Introduction

A wide range of psychiatric symptoms has been associated with pernicious anemia. A number of factors indicate a causal relationship between B12 deficiency and cerebral dysfunction and consequent organic mental change.

Deana (1977) demonstrated that vitamin B12 deficiency in the rat has profound effects on several neurotransmitter systems and results in significantly reduced norepinephrine levels in the brain.

Uncorrected vitamin B12 deficiency may result in dementia and cerebral lesions similar to spinal cord lesions in subacute combined degeneration of the cord (Mac-Donald, 1956; Roos and Willanger, 1977; Dreyfus and Geel, 1972). In the presence of haematological and/or neurological signs a vitamin B12 deficiency is generally recognized as a contributing if not causative factor for psychiatric symptoms in patients with organic mental disorder.

It is less well known that psychiatric symptoms may be the first symptoms of vitamin B12 deficiency and may antedate haematological and neurological symptoms by a long period. Recently Evans (1983) described two such cases, pointing to the importance of serum B12 determinations in patients with organic psychiatric symptoms.

However, an intriguing question remains as to what extent B12 in serum is a real reflection of the B12 status of brain tissue. Dreyfus (1970) gave evidence that a low serum B12 status results in low B12 levels in brain tissue. Several authors (Worm-Petersen and Poulsen, 1961; Ukyo, 1971; Taguchi et al., 1977) have suggested the existence of a selective control mechanism for the passage of B12 across the blood-brain-barrier. Ordonez (1977) reviewing the data, speculates that B12 is transferred to the brain at the choroid plexus, which has a very high concentration of B12. Through an active transport mechanism B12 is released to the cerebrospinal fluid (CSF). The protein-B12 complex in the CSF then delivers the B12 to the brain cells. Ordonez states that additional direct uptake by the blood-brain-barrier may be involved.

Circumstantial evidence is available indicating that CSF B12 levels can be regarded as indicative for brain tissue B12 status:

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Dreyfus (1970) demonstrated that low serum B12 results in reduced brain tissue levels, whilst Frenkel (1973) demonstrated that patients with pernicious anemia and low serum B12 levels (n = 22) had CSF B12 levels lower than 5 pg/ml. In a control group of healthy people he found a mean CSF B12 level of 19 pg/ml. Frenkel (1973) was also able to demonstrate that normal serum B12 levels do not necessarily indicate normal CSF B12 levels: in his group of patients with long-term diphosphine use he found normal B12 levels in serum and pathologically low levels of B12 in CSF. Parenteral vitamin B12 medication improved the mentation in this group of patients. Based on this information we have set out to determine whether in groups of selected patients with organic mental disorder a linear correlation exists between serum B12 and CSF B12. The main goal was to find out whether the finding of a normal serum B12 level in a patient with organic mental disorder really rules out the possibility of reduced B12 level in CSF and consequently rules out cerebral B12 deficiency.

Conflicting reports on CSF levels of B12 in neurological patients measured with the bacteriological method were available (Worm-Petersen, 1962; Schrumpf and Bjelke, 1970; Taguchi et al., 1977).

Secondly we have set out to assess the effect of parenteral vitamin B12 (Hydroco-balamine, 1 mg i.m. twice weekly for 6 weeks) medication in a group of twelve patients with organic mental disorder, comparing the pathologically low B12 levels in CSF prior to medication with the levels after 6 weeks medication.

Material and Methods

Methods: The determination of vitamin B12 and folic acid in cerebro-spinal-fluid by a radio-assay method (Gijzen et al., 1983).

The most important problem to be solved for the determination of vitamin B12 in cerebro-spinal-fluid is the low concentration level necessary for diagnostic purposes.

We solved this problem by a preconcentration step. Preconcentration without any damage to the component to be determined can be achieved by vacuum evaporation at room temperature of 5.0 ml. of CSF until dryness. The residue is dissolved in 0.50 ml. of a vitamin B12 and folic acid-free serum. In this way the matrix of the sample is comparable to that of the standard materials used in the method. Experiments showed acceptable parallelism on dilutions and spiking and the non-specific binding of the CSF-samples treated that way did not differ significantly from normal ones.

The lowest measurable-concentration by this technique is as low as 5 pg/ml. The reagents used for the analytical procedure are the Dualcount reagents of the Diagnostic Products Corporation with the purified B12 binder.

Determinations were carried out in the Laboratory for Nuclear Medicine, Vught. (Head: J.F.W. Tertoolen).

Venapuncture and lumbal puncture to obtain serum and CSF for the determination of B12 levels were carried out on the same day, usually simultaneously. We obtained informed consent from the patients and/or their relatives after adequate explanation of the experimental nature of the proceedings.

Patient selection:

We selected 3 groups of patients and 1 control group.

Group 1:

Group 1 is a group of geriatric patients (age 60-85): 23 patients with the diagnosis of dementia on admission to the in-patient department: as to underlying etiology of the dementia the group could be divided into:
- 6 patients with alcohol related brain damage.
- 5 patients with multi-infarct-dementia or Parkinson-related dementia.
- 12 patients with senile dementia (Alzheimer Type), some of them with coexistent depressive reaction.

None of these patients were suffering from any acute physical disease, all were normal on liver function and kidney function tests. They displayed no haematological abnormalities. On neurological examination all these patients had soft neurological symptoms of encephalopathy and polyneuropathy, confirmed in all patients by the finding of cerebral atrophy and widening of the ventricles on the CAT-scan, whilst in 17 of the 23 patients on which an electromyography was done, the existence of polyneuropathy was confirmed.
Group 2:

Group 2 is a group of 16 patients (age 30-60) with a diagnosis of organic affective syndrome (DSM-III) on admission to the out-patient department.

In all these patients exposure to toxic chemicals such as alcohol, industrial solvents, halogenated hydrocarbons (herbicides, pesticides) was considered to be etiologically involved in the development of the neurasthenic depressive syndrome. All patients were in good physical health, had normal haematology, normal liver function, normal kidney function. They displayed soft neurological signs of encephalopathy and neuropathy. In 11 of these patients electromyography was done, revealing a polyneuropathy in 8 patients.

Group 3:

Group 3 is a group of 10 female patients (age 25-40) with a diagnosis of organic affective syndrome (DSM-III), presenting at the out-patient department as post-natal depressions with mainly neurasthenic complaints.

All patients had good physical health, no signs of abnormal liver or kidney function. All patients had complaints of neurasthenia, all patients had soft neurological signs of encephalopathy and neuropathy. In 6 patients an electromyography was done, revealing a polyneuropathy in 3 out of 6 patients. From this group of women with long-standing postnatal depression (duration 2-12 years), 8 out of 10 women had been taking the oral contraceptive pill for more than 2 years prior to the last pregnancy.

Group 4:

Group 4 is a control group of 12 patients attending the outpatient clinic, who underwent lumbar puncture for diagnostic reasons, mainly radicular symptomatology.

These 12 patients were in good physical health, had no symptoms of depression, no symptoms of acute physical diseases, no symptoms of encephalopathy or neuropathy as confirmed by CAT-scan and electromyography, (age 25-50).

Results

The tables show clearly that there is no correlation between serum B12 and CSF B12 in patients with organic brain damage selected according to the criteria.

Table 1 shows that out of the 6 patients with alcohol dementia 5 patients had a normal serum B12 level, whilst in 5 patients the CSF B12 level was in the pathologically low range. Of twelve patients with senile dementia, 3 appeared to have a low or pathological low serum B12 level.

All three patients had a CSF level below 5 pg/ml, whilst of the remaining 9 patients with senile dementia another 6 had a CSF level below 5 pg/ml.

The remaining 3 patients of this subgroup, who had a normal serum B12 level, all had a CSF B12 level in the sub-normal range, between 5 and 10 pg/ml.

The table shows in group 2 that all patients with an organic affective syndrome, selected for neurasthenic symptomatology and possible exposure to potentially neurotoxic chemicals, had a normal serum B12 level.

However it is shown that 8 out of 16 patients had a pathologically low level of B12 in CSF, whilst another 5 patients had a level in the sub-normal range.

The remaining 3 patients had levels resp. of 10, 16 and 18 pg/ml, which is still below the arithmetic mean of the control-group. In group 3 of table 1 it is shown that of the 10 patients with post-natal depression, who all had normal serum B12 levels (range 250-500 pg/ml), 8 patients had a pathologically low CSF B12 level, lower than 5 pg/ml, whilst the remaining 2 patients had both a level of 12 pg/ml.

Table 2 shows that in the 12 controls all patients had a level of B12 serum between 200 and 800 pg/ml, whilst the level in CSF showed an arithmetic mean of 22 pg/ml, ranging from 12 to 57 pg/ml.

Table 3 shows that after 6 weeks of treatment with parenteral vitamin B12, given twice weekly, 1 mg Hydrocobalamine i.m. with 50 mg zinc-DL-Aspartate and 250 mg Taurine combined in a capsule TDS, results in a significant increase of vitamin B12 levels in CSF.

Table 4 shows that after 6 weeks of medication, given in a capsule TDS, containing: 0.1 mg Cyanocobalamine; 50 mg Zinc-DL-Aspartate; 250 mg Taurine, such impressive increases in vitamin B12 in CSF were not found.
<table>
<thead>
<tr>
<th>Group</th>
<th>No.</th>
<th>se-B 12 pg/ml</th>
<th>CSF- B12 pg/ml</th>
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<tr>
<td></td>
<td></td>
<td>0-100</td>
<td>100-200</td>
</tr>
<tr>
<td>1. Alc. dementia: Multi-inf. dementia Senile dementia:</td>
<td>6</td>
<td>1 0 2</td>
<td>0 0 1</td>
</tr>
<tr>
<td>2. Org. aff. syndrome:</td>
<td>23</td>
<td>3 0 0</td>
<td>1 0 0</td>
</tr>
<tr>
<td>3. Post-natal depr.:</td>
<td>16</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>TOTAL GROUP 1, 2, 3</td>
<td>49</td>
<td>3 1</td>
<td>4 5</td>
</tr>
<tr>
<td>controls</td>
<td></td>
<td></td>
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<tr>
<td>No.</td>
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<td>CSF- B12 pg/ml</td>
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<tr>
<td></td>
<td></td>
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<td>0</td>
</tr>
<tr>
<td>range</td>
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<table>
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<th>10 patients</th>
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<th>Post-treatment</th>
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<tr>
<td>se-B12</td>
<td>CSF-B12 pg/ml</td>
<td>se-B12</td>
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<tr>
<td>Arithmetic mean</td>
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<td>&lt;5</td>
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<tr>
<td>range</td>
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TABLE 4
Cyanocobalamin TDS for 6 weeks:

<table>
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<th>Patient</th>
<th>Pre-treatment</th>
<th>Post-treatment</th>
</tr>
</thead>
<tbody>
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<td>I</td>
<td>se-B12 430</td>
<td>&gt;2400</td>
</tr>
<tr>
<td>II</td>
<td>CSF-B12 450</td>
<td>21 9.6</td>
</tr>
</tbody>
</table>

Discussion

Our results are generally in agreement with findings presented by other authors. The level found for the controls in our group (n = 12) is comparable with the levels found by Frenkel (1973), Schrumpf and Bjelke (1970) and Taguchi et al. (1977). The finding of a reduced vitamin B12 level in CSF in patients with brain atrophy was also reported by Schrumpf (1970), though not as clearly as in our group of patients, which might be related to the strict selection of our patient group or may be related to the use of the radio-assay-method (RA) instead of the biological assay-method, because it has been reported that the RA method is more reliable in the lower concentration range.

If and when the circumstantial evidence that CSF B12 level is indicative of cerebral B12 status can be accepted, then our findings have far reaching consequences.

Of our total number of 49 patients with organic mental disorder only 4 patients would have been detected with determination of vitamin B12 levels in serum, whilst in fact 30 of these 49 patients have a pathologically low level of vitamin B12 in CSF and could be treated effectively with parenteral vitamin B12 as has been demonstrated.

In agreement with Frenkel (1973) and MacDonald Holmes (1956) we found clear clinical improvement after long term treatment with vitamin B12, which will be reported elsewhere.

Regarding the group of geriatric patients with dementia syndrome it is particularly fascinating that in the group of patients with multi-infarct-dementia close to normal levels of B12 in CSF were found, whilst very low levels of CSF B12 were found in the group of patients with alcohol dementia and senile dementia.

Particularly fascinating, because the presence of polyneuropathy in the alcoholics is well known, but Levy (1966) has pointed at the interesting fact that in patients with senile dementia also a relation can be found between the development of peripheral polyneuropathy and progress of senile dementia.

This finding is suggestive of a correlation between cerebral B12 deficiency and development of encephalopathy in a sub-group of patients with senile dementia, supported by our findings. At this moment one can only speculate on the mechanism involved, but we have put forward strong evidence (Tiggelen, 1983) that zinc-deficiency could be an important factor in the development of the dichotomy between normal levels of B12 in serum and pathologically low levels of B12 in CSF.

In zinc deficient status the corresponding relatively high levels of copper could block the transport of B12 in the choroid plexus, similar to the effects of known free radical chain reaction inducers as mercury, cadmium and possibly other neurotoxins (Pardridge, 1976; Rapoport, 1964). A state of zinc deficiency can develop due to: reduced dietary intake and/or absorption of zinc metabolic conditions such as diabetes mellitus, pregnancy, chronic hepatic failure, chronic renal failure; medication such as corticosteroids, anti-phlogistics, chelating agents, diuretics, estrogens; intoxication e.g. in chronic alcoholism and possibly due to chronic exposure to halogenated hydrocarbons with estrogen-receptor binding capacity (Eroschenko and Palmiter, 1980).

The hard evidence of zinc deficiency in our group of geriatric patients, which will be
presented in detail elsewhere and has been demonstrated in earlier work (Tiggelen, 1983; Srinivasan et al., 1982), was the rationale behind the combination of parenteral vitamin B12 medication with zinc-DL-Aspartate.

We think that the here presented results on vitamin B12 status in geriatric patients with a dementia syndrome do warrant further investigations of a possibly causal relationship between the development of senile dementia and cerebral B12 deficiency, as measured by estimation of CSF B12 levels.

This could have far reaching preventive aspects regarding the threatening epidemic of the 21st century: senile dementia. Equally intriguing are the results that we found in the group of patients with organic affective syndrome and post-natal depressions. Too frequently in my opinion these patients are regarded as suffering from a depression caused by psycho-social factors and are treated by psycho-therapy, supported by anti-depressants. Our findings suggest that especially when soft neurological signs of encephalopathy and/or neuropathy are found, estimation of vitamin B12 levels in CSF is rewarding.

Wertalik (1982) pointed to the effects of estrogens in oral contraceptives on B12 metabolism, our findings in a group of 10 patients with post-natal depression are equivocal in indicating a vitamin B12 problem. The mechanism involved is not clear and it remains to be seen whether estrogens and estrogen-receptor binding chemicals as halogenated hydrocarbons (Eroschenko and Palmiter, 1980) only have an effect on B12 transportation through blood-brain-barrier and choroid plexus: it might well be that other vitamins such as vitamin B1, B6, possibly even the transport of amino-acids is affected. Further research will have to clarify this issue, but our findings in post-natal depressions and also in patients with an organic affective syndrome, presenting as the classical untreatable neurasthenic depressive patient, who drives the doctor insane by blaming pregnancy and environmental pollution for her depressive complaints, may give more endorsement for the patient's "organic" feelings than for the doctor's "psycho-therapeutic" endeavours.

A classical example of such an organic affective syndrome, now discarded as postwar neurosis, is the plight of the "agent Orange" victims, where careful examination should be conducted into CSF B12 status, especially in the light of a publication by Filippine (1981) reporting polyneuropathy after exposure to dioxine.

**Conclusion**

In patients with a suspected organic mental disorder assessment of vitamin B12 status by determining serum B12 levels is insufficient.

Estimation of CSF B12 levels in these conditions is mandatory, particularly in view of the treatability of a vitamin B12 deficient status and in view of the irreversible damage to the central nervous system which develops when the cerebral B12 deficiency is not detected.

Further research into this matter will reveal whether prevention of the development of dementia in a sub-group of patients with senile dementia is a real possibility by assessment and manipulation of cerebral vitamin B12 status.

Based on our findings, it is furthermore suggested that a considerable number of patients is classified and treated as dysthymic disorder (DSM-111) in psychiatric institutions and by psychiatric methods of expensive psycho-social therapy, whereas in fact these patients are suffering from an undetected organic affective syndrome, to which cerebral B12 deficiency is at least a contributing, if not a causative factor. In this respect we mention the post-natal depression and the possibly toxic neurasthenic depression.

**Summary**

Vitamin B12 levels in serum and cerebrospinal fluid (CSF) were assayed with radio-assay method in samples from 49 patients with organic mental disorder (dementia n = 23, organic affective syndrome n = 16, post natal depression n = 10) and from 12 controls.

In controls normal serum levels (ref. 200-800 pg/ml) correlated with normal levels in CSF (mean: 22 pg/ml, range 12-57).

In the patient group 4 had a serum level below normal, whereas their CSF level was lower than 5 pg/ml, reportedly the level found in patients with untreated pernicious anemia.

Of the remaining group of 45 patients all had a normal serum level, while 26 patients appeared to have an abnormally low level of B12 in CSF (<5 pg/ml).
In 10 patients 6 weeks of hydrocobalamin medication intramuscularly (twice weekly 1 mg) increased the abnormally low pre-treatment levels in CSF to levels far higher than in the controls.

These results indicate that a potentially treatable condition of vitamin B12 deficiency will be overlooked in a significant proportion of patients with organic mental disorder when determination of CSF vitamin B12 is not included in the assessment.

Some diagnostic, therapeutic and preventive aspects are briefly discussed.

Acknowledgements

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References


