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Vitamin B_{12}-Induced Reduction of Platelet Monoamine Oxidase Activity in Patients with Dementia and Pernicious Anaemia

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Summary. Platelet monoamine oxidase (MAO) activity has previously been shown to be increased in patients with senile dementia of Alzheimer type (SDAT) and in patients with megaloblastic anaemia. Moreover, low serum B_{12} levels were found to be 4–5 times more frequent in SDAT compared with an unselected population of similar age. In the present investigation, platelet MAO activity was estimated in 14 SDAT patients with relatively low serum B_{12} levels and in 4 patients with pernicious anaemia. Before B_{12} therapy, platelet MAO activity was significantly increased in both patient groups compared with a control group. After B_{12} therapy, platelet MAO activity was significantly reduced in both patient groups to apparently normal levels. The present results show that B_{12} status is a controlling factor of platelet MAO activity and confirm that a significant connection exists between vitamin B_{12} deficiency and primary degenerative dementia disorders, such as SDAT.

Key words: Senile dementia of Alzheimer type – Pernicious anaemia – Vitamin B_{12} deficiency – Platelet monoamine oxidase activity

Introduction

Monoamine oxidase (MAO; E.C.1.4.3.4.) is a key enzyme in the degradation of monoamines. There are two forms of the enzyme, MAO-A and MAO-B, which are characterized by their sensitivity to the selective MAO-A inhibitor clorgyline.

Brain MAO-B activity increases with age in most brain areas and is, in some regions, further increased in patients with senile dementia of Alzheimer type (SDAT) when compared with age-matched controls [1]. The increase in brain tissue MAO-B activity is thought to reflect a reactive gliosis involving cells with a high content of MAO-B molecules [10, 21, 22].

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In human platelets there is MAO of the B type, which, however, in contrast to the brain enzyme, does not seem to increase with age [18]. An increased platelet MAO activity has, on the other hand, been reported in different degenerative dementing disorders such as Huntington's chorea [17], Parkinson's disease [9] and primary degenerative dementia [1, 3, 9, 17]. Thus, increased platelet MAO activity cannot be considered a specific feature of SDAT, but it has been suggested that it reflects a predisposition to the development of a dementia syndrome, regardless of the underlying disorder [4].

Glover et al. [12] have previously reported a highly significant increase in platelet MAO activity in patients with megaloblastic anaemia. They also observed a significant correlation between the platelet MAO activity and the severity of the bone marrow megaloblastic change, as assessed by the deoxyuridine suppression test and bone marrow morphology. Megaloblastosis is usually associated with deficiencies of vitamin B_{12} and/or folate.

Serum B_{12} levels below the lower reference limit were found to occur in 29% of cases of primary degenerative dementia [15]. In our own study [25], 23% of patients with SDAT had level of serum B_{12} lower than 130 pmol/l, which greatly exceeds the 5.6% prevalence of low serum B_{12} levels (< 130 pmol/l) in an unselected population of 75-year-old individuals [20]. The mean serum B_{12} level for the SDAT group was significantly lower than the mean value for presenile Alzheimer's disease and vascular dementia. Moreover, in that study of demented patients [25], we found a significant inverse correlation between platelet MAO activities and serum levels of vitamin B_{12}.

The aim of the present study was to explore further the relationship between platelet MAO activity and the vitamin B_{12} status in SDAT patients.

Subjects and Methods

Subjects. Included in the study were 14 consecutive SDAT patients (aged 80 ± 4 years), 9 females and 5 males, with relatively low serum B_{12} levels (range 6–181 pmol/l). After drawing a blood sample for MAO estimation, the patients were treated with intramus-

cular injections of 1 mg hydroxocobalamin daily, with up to 7 injections within 10 days. At least 4 weeks after the first injection of B_{12}, a new blood sample was drawn for MAO estimation.

To elucidate further the impact of B_{12} deficiency on MAO activity in platelets, we also studied 4 patients with pernicious anaemia in the same way. Apart from blood analyses, the diagnosis of pernicious anaemia was confirmed with a sternal bone marrow puncture showing megaloblastic erythropoiesis.

Control values for MAO activity in platelets were obtained from 47 healthy adults (aged 72 ± 5 years).

Laboratory Methods. Assessment of MAO activity in platelets was performed as described previously with beta-phenylethylamine as substrate and expressed as nanomoles of substrate oxidized/10^{10}

Table 1. Fourteen patients with senile dementia of Alzheimer type (SDAT) and 4 patients with pernicious anaemia, in whom were determined mean ± standard deviation for age, MAO-B in platelets, vitamin B_{12} in serum, haemoglobin in blood and erythrocytal mean corpuscular volume (MCV)

	SDAT ($n = 14$)	Pernicious anaemia ($n = 4$)
Age (years)	80 ± 4	75 ± 9
MAO-B (nmol × 10^{-10} platelets/min)	15 ± 6	33 ± 5
Vitamin B_{12} (pmol/l)	108 ± 51	12 ± 4
Haemoglobin (g/l)	134 ± 16	67 ± 13
MCV (fl)	93 ± 4	138 ± 4

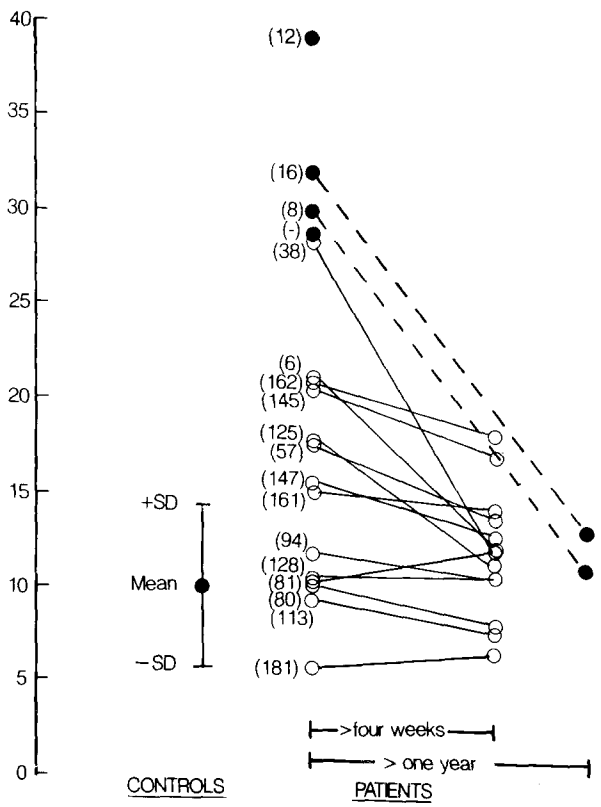

Fig. 1. Monoamine oxidase (MAO) activity in platelets measured with beta-phenylethylamine as substrate (nmol × 10^{-10} thrombocytes/min) in 14 patients with senile dementia of Alzheimer type (○) and 4 patients with pernicious anaemia (●), before and after vitamin B_{12} supplementation. The MAO activity is compared with healthy adult controls (mean and standard deviation). Initial serum B_{12} levels within parentheses

platelets per minute [13]. Vitamin B_{12} was determined by a radioligand assay (Diagnostic Prod. Corp., Los Angeles, Calif.), and 130 pmol/l considered the lower limit of normal distribution for serum B_{12}.

Statistics. Statistical significance was assessed with Student's *t*-test and the Wilcoxon signed rank test for paired data.

Results

In the SDAT group, mean ± standard deviation (SD) for serum B_{12} levels was 108 ± 51 pmol/l, for blood haemoglobin (Hb) 134 ± 16 g/l and for erythrocyte mean corpuscular volume (MCV) 93 ± 4 fl, indicating neither anaemia nor macrocytosis of clinical significance (Table 1). Reference limits were Hb < 110 for anaemia and MCV > 100 for macrocytosis. The platelet MAO activity was 15 ± 6 nmol × 10^{-10} platelets per minute as compared with 10.2 ± 4.3 for the controls, which was a significant difference ($P < 0.002$). The four patients with pernicious anaemia had very low serum B_{12} values (12 ± 4), severe anaemia (Hb = 66 ± 13), prominently macrocytic erythrocytes (MCV = 138 ± 4) and very high platelet MAO activities (33 ± 5).

After treatment with vitamin B_{12}, the MAO activity in platelets was significantly reduced ($P = 0.004$) in the SDAT group (Fig. 1). All MAO activities above the mean of the controls decreased after treatment.

Two patients with pernicious anaemia were available for a follow-up 1 year later. Their MAO activities were reduced to the normal range after treatment with vitamin B_{12} (Fig. 1).

Discussion

Platelet MAO activity is mainly under genetic control, as appears from studies on twins [23] and families [24]. However, non-genetic factors, such as changes in platelet number, volume and protein content, which may be associated with various forms of stress, haematological abnormalities and drug effects, could also affect the MAO activity of platelets [11, 19]. Iron deficiency is related to microcytosis and low platelet MAO activity [5], while deficiency states of vitamin B_{12} or folate are related to megaloblastosis and increased platelet MAO activities [12].

In a retrospective study on demented patients, we recently reported a significantly negative correlation between the level of B_{12} in serum and the platelet MAO activity [25]. In that study the MAO activity was related to the platelet protein, while in the present study the activity was related to the number of platelets. In both studies, however, a relationship between low levels of B_{12} in serum and high platelet MAO activities in SDAT patients was found. The patients with pernicious anaemia had very low serum B_{12} levels as well as very high platelet MAO activities. A causal relationship was confirmed, since administration of vitamin B_{12} significantly reduced the platelet MAO activity in the SDAT patients as well as in 2 patients with pernicious anaemia.

Although the present results strongly indicate a causal relationship between low serum B_{12} levels and increased MAO activity in platelets, 3 of 14 SDAT patients did not respond with a decrease in the MAO activity after treatment with vitamin B_{12}. It is possible that the non-responding patients, all of whom were in the normal range of MAO activity, did not have a B_{12} deficiency from a functional point of view, at least not in the bone marrow. Serum levels of vitamin B_{12} are probably not reliable guides to the degree of true deficiency. This issue could be evaluated with a deoxyuridine suppression test [7] or, possibly, the determination of serum homocysteine concentration [16].

The SDAT patients had a rather modest reduction in serum B_{12} levels as well as a modest increase in platelet MAO activity in comparison with the patients with pernicious anaemia. Nevertheless, the significant response to B_{12} treatment, as reflected by a reduction in platelet MAO activity, implicates some physiological effects of the B_{12} deficiency, although evidently not to the extent of causing anaemia or macrocytosis. This is in agreement with the recent findings by Lindenbaum et al. [16], who studied the association between vitamin B_{12} deficiency and neuropsychiatric disorders. They pointed out that cases with clinically significant B_{12} deficiency are often lacking anaemia and macrocytosis, although erythrocyte MCV, within reference limits (< 100 fl.), is most often reduced after treatment with vitamin B_{12}. Others [6, 8], too, have emphasized the importance of recognizing this atypical form of vitamin B_{12} deficiency, lacking the classical signs of megaloblastic pernicious anaemia.

It is impossible, from our results, to draw any conclusions as to a causal relationship between dementia in our patients and the biochemical findings. Although evidence for an effect of vitamin B_{12} deficiency on the nervous system is generally convincing [2, 14, 16, 27, 28], different possibilities must be considered as to the role of low serum B_{12} levels in degenerative dementia with subtle signs of B_{12} deficiency. One possibility is that low B_{12} levels might occur because of poor dietary intake in demented patients. However, this explanation is contradicted by the findings that low serum B_{12} levels in patients with SDAT are mainly determined by malabsorption due to gastric mucosal atrophy [26]. These findings might also relate to another possible explanation; low serum B_{12} levels are epiphenomena in an atrophic process involving both the gastric mucosa and the brain.

The present study was not designed to evaluate the clinical effects of vitamin B_{12} therapy with respect to the mental state of the patients. Future prospective studies will need to address this important issue.

Conclusion

The results confirm that vitamin B_{12} deficiency is a determinant of increased platelet MAO activity, which is often found in patients with primary degenerative dementia [1, 3, 9, 17]. They also confirm the previous conclusion [15] that a significant connection exists between functional vitamin B_{12} deficiency and primary degenerative dementia disorders, such as SDAT.

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