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Review Article

Metabolic vitamin B12 deficiency: a missed opportunity to prevent dementia and stroke

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ABSTRACT

The purpose of this narrative review is to highlight insights into the importance and frequency of metabolic vitamin B12 (B12) deficiency, reasons why it is commonly missed, and reasons for the widespread but mistaken belief that treatment of B12 deficiency does not prevent stroke or improve cognitive function. Metabolic B12 deficiency is common, being present in 10%-40% of the population; is frequently missed; is easily treated; and contributes importantly to cognitive decline and stroke in older people. Measuring serum B12 alone is not sufficient for diagnosis; it is necessary to measure holotranscobalamin or functional markers of B12 adequacy such as methylmalonic acid or plasma total homocysteine. B-vitamin therapy with cyanocobalamin reduces the risk of stroke in patients with normal renal function but is harmful (perhaps because of thiocyanate accumulation from cyanide in cyanocobalamin) in patients with renal impairment. Methylcobalamin may be preferable in renal impairment. B12 therapy slowed gray matter atrophy and cognitive decline in the Homocysteine and B Vitamins in Cognitive Impairment Trial. Undiagnosed metabolic B12 deficiency may be an important missed opportunity for prevention of dementia and stroke; in patients with metabolic B12 deficiency, it would be prudent to offer inexpensive and nontoxic supplements of oral B12, preferably methylcobalamin or hydroxycobalamin. Future research is needed to distinguish the effects of thiocyanate from cyanocobalamin on hydrogen sulfide, and effects of treatment with methylcobalamin on cognitive function and stroke, particularly in patients with renal failure.

1. Introduction

There is widespread misunderstanding of the complexity of interpreting clinical trial results of vitamin B12 (B12) for prevention of stroke and dementia. In this narrative review, insights into reasons why many of the randomized trials appeared to be negative are discussed. The literature reviewed was from reference databases of the author and of Profs David Smith and Helga Refsum, who advised the author on early drafts. Randomized trials, although rightly regarded

Abbreviations: B12, vitamin B12; CSPPT, China Stroke Primary Prevention Trial; GFR, glomerular filtration rate; H2S, hydrogen sulfide; MMA, methylmalonic acid; NHANES, National Health and Nutrition Examination Survey; tHcy, plasma total homocysteine; VISP, Vitamin Intervention for Stroke Prevention trial.

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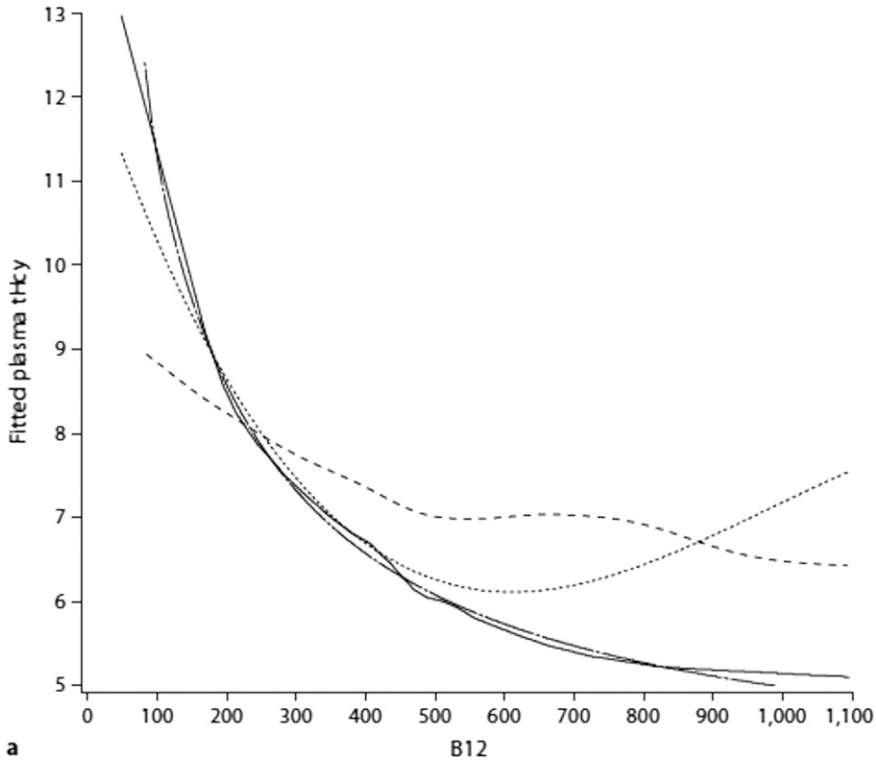

Fig. 1 – Relation of serum B12 to plasma total homocysteine. Based on data from 8832 participants in the NHANES. Polynomial and inverse regression, spline, loess fits for plasma tHcy with B 12. Solid, dotted, long dashed, and short dashed lines represent loess, cubic polynomials, cubic polynomials of the inverse covariate, and smooth splines, respectively. (Reproduced by permission of Karger from Bang H, Mazumdar M, Spence D. Tutorial in biostatistics: analyzing associations between total plasma homocysteine and B vitamins using optimal categorization and segmented regression. *Neuroepidemiology*. 2006;27(4):188-200).

as first-tier evidence, are blunt instruments for studying vascular biology; they must be interpreted with knowledge of the biology of the conditions being studied.

2. Importance of metabolic B12 deficiency

Both stroke and dementia increase steeply with age. With the aging of the population, the burden of dementia and stroke, in both human and economic terms, is expected to increase markedly. A policy statement from the American Heart Association [1] predicted that stroke in the United States will more than double by 2030, with total annual costs of stroke of ~$240 billion. In view of recent calls for integrated approaches to prevention of dementia [2], it is timely to address a potentially treatable contributory factor for both dementia and stroke: inadequate B12 status. Underdiagnosis of this condition results largely from failure to understand that a normal serum B12 may not reflect an adequate functional B12 status [3,4]. Only ~25% of serum total B12 is in the active form of holotranscobalamin [5]. Thus, total serum B12 determination is not sensitive for B12 deficiency. A potentially more accurate way to diagnose functional adequacy of B12 is to measure holotranscobalamin [5–7] or to use functional or metabolic markers of B12 such as plasma methylmalonic acid (MMA) or total homocysteine (tHcy) [3,8].

Metabolic B12 deficiency is strictly defined by elevation of MMA levels or by elevation of Hcy in folate-replete individuals [3]. The prevalence varies markedly in different populations but is typically in the range of 10%-40% [3,9]. The majority of people with metabolic deficiency of B12 have normal or low-normal serum B12 concentrations [3].

3. Level of serum B12 that would define adequacy of functional B12

Vogiatzoglou et al [10] reported in the Hordaland study that levels of MMA and tHcy begin to rise already at a serum B12 of 350-400 pmol/L, with a much steeper rise in MMA in the elderly. That level coincides with the inflection point of serum B12, 400 pmol/L, below which tHcy levels began to rise in the National Health and Nutrition Examination Survey (NHANES) [11] (Fig. 1). A more complex relationship between serum B12 and MMA has recently been described in the NHANES cohort, with 33% of those studied having serum B12 between 126 and 287 pmol/L and so considered intermediate between deficiency and sufficiency [12]. Both these large cohorts indicate that B12 sufficiency is first obtained with at least 300-350 pmol/L in serum B12. In the zone below 300-400 pmol/L but within the normal range of serum B12, metabolic B12 deficiency is common but is seldom accompanied by the classical markers