Editorial

Homocysteine, Stroke, and Dementia
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The increase in aging population worldwide is expected to cause an elevation in the prevalence of vascular diseases, including atherosclerosis, hypertension, diabetes mellitus, and hyperlipidemia, as well as their consequences: ischemic heart disease, peripheral vascular disease, and stroke. This will unavoidably result in an increase in the frequency of vascular dementia, which will only be enhanced because of the frequency of Alzheimer disease (AD) changes in these age groups. However, preventive strategies, which should be the best solution to these problems, are hampered by the fact that both disorders may be caused by several etiologies, such as primary lesions elsewhere in the body (heart, blood vessels), genetic factors, and primary degeneration of the brain and its vasculature.

It has been known for several decades that deficiency of certain vitamins, particularly vitamin B₁₂, can cause neurological dysfunction, including cognitive impairment, which can be reversed by correcting the deficiency. The neurological effects may well result from dysfunction of several metabolic pathways. However, the homocysteine pathway, in which vitamin B₁₂ and folic acid, as well as pyridoxine (vitamin B₆), function as cofactors, seems to play a central role. Deficiency of either of these vitamins causes a reduced methylation capacity, which could affect several metabolic processes in the central nervous system and elsewhere.

Hyperhomocysteinemia, or increased serum concentration of total homocysteine, has been identified as being associated with vascular disease, including cerebrovascular disease in general, particularly in subjects with significant carotid stenosis.¹² The term total homocysteine refers to the fact that in the body a dynamic equilibrium exists between levels of homocysteine, its oxidized product homocystine, and a dimer form of homocysteine with cysteine, either free or bound to proteins.) Unexpectedly, AD is also related to hyperhomocysteinemia.³⁴ Thus, the findings of McIlroy and colleagues reported in this issue of Stroke are highly relevant.

While there is a strong correlation between hyperhomocysteinemia on the one hand and cerebrovascular disease and dementia on the other, as all epidemiologists know, a correlation should never be taken to indicate causation. Homocysteine itself is thought to be toxic to blood vessels and can be shown in vitro to cause excitotoxic damage, similar to excessive glutamate.⁵ One mechanism that may be involved is endothelial dysfunction resulting from oxidative stress.⁶ The latter could affect endothelial cells in large vessels (e.g., the carotid arteries) or smaller-caliber arterioles (such as penetrating blood vessels in the brain), resulting in local thrombosis and cerebral ischemia. However, there is no ultimate proof that either of these processes is directly causative in the diseases associated with hyperhomocysteinemia. Is it possible that the elevated total homocysteine levels are the consequence of stroke and dementia, rather than its cause? Poor diet is common in old age, particularly among sick people, such as those with dementia. A recent study showed a correlation between low folic acid and high homocysteine levels with cognitive functions in vascular dementia and AD,⁷ which is consistent with the idea of secondary elevation of total homocysteine in demented people. While this could be a contributory factor, data from several incidence studies show that levels in normal elderly people prognosticate the occurrence of stroke and dementia.⁸ Moreover, it is possible that deficiency of vitamin B₁₂ or folic acid could result in metabolic derangements other than hyperhomocysteinemia. Thus, hyperhomocysteinemia should, at the present time, be regarded only as an indicator of susceptibility to disease, and therapies that could reduce homocysteine levels are not guaranteed to reduce the incidence of either strokes or dementia. Treatment of hyperhomocysteinemia should therefore be considered a rational approach like that addressed against other biochemical markers of disease vulnerability, such as hypercholesterolemia.

Treatment with several B group vitamins has been shown to reduce the level of homocysteine in the blood, even in persons whose serum levels of these vitamins is in the range currently considered normal. It is still not known whether therapy with any of these vitamins would reduce the incidence of cerebrovascular disease, AD, or vascular dementia, but this is quite possible.

Several issues are still unknown. What level of total homocysteine should be considered “excessive”? At present, a level of approximately 15 μmol/L is considered the border between normal and mildly elevated, levels >30 μmol/L are considered moderately elevated, and levels >100 μmol/L are considered severely elevated. However, it is doubtful whether defining a clear value is helpful because vascular damage can result from the cumulative action of many factors; therefore, in smokers, or in older people, a different definition may need to be applied. A related issue is when and how often to measure serum total homocysteine levels and whether this measurement is helpful at all. The measured values depend on the type of food consumed before the test and on the handling of the blood (which should ideally be separated and refrig-
ated immediately, and in any case should be cooled after collection and separated within 4 hours). Given this difficulty, it may be simpler if all older people, and particularly those with higher risk of vascular disease or dementia, receive supplemental folic acid and vitamin B₁₂. While folic acid seems to be more important than vitamin B₁₂, treatment with both is probably preferred because the use of folic acid alone may obscure the expression of vitamin B₁₂ deficiency. The dose of either vitamin that should be recommended is undetermined. However, since the natural source of either vitamin is food, and because dietary habits are so different among people, it may be appropriate to recommend a higher dose, such as 2 to 5 mg folic acid and a slightly lower dose of vitamin B₁₂ daily. This recommendation is based on the known safety of both vitamins, even if used in excessive amounts, and their low cost. While the addition of folic acid to the diet by providing it as a food additive (eg, in flour) may be helpful, the benefit depends on the amount and type of food consumed. Of course, only prospective controlled studies can prove the efficacy of vitamin supplementation. Such studies are currently under way.

Despite all the limitations, we see once more how results of epidemiological studies can have a marked effect on health by providing tentative directions to treatments that can prevent the enormous problems we face. Many of the most significant advances in medicine were due to preventive, rather than curative, measures. The use of these vitamins, at doses higher than regarded necessary in the past, may thus have a significant effect on the health and well-being of the elderly population.

References

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