A revised guide to the diagnosis of polycythaemia

In this series, we present authoritative advice on the investigation of a common clinical problem, specially commissioned for family doctors by the Board of Continuing Medical Education of the Royal Australasian College of Physicians.

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Just as anaemia can be the presenting sign of many underlying illnesses, an elevated haemoglobin level can be due to one or more of many causes and the management of a high haemoglobin level can vary. Sometimes the cause will be clear and the management simple, such as in the case of dehydration or smoking. In more difficult cases, referral of patients to a haematologist will be required for diagnosis and appropriate treatment.

True polycythaemia (polycythaemia vera) is a myeloproliferative disorder characterised by an increase in the number of red cells in the blood. It results in an increase in the haemoglobin level, haematocrit and red cell count and, in some patients, increases in granulocyte and platelet counts. Clinical features include pruritus (which is related to the release of histamine from basophils) and splenomegaly.

Diagnosing polycythaemia vera

Since the publication of the previous article on this topic in *Medicine Today*,[1] a significant advancement in the diagnosis of polycythaemia vera has occurred with the discovery of an acquired somatic mutation in the bone marrow and blood cells of almost all patients with the disorder.

In 2005, the JAK2-V617F mutation was described in the *JAK2* (Janus kinase 2) gene. This mutation occurs in about 95% of patients with polycythaemia vera and is detected using a sensitive allele-specific polymerase chain reaction.[2] Overall, 98% of patients with polycythaemia vera have the JAK2-V617F mutation or another mutation of the *JAK2* gene, the exon 12 mutation. These mutations can also occur in patients with other myeloproliferative diseases, such as primary myelofibrosis or essential thrombocythaemia, although they do not occur in the general population. They

IN SUMMARY

- **Polycythaemia vera is a myeloproliferative disorder that needs to be distinguished from other causes of an elevated haemoglobin level. A reduction in the plasma volume (relative polycythaemia), an increase in erythropoietin secretion (secondary polycythaemia) and smoking (smoker's polycythaemia) can all increase the haemoglobin level.**
- **The diagnosis of polycythaemia vera has been simplified with the finding of a gene mutation present in 95% of patients with this condition.**
- **If a patient's haemoglobin level is borderline between normal and high, look for possible clinical causes such as dehydration or smoking. Remember that such findings may be normal in young men.**
- **A high haemoglobin level is more important if intercurrent vascular disease is present because polycythaemia vera is a risk factor for both arterial and venous thrombosis.**

Diagnosis of polycythaemia vera

The presence of both major criteria and at least one minor criterion, or the first major criterion and at least two minor criteria is required for a diagnosis of polycythaemia vera.

The major criteria are:

- raised haemoglobin level, haematocrit or red cell count
- the presence of a *JAK2* gene mutation.

The minor criteria are:

- typical bone marrow histology
- low serum erythropoietin level
- formation of endogenous erythroid colonies on marrow culture.

are therefore highly specific for the diagnosis of myeloproliferative diseases and have brought the diagnosis of polycythaemia vera into the molecular era.

As a result, the 1997 modifications of the clinical criteria of the Polycythemia Vera Study Group have been revised by an international expert panel and have led to the current WHO diagnostic criteria.[3] The diagnosis of polycythaemia vera requires the presence of both major criteria and at least one minor criterion, or the first major criterion of a raised haemoglobin, haematocrit or red cell count and at least two minor criteria (see the box above).

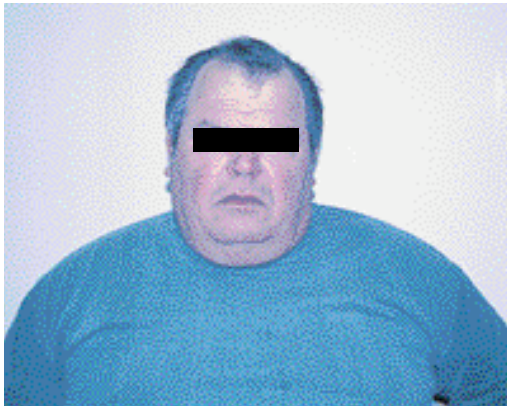

Figure. Plethoric facies of a man with a haemoglobin level of 199 g/L caused by sleep apnoea.

Table. Causes of a high haemoglobin level

	Red cell mass	Plasma volume	Erythropoietin level
Polycythaemia vera	Increased	No change	Decreased
Relative polycythaemia	No change	Decreased	No change
Secondary polycythaemia	Increased	No change	Increased
Smoker's polycythaemia	Increased	Decreased	Increased

Differential diagnoses

Polycythaemia vera needs to be distinguished from other causes of an elevated haemoglobin concentration (Table). A high haemoglobin level can also be caused by a reduction in the plasma volume (relative polycythaemia) or an increase in erythropoietin secretion (polycythaemia secondary to cyanotic heart disease, hypoxic lung disease, and renal or other tumours). Less common causes include sleep apnoea (Figure), androgen therapy and blood doping in athletes. Smoking causes another type of polycythaemia (smoker's polycythaemia).

If a patient's haemoglobin level seems to be borderline between normal and high, look for possible clinical causes such as dehydration or smoking. Remember that such findings may be normal in young men. Polycythaemia vera occasionally presents with a borderline high haemoglobin level if masked by iron deficiency, if inapparent due to increased plasma volume or in the spent phase when myelofibrosis develops. The finding of a borderline high haemoglobin level is more important clinically if intercurrent vascular disease is present.

A high haemoglobin level is more likely to be due to a myeloproliferative disease when associated with increased levels of neutrophils and platelets or with other symptoms and signs of polycythaemia vera. A practical approach to the investigation of a high haemoglobin finding that addresses the diagnostic criteria for polycythaemia vera is suggested in the flowchart on page 48.

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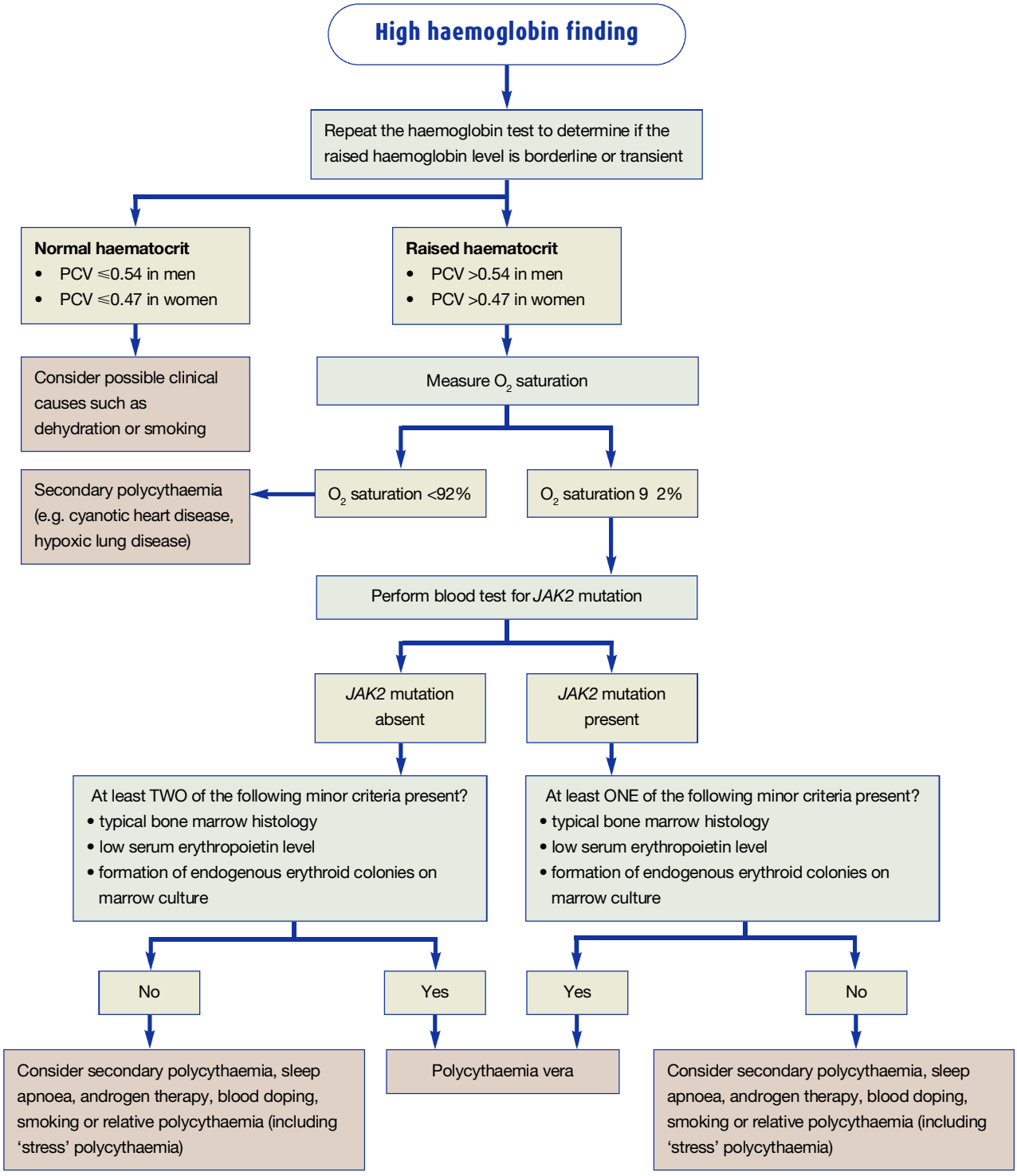
Investigating the patient with a raised haemoglobin level



ABBREVIATION: PCV = packed cell volume.

Clinical approach to diagnosis

A full medical history of the patient should be taken on presentation. Pruritus, usually worse after a hot bath or shower, is a typical symptom of polycythaemia vera. Possible causes of secondary polycythaemia can also be elicited from the history.

Examination can reveal the presence of splenomegaly in polycythaemia vera, or signs of heart or lung disease in secondary polycythaemia. Measurement of oxygen saturation is an important factor when discriminating between polycythaemia secondary to chronic hypoxic lung disease or cyanotic heart disease, and other causes of polycythaemia.

Blood tests should then be performed. The co-existence of neutrophilia and/or thrombocytosis with a raised haemoglobin level makes the diagnosis of polycythaemia vera more likely. The blood film may show morphological abnormalities such as abnormal large platelets. Polycythaemia vera can be associated with iron deficiency, due to a depletion of iron stores by increased red cell production, and it is impor-tant that iron replacement not be given, since the haematocrit could rise dangerously.

If at this point in the investigations polycythaemia vera is the likely diagnosis, a blood test for the JAK2-V617F mutation can provide another major diagnostic criterion. Then either a low serum erythropoietin level or a characteristic bone marrow biopsy confirms the diagnosis.

Concluding remarks

The diagnosis of polycythaemia vera has been simplified by the discovery of a sensitive molecular test for the presence of myeloproliferative disease. However, the finding of an elevated haemoglobin level has a wide differential diagnosis that includes many organ systems. MT

References

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COMPETING INTERESTS: None.