Alzheimer's Dementia

Some possible mechanisms related to vitamins, trace elements and minerals, suggesting a possible treatment

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Summary

It *is postulated that in some elderly people there is a diminution of transport of most vitamins, minerals and essential trace elements at the blood/brain barrier and, possible, in the gut; this leads to deficiencies in brain cells. It is postulated that these deficiencies in brain cells are the primary causes of the formation of lipofuscin and neurofibrillary tangles, finally leading to cell death. It is suggested that administration of vitamins and trace elements at higher than recommended intakes might halt the process at an early age, or slow the rate of development of the disease process.*

Introduction

This paper is based on a review of the literature with particular reference to the role of vitamins, trace elements and minerals in the pathology of dementia, particularly of the Alzheimer's type. Non-essential trace elements have also been covered and, of these, aluminium has received the highest attention in recent years.

It is a common theme that theories of the pathology of senile dementia overlap with theories of ageing. The implication is that persons who present with symptoms have premature brain ageing and that the processes involved may be similar to those occurring in non-demented persons, but these processes are proceeding at a faster rate (and/or with an earlier beginning) in persons with symptoms.

Vitamins

Shaw et al. (1,2) showed that low plasma vitamin C, folate and tryptophan levels were found more often in demented patients than in non-demented controls. Also they showed that the intake, relative to the recommended daily allowance (RDA) was low for thiamine, folate, pyridoxine, vitamin C and vitamin D, although this was true also for non-demented controls. Schorah et al. (3) have shown that vitamin C levels tend to be low in psychiatric in-patients. While there may be inadequate vitamin provision in the diet in some long-stay hospitals, it is unlikely that this is a cause of dementia since many patients have developed their illness before admission to hospital. Lehmann (4) has suggested that there may be a degree of malabsorption of tryptophan in demented patients. It is possible also that decreased activity of vitamin receptor sites or binding proteins occurs and Inada et al. (5) have observed low vitamin B12 binding proteins in brains from patients with dementia, neuronal loss and other changes. Cole and Prchal (6) showed that serum vitamin B12 levels were low in Alzheimer-type dementia and were independent of folate deficiency while Evans et al. showed that reversible organic mental changes could be an early sign of vitamin B12 deficiency in some patients. Enk et al. (8) have described a patient who developed dementia and peripheral neuropathy sixteen years after partial gastrectomy. This patient's symptoms improved after treatment with folic acid following unsuccessful treatment with vitamin B12 alone. Yatzidis et al. (9) found that biotin administration gave a marked improvement in patients suffering from encephalopathy and peripheral neuropathy due to chronic haemodialysis. These studies indicate that several vitamins influence brain function and that some could be involved in the pathology of dementia. It is possible that transport of some vitamins and aminoacids may be diminished, in old age, at the blood/brain barrier and, perhaps, in the gut also.

Lipofuscin is thought to be the end-product of auto-oxidation of polyunsaturated

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fatty acids in the central nervous system, and Dowson (10) has related the increased intraneuronal lipofuscin in Alzheimer's dementia to vitamin E deficiency. Clausen (11) has reviewed the auto-oxidation theory in relationship to the pathology of dementia. Lipofuscin deposition is not specific to Alzheimer's disease — it occurs in other syndromes which have a demential aspect e.g. Parkinson's disease and the rare inherited lipofuscinoses (Batten-Bielchowsky, Spielmeyer-Vogt and Kufs diseases); but it also occurs, usually to a lesser extent, in non-demented ageing brains. Lipofuscin is formed by a complex series of reactions which involve reaction of hydrogen peroxide with polyunsaturated fatty acids followed by auto-oxidation, with the formation of organic peroxides, organic free radicals and other reactive intermediates. The final product, lipofuscin, is a polymerisation product of phospholipids, proteins and reactive intermediates. Lipofuscin may have a direct toxic effect on brain cells, but, also, the peroxides, free radicals and other intermediates are reactive compounds which could damage neuronal DNA as well as membrane structures. These reactive, damaging, intermediates are inactivated by catalase, vitamin E, superoxide dismutase (a zinc-copper enzyme), glutathione peroxidase (a selenium enzyme), mitochondrial superoxide dismutase (a manganese enzyme) and, possibly, vitamin C also. Clausen (11) has discussed the possibility of vitamin E, selenium and vitamin C supplementation as a treatment for dementia. The auto-oxidation theory is a general theory of brain ageing as well as a theory of dementia and is probably at least part of the mechanisms involved. Finally, Scileppi et al. (12) found no difference in plasma vitamin C status in patients with Alzheimer's disease compared with patients who had other types of dementia. However, this does not exclude the possibility of differences within the brain cells.

Trace Elements

Trace elements could play a part in the mechanisms of dementia either because an excess of a non-essential, toxic, element occurs or because a deficiency (or an excess) of an essential trace element occurs.

The deficiency of trace elements theory has been expounded in detail for zinc by Burnet (13), who pointed out that most of the enzymes concerned with DNA replication, repair and transcription are zinc metallo-enzymes. If there were an age-associated loss of incorporation of zinc into these enzymes in neurones, perhaps with zinc being replaced by other metal ions, then a loss of enzyme activity would occur and loss of neurones could result. The loss of each neurone was envisaged as a result of a cumulative, and, finally, a catastrophic cascade of errors in DNA, RNA and protein synthesis leading to cell death. This mechanism would have a genetically-determined resistance to error accumulation before the final cascade of errors leading to cell death. The theory of Burnet on dementia is closely related to his theory that ageing, in general, is essentially the accumulation of genetic error in somatic cells (14, 15).

That zinc may have a role in the pathology of dementia has been supported by Hullin (16) and Van Tiggelen (17) (who thought that cerebral vitamin B12 was an important factor also). Van Tiggelen thought that the transport of vitamin B12, other vitamins and aminoacids into the brain may be impaired by a combination of zinc deficiency and a relative increase in copper toxicity. There is evidence that the activities of zinc metallo-enzymes in animal tissues are refractory to changes in dietary supply and that non-enzymic functions of zinc may be very important (18). Some of this animal work shows that lipid peroxidation is inversely related to zinc status, and that stabilisation of membranes could be a major function for zinc (18). These studies were not on brain cells, but there is a possibility that zinc is important in the stabilisation or protection from damage of brain cell membranes. Yoshimasu et al. (19) have suggested" that brain manganese may be increased in Alzheimer's disease, but the studies of Markesbury et al. (20) showed no changes of brain manganese with ageing or the development of dementia.

Aluminium is thought to be a nonessential trace element and its neurotoxicity in man has been demonstrated by outbreaks of dementia in patients on renal dialysis (dialysis dementia or dialysis encephalopathy)(21). The excess brain tissue aluminium stems from the dialysate with some contribution by absorption of aluminium hydroxide. It has been shown (22, 23) that both normal subjects and chronic

renal failure patients showed positive aluminium balance on oral aluminium hydroxide, with the chronic renal failure patients retaining more than normal subjects. The contribution of cooking in aluminium cookware to the daily aluminium load can be significant (9-17% for some foods) (24). However, aluminium is normally present in raw surface water and domestic tap water can contain high aluminium concentration, either naturally or because aluminium has been added as a flocculant in the purification process. The relationship of long-term ingestion of aluminium in the diet to the development of senile dementia is unknown. But Perl et al. (25, 26) observed that foci of aluminium can be detected in the nuclear region of a high percentage of neurones containing neurofibrillary tangles both in patients with senile dementia and in elderly controls. Yoshimasu et al. (19) have found increased aluminium and calcium in CNS tissue in Alzheimer's disease and amytrophic lateral sclerosis. Gar-ruto et al. (27) have related the high incidence of amytrophic lateral sclerosis and parkin-sonism-dementia among the Chammoros of Guam to nutritional deficiencies of calcium and magnesium with the deposition of calcium and aluminium in the neurones. However, Yanigihara et al. (28) found that changes in calcium metabolism in these patients were small; some, but not all, patients had elevation of parathyroid hormone and there was a tendency to have a low plasma 25-hydroxy vitamin D. It is thought that elevated parathyroid hormone may lead to enhanced aluminium absorption and that this is an important step in the pathogenesis of the demential syndromes among the Chammoros of Guam (28) and of renal osteodystrophy (29). Also, it has been shown that osteomalacia and osteitis fibrosa can result from the long-term ingestion of aluminium hydroxide in persons without renal failure. Aluminium has been found in the osteoid seams of some of these patients (30): also, not all of these patients had raised parathyroid hormone levels and phosphate deficiency has been postulated to be the main factor (30). It is fair to conclude that the relationships between vitamin D, parathyroid hormone, and the metabolism of calcium, magnesium, and aluminium (as hydroxide and as 'natural' aluminium in the diet) remain to defined. However, Deary and Hendrikson (31) have suggested also that calcium deficiency increases the likelihood of senile plaque and neurofibrillary tangle formation. Perry and Perry (32) have shown that senile plaque contains relatively abundant aluminium and silicon, probably in the form of an alumino-silicate associated with the amyloid protein known to be at the core of senile plaques. It is interesting that Hershey et al. (33) found elevated CSF silicon levels in a high proportion of patients with Alzheimer's disease, but found no relationship between CSF aluminium, arsenic, lead or manganese and dementia. However, the increased silicon concentrations in CSF were not confirmed by Bourrier-Guerin et al. (34), although a tendency for low CSF zinc concentrations was found. All in all, there is some evidence that deficiencies of calcium, magnesium and some trace elements may be related to the development of dementia. Possibly as a result of these deficiencies, aluminium accumulation may be an important aetiological step.

Finally, other studies have suggested that the absolute or relative amounts of trace elements may be related to other forms of mental illness. Thus, copper excess relative to zinc has been related to schizophrenia (36) although this has been disputed (35). A relative excess of vanadium has been related to depressive illness (37).

Other Studies

It is now quite well established that a cholinergic deficiency occurs in Alzheimer's disease (34). This deficit is particularly involved in the memory impairment of Alzheimer's disease and parkinsonism-dementia, although it is possible that other neurotransmitters may be involved also (38, 39). The memory impairment is, in part, related to the reduction in the activity of the pyruvate dehydrogenase complex and choline acetyl transferase. The cholinergic hypothesis has been invoked also for alcoholic dementia (40), although zinc deficiency and B12 deficiency have been suggested as being important (17). In alcoholism, thiamine deficiency sometimes occurs. This would result in a decrease in activity of the pyruvate dehydrogenase complex, since thiamine pyrophosphate is a co-factor. It is possible that thiamine deficiency in brain cells could contribute to the cholinergic deficiency of

Alzheimer's disease also.

Discussion

In this field it is difficult to decide whether any observed changes reflect the primary disease process or are secondary to a primary disease process or mechanism. For example, it has been suggested (41) that the accumulation of aluminium in brain tissue in Alzheimer's disease may be secondary, and represents a "marker" of degenerating neurones. On the other hand, aluminium accumulation may be an important aetiological factor. It is not until all the steps in the pathogenesis of the disease are known that these issues can be resolved; we are far from this ideal state of knowledge. The evidence reviewed in this paper, taken with the speculations of other authors, suggests a hypothesis.

It is postulated that a proportion of elderly persons gradually develop a reduction in the efficiency of transport of vitamins, trace elements and minerals into the brain. The reduction of transport mechanisms in the brain may be reflected in a reduction of transport mechanisms in the gut also. The reduction in transport of trace elements and minerals may allow an increased absorption of more toxic substances e.g. aluminium. Intracellularly, the result is decreased enzyme activities and increased auto-oxidation of unsaturated fatty acids leading to an accumulation of damage to membrane structures and DNA, together with the formation of lipofuscin and neurofibrillary tangles. The damaged cell then retains more toxic substances (aluminium, in particular) and damage accrues to a critical point such that any further damage leads to cell death. The resistance of any individual to neuronal cell death by these mechanisms and, hence, resistance to the development of the syndrome of dementia is genetically determined. Thus, the development of dementia in any individual is a combination of genetic factors with environmental and dietary factors.

The hypothesis suggests that a therapeutic trial of a mixture of vitamins, trace elements and minerals should be tried in patients who have evidence of early dementia, with the hope that the process will be slowed. Patients with early dementia are more likely to respond to treatment than patients with late dementia; the other group of patients who may be included are those with mild dementia associated with Parkinson's disease. Psychometric testing of patients and matched controls over a 6-12 months period of supplementation (or placebo) may be necessary to assess the benefit of supplementation.

The therapeutic problem is to decide on the amounts to be given. It is suggested that in order to get concentrations in the brain that are optimal for brain function, vitamins, trace elements and minerals will need to be administered at increased amounts in the diet. While some trace elements are safely administered (e.g. zinc is said to be safe up to 25 times the RDA (42)) other trace elements, e.g. copper (36) and vanadium (37), have been related to mental illness because they have been found to be in relative excess. Hence, it is suggested that trace elements should be given at no more than twice the RDA. Also, a mixture of trace elements should be given together since it is known that there is interaction between some trace elements e.g. administration of zinc has led to copper deficiency, although large amounts of zinc were given. Other, yet unknown, interactions may occur. If a mixture of trace elements is given at no more than twice the RDA's then it is likely that such interactions would be avoided.

It has been suggested that, for some persons, optimum brain function can be achieved only by giving large doses of some vitamins; large doses of nicotinamide, vitamin C, Pyridoxine and vitamin E have been advocated in the treatment of schizophrenia and autistic children (43). It is clear that most vitamins, with the exception of vitamins A and D, have very large safety factors (43). Harrell et al. (44) gave dietary supplements to mentally retarded children for eight months, which resulted in gains in I.Q. of up to 25 units (mean 16 units). Eight minerals and trace elements were given in moderate amounts (mostly twice the RDA's) and eleven vitamins (mostly in large amounts) were given to the subjects studied. Multi-supplementation, similar to that used by Harrell et al. (44), should be tried in early Alzheimer's disease, since it is unlikely that any single vitamin, trace element or mineral is responsible for the syndrome. The evidence is that it is a combination of deficiencies in brain cells that could cause the syndrome.

The last paragraph in the late Sir Mac-

Farlane Burnet's book (14) is as follows: — "I believe that there is a wide scope for research on the best means of minimizing the depression and misery of pre-death in the old. Here at least is one region where the physician need have no fear of addiction just as he accepts the necessity to use doses of morphia to control the pain of terminal cancer. And if the drugs needed to bring even an artificial serenity to the aged and dependant will shorten life significantly, it may be hard to say that this is a loss rather than a gain. In my opinion this is the most important area for psychopharmacological research at the present — and at the same time probably the most potentially fruitful field in geriatrics". I support this view and hope that the therapeutic trial advocated in this paper will show an effect on brain function in mildly demented elderly patients.

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