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Five out of 16 plasma signaling proteins are enhanced in plasma of patients with mild cognitive impairment and Alzheimer's disease[☆]

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Abstract

Alzheimer's disease (AD) is a progressive neurodegenerative disorder with characteristic neuropathological changes of the brain. Great efforts have been undertaken to determine the progression of the disease and to monitor therapeutic interventions. Especially, the analysis of blood plasma had yielded incongruent results. Recently, Ray et al. identified changes of 18 signaling proteins leading to an accuracy of 90% in the diagnosis of AD. The aim of the present study was to examine 16 of these signaling proteins by quantitative Searchlight multiplex ELISA in order to determine their sensitivity and specificity in our plasma samples from AD, mild cognitive impairment (MCI), depression with and without cognitive impairment and healthy subjects. Quantitative analysis revealed an increased concentration in Biocoll isolated plasma of 5 out of these 16 proteins in MCI and AD patients compared to healthy subjects: EGF, GDNF and MIP1 δ (in AD), MIP4 (in MCI) and RANTES (in MCI and AD). ROC analysis predicted a sensitivity of 65–75% and a specificity of 52–63% when comparing healthy controls versus MCI or AD. Depression without any significant cognitive deficits did not cause any significant changes. Depressed patients with significant cognitive impairment were not different from MCI patients. In conclusion, we detected a number of altered proteins that may be related to a disease specific pathophysiology. However, the overall expression pattern of plasma proteins could not be established as a biomarker to differentiate MCI from AD or from depression.

Keywords

Diagnosis; Blood; Plasma; Biomarker; Alzheimer; Mild cognitive impairment; Dementia; Multiplex ELISA

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.neurobiolaging.2009.03.011.

Patients were recruited from an outpatient clinic located at the Department of Psychiatry in Innsbruck, Austria. The study was approved by the local ethical committee. Healthy controls, patients with mild cognitive impairment or Alzheimer's disease and patients with depression with or without cognitive impairment were diagnosed according to international standards. Blood was collected, centrifuged on a Biocoll gradient and the plasma was frozen. The detection of 16 biomarkers was performed using the Thermo Scientific SearchLight Protein Array Technology (THP Medical Products, Vienna). Statistical analysis was performed by One Way ANOVA and receiver-operating characteristic (ROC) analysis.

Healthy controls ($n = 19$) had an age of 72.1 ± 1.3 years and a MMSE of 28.4 ± 0.3 . The mean ($\pm$ SEM) plasma control levels of the 16 measured biomarkers were (in pg/ml): ANG-2: 2168 ± 534 ; EGF: 2.4 ± 0.5 ; G-CSF: 7.8 ± 1.4 ; GDNF: 10.8 ± 2.1 ; ICAM1: $242,370 \pm 28,580$; IL1 α : 3.2 ± 0.4 ; IL3: 8.1 ± 0.7 ; IL8 (CXCL8): 2.3 ± 0.5 ; IL11: 16.6 ± 1.9 ; MCP3 (CCL7): 3.3 ± 0.6 ; M-CSF: 1680 ± 416 ; MIP1 δ (CCL15): 3890 ± 510 ; MIP4 (CCL18): $65,900 \pm 9300$; PDGF-BB: 228 ± 65 ; RANTES (CCL5): 9823 ± 2418 and TNF α : 9.5 ± 0.7 . No statistically significant difference was observed in any of the 16 measured plasma biomarkers between non-depressive healthy controls and depressive patients without cognitive impairment ($n = 16$) without any other neurological or psychiatric disorder. In MCI two proteins out of those 16 tested biomarkers were significantly increased compared to healthy controls: MIP4 and RANTES (Table 1). Out of 16 measured biomarkers 4 were significantly elevated in AD compared to healthy controls: EGF, GDNF, MIP1 δ and RANTES (Table 1). When healthy controls and depressive patients without cognitive impairment were pooled in addition also ICAM1 and MIP1 δ were enhanced in MCI and TNF α in MCI and AD (Table 1). Depressive patients with cognitive impairment were not different from MCI patients (Table 1). ROC analysis yielded a sensitivity of 75% and a specificity of 63% to discriminate healthy controls from MCI patients. Discrimination between healthy controls and AD subjects was somewhat lower showing a sensitivity of 66% and a specificity of 53%. No useful discrimination between MCI and AD patients was seen (60% sensitivity and 59% specificity).

In the present study, we detected significant increases in the expression levels in 5 out of 16 proteins in AD and MCI: EGF, GDNF, MIP1 δ , MIP4 and RANTES. The protein expression profile revealed that certain proteins were significantly increased in MCI and AD. In general, neither MCI patients, AD patients or patients suffering from depression with cognitive impairment exhibited a protein expression profile that was specific and sensitive enough to be used as diagnostic biomarkers.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Table 1

Plasma biomarkers in mild cognitive impairment (MCI), Alzheimer's disease (AD), depression with or without cognitive impairment (CI).

	Mild cognitive impairment			Alzheimer's disease			Depression + CI			Depression		
	Mean	Median	p1	Mean	Median	p2	Mean	Median	p3	Mean	Median	p1
<i>n</i>	44			96	26	16						
Age	73.5 ± 1.2			77.0 ± 0.8*	71.0 ± 1.6	69.1 ± 1.6 ns						
MMSE	27.1 ± 0.2			18.8 ± 0.6*	24.8 ± 0.6	29.3 ± 0.1 ns						
	Mild cognitive impairment			Alzheimer's disease			Depression + CI			Depression		
	Mean	Median	p1	Mean	Median	p2	Mean	Median	p3	Mean	Median	p1
EGF	106 ± 12	75	ns	181 ± 16	81	0.015	68 ± 14	67	ns	179 ± 32	122	ns
G-CSF	186 ± 30	166	ns	167 ± 18	125	ns	181 ± 27	138	ns	67 ± 16	69	ns
GDNF	134 ± 12	203	ns	239 ± 14	221	0.044	305 ± 36	295	ns	99 ± 26	68	ns
ICAM1	121 ± 4	134	0.054	111 ± 4	122	ns	108 ± 8	110	ns	94 ± 9	136	ns
IL1α	105 ± 5	113	ns	108 ± 5	112	ns	112 ± 11	105	ns	97 ± 13	123	ns
IL3	94 ± 6	106	ns	94 ± 4	90	ns	91 ± 6	93	ns	129 ± 19	139	ns
IL8	266 ± 45	205	ns	257 ± 26	226	ns	138 ± 24	195	ns	246 ± 34	150	ns
IL11	78 ± 4	94	ns	88 ± 4	95	ns	97 ± 13	110	ns	138 ± 31	111	ns
MCP3	116 ± 11	165	ns	143 ± 15	157	ns	126 ± 13	144	ns	77 ± 20	67	ns
M-CSF	113 ± 18	107	ns	86 ± 7	101	ns	84 ± 12	101	ns	81 ± 22	113	ns
MIP1δ	123 ± 7	128	ns	134 ± 5	145	0.032	128 ± 8	149	ns	105 ± 17	101	ns
MIP4	138 ± 8	169	0.016	124 ± 7	127	ns	179 ± 31	136	ns	118 ± 18	134	ns
PDGF-BB	142 ± 16	139	ns	129 ± 10	138	ns	104 ± 17	95	ns	96 ± 23	152	ns
RANTES	212 ± 22	131	0.013	237 ± 16	148	0.026	183 ± 23	161	ns	88 ± 22	110	ns
TNFα	150 ± 7	140	ns	158 ± 7	145	0.007	188 ± 11	173	ns	81 ± 11	86	ns

Plasma biomarkers were analyzed by Searchlight Multiplex ELISA as described in Methods. Values are presented as % of controls. Statistical analysis: p1, versus healthy control (*n* = 19); p2, versus mixed controls and depression (*n* = 35); p3, versus MCI. Statistical significance *p* < 0.05 (* or bold values).