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Use of plasma methylmalonic acid in diagnosing vitamin B-12 deficiency in general practice

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***Objectives* – To examine the reasons why general practitioners (GPs) request plasma methylmalonic acid (MMA) tests and how they respond to a result above the reference interval.**
***Design* – Retrospective study of medical records.**
***Setting* – Primary health care, Aarhus County, Denmark.**
***Subjects* – 181 patients with increased concentrations of plasma MMA (> 0.28 μmol/l) attending 10 GPs.**
***Main outcome measures* – Reasons for requesting the analysis and reactions to a plasma MMA level above the reference interval.**
***Results* – A reason for requesting plasma MMA was stated in 129 (71%) of the 181 medical records, screening being the most frequent. A reaction to an increased concentration of plasma MMA was recorded in 128 (71%) patients, and vitamin B-12 treatment was initiated in 102 (80%) of them. Among the 105 patients with marginally elevated plasma MMA level (0.29–0.44 μmol/l), vitamin B-12 treatment was initiated in 38 (36%).**
***Conclusion* – Plasma MMA was frequently used as a screening test. Treatment with vitamin B-12 was initiated when MMA level was increased, and often when plasma MMA level was slightly above the reference interval. This strategy is likely to promote over-treatment with vitamin B-12.**

***Key words:* general practice, diagnostic decision, vitamin B-12 deficiency, vitamin B-12, plasma methylmalonic acid.**

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The often diffuse and non-specific symptoms in the early phase of vitamin B-12 deficiency, and the irreversible damage to the central nervous system that may result from delayed diagnosis (1), have been strong incentives to establish sensitive diagnostic tests. Plasma methylmalonic acid (MMA), which accumulates in vitamin B-12 deficiency, is the most recent test introduced.

Currently under discussion is how measurement of MMA should be used in diagnosing vitamin B-12 deficiency (2). Several authors have suggested that vitamin B-12 deficiency could be defined as an increased MMA level with a significant reduction after vitamin B-12 treatment (3,4), and others have recommended the initiation of vitamin B-12 treatment when MMA level is above 0.44 μmol/l (3). General practitioners (GPs) in Denmark have received this recommendation along with the test result, but until now no one has examined whether they are following the recommendations supplied.

In Denmark generally, and in Aarhus County in particular, MMA concentration has been used increasingly, especially among GPs. This is probably because GPs in Aarhus County work nearby Aarhus University Hospital, where the test was developed and is currently performed (5). Since the GPs included in this study might very well be not too distant future users of MMA, we considered it relevant to examine the reasons given by GPs in Aarhus County for requesting an MMA measurement, and also how they react to an MMA concentration above the reference interval; in this way determining whether GPs are adhering to the recommendation concerning treatment of patients with an MMA level above 0.44 μmol/l.

MATERIAL AND METHODS

Using the laboratory information system of Aarhus University Hospital, we obtained information on patients with a concentration of MMA above the reference interval (> 0.28 μmol/l). They were all registered at one of 10 GPs in Odder Municipality (20 000 inhabitants), Aarhus County. Two of the 12 GPs in Odder Municipality declined to attend the study. Sociodemographically, Odder Municipality is similar to Aarhus County.

We identified 181 patients who had an increased MMA concentration measured during 1997–99 after a request from their GP. For each patient, we used the first increased MMA concentration and excluded patients who received vitamin B-12 treatment when the analysis was requested. Examination of the medical records was performed during May 2000 by AMH.

In relation to the reasons for GPs requesting MMA level, we registered explicit statements about a suspicion of vitamin B-12 deficiency, classified as

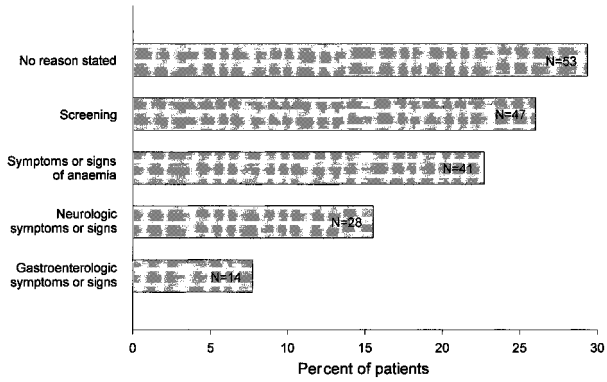

Fig. 1. General practitioners' reasons for requesting determination of plasma methylmalonic acid level among 181 patients. The sum exceeds 100% because categories are not exclusive, and for 2 patients 2 reasons were recorded.

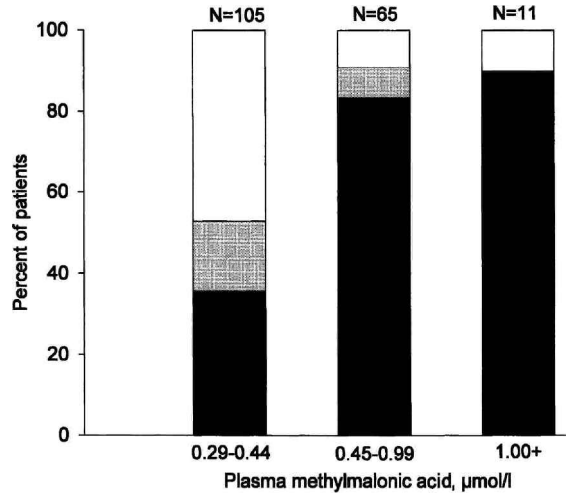

Fig. 2. General practitioners' reaction to an increased level of plasma methylmalonic acid among 181 patients. ■ = B-12 treatment; ▨ = other reaction; □ = no reaction.

anaemia, signs of neurologic disease, gastrointestinal disease, or screening (screening covers routine consultations for the elderly). Concerning reactions to an increased MMA level, we searched for: 1) initiation of vitamin B-12 treatment, 2) additional examinations related to vitamin B-12 deficiency, 3) a repeated MMA determination, or 4) the MMA result mentioned in the record (for instance "normal MMA"). We recorded "no reaction" when none of these reactions was found.

We used the chi-squared test for trend, and p-values less than 5% were regarded as statistically significant.

RESULTS

During the study period (1997–99), the annual number of MMA measurements requested from GPs was 18 per 1000 inhabitants in Aarhus County and 20 per 1000 inhabitants in Odder Municipality. Of the 181 patients with an increased MMA level the median was 0.40 µmol/l (range 0.29–5.90 µmol/l); the majority (94%) had an MMA concentration between 0.29 and 1.00 µmol/l. The median age was 81.7 years (range 26–98 years) and 54% were women.

One or more explicit reasons for requesting MMA level were stated in 129 (71%) of the 181 medical records, and screening was the most frequently stated reason (Fig. 1). Relevant laboratory tests requested before and simultaneously with MMA level are given in Table I. A reaction was recorded in 128 (71%) patients and no reaction in 53 (29%) (median MMA = 0.34 µmol/l). Vitamin B-12 treatment was initiated in 102 (56%) patients (median MMA = 0.51 µmol/l). In 19 patients the GPs repeated MMA tests, and in 7 medical records other reactions were stated.

We found a significant association between level of MMA and a reaction ($p < 0.001$) (Fig. 2). Among the 76 patients with an MMA concentration above 0.44 µmol/l, 64 (84%) had started treatment with vitamin

Table I. Laboratory tests in relation to plasma methylmalonic acid determination in 181 patients with an initial plasma methylmalonic acid level above 0.28 µmol/l.

	More than 1 year before MMA	Up to 1 year prior to MMA determination n (%)	At the same time as MMA determination n (%)	Not measured n (%)
Plasma cobalamins	6 (3)	3 (2)	36 (20)	136 (75)
Blood haemoglobin	20 (11)	23 (13)	105 (58)	33 (18)
Erythrocyte mean cell volume	18 (10)	21 (12)	89 (49)	53 (29)
Erythrocyte folate	3 (2)	1 (1)	38 (21)	139 (76)
Plasma creatinine	4 (2)	24 (13)	150 (83)	3 (2)

Patients who had a laboratory test performed more than once were placed according to the most recent test.
Plasma homocysteine was measured in one patient.

B-12. However, of the remaining 105 patients with a marginally elevated MMA level (0.29–0.44 μmol/l), 38 (36%) had started treatment. Treatment response was evaluated by repeating the MMA test after the start of treatment in 61 (60%) patients.

Plasma gastrin, plasma pepsinogen, antibodies against parietal cells, and antibodies against intrinsic factor were not measured in any of the patients, and no patients were referred for further investigations, such as the Schilling test, upper gastrointestinal endoscopy, or bone marrow examination.

DISCUSSION

Among the GPs examined, MMA level was frequently used as a screening test, and in general the GPs followed the current recommendations regarding initiation of vitamin B-12 treatment. We chose to examine GPs in a region where the use of MMA is well established and thereby representative of future use of this test. Since the information in the medical records was not written specifically for this purpose, it may be limited in certain relevant respects.

When a patient has anaemia, neurologic or gastroenterologic symptoms or signs, it has become universally accepted practice to request laboratory tests for diagnosing vitamin B-12 deficiency. It appears from the present study that MMA level was requested on a much broader indication, namely also in screening of the elderly. There is no evidence of MMA being used like this, and we agree with others who have expressed concern regarding its use as a screening test (2,6).

In Denmark, the result of an MMA test is supplied along with guidance suggesting that a concentration above 0.44 μmol/l indicates vitamin B-12 deficiency. In general, GPs have followed this recommendation, as they initiated treatment in 84% of individuals with an MMA level above 0.44 μmol/l. However, among patients with a moderately elevated MMA level of 0.29–0.44 μmol/l, 36% were treated, which might indicate over-treatment (3). These findings are in marked contrast to a similar study among hospitalized patients, in whom an increased MMA level was ignored in 62% of cases and physicians tended to react only to an MMA concentration above 1.00 μmol/l (7). Today, we do not know which of these two approaches benefits patients most, but in a recent study we found that an increased MMA level was not always a marker of a stable or progressive condition (8).

The risks of administering vitamin B-12 might be minor, as the preparation is non-toxic and there are no side effects. However, over-treatment means treating patients throughout life for a disease they do not have and, furthermore, it may mask other diseases. We therefore consider it important to stress that the clinical benefits of vitamin B-12 treatment of individuals with a moderate increase in MMA level is questionable (9).

In conclusion, we found that among the GPs examined MMA was used as a first-line test for diagnosing vitamin B-12 deficiency, and often as a screening test. In general, the current recommendations were followed, but vitamin B-12 treatment was frequently initiated also among patients with slightly elevated MMA level. The benefit of using MMA measurement as a screening test is unknown, and the benefit of treating patients with moderately increased MMA level is questionable.

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