

Correlations between cognitive, behavioural and psychological findings and levels of vitamin B₁₂ and folate in patients with dementia

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SUMMARY

Background Associations between low levels of folate and vitamin B₁₂ and cognitive impairment in patients with dementia have been reported. Some studies revealed correlations between low levels of vitamin B₁₂ and behavioural and psychological signs and symptoms of dementia (BPSD) in Alzheimer's disease (AD) patients. Given the lack of studies in frontotemporal dementia (FTD) and on folate and given the methodological shortcomings of former publications, we set up a prospective study.

Methods At inclusion, AD ($n = 152$) and FTD ($n = 28$) patients underwent a neuropsychological examination. Behaviour was assessed using a battery of behavioural assessment scales. Determination of serum vitamin B₁₂ and red cell folate levels were performed within a time frame of two weeks of inclusion.

Results In both patient groups, significantly negative correlations between levels of serum vitamin B₁₂ and red cell folate and the degree of cognitive deterioration were found. No correlations with BPSD were found in the AD patient group. In FTD patients, levels of vitamin B₁₂ were negatively correlated with both hallucinations ($p = 0.022$) and diurnal rhythm disturbances ($p = 0.036$).

Conclusions The observed negative correlations between levels of vitamin B₁₂ and folate and cognitive impairment in both AD and FTD patients, raise the possibility of a non-specific etiological role. Although levels of vitamin B₁₂ and folate did not correlate with BPSD in AD patients, negative correlations between serum vitamin B₁₂ levels and BPSD in FTD patients were revealed. Decreased serum vitamin B₁₂ levels may predispose FTD patients to develop hallucinations and diurnal rhythm disturbances. Copyright © 2004 John Wiley & Sons, Ltd.

KEY WORDS — dementia; behaviour; BPSD; Alzheimer's disease; frontotemporal dementia; vitamin B₁₂; folate

INTRODUCTION

Some studies have shown that low serum vitamin B₁₂ levels are associated with greater cognitive impairment in patients with probable and confirmed Alzheimer's

disease (AD) (Levitt *et al.*, 1992; Clarke *et al.*, 1998; Whyte *et al.*, 2002) which has, however, been denied by others (Basun *et al.*, 1994; Eastley *et al.*, 2000). Associations between low levels of folate and cognitive impairment in patients with AD, vascular and unspecified dementias have been described (Sneath *et al.*, 1973; Botez *et al.*, 1977; Sommer *et al.*, 1988; Leblhuber *et al.*, 2000), but again several negative reports have been published as well (Bell *et al.*, 1990; Levitt *et al.*, 1992). More recent findings, however, support the hypothesis of a pathophysiologically significant interaction between low levels of serum

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folate or vitamin B₁₂ and increased risk of AD (Clarke *et al.*, 1998; Wang *et al.*, 2001). Moreover, low serum folate levels were strongly associated with atrophy of the cerebral cortex in AD patients (Snowdon *et al.*, 2000). A possible explanation for these findings is that lowered vitamin B₁₂ and folate levels lead to increased plasma homocysteine concentrations (Clarke *et al.*, 1998). There is indeed evidence that increased plasma homocysteine concentrations are a risk factor for dementia in general (Seshadri *et al.*, 2002) and are inversely associated with cognitive functioning (Bell *et al.*, 1992; Riggs *et al.*, 1996; Lehmann *et al.*, 1999; Morris *et al.*, 2001). If this hypothesis is correct, low levels of folate and vitamin B₁₂ should correlate with increased cognitive impairment in other forms of dementia like frontotemporal dementia (FTD) as well, which has not been tested yet.

Since associations between decreased (serum, red cell and cerebrospinal fluid) folate and vitamin B₁₂ levels and (worsening of) psychiatric disorders like depression have been described (Reynolds *et al.*, 1970; Carney *et al.*, 1990; Bottiglieri *et al.*, 2000; Reynolds, 2002), one could expect an association with behavioural and psychological signs and symptoms of dementia (BPSD) as well. However, studies in this domain are very sparse, produced conflicting results and only focused on AD and vitamin B₁₂ (Meins *et al.*, 2000; Whyte *et al.*, 2002). Methodological shortcomings of formerly published studies (lack of time-linked and extensive behavioural observations, poorly defined patient populations, lack of data on nutritional status of patients) hamper interpretation of the reported results. We therefore set up a prospective study to test for possible correlations of decreased serum vitamin B₁₂ and red cell folate levels with the degree of cognitive impairment and extent of BPSD in a population of AD and FTD patients.

MATERIALS AND METHODS

Study population

The study population consisted of consecutively hospitalised patients who were admitted for a diagnostic work-up of dementia. Patients with probable AD ($n = 152$) and probable FTD ($n = 28$) were included in this prospective study. All patients were hospitalised and underwent a general physical and neurological examination, routine blood screening (including serum vitamin B₁₂, red cell folate, haematological parameters and several biochemical indices of nutrition), neuroimaging consisting of CT scan and/or MRI, electroencephalogram and an extensive neuropsychological examination as routinely performed in the differential diagnostic work-up in our Memory Clinic (De Deyn *et al.*, 2003). The diagnosis of probable AD was based on NINCDS/ADRDA criteria (McKhann *et al.*, 1984). The patients also fulfilled the DSM-IV criteria (American Psychiatric Association, 1994). Diagnosis of probable FTD was based on clinical diagnostic criteria for FTD (Neary *et al.*, 1998). Mini-Mental State Examination (MMSE) scores were obtained according to Folstein *et al.* (1975). The Hierarchic Dementia Scale (HDS) is an instrument that allows quantifying the degree of cognitive deterioration (Demonet *et al.*, 1990). Staging of dementia was assessed by means of the Global Deterioration Scale (GDS) (Reisberg *et al.*, 1982).

Patients on any kind of vitamin supplementation, patients with alcohol abuse or patients, who had to be artificially fed, were not included in the study.

The local ethics committee (OCMW Antwerp IRB) approved this study. All patients and their caregivers gave informed consent for participation to the study.

Behavioural assessment

Behaviour was assessed covering a period of two weeks prior to inclusion using a battery of behavioural assessment scales. The Middelheim Frontality Score (MFS) is indicative of frontal lobe features and is obtained by summing the scores obtained on ten items as described earlier (Pickut *et al.*, 1997). The Behavioral Pathology in Alzheimer's Disease Rating Scale (Behave-AD) is a 25-item scale that measures behavioural symptoms in seven clusters scored on a four-point scale of increasing severity (Reisberg *et al.*, 1987). As all subjects included were in-patients, the nursing home variant of the Behave-AD was used (De Deyn *et al.*, 1999). The Cohen-Mansfield Agitation Inventory (CMAI) assesses 29 agitated behaviours on a seven-point scale of increasing severity (Cohen-Mansfield *et al.*, 1989). The Cornell Scale for Depression in Dementia (CSDD) is a 19-item scale that is rated on a three-point score of absent, mild or intermittent and severe (Alexopoulos *et al.*, 1988). When a deficiency was diagnosed, vitamin supplementation was started immediately following behavioural and neuropsychological assessments.

Serum vitamin B₁₂, red cell folate, haematological parameters and biochemical indices of nutrition

Blood sampling was performed after overnight fasting and within a time frame of two weeks of inclusion. Haematological parameters and biochemical

nutritional indices (see Table 2) were obtained through routine laboratory tests. Levels of serum vitamin B₁₂ and red cell folate were determined by use of solid phase radioassay kits (SIMUL-TRAC SNB[®]).

Statistical analyses

Distributions of male/female ratios were compared using Chi-square statistics. All two-group comparisons of demographic, clinical and behavioural data were made with the *t*-test or—when lacking normal distribution—the Mann–Whitney Rank Sum Test (RST). Spearman Rank-Order was used for calculating correlations. A probability level of $p < 0.05$ was considered significant. Analysis was performed using the Sigma-Stat software (SPSS Science, Erkrath, Germany).

RESULTS

AD patients were significantly older and more severely cognitively deteriorated at inclusion than FTD patients (Table 1). FTD patients displayed more frontal lobe features as reflected by a significantly higher mean MFS score. AD patients had higher total Behave-AD scores. Biochemical indices of nutrition and haematological parameters are displayed in Table 2. Mean levels of serum vitamin B₁₂ or red cell folate were not significantly different between the two disease groups (folate: $p = 0.475$; vitamin B₁₂: $p = 0.543$). Five FTD patients had vitamin B₁₂ levels that were deficient (values: 184, 179, 177, 152, 101 pg/ml) according to the reference range of our laboratory (< 193 pg/ml). No correlations between levels of vitamin B₁₂ and folate were found either (AD: $r = 0.049$, $p = 0.547$; FTD: $r = 0.215$, $p = 0.267$). With exception of correlations between MMSE and serum glucose ($r = -0.169$, $p = 0.05$) and HDL cholesterol levels ($r = 0.188$, $p = 0.04$), none of the biochemical nutritional indices correlated significantly with the MMSE or HDS scores in the AD group. No correlations between biochemical nutritional indices and cognitive functioning were revealed in the FTD patient group.

In the AD and FTD patient groups, correlations between cognitive (MMSE, HDS and GDS) and behavioural (MFS, CSDD, Behave-AD cluster, total and global scores and CMAI cluster and total scores) test scores and levels of serum vitamin B₁₂ and red cell folate were calculated. Statistically significant correlations are summarized in Table 3.

In AD patients, significant positive correlations between red cell folate levels and MMSE scores were found. Red cell folate and serum vitamin B₁₂ levels

Table 1. Demographic, clinical and behavioural data for AD and FTD patients

	AD (<i>n</i> = 152)	FTD (<i>n</i> = 28)	<i>p</i>
Sex (M/F)	49/103	14/14	$p = 0.111$ (Chi ²)
Mean age at inclusion (years)	79 ± 7 (55–98)	69 ± 11 (41–90)	<0.001 (RST)
Mean age at onset (years)	76 ± 8 (50–96)	63 ± 10 (40–82)	<0.001 (RST)
Disease duration (years)	4 ± 3 (0–16)	6 ± 4 (1–19)	<0.001 (RST)
MMSE score (/30)	12.7 ± 6.9 (0–28.0)	16.3 ± 8.3 (0–30.0)	= 0.020 (<i>t</i> -test)
HDS score (/10)	7.0 ± 1.6 (1.5–9.4)	7.4 ± 1.3 (4.9–9.8)	= 0.527 (RST)
Global Deterioration Scale	5.5 ± 0.9 (3.0–7.0)	5.0 ± 1.2 (3.0–7.0)	= 0.015 (RST)
Middelheim Frontality Score	3.9 ± 1.6 (0–8.0)	6.3 ± 1.2 (3.0–8.0)	<0.001 (RST)
Behave-AD	2.0 ± 3.0 (0–17.0)	0.9 ± 2.0 (0–9.0)	= 0.031 (RST)
Cluster paranoid and delusional ideation			
Behave-AD	0.5 ± 1.2 (0–7.0)	0.3 ± 0.9 (0–3.0)	= 0.352 (RST)
Cluster hallucinations			
Behave-AD	2.6 ± 3.5 (0–17.0)	1.1 ± 2.4 (0–9.0)	= 0.027 (RST)
Cluster psychosis			
Behave-AD	2.8 ± 2.2 (0–9.0)	2.1 ± 1.8 (0–5.0)	= 0.207 (RST)
Cluster activity disturbances			
Behave-AD	3.2 ± 2.8 (0–9.0)	2.3 ± 2.3 (0–8.0)	= 0.149 (RST)
Cluster aggressiveness			
Behave-AD	0.7 ± 0.8 (0–3.0)	0.3 ± 0.4 (0–1.0)	= 0.036 (RST)
Cluster diurnal rhythm disturbances			
Behave-AD	1.1 ± 1.4 (0–5.0)	0.9 ± 1.3 (0–4.0)	= 0.537 (RST)
Cluster affective disturbances			
Behave-AD	0.7 ± 1.4 (0–10.0)	0.2 ± 0.7 (0–3.0)	= 0.055 (RST)
Cluster anxieties and phobias			
Behave-AD	11.0 ± 7.4 (0–40.0)	6.9 ± 4.7 (0–18.0)	= 0.006 (RST)
Total score			
Behave-AD	1.6 ± 0.8 (0–3.0)	1.4 ± 0.8 (0–3.0)	= 0.311 (RST)
Global score			
Cohen-Mansfield Agitation Inventory	13.2 ± 7.3 (10.0–54.0)	10.9 ± 2.0 (10.0–17.0)	= 0.141 (RST)
Aggressive behaviour			
Cohen-Mansfield Agitation Inventory	20.4 ± 8.4 (10.0–53.0)	18.9 ± 7.4 (11.0–37.0)	= 0.461 (RST)
Physically non-aggressive behaviour			
Cohen-Mansfield Agitation Inventory	14.1 ± 7.2 (8.0–44.0)	12.7 ± 5.2 (8.0–25.0)	= 0.466 (RST)
Verbally agitated behaviour			
Cohen-Mansfield Agitation Inventory	47.3 ± 18.0 (8.0–126.0)	42.2 ± 11.0 (29.0–69.0)	= 0.264 (RST)
Total score			
Cornell Scale for Depression in Dementia	6.2 ± 4.2 (0–21.0)	6.7 ± 3.0 (1.0–14.0)	= 0.233 (RST)

Data are given as mean ± SD. Ranges are represented between brackets. RST = Mann–Whitney Rank Sum Test.

Table 2. Biochemical nutritional indices, haematological parameters and levels of vitamin B₁₂ and red cell folate for AD and FTD patients

	AD (n = 152)	FTD (n = 28)	Reference range
Vitamin B ₁₂ (pg/ml)	382.8 ± 257.8 (95.0–1666.0)	316.6 ± 120.0 (101.0–593.0)	193–982
Red cell folate (ng/ml)	245.5 ± 197.5 (67.0–1381.0)	277.2 ± 195.2 (79.0–853.0)	93–641
Total protein (g/l)	69.2 ± 6.4 (48.0–86.0)	69.3 ± 5.5 (60.0–80.0)	58–76
Albumin (g/l)	38.7 ± 5.8 (26.6–57.1)	40.0 ± 6.0 (29.8–52.8)	35–50
Calcium (meq/l)	4.62 ± 0.26 (4.06–5.94)	4.49 ± 0.18 (4.13–4.91)	4.2–5.1
Glucose (mg/dl)	103.7 ± 34.1 (58.0–289.0)	90.8 ± 14.4 (69.0–127.0)	76–110
Ureum (mg/dl)	37.5 ± 13.1 (7.0–83.0)	34.2 ± 15.8 (17.0–94.0)	19–43
Creatinine (mg/dl)	0.92 ± 0.23 (0.50–1.70)	0.91 ± 0.38 (0.60–2.20)	0.5–1.2
Total cholesterol (mg/dl)	206.0 ± 42.7 (116.0–333.0)	200.9 ± 35.3 (135.0–284.0)	150–200
HDL cholesterol (mg/dl)	56.5 ± 18.4 (28.0–112.0)	51.7 ± 12.9 (30.0–81.0)	40–70
LDL cholesterol (mg/dl)	128.7 ± 38.9 (46.0–247.0)	123.0 ± 32.6 (56.0–193.0)	60–120
Triglycerides (mg/dl)	105.7 ± 40.5 (36.0–280.0)	137.3 ± 69.4 (67.0–409.0)	<180
Haematocrit (%)	40.1 ± 4.5 (26.6–52.6)	41.6 ± 4.2 (28.6–48.1)	36.1–45.4
Red cell count (×10 ⁶ /mm ³)	4.4 ± 0.5 (3.1–6.2)	4.7 ± 0.3 (4.0–5.2)	4.07–5.58
Haemoglobin (g/dl)	13.5 ± 1.7 (8.8–18.7)	13.9 ± 1.8 (8.1–16.3)	12.9–15.9
Mean corpuscular volume (fl)	90.9 ± 5.2 (81.1–109.0)	89.4 ± 6.3 (71.9–98.5)	81.3–96.7

Data are given as mean ± SD. Ranges are represented between brackets.

correlated positively with MMSE and HDS scores respectively in the FTD patient group. No significant correlations with the behavioural data were revealed in AD patients. In FTD patients, however, we found statistically significant negative correlations between

hallucinations and diurnal rhythm disturbances and levels of vitamin B₁₂.

DISCUSSION

This study is the first evaluating possible associations between vitamin B₁₂/folic acid and cognition and behaviour in FTD patients. The use of strict diagnostic criteria, the determination of both red cell folate and vitamin B₁₂ levels in one and the same patient population, the determination of several biochemical nutritional indices and haematological parameters and a time-linked and extensive behavioural observation using a battery of behavioural assessment scales are major advantages of this prospective study compared to other publications in AD patients. The small FTD sample size is a drawback of the study, limiting firm interpretation of the positive associations in this patient group.

Although the cognitive tests (MMSE, HDS) used in this study are not as sensitive in FTD patients as in AD patients, we found negative correlations between levels of vitamin B₁₂ and red cell folate and severity of dementia in FTD patients. Red cell folate levels were negatively correlated with severity of dementia in AD patients, thus confirming formerly published studies (Sneath *et al.*, 1973; Leblhuber *et al.*, 2000). In contrast to the reports of Levitt *et al.* (1992), Clarke *et al.* (1998) and Whyte *et al.* (2002), we did not reveal correlations between levels of vitamin B₁₂ and cognitive functioning of AD patients, which is in accordance with other studies (Basun *et al.*, 1994; Eastley *et al.*, 2000). Indeed, our results may indicate a negative influence of lowered vitamin B₁₂ and/or red cell folate levels on cognitive functioning in both patient groups. As the vast majority of the biochemical indices of nutrition we analysed were not significantly related with the degree of cognitive deterioration, we consider it to be unlikely that the reported associations are caused by a decline in

Table 3. Statistically significant correlations between cognitive and behavioural test scores and levels of vitamin B₁₂ or red cell folate (RC FA) (Spearman Rank-Order)

Cognitive and behavioural testing	Vit B ₁₂ or RC FA	r	p
AD			
Hierarchic Dementia Scale	RC FA	r = 0.205	p = 0.028
FTD			
Mini-Mental State Examination	RC FA	r = 0.443	p = 0.023
Hierarchic Dementia Scale	Vit B ₁₂	r = 0.538	p = 0.014
Behave-AD	Vit B ₁₂	r = -0.432	p = 0.022
Cluster hallucinations			
Behave-AD	Vit B ₁₂	r = -0.398	p = 0.036
Cluster diurnal rhythm disturbances			

nutritional state due to progression of dementia. These findings raise the possibility of a non-specific etiological or contributory role of lowered vitamin B₁₂ and folate levels in the pathophysiology of dementia and may support the hypothesis of increased plasma homocysteine levels as a risk factor for dementia in general and AD in particular (Seshadri *et al.*, 2002). Indeed, a case-control study of 164 patients with dementia revealed an association between cognitive decline and raised plasma homocysteine and lowered serum folate and vitamin B₁₂ levels (Clarke *et al.*, 1998). Unfortunately, plasma homocysteine levels have not been analysed in our patient population, which is a drawback of the present study.

The lack of associations between BPSD and serum vitamin B₁₂ and folate levels in AD patients is in concordance with a former study (Whyte *et al.*, 2002). However, Whyte and colleagues study has major drawbacks: although the study population consisted of 643 subjects, both possible and probable AD patients were included; indices of nutritional status were not determined; and moreover, vitamin B₁₂ levels were retrospectively gathered (by primary care physicians). This implicated that different analytical laboratories, using different analytical techniques and applying different reference values, have performed vitamin B₁₂ determinations. On the other hand, Meins *et al.* (2000) observed an association between low serum vitamin B₁₂ levels and BPSD (irritability, disturbed behaviour) in a prospective study with 73 probable AD patients. The rather limited population and the lack of documentation of the nutritional status of the included patients, hampers firm interpretation of these positive findings.

Although hallucinations are rare in patients with FTD, the significant negative correlation with serum levels of vitamin B₁₂ could indicate that lower levels of vitamin B₁₂ predispose to the development of hallucinations. The significant negative correlation between diurnal rhythm disturbances and levels of vitamin B₁₂ in FTD patients could be meaningful as positive effects of vitamin B₁₂ treatment on sleep-wake rhythm in patients with sleep disorders and AD have been reported (Ito *et al.*, 2001). As a correlation does not necessarily imply a causative relation, the pathophysiological mechanisms underlying these findings remain to be elucidated. Given the role of vitamin B₁₂ and folate in the synthesis of monoamine neurotransmitters (Bottiglieri, 1996; Bottiglieri *et al.*, 2000) and given the existence of neurochemical correlates of BPSD (Engelborghs and De Deyn, 1997), one could hypothesize that lowered vitamin B₁₂ leading to altered monoaminergic neurotransmission

predispose to BPSD which is the subject of a longitudinal, prospective study in progress. This hypothesis does not, however, explain the lack of statistically significant findings in AD patients and the lack of associations with lowered folate levels in both patient groups.

In conclusion, we observed associations between low levels of vitamin B₁₂ and folate and increased severity of dementia in both AD and FTD patients, raising the possibility of a non-specific etiological role. No associations of behavioural data and levels of red cell folate or serum vitamin B₁₂ were observed in AD patients whereas negative correlations between serum levels of vitamin B₁₂ and BPSD (hallucinations and diurnal rhythm disturbances) in FTD patients were revealed. The underlying pathophysiological mechanisms remain to be elucidated.

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