J Neural Transm (1998) 105: 59–68

Journal of Neural Transmission

Increased blood mercury levels in patients with Alzheimer's disease

C. Hock[1], **G. Drasch**[2], **S. Golombowski**[1], **F. Müller-Spahn**[1], **B. Willershausen-Zönnchen**[3], **P. Schwarz**[3], **U. Hock**[1], **J. H. Growdon**[4], and **R. M. Nitsch**[5]

[1] Department of Psychiatry, University of Basel, Switzerland
[2] Department of Forensic Medicine, University of Munich, and
[3] Department of Dentistry, University of Mainz, Federal Republic of Germany
[4] Department of Neurology, Massachusetts General Hospital, Boston, MA, U.S.A.
[5] Center for Molecular Neurobiology, University of Hamburg, Federal Republic of Germany

Accepted November 4, 1997

Summary. Alzheimer's disease (AD) is a common neurodegenerative disorder that leads to dementia and death. In addition to several genetic parameters, various environmental factors may influence the risk of getting AD. In order to test whether blood levels of the heavy metal mercury are increased in AD, we measured blood mercury concentrations in AD patients (n = 33), and compared them to age-matched control patients with major depression (MD) (n = 45), as well as to an additional control group of patients with various non-psychiatric disorders (n = 65). Blood mercury levels were more than two-fold higher in AD patients as compared to both control groups ($p = 0.0005$, and $p = 0.0000$, respectively). In early onset AD patients (n = 13), blood mercury levels were almost three-fold higher as compared to controls ($p = 0.0002$, and $p = 0.0000$, respectively). These increases were unrelated to the patients' dental status. Linear regression analysis of blood mercury concentrations and CSF levels of amyloid β-peptide (Aβ) revealed a significant correlation of these measures in AD patients (n = 15, $r = 0.7440$, $p = 0.0015$, Pearson type of correlation). These results demonstrate elevated blood levels of mercury in AD, and they suggest that this increase of mercury levels is associated with high CSF levels of Aβ, whereas tau levels were unrelated. Possible explanations of increased blood mercury levels in AD include yet unidentified environmental sources or release from brain tissue with the advance in neuronal death.

Keywords: Dementia, biochemical markers, heavy metals, neurodegeneration.

Abbreviations

AD Alzheimer's disease, *MD* major depression, *f* female, *m* male, *ELISA* enzyme-linked immunosorbent assay, *APP* amyloid precursor protein, *A*β amyloid β-peptide.

Introduction

Alzheimer's disease (AD) is the most common neurodegenerative disorder. In addition to several genetic parameters, such as mutations in the amyloid precursor protein (APP) and presenilin genes, or allelic variances of the apolipoprotein E gene (for review see: Hardy, 1996), various environmental factors may influence the risk of getting AD. These include such metals as iron, aluminium, zink, copper, lead, cadmium, mercury (Basun et al., 1991). Iron and zinc levels were shown to be significantly increased in post mortem AD hippocampus and amygdala (Deibel et al., 1996). Serum levels of the iron binding protein p97 were shown to be elevated in AD patients compared to controls (Kennard et al., 1996). Several preliminary reports noted that mercury levels were elevated in post mortem AD brain tissue (Ehmann et al., 1986; Thompson et al., 1988), and in plasma of AD patients (Basun et al., 1991). Elemental mercury can be derived from amalgam restorations that are in widespread use. To examine whether mercury is increased and to determine the relevance of this finding to AD, we determined blood mercury levels in patients with probable AD, and compared them to age-matched patients with major depression (MD), and to an additional control group of patients with various non-psychiatric disorders.

Subjects and methods

Subjects

The diagnosis of probable AD was made according to the NINCDS-ADRDA criteria (McKhann et al., 1984). MD was diagnosed according to ICD10 (F32.0x/1x, F33.0x/1x) and DSM-IIIR (296.20–22, 296.30–32). Blood mercury levels were measured in 33 AD patients (15 m, 18 f, mean age 70.7 ± 11.3 yrs, Mini Mental State (MMS, Folstein et al., 1975). Score 17.5 ± 6.4), and in 45 patients with MD (6 m, 39 f, 73.3 ± 10.0 yrs, MMS 28.0 ± 1.5). AD patients with early onset (<65 years, n = 13, 6 m, 7 f, 59.2 ± 6.8 yrs, MMS 17.3 ± 6.1) were compared to AD patients with late onset (≥65 years) of the disease (n = 20, 9 m, 11 f, 78.2 ± 6.0 yrs, MMS 17.9 ± 6.7). None of the early onset AD patients had a family history of AD. In no case was an occupational exposure to mercury, or excessive fish consumption reported. Neither clinical signs nor laboratory values indicated that patients were malnourished or had renal disorders. All patients were community-dwelling in Munich and environs, and were refered to the research ward of the Department of Psychiatry, University of Munich, from general practioners, neurologists and psychiatrists for diagnostic purposes and screening for clinical trials. None of the patients was institutionalized. Patients were selected from this research ward during a period of one year. Occupational exposure to heavy metals and dietary history were recorded in a clinical interview and documented in case report forms. The nutritional status of all patients was within the normal range. All patients received food from the clinic during the period of investigations. An additional group of control patients was recruited from the Munich University Hospitals. 65 patients with various nonpsychiatric disorders including intestinal and renal disturbances, gastroenteritis,

dermatitis, tremor and chronic pain, were examined ("mixed control group", n = 65, mean age 36.1 yrs).

Ethics

Informed consent was taken from each patient and their caregivers before the investigation. The study was approved by the local ethical committee. All procedures were in accordance with the Helsinki Declaration of 1975, as revised in 1983.

Protocol

35 of the 78 patients were selected at random to undergo complete dental assessment. The dental status work up included counts of amalgam fillings in 17 AD patients (7 m, 10 f, mean age 72.8 ± 9.7 yrs) and 18 control patients with MD (1 m, 17 f, 74.9 ± 9.9 yrs). 88% (15/17) of AD, and 33% (6/18) of MD had dentures at the time of mercury determinations. 71% (12/17) of AD, and 83% (15/18) of the patients with MD had no amalgam fillings, and 28% (5/17) of AD, and 17% (3/18) of MD patients had one or more amalgam filling at the time of mercury measurements.

CSF was obtained for diagnostic purposes in a subset of the AD patient group in which a lumbar puncture was performed during the diagnostic work-up. This fact explains the differences in sample sizes. All available CSF samples were used for the analyses. For Aβ measurements, CSFs were obtained from 15 AD patients (7 m, 8 f, 68.1 ± 7.5 yrs, MMS 18.7 ± 5.7). For tau measurements, CSFs were available from 18 AD patients (9 m, 9 f, 69.1 ± 8.1 yrs, MMS 18.3 ± 6.0). CSFs were obtained by lumbar puncture within one week of both dementia testing, and blood mercury measurements. To avoid possible influences of a ventriculo-lumbar gradient, lumbar punctures were done between 7.30 and 8 a.m. before patients assumed an erect posture. CSF samples were frozen (−80°C) at the bedside in 0.5 ml aliquots, and stored at −80°C until biochemical analyses.

AD patients were free of psychotropic medication. Control subjects with MD were treated with such antidepressants as serotonin reuptake inhibitors, reversible monoaminoxidase A inhibitors and tricyclics. It is currently unknown whether these treatments can influence blood levels of mercury or CSF levels of Aβ and tau.

Mercury assay

Blood was collected in disposable Hg-free EDTA coated plastic tubes and stored for a maximum of 3 days at +4°C until analysis. It is mandatory to measure mercury levels within a few days of blood collection because storage of mercury-containing specimens in plastic test tubes over several months leads to deposition of mercury in the test tube walls, and to a loss of mercury in the specimen (Schaller, 1985; Drasch et al., unpublished observations). Therefore, blood samples were assayed for mercury levels consecutively and diagnoses were blinded to the investigators. Blood mercury levels were determined by cold vapour atomic absorption spectrometry after enrichment on a gold-platinum-net according to a recently described protocol (Schaller, 1985; Drasch et al., 1994) using the Perkin-Elmer 1,100 B atomic absorption spectrometer with HGA 20 (Perkin-Elmer, Überlingen, Germany). 1.0 ml of whole blood were analysed in duplicates, and Seronorm™ Trace Element Whole Blood (Nycomed, Torshov, Norway) was used as matrix-matched control. The detection limit was 0.3 μg/l, and the assay was linear over the range of 0.3–30 μg/l. The within series imprecision of the method used was specified with 3.2% in relation to the standard deviation, the day to day imprecision with 3.6% (Schaller, 1985). Our own investigations and quality controls confirmed within series imprecision and day to day imprecision ranging from 3–4% (Drasch et al., unpublished observations).

Amyloid β-peptide (Aβ) ELISA

CSF levels of Aβ were measured by an ELISA as described recently (Seubert et al., 1992). This assay measures the sum of $A\beta_{1-40}$ and $A\beta_{1-42}$. In a typical human CSF sample, there is approximately 10 to 20 times more $A\beta_{1-40}$ than $A\beta_{1-42}$. Data represent the mean of triplicate determinations. The sensitivity was ≤0.1 ng/ml (for details see: Seubert et al., 1992).

Tau ELISA

CSF levels of tau protein were determined by an ELISA as described previously (Vandermeeren et al., 1993; Hock et al., 1995). The detection limit was 10 pg/ml, the mean recovery 92%, the assay was linear in the range of 10 to 160 pg/ml, and the intra-assay variance was below 11%.

Statistical analyses

Statistical analysis of data was performed using the independent-samples t-test (when normal distribution was demonstrated) or Mann-Whitney U test for group comparisons. Correlation analyses were performed by multiple regression using CSF levels of Aβ and tau, as well as Mini Mental State, duration of illness and age of onset. Regression analysis was complemented by ANOVA. Statistical significance was assumed at $p < 0.05$. Bonferroni correction for multiple testing was applied.

Results

Blood mercury levels were more than two-fold higher in the AD group as compared to control patients with MD (mean ± SEM: 2.64 ± 0.38 μg/l, n = 33, range: 0.00–8.66 μg/l, and 1.20 ± 0.20 μg/l, n = 45, range: 0.00–6.12 μg/l, respectively, p = 0.0005, t-test). Blood mercury concentrations in AD patients with early onset of the disease were almost three-fold higher (3.32 ± 0.73 μg/l, n = 13, range: 0.60–8.66 μg/l) as compared to control patients with MD (p = 0.0002). Blood mercury concentrations in AD patients with late onset of the disease were also significantly higher (2.20 ± 0.39 μg/l, n = 20, range: 0.00–7.10 μg/l) as compared to the controls (p = 0.0138), although the elevation was only 1.8 fold (Fig. 1). The comparison of mean blood mercury levels between AD with early and late onset of the disease was statistically not significant (p = 0.1502). In order to exclude a systematic error caused by abnormally low blood levels of mercury in our group of control patients with MD, e.g. due to treatment with antidepressants, mean blood levels of mercury were measured in an additional group of mixed control patients with various non-psychiatric disorders. Mean blood levels of mercury in the AD group were clearly higher than in this additional control group (n = 65, 1.09 ± 0.12 μg/l, range: 0–3.3 μg/l). Comparison to the AD group: p = 0.0000, to AD with early onset: p = 0.0000, to AD with late onset: p = 0.0004 (Fig. 1). The results remained significant using Bonferroni-corrected α-values.

Figure 2 shows a scattergram of the individual mercury values and boxplots (showing median, 5%, 10%, 25%, 75%, 90% and 95th percentiles) in the AD, MD mixed control patients (median: 2.00 μg/l, n = 33, 0.80 μg/l, n = 45, and 0.80 μg/l, n = 65, respectively). In all groups normal distribution was demonstrated (Kolmogorov-Smirnov test of normality: AD, p = 0.005, MD,

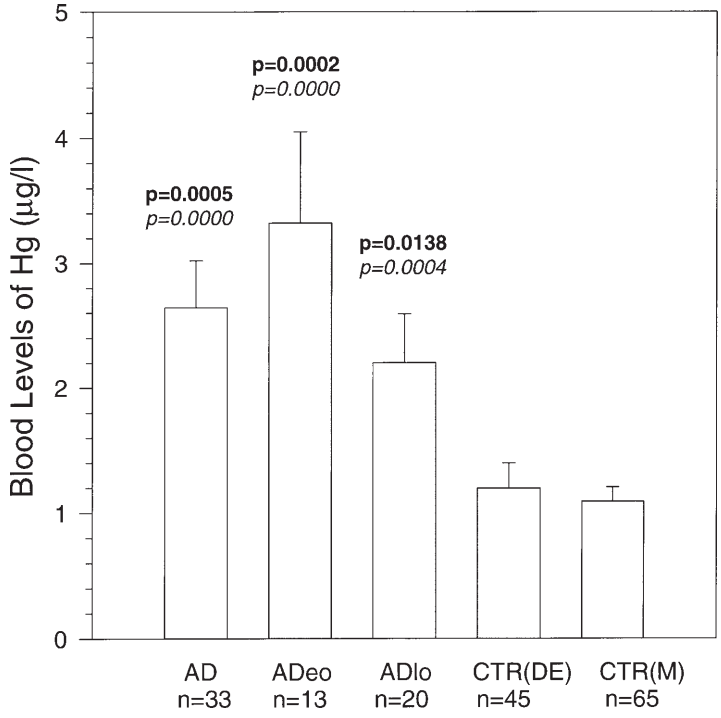

Fig. 1. Bars show blood mercury levels (mean ± SEM) in the AD group (2.64 ± 0.38 µg/l, n = 33, range: 0.00–8.66 µg/l), AD patients with early onset of the disease (ADeo, 3.32 ± 0.73 µg/l, n = 13, range: 0.60–8.66 µg/l), AD patients with late onset of the disease (ADlo, 2.20 ± 0.39 µg/l, n = 20, range: 0.00 to 7.10 µg/l), control patients with MD (CTR(DE), 1.20 ± 0.20 µg/l, n = 45, range: 0.00–6.12 µg/l), and control patients with various non-psychiatric disorders (CTR(M, mixed), 1.09 ± 0.12 µg/l, n = 65, range: 0–3.3 µg/l). P values are given in bold, when compared to CTR(DE), in italics, when compared to CTR(M). The independent-samples t-test was used. The results remained significant using Bonferroni-corrected α-values

p = 0.000, mixed control patients, p = 0.005). The 95% Confidence Interval (CI) for the mean was 1.87–3.41 in AD, 0.79–1.60 in MD, and 0.86–1.32 in the mixed control patients.

In order to evaluate effects of dental status on blood mercury levels, patients with AD and AD were grouped according to the presence of amalgam filling(s): MD patients without denture and without fillings, 2.82 ± 1.30 µg/l (mean ± SD), n = 12, AD patients with ≥1 amalgam filling(s), 3.15 ± 3.24 µg/l, n = 5 (p = 0.5268), indicating that these groups were not significantly different. Patients with MD without denture or fillings, 1.96 ± 1.53 µg/l, n = 15, had similar levels as control patients with ≥1 amalgam filling(s) 2.55 ± 2.10 µg/l, n = 3 (p = 0.5145). No differences in blood mercury levels between all patients without denture or fillings, 2.34 ± 1.47 µg/l, n = 27, and those with more than one amalgam filling(s), 2.93 ± 2.71 µg/l, n = 8 (p = 0.8443) (Mann-Whitney U test).

Linear regression analysis of blood mercury concentrations of AD patients and CSF levels of Aβ showed that these measures were significantly

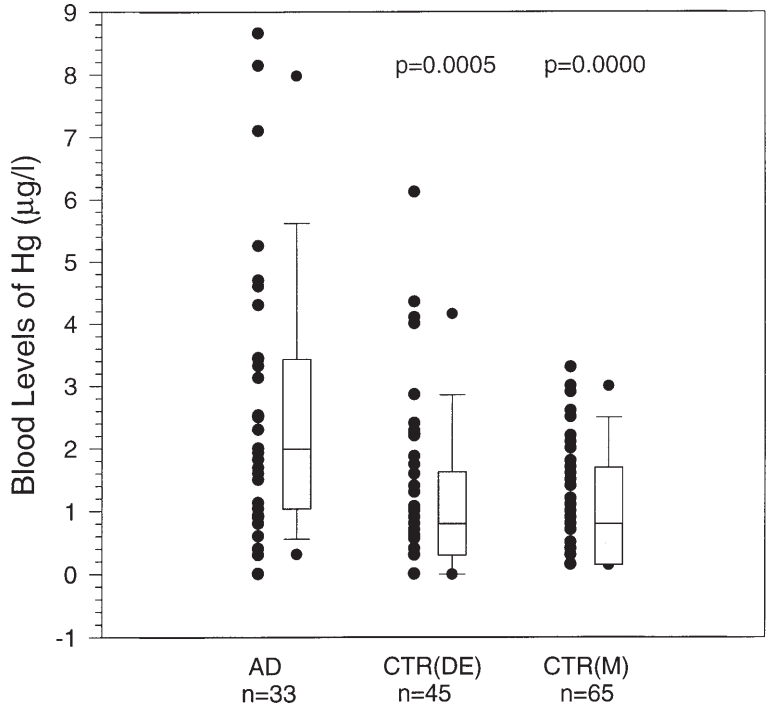

Fig. 2. Scattergram of the individual mercury values (shown as dots) and boxplots (showing median, 5%, 10%, 25%, 75%, 90% and 95th percentiles) in the AD patients and the control patients with MD (median: 2.00 µg/l, n = 33, and 0.80 µg/l, n = 45, and 0.80 µg/l, n = 65, respectively)

correlated (n = 15, r = 0.7440, p = 0.0015, Pearson type of correlation, p = 001, ANOVA) (Fig. 3). In contrast, there was no correlation with CSF levels of tau (n = 18, r = 0.465, p = 0.0517, Pearson type of correlation). Blood mercury levels did not correlate with age, sex, age of disease onset and MMS scores.

Discussion

The major finding of this study indicates that mean blood mercury concentrations are more than two-fold higher in AD patients, and even three-fold higher in AD patients with early onset of the disease, as compared to age-matched control patients with MD. For comparison: Normal blood mercury levels in the German population reportedly are 0.74 ± 0.80 µg/l (n = 2,294, age range, 25–69 yr, highest value: 11.1 µg/l) (Krause et al., 1989). The highest levels in our study were 8.66 µg/l for the AD group, 6.12 µg/l for the MD, and 3.30 for the mixed control group. These levels were clearly below the concentrations that are known to cause acute (>200 µg/l) or chronic (>35 µg/l) neurotoxicity. Since there is substantial overlap with the control subjects, blood mercury levels do not constitute a diagnostic tool for the AD patient group. One reason for this overlap might be that a considerable portion of the age-

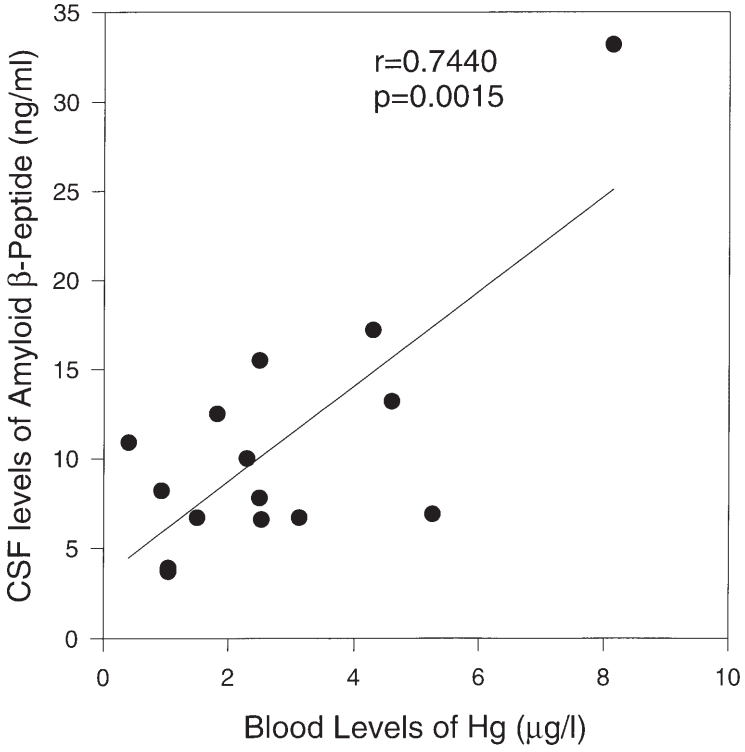

Fig. 3. Correlation of blood mercury concentrations and CSF levels of Aβ in AD patients by linear regression analysis (n = 15, r = 0.7440, p = 0.0015, Pearson type of correlation)

matched healthy controls might be preclinical AD patients. It is assumed that the specific neuropathology of AD precedes the clinical manifestation of the disease for years, or even decades (Davies et al., 1988; Rumble et al., 1989). In addition, patients with MD were shown to have an increased risk for AD as compared to the general population (Steffens et al., 1997). The higher overlap of the AD with the MD group than with the mixed controls, as shown in Fig. 2, would be consistent with these reports. However, to date, no preclinical markers are available that definitely ecxlude preclincal AD patients in such studies. Nevertheless, the increase in mean blood mercury levels might be specific for the AD group, because a similar difference was observed by comparison to the other control group of patients with various non-psychiatric disorders. Further comparative studies that include other neurological illnesses associated with neurodegeneration are needed to clarify the specificity of increased mercury levels. In addition, further studies in larger samples may provide insight whether subgroups of AD patients that show higher blood mercury levels than the average levels in age-matched controls can be associated with specific clinical characteristics.

The finding of increased blood levels of mercury in AD patients is in agreement with a previous report of Basun et al. (1991) who showed that

plasma levels of mercury were increased in 12 patients with AD as compared to 25 healthy age-matched volunteers (mean ± SD: 14.7 ± 6.5 nmol/l, and 8.0 ± 3.7, respectively). In contrast to our finding and the results of Basun et al., Fung et al. (1995) reported no differences in blood mercury levels in institutionalized AD patients as compared to controls. However, in that study, blood specimens were stored at −70° until assayed. As stated above, it is mandatory to measure mercury levels within a few days of blood collection because storage of mercury-containing specimens in plastic test tubes over several months leads to deposition of mercury in the test tube walls, and to a loss of mercury in the specimen. For this reason we were not able to detect mercury in stored CSF and serum samples. This might explain why Fung et al. (1995) did not replicate the finding of Basun and colleagues (1991).

In our sample, 70% of the AD patients showed higher blood mercury levels than the average levels in the control group with MD, and 83% higher than the mixed control group. However, it is important to note that our correlative data provide no evidence for a causal effect of mercury in the pathogenesis of AD. Prospective population-based studies are required to determine whether increased blood mercury levels are a risk factor for the development of AD. Alternatively, increased levels of mercury may be a marker of neurodegeneration in a subgroup of AD patients. It may be speculated that sequestered mercury is released from brain tissue with the advance in neuronal death in AD, known to be more marked in patients with early onset of the disease.

Mercury in whole blood comprises the sum of organic (methylmercury) and inorganic mercury (elemental mercury, mercury salts). Potential sources of mercury in human subject arise from environmental exposure to mercury (industrial discharge, chloralkali production, fungicides, germicides), as well as from the intake of fish and seafood (Halbach, 1994). The potential environmental source of elevated mercury levels in AD patients is unclear. In selected individuals, amalgam restorations can contribute for up to two thirds of the total body load of mercury (Halbach, 1994). In the present study, blood mercury levels were not significantly different in patients with AD and MD grouped according to the presence of amalgam filling(s). Our data exclude the possibility that the patients studied had a history of occupational exposure to mercury, or of excessive consumption of sea food. Thus, other environmental sources of mercury need to be identified.

The second finding of this study was that increased blood mercury levels correlated with CSF levels of Aβ suggesting the possibility of a direct or indirect interaction of these two measures, provided that blood mercury concentrations correspond constantly to levels in CSF and brain. Recent studies suggest that this is the case. The ratios of mercury concentrations between lumbar CSF and plasma were 0.35 ± 0.32 in AD patients, and 0.42 ± 0.68 in healthy controls (statistically not different, Basun et al., 1991). Nielsen et al. (1994) found that blood and brain mercury levels were correlated, and that in mice blood mercury levels may be used as an estimate of brain tissue concentrations of mercury. However, systematic correlative measurements of mer-

cury in blood, CSF and brain tissue derived from the same individuals are required to determine whether blood levels of mercury consistantly reflect tissue levels in the central nervous system. Since mercury is a potent inhibitor of protein kinase C (PKC) activity and phorbol ester binding to PKC (Rajanna et al., 1995), it is tempting to speculate that mercury might alter proteolytic processing of APP, because α-secretase processing by cleavage within the Aβ domain is readily increased by PKC (for review see: Nitsch and Growdon, 1994). Tissue culture experiments that are under way in our group, suggest that mercury decreases APPs secretion in a dose-dependent manner (Hock et al., in preparation).

Neurofibrillary tangles are another important histopathological hallmark of AD. Increased mercury concentration may interfere with microtubule assembly in that $HgCl_2$ markedly inhibits the ADP-ribosylation of tubulin and actin (Lorscheider et al., 1995). CSF levels of tau, however, were not correlated to blood levels of mercury in our study.

In summary, we found that blood mercury concentrations were more than two-fold higher in AD patients as compared to age-matched control patients with MD, or as compared to a group of control patients with various non-psychiatric disorders. Blood mercury levels positively correlated with CSF levels of Aβ. Increased mercury levels might interfere with the metabolism of proteins that play a role in the pathogenesis of AD. Possible explanations of increased blood mercury levels in AD patients include yet unidentified environmental sources or release from brain tissue with the advance in neuronal death.

Acknowledgements

C. Hock, MD, and F. Müller-Spahn, MD, are supported by the Schweizerischer Nationalfonds, grant no. 3200-043592.95/l. We thank D. Schenk, PhD, and C. Vigo-Pelfrey, PhD, Athena Neurosciences, South San Francisco, CA, for performing Aβ ELISAs and for stimulating discussions.

References

Basun H, Forssel LG, Wetterberg L, Winblad B (1991) Metals and trace elements in plasma and cerebrospinal fluid in normal aging and Alzheimer's disease. J Neural Transm [P-D Sect] 4: 231–258

Davies L, Wolska B, Hilbich C, Multhaup G, Martins K, Simms G, Beyreuther K, Masters CL (1988) A4 amyloid protein deposition and the diagnosis of Alzheimer's disease. Neurology 38: 1688–1693

Deibel MA, Ehmann WD, Markesbery WR (1996) Copper, iron, and zinc imbalances in severely degenerated brain regions in Alzheimer's disease – possible relation to oxidative stress. J Neurol Sci 143(1–2): 137–142

Drasch G, Schupp I, Höfl H, Reinke R, Roider G (1994) Mercury burden of human fetal and infant tissues. Eur J Pediatr 153: 607–610

Ehmann WD, Markesbery WR, Alauddin M, Hossain TIM, Brubaker EH (1986) Brain trace elements in Alzheimer's disease. Neurotoxicology 7(1): 197–206

Folstein MF, Folstein SE, McHugh PR (1975) Mini Mental State. A practical method for grading the cognitive state of patients for the clinician. J Psychiatry Res 12: 189–198

Fung YK, Meade AG, Rack EP, Blotcky AJ, Claassen JP, Beatty MW, Durham T (1995) Determinations of blood mercury concentrations in Alzheimer's patients. Clin Toxicol 33(3): 243–247

Halbach S (1994) Amalgam tooth fillings and man's mercury burden. Hum Exp Toxicol 13: 496–501

Hardy J (1996) New insights into the genetics of Alzheimer's disease. Ann Med 28(3): 255–258

Hock C, Golombowksi S, Naser W, Müller-Spahn F (1995) Increased levels of tau-protein in cerebrospinal fluid of patients with Alzheimer's disease – correlation with degree of cognitive impairment. Ann Neurol 37(3): 414–415

Kennard ML, Feldman H, Yamada T, Jefferies W (1996) Serum levels of the iron binding protein p97 are elevated in Alzheimer's disease. Nature Med 2(11): 1230–1235

Krause C, Chutsch M, Henke M, Huber M, Kliem C, Schulz C, Schwarz E (1989) Studienbeschreibung und Humbanbiologisches Monitoring. Umwelt-Survey, vol I. Institut für Wasser-, Boden- und Lufthygiene des Bundesgesundheitsamtes, Berlin

Lorscheider FL, Vimy MJ, Summers AO, Zwiers H (1995) The dental amalgam mercury controversy–inorganic mercury and the CNS; genetic linkage of mercury and antibiotic resistances in intestinal bacteria. Toxicology 97(1–3): 19–22

McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM (1984) Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. Neurology 34(7): 939–944

Nielsen JB, Andersen O, Grandjean P (1994) Evaluation of mercury in hair, blood and muscle as biomarkers for methylmercury exposure in male and female mice. Arch Toxicol 68(5): 317–321

Nitsch RM, Growdon JH (1994) Role of neurotransmission in the regulation of amlyoid β-protein precursor processing. Biochem Pharmacol 47(8): 1275–1284

Rajanna B, Chetty CS, Rajanna S, Hall E, Fail S, Yallapragada PR (1995) Modulation of protein kinase C by heavy metals. Toxicol Lett 81(2–3): 197–203

Rumble B, Retallack R, Hilbich M, Simms G, Multhaup G, Martins R, Hockey A, Montgomery P, Beyreuther K, Masters CL (1989) Amyloid A4 protein and its precursor in Down's syndrome and Alzheimer's disease. N Engl J Med 320(22): 1446–1452

Schaller KH (1985) Mercury. In: Angerer J, Schaller KH (eds) Analyses of hazardous substances in biological material – methods for biological monitoring, vol 2. VCH-Verlag, Weinheim, pp 195–207

Seubert P, Vigo-Pelfrey C, Esch F, Lee M, Dovey H, Davis D, Sinha S, Schlossmacher M, Whaley J, Swindlehurst C, McCormack R, Wolfert R, Selkoe DJ, Lieberburg I, Schenk D (1992) Isolation and quantification of soluble Alzheimer's β-peptide from biological fluids. Nature 359: 325–327

Steffens DC, Plassman BL, Helms MJ, Welsh-Bohmer KA, Saunders AM, Breitner JCS (1997) A twin study of late-onset depression and apolipoprotein E ε4 as risk factors for Alzheimer's disease. Biol Psychiatry 41: 851–856

Thompson CM, Markesbery WR, Ehmann WD, Mao YX, Vance DE (1988) Regional brain trace-element studies in Alzheimer's disease. Neurotoxicology 9: 1–8

Vandermeeren M, Mercken M, Vanmechelen E, Six J, van de Voorde A, Martin JJ, Cras P (1993) Detection of tau proteins in normal and Alzheimer's disease cerebrospinal fluid with a sensitive sandwich enzyme-linked immunosorbent assay. J Neurochem 61(5): 1828–1834

Authors' address: Dr. C. Hock, Department of Psychiatry (PUK), University of Basel, Wilhelm-Klein-Strasse 27, CH-4025 Basel, Switzerland.

Received August 10, 1997