

Retrospective Study of High Hemoglobin Levels in 56 Young Adults

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Abstract

Background: Erythrocytosis is a frequent request for consultation in the hematologic field. The diagnostic approach is well established in the general population but in a young adult, finding the etiology of erythrocytosis can be a real diagnostic challenge.

Methods: This is an observational retrospective unicentric study made at the Sherbrooke University Hospital Center, over a period of 20 years (1995 - 2015). Every patient aged between 16 and 35 years old with a significant elevation of hemoglobin or hematocrit was included (hemoglobin > 185 g/L and/or hematocrit > 0.52 in men; hemoglobin > 165 g/L and/or hematocrit > 0.48 in women).

Results: Totally, 426 patients met the inclusion criteria (over a total of 113,453 complete blood counts) but only 56 entered the study for investigations. The majority of patients were of male gender, 43% of the patients were obese, 59% were smokers and 38% used excess alcohol or recreational drugs. Twenty-five patients had the diagnosis of absolute erythrocytosis. Seven patients had the diagnosis of relative erythrocytosis and no cause could be identified in 24 patients. No primary erythrocytosis was found in this cohort. Among the 25 patients with secondary erythrocytosis, hypoxia was the most frequent etiology identified. Less than half of the patients in the cohort had long term follow-up. Search for *JAK2* mutation and serum EPO dosage were performed in 17.9% and 23.2% of cases respectively. Seven patients were treated with aspirin and five patients had phlebotomies.

Conclusions: This retrospective study reveals an actual clinical management that is often discordant with the current recommendations and a frequent lack of follow-up after initial investigations. Harmonization of management of erythrocytosis appears to be highly desirable.

Keywords: Hematology; Erythrocytosis; Young adults; Epidemiology

Introduction

Erythrocytosis represents a frequent request for consultation in the hematologic field. Frequently, it is an incidental finding secondary to a persistent elevation of hemoglobin and hematocrit. Erythrocytosis is suspected when repeated values of hemoglobin are above 165 g/L in female and 185 g/L in male, or when hematocrit values exceed 48% in female and 52% in male. However, the term absolute erythrocytosis is used when an erythrocytic mass exceeds 125% of the predicted value [1-4]. When the erythrocytic mass is not increased, erythrocytosis is said to be “relative” [5].

Erythrocytosis is subsequently classified according to its etiology, whether primary or secondary. Primary erythrocytosis is due to a direct defect within the red blood cell (RBC) progenitors [3]. Secondary erythrocytosis is due to external factors stimulating the RBC production. The latter type is more common in the general population [6]. Its differential diagnosis is broad and encompasses notably cardio-pulmonary pathologies, smoking and exogenous androgens. (Table 1, [1, 3, 4, 7-18]) It is important to use a systematic approach to identify the underlying etiology and to manage it accordingly. Many diagnostic algorithms have been proposed in the literature [19]. Proper management depends on the underlying cause. Phlebotomies may be proposed to patients presenting with hyperviscosity related symptoms [20] (Fig. 1). Even though general etiological profile and clear management indications are already established in medical literature, data is still lacking regarding the etiologic profile on the population level, especially in young adults. The purpose of this study was to answer this very question by interrogating the population of young adults at the Sherbrooke University Hospital Center (CHUS), in Quebec. The secondary outcome was to compare the actual clinical management of these patients with the current recommendations in the literature.

Methods

Study design

In this observational study design, every case of erythrocytosis identified at the CHUS between January 1, 1995 and

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Table 1. Main Etiologies of Erythrocytosis ([1, 3, 4, 7-18])

Primary
Acquired
Myeloproliferative syndrome (polycythemia vera) [1, 3, 4, 7, 8, 9]
Hereditary
<i>EPO</i> <i>r</i> -mutations [10, 11]
Secondary
Hereditary
Low P50
High oxygen affinity hemoglobin [12]
Congenital methemoglobinemia [13, 14]
2,3-BPG deficiency [15]
Normal P50
Mutation of <i>VHL</i> (Chuvash disease) [16]
Mutation of <i>PHD2</i> [17]
Mutation of <i>HIF2-α</i> [18]
Acquired
Hypoxia
Smoking
Carbon monoxide intoxication
Living in high altitude
Lung disease
Obstructive sleep apnea syndrome
Intracardiac shunt and cyanotic heart disease
Renal impairment
Renal artery stenosis
Renal cyst
Post kidney transplant
Neoplasia
Renal carcinoma
Hepatocellular carcinoma
Cerebellum hemangioblastoma
Pheochromocytoma
Uterine leiomyoma
Endocrinopathy
Cushing disease
Drugs
Diuretics
Exogenous androgens
Exogenous EPO

December 31, 2015, was examined retrospectively through computerized medical files. Patients had to be between 16 and 35 years old at the time of the erythrocytosis diagnosis. Within this specified window, patients had to have at least

one complete blood count performed at the CHUS with a hemoglobin value of 185 g/L or higher for men and 165g/L or higher for women or a hematocrit value of 52% or higher for men and of 48% or higher for women. The protocol of this study was approved by the institutional scientific and ethical committees.

Patients

All patients were aged between 16 and 35 years old and had at least one criteria of suspicion for erythrocytosis at one time during the specified window. After the review of every collected file, patients were excluded if they didn't have their investigation and/or follow-up for the erythrocytosis performed at the CHUS and if the computerized medical files contained no more information than the initial complete blood count. Based on the available data, a consensus was reached between the main authors for cases whose inclusion in the cohort was debatable.

Data collection

Data collected in the computerized medical files were: anthropometric measurements, comorbidities, laboratory tests (dates and results) and imaging tests (dates and results). Additional data were collected through manual extraction of the medical files and consisted of the following: lifestyle habits (tobacco use, alcohol intake and recreational drug use), medications (androgens, steroids, and erythropoietin), data on medical follow-up and treatments offered.

Variable and objectives

The main outcome of this study was to establish the etiological profile of erythrocytosis among the population of young adults at a Canadian university hospital center. The etiology was determined following an analysis of the medical files. When no etiology was clearly established during follow-up, patients were classified according to the most likely etiology determined by a consensus among the main authors. Sometimes, no cause could be identified even after thorough review of the medical files. The secondary outcome was to evaluate the management of these patients and compare it to the current recommendations in the medical literature, with the purpose of improving the quality of care.

Statistical analyses

Statistical analyses were of a descriptive type in this study. Categorical variables were described using frequencies and proportions. Continuous variables were described using means and standard deviation if they were normal in type or using medians and interquartile ranges if normality was not respected.

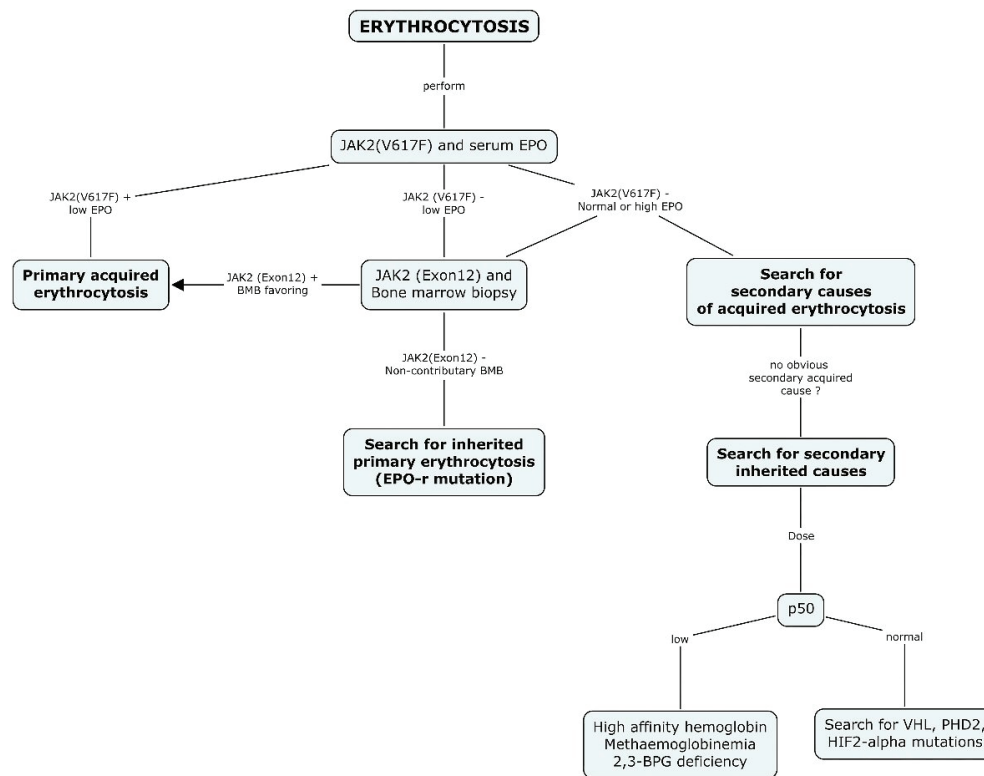


Figure 1. Diagnostic algorithm suggested for erythrocytosis. The current diagnostic approach recommended for the investigation of erythrocytosis systematically includes a search for *JAK2* (V617F) mutation and serum EPO as the first step in every patient. A positive *JAK2* (V617F) result should orient the diagnosis and management towards a diagnosis of primary acquired erythrocytosis. A normal or high EPO should guide the clinician towards the search for a secondary cause of acquired erythrocytosis, and when no cause is found, the search for a secondary inherited cause. A negative result for *JAK2* (V617F) mutation and a low EPO level should be further investigated with a bone marrow biopsy and a search for *JAK2* (exon12), and when non-contributory, should prompt a search for inherited primary erythrocytosis. EPO: erythropoietin; BPG: bisphosphoglycerate; HIF-2: hypoxia inducible factor 2; PHD2: prolyl hydroxylase domain protein 2; VHL: von Hippel-Lindau.

Results

Patients

A total of 113,453 complete blood counts were performed in the young adult population at the CHUS between January 1995 and December 2015. Among these, 426 patients met the criteria for suspicion of erythrocytosis. Within that number, 56 patients were selected for the study, having been investigated and monitored for their erythrocytosis.

The majority of these patients were male. In this cohort, 43% were obese and a third of these had a morbid obesity (class III obesity). As for lifestyle habits, 59% of patients were smokers and 38% were taking alcohol (11%) or using recreational drugs (27%) daily (Tables 2-4).

Etiological data

Even with a preselection of patients being investigated for erythrocytosis detected with a complete blood count, no cause could be identified for 24 of these young adults. Even after

a complete review of the computerized medical files by the authors, the diagnosis still remained uncertain. A diagnosis of relative erythrocytosis was made in seven cases. As for the remaining 25 cases of absolute erythrocytosis in the cohort, no case of primary erythrocytosis was found. Thus, there was no case of myeloproliferative syndrome, including polycythemia vera (PV), for the period studied in the young adults at the CHUS (Table 5).

The 25 cases of absolute erythrocytosis had a secondary etiology. Of these 25 patients, the diagnosis was either clearly identified in the medical records or attributed as most likely after a review of the records by the authors. The two hereditary cases were diagnosed as high oxygen affinity hemoglobin. No genetic mutation was found among patients for whom genetic mutation tests were done, which represents 17.9% of the cohort. Hypoxia was the most frequent extrinsic factor responsible for erythrocytosis [21] in our population of young adults. Of these 13 patients, four had a heart disease, five had a lung disease and eight were smokers. No tumour secreting erythropoietin was found within this cohort. Exogenous androgens prescribed in the context of transgender hormonal therapy were responsible for the four cases of absolute erythrocytosis (Table 6).

Table 2. Distribution of Cases per Year

Year of diagnosis (year)	Number of cases (n)
1995	4
1996	2
1997	2
1998	1
1999	1
2000	0
2001	1
2002	0
2003	2
2004	7
2005	5
2006	4
2007	3
2008	1
2009	4
2010	1
2011	3
2012	1
2013	3
2014	5
2015	6

Secondary outcomes

Every patient included in this study was questioned and a physical exam was performed following the discovery of erythrocytosis. Almost half of these patients (n = 26) were not evaluated by a specialist following the discovery of an abnormal hemoglobin or hematocrit value in the complete blood count. Five patients were dismissed after a single visit with a specialist (four with hematologists and one with pneumologist). For the 25 patients who had long-term follow-up, the median length was 42 months. Among these 25 patients, 10 had a follow-up with a hematologist and six with an internist. The other patients had a follow-up in the medical speciality related to their other comorbidities; either in cardiology, pneumology, nephrology or endocrinology.

The *JAK2* mutation assay and the serum erythropoietin dosage were performed in 17.9% and 23.2%, respectively. The *JAK2* mutation assay, which is available at the CHUS since 2005, was performed in 10 of the 31 patients investigated after 2005 (32.3%). In the majority of patients, an investigation for secondary causes seems to have been performed with complementary laboratory and imaging tests, such as urine analysis, liver function tests, chest radiography and abdominal ultrasound. Although two cases of high oxygen affinity hemoglobin were diagnosed in the context of a positive family history, measurement of P50 was never performed (Table 7).

Table 3. Demographic and Clinical Characteristics of Patients

Characteristics (n = 56)	Value
Age at diagnosis, median value (extremes)	27 (16 - 35)
Gender	
Female, n (%)	21 (37.5)
Male, n (%)	35 (62.5)
Comorbidities	
Heart disease ^a , n (%)	4 (7.1)
Lung disease ^b , n (%)	5 (8.9)
Kidney disease ^c , n (%)	6 (10.7)
Hemoglobinopathy ^d , n (%)	2 (3.6)
Obesity ^{e*} , n (%)	23 (41.1)
Lifestyle habits	
Tobacco use, n (%)	33 (58.9)
Alcohol, n (%)	6 (10.7)
Recreational drugs, n (%)	15 (26.8)
Body mass index ^{f*} , median value (extremes)	28.3 (13.5 - 57.0)
Underweight, n (%)	4 (7.1)
Normal weight, n (%)	13 (23.2)
Overweight, n (%)	9 (16.1)
Obesity - class I, n (%)	14 (25.0)
Obesity - class II, n (%)	3 (5.4)
Obesity - class III, n (%)	7 (12.5)
Drugs	
Exogenous androgens, n (%)	4 (7.1)
Anabolic steroids, n (%)	0 (0)
Diuretics, n (%)	1 (1.9)
Exogenous erythropoietin, n (%)	0 (0)

^aIntracardiac shunt, cyanotic heart disease. ^bChronic obstructive pulmonary disease, sleep apnea syndrome. ^cPost-kidney transplant. ^dHigh oxygen affinity hemoglobin. ^eBody mass index (BMI) $\geq 30\text{kg/m}^2$. ^fUnderweight (BMI $< 18.5\text{kg/m}^2$), normal weight (BMI 18.5 - 24.95kg/m²), overweight (BMI 25.0 - 29.95kg/m²), class I obesity (BMI 30.0 - 34.95kg/m²), class II obesity (BMI 35.0 - 39.95kg/m²), class III obesity (BMI $> 40.05\text{kg/m}^2$). *Data of six patients missed.

Aspirin was prescribed to seven patients following erythrocytosis diagnosis. Five patients had phlebotomies for their symptoms. No death due to erythrocytosis occurred during the follow-up period. Only one patient had a major complication attributable to blood hyperviscosity. This patient was monitored in cardiology for cyanotic heart disease with known as secondary erythrocytosis, but untreated. This patient developed a pulmonary artery thrombosis and was subsequently treated with phlebotomies and a long-term anticoagulation with Coumadin. Hemoglobin and hematocrit values at the time of the thrombotic event were 202 g/L and 0.624, respectively. One patient had hemoptysis in the context of pneumonia and his hemoglobin and hematocrit values at the time were in the normal range at 175 g/L and 0.515 respectively. No association

Table 4. Erythrocytosis Criteria

	Men	Women
Hemoglobin, median value		
At diagnosis (g/L)	186	170
Highest value during follow-up (g/L)	194	177
Hematocrit, median value		
At diagnosis (%)	53.2	49
Highest value during follow-up (%)	55.5	51.6

Table 5. Major Etiologies of Erythrocytosis

Etiologies (n = 56)	Value
Relative erythrocytosis, n (%)	7 (12.5)
Absolute erythrocytosis, n (%)	25 (44.6)
Primary, n (%)	0 (0)
Secondary, n (%)	25 (44.6)
No identifiable cause, n (%)	24 (42.9)

between hemoptysis and erythrocytosis was made by the specialists who evaluated this patient. Four cases of gout arthritis occurred, without any clear association with the underlying erythrocytosis.

Discussion

The main conclusion emerging from this study is that erythrocytosis in young adults is predominantly secondary to an external factor that stimulates erythropoiesis. Poor lifestyle habits such as smoking and obesity are over-represented in this particular population in comparison with the general population.

Table 7. Patients Management

Tests and analyses	Number of patients	Abnormal values
Clinical history and physical examination, n (%)	56 (100)	-
Oxygen saturation, n (%)	51 (91.1)	7 (12.5)
Complete blood count, n (%)	56 (100)	56 (100)
Red blood cell mass, n (%)	4 (7.1)	3 (5.4)
Liver function tests ^a , n (%)	53 (94.6)	18 (32.1)
Chest X-ray, n (%)	48 (85.7)	9 (16.1)
Abdominal echography, n (%)	32 (57.1)	12 (21.4)
Search for <i>JAK2</i> mutation, n (%)	10 (17.9)	0 (0)
Search for other genetic mutations ^b , n (%)	0 (0)	0 (0)
Serum EPO, n (%)	13 (23.2)	0 (0)
Bone marrow aspirate and biopsy, n (%)	2 (3.6)	1 (1.8)
P50, n (%)	0 (0)	0 (0)
Carboxyhemoglobin, n (%)	12 (21.4)	0 (0)

^aAST, ALT, and bilirubin. ^bVHL, PDH2, HIF- α , EPO-r.

Table 6. Detailed Etiologies of Secondary Erythrocytosis Cases

	Value
Hereditary, n (%)	
Low P50, n (%)	2 (3.6)
Normal P50, n (%)	0 (0)
Acquired, n (%)	
Hypoxia, n (%)	13 (23.2)
Renal impairment, n (%)	6 (10.7)
Neoplasia, n (%)	0 (0)
Endocrinopathy, n (%)	0 (0)
Drugs, n (%)	4 (7.1)

The percentage of obese patients (43%) is more than twice the one of the general population which was 18% (self-reported) in the province of Quebec in 2014 [22]. In the study, 59% patients were smokers, which is far more than what is reported in the general population which was 19.6% in the province of Quebec in 2014 [23]. More than half of the reported cases of erythrocytosis were actually related to hypoxia, which suggests that poor lifestyle habits have a significant etiological role.

Conversely, no case of primary erythrocytosis was diagnosed in this population. The prevalence of PV in the general population reported in the medical literature is 44 to 57 per 100,000 people [7]. The incidence of PV in childhood and adolescence is extremely rare. Only about 50 cases of pediatric PV have been reported in all the medical literature [24]. An epidemiological study made in United Kingdom found an incidence of 0.49 cases of PV per 100,000 people among adults aged between 15 and 34 [25]. This data may explain, at least partially, the absence of PV in our cohort.

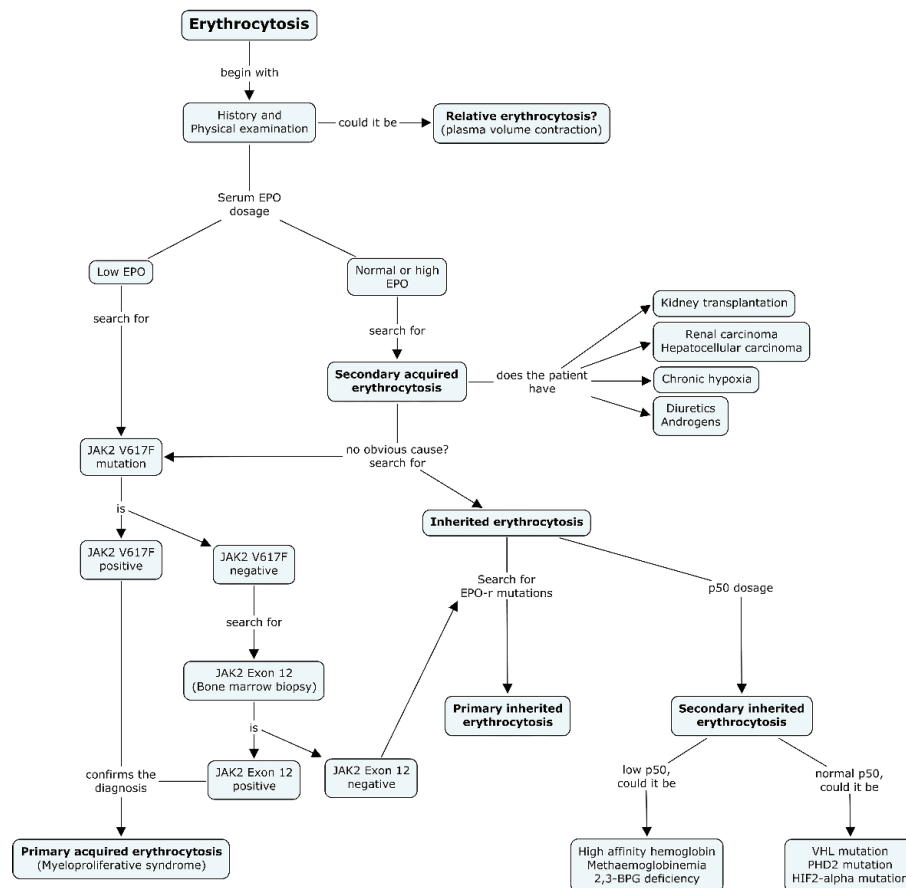


Figure 2. New diagnostic algorithm suggested for erythrocytosis. After exclusion of relative erythrocytosis, serum erythropoietin dosage should be undertaken early in the diagnostic course before concluding of a secondary cause for erythrocytosis in the young adult. In the case of low EPO, *JAK2* (V617F) mutation should systematically be searched. A bone marrow biopsy for *JAK2* exon 12 search should be undertaken with a negative *JAK2* (V617F) mutation. In the case of normal or high EPO, and when no obvious cause for secondary acquired erythrocytosis could be found, a search for inherited erythrocytosis should be undertaken. A search for *EPO-r* mutations and P50 dosage must then be taken into consideration to complete the diagnostic evaluation.

Furthermore, it should be noted that no cause could be identified in a large proportion of patients despite follow-up and management by a specialist. The prevalence of idiopathic erythrocytosis in the general population is estimated to be 110 per 100,000 people [26, 27]. The prevalence in our cohort was lower, with 21 cases per 100,000 people. Among these cases of idiopathic erythrocytosis, nearly a third of patients were hospitalised in a psychiatric unit at the time of the first complete blood count. A decompensation of the underlying psychiatric illness and deliberate intoxications with drugs or medications were frequently mentioned as the reasons for admission on the hospitalisation summary. This suggests that some of these patients probably had a relative erythrocytosis.

The etiological profile of erythrocytosis in young adults that has been revealed in this study sheds a new light over the distribution of the different causes in this particular population. In the future, this would allow us to better guide the diagnosis and management of this entity. In our opinion, hereditary erythrocytosis deserves mention in the differential diagnosis, although it should be kept in mind that it represents only a

small minority of the etiologies in this population, unlike the acquired causes of erythrocytosis.

This study also highlighted the fact that a rise in hemoglobin is often trivialized. Indeed, more than half of these young adults had no referral or follow-up by any specialist. It should also be noted that of the 426 records of young adults who met the inclusion criteria that the computer program identified, 370 had to be rejected because of an incomplete record or lack of management of erythrocytosis. Even when a follow-up was undertaken, the management was often disorganised and discordant with the algorithms suggested in the literature. A secondary cause for erythrocytosis was often assumed but weakly proven. In our opinion, the search for *JAK2* mutation as well as serum erythropoietin dosage should be performed in the very beginning of investigations. Less than one in four patients had those tests performed in this study. Even after it became available in 2005 at the CHUS, the *JAK2* mutation was searched only in a third of patients with erythrocytosis. This fact could partially explain the absence of primary absolute erythrocytosis diagnosed in our study. No other genetic mutations that could be associated with elevated hemoglobin were

investigated. Even the P50 was never measured. The two cases of high oxygen affinity hemoglobin were diagnosed based on family history, but not confirmed. Laboratory and imaging tests were requested in patients as part of their long-term follow-up, probably in search of a secondary cause of erythrocytosis or in the assessment of their underlying disease. This study therefore reveals the lack of structure in the diagnostic approach and follow-up of patients presenting with erythrocytosis when compared with the current recommendations. However, the diagnostic approach and criteria have evolved during the last 20 years. From 1970 to 2001, the criteria used for the diagnosis of PV were those of the Study Group on Polycythemia. These criteria were revised for the first time in 2001 by the World Health Organisation (WHO) [28]. One of the hypotheses that can explain the disparate care between the patients is the evolution of diagnostic criteria and the availability of new tests during the period under study.

In light of the results of our study, we suggest a new management algorithm adapted to the etiological profile of the young adult (Fig. 2).

Conclusions

To the best of our knowledge, this is the first study to investigate the etiological profile of erythrocytosis in the young adults (16 - 35 years old). Despite its retrospective nature, it reveals a management that is often discordant with the current algorithms recommended in the literature for management of erythrocytosis at all ages and a frequent absence of follow-up after the initial investigations. Hereditary erythrocytosis deserves to be systematically mentioned in this age group, although it represented only a minority of cases in our cohort. Secondary acquired causes of erythrocytosis were the etiologies most frequently diagnosed, whereas myeloproliferative syndromes were not represented in our study. The symptoms which can become important and the thrombotic and hemorrhagic complications associated with blood hyperviscosity require a regular follow-up, especially in a young population [29]. We suggest that modifications be made in the diagnostic approach and management of erythrocytosis in this population. We adapted the current algorithm in light of the results of this study and believe it might better guide clinical decisions in the future.

Acknowledgments

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Author Contributions

AD and MP designed the search protocol. AD collected and analysed the data. AD and MP wrote the manuscript. PMH translated the manuscript. JFC, PB, LD, RL, JD, JAB and VE contributed to data collection and analysis.

Conflict of Interest

The authors do not declare any conflict of interest.

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