

Nutritional Aspects of Senile Dementia of the Alzheimer Type (SDAT)

C. J. M. van Tiggelen, M.D.¹

It is generally accepted that senile dementia of the Alzheimer type, the most common form of dementia with late onset, should be considered as a multifactorial condition, in which a variety of causative factors are involved, such as genetic factors, toxic-metabolic-nutritional factors, vascular factors and depression-related factors.

I am putting forward the hypothesis that variable interaction of the above mentioned factors results in altered activity of microsomal P-450 liver enzyme systems. For an enlightening review on microsomal liver enzyme function see Conney (1986).

The altered microsomal liver enzyme function can result in increased levels of Ammonia in blood, described in SDAT. It will also result in alterations in drug metabolism, due to changes in toxifying and detoxifying capacity of the liver, whilst changes in metabolism of endogenous substances such as thyroid-hormones and steroid-hormones can be observed as well.

There is abundant literature indicating that alterations in microsomal liver enzyme function has a profound effect on the biological availability of nutrients such as trace-elements, vitamins and amino-acids.

I refer here in particular to the nutritional data collected in patients with well-known altered microsomal liver enzyme status such as chronic phenylhydantion users and chronic alcoholics: selective nutritional deficiencies in the central nervous system have been described in these groups, in my opinion caused by defective activation in the affected liver of the processes that convert certain vitamins into the form with access through the blood-brain barrier and/or plexus chorioideus to the central nervous system: this problem arises in particular with vitamin B₁, vitamin B₁₂ and with folic acid.

Extensive evidence of compromised vitamin

vitamin B₁₂ and folate status in relation to neuro-psychiatric pathology is available, to some extent even documenting cerebral deficits of these vitamins in SDAT. Animal experiments have shown profound neurotransmitter changes in the brain of animals made deficient in vitamin B₁₂, vitamin B₁ and folate, including considerable reduction of Acetylcholine levels, a crucial finding in SDAT.

Recently much attention has been given to the possible role of glutamic acid as a neurotoxic agent contributing to the development of typical Alzheimer neuropathology. Increase in glutamic acid levels can be secondary to the altered microsomal liver enzyme activity and hyperammonaemia, which influences strongly levels and access of amino-acids (precursors of neurotransmitters) to the brain, in that way influencing brain function, whilst it also influences access of other potentially neurotoxic amino acids such as quinolinic acid and homocystein.

Glutamic acid neurotoxicity is strongly potentiated by neuronal hypoxia, whilst the combined neurotoxic effect of glutamic acid and hypoxia can be modified by zinc, glutamine and taurine.

These considerations open up a perspective for a potentially effective preventive nutritional strategy in dementing disorders: application of the suitable forms of parenteral vitamin B₁, vitamin B₁₂, folic acid and taurine, supported by oral administration of a balanced trace-element preparation containing zinc, selenium, molybdenum, jodine, traces of manganese and copper, iron, magnesium, calcium, chromium, boron and glutamine.

In my clinical experience this combination appears to be very effective, resulting in arresting dementia-syndromes and improving conditions of alcohol or other toxic chemical induced neuropsychiatric pathology (van Tiggelen 1987).

1. Farmers Road, Meeniyan, Australia, 3956. B₁,

Neurotoxicity of glutamic acid in SDAT, its modulation by zinc, taurine, glutamine

Recently the neurotoxicity of the excitatory amino acid glutamic acid has been suggested as being involved in the development of senile dementia of the Alzheimer type and possibly in other organic mental disorders (Greenamyre 1986, Greenamyre 1988, Hardy 1987, Cross 1987).

Convincing evidence is available demonstrating that the neurotoxicity of glutamate is strongly potentiated by neuronal hypoxia (Jorgensen 1982, Simon 1984, Schwarcz 1985, Rothman 1986, Petito 1986, Nehls 1988), whilst a potentiating effect of corticosteroids is also possible (Sapolsky 1985).

The potentiating hypoxia can be of cardiovascular or cerebrovascular origin, in this respect a recent publication (Brun 1986) deserves attention. The neuronal hypoxia can also be of metabolic origin, eg. secondary to metabolic disturbances in cerebro as in vitamin B₁₂ deficiency (Hirsch 1984, Gibson 1988). Glutamate neurotoxicity can be modified by specific ions (Olney 1986), in particular the trace-element zinc can play a modulating role (Peters 1987, Koh 1988). This is interesting against the background of observation on the role of zinc in alcohol-related dementia syndromes (van Tiggelen 1979, Kasarskis 1985) and rekindles the potential role of zinc in senile dementia (Burnet 1981). The study of alcohol-induced encephalopathy as a model for the study of senile dementia of the Alzheimer type, originally suggested by Burnet (personal communication) will appear to be far more fruitful than assumed in particular in regard to the possible involvement of subtle and sub-clinical liver dysfunction caused by altered microsomal liver enzyme activity and resulting in hyperammonemia and secondary nutritional deficiencies in cerebro. In this respect the favourable results of oral zinc supplementation in patients with alcohol-induced encephalopathy (Reding 1984) deserve duplication.

Furthermore a protective role against neuronal hypoxia (a factor strongly potentiating neurotoxicity of excitatory amino acids) can be attributed to the amino acid glutamine (Schurr 1987a) and to the amino acid taurine (Schurr 1987b). The interaction between taurine and

excitatory amino acids is extensively studied (Lehmann 1987 and ref there), but more indications are coming forward that taurine plays a protective role in particular in highly excitable tissue of nervous origin (Lake 1986), supporting clinically interesting observations in the Japanese literature in the use of taurine in cardiovascular pathology, which favourable clinical experiences with taurine will find probably more application in cerebral pathology when a lipophilic taurine-derivative such as MY-117 (Oja 1982) can be applied parenterally.

Summarized: glutamate neurotoxicity seems to play a role in SDAT, and most likely in other chemical induced organic mental syndromes and dementia syndromes, such as alcohol related brain damage, solventia dementia and industrial chemical induced neurasthenia.

Neuronal hypoxia plays a potentiating role and should be minimized by optimizing cardiovascular, cerebrovascular and blood-viscosity status. A combination of zinc-ions, taurine and glutamine may provide considerable protection against the combined neurotoxic effect due to excitotoxicity and hypoxia.

The role of vitamin B₁₂ in SDAT considering a role for folic acid in biological activation of vitamin B₁₂

Extensive information is available in the literature on compromised vitamin B₁₂ status in patients with SDAT: Inada 1982 described reduced levels of vitamin B₁₂ in brain tissue of dementia sufferers, van Tiggelen (1984a, 1984b) described reduced levels of vitamin B₁₂ in the cerebrospinal fluid of SDAT patients, notwithstanding normal serum levels. Later vitamin B₁₂ anomalies in SDAT patients were described by other groups (Cole 1984, Karnaze and Carmel 1987), increasingly the picture is becoming clear that the biological availability of vitamin B₁₂ can be compromised resulting in neuro-psychiatric pathology in the absence of haematological pathology (Kanazawa 1985, Herbert 1988, Carmel 1988a, Carmel 1988b, Hallam 1987, Levitt 1988).

It may well be that indeed the only form

of vitamin B₁₂ in the central nervous system with biological activity is methyl-cobalamine (Goto 1987), which is possibly also the biologically active component in the immune system (Kubota 1987, Taki-moto 1982) and in osteoblasts (Carmel 1988c) which raises the possibility that methyl-cobalamine deficiency can result in reduced intestinal alkaline phosphatase levels interfering with intestinal absorption and possibly biological activation of vitamin B, (Schaller 1975).

In this respect the interaction between vitamin B₁₂ and folic acid should be mentioned (Stokstad 1988) (Botez 1979, Fi-gueroa 1980, Botez 1982a, Botez 1982b), which could suggest a role for folic acid or rather methyl-tetra-hydro-folate in the conversion of cobalamine in the biologically highly active form of methyl-cobalamine. This concept is supported by clinical observations in patients with folate responsive neuro-psychiatric pathology who showed improvement in vitamin B₁₂ status after being medicated with folic acid.

It has been demonstrated that cerebral vitamin B₁₂ deficiency has profound effects on neurotransmitter levels in cerebro in animal experiments (Deana 1977, Hakim 1983) affecting Noradrenaline and Acetylcholine levels as well as regional glucose utilization.

Summarized, there seems to be an indication that in SDAT and possibly a variety of organic mental disorders the biological activity of vitamin B₁₂ is impaired in the central nervous system, possibly due to reduced availability of methyl-cobalamine, which may be associated with complex folic acid abnormalities. The possibility that a functional vitamin B₁₂ deficiency can interfere with vitamin B₁, absorption, transport and biological activity should not be under-estimated.

The role of vitamin B₁ in SDAT.

Recently attention has been drawn to the defective thiamine status, presenting as defects in vitamin B₁ dependent enzymes, in the brains of patients with senile dementia of the Alzheimer type (Blass 1988, Gibson 1988, Kwan-Fu Rex Sheu 1988).

Therapeutic trials with oral thiamine in demented patients were ineffective. This may be due to malabsorption of the oral thiamine or

inability of the conversion in the liver of thiamine in the form which passes readily the blood-brain barrier of the dementia patients.

It has been demonstrated (Baker 1983) that fat-soluble allithiamines (Thomson 1971) are better absorbed and penetrate into the CNS compartment far more readily: the components suggested are thia-mine-propyl-disulphide and thiamine-te-trahydrofurfuryl-disulphide.

However biological activity of these components is most likely dependent on liver function, as suggested by Oda (1984).

Deficiency of biologically active thiamine in the brain is associated with a wide range of neuropathology in cerebro as is known from study of the brains of chronic alcoholics.

It has been suggested (Gibson 1988) that vitamin B₁ deficiency in cerebro can contribute to the neurotoxicity of glutamate by contributing to tissue hypoxia and in disturbing the balance between glutamic acid and glutamine.

Furthermore it has been demonstrated that cerebral B₁ deficiency results in a considerable reduction of acetyl-choline levels in the brain (Heinrich 1973), whilst interaction with other transmitters has been noticed (Freye 1982), as reported by Florence (1988) involving reduction of dopamine levels in case of thiamine deficiency due to the role of thiamine in the blockade of dopamine oxidation to hydroxy-dopamine, which in itself is a neurotoxic agent for the noradrenergic neurons in the locus coeruleus and in the dorsal noradrenergic bundle.

This indicates a possible therapeutic or rather preventive role for application of parenteral thiamine or parenteral allithia-mine in an endeavour to correct thiamine function in cerebro, which may have a beneficial effect in SDAT and in a variety of other neuro-psychiatric disorders such as several dementia's, tardive dyskinesia, manifestation of manganese toxicity (Florence 1988), minimal brain dysfunction in children, toxic neuro-myelo-en-cephalopathy, Gille de la Tourette syndrome, post-traumatic stress disorder, stress related psychosomatic diseases, immune disorders, chemical allergies, myalgia en-cephalopathica, depressive disorders, osteoporosis.

Most likely parenteral vitamin B₁, parenteral vitamin B₁₂, parenteral folic acid have to be combined in parenteral application in a physiological dose, possibly in combination with the lipophilic taurine, whilst support by a glutamine-based well balanced trace element preparation containing minimal amounts of copper and manganese, but twice the recommended daily allowance of zinc, selenium, molybdenum, chromium, iodine and substantial amounts of calcium, magnesium (as Pho-setamin) and iron and vitamin C, may increase the therapeutic effectiveness.

The main aim of the supporting trace element preparation is to normalize the altered microsomal liver enzyme activity. And this preparation may even facilitate suppression of genetic predisposition to alterations of microsomal liver enzyme function under otherwise inducing circumstances.

References

1. Baker H, Frank O, deAngelis B, Feingold S: Vitamins in human blood and CSF after intramuscular administration of several B vitamins. *Nutrition Reports International* 27(/): 661-670, 1983.
2. Blass JP et al: Thiamine and Alzheimers disease, a pilot study. *Arch. Neurol.* 45:833-836, 1988.
3. Botez MI et al: Relapsing neuropathy, cerebral atrophy and folate deficiency. *Appl. Neurophysiol.* 42: 171-183, 1979.
4. Botez MI, Young SN, Bachevalier J, Gauthier S: Effect of folic acid and vitamin B₁₂ deficiencies on 5-Hydroxyindoleacetic acid in human CSF. *Ann. Neurol.* 12: 479-484, 1982a.
5. Botez MI, Joyal C, Maag U, Bachevalier J: Cerebrospinal fluid and blood thiamine concentrations in phenytoin-treated epileptics. *Le Journal Canadien des Sciences Neurologiques* 9(1): 37-39, 1982b.
6. Brun A and Englund E: A white matter disorder in dementia of the Alzheimer type. *Ann. Neurol.* 19: 253-262, 1986.
7. Burnet FM: A possible role of zinc in the pathology of dementia. *Lancet* 1981 i:186-188.
8. Carmel R, Sinow RM, Siegel ME, Samloff M: Food cobalamin malabsorption occurs frequently in patients with unexplained low serum cobalamin levels. *Archives Intern. Med.* 148: 1715-1719, 1988a.
9. Carmel R: Pernicious anaemia, the expected findings of very low serum cobalamin levels, anemia and macrocytosis are often lacking. *Archives Intern. Med.* 148: 1712-1714, 1988b.
10. Carmel R, Lau KHW, Baylink DJ, Saxena S, Singer FR: Cobalamin and osteoblast specific proteins. *N. Engl. J. Med.* 319: 70-5, 1988.
11. Cole MG, Prchal JF: Low serum vitamin B₉ in Alzheimer type dementia. *Age and Ageing* 13: 101-105, 1984.
12. Conney Allen H: Induction of microsomal cytochrome P-450 enzymes. *Life Sciences* 39: 2493-2518, 1986.
13. Cross AJ et al: Glutamate deficits in Alzheimers disease. *J. Neurol. Neuro-surg. and Psychiat.* 50: 357-358, 1987.
14. Deana R, Vincenti E, Deana A Donella: Levels of neurotransmitters in brain of vitamin B₁₂ deficient rats. *Int. J. Vit. Nutr. Res.* 47: 119-122, 1977.
15. Figueroa AM, Johnson RH, Lambie DG, Shakir RA: The role of folate deficiency in the development of peripheral neuropathy caused by anticonvulsants. *Journal of Neurological Sciences* 48: 315-323, 1980.
16. Florence TM and Stauber JL: Neurotoxicity of Manganese. *Lancet* 1988, i 963.
17. Freye E, Hartung E: The potential use of thiamine in patients with cardiac insufficiency. *Acta. Vitaminol. Enzy-mol.* 4: 285-290, 1982.
18. Gibson GE et al: Reduced activities of thiamine dependent enzymes in the brains and peripheral tissues of patients with Alzheimer disease. *Arch. Neurol.* 45: 836-840, 1988.
19. Goto I et al: Effects of methylcobalamin on vitamin B₁₂ and B₁₂-deficient encephalopathy in rats. *Journal of the Neurological Sciences* 77-97/102, 1987.
20. Greenamyre JT: The role of glutamate in neurotransmission and in neurological disease. *Arch. Neurol.* 43: 1068-1063, 1986.
21. Greenamyre JT et al: Glutamate transmission and toxicity in Alzheimers disease. *Prog. Neuro-Psychopharmacol. Er Biol. Psychiat.* 12: 421-430, 1988.
22. Hakim AM, Cooper BA, Rosenblatt DS et al: Local cerebral glucose utilization in two models of B₁₂ deficiency. *J. Neurochem.* 40: 1155-, 1983.
23. Hallam LJ, Sawyer M, Clark ACL, Van Der Weyden MB: Vitamin B₁₂ responsive neonatal megaloblastic anemia and homocystinuria with associated reduced

- methionine synthase activity. *Blood* 69(4): 1128-1133, 1987.
24. Hardy J et al: Glutamate deficits in Alzheimers disease. *J. Neurol. Neuro-surg. and Psychiat.* 50: 356-357, 1987.
 25. Heinrich CP, Stadler H, Weiser H: The effect of thiamine deficiency on the acetylcoenzyme-A and acetylcholine levels in the rat brain. *Journal of Neuro-chemistry* 21: 1273-1281, 1973.
 26. Herbert F: Don't ignore low serum cobalamin (vitamin B₁₂ levels. Editorial. *Archives Intern. Med.* 148: 1705-1707, 1988.
 27. Hirsch JA, Gibson GE: Selective alteration of neurotransmitter release by low oxygen in vitro. *Neurochem. Res.* 9: 1037-1047, 1984.
 28. Inada M, Toyoshima M, Kameyama M: Cobalamin contents of the brains in some clinical and pathologic states. *Int. J. Vit. Nutr. Res.* 52(4) 423-9, 1982.
 29. Jorgensen MB, Diemer NH: Selective neuron loss after cerebral ischemia in the rat: possible role of transmitter glutamate. *Acta. Neurol. Scandinav.* 66: 536-546, 1982.
 30. Kanazawa S, Herbert V: Total corrinoid, cobalamin (vitamin B₁₂), and cobalamin analogue levels may be normal in serum despite cobalamine in liver depletion in patients with alcoholism. *Laboratory Investigation* 53(1): 108-110, 1985.
 31. Karnaze DS, Carmel R: Low serum cobalamin levels in primary degenerative dementia. Do some patients harbor atypical cobalamin deficiency states? *Archives Intern. Med.* 147: 429-431, 1987.
 32. Kasarskis EJ et al: Effects of alcohol ingestion on zinc content of human and rat central nervous systems. *Experimental Neurology* 90: 81-95, 1985.
 33. Koh J-y, Choi DW: Zinc alters excitatory amino acid neurotoxicity on cortical neurons. *Journal of Neuroscience* 8(6): 2164-2172, 1988.
 34. Kubota Ketal: Restoration of decreased suppressor cells by vitamin B₁₂ therapy in a patient with pernicious anemia. *American Journal of Hematology* 214: 221-3, 1987.
 35. Kwan-Fu Rex Sheu et al: Studies of Transketolase abnormality in Alzheimer disease. *Arch. Neurol.* 45: 841-846, 1988.
 36. Lake N, de Roode M, Nattel S: Effects of Taurine on rat cardiac electrophysiology: in vivo and in vitro studies. *Life Sciences* 40: 997-1005, 1987.
 37. Lehmann A, Hagberg H, Hustable RJ, Sandberg M: Reduction of brain taurine: effects on neurotoxic and metabolic actions of kainate. *Neurochem. Int.* 10(3): 265-274, 1987.
 38. Levitt AJ, Joffe RT: Vitamin B₁₂ in psychotic depression. *Brit. J. Psychiatry*, 153: 266-7, 1988.
 39. Nehls DG, Kuramaji A, Park CK, McCulloch J: Differential effects of competitive and non-competitive N-methyl-D-aspartate antagonists on glucose use in the limbic system. *Neuroscience Letters* 91: 204-210, 1988.
 40. Oda R, Okumura M, Yamano S, Yoshi-mura H: Measurement of urinary thiamine propyl disulfide metabolites as an index of liver function. *Int. J. Clin. Pharmacol. Ther. Toxicol.* 11:591-594, 1984.
 41. Oja SS, Kontro P, Linden I-B, Andersen L, Gothoni G: A new Taurine derivative with anticonvulsant effect. *Act. Neurol. Scandinav.* 65, suppl. 90: 188-9, 1982.
 42. Olney JW, Price MT, Samson L, Labru-yere J: The role of specific ions "in glutamate neurotoxicity. *Neuroscience Letters* 65: 65-71, 1986.
 43. Peters S, Koh J, Choi DW: Zinc selectively blocks the action of N-methyl-D-Aspartate on cortical neurons. *Science* 236: 589-593, 1987.
 44. Petito CK et al: Delayed hippocampal damage in humans following cardiorespiratory arrest. *Neurology* 37: 1281-1286, 1987.
 45. Sapolsky RM: Glucocorticoid toxicity in the hippocampus: temporal aspects of neuronal vulnerability. *Brain Research* 359: 300-305, 1985.
 46. Schaller H and Holler K: Thiamine absorption in the rat. *Int. J. Vitam. Nutr. Res.* 45: 31-38, 1975.
 47. Schurr A, Changaris DG, Rigor BM: Glutamine protects neuronal function against cerebral hypoxia: a study using the in vitro hippocampal slice preparation. *Brain Research* 412: 179-181, 1987a.
 48. Schurr A, Tseng MT, West CA, Rigor BM: Taurine improves the recovery of neuronal function following cerebral hypoxia: an in vitro study. *Life Sciences* 40: 2059-2066, 1987b.
 49. Schwarcz R and Meldrum B: Excitatory amino acid antagonists provide a therapeutic approach to neurological disorders. *Lancet* 1985 ii: 140-144.
 50. Simon RP, Swan JH, Griffiths T, Meldrum BS: Blockade of N-methyl-D-Aspartate Receptors may protect against ischemic damage in the brain. *Science*

- 226: 850-852, 1984. 51. Stokstad ELR, Reisenauer A, Kusano G, Keating JN: Effect of high levels of dietary folic acid on folate metabolism in vitamin B₁₂ deficiency. *Archives of Biochemistry and Biophysics* 265 (2): 407-414, 1988.
52. Reding P, Duchateau J, Bataille Chr: Oral zinc supplementation improves hepatic encephalopathy, results of a randomized controlled trial. *Lancet* 1984 ii: 493-5.
53. Rothman SM and Olney J W: Glutamate and the physiology of hypoxic-ischemic brain damage. *Ann. Neurol.* 19: 105-111, 1986.
54. Takimoto G, Yoshimatsu K et al: The modulation of murine immune responses by methyl-B₁₂. *Int. J. Tiss. Reac.* IV(2): 95-101, 1982.
55. Thomson Allan D, Frank O, Baker H: Thiamine propyl disulfide, absorption and utilization. *Annals of Internal Medicine* 74: 529-534, 1971.
56. Van Tiggelen CJM, Siemensma N, Simons M: The trace element zinc and alcohol brain damage, pp. 81-92 in *Zinkstoffwechsel*, Ed: JD Druse-Jarres, Publ: TM Verlag Bad Oeynhausen (Germany) 1979.
57. Van Tiggelen CJM, Peperkamp JPC, Tertoolen HJFW: Assessment of vitamin B₁₂ status in CSF. *Am. J. Psychiatry* 141(1): 136-137, 1984a.
58. Van Tiggelen CJM: Alzheimers disease/ alcohol dementia: association with zinc deficiency and cerebral vitamin B₁₂ deficiency. */. Orthomolecular Psychiatry* 13(2): 97-104, 1984b.
59. Van Tiggelen CJM: Trace elements, micorsomal liver enzyme induction and amino acids: a new perspective in biological psychiatry, pp. 419-431 in: *Trace Element Analytical Chemistry in Medicine and Biology*, Vol. 4, Ed: P. Bratter and Peter Schramel, Publ: Walter de Gruyter & Co., Berlin-New York, 1987.