Dementia
and Geriatric
Cognitive Disorders

Dement Geriatr Cogn Disord 2016;41:273–280
DOI: 10.1159/000446275
Accepted: April 16, 2016
Published online: June 16, 2016

1420–8008/16/0416–0273$39.50/0
www.karger.com/dem

Original Research Article

Serum Soluble Tumor Necrosis Factor-Related Apoptosis-Inducing Ligand Levels in Older Subjects with Dementia and Mild Cognitive Impairment

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Key Words
Circulating TRAIL · Late-onset Alzheimer's disease · Vascular dementia · Mild cognitive impairment

Abstract
Background: The tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) has been involved in both physiological and pathological conditions, including vascular pathologies and pathologies of the central nervous system. Nonetheless, the knowledge about the role of systemic TRAIL in patients affected by different types of dementia and mild cognitive impairment (MCI) is still limited. ***Objective:*** We assessed serum TRAIL levels in a large cohort of older individuals (n = 644) including patients with late-onset Alzheimer's disease (LOAD), vascular dementia (VAD), 'mixed' dementia (MIX), MCI, and healthy controls. ***Methods:*** Circulating TRAIL was measured by ELISA. ***Results:*** At univariate analysis, TRAIL levels were higher in VAD, MIX, and MCI patients compared with LOAD patients and controls. Using the multiple linear regression model, we found that TRAIL levels were associated with VAD and MCI, but not MIX, independent of potential confounding factors. ***Conclusion:*** The finding of high levels of circulating TRAIL in VAD and MCI seems to suggest that both of these conditions are characterized by a significant vascular damage with respect to LOAD.

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Introduction

Late-onset Alzheimer's disease (LOAD) and vascular dementia (VAD) are the two most common forms of dementia in older individuals living in Western countries [1, 2], and inflammatory mechanisms have already been linked to their pathogenesis [3–6]. We have previously observed that older individuals affected by LOAD or VAD are characterized by increased serum levels of IL-1β and TNF-α, independent of potential confounders [7]. Interestingly, the pattern of systemic inflammation observed in LOAD and VAD was similar, but not identical since IL-6 levels were higher in VAD compared with LOAD [7].

Soluble tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) is a member of the TNF ligand superfamily expressed as a type II transmembrane protein with an extracellular domain that can be cleaved and act as soluble cytokine [8]. Experimental evidence suggests that soluble TRAIL is active on normal cells, including vascular cells [9–12]. It has been demonstrated that this cytokine is not typically expressed in the central nervous system (CNS) of healthy subjects, and that the different TRAIL receptors are differently distributed among the CNS-resident cell types. Emerging data show that TRAIL can be induced by immune stimuli on macrophages and microglia, and may be involved in neuronal apoptosis through direct interaction with TRAIL receptors on neurons or through macrophage death-mediated release of neurotoxins [13]. TRAIL expression is induced on neurons by β-amyloid protein, the most important triggering factor for Alzheimer's disease (AD) [14]; similarly, it has been demonstrated that TRAIL is involved in the pathogenesis of several CNS disorders, including AD [15]. In particular, TRAIL is specifically expressed in the brain of AD patients, while it is absent in the brain of non-demented subjects [16]. Moreover, the contribution of TRAIL to β-amyloid protein neurotoxicity has been demonstrated in vitro, showing that a TRAIL-neutralizing monoclonal antibody protects neuronal cells from neurotoxicity [17], and that exposure of neuronal cells to TRAIL led to cell death, suggesting a direct neurotoxic effect of TRAIL [17]. In this context, a previous study reported that serum TRAIL levels of AD patients were not different from those of healthy controls; in the same study, TRAIL was not found in the cerebrospinal fluid of both controls and AD patients [18]. At present, very few data are available about the possible role of systemic TRAIL levels in patients affected by dementia. In order to clarify this issue, we evaluated the circulating TRAIL levels in a large cohort of older individuals including patients affected by different types of dementia [LOAD, VAD, and 'mixed' dementia (MIX)], patients with mild cognitive impairment (MCI), and healthy controls.

Methods

Subjects

Six hundred and forty-four consecutive subjects referring to the Day Service for Cognitive Decline (University Hospital of Ferrara, Ferrara, Italy) from 2007 to 2014 were enrolled and divided into groups as described below.

Group 1 consisted of 168 elderly patients with LOAD by the NINCDS-ADRDA criteria [19]. Only patients with 'probable' AD were included. The Global Deterioration Scale ranged from stage 3 to 6.

Group 2 consisted of 63 elderly patients with VAD by the NINDS-AIREN criteria [20]. Only patients with 'probable' VAD were included. The Global Deterioration Scale ranged from stage 4 to 6.

Group 3 consisted of 106 older patients with MIX. In these patients, a definite diagnosis of probable VAD or LOAD was not possible since both clinical characteristics of LOAD and VAD were present. In particular, while the CT scan or MRI demonstrated significant cerebrovascular disease, the evolution of the symptoms was slow and progressive. The Global Deterioration Scale ranged from stage 4 to 6.

Group 4 consisted of 251 older subjects with MCI [21] defined as the presence of short-/long-term memory impairment with/without impairment in other single or multiple cognitive domains, in individuals who did not meet the standardized criteria for dementia. An additional requirement for MCI patients was

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independency in the instrumental activities of daily living. The majority of these individuals were affected by amnestic multidomain MCI. Subjects with MCI due to recognized causes (e.g. major depression and severe vitamin B_{12} deficiency) were excluded.

Group 5 consisted of 56 normal older individuals (controls) without evidence of dementia and without any disability attributable to cognitive impairment.

All subjects (and/or their caregivers) were informed in detail about the research project and research protocols, and gave their written consent to participate in the study. The study was carried out according to the Declaration of Helsinki (World Medical Association, http://www.wma.net) and the guidelines for Good Clinical Practice (European Medicines Agency, http://www.ema.europa.eu).

Clinical Evaluations

The diagnosis of dementia was made by trained geriatricians. Personal data and medical history were collected by interviewing patients and caregivers. All patients underwent a general and neurological examination. For neuropsychological assessment, all subjects were given a battery of tests as previously described [7]. The basic activities of daily living were evaluated using the Barthel Index (BI) [22]. Instrumental activities of daily living were evaluated using a modified version of the Lawton Brody Scale [23]. Clinical chemistry analyses were routinely performed to exclude other causes of cognitive impairment, including serum B_{12} vitamin, serum folate, liver, kidney, and thyroid function tests, complete blood cell count, and arterial oxygen saturation. Subjects affected by severe congestive heart failure, severe liver or kidney disease, severe chronic obstructive pulmonary disease (COPD) and cancer were excluded. There was no evidence of acute illnesses at the time of clinical observation and blood sampling. No subject was taking NSAIDS, antibiotics or steroids at the time of recruitment. The diagnoses of diabetes, hypertension, and cardiovascular disease were performed as described previously [7]. Smokers were defined as patients with present/previous significant smoking history (>10 packs/years).

Brain CT Scan

All subjects underwent brain CT by using a 64-slice volumetric scanner (GE LightSpeed VCT). The reconstructed slice thickness was 5 mm. CT images were evaluated by 2 trained radiologists. The CT scan information supported the clinical diagnosis and the evaluation of the presence of brain pathologies associated with cognitive impairment (e.g. cerebrovascular disease and normal pressure hydrocephalus). When necessary, subjects underwent brain MRI (Philips Achieva 1.5 T).

Evaluation of Biochemical Parameters

Venous blood was collected upon overnight fast, centrifuged at 3,000 rpm for 10 min, and serum was stored in aliquots at –80°C. Total and high-density lipoprotein (HDL) cholesterol was determined using an enzymatic colorimetric method (Roche Diagnostics, Mannheim, Germany; sensitivity: 3 mg/dl). Low-density lipoprotein (LDL) cholesterol was estimated using the Friedewald equation. Triglycerides were determined using an enzymatic colorimetric method (Roche Diagnostics; sensitivity: 4 mg/dl). Glycemia was measured using an enzymatic colorimetric method based on the Trinder reaction [Far, Verona, Italy; sensitivity: 3 mg/dl; intra- and interassay coefficients of variation (CV) were 2.5 and 2.7 respectively]. High-sensitivity C-reactive protein (hsCRP) was measured using an enzymatic colorimetric method (Roche Diagnostics; sensitivity: 0.03 mg/l; intra- and interassay CV were 0.8 and 4.1, respectively). Circulating TRAIL was measured using an ELISA kit (R&D Systems, Minneapolis, Minn., USA; sensitivity: 2.9 pg/ml; intra- and interassay CV were 3.9 and 6%, respectively), as previously described [24]. Selected serum samples were run in each ELISA plate as internal controls.

Statistical Analyses

Data were expressed as mean (standard deviation) or median (interquartile range) when necessary. Means were compared by ANOVA (Bonferroni post hoc test). Medians were compared by the Kruskal-Wallis test. Prevalence was compared by the Fisher exact test. The association between TRAIL serum levels and cognitive diagnosis in the five groups was tested by multivariate linear regression analysis after adjusting for age, gender, total cholesterol, triglycerides, hsCRP, creatinine, previous stroke, COPD, cognitive performance (Mini-Mental State Examination – MMSE score), and functional status (BI).

Table 1. Principal characteristics of the subjects divided according to cognitive diagnosis

Parameter	Controls (n = 56)	VAD (n = 63)	LOAD (n = 168)	MIX (n = 106)	MCI (n = 251)	p
Age, years[a]	74 [67; 79]	79 [75; 84]	79 [75; 83]	81 [78; 84]	77 [73; 80]	<0.001
Males, n	18 (32)	28 (44.5)	46 (27)	34 (32)	103 (41)	0.024
Education, years[a]	8 [5; 12]	5 [3; 7]	5 [3; 5]	5 [4; 8]	5 [5; 8]	<0.001
Smoking habit						0.56
Never, n	32 (57.1)	34 (53.9)	106 (64.2)	57 (55.3)	129 (51.8)	
Previous, n	18 (32.1)	23 (36.5)	47 (28.4)	37 (35.9)	95 (38.1)	
Current, n	6 (10.7)	6 (9.5)	1 (7.2)	9 (8.7)	25 (10.0)	
MMSE, /30[a]	27.0 [26; 28.9]	21.5 [19.0; 24]	20.9 [18.4; 23.5]	20.7 [18.0; 23.4]	24.4 [22.3; 26.6]	<0.001
BI, /100[a]	100 [98; 100]	95.5 [80; 100]	98 [83; 100]	95.5 [82; 98]	100 [94; 100]	<0.001
Lawton-Brody scale, /19[a]	19 [18; 19]	11.5 [8; 17]	12 [9; 16]	11.5 [9; 14]	17 [13; 19]	<0.001
Hemoglobin, g/dl	13.4±1.2	13.1±1.6	13.1±1.4	13.2 ±1.4	13.3±1.4	0.59
Creatinine, mg/dl[a]	0.81 [0.78; 1.00]	1.10 [0.89; 1.30]	0.90 [0.76; 1.10]	0.90 [0.77; 1.10]	0.90 [0.78; 1.10]	0.002
Albumin, g/dl[a]	4.2 [3.9; 4.4]	4.0 [3.8; 4.3]	4.1 [3.9; 4.3]	4.0 [3.8; 4.2]	4.0 [3.8; 4.3]	0.06
Uric acid, mg/dl	4.3±1.2	5.2±1.6	5.0±1.5	5.2±1.7	5.2±1.5	0.11
Total cholesterol, mg/dl	207±34.9	207±39.4	213±41.9	204±38.7	209±41.2	0.47
Triglycerides, mg/dl[a]	100 [81.5; 130]	117 [86; 155]	100 [82; 142]	107 [85; 133]	109 [82; 149]	0.32
HDL cholesterol, mg/dl	63±17	59.5±16	62±16	60±16	59.5 ±16	0.43
LDL cholesterol, mg/dl	124±32	124±35	128±35	121±34	12±36	0.53
Fasting glucose, mg/dl[a]	93 [86; 108]	92 [86; 103]	95 [87; 105]	95.5 [84; 108]	96.5 [87; 111]	0.93
hsCRP, mg/l[a]	0.13 [0.07; 0.21]	0.30 [0.11; 0.63]	0.17 [0.08; 0.4]	0.18 [0.1; 0.38]	0.19 [0.1; 0.445]	0.05
Hypertension, n	33 (58.9)	44 (69.8)	106 (63.1)	70 (66)	158 (62.9)	0.75
CHD, n	7 (12.5)	15 (23.8)	21 (12.5)	18 (16.9)	39 (15.5)	0.28
Diabetes, n	10 (17.8)	17 (26.9)	22 (13.1)	17 (16.0)	39 (15.5)	0.15
Previous stroke, n	1 (1.7)	10 (15.8)	0	7 (6.6)	16 (6.3)	<0.001
COPD, n	2 (3.6)	4 (6.3)	17 (10.1)	9 (8.5)	23 (9.1)	0.58
TRAIL, pg/ml[a]	62.4 [54.5; 76.0]	73.4 [56.0; 90.8]	67.5 [52.2; 87.3]	73.1 [61.2; 90.4]	74.9 [59.8; 97.3]	<0.009

CHD = Coronary heart disease. Figures in parentheses indicate percentages. [a] Median [interquartile range].

Results

The main characteristics of patients according to the cognitive diagnosis are reported in table 1. As expected, the MMSE, BI, and Lawton-Brody scale scores were lower in patients with dementia compared with controls and MCI patients. Serum creatinine was higher in the VAD group compared with other groups, while hsCRP was higher in the VAD group compared with controls. There were no significant differences in total LDL and HDL cholesterol, triglyceride, uric acid, fasting glucose, or hemoglobin levels (table 1). Moreover, no significant differences were noted in the prevalence of hypertension, coronary heart disease, diabetes, or COPD. A history of previous stroke was more frequent among subjects with VAD or MCI (table 1). Finally, serum TRAIL levels were significantly higher in VAD, MIX, and MCI patients compared with controls and LOAD patients.

When the sample was analyzed according to serum TRAIL tertiles (see online suppl. table 1, for all online suppl. material, see www.karger.com/doi/10.1159/000446275), a significant trend toward a lower prevalence of male gender in the III tertile (TRAIL levels >82.0 pg/ml) was observed, while no associations were found with age, formal education or smoking habit, or MMSE, BI or Lawton-Brody scale scores. In agreement with a previous study [25], uric acid, total cholesterol, and triglycerides were higher in subjects belonging to the III TRAIL tertile. In contrast with a previous report [26], hemoglobin, creatinine, albumin,

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Table 2. Multiple linear regression model for TRAIL serum levels

Variable	Coefficient	95% CI	p
Diagnosis			0.02
VAD	16.21	2.37; 30.05	
LOAD	5.31	–6.51; 17.12	
MIX	8.87	–4.03; 21.78	
MCI	13.26	3.20; 23.32	
Male gender	–10.80	–17.30; –4.31	0.001
Age	–0.122	–0.575; 0.331	0.59
Total cholesterol	0.018	–0.058; 0.094	0.63
Triglycerides	0.025	–0.031; 0.081	0.37
hsCRP	–1.70	–4.14; 0.74	0.17
Creatinine	6.32	–1.29; 13.92	0.10
Stroke	–5.71	–17.92; 6.50	0.35
COPD	–12.45	–22.32; –2.57	0.01
MMSE score	0.566	–0.200; 1.331	0.14
BI score	0.027	–2.10; 2.15	0.98

HDL and LDL cholesterol, fasting glucose and hsCRP were not associated with serum TRAIL levels. Concerning comorbidities, the prevalence of COPD was inversely associated with TRAIL levels, as previously reported [27]. Of interest, TRAIL levels were significantly correlated with total cholesterol ($r = 0.11$; $p = 0.002$), triglycerides ($r = 0.11$; $p = 0.003$), LDL cholesterol ($r = 0.07$; $p = 0.05$), and uric acid ($r = 0.14$; $p = 0.049$). Finally, the multiple linear regression analysis for TRAIL levels highlighted that the diagnosis of VAD and MCI were associated with TRAIL levels, independent of several potential confounders (table 2).

Discussion

In the present study, we analyzed the circulating levels of TRAIL in a sample of 644 older individuals, including patients affected by different types of dementia and MCI, and controls. The first interesting finding is that TRAIL was not increased in LOAD, confirming in a much larger sample the previous preliminary observation reported by Genc et al. [18]. Our results suggest that, although TRAIL might be implicated in the pathogenesis of LOAD [14–16], its involvement might be limited to the CNS through the local production of TRAIL by resident cells, in the absence of a systemic contribution. The second interesting finding is the evidence that MCI patients show increased systemic TRAIL levels. MCI has been considered a prodromal phase of dementia, although less than 40% of MCI subjects convert to dementia after 10 years of follow-up [28]. Depending on its pathogenesis, MCI may therefore convert to different types of dementia including LOAD and VAD; unfortunately, data about the possible conversion to dementia were not available at the time of the study. Since in our sample the majority of MCI cases had 'amnestic multidomain' MCI, a condition that may progress to LOAD or VAD, the finding of higher levels of serum TRAIL seems to indicate that MCI might be a pathological condition much closer to VAD than LOAD, at least in our sample. This might theoretically depend on the higher prevalence of previous stroke in the MCI group (similar to MIX); however, TRAIL levels were not higher in MCI patients with previous stroke (data not shown). More generally, by highlighting the possible link between TRAIL and the diagnosis of MCI [29–31], our data might support previous results of other groups underlining the important role of vascular factors in the pathogenesis of cognitive impairment in the elderly, independent of the final etiological diagnosis.

The finding of higher levels of TRAIL in VAD compared with controls also deserves a particular comment. By definition, VAD represents a dementia syndrome caused by a damage of the CNS secondary to a deficit in blood supply. Most frequently, this deficit is due to impairment of the large cerebral arteries and/or of the small perforating arteries supplying blood to white matter and basal nuclei. TRAIL concentrations have been associated with several vascular risk factors [32, 33] that, in turn, have been associated with VAD and ischemic stroke [34]. Although the mechanisms of this association have not been clarified, we could confirm in our sample a positive significant correlation between TRAIL and LDL cholesterol, triglycerides, and uric acid. However, it has to be underlined that: (a) the association between TRAIL concentrations and VAD diagnosis was independent of these risk factors at multivariate analysis, and (b) these risk factors were not different between the groups, at least at the time of our observation. On the other hand, higher TRAIL levels might represent a sort of an adaptive mechanism aiming at counteracting atherosclerosis and systemic inflammation (confirmed in VAD patients by increased hsCRP values), which represent two main physiopathological features of VAD. In this context, we have previously shown that circulating TRAIL has protective effects on the vascular system [35]. Experimental studies have indeed demonstrated that TRAIL may exert antiatherosclerotic and anti-inflammatory activity both in vitro and in animal models [36]. Overall, the different findings about the systemic concentration of TRAIL seem to underline some important differences in the pathogenesis of LOAD and VAD. More intriguing is the observation that in MIX, TRAIL levels are as high as in VAD, although serum TRAIL levels were not independently associated with this diagnosis at multivariate analysis. This finding might suggest that MIX is actually a clinical condition different from VAD and LOAD or, alternatively, that other factors might mediate the association between TRAIL and this diagnosis.

In conclusion, although we are aware of the limitations of the study (the cross-sectional design does not allow to infer a cause-effect relationship), to our knowledge, this is the first study reporting serum TRAIL levels in a large sample of older patients with LOAD, VAD, MIX, and MCI. Our results show that circulating TRAIL levels are increased in VAD but not in LOAD, underlying some physiopathological differences between these two forms of dementia. Moreover, although the lack of data about possible conversion of MCI to dementia did not allow us to speculate further, the evidence that circulating TRAIL levels are increased in MCI represents an issue that definitely deserves further investigation.

Acknowledgments

This work was supported by Regione Emilia Romagna (Programma di ricerca Regione-Università 2010–2012, Area 1-Strategic Programme, Thematic Area of Rehabilitation, Project PRUA1RI-2012-005).

Disclosure Statement

The authors declare that there are no conflicts of interest regarding the publication of this article.

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Filename: DEM446275
Article-No: 446275, Fig.: 0, Tab.: 2
<Issueid>5-6</Issueid>
Suppl. Materials

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<BezNr>366098</BezNr><I>S.</I><F>Stefano</F><S>Volpato</S><F16_Sup>c</F16_Sup>
<BezNr>366099</BezNr><I>A.</I><F>Amedeo</F><S>Zurlo</S><F16_Sup>d</F16_Sup>
<BezNr>366100</BezNr><I>G.</I><F>Giorgio</F><S>Zauli</S><F16_Sup>a</F16_Sup>
<BezNr>366101</BezNr><I>P.</I><F>Paola</F><S>Secchiero</S><F16_Sup>a</F16_Sup>
<BezNr>366102</BezNr><I>G.</I><F>Giovanni</F><S>Zuliani</S><F16_Sup>c</F16_Sup>