CSF YKL-40 and GAP-43 are related to suicidal ideation in older women

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Running title: CSF YKL-40 and GAP-43 are related to suicidality

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Abstract

Objective: To investigate possible relationships between suicidal ideation and cerebrospinal fluid (CSF) levels of gliamarkers YKL-40 (also known as chitinase-3-like protein 1), growth-associated protein-43 (GAP-43) and myelin basic protein (MBP).

Method: The sample was obtained from the Prospective Population Study of Women and included 86 women without dementia who underwent both psychiatric examinations and lumbar puncture (LP). Eight of these women reported past month suicidal ideation.

Results: Significantly higher CSF levels of both YKL-40 and GAP-43 were detected in women with past month suicidal ideation. Associations with suicidal ideation remained for both YKL-40 and GAP-43 in regression models adjusted for smoking status, BMI and age. CSF levels of YKL-40, GAP-43 and MBP did not differ by depression status. Higher levels of CSF GAP-43 were associated with feelings of worthlessness; a strong relationship was demonstrated in the fully adjusted model (OR 5.95 CI [1.52-23.20], *P*=0.01).

Conclusion: Our findings of elevated CSF concentrations of both YKL-40 and GAP-43 in women with suicidal ideation, compared to those without, suggest that a disrupted synaptic-glial functioning and inflammation may be related to the etiology of suicidal ideation in older adults.

Key words: suicide, depression, old age

Significant outcomes

- In a population-based sample of women, higher CSF levels of GAP-43 and YKL-40 were observed in those with suicidal ideation, compared to those without.
- Associations remained in models adjusted for smoking status, BMI and age.
- Relationships could not be explained by depression status.

Limitations

- The sample consists of older adult women and cannot be extrapolated to other populations.
- Albeit the number of participants with CSF data being relatively large, the number of cases with suicidal ideation was limited, reflecting the population-based study design.
- The study design limits the possibility to draw conclusions about directionality since we have CSF data from one time point only and some of the women may have had episodes of suicidal behavior prior to baseline.

Introduction

According to the World Health Organization, over 800 000 people die by suicide each year (1). High suicide rates are observed in older adults in most parts of the world, yet very little is known about the neurobiology of suicidal behavior in this age group (2). Being a serious health problem, the possibility of more quantitative and objective tools, such as biomarkers, for predicting and tracking suicidal states would be of clinical value.

A growing body of literature speaks for the involvement of inflammatory mediators in the pathophysiology of suicidal behavior in non-elderly cohorts (3, 4). The authors of a recent meta-analysis reviewed the literature on blood, CSF, and post mortem brain samples, highlighting robust associations between suicidality and IL-1β and IL-6 (5). The mechanisms of these associations remain to be elucidated. The role of microglial cells and astrocytes is of interest in this connection as the impact of cytokines on neurotransmitter storage and release by these cells are to a large extent involved in the general immunosurveillance and mediation of inflammation in the central nervous system (CNS) (6, 7). It has been suggested that abnormalities of proteins involved in neurotransmission and neural plasticity at synapses may be markers of dysregulated neural connectivity (8). At the same time, a dynamic interplay between neural and oligodendroglial mechanisms in regulating synaptic plasticity and sprouting has been shown when studying brain development and neural regeneration (9). Study of CSF microglial markers may help to shed light on neuropathological mechanisms associated with suicidality. One potential marker of interest is YKL-40, also known as chitinase-3-like protein 1 (CHI3L1), which has proven to be a very stable marker for monitoring inflammation and microglial activation in the CNS (10). To date, YKL-40 has been studied in the context of psychiatric morbidity in clinical samples with neurological disorders (11, 12). It has yet to be examined in relation to suicidal behavior. Growth associated protein 43 (GAP-43) is a marker of neuronal plasticity, critical to the regulation of

neuronal morphology and communication where it plays an important role in neuronal sprouting, synaptic reorganization and alternation of neuronal morphology (13, 14). An early post-mortem study showed slightly increased levels of GAP-43 in the anterior frontal cortex of depressed persons who died by suicide (9). Further, abnormalities in the myelination process of these subjects was suggested by the finding of reduced myelin basic protein (MBP) immunoreactivity in that same study. MPB is found in oligodendrocytes and myelin sheets and plays an important role in neuroinflammatory processes leading to neuronal damage (15). MBP was recently highlighted as a biomarker of potential importance for the clinical prediction of suicide (16).

Many studies that examine relationships between CNS biomarkers and suicidal behavior are based on clinical cohorts with major depression. While associations between markers of inflammation and suicidal behavior might in part be explained by associations with depression (17, 18), differential results for affective disorders and suicidal behavior have been reported (19). Further, although major depression is the most common psychiatric disorder observed among persons who die by suicide, many of those who think about suicide or engage in suicidal behavior do not meet criteria for this condition. CSF biomarker studies using population-based cohorts can thus help to provide insights into neuropathological mechanisms related to suicidal ideation in a broader context. To our knowledge, there are to date no studies examining relationships between CSF microglial markers and suicidal ideation in population-based samples.

Aims of the study

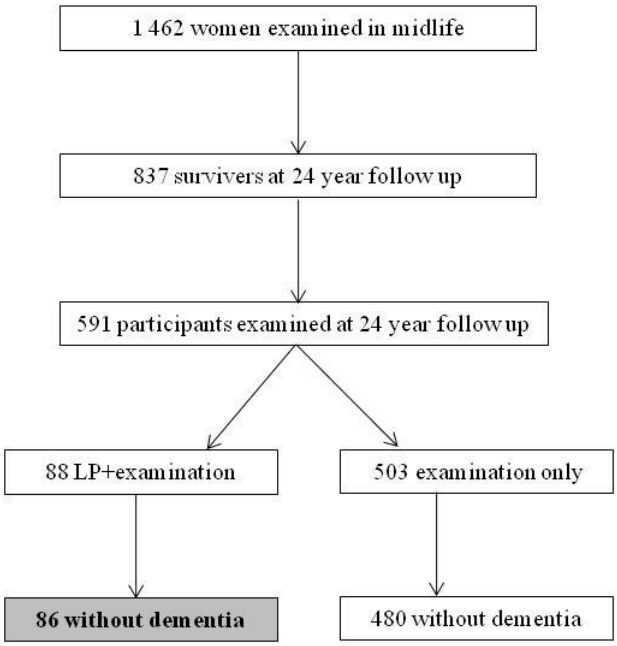
The aim of this study was to investigate associations between CSF markers (YKL-40, GAP-43 and MBP) and suicidal ideation in a population-based sample of older women. A second aim was to test for relationships between these biomarkers and depression status.

Materials and methods

Subjects

The study sample was obtained from the Prospective Population Study of Women (PPSW), a population-based survey in Gothenburg, Sweden (20). The sample was collected from the Swedish Population Register, based on birth date, and included women living in private households as well as those in residential care (20, 21). The study began in 1968-1969 and included a representative sample of 1462 women living in Gothenburg, Sweden born on certain dates in 1908, 1914, 1918, 1922 and 1930 (Figure 1).

Figure 1. Participant flow



In 1992-1993, 837 surviving women were invited to participate in a psychiatric examination and among those 591 who agreed to take part, 88 women aged 62-84 years consented to undergo a lumbar puncture (LP). Two of these women were diagnosed with dementia at the time of the LP. As higher values of CSF YKL-40 have been associated with development of

dementia (22) these women were excluded leaving 86 non-demented women born in 1908 (*n*=2), 1914 (*n*=7), 1918 (*n*=33), 1922 (*n*= 43) and 1930 (*n*=1).

No differences were observed between non-demented women with (n=86) and without (*n*=480) lumbar puncture with regard to age at examination, Mini Mental State Examination (MMSE) score, age at death, alcohol consumption, body mass index (BMI), systolic and diastolic blood pressure, levels of cholesterol in serum, level of education and smoking status (Supplementary Table 1). The proportion of women with major depression was numerically higher in the CSF group but the difference did not reach significance.

The study was approved by the Ethics Committee for Medical Research at the University of Gothenburg. Written informed consent was obtained from all participants at each examination wave.

Procedures

The clinical examination, which was carried out at a geriatric outpatient department or in the participant's home, included comprehensive social, functional, physical, neuropsychiatric and neuropsychological examinations, as well as close informant interviews. Information about medication use was gathered at each study wave and classified according to the Anatomical Therapeutic Chemical Classification codes (ATC). The psychiatric examination was semi-structured and performed by psychiatrists.

Diagnoses

The Comprehensive Psychological Rating Scale (CPRS) (23) was used to rate psychiatric symptoms. The Montgomery Åsberg Depression Rating Scale (MADRS) (23), a subscale of the CPRS, was used to rate symptoms of depression. Ten symptoms are rated 0 (symptom not present) to 6 (severe symptom level). None of the women had scores indicating severe depression. Past month suicidal thoughts were assessed with the MADRS suicidality item,

which employs the following anchor points: 0-1) Enjoys life or takes it as it comes. 2-3) Weary of life. Only fleeting death wishes. 4-5) Much better off dead. Suicidal thoughts are common, and suicide is considered as a possible solution, but without specific plans or intention. 6) Explicit plans for suicide when there is an opportunity. Active preparations for suicide. For the purpose of this study, a woman with a rating of 4-6 was considered to have suicidal ideation. Major depression was diagnosed in accordance with DSM-IV criteria (24) but the bereavement criterion was not applied, making the diagnosis compatible to DSM-5 (25). Minor depression was diagnosed according to DSM-IV research criteria (either a sad or depressed mood or loss of interest or pleasures in nearly all activities, and in total at least 2 but less than 5 additional symptoms).

Neuropsychiatric examinations and interviews

The exam included the MMSE (26) and tests of short- and long term memory, aphasia, apraxia, agnosia and abstract thinking. The diagnosis of dementia was made on the basis of the neuropsychological examination and the interview with the close informant, with each considered separately, using DSM-III-R criteria (27). Each symptom had to have reached a level at which it caused the subject substantial difficulty in social functioning and the duration of dementia had to be at least six months. A final diagnosis was made on the basis of the combined information. In the current study, dementia was an exclusion criterion only.

CSF analysis

Lumbar punctures were carried out in 1992-1993 and where CSF-samples (12 ml) were taken through the L3/L4 interspace and gently mixed to avoid gradient effects. The samples were promptly centrifuged at 2000g for 10 minutes to eliminate cells and other insoluble materials, aliquoted in 1 ml portions, snap frozen at -80 ^{o}C, stored at that temperature and brought in an

unbroken freeze chain to the laboratory for analyses. The CSF samples in this study did not undergo any freeze thaw cycles prior to analysis. CSF YKL-40 concentrations were measured using the Human Chitinase 3-like 1 Quantikine ELISA Kit (R&D Systems, Minneapolis, MN). The intra-assay coefficient of variation was 3.3% and the inter-assay coefficient of variation was 9.1%. The detection limit was 6.25 ng/ml. CSF GAP-43 was determined by ELISA (28). NM2 was used as capturing antibody, biotinylated NM4 as detecting antibody, and recombinant GAP-43 as standard. The detection limit was 140 pg/ml. CSF MBP concentrations were measured using the Active® MBP ELISA kit (Diagnostic Systems Laboratories Inc., Webster, TX). The detection limit was 0.1 ng/ml. All analyses were performed in one round of experiments using one batch of reagents by board-certified laboratory technicians who were blinded to clinical data.

Statistical analysis

Differences in mean CSF levels of YKL-40, GAP-43 and MBP by suicidal ideation were first tested with Student's t-test. As associations might be impacted by smoking, BMI and age, binary logistic regressions were carried out adjusting for each of these variables, and results are then presented for fully adjusted models. *F*-tests were used for investigating differences in biomarker levels among those with no, minor and major depression.

In an explorative set of analyses, we used Fisher's exact test to analyze relationships between the three CSF-markers and each of the specific symptoms included in the MADRS (with the exclusion of the suicide item): 1) Apparent sadness, 2) Reported sadness, 3) Inner tension, 4) Reduced sleep, 5) Reduced appetite, 6) Concentration difficulties, 7) Lassitude, 8) Inability to feel, and 9) Feelings of worthlessness. Binary logistic regressions were used to examine these associations while adjusting for smoking status, BMI and age. Missing data for smoking status (n=2) and BMI (n=1) were handled by listwise deletion. Statistical tests were carried

out using SPSS for Windows (version 17, SPSS Chicago, IL.). All tests were two-tailed and significance was reported where *P* values were less than 0.05.

Results

Participant characteristics are presented in Table 1. Eight women reported past month suicidal ideation. As expected, these women scored higher on the MADRS. MMSE scores were similar in women with and without suicidal ideation. Table 1 shows further mean values for the investigated CSF-markers. Levels of both YKL-40 and GAP-43 were significantly higher in women with past month suicidal ideation. Levels of MBP were similar in women with and without such ideation.

Table 1. Participant characteristics and CSF biomarkers by suicidal ideation in a population-based sample of older women without dementia

	All	Past month suicidal ideation			
	N =86	No (*N* =78)	Yes (*N* =8)		
	Mean (SD)	Mean (SD)	Mean (SD)	t-statistic	*P*
Age (years)	72.5 (3.3)	72.7 (3.1)	70.6 (4.2)	1.7	0.096
MADRS	7.0 (8.3)	5.1 (6.0)	25.3 (5.3)	-9.2	<0.001
MMSE	28.3 (1.4)	28.4 (1.4)	28.1 (1.6)	0.5	0.639
YKL-40 (10^{-8}g/ml)	17.9 (6.1)	17.5 (5.9)	22.0 (6.2)	-2.0	0.047
GAP-43 (ng/ml)	1.2 (0.6)	1.2 (0.5)	1.6 (0.6)	-2.1	0.037
MBP (ng/ml)	0.98 (0.3)	0.97 (0.3)	1.10 (0.3)	-0.9	0.385

MADRS, Montgomery-Åsberg Depression Scale
MMSE, Mini Mental State Examination

Results of the binary regression models are shown in Table 2. The relationship between YKL-40 and suicidal ideation remained in the model adjusted for smoking status, BMI and age. A one unit increase in GAP-43 was associated with a more than four-fold increase in odds of suicidal ideation in the fully adjusted model.

Table 2. CSF biomarker associations with suicidal ideation from logistic regression models with smoking status, BMI and age in a population-based sample of older women without dementia

	Smoking				BMI				Age				Fully adjusted			
	OR	CI (95%)		*P*	OR	CI (95%)		*P*	OR	CI (95%)		*P*	OR	CI (95%)		*P*
YKL-40 (10^{-8}g/ml)	1.15	1.01	1.30	0.034	1.15	1.01	1.30	0.035	1.12	1.00	1.25	0.059	1.17	1.02	1.34	0.026
GAP-43 (ng/ml)	3.42	1.07	11.01	0.039	4.48	1.30	15.41	0.018	3.22	0.97	10.69	0.056	4.61	1.29	16.49	0.019
MBP (ng/ml)	3.70	0.31	44.15	0.300	5.44	0.36	82.17	0.222	2.83	0.23	34.98	0.417	5.94	0.37	96.49	0.211

We could not test for associations between CSF markers and ongoing medication due to limited study power. Five women were on antidepressants and two of these had suicidal ideation. One woman (without suicidal ideation) had ongoing antipsychotic treatment. Anti-inflammatory medication was currently prescribed to eight women, none of whom reported suicidal ideation. Finally, one woman with suicidal ideation had ongoing cortisone treatment. As previously reported (17), one fifth of the women fulfilled criteria for depression (major depression, *n*=10, minor depression, *n*=9). As presented in Table 3, CSF levels of YKL-40, GAP-43 and MBP did not differ by depression status.

Table 3. Characteristics and CSF biomarkers by depression status in a population-based sample of older women without dementia (*n*=86)

	No depression (*N* =67)	Minor depression (*N* =9)	Major depression (*N* =10)	
	Mean (SD)	Mean (SD)	Mean (SD)	*P*
Age	72.4 (3.1)	75.1 (4.4)	70.8 (1.7)	0.013
MADRS	4.0 (4.8)	9.4 (4.2)	24.8 (6.3)	<0.001
MMSE	28.5 (1.4)	28.0 (1.5)	27.9 (1.3)	0.369
YKL-40 (10^{-8}g/ml)	17.8 (6.0)	18.3 (8.3)	18.8 (4.2)	0.876
GAP-43 (ng/ml)	1.1 (0.5)	1.2 (0.6)	1.5 (0.6)	0.267
MBP (ng/ml)	1.1 (0.3)	1.0 (0.3)	1.1 (0.3)	0.527

We also tested whether a "dose-response" relationship might be observed for any of the three CSF markers in relation to depression severity level as measured by the MADRS severity groups: no depression (0-12), mild depression (13-19) and moderate depression (20-34), but no such association could be observed (data not shown).

In a set of exploratory analyses, relationships were tested between each of the CSF markers and each of the 9 other (non-suicide) MADRS items. As shown in Table 4, relationships could be shown for neither YKL-40 nor MBP.

Table 4. CSF biomarkers by MADRS items in a population-based sample of older women without dementia (*n*=86)

MADRS items	Rating		YKL-40 (10^{-8}g/ml)		GAP-43 (ng/ml)		MBP (ng/ml)	
	0-1	2-6	0-1	2-6	0-1	2-6	0-1	2-6
	N	*N*	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Apparent sadness (observed)	70	16	17.7 (5.9)	18.8 (6.8)	1.1 (0.5)	1.4 (0.6)	0.97 (0.3)	1.03 (0.3)
Reported sadness	76	10	17.7 (5.9)	19.6 (7.4)	1.2 (0.5)	1.4 (0.6)	0.98 (0.3)	0.96 (0.2)
Inner tension	69	17	17.6 (6.2)	19.5 (5.5)	1.1 (0.6)	1.4 (0.5)	0.98 (0.3)	0.99 (0.2)
Reduced sleep	56	30	18.2 (6.1)	17.4 (6.0)	1.2 (0.6)	1.1 (0.5)	0.99 (0.3)	0.96 (0.2)
Reduced appetite	82	4	17.9 (6.0)	19.4 (8.6)	1.2 (0.6)	1.2 (0.2)	0.97 (0.3)	1.10 (0.2)
Concentration difficulties	56	30	17.9 (6.3)	18.0 (5.6)	1.2 (0.6)	1.2 (0.5)	0.99 (0.3)	0.95 (0.2)
Lassitude	42	44	18.2 (6.9)	17.7 (5.2)	1.2 (0.6)	1.2 (0.5)	1.00 (0.3)	0.96 (0.2)
Inability to feel	75	11	17.9 (6.3)	17.8 (4.4)	1.2 (0.6)	1.3 (0.6)	0.97 (0.3)	1.06 (0.2)
Feelings of worthlessness	69	17	17.4 (6.1)	20.0 (5.6)	1.1 (0.5)*	1.5 (0.5)	0.96 (0.3)	1.04 (0.2)

*p<0.05 using Student's t-test.

Higher levels of CSF GAP-43 were associated with feelings of worthlessness; a strong relationship was demonstrated in a binary logistic regression model that included smoking status, BMI and age (OR 5.95 CI [1.52-23.20], *P*=0.01).

Discussion

We found higher CSF levels of both GAP-43 and YKL-40 in women with suicidal ideation compared with those without such thoughts. To our knowledge, this is the first population-

based study to show findings suggesting that disrupted synaptic-glial functioning and inflammation may be related to the etiology of suicidal ideation in older adults. Also, our data suggest that the elevation of CSF YKL-40 and GAP-43 seen in women with suicidal ideation was not directly mediated by depression status. The impact of age on associations between the CSF markers and suicidal ideation appeared greater for age than for smoking status and BMI, but associations with suicidal ideation remained in the fully adjusted model. The microglial marker YKL-40 has not been studied previously in the context of suicidal behavior and depression. Data are thus lacking for comparison. YKL-40 is a known marker of inflammatory processes and microglial activation (11) and we know from previous studies that inflammatory processes contribute to the pathogenesis of suicidal behavior (29, 30).

While not directly comparable, as we investigated suicidal ideation rather than suicide death, our findings showing elevated levels of GAP-43 in suicidal women point in the same direction as a previous study indicating a slightly increased GAP-43 immunoreactivity in depressed suicides (9). As GAP-43 is known to be involved in the maintenance of synapses and neuritic regeneration it may be regarded as a neurodegenerative marker - a sign of neurodegeneration (31). Our findings on elevated GAP-43 in suicidal women may indicate changes in neuronal structure, signaling that neuronal plasticity is either compromised or deficient in the presence of suicidality. However, there are conflicting results with another post mortem study showing decreased levels of GAP-43 in depressed suicides (32). Animal research suggests that elevated levels of GAP-43 might be related to antidepressant exposure (33). While our study lacked power to address this question, antidepressant treatment could not explain the elevated rates observed in the suicidal women, because few of these were on treatment.

No significant difference in MBP levels could be established in the current study. This needs to be tested in larger population-based samples. Reduced levels of MBP have previously

been shown in patients with schizophrenia and depression who died by suicide (9), indicating abnormalities in the myelination state or process.

While no relationships could be shown for YKL-40 or MBP in the exploratory analyses involving the other MADRS items, an association was observed between higher levels of GAP-43 and feelings of worthlessness. Further correction for multiple testing could not be performed due to the small size of our sample but this result may nevertheless provide an interesting lead for further investigation. In a recent clinical study focusing on patients with a single complicated episode of major depression, worthlessness was the only depressive symptom that predicted future post remission suicide attempts (34).

Strengths and limitations

Results from the current study cannot be extrapolated to male populations. Males may show up to 10% higher levels of GAP-43 compared to females (14). In clinical samples, no correlations between age and expressions of GAP-43 or MBP have been detected (9, 14). The effect of age needs to be clarified, however, when it comes to older adult populations. In persons with Alzheimer's disease (AD), decreased levels of GAP-43 are observed in the prefrontal cortex and the hippocampus while increased levels are seen in the CSF (35), indicating synaptic degeneration or plasticity. It is possible that CNS GAP-43 may in the case of suicidal ideation be a marker of neurodegeneration of cortical areas (frontal-subcortical connectivity) that are also affected in AD. While established AD does not appear to be associated with increased risk of suicide (36), clinical studies suggest that cognition may be impaired in older adults with suicidal behavior (37), and further studies are needed to clarify possible mechanisms.

Strengths of the study include the population-based sample and the comprehensive neuropsychological examinations. The latter made it possible to exclude persons with

dementia, and to diagnose both major and minor depression. Some limitations need to be addressed. The samples were stored for several decades and the long-term stability of the three biomarkers examined in our study is not known. If changes did occur, this would be anticipated to decrease the likelihood of finding significant differences between subgroups with and without suicidal ideation. While the number of participants with CSF data is relatively large, the number of cases with suicidal ideation was limited, reflecting the population-based study design. Another important limitation is that we have CSF data from one time point only. Some of the women may have had episodes of suicidal behavior prior to baseline. We can thus not make conclusions about the directionality of the observed relationships. Finally, a common limitation in population-based studies is that there is an underlying risk of attracting those who may be healthier than the general public. This type of selection bias decreases the likelihood of finding significant differences.

Acknowledgements

The Swedish Research Council (11267, 2005-8460, 825-2007-7462, 825-2012-5041, 2013-2699, 2013-8717, 2015-02830, 2016-01590), Swedish Research Council for Health, Working Life and Welfare (no 2001-2646, 2001-2835, 2003-0234, 2004-0150, 2006-0020, 2008-1229, 2004-0145, 2006-0596, 2008-1111, 2010-0870, 2012-1138, 2016-07097, AGECAP 2013-2300, Epilife 2006-1506), Swedish Brain Power, the Knut and Alice Wallenberg Foundation, the Alzheimer's Association Zenith Award (ZEN-01-3151), the Alzheimer's Association Stephanie B. Overstreet Scholars (IIRG-00-2159), the Bank of Sweden Tercentenary Foundation, Eivind och Elsa K:son Sylvans stiftelse, Stiftelsen Söderström-Königska Sjukhemmet, Konung Gustaf V:s och Drottning Victorias Frimurarstiftelsen, Stiftelsen för Gamla Tjänarinnor, Handlanden Hjalmar Svenssons Forskningsfond, Demensförbundet, Stiftelsen Längmanska kulturfonden.

Conflict of interest

KB is a co-founder of Brain Biomarker Solutions in Gothenburg AB, a GU Venture-based platform company at the University of Gothenburg, and has served as a consultant or at advisory boards for IBL International, Roche Diagnostics, Eli Lilly, Fujirebio Europe and Novartis. All other authors declare no conflict of interest.

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