



CSF tau and amyloid β_{42} levels in Alzheimer's disease—A meta-analysis

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ABSTRACT

Alzheimer's disease International (ADI) estimates that there are currently 30 million people with dementia in the world. The main objective was to perform meta-analysis of studies of CSF tau and Amyloid β_{42} ($A\beta_{42}$) levels in Alzheimer's disease (AD) patients and controls. In the present study MEDLINE was reviewed from 1995 to 2009, supplemented by citation analysis from retrieved articles to select case control studies. Descriptive statistics showed that median effect size (raw mean difference) of CSF tau and $A\beta_{42}$ levels were 301 pg/ml (Range: 22 to 614 pg/ml) and – 352 pg/ml (Range: – 969 to 203 pg/ml) respectively. The pooled effect size CSF tau and $A\beta_{42}$ was 289.14 pg/ml (95% CI 253.278 to 325.013 pg/ml) and – 329.02 pg/ml (95% CI – 387.740 to – 270.445 pg/ml) respectively. Heterogeneity in effect size of selected studies was present for both parameters (CSF tau: Q statistics = 1816.596, DF = 40, P = 0.000 and CSF $A\beta_{42}$: Q-statistics = 1259.358, DF = 24, p < 0.001). Based on the findings of meta-analysis in the present study, CSF tau and $A\beta_{42}$ levels in AD and controls may be considered as potential biomarker along with the clinical phenotype to perform them during high quality diagnostic testing in dementia.

KEYWORDS

Alzheimer's Disease; Dementia; CSF Amyloid β_{42} ; CSF Tau; Meta-Analysis

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References

- [1] Estimate of worldwide prevalence of Alzheimer's disease. <http://www.emaxhealth.com/91/12843.html>
- [2] Agarwal, R., Kushwaha, S.S. and Gupta, M. (2006) Role of biomarkers in diagnosis of Alzheimer's disease. *Indian Journal of Medical Biochemistry*, 10, 25-30.
- [3] Albert, M.S., DeKosky, S.T. and Dickson, D., et al. (2011) The diagnosis of mild cognitive impairment due to Alzheimer's disease: Recommendations from national institute on aging-Alzheimer's association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer's & Dementia*, 7, 270-279. doi: 10.1016/j.jalz.2011.03.008
- [4] Jack Jr., C.R., Albert, M.S. and Knopman, D.S., et al. (2011) Introduction to the recommendations from the national institute on aging-Alzheimer's association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer's & Dementia*, 7, 257-262. doi: 10.1016/j.jalz.2011.03.004
- [5] Fagan, A.M., Roe, C.M. and Xiong, C., et al. (2007) Cerebrospinal fluid tau/beta-amyloid (42) ratio as a prediction of cognitive decline in nondemented older adults. *Archives of Neurology*, 64, 343-349. doi: 10.1001/archneur.64.3.noc60123
- [6] Forman, M.S., Farmer, J. and Johnson, J.K., et al. (2006) Frontotemporal dementia: Clinicopathological correlations. *Annals of Neurology*, 59, 952-962. doi: 10.1002/ana.20873
- [7] Blennow, K. and Hampel, H. (2003) CSF markers for incipient Alzheimer's disease. *Lancet*

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- [8] McKahn, G.M., Knopman, D.S. and Chertkow, H., et al. (2011) The diagnosis of dementia due to Alzheimer' s disease: Recommendations from the national institute on aging-Alzheimer' s association workgroups on diagnostic guidelines for Alzheimer' s disease. *Alzheimer' s & Dementia*, 7, 263-269. doi:10.1016/j.jalz.2011.03.005
- [9] Blennow, K., Wallin, A. and Agren, H., et al. (1995) Tau protein in cerebrospinal fluid: a biochemical marker for axonal degeneration in Alzheimer' s disease? *Molecular and Chemical Neuropathology*, 26, 231-245. doi:10.1007/BF02815140
- [10] Vigo-Pelfrey, C., Seubert, P. and Barbour, R., et al. (1995) Elevation of microtubule-associated protein tau in the cerebrospinal fluid of patients with Alzheimer' s disease. *Neurology*, 45, 788-793. doi:10.1212/WNL.45.4.788
- [11] Andreasen, N., Hesse, C. and Davidsson, P., et al. (1999) Cerebrospinal fluid β -amyloid₍₁₋₄₂₎ in Alzheimer' s disease: Differences between early- and late- onset AD and stability during the course of disease. *Archives of Neurology*, 56, 673- 680. doi:10.1001/archneur.56.6.673
- [12] Motter, R., Vigo-Pelfrey, C. and Kholodenko, D., et al. (1995) Reduction of β -amyloid peptide₄₂ in the cerebrospinal fluid of patients with Alzheimer' s disease. *Annals of Neurology*, 38, 643-648. doi:10.1002/ana.410380413
- [13] Galasko, D., Clark, C. and Chang, L. et al. (1998) High cerebrospinal fluid tau and low amyloid β_{42} levels in the clinical diagnosis of Alzheimer' s disease and relation to apolipoprotein E genotype. *Archives of Neurology*, 55, 937-945. doi:10.1001/archneur.55.7.937
- [14] The Ronald & Nancy Reagen Research Institute of the Alzheimer' s Association & the National Institute on Aging Working Group (1998) Consensus report of the working group on: Biological markers of Alzheimer' s disease. *Neurobiology of Aging*, 19, 109-116. doi:10.1016/S0197-4580(98)00022-0
- [15] Frank, R.A., Galasko, D. and Hampel, H., et al. (2003) Biological markers for therapeutic trials in Alzheimer' s disease—Proceedings of the biological measures working group: NIA initiatives on neuroimaging in Alzheimer' s disease. *Neurobiology of Aging*, 24, 521-536. doi:10.1016/S0197-4580(03)00002-2
- [16] Andreasen, N., Hesse, C. and Davidsson, P., et al. (1999) Cerebrospinal fluid β -amyloid₍₁₋₄₂₎ in Alzheimer' s disease: Differences between early- and late- onset AD and stability during the course of disease. *Archives of Neurology*, 56, 673-680. doi:10.1001/archneur.56.6.673
- [17] Huedo-Medina, T.B. and Sanchez-Meca, J., et al. (2006) Assessing heterogeneity in meta-analysis: Q statistics or I² index? *Psychological Methods*, 11, 193-206. doi:10.1037/1082-989X.11.2.193
- [18] Begg, C.B., Cooper, H. and Hedges, L.V. (1994) *The handbook of research synthesis*. Russell Sage Foundation, New York.
- [19] Sunderland, T., Linker, G. and Mirza, N., et al. (2003) Decreased β -amyloid₍₁₋₄₂₎ and increased tau levels in cerebrospinal fluid of patients with Alzheimer' s disease. *Journal of the American Medical Association*, 289, 2094- 2103. doi:10.1001/jama.289.16.2094
- [20] Andreasen, N., Minthon, L. and Davidsson, P., et al. (2001) Evaluation of CSF-A β ₄₂ as diagnostic markers for Alzheimer' s disease in clinical practice. *Archives of Neurology*, 58, 373-379. doi:10.1001/archneur.58.3.373
- [21] Arai, H., Terajima, M. and Miura, M., et al. (1995) Tau in cerebrospinal fluid. *Annals of Neurology*, 38, 649-652. doi:10.1002/ana.410380414
- [22] Mori, H., Hosoda, K. and Matsubana, E., et al. (1995) Tau in cerebrospinal fluids. *Neuroscience Letters*, 186, 181-183. doi:10.1016/0304-3940(95)11291-4
- [23] Munroe, W.A., Southwick, P.C. and Chang, L., et al. (1995) Tau protein in cerebrospinal fluid as an aid in the diagnosis of Alzheimer' s disease. *Annals of Clinical Laboratory Science*, 25, 207-217.
- [24] Skoog, I., Vanmechelen, E. and Andreasson, L.A., et al. (1995) A population-based study of tau protein and ubiquitin in cerebrospinal fluid in 85 years olds. *Neurodegeneration*, 4, 433-442. doi:10.1006/neur.1995.0052
- [25] Tato, R.E., Frank, A. and Hernanz, A. (1995) Tau protein concentrations in cerebrospinal fluid of patients with dementia of the Alzheimer type. *Journal of Neurology, Neurosurgery and Psychiatry*,

- [26] Arai, H., Terajima, M. and Miura, M., et al. (1997) Effect of genetic risk factors and disease progression on the cerebrospinal fluid tau levels in Alzheimer' s disease. *Journal of the American Geriatrics Society*, 45, 1228- 1231.
- [27] Golombowski, S. and Muller-Spahn, F., et al. (1997) Dependence of cerebrospinal fluid Tau protein levels on apolipoprotein E4 allele frequency in patients with Alzheimer' s disease. *Neuroscience Letters*, 225, 213-215. doi: 10.1016/S0304-3940(97)00228-0
- [28] Andreasen, N., Vanmechelen, E., Van de Voorde, A., et al. (1998) Cerebrospinal fluid tau protein as a biochemical marker for Alzheimer' s disease. *Journal of Neurology, Neurosurgery and Psychiatry*, 64, 298-305. doi: 10.1136/jnnp.64.3.298
- [29] Arai, H., Satoh-Nakagawa, T. and Higuchi, M. et al. (1998) No increase in cerebrospinal fluid tau protein levels in patients with vascular dementia. *Neuroscience Letters*, 256, 174-176. doi: 10.1016/S0304-3940(98)00781-2
- [30] Kurz, A., Riemenschneider, M. and Buch, K. et al. (1998) Tau protein in cerebrospinal fluid is significantly increased at the earliest clinical stage of Alzheimer disease. *Alzheimer Disease and Associated Disorders*, 12, 372- 377. doi: 10.1097/00002093-199812000-00020
- [31] Mecocci, P., Cherubini, A. and Bregnocchi, M., et al. (1998) Tau protein in cerebrospinal fluid. *Alzheimer Disease and Associated Disorders*, 12, 211-214. doi: 10.1097/00002093-199809000-00015
- [32] Nishimura, T., Takeda, M. and Nakamura, Y., et al. (1998) Basic and clinical studies on the measurement of tau protein in cerebrospinal fluid as a biological marker for Alzheimer' s disease and related disorders. *Methods & Findings in Experimental & Clinical Pharmacology*, 20, 227- 235.
- [33] Shoji, M., Matsubara, E. and Kanai, M., et al. (1998) Combination assay of CSF tau, Abeta₍₁₋₄₀₎ and Abeta₁₋₄₂₍₄₃₎ as a biochemical marker of Alzheimer' s disease. *Journal of the Neurological Sciences*, 158, 134-140. doi: 10.1016/S0022-510X(98)00122-1
- [34] Kanai, M., Matsubara, E. and Isoe, K., et al. (1998) Longitudinal study of cerebrospinal fluid levels of tau, Abeta₁₋₄₀, and Abeta₁₋₄₂₍₄₃₎ in Alzheimer' s disease. *Annals of Neurology*, 44, 17-26. doi: 10.1002/ana.410440108
- [35] Andreasen, N., Minthon, L. and Clarberg, A., et al. (1999) Sensitivity, specificity, and stability of CSF-tau in AD in a community-based patient sample. *Neurology*, 53, 1488- 1494. doi: 10.1212/WNL.53.7.1488
- [36] Burger nee Buch, K. and Padberg, F., et al. (1999) Cerebrospinal fluid tau protein shows a better discrimination in young old (<70 years) than in old patients with Alzheimer' s disease compared with controls. *Neuroscience Letters*, 277, 21-24.
- [37] Green, A.J., Harvey, R.J. and Thompson, E.J., et al. (1999) Increased tau in the cerebrospinal fluid of patients with frontotemporal dementia and Alzheimer' s disease. *Neuroscience Letters*, 259, 133- 135. doi: 10.1016/S0304-3940(98)00904-5
- [38] Hampel, H., Teipel, S.J. and Padberg, F., et al. (1999) Discriminant power of combined cerebrospinal fluid tau protein and of the soluble interleukin-6 receptor complex in the diagnosis of Alzheimer' s disease. *Brain Research*, 823, 104-112. doi: 10.1016/S0006-8993(99)01146-4
- [39] Molina, L., Touchon, J. and Herpe, M., et al. (1999) Tau and apo E in CSF: Potential aid for discriminating Alzheimer' s disease from other dementias. *Neuroreport*, 10, 3491-3495. doi: 10.1097/00001756-199911260-00005
- [40] Kahle, P.J. Jakowec, M. and Teipel, S.J., et al. (2000) Combined assessment of tau and neuronal thread protein in Alzheimer' s disease CSF. *Neurology*, 54, 1498-1504. doi: 10.1212/WNL.54.7.1498
- [41] Kanemaru, K., Kameda, N. and Yamanouchi, H. (2000) Decreased CSF amyloid beta₄₂ and normal tau levels in dementia with Lewy bodies. *Neurology*, 54, 1875-1876. doi: 10.1212/WNL.54.9.1875
- [42] Sjogren, M., Minthon, L. and Davidsson, P., et al. (2000) CSF levels of tau, beta-amyloid₍₁₋₄₂₎ and GAP-43 in frontotemporal dementia, other types of dementia and normal aging. *Journal of Neural Transmission*, 107, 563-579. doi: 10.1007/s007020070079
- [43] Hampel, H., Buerger, K. and Kohnken, R., et al. (2001) Tracking of Alzheimer' s disease progression with cerebrospinal fluid tau protein phosphorylated at threonine 231. *Annals of Neurology*, 49, 545-

- [44] Itoh, N., Arai, H. and Urakami, K., et al. (2001) Largescale, multicenter study of cerebrospinal fluid tau protein phosphorylated at serine 199 for the antemortem diagnosis of Alzheimer' s disease. *Annals of Neurology*, 50, 150- 156. doi:10.1002/ana.1054
- [45] Rosler, N., Wichart, I. and Jellinger, K.A. (2001) Clinical significance of neurobiochemical profiles in the lumbar cerebrospinal fluid of Alzheimer' s disease patients. *Journal of Neural Transmission*, 108, 231-246. doi:10.1007/s007020170091
- [46] Shoji, M., Matsubara, E. and Murakami, T., et al. (2002) Cerebrospinal fluid tau in dementia disorders. *Neurobiology of Aging*, 23, 363-370. doi:10.1016/S0197-4580(01)00309-8
- [47] Sjogren, M., Davidsson, P., Wallin, A., et al. (2002) Decreased CSF-beta-amyloid₄₂ in Alzheimer' s disease and amyotrophic lateral sclerosis may reflect mismetabolism of beta amyloid induced by disparate mechanisms. *Dementia and Geriatric Cognitive Disorders*, 13, 112-118. doi:10.1159/000048642
- [48] Csernansky, J.G., Miller, J.P. and McKeel, D., et al. (2002) Relationships among cerebrospinal fluid biomarkers in dementia of the Alzheimer type. *Alzheimer Disease and Associated Disorders*, 16, 144-149. doi:10.1097/00002093-200207000-00003
- [49] Maddalena, A., Papassotiropoulos, A., Muller-Tillmanns, B., et al. (2003) Biochemical diagnosis of Alzheimer' s disease by measuring the cerebrospinal fluid ratio of phosphorylated tau protein to β -amyloid peptide₄₂. *Archives of Neurology*, 60, 1202-1206. doi:10.1001/archneur.60.9.1202
- [50] Grossman, M., Farmer, J. and Leight, S., et al. (2005) Cerebrospinal fluid profile in frontotemporal dementia and Alzheimer' s disease. *Annals of Neurology*, 57, 721- 729. doi:10.1002/ana.20477
- [51] Herukka, S.K., Hallikainen, M. and Soininen, H., et al. (2005) CSF A β ₄₂ and tau or phosphorylated tau and prediction of progressive mild cognitive impairment. *Neurology*, 64, 1294-1297. doi:10.1212/01.WNL.0000156914.16988.56
- [52] De Jong, D., Jansen, R.W.M., Kremer, B.P.H., et al. (2006) Cerebrospinal fluid amyloid β ₄₂/phosphorylated tau ratio discriminates between Alzheimer' s disease and vascular dementia. *Journal of Gerontology: Medical Sciences*, 61, 755-758. doi:10.1093/gerona/61.7.755
- [53] Bibl, M., Esselmann, H. and Mollenhauer, B., et al. (2007) Blood-based neurochemical diagnosis of vascular dementia: A pilot study. *Journal of Neurochemistry*, 103, 467- 474. doi:10.1111/j.1471-4159.2007.04763.x
- [54] Shaw, L.M., Vanderschueren, H., Knapik-Czajka, M., et al. (2009) Cerebrospinal fluid biomarker signature in Alzheimer' s disease neuroimaging initiative subjects. *Annals of Neurology*, 65, 403-413.
- [55] Thomann, P.A., Kaise, E. and Schonknecht, P., et al. (2009) Association of total tau and phosphorylated tau 181 protein levels in cerebrospinal fluid with cerebral atrophy in mild cognitive impairment and Alzheimer' s disease. *Journal of Psychiatry and Neuroscience*, 34, 136- 142.
- [56] Hulsaert, F., Blennow, K., Ivanoic, A., Schoonderwaldt, H.C., et al. (1999) Improved discrimination of AD patients using β -amyloid₍₁₋₄₂₎ and tau levels in CSF. *Neurology*, 52, 1555-1562. doi:10.1212/WNL.52.8.1555
- [57] Tamaoka, A., Sawamura, N. and Fukushima, T., et al. (1997) Amyloid beta protein 42(43) in cerebrospinal fluid of patients with Alzheimer' s disease. *Journal of Neurological Sciences*, 148, 41-45. doi:10.1016/S0022-510X(96)00314-0
- [58] Jensen, M., Schroder, J. and Blomberg, M., et al. (1999) Cerebrospinal fluid Abeta₄₂ is increased early in sporadic Alzheimer' s disease and declines with disease progression. *Annals of Neurology*, 45, 504-511. doi:10.1002/1531-8249(199904)45:4<504::AID-ANA12>3.0.CO;2-9
- [59] Fukuyama, R., Mizuno, T. and Mori, S., et al. (2000) Age-dependent change in the levels of Abeta₄₀ and Abeta₄₂ in cerebrospinal fluid from control subjects, and a decrease in the ratio of Abeta₄₂ to Abeta₄₀ level in cerebrospinal fluid from Alzheimer' s disease patients. *European Neurology*, 43, 155-160. doi:10.1159/000008156
- [60] Mehta, P.D., Pirtila, T. and Mehta, S.P., et al. (2000) Plasma and cerebrospinal fluid levels of amyloid beta proteins 1-40 and 1-42 in Alzheimer disease. *Archives of Neurology*, 57, 100-105. doi:10.1001/archneur.57.1.100

- [61] Otto, M., Esselmann, H. and Schulz-Shaeffer, W., et al. (2000) Decreased beta-amyloid₁₋₄₂ in cerebrospinal fluid of patients with creutzfeldt-jakob disease. *Neurology*, 54, 1099-1102. doi:10.1212/WNL.54.5.1099
- [62] Riemenschneider, M., Schmolke, M. and Lautenschlager, N., et al. (2000) Cerebrospinal beta-amyloid (1-42) in early Alzheimer' s disease: Association with apolipoprotein E genotype and cognitive decline. *Neuroscience Letters*, 284, 85-88. doi:10.1016/S0304-3940(00)00976-9
- [63] Mayeux, R., Tang, M.-X. and Stern, Y., et al. (2003) Plasma A β 40 and A β 42 and Alzheimer' s disease—Relation to age, mortality, and risk. *Neurology*, 61, 1185-1190. doi:10.1212/01.WNL.0000091890.32140.8F
- [64] Skoog, I., Davidsson, P., Aevarsson, O., Vanderstichele, H., Vanmechelen, E. and Blennow, K. (2003) Cerebrospinal fluid beta-amyloid₄₂ is reduced before the onset of sporadic dementia. *Dementia and Geriatric Cognitive Disorders*, 15, 169-176. doi:10.1159/000068478
- [65] van Harten, A.C., Kester, M.I., Visser, P.J., Blankenstein, M.A., Pijnenburg, Y.A.L., van der Flier, W.M. and Scheltens, P. (2011) Tau and p-tau as CSF biomarkers in de- mentia: A meta-analysis. *Clinical Chemistry and Laboratory Medicine*, 49, 353-366. doi:10.1515/cclm.2011.086
- [66] Ravaglia, S., Bini, P. and Sinforiani, E., et al. (2008) Cerebrospinal fluid levels of tau phosphorylated at threonine 181 in patients with Alzheimer' s disease and vascular dementia. *Neurological Sciences*, 29, 417-423. doi:10.1007/s10072-008-1023-1
- [67] Brockwell, S.E. and Gordon, R.I. (2001) A comparison of statistical methods for meta-analysis. *Statistics in Medicine*, 20, 825-840. doi:10.1002/sim.650
- [68] Erez, A., Bloom, M.C. and Wells, M.T. (1996) Using random rather than fixed effect models in meta-analysis: Implications for situational specificity and validity generalization. *Personnel Psychology*, 49, 275-306. doi:10.1111/j.1744-6570.1996.tb01801.x
- [69] Hunter, J.E. and Schmidt, F.L. (2000) Fixed effects vs random effects meta-analysis models: Implications for cumulative research knowledge. *International Journal of Selection & Assessment*, 8, 275-292. doi:10.1111/1468-2389.00156
- [70] Field, A.P. (2003) The problems in using fixed effect models of meta-analysis on real world data. *Understanding statistics*, 2, 77-96. doi:10.1207/S15328031US0202_02
- [71] Borenstein, M., Higgins, J.P., Rothstein, H.R. and Sutton, A.J. (2009) Introduction to meta-analysis. John Wiley & Sons, Ltd., Hoboken, 277-278. doi:10.1002/9780470743386.ch30
- [72] Kapaki, E., Paraskevas, G.P., Zalonis, I., et al. (2003) CSF tau protein and β -amyloid (1- 42) in Alzheimer' s disease diagnosis: Discrimination from normal ageing and other dementias in the Greek population. *European Journal of Neurology*, 10, 119-128. doi:10.1046/j.1468-1331.2003.00562.x
- [73] Hock, C., Golombowski, S. and Naser, W., et al. (1995) Increased levels of tau protein in cerebrospinal fluid of patients with Alzheimer' s disease—Correlation with degree of cognitive impairment. *Annals of Neurology*, 37, 414-415. doi:10.1002/ana.410370325
- [74] Skoog, I., Vanmechelen, E. and Andreasson, L.A., et al. (1996) A population-based study of tau protein and ubiquitin in cerebrospinal fluid in 85-year-olds. *Neuroscience Letters*, 214, 163-166.
- [75] Schmand, B., Huizenga, H.M. and van Gool, W.A. (2010) Meta-analysis of CSF and MRI biomarkers for detecting preclinical Alzheimer' s disease. *Psychological Medicine*, 40, 135-145. doi:10.1017/S0033291709991516
- [76] Sharpe, D. (1997) Of apples and oranges, file drawers and garbage: Why validity issues in meta-analysis will not go away. *Clinical Psychology Review*, 17, 881-901. doi:10.1016/S0272-7358(97)00056-1