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ORIGINAL ARTICLE

Vitamin B12 deficiency associated with symptoms of frontotemporal dementia

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Abstract We report the case of an elderly patient with cobalamin deficiency who progressively developed cognitive and behavioral symptoms associated with neuropsychiatric disturbances. His neuropsychological profile showed many features suggestive for a frontal-dysexecutive syndrome and was related to a predominant asymmetric (right > left) frontal lobe hypoperfusion. He completely recovered after a treatment with vitamin B12 and follow-up of 7 years showed that his improvement remained stable. Along with the other cases reported in the literature, our case also proves that there are some cases of vitamin B12 deficiency that can manifest with the symptoms of frontotemporal dementia and that they are completely reversible after substitution therapy.

Keywords Vitamin B12 · Dementia · Frontal-dysexecutive symptoms

Introduction

Vitamin B12 deficiency has long been documented in haematological disorders and can be associated with neurological impairments and mental changes including dementia [1–3]. The role of vitamin B12 deficiency as a cause of dementia, however, is still unclear [3, 4]. Some studies have found that serum cobalamin levels were normal in patients affected by Alzheimer's disease (AD) [4], whereas others have evidenced a vitamin B12 deficiency [3, 5]. The question, which cases of dementia are reversible after vitamin B12 treatment is also controversial [2, 3, 6]. Moreover, the clinical profile of dementia linked to low vitamin B12 serum level is not yet well defined because only few published studies report detailed neuropsychological assessment and specify the diagnostic criteria of dementia applied [2–4, 6–9].

In this study, we report the clinical case of an elderly patient affected by a frontal-dysexecutive syndrome with additional psychiatric symptoms reversed after vitamin B12 replacement. The neuropsychological and SPECT findings contributed to the differentiation of the clinical pattern of his cognitive and behavioral disturbances from that of AD.

Case report

The patient was a 72 year old male retired physician with no significant past medical or psychiatric history. His relatives reported that since June of 2000, he had started to show apathy, irritability, deterioration of attention and memory, and 1 year later association with psychotic episodes characterized by paranoid thoughts and jealous delusions regarding his spouse. Initially, the patient was seen in an outpatient's psychiatric unit and diagnosed as affected by a late onset psychosis. He received a neuroleptic therapy that had only little efficacy for his delusional disorder. In July 2001, due to the worsening of his mental status, treatment with donepezil was added because of the

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clinical suspicion that he was affected by AD. At that time the patient was clinically diagnosed with AD by his psychiatrist but neuropsychological testing was not performed. In November 2001 because of the persistence of cognitive impairment and symptoms of peripheral neuropathy, the patient was admitted to the neurological department of our hospital. On admission he was awake but appeared disoriented, slow in thinking, and long-term memory was impaired. His facial expressions, speech and spontaneous movements were reduced, emotional unconcern was present. As a result, his ability to initiate activities of daily living was impaired. Clinically, the patient presented executive and affective symptoms which met four out of five core diagnostic features (insidious onset and gradual progression, early impairment in regulation of personal conduct, early emotional blunting and early loss of insight) for fronto-temporal dementia as proposed by the consensus criteria for such type of dementia [10]. Moreover, his behaviour was often marked by distractibility and impersistence which are symptoms belonging to the behavioural supportive diagnostic features of FTD [10].

The neurological examination showed normal tendon reflexes but a decreased sense of proprioception and vibration in the legs. Flexor plantar responses were bilaterally present. He showed oscillations during Romberg testing and his gait was moderately ataxic. He complained of a mild paresthesias in his lower limbs. CT scan and MRI showed a generalized cerebral atrophy and an hypodense area in the right lenticular nucleus due to an old silent cerebral infarct. EEG showed a 6–8 c/s activity mixed with sporadic bilateral theta waves. Doppler sonography of the cerebral arteries showed a slight thickness of the walls without significant stenosis. The serum vitamin B12 level was significantly below the normal range (54 pg/ml, normal range 200–1,200 pg/ml); folate serum level was slightly higher than the normal range (18.2 ng/ml, normal range 2.5–16.9); red blood count showed anemia with macrocytosis (RBC 2.52, HGB 9.3 g/dl, MCV 104.8 fl); the homocysteine result was elevated (18 ng/ml); methylmalonic acid serum was not evaluated. Thyroid hormone levels were normal. Titers of antibodies specific for parietal cells were in the normal range. Genomic investigation did not reveal MTHFR deficiency. Gastroscopy revealed gastritic atrophy confirmed by biopsy. EMG showed delayed nerve conduction and reduced action potentials. An assessment of cognitive functions was performed before starting the parenteral vitamin B12 therapy.

The patient began a treatment with parenteral vitamin B12 1,000 mcg three times weekly for 45 days followed by a progressive weekly reduction of 1,000 mcg every 45 days, reaching a maintenance dose of 1,000 mcg every month. After 4 weeks of treatment the patient's ataxic gait improved, his psychotic symptoms disappeared and his cognitive disturbances significantly decreased. Serum B12 and homocysteine levels returned progressively to the normal range.

Neuropsychological evaluation

Table 1 shows the scores of the patient's neuropsychological tests, before and after the therapy with vitamin B12. On admission, the patient's neuropsychological profile revealed that his attention/working memory measured by digit span both forward and backward and by repetition of months of year backward, was severely impaired. Verbal long-term memory at the delay recall of the Rey's list (RAVLT) was reduced; severe disturbance of executive functions was evident as manifested by the abnormal scores of the clock drawing test (see Fig. 1-test A), word fluency test and Weigl's test (WST). The score of the Raven's matrices (RCPM) was also impaired. The score of the mini mental state examination (MMSE) was 25 [11]. One month after starting the therapy with vitamin B12 the patient showed a significant improvement in his attentional, reasoning and executive functions along with a normal performance in the delayed free recall of Rey's 15 words [12]. His MMSE score returned to a normal value of 28. The patient successfully completed the clock drawing test [13] (see Fig. 1-test B). Three months after initiating therapy, only the Verbal Fluency score was slightly below the mean range. Six months later the scores of the neuropsychological tests were all in the normal range. His MMSE was 30. At the last retest performed approximately 7 years later, his cognitive performances remained unchanged.

Functional neuroimaging

Before starting vitamin B12 therapy, brain single photon emission computer tomography (SPECT) (99mTcECD) showed bilaterally fronto-parietal and anterior temporal hypoperfusion, much more marked and widespread in the anterior frontal regions. The hypoperfusion was greater on the right side than on the left (Fig. 2a). Six months after starting B12 therapy, a control SPECT revealed diffused improvement of cerebral perfusion also with a quite complete normalization of the blood flow in the right frontal cortex (Fig. 2b). Another SPECT performed 1 year later showed that this improvement remained stable.

Discussion

The patient's behavioural and cognitive profile was characterized by attention and concentration deficit, slow

Table 1 Neuropsychological tests results

Domain	Test	Admission	1 month later	3 months later	6 months later	7 years later
General mental status	MMSE	25/30[a]	28/30	29/30	30/30	30/30
Digit span	Digit span forward	3[a]	5	5	6	5
	Digit span backward	2[a]	5	5	5	5
Attention	Months of year backward	6/12[a]	12/12	12/12	12/12	12/12
Reasoning/executive functions	RCPM	13/36[a]	23/36	22/36	24/36	27/36
	Verbal fluency (FAS words/min)	14[a]	18[a]	21[a]	25	35
	Clock drawing test	3/10[a]	10/10	10/10	10/10	10/10
	WST	3/15[a]	7/15	7/15	8/15	8/15
Memory	RAVLT immediate recall	33/75	33/75	38/75	40/75	39/75
	RAVLT delay recall	2/15[a]	6/15	7/15	7/15	9/15
	RAVLT multiple recognition[b]	13/15	14/15	15/15	15/15	15/15
Constructive	CD	3.1/12[a]	5.4/12[a]	8.4/12	7.4/12	7.6/12
	CDL	30.3/70[a]	41.6/70[a]	69.3/70	62.3/70	59.7/70
Language	BNT 20 figures	20/20	20/20	20/20	20/20	20/20
	Phrase construction	21/25	25/25	25/25	25/25	25/25
Depression	BDI	ND	7/63	9/63	8/63	6/63

MMSE mini mental state examination (Measso et al. [11]); digit span forward and backward (Orsini et al. [18]); *RCPM* Raven's coloured progressive matrices (Basso et al. [19]); *FAS* word generation test (Carlesimo et al. [12]); clock drawing test (Shulman et al. [13]); *WST* Weigl's sorting test (Spinnler and Tognoni [20]); *RAVLT* Rey auditory verbal learning test (Carlesimo et al. [12]); *CD* copying drawings (Carlesimo et al. [12]); *CDL* copying drawings with guiding landmarks (Carlesimo et al. [12]); *BNT* Boston naming test (Kaplan et al. [21]); phrase construction (Carlesimo et al. [12]); *BDI* Beck depression inventory (Beck et al. [22]); *ND* not done

[a] Abnormal scores (test references and normative data are available in the literature reported in brackets)

[b] Seventeen healthy elderly matched for age and level of education to our patient were enrolled to calculate z score on multiple recognition trial: raw score 13/15; z −1.36; z_c ±1.64 for $p < 0.05$ (n.s.); raw score 14/15; z −0.47; z_c ±1.64 for $p < 0.05$ (n.s.); raw score 15/15; z 0.41; z_c ±1.64 for $p < 0.05$ (n.s.)

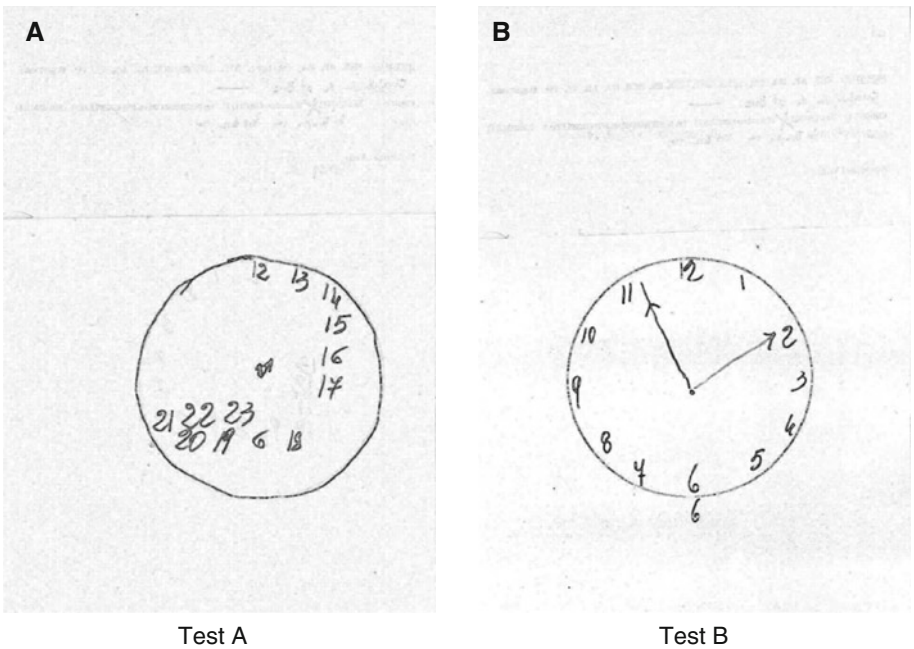

Fig. 1 The patient's performance at the clock drawing test before the treatment with vitamin B12 (A-score 3/10) and 1 month later (B-score 10/10). **a** Test A and **b** Test B

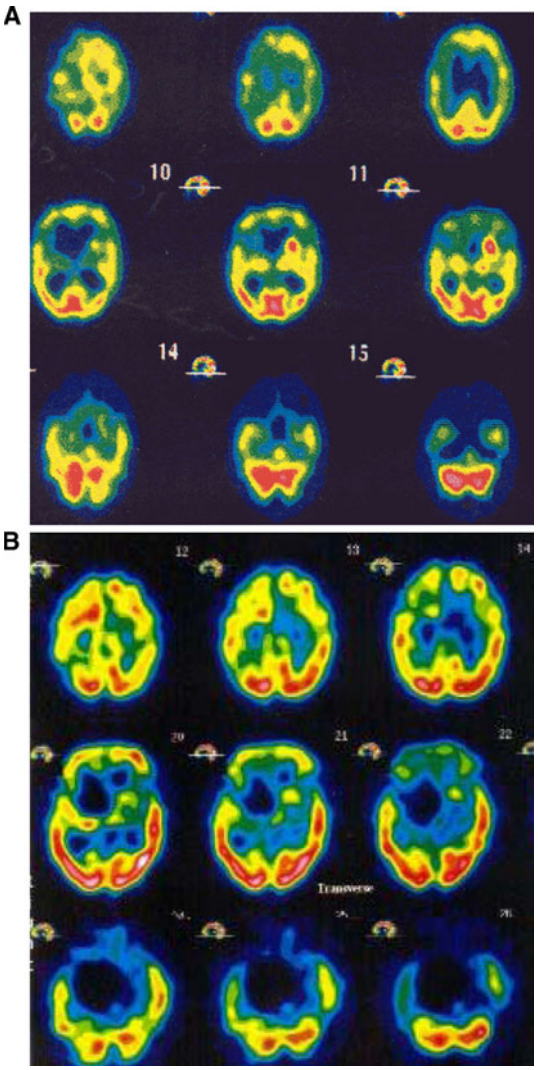

Fig. 2 Functional imaging with SPECT before (**a**) and 6 months after vitamin B12 replacement (**b**)

thinking process, impairment of executive functions, loss of insight, decreased spontaneous movements and facial expression, apathy, irritability and paranoid delusional symptoms. The patient's general level of mental functioning was relatively preserved (the MMSE score was 25). He was able to recall 13/15 words in a recognition trial of the words in the Rey auditory verbal learning test (RAVLT), a score that was more congruent with retrieval difficulties due to executive and attention disorders than with storing impairment as observed in AD. Language abilities that are usually impaired in AD were preserved. In conclusion, our patient's neuropsychological assessment showed a significant impairment on frontal-executive tests in the absence of general mental deterioration and aphasia, with preservation of spatial orientation, praxis and long-term memory storage.

In our patient, SPECT showed widespread hypoperfusion on the bilateral anterior cortex which was greater on the right dorsolateral prefrontal cortex and much less evident on the posterior association cortex. This pattern is consistent with a frontal lobe dysfunction and it is different from that of AD where the greatest reduction in cerebral blood flow is in the temporo-parietal association cortex. Literature reports on blood flow changes found with SPECT in patients with cognitive abnormalities due to cobalamin deficiency dementia are rare and controversial. Nilsson et al. [7] reported 15 patients with dementia associated with cobalamin deficiency, who improved clinically, and also showed a concomitant increase in their general cerebral perfusion after treatment. On the contrary, Behrens et al. [14] found a normal SPECT in a patient affected by vitamin B12 dementia. Schreinzer et al. [8] in their patient with frontotemporal dementia (FTD) due to vitamin B12 deficiency found hypoperfusion in the left parietal and temporal lobe but not in the frontal lobes. Recently, Akdal et al. [9] described a similar patient with FTD-like dementia who showed bilateral fronto-temporo-parietal hypoperfusion greater on the right side.

The patient was affected by an atrophic gastritis that produced a reduction of gastric acid and pepsinogen secretion with a consequent decrease in the intestinal digestion and absorption of vitamin B12. Our patient's elevated homocysteine was related to his B12 deficiency, as his folate serum level was normal and genetic defects were absent. Both cobalamin and folate are needed for the methylation of homocysteine to methionine and in the synthesis of *S*-adenosylmethionine (SAM) the major donor in numerous methylation reactions which is essential for the transmethylation of neuroactive substances (myelin, neurotransmitters) in the central nervous system [15]. In addition, elevated levels of homocysteine are metabolized to *S*-adenosylhomocysteine (SAH) which disrupts the methylation pathway, competing with SAM for the active site on the methyltransferase enzyme protein [15]. Therefore, methylation reactions play a fundamental role in CNS functions and a defect in these processes is associated with neuropsychiatric impairments [1]. Abnormalities in central myelin have been linked to cobalamin deficiency but both mechanisms of myelin damage as well as effects of vitamin B12 replacement on these lesions are unknown [16]. In our patient, the lack of signs of white matter lesions at the MRI and the rapid remission after parenteral vitamin B12 substitution let us to presume that his mental malfunctioning was associated with more than a myelin damage, to a reversible deficit of neurotransmitters caused by the impaired transmethylation reactions that are involved in the synthesis and metabolism of biogenic amines.

The complete clinical recovery in our patient in face of the lack of pre-existing cognitive impairment indicates that cobalamine deficiency was likely a sufficient causative factor of his reversible dementia. His clinical manifestations

characterized by frontal-dysexecutive disturbances, behavioral and affective disorders met many of the diagnostic criteria for fronto-temporal dementia (FTD) proposed by the Lund and Manchester Groups [17]. In comparison with the other two published cases of FTD-like dementia linked to vitamin B12 deficiency [8, 9] and presenting as a disinhibited behavioural syndrome, the cognitive profile of our patient was mainly characterized by an apathetic and dysexecutive behaviour. This kind of behaviour reflected the marked hypoperfusion of his frontal dorsolateral cortex whereas his psychotic disturbance was likely related to the anterior temporal involvement. Such a neuropsychological pattern is different from that of AD even when this disorder is associated with a low cobalamine level. To this regard, Whyte et al. [4] demonstrated in a cohort of AD patients that those with low B12 levels showed a greater overall cognitive impairment than normal B12 patients but the pattern of mental deterioration was not different in both groups. On the other hand, Osimani et al. [3] found that demented patients who improved after vitamin B12 replacement presented neuropsychological manifestations different from those of AD patients consisting of psychotic symptoms, concentration and visuospatial deficits, and dysexecutive abnormalities.

In summary, the present study, along with others reported in the literature, would suggest that within the heterogeneous group of patients with dementia and vitamin B12 deficiency, there are some individuals who present FTD-like cognitive and behavioural changes that disappear after cobalamin replacement. More studies are needed to better characterize the clinical diagnostic features of this form of reversible dementia and to distinguish it from other dementia cases associated with vitamin B12 deficiency but not reversible after substitution therapy.

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