

## Commentary

### Vitamin B<sub>12</sub> deficiency & cognitive impairment in elderly population

Dementia, considered as disease of old age, is growing at an alarming rate and becoming a public health problem, increasing the financial and personal costs with an adverse impact on health care expenditure, and on families. It is well known that age is a risk factor for dementia<sup>1</sup>; and the prevalence increases with advancing age<sup>2</sup>. In Europe, prevalence of dementia among people older than 65 yr is about 10 per cent<sup>3</sup>. Preservation of cognitive ability well in old age is essential not only to promote an adequate health status but also to delay the onset of dementia and slow down its progress, thereby, reducing the societal costs each year for chronic care and lost productivity. As a curative treatment is currently not possible for dementia, a number of attempts have been made to find out the non genetic risk factors that may be modified to limit it<sup>4</sup>. Increased homocysteine levels in conjunction with low levels of folate, vitamin B<sub>12</sub> and B<sub>6</sub>, which interact to control homocysteine, have been found to correlate with decreased cognitive performance<sup>5-7</sup>. The prevalence of high total serum homocysteine is age related and hyperhomocysteinemia is common in elderly population<sup>8</sup> which negatively correlates with cognitive status. Deficiency of the B vitamins (folate, vitamin B<sub>6</sub> and vitamin B<sub>12</sub>) may play a role in pathogenesis of cognitive impairment in the elderly through hyperhomocysteinemia. On the other hand, elevated plasma homocysteine concentrations are a sensitive marker for vitamin B<sub>12</sub> and folate deficiency<sup>9</sup>. Homocysteine is produced from the methylation cycle, as it is totally absent from any dietary source. Both folate and vitamin B<sub>12</sub> are required in the methylation of homocysteine to methionine and in the re-methylation and synthesis of S-adenosylmethionine, a major methyl donor in the central nervous system. Hence, research to date suggests that hyperhomocysteinemia due to disturbed monocarbon metabolism may contribute to cognitive impairment and Alzheimer's

disease<sup>10</sup> and can be considered a sensitive marker of cognitive impairment. On the other hand, raised plasma homocysteine concentrations are a sensitive marker for cobalamin and folate deficiency. Findings suggest that decreased vitamin B<sub>12</sub> dependent transmethylation reactions might be involved in the pathogenesis of dementia<sup>11</sup>. Hence, increased homocysteine levels in association with low levels of folate, vitamin B<sub>6</sub> and vitamin B<sub>12</sub>, shows significant correlation with decreased performance on cognitive tests<sup>5-7</sup>. For these reasons, B vitamin supplementation has been shown to prevent or reverse cognitive decline. However, effect of vitamin B<sub>12</sub> oral supplementation shows heterogeneous results and is found related to the dose, route of administration and duration of treatment. A few trials have been conducted to assess the effect of vitamin B<sub>12</sub> supplementation on cognitive function in humans<sup>12,13</sup>, with duration of supplementation varying from 4 wk to 6 months. For most of the cognitive tests performed, no improvement was observed for vitamin B<sub>12</sub>. Only a few cognitive tests showed statistically significant improvement<sup>12</sup>. At least two studies are available in literature showing statistically significant worsening of cognitive functions after vitamin B<sub>12</sub> supplementation<sup>12,13</sup>. In case of folic acid supplementation, studies found cognitive improvement after folic acid intervention which correlated in linear fashion with the low levels of folate at baseline (< 6.8 nmol/l)<sup>14</sup>.

Several studies have found high incidence of vitamin B<sub>12</sub> and folate deficiency in elderly in western population<sup>15,16</sup>. However, no such data are available in elderly Indian population. With increasing ageing population, varied socio-economic strata and high prevalence of *Helicobacter pylori* infection along with vegetarian diet followed in majority of Indian households, the prevalence of vitamin B<sub>12</sub> and folate deficiency may be much higher in Indian population.

There are two studies so far in India showing prevalence of vitamin B<sub>12</sub> and folate deficiency. One study conducted by Yagnik *et al*<sup>17</sup>, investigated the prevalence of low vitamin B<sub>12</sub> concentration and hyperhomocysteinemia in rural and urban Indian men living in and around Pune, Maharashtra. They reported vitamin B<sub>12</sub> level of 150 pmol/l in 67 per cent of men and hyperhomocysteinemia (<15 umol/l) in 58 per cent subjects. They also reported 4.4 and 3.0 times higher risk of low vitamin B<sub>12</sub> concentration and hyperhomocysteinemia respectively in vegetarians.

Shobha *et al*<sup>18</sup> in the present study have highlighted the relationship of dietary habits of urban south Indian elderly subjects and plasma vitamin B<sub>12</sub>, folate and homocysteine levels with cognitive status and impact of vitamin supplementation on the normalization of the same. They found that daily vitamin B<sub>12</sub> intake was 3.5 times higher than the FDA recommendation contrary to belief that dietary intake would be low in Indian population being majority population vegetarian (57%). Also, average daily dietary folate intake was almost equal to the FDA recommended daily intake of folate. There was low occurrence of vitamin B<sub>12</sub> deficiency and vitamin supplementation had a significant impact on the normalization of the plasma B<sub>12</sub>, MMA, folate and homocysteine. However, no correlation was detected between plasma vitamin B<sub>12</sub> and cognitive status in elderly population.

Cognitive impairment is multifactorial in origin sharing modifiable and non modifiable risk factors. As there are no curative treatments for it, the only possibility is that treatment may delay or slow down disease progression. It is highly appropriate to detect such modifiable risk factors like hyperhomocysteinemia, vitamin B<sub>12</sub> and folate deficiency, *etc.* These nutrition related risk factors not only have been associated with lower cognitive function in old age, but incipient dementia may also change dietary habits, that is, malnutrition can be a consequence rather than a cause of cognitive impairment. In the absence of curative treatment for dementia, vitamin B<sub>12</sub> and folate may be relevant to the clinical course of dementia and should be considered for therapeutic intervention. However, more therapeutic research is needed. Clinical trials must be initiated in high risk population to determine whether, lowering of blood homocysteine levels by vitamin B supplementation reduces the risk of cognitive impairment, the clinical onset of dementia. Longitudinal studies should also be undertaken to explore the association between nutrition status and cognitive

impairment, and whether it is possible to inhibit or delay the onset of dementia by dietary modifications. Hence, at present, B vitamin supplementation should be reserved for the treatment of documented deficiency states.

**Rachna Agarwal**

Department of Neurochemistry  
Institute of Human Behaviour &  
Allied Sciences (IHBAS)  
Jhilmil, Dilshad Garden  
Delhi 110 095, India  
rachna1000@hotmail.com

### References

1. Carr DB, Goate A, Phil D, Morris JC. Current concepts in the pathogenesis of Alzheimer's disease. *Am J Med* 1997; 103 : 3S-10S.
2. Callahan CM, Hendrie HC, Tierney WM. Documentation and evaluation of cognitive impairment in elderly primary care patients. *Ann Int Med* 1995; 122 : 422-9.
3. Gonzalez-Gross M, Marcos Ascension, Pietrzik K. Nutrition and cognitive impairment in the elderly. *Br J Nutr* 2001; 86 : 313-21.
4. Agarwal R, Chhillar N, Khushwaha S, Singh NK, Tripathi CB. Role of vitamin B12, folate and thyroid stimulating hormone in dementia: A hospital-based study in north Indian population. *Ann Indian Acad Neurol* 2010; 13 : 257-62.
5. Wardlaw GM, Kessel M. *The water soluble vitamins: Perspectives in nutrition*. 5<sup>th</sup> ed. New York: McGraw-Hill; 2002. p. 364-417.
6. Riggs KM, Spiro A III, Tucker K, Rush D. Relation of vitamin B-12, vitamin B-6, folate and homocysteine to cognitive performance in the Normative Aging study. *Am J Clin Nutr* 1996; 63 : 306-14.
7. Wang HX, Wahlin A, Basum H, Fastbom J, Winbind B, Fratiglioni L. Vitamin B (12) and folate in relation to the development of Alzheimer's disease. *Neurology* 2001; 56 : 1188-94.
8. Gottfries CG, Lehman W, Regland B. Early diagnosis of cognitive impairment in the elderly with the focus on Alzheimer's disease. *J Neural Transm* 1998; 105 : 773-86.
9. Parnetti L, Bottiglieri T, Lowenthal D. Role of homocysteine in age-related vascular and non vascular diseases. *Ageing (Milano)* 1997; 9 : 241-57.
10. Clarke R, Smith AD, Jobst KA, Refsum H, Sutton L, Ueland PM. Folic acid, vitamin B<sub>12</sub> and serum homocysteine levels in confirmed Alzheimer's disease. *Arch Neurol* 1998; 55 : 1449-55.
11. Swain R. An update of vitamin B<sub>12</sub> metabolism and deficiency states. *J Fam Prac* 1995; 41 : 595-600.
12. Hvas AM, Juul S, Lauritzen L, Nexø E, Ellegaard J. No effect of vitamin B-12 treatment on cognitive function and depression: a randomized placebo controlled study. *J Affect Disord* 2004; 81 : 269-73.

13. Eussen SJ, deGroot LC, Joosten LW, Bloo RJ, Clarke R, Ueland PM, *et al.* Effect of oral vitamin B-12 with or without folic acid on cognitive function in older people with mild vitamin B<sub>12</sub> deficiency: a randomized, placebo-controlled trial. *Am J Clin Nutr* 2006; 84 : 361-70.
14. Fioravanti M, Ferrario E, Massaia M, Cappa G, Rivolta G, Grossi E, *et al.* Low folate levels in the cognitive decline of elderly patients and the efficacy of folate as a treatment for improving memory deficits. *Arch Gerontol Geriatr* 1997; 26 : 1-13.
15. Hitzhusen JC, Taplin ME, Stepenson WP, Ansell JE. Vitamin B<sub>12</sub> levels and age. *Am J Clin Pathol* 1986; 85 : 32-6.
16. Garry PJ, Goodwin JS, Hunt WC. Folate and vitamin B<sub>12</sub> status in a healthy elderly population. *J Am Geriatr Soc* 1984; 32 : 719-26.
17. Yagnik CS, Deshpande SS, Lubree HG, Naik SS, Bhat DS, Uradev BS, *et al.* Vitamin B<sub>12</sub> deficiency and hyperhomocystenemia in rural and urban Indians. *J Assoc Physicians India* 2006; 54 : 775-82.
18. Shobha V, Tarey SD, Singh RG, Shetty P, Unni US, Srinivasan S, *et al.* Vitamin B<sub>12</sub> deficiency & levels of metabolites in an apparently normal urban south Indian elderly population. *Indian J Med Res* 2011; 134 : 432-9.