



Macrocytosis

An Australian general practice perspective

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BACKGROUND

Clinicians' approaches to identifying and investigating red blood cell macrocytosis are variable. There is little literature on the Australian primary care approach.

METHODS

Mean corpuscular volume (MCV) in blood counts from an urban Australian general practice were calculated and general practitioners in the surrounding division were surveyed on their experience of and approach to investigating macrocytosis.

RESULTS

Mean corpuscular volume above 100 fL was found in 1.7% of patients, and 7.3% had an MCV above 96 fL. Ninety-four percent of responding GPs replied they would further investigate this clinical finding, particularly at levels above 100 fL. Alcohol excess and vitamin B12 deficiency were the most common single causes of macrocytosis in their experience.

DISCUSSION

Macrocytosis can be a marker for disease and it is important to identify and investigate its presence. Further research is needed to clarify the reference range for healthy adults in general practice and to formulate evidence based clinical guidelines for investigating isolated macrocytosis.

The average volume of red blood cells in a sample is expressed as the mean corpuscular volume (MCV) and is measured in femtolitres (fL). Mean corpuscular volume is routinely reported as part of a full blood count along with other red blood cell indices. An elevated MCV is referred to as (erythroid) macrocytosis. The upper reference limit for MCV quoted varies from 95–100 fL.^{1–3}

Macrocytosis may or may not be associated with anaemia; isolated macrocytosis refers to an elevated MCV in the absence of associated abnormalities of the haemoglobin, white cell and platelet counts. Guidelines exist for investigating macrocytic anaemia, but it is unclear whether these guidelines can be used for isolated macrocytosis.

The presence of macrocytosis can be an indicator of underlying disease. Potential causes of macrocytosis are listed in *Table 1*;^{1,2,4,5} several have serious health consequences. The investigation of macrocytosis may provide an opportunity to identify and manage these conditions. However, hospital based research suggests that primary care clinicians' approaches to identifying and investigating macrocytosis are variable.⁶ Seppa et al⁷ stated that 'evaluation of macrocytosis, when undertaken, was well done by general practitioners. However, it was performed too seldom and, thus, several diseases,

especially alcohol abuse, may have been overlooked'.

The authors sought to explore this subject in an Australian primary care setting. Funding was provided by the Commonwealth Department of Health and Ageing's Primary Health Care Research Development Program; ethics approval was obtained from the University of Newcastle Human Research Ethics Committee.

Phase 1: frequency of macrocytosis in a general practice

Method

Mean corpuscular volume values were obtained for 2801 patients aged over 16 years at time of testing who were referred to the main pathology provider for a full blood count by a single urban group practice over a 5 year time period. There was no upper age limit. Initial blood counts were used so that each patient was included only once.

Results

The MCV values had a normal distribution with a mean of 90.3 fL and standard deviation of 4.8. This is comparable with another population based Australian study⁸ as well as the laboratory's mean that sets an upper reference limit of 100 fL for MCV.

The proportion of initial blood counts with an MCV above 96, 100 and 105 fL is shown in *Table 2*.

Phase 2: GP questionnaire

Method

A one page survey was sent to the 408 members of an urban Australian division of general practice in 2005. An item was placed in the division newsletter advising the intended research so as to increase the rate of completion and return of the questionnaire. A second copy of the survey was mailed with a modified cover letter asking GPs to disregard the survey if they had replied the first time. One hundred and fifty of 408 (37%) surveys were returned.

The survey employed both open ended and multiple choice questions asking about the most common cause of macrocytosis in the GP's experience, investigating isolated macrocytosis in an otherwise well adult patient, frequency of investigation of macrocytosis at various MCV levels, and general comments.

Results

Eighty-one percent of respondents identified excessive alcohol intake or vitamin B12 deficiency as the most common causes of macrocytosis in their clinical experience. 'Idiopathic' causes, liver

Table 1. Potential causes of macrocytosis

Vitamin B12 and folate deficiency
Alcohol
Liver disease
Bone marrow disorders (myelodysplasia, aplastic, dyserythropoietic and sideroblastic anaemias and leukaemia)
Medications
Physiological (neonates, pregnancy)
Hypothyroidism
Artifact (cold agglutinins, hyperglycaemia)
Hyperlipidaemia
Reticulocytosis
Postrenal transplant

Table 2. Proportion of patients with MCV over 96, 100 and 105 fL

MCV (fL)	Number of patients (%)
	N=2801
96.0–99.9	205 (7.32)
100.0–104.9	48 (1.71)
105+	15 (0.54)

disease, folate deficiency and age were reported less frequently.

When asked to consider an otherwise well adult with isolated macrocytosis, 94% of respondents indicated that they would investigate this finding. *Figure 1* shows the frequency with which these GPs reported they would investigate an otherwise well adult with differing MCV levels given a reference range of 80–100 fL.

Respondents raised some important issues in regard to macrocytosis:

- the value of 'watchful waiting', repeating the blood count after a period of time
- the role of history, medication use and alcohol assessment
- the importance of the patient's general health
- discussing the case with a haematologist
- a request for a cost effective approach to investigating persistent macrocytosis with no clear underlying cause
- the importance of clinical judgment and 'treating the patient, not the numbers'.

Information on respondent demographics was not collected. Limitations to this phase of the research include the low overall response rate and the potential for responder bias. This limits the generalisability of the findings.

Discussion

The variability between doctors' investigations of macrocytic patients reported in the literature⁶ was reflected in the stated practices of respondents to the questionnaire.

Guidelines exist for the investigation of macrocytic anaemia. However, there is little clinical information on investigating isolated macrocytosis where an elevated MCV exists without associated abnormalities of other full blood count indices.

An elevated MCV may be a useful indicator of alcoholic liver disease and B12 deficiency although in the latter the MCV elevation may rise only once the B12 levels are quite low.^{7,9}

To estimate the reference range on normally distributed data, laboratories usually take the two standard deviations either side of the mean, which includes 95% of all results. The range determined may then be modified to reflect clinical utility. There are differing opinions regarding the upper

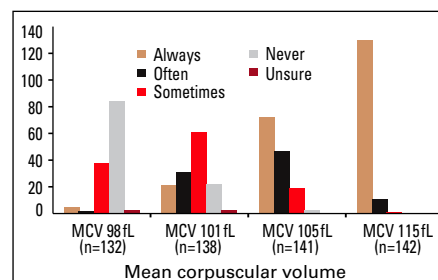


Figure 1. Number of responses investigating macrocytosis at different MCV levels

limit of normal for MCV.^{1–3} Laboratories often quote an upper reference limit of 100 fL⁵, however this does not necessarily reflect the upper limit of MCV in healthy adults and therefore the level beyond which investigations should be considered; 96 fL may be a more appropriate reference limit.³ A number of the GPs surveyed replied that they would investigate patients with an MCV below 100 fL.

Patients need to obtain the right tests at the right time if they are to receive quality primary health care. We question the appropriateness of using 100 fL as a universal upper reference limit for MCV and suggest that guidelines for the investigation of isolated macrocytosis in primary care be developed.

Conflict of interest: none declared.

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