Alzheimers Disease/Alcohol Dementia: Association with Zinc Deficiency and Cerebral Vitamin B12 Deficiency

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Abstract

It is demonstrated that patients with senile dementia Alzheimer's type (SDAT) and alcohol related brain damage (AD) show a significant increase in ratio se-Cu/se-Zn when compared with patients with multi-infract dementia (MID) and when compared with a matched control group.

This is regarded as an indicator of zinc deficiency and relative copper toxicity in SDAT and AD, not in MID.

In the same groups with SDAT and AD a high incidence of pathologically low levels of vitamin B12 in cerebrospinal fluid (CSF) was found, despite normal serum B12 levels. In MID the normal serum *B12 corresponded with a normal CSF B12.*

This indicates abnormal function of the choroid plexus and possibly of the blood-brain barrier in SDAT and AD, not in MID.

Discussed is the possibility that in a large sub-group of SDAT and AD the clinical, neurochemical and neuropathological data can be explained by the hypothesis that the combination of zinc deficiency and copper toxicity results in limbic disinhibition and defective central noradrenergic neurotrans-mission. The neuroendocrine effects of the limbic disinhibition and the impaired regulation of the cerebral micro-circulation by the defective noradrenergic *system will result in dysfunction of the blood-brain barrier and the choroid plexus, resulting as has been demonstrated in a CSF B12 deficiency. Such an effect is strongly potentiated by a co-existent depression.*

Due to the reduced plasticity of the aging brain the presentation of this organic affective syndrome and/or depression is under a "dementia" disguise, facilitated by organic cerebral changes caused primarily by zinc deficiency and copper toxicity, secondarily by the cerebral B12 deficiency.

Early recognition and adequate treatment with nutritional supplementation can possibly prevent irreversible damage in subgroups of SDAT and AD. Primary prevention by nutritional strategies can be a realistic perspective. The need for further research into this challenging hypothesis is stressed.

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Presented at Victorian State Geriatric Conference, La Trobe University, Melbourne, Australia. 1983.

Introduction

In recent years a possible association between zinc deficiency and development of dementia has been suggested (Burnet, 1981; van Tiggelen, 1983) and the need to investigate zinc status in senile dementia of the Alzheimer's type has been stressed (Mann, 1982). Evidence of zinc depletion in the hippocampus of chronic alcoholics has been given (McLardy, 1975), whilst zinc deficiency in chronic alcoholics without liver damage could be demonstrated in serum (van Tiggelen et al., 1979). In rats with hepatic encephalopathy a decrease of hippocampal zinc was demonstrated (Baraldi et al., 1983). Constantinidis (1977) reported on abnormalities in zinc transport and metabolism in Pick's and Alzheimer's disease, while two recent reports demonstrated significant decreases in serum zinc levels in chronic alcoholics and in patients with undifferentiated dementia (Srinivasan et al., 1982; van Tiggelen, 1983).

Assessment of zinc status by measuring serum zinc is of disputable value (Prasad, 1981) even when standardized methods are used (Kiilerich and Christensen, 1981). The ratio se-Copper/se-Zinc has been demonstrated to be a rather reliable parameter of zinc status in man (Abdulla and Svensson, 1979), taking into account that zinc deficiency potentiates relative copper toxicity (Underwood, 1977).

The connection between vitamin B12 deficiency, established by measuring serum B12, and dementia is generally accepted (Roos and Willanger, 1977; Dreyfus and Geel, 1981). Frenkel (1973) found a discrepancy between normal levels of serum B12 and pathologically low levels of B12 in cerebrospinal fluid (CSF) in two groups of patients with organic mental symptoms, both exposed to potentially neurotoxic chemicals: a group of chronic alcoholics and a group of patients on long-term anti-epileptic medication with phenytoin. Layzer (1978) presented evidence on the development of a neuromyelopathy in man after exposure to nitrous oxide, which chemical has been shown to induce a vitamin B12 deficiency in bone marrow and brain (Scott et al., 1981). The neuropathy following nitrous oxide exposure develops despite normal levels of B12 in serum (Layzer et al., 1978). Recently a similar discrepancy between normal serum B12 and pathologically low CSF B12 was reported in patients with organic mental symptoms (toxic neurasthenic depression, post-natal depression, dementia) (van Tiggelen et al., 1984). Schrumpf and Bjelke (1970) reported earlier on the reduced levels of CSF B12 in patients with brain atrophy.

We explored the possible connection between zinc deficiency and copper toxicity, as measured by the ratio se/Cu/se-Zn, and a discrepancy between normal serum B12 and low CSF B12 in patients with senile dementia Alzheimer's type (SDAT), alcohol related brain damage (AD) and multi-infarct dementia (MID).

Material and Methods

In 136 consecutive patients, admitted under the preliminary diagnosis of dementia (DSM-111) to a psychogeriatric assessment unit, serum levels of zinc and copper were estimated in the first week of admission, conforming to Kiilerich (1981). The mean age was 74, 70 percent female. A control group of 28 elderly people, matched for age and sex, living in the community and rated by their general practitioner as healthy, was available for comparing serum levels of copper and zinc. From a series of 52 consecutive admissions, part of the above mentioned patient group, we were able to select 3 sub-groups with the most likely diagnosis of senile dementia of the Alzheimer's type (SDAT, n=24), alcohol related brain damage and alcohol dementia (AD, n=9), multi-infarct-dementia (MID, n=10). In the selection the strict inclusion and exclusion criteria as described by Glen and Christie (1979) were followed. Consequently all patients included in the sub-groups SDAT, AD, and MID had normal serum B12 levels (ref. 200-800 pg/ml, radio-assay method), (Gyzen et al., 1983).

In the routine neurological examination the linguo-mental reflex was included, described as an early sign of temporal lobe dysfunction (Bracha, 1978) and organic limbic dysfunction (van Tiggelen, 1983). After explanation of the experimental and investigative nature of the procedure, informed consent was obtained from patients and/or relatives to carry out a lumbal puncture in 50

percent of the patients in order to obtain cerebrospinal fluid for B12 testing. The method is described elsewhere (van Tiggelen et al., 1983). On the same day serum B12 was retested.

For ethical reasons we were not able to obtain vitamin B12 levels in a matched control group. Normal levels of CSF B12 presented in the literature are from 10-30 pg/ml (Frenkel et al., 1973; van Tiggelen et al., 1983; Taguchi et al., 1977 and Baker et al., 1983). In the accessible literature I have not been able to trace figures indicating a decrease of CSF B12 in elderly controls.

Student's t-test was used for analysis of the appropriate date to assess the significance of the differences between the various groups.

Results

Table 1 shows that the patient group as a whole differs significantly from the control group: a significant decrease in se/Zn, a significant increase in se/Cu and in ratio se-Cu/se-Zn.

Compared with the controls the SDAT group shows a significant reduction of se-Zn, a significant increase in se-Cu and a significant increase in ratio se-Cu/se-Zn.

Comparing the AD group with the controls shows a significant decrease of se-Zn, a less significant increase in se-Cu, whilst the ratio se-Cu/se-Zn is significantly higher than in the control-group.

Comparing the MID group with the control group shows a decrease of both se-Cu and se-Zn with low statistical significance, while the ratio se-Cu/se-Zn is not different from the control group.

Comparing the patient sub-groups with one another demonstrates a strong similarity between SDAT and AD.

The very high standard deviation in se-Cu in the SDAT group raises the suggestion that measurements in a larger group of SDAT patients may be able to confirm our preliminary impression that this group can be subdivided in two groups: one sub-group with se-Cu levels in the same range as AD, while the second sub-group has far higher se-Cu levels.

Table 2 shows that SDAT and AD, the groups with a significant rise in ratio se-Cu/se-Zn, demonstrate a clear discrepancy between normal serum B12 and pathologically low CSF B12 levels: 13 out of 17 patients with SDAT/AD have a CSF level lower than 5 pg/ml, according to Frenkel et al. (1973) the pathological level found in patients with untreated pernicious anemia.

The MID patients show normal levels of CSF B12.

Table 3 shows that finding a positive linguo-mental reflex is associated with an abnormal high ratio se-Cu/se-Zn and with an abnormal low CSF B12, despite normal serum B12.

Table 1

Serum-Cu, serum-Zn and ratio se-Cu/se-Zn in controls, SDAT, AD, MID, and undifferentiated dementia patients.

n	**Controls**	**SDAT 24**	**AD** 9	**MID**	"dementia 136
se-Cu-SD	**28**	[a]23.6-3.9	[b]20.1-2.0	10	[a]21.8-3.6
micromol/L	18.5-1.9			[c]16.9-2.4	
se-ZN-SD	18.0-1.9	[a]13.9-1.8	[a]12.8-2.6	[c]15.9-2.1	[a]14.7-2.6
micromol/L					
se-CU-se-Zn	1.04-0.16	. [a]1.70-0.26	[a]1.61-0.29	1.07-0.12	[a]l.48-0.30
ratio-SD					
Statistical evaluation:		Student's t-test	: compared with	controls.	

[a]: significant, p<0.001 : significant, p<0.01 [c]: significant, p<0.05

Table 2

Serum and CSF levels of vitamin B12 in patients with SDAT, AD, MID who gave informed consent for lumbal puncture.

Group	Consent	Se-B12 pg/ml (ref 200-800)	CSF B12 pg/ml 0-5	5-10	above 10
SDAT (N=24)	11	220-620	**8**	**2**	**1**
AD (n=9)	**6**	220-460	**5**	**-**	**1**
MID (n=10)	**5**	220-430		**5**	

Table 3

Presence of linguo-mental reflex in SDAT, AD and MID considering CSF B12 levels.

	CSF B12 level	Linguo-mental reflex positive	negative
SDAT: (n=24)	not tested: 13 0-5 pg/ml 8 5-10 pg/ml 2 above 10 pg/ml 1	**12 8 2**	**1 1**
AD: (n=9)	not tested: 3 0-5 pg/ml 5 above 10 pg/ml 1	**3 5**	**1**
MID: (n=10)	not tested: 5 over 10 pg/ml 5	**2 1**	**3 4**

Discussion

The demonstrated similarity between SDAT and AD in copper and zinc status, indicative of a zinc deficiency and possibly a relative copper toxicity being involved in SDAT, underlines strongly the similarity demonstrated by Carlsson et al. (1980) in neurotransmitter changes in SDAT and AD. Zinc deficiency in chronic alcoholism is widely accepted and our results support the hypothetical effects of cerebral zinc deficiency on neuronal protein metabolism, as suggested by Burnet (1981) and as discussed by Mann (1982). The demonstrated zinc deficiency in SDAT will result in a decrease of zinc in the hippocampus, as has been documented earlier (McLardy, 1975) in chronic alcoholics and has been published recently in hepatic encephalopathy (Baraldi et al., 1983). Evidence has been presented that hippocampal zinc is involved in enkephalin receptor function (Stengaard-Pedersen et al., 1981; Stengaard-Pedersen, 1982), in glutamic acid function and metabolism (Dreosti et al., 1981) in glutaminergic neurotransmission (Moroni et al., 1983), in GABA-receptor sensitivity (Baraldi and Zeneroti, 1982). Taking this in consideration, zinc depletion in the hippocampus will result in hippocampal, possibly even limbic disinhibition, as argued by Segal (1982) a distinct feature of SDAT and AD. Partial therapeutic effect of treatment with the opioid antagonist Naloxone and with GABA-ergic medication in SDAT can be explained in this way (Reisberg et al., 1982). Another effect of hippocampal zinc depletion has been suggested by Barbeau and Donaldson (1974) through an effect of the imbalance between zinc and copper on the activity of Na-K-ATPase, possibly by interference with the regulatory role of a zinc-taurine complex, postulated by van

Gelder (1983), resulting in defective osmo-regulation and changes in excitation threshold.

An important role in the development of limbic disinhibition in SDAT and AD is attributed to defective noradrenergic neuro-transmission, in particular in the dorsal nor-adrenergic bundle originating in the locus coeruleus. Cell loss in the locus coeruleus has been demonstrated in a large sub-group of SDAT (Mann, 1980; Tomlinson et al., 1981; Bondareff et al., 1982) and strongly suggested in AD (Mason et al., 1983; Mair and McEntee, 1983). Defective noradrenergic function was not found in multi-infarct-dementia (Mann et al., 1982).

In this respect our reported findings on zinc deficiency in SDAT, but not in MID, can be relevant: Wenk and Stemmer (1982) demonstrated a significant reduction of dopamine-beta-hydroxylase in the zinc defi-cient rat; copper toxicity impairs the function of dopamine-beta-hydroxylase (Molinoff and Orcutt, 1973). Cross et al. (1981) reported on the loss of this noradrenaline producing dopamine-beta-hydroxylase in the brains of SDAT patients.

The evidence brought forward indicates strongly a role for the found zinc deficiency in SDAT and AD; in particular the limbic dysfunction can be strongly connected with cerebral and hippocampal zinc depletion. The reportedly high prevalence of non-suppression in the dexamethasone suppression test amongst SDAT (Spar and Gerner, 1982; Raskind et al., 1982) an indicator of limbic dysfunction, appears to be more closely connected with assumed cerebral zinc deficiency than with depression, as is indicated by our preliminary results (unpublished).

The results, presented in table 2, indicate a high incidence of CSF B12 deficiency, despite normal levels of B12 in serum. When indirect evidence (Dreyfus, 1970; Frenkel et al., 1973) is accepted it indicates a cerebral B12 defi-ciency in a large proportion of patients with SDAT and AD. The implications are manifold. From the clinical point of view it explains a range of neuro-psychiatric and neuro-physiological phenomena found in patients with SDAT and AD., similar to findings in patients with a cerebral B12 deficiency as manifested in a serum B12 deficiency: peri-pheral neuropathy (Levy, 1975) abnormal visual evoked potential in pernicious anemia (Troncoso et al., 1979) and in SDAT (Coben et al., 1983), autonomous neuropathy, psychiatric manifestations (McDonald Holmes, 1956), even in the absence of any haematolo-gical or neurological signs (Evans et al., 1983). It is intriguing that some of the psychiatric phenomena in SDAT and AD can be related to the not recognized and not treated state of cerebral B12 deficiency. Even more intriguing is the question to what extent irreversible damage to the central nervous system is caused by the failure to recognize the cerebral B12 deficiency.

The demonstrated B12 deficiency in CSF even allows an explanation for neurotransmitter changes found in SDAT and AD, particularly involving the reported defective noradrenergic and acetylcholinergic aspects. Deana et al. (1977) reported a significant decrease of noradrenaline in the brains of rats with a confirmed B12 deficiency, while in the same animals a significant reduction of plasma acetylcholinesterase was found. Hakim et al. (1983) demonstrated recently in rats with a nitrous oxide induced B12 deficiency a significantly decreased glucose utilisation in selected areas of the brain, including the limbic cortex. Gibson and Duffy (1981) have reported suppression of cerebral acetylcholine synthesis after exposure to nitrous oxide. Hakim et al. (1983) suggested that the reduced activity of methionine-synthetase,' shown to be the result of induced B12 deficiency, causes defective methylation in the liver and leads to insufficient formation of choline, the necessary precursor of acetylcholine in the brain. Further research in the nitrous oxide induced B12 deficient rat should clarify to what extent B12 deficiency affects the noradrenergic system and the locus coeruleus. The demonstrated zinc deficiency and copper toxicity in SDAT and AD and the documented cerebral B12 deficiency can explain many of the clinical and neurochemical features. It remains very interesting to speculate on a possible correlation.

Recently we (van Tiggelen et al., 1983) reported a discrepancy between normal serum B12 and low CSF B12 in younger patients with exposure to toxic chemicals. A possible explanation is a toxic effect of chemicals or their toxic intermediate meta-

bolites on the choroid plexus, the main transport route for B12 from blood to brain. Such effects have been demonstrated for Hg (Pardridge, 1976) for solvents (Rapoport, 1964), whilst Friedheim et al. (1983) suggested that the choroid plexus acts as a protective sink for heavy metals. A relatively high level of copper in the case of zinc deficiency can have a toxic effect on the enzyme-systems in the choroid plexus (Masuzawa and Sato, 1983) e.g. Na-K-ATPase, thus impairing the active transport of nutrients and metabolites such as B12, but possibly also other vitamins and aminoacids.

A second, presently more speculative explanation is that excess copper in tissue with a high oxidative status as brain or liver can exert a strong oxidative effect, as has recently been documented by Sasaki et al. (1983). This suggests a mechanism similar to the effect of nitrous oxide on B12 (Deacon et al., 1983): inactivation of B12 by oxidation of the monovalent Cobalt to tri-valent cobalt.

The third and most elegant possibility is that the copper-zinc imbalance causes a defective noradrenergic neurotransmission, including the failing autonomous innervation of intracerebral vessels, as described by Mann (1982; et al. 1980). This will imply an effect on the blood-brain barrier, as has been demonstrated (Preskorn et al., 1982). To what extent defective noradrenergic neurotransmission affects the transport of e.g. B12 through the choroid plexus should be investigated.

Whichever of the explanations is favoured, it will be clear that zinc deficiency will facilitate the process (Bettger and O'Dell, 1981) and that reduced free radical scavenging or anti-oxidative potential can potentiate the process.

The results in table 3, combined with earlier observations on the strong relation between the linguo-mental reflex as a soft neurological sign and CSF B12 deficiency (van Tiggelen et al., 1983), suggest that a positive linguo-mental reflex can be considered as an indicator of pathologically low CSF B12. The exact reliability has to be evaluated in further research.

Conclusion

The results presented, in combination with the above mentioned considerations have resulted in the following working-hypothesis: A multifactorial process, including genetic, nutritional, toxic and stress-related factors, can lead to the development of a zinc deficiency usually accompanied by a relative copper toxicity. For lack of a better method we consider an abnormal high ratio se-Cu/se-Zn as a biochemical indicator of this condition.

The effects on the brain can be summarized as initially the development of hippocampal/limbic disinhibition, facilitated by neurotransmitter changes. In particular the effect on the noradrenergic system results through its regulation of the cerebral microcirculation in effects on the blood-brain-barrier and the choroid plexus, impairing the transport as has been demonstrated of vitamin B12.

The consequently developing cerebral B12 deficiency results in the development of an organic affective syndrome, which presents itself due to the zinc deficiency and copper toxicity induced cerebral dysfunction as an "amnestic-demential syndrome". When a co-existing depression is present, severe behavioural disorder and psychotic features may develop. Early recognition of the condition is possible by means of the linguo-mental reflex. A co-existing depression must not be missed.

Early treatment is necessary to prevent the development of irreversible neurological and cerebral damage.

Our results with treatment of early SDAT and AD, supplementing parenteral vitamin B12 for a long period in a high dose, prescribing zinc-aspartate and taurine for a long period in a low dose, are suggesting a hopeful perspective in arresting the process or even in prevention.

Further clinical research involving double blind trials and examining the preventive effect of medication with zinc and taurine are envisaged.

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