

Screening of Psychiatric Patients for Hypovitaminosis B₁₂

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Summary: Vitamin B₁₂ assays and inspection of peripheral blood films performed on 1,004 consecutive new patients over the age of 50 admitted to mental hospital led to the discovery of pernicious anaemia in only two cases. It is concluded that routine vitamin B₁₂ assays are justified only when fully-automated techniques have become available.

Introduction

It has long been known that deficiency of vitamin B₁₂ may be associated with psychiatric symptoms which are so severe as to dominate the clinical picture of the deficiency and lead to the patient's admission to a mental hospital. In most instances such patients are anaemic, but cases in which there was no overt anaemia and cases in which mental illnesses were associated with normal haemoglobin levels and normal red cell and white cell morphology, but with low serum levels of vitamin B₁₂ and impaired absorption of vitamin B₁₂, have been reported (Strachan and Henderson, 1965). Such instances of haematologically latent pernicious anaemia would seem to be rare. There has been much discussion about screening procedures for hypovitaminosis B₁₂ in psychiatric cases, and the present investigation was undertaken to compare the value of inspection of peripheral blood film morphology with vitamin B₁₂ and folate assays in the routine screening of psychiatric patients.

Inspection of peripheral blood films and assays of serum vitamin B₁₂ and folate were performed on 1,004 patients aged 50 or over admitted between July 1967 and March 1969 to a large mental hospital. In the case of 37 patients in this age group the peripheral films were inspected but the serum vitamin B₁₂ level was not estimated, while in six cases the serum vitamin B₁₂ was assayed but no blood films were available. In a further 23 cases the patient had died or had been discharged before any specimens could be obtained.

Methods

Peripheral films were examined for the presence of hypersegmentation of the neutrophils and macrocytosis. Neutrophils counted as hypersegmented contained at least five nuclear lobes, which were usually connected by very fine filaments. Percentage counts of hypersegmentation were not done, but the films were scored as showing hypersegmentation ±, +, or ++. This scoring method was found to be, with experienced observers, as adequate as, and more economical in time than, the percentage hypersegmented cell count.

Assays.—The serum levels of vitamin B₁₂ were assayed either by the microbiological (*Euglena gracilis*) method (Anderson, 1964) or, in some cases, by an isotopic method (Lau *et al.*, 1965). Serum vitamin B₁₂ concentrations of 100-150 pg./ml. measured by the *E. gracilis* method were considered to be in the "intermediate" range, and concentrations less than 100 pg./ml. were regarded as "low." Every vitamin B₁₂ level found to be below 200 pg./ml. by the isotopic method was confirmed microbio-

logically. Serum folate was estimated initially by the method of Waters and Mollin (1961), but later by the aseptic addition method (Herbert, 1966). Red blood cell folate was assayed by the method of Hoffbrand *et al.* (1966).

Vitamin B₁₂ Absorption Tests.—The method of Coupland (1966) was used and the eight-hour plasma concentration, expressed as percentage of the oral dose of ⁵⁸Co B₁₂ per litre of plasma, was measured. Whenever possible the 24-hour urinary excretion of ⁵⁸Co B₁₂ was also measured.

Results

The results are summarized in Table I. Some degree of macrocytosis of the red blood cells was seen in six cases. Of these six films there was an associated ++ neutrophilic hypersegmentation in five cases and + hypersegmentation in one case. In all these cases the serum folate was less than 3 ng./ml. and in one case the serum vitamin B₁₂ was also low.

Vitamin B₁₂ Absorption Studies.—Tests of vitamin B₁₂ absorption were carried out in 7 of the 25 patients with serum vitamin B₁₂ levels between 100 and 150 pg./ml. (when pressure of laboratory work permitted, and the patient was co-operative). In all seven instances absorption was normal. The results in nine patients with a serum vitamin B₁₂ value of less than 100 pg./ml. are shown in Table II. It can be seen that two of the nine patients (Cases 3 and 6) had the vitamin B₁₂ absorption pattern of pernicious anaemia—that is, defective absorption of vitamin B₁₂ was corrected by a potent preparation of hog intrinsic factor.¹

Discussion

In this series of 1,004 patients routine examination of the peripheral blood films combined with serum vitamin B₁₂ estimations led to the discovery of two cases (Cases 3 and 6) of pernicious anaemia. One patient (Case 4) who had an abnormal peripheral film and a low serum vitamin B₁₂ level died before the ⁵⁸Co B₁₂ absorption test could be undertaken.

As the incidence of pernicious anaemia in people of a comparable age group (over 60) is 7 per 1,000 (Mosbech, 1967) there is no evidence from this series that pernicious anaemia is unduly frequent in elderly psychiatric cases.

In each of these three instances the peripheral blood picture was abnormal, and had inspection of the peripheral film been used as the sole screening procedure these cases would not have been missed. In one instance (Case 1) the serum vitamin B₁₂ was in the low range (100 pg./ml.) but the film was normal; the absorption of ⁵⁷Co B₁₂ was, however, normal.

In most cases hypersegmentation of the neutrophils was not due to vitamin B₁₂ deficiency, but the more pronounced the hypersegmentation the more likely was it due to vitamin B₁₂ deficiency. One-third of the cases with + or ++ degree of hypersegmentation had both normal vitamin B₁₂ and serum folate levels below 3 ng./ml. (Table I). Many patients (25%) with normal blood films had serum folate levels below 3 ng./ml. Furthermore, hypersegmentation of the neutrophils was

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noted when the films of patients with normal folate levels were inspected. Hypersegmentation of the neutrophils may be seen with serum folate levels higher than 3 ng./ml., probably as an expression of early folate deficiency (Hoffbrand and Newcombe, 1967). In the six instances where macrocytosis was noted hypersegmentation was always present.

If the criterion for further investigation of a patient—by assaying the serum vitamin B₁₂ and then, if indicated, performing tests of vitamin-B₁₂ absorption—had been the presence of at least + of neutrophil hypersegmentation vitamin B₁₂ assays would have been required in 71 patients. This would represent a considerable saving in time and expense. The use of the investigation for antigastric antibodies described by Henderson *et al.* (1966) also cuts down the number of patients requiring further investigations to less than 10%. It has, however, the disadvantage that if it were used as the only screening procedure cases of vitamin B₁₂ deficiency following gastrointestinal surgery might be missed (Weir and Webb, 1966; Hunter *et al.*, 1967) and peripheral blood film abnormalities, besides those due to vitamin B₁₂ or folate deficiency, would not be seen. Thus as regards primary screening of patients for vitamin-B₁₂ deficiency the inspection of the peripheral films was satisfactory. This accords with Shulman's (1967a; 1967b) findings.

With respect to folate deficiency, however, the position is quite different. Minor degrees of neutrophilic hypersegmentation were associated with serum folate levels above 3 ng./ml. in several instances and in many others the serum folate level was low without there being any findings in the blood films suggestive of folate deficiency. It would seem that low serum folate levels (<3 ng./ml.) are very common in elderly patients admitted to the psychiatric hospital, but it is hard to know what significance should be attached to this finding. It is likely that most of these low levels were due to dietary deficiency resulting presumably from the capricious appetites and apathy of the patients. A good hospital diet might well rectify the folate deficiency, but ensuring that the patient eats the diet is, of course, difficult.

Hence, vitamin B₁₂ estimation in the older psychiatric patient would be useful mainly to allow folate supplements to be given where the serum vitamin B₁₂ level is normal and grounds for suspecting folate deficiency exist.

In the Sheffield Regional Hospital Board's area, covering 4,600,000 people, there were 5,861 admissions of patients aged 50 or over during 1967. Routine screening of these patients would be impracticable unless a reliable fully automated method for vitamin B₁₂ assays was available. At the present time careful inspection of the peripheral film appears to be the most

economical primary screening test for vitamin B₁₂ deficiency. Based on our experience of over 1,000 consecutive new patients admitted to a mental hospital over the age of 50 routine vitamin B₁₂ assays in psychiatric patients are no more indicated than in the population at large. Indications for assays should be based on haematological grounds (Varadi *et al.*, 1966).

It is not the purpose of this paper to discuss the clinical findings, but of the patients in whom the serum vitamin B₁₂ levels were less than 50 pg./ml. two (Cases 1 and 3) are still in the mental hospital with essentially unchanged symptomatology (depression). The third patient (Case 6), who was found to have pernicious anaemia, had a good haematological response to vitamin B₁₂, but though discharged from hospital still remained rather depressed. Thus the hypovitaminosis B₁₂ may have been coincident with rather than responsible for the mental illness in these instances. In those patients with low vitamin B₁₂ levels but normal absorption (13 out of 15 examined) the hypovitaminosis was presumably secondary to inadequate diet.

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TABLE I.—Results in 1,004 Cases

Total No. of Cases	Hypersegmentation	Serum B ₁₂ Levels in pg./ml.			Serum Folate Levels in ng./ml.				Normal B ₁₂ and > 3 ng./ml. Folate Levels
		> 150	100–150	< 100	> 3	2–3	1–2	< 1	
809	Absent	787 (97.3%)	19 (2.3%)	3 (0.4%)	608	132	64	5	0
124	±	119 (96.8%)	3 (2.4%)	2 (1.8%)	77	29	16	2	76 (70%)
51	+	47 (92.1%)	3 (5.9%)	1 (2%)	19	15	14	3	16 (31.2%)
20	++	17 (85%)	0	3 (15%)	8	3	8	1	6 (30%)

TABLE II.—Results in Nine Cases with Serum Vitamin B₁₂ Less than 100 pg./ml.

Case No.	Age	Hb (g./100 ml.)	P.C.V. (%)	Hypersegmentation	Bone Marrow	Serum B ₁₂ pg./ml.	Serum Folate		R.C. Folate	B ₁₂ Absorption	
							ng./ml.			Without I.F.	With I.F.
1	67	13.0	41	0	N.D.	46	2.3	237	Normal		
2	61	13.3	36	±	N.D.	97	7.6	73	Normal		
3	79	13.3	42	+	Normoblastic. Few G.M.	30	15.0	134	Low	Corrected	
4	68	12.5	38	++	N.D.	68	9.0	214	N.D. (died)		
5	70	12.2	38	0	N.D.	83	4.3	147	Normal		
6	75	11.8	36	++	Had B ₁₂ before B.M. responded (P.C.V. 45%)	30	17.0	200	Low	Corrected	
7	79	14.4	48	++	N.D.	94	2.1	75	Normal		
8	76	13.7	45	0	N.D.	88	4.4	128	Normal		
9	89	12.6	41	±	Normal	72	1.7	78	Normal		

G.M. = Giant metamyelocyte. N.D. = Not done.