patients were followed for a median of 3.5 years (range 1–23) and 23 of them (31%) were followed for more than 8 years. Treatment included phlebotomy to maintain hematocrit below 45% and aspirin, 100 mg/day, in 24 patients (32%) with previous thrombosis, microvascular symptoms, or cardiovascular risk factors. No cytotoxic drugs were given. During follow-up, no hematological transition to overt PV, myelofibrosis, or acute leukemia was observed and no disease potentially associated with secondary erythrocytosis emerged. Two thrombotic events (one cerebral ischemia and one deep vein thrombosis) occurred, with an incidence of 0.8% per patient-year, significantly lower than the 3.5% per patient-year (p < 0.05) incidence of major vascular complications observed in 205 patients with PV followed during the same period in one of the two institutions (Bergamo).

Other case series have been recently reported. Kiladjian et al in a prospective study, evaluated 140 patients with PV (median age 62 years, male:female ratio of 1.46) and 39 with IE (median age 57 years, male:female ratio 3.33) treated with pipobroman. Diagnosis of IE was based on elevated RCM, normal platelet and leukocyte counts, no splenomegaly, and no evidence of secondary erythrocytosis. After 11.4 years of median follow-up (range 1–28), six IE patients (15.4%) developed leukemia, which did not differ from the PV group (18.6%). Four patients with IE (10.2%) and 28 with PV (20%) presented with a major vascular event. Although this difference was not statistically significant, the rate of thrombosis in IE was about half that in PV; more interestingly, the calculated incidence of thrombosis per year in IE was approximately 0.9%, very close to the 0.8% observed in our study, and the development of leukemia in this group raises the question of a pipobroman induced complication.

Peter Johansson in Sweden (personal communication) is currently following 13 patients with IE (median age 58 years, nine males, four females) without apparent cause and treated with phlebotomy alone, aiming for the target hematocrit <50%. After 6 years median follow-up (range 2–22), one case of myocardial infarction was observed with an estimated incidence of major thrombosis of 1.2% patients per year. None of the patients developed PV or any other hematological progression. The main clinical findings of IE patients included in these recent prospective case series are summarized in Table 2.

**TREATMENT RECOMMENDATIONS**

Some patients with IE have been treated with myelosuppressive agents, assuming that this condition was a variant of PV; similarly, many patients with PFCP (JTP personal observation) as well as many patients with Chuvash polycythemia were also treated by chemotherapy. However, acute leukemia developed in 8–10% of patients treated with P32 and in 15% of those given long-term pipobroman therapy. By contrast, leukemic transition was not observed in those patients in whom treatment was restricted to phlebotomy. Thus, we feel it is imperative that potentially leukemogenic agents should be avoided in IE.
Phlebotomy has been the treatment most frequently used in these patients, although there is no controlled study to show that this therapy reduces the incidence of vascular occlusive events compared to an untreated group. In addition, there is uncertainty regarding the threshold value of hematocrit to be used for starting phlebotomy and the target hematocrit to reach and to maintain. Translating evidence from PV management strategies, reduction of cerebral blood flow in IE at raised hematocrit values has been without much evidence interpreted as a predictor of cerebral thrombosis; thus, some of us (GF and TB) feel that judicious phlebotomy to maintain hematocrit at least below 0.50 can be recommended. However, an increased risk of thrombosis has been seen with or without control of hematocrit in PFCP and in Chuvash polycythemia; perhaps due to augmented Epo sensing in PFCP and augmentation of transcription of hypoxia controlled genes such VEGF and plasminogen inhibitor of activation (PIA) in Chuvash polycythemia. Thus, we on the other side of the Atlantic (XG and JP) are skeptical of this recommendation and perform phlebotomies only in those patients with symptoms of hyperviscosity syndrome and in those who unequivocally feel better after therapeutic phlebotomy.

Low-dose aspirin (100 mg daily) has been recently found to reduce the incidence of major vascular complications in a randomized clinical trial in PV, leading to the recommendation to introduce this drug in the initial therapy of all PV patients. Whether this advice should also be applied to patients with IE is not formally proven. For the time being, aspirin can be recommended to patients at increased risk of occlusion, such as those with evidence of ischemia, previous history of thrombosis, peripheral vascular disease, diabetes mellitus and hypertension.

**SUMMARY**

At variance with earlier reports, recent prospective studies show that IE is a frequent condition, stable over time, with a low inherent tendency to progress into PV or other clonal myeloproliferative disorders. The thrombotic risk is lower than observed in PV.
but still present in about 1% patients per year. Myelosuppressive agents should be avoided and phlebotomy as well as low-dose aspirin should be considered when hyperviscosity suspected. It is possible some of the patients have otherwise unrecognized PFCP, VHL mutations causing congenital polycythemia, and other yet to be recognized molecular defects. A better assessment of the natural history of disease in prospective cohorts of well-characterized patients by detailed laboratory tests and controlled clinical studies to establish the value and the risk/benefit ratio of the optimal hematocrit target of phlebotomy and other therapies is needed.

Practice points

- idiopathic erythrocytosis is a frequent condition, with an estimated prevalence of 1.1 cases every 1000 normal subjects
- diagnosis is based on a careful exclusion of other causes of absolute erythrocytosis, such as PV, secondary polycythemias and congenital erythrocytosis
- the clinical course is characterized by a lower rate of thrombotic complications than observed in PV and a low, if any, spontaneous transition to acute leukemia
- phlebotomy is the therapy of choice, whereas myelosuppressive agents should be avoided because of the risk to increase the leukemic transformation

Research agenda

- the underlying mechanism driving erythropoiesis in IE remains to be identified
- the natural history of disease should be evaluated in long-term prospective studies of well-characterized cohort of patients
- optimization of phlebotomy therapy is a major therapeutic goal to be pursued

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