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Longstanding psychological stress in relation to biomarkers of neuronal dysfunction in cerebrospinal fluid: a 25-year follow-up study in women

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ABSTRACT

Longstanding psychological stress has been associated with increased risk of neurodegenerative disorders, such as dementia and Alzheimer's disease. In a prospective population study of women ($n = 81$), we tested if midlife stress (mean age 49 years) was associated with late-life biomarkers of neurodegeneration in cerebrospinal fluid (CSF) (mean age 74 years) in linear regression models. It was found that women who report of stress at baseline ($n = 20$) had higher levels of CSF visinin-like protein-1 (VILIP-1) (age adjusted $\beta = 0.113$, $p = 0.017$) and CSF myelin basic protein ($\beta = 0.060$, $p = 0.030$) compared with women without midlife stress ($n = 61$). There was also a trend observed for higher CSF neurofilament light ($\beta = 0.133$, $p = 0.056$). In addition, longer periods of stress (i.e., stress at 2–3 midlife examinations) were associated with higher levels of CSF VILIP-1. The results suggest that longstanding stress might be associated with neurodegenerative processes in the brain, as CSF VILIP-1 is an unspecific marker for neuronal injury and CSF myelin basic protein reflects neuroaxonal demyelination.

1. Introduction

Increasing evidence suggests that longstanding psychological stress may trigger pathologic processes in the human brain and increase the risk for neurodegenerative disorders. In a large population-based sample of women we earlier found that longstanding midlife stress was associated with late-life dementia and Alzheimer's disease (AD) (Johansson et al., 2010), as well as structural brain changes, such as temporal lobe atrophy and white matter lesions (Johansson et al., 2012). In addition, stressful life-events and stress-prone personality (high neuroticism) were related to increased risk of AD (Johansson et al., 2013, 2014). Other longitudinal studies have reported associations between post-traumatic stress disorders, perceived stress, and neurodegenerative disorders (Greenberg et al., 2014).

Little is known about the underlying biological mechanisms of those associations. Recently, we showed that longstanding midlife stress was associated with higher levels of tau proteins in cerebrospinal fluid (CSF), in a sample of women followed up for more than 25 years (Johansson et al., 2018). Increased CSF tau concentration primarily represents AD-type degeneration (Zetterberg, 2018). However, we saw no association between stress and levels of CSF beta amyloid 1–42 (Aβ42) (Johansson et al., 2018), the main marker of amyloid plaques in AD (Blennow et al., 2006; Jack et al., 2013). Moreover, a clinicopathologic study found that persons with stress-prone personality had more advanced neurofibrillary tangles in brain (Terracciano et al., 2013) and 2 preclinical studies found that chronic stress was associated with accumulation of tau proteins in mice (Kang et al., 2007; Sotiropoulos and Sousa, 2016).

Neurodegeneration is often a consequence of long-lasting progression of loss of neurons and synapses in the cerebral cortex and subcortical regions. Trajectories to the neuronal loss can be because of, for example, aggregation of misfolded proteins, myelin injury, or oxidative stress (Lupien et al., 2018). Several CSF measures reflect structural and functional injuries of the nerve

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cells and are used as prognostic and diagnostic biomarkers of neuropathologic changes in the brain. Three such biomarkers are visinin-like protein-1 (VILIP-1), myelin basic protein (MBP), and neurofilament light (NF-L) (Fagan et al., 2014; Tarawneh et al., 2012, 2015). VILIP-1 is part of the calcium-sensor protein family and is expressed in high abundance in central nervous system neurons (Braunewell and Klein-Szanto, 2009; Kiyama et al., 1985). It is excessively released during neuronal degeneration (Lee et al., 2008) and has been shown to correlate well with AD progression (Tarawneh et al., 2012). MBP is a main component of the neuromyelin (Zhan et al., 2018), and increased concentrations of CSF MBP are associated with demyelination in central nervous system and an increased amount of cytokines and oxidative stress (Zhan et al., 2018). NF-L is one of the components in neurofilaments, which is a main structure in the cytoskeleton, particularly in large myelinated axons (Zetterberg et al., 2016). High levels of NF-L in CSF indicate structural damage of nerve cells and are associated with white matter damage and general brain atrophy (Zetterberg et al., 2016).

There is a lack of studies investigating the long-term effects of psychological stress on neurodegenerative biomarkers in CSF. Therefore, we examined the relationship between longstanding psychological stress in midlife and late-life levels of CSF VILIP-1, MBP, and NF-L in a sample of 81 women followed up for more than 25 years.

2. Materials and methods

2.1. Study population

The study is part of the Prospective Population Study of Women in Gothenburg, Sweden, which was initiated in 1968 ($n = 1462$, participation rate 90%) (Bengtsson et al., 1973; Johansson et al., 2010). The study was designed to investigate a number of somatic and psychological health aspects in women before and after the menopause, and the participants were sampled from the Swedish Population Register based on specific birth dates to yield a representative sample at the ages studied. A question about psychological stress was included at the baseline examination in 1968–1969 (mean age 46 years) and in the follow-up examinations in 1974–1975 (mean age 52 years) and in 1980–1981 (mean age 58 years). At the follow-up examination in 1992–1994, a subsample of 590 women participated in an extensive neuropsychiatric examination and among these 87 underwent lumbar puncture (LP) (Gustafson et al., 2007; Mielke et al., 2006).

Participants and nonparticipants in the LP examination were similar regarding baseline systolic and diastolic blood pressure, body mass index (BMI), smoking habits, cardiovascular disorders (CVDs), depressive symptoms, and report of longstanding stress. They were also similar regarding the Mini-Mental State Examination (MMSE) score in 1992–1994. The LP participants were younger ($p < 0.01$), had higher education ($p = 0.04$), and lower 5-year mortality rate ($p = 0.02$) compared with nonparticipants. The present study consists of 81 women (i.e., all who had stress data from the baseline examination). They were born in 1908 ($n = 3$), 1914 ($n = 7$), 1918 ($n = 33$), and 1922 ($n = 38$). At the time of the LP study, the women were in their early late-life (mean age 74 years) and most of the samples were cognitively healthy. All except 1 women had the MMSE score ≥25 (mean 28.4 ± 1.4). Two women had dementia onset at the time of the study start (i.e., in 1991 vs. 1993). The Ethics Committee for Medical Research at the University of Gothenburg approved the study, and informed consent was obtained from all participants, in accordance with the provisions of the Helsinki Declaration.

2.2. Assessment of longstanding psychological stress

The question about psychological stress was asked by a physician and was as follows: “Have you experienced any period of stress, 1 month or longer, in relation to circumstances in everyday life, such as work, health, or family situation?” Stress was defined as feelings of irritability, tension, nervousness, fear, anxiety, or sleep disturbances. The responses were categorized as follows: 0, never a period of stress; 1, period/s of stress more than 5 years ago; 2, one period of stress during the last 5 years; 3, several periods of stress during the last 5 years; 4, constant stress during the last year; or 5, constant stress during the last 5 years. For the purpose of this study, women who endorsed responses 3, 4, or 5 were considered to have psychological stress.

2.3. Assessment of CSF biomarkers

LPs were conducted between January 1993 and March 1994. CSF samples (12 mL) were taken through the L3/L4 interspace. To eliminate cells and other insoluble material, the samples were centrifuged at 2000 *g* for 10 minutes. The liquid was then stored at −80 °C in 1 mL polypropylene vials until analysis. Commercially available kits were used for measuring the concentrations of VILIP-1 (Human VILIP-1 ELISA; BioVendor GmbH, Heidelberg, Germany), MBP (Active MBP; Diagnostic Systems Laboratories Inc, Webster, TX, USA), and NF-L (NF-light ELISA; IBL international, Hamburg, Germany), following the manufacturers’ protocols. All measurements per assay were performed in 1 round of experiments using 1 batch of reagents by board-certified laboratory technicians who were blinded to clinical data. The CSF data set has been described in several previous studies (Gudmundsson et al., 2010; Gustafson et al., 2007; Johansson et al., 2018; Kern et al., 2014; Mielke et al., 2006).

2.4. Assessment of covariates

Information on depression, CVDs, education, physical activity, BMI, and socioeconomic status was obtained at the baseline examination in 1968–1969. Depression was diagnosed using information from the psychiatric interview at baseline and was compatible with the DSM-III criteria (Hallstrom, 1984). CVDs were defined as hypertension and/or stroke, that is, systolic blood pressure ≥160 mm Hg and/or diastolic blood pressure ≥95 mm Hg, and/or taking antihypertensive medications and (or) information on stroke from the examination or the Swedish Hospital Discharge Registry. Education was dichotomized as compulsory (6 years) or more than compulsory. Physical activity during leisure time was rated as low (<4 h/wk) versus medium-high (≥4 h/wk). BMI was calculated using the formula person’s weight in kilogram by height in meters squared. Socioeconomic status was based on husband’s occupation for married women and own occupation for unmarried women, and was defined as low versus medium-high (Carlsson, 1958). MMSE was administered at the follow-up examination in 1992–1994.

2.5. Statistical analyses

Because of skewed distributions, all CSF values, that is, VILIP-1, MBP, and NF-L, were natural log transformed to improve symmetry. Pearson’s correlation coefficients estimated linear relationships between age and stress, age and CSF markers, and between the 3 CSF biomarkers. The relations between psychological stress in midlife and CSF markers in late-life were analyzed using linear regression models. Model 1 was adjusted for age and model 2 was additionally adjusted for depression and CVDs. The CSF variable was used as dependent variable, and the results were presented as β-

Table 1
Characteristics of the study participants ($n = 81$)

Characteristics	Mean ± SD or n (%)
Age at baseline (y)	48.8 ± 3.4
Psychological stress	
Baseline	20 (24.7)
1st follow-up, 6 y after baseline	18 (22.2)
2nd follow-up, 12 y after baseline[a]	12 (14.8)
Depression[b,c]	10 (18.9)
Cardiovascular disorders[b]	27 (24.5)
Body mass index[b]	24.4 ± 3.8
Education level[b]	
Compulsory	57 (70.4)
More than compulsory	24 (29.6)
Physical activity[b]	
Low	15 (18.5)
Medium-high	66 (81.5)
Socioeconomic status[b,c]	
Low	21 (39.6)
Medium-high	32 (60.4)
Mini-Mental State Examination[d,e]	28.4 ± 1.4
Cerebrospinal fluid biomarkers[d]	
VILIP-1 (ng/L)	13.4 ± 5.4
MBP (ng/mL)	0.99 ± 0.28
NF-L (ng/L)	324.7 ± 243.8

Key: MBP, myelin basic protein; NF-L, neurofilament light; SD, standard deviation; VILIP-1, visinin-like protein-1.
[a] Two missing, $n = 79$.
[b] Measured at baseline examination in 1968–1969.
[c] Twenty-eight missing, $n = 53$.
[d] Measured at follow-up examination in 1992–1994.
[e] One missing, $n = 80$.

coefficients (unstandardized) and 95% confidence intervals. The statistical significance was defined as a $p < 0.05$ (two-tailed) in all analyses.

We further examined whether the number of examinations when participants' reported psychological stress influenced the association to CSF measures. Stress data from the 3 midlife examinations were combined and the sample was divided into 3 groups: 1, no report of stress at any examinations; 2, report of stress at 1 examination; and 3, report of stress at 2 or 3 examinations. All analyses were performed with IBM Statistical Package for the Social Sciences version 24 statistical software (Armonk, NY, USA).

3. Results

Table 1 presents the characteristics of the 81 participants. Twenty-five percent ($n = 20$) reported psychological stress at the baseline examination in 1968–1969. At the first follow-up, in 1974–1975, participants reported 22% stress and in the second follow-up, in 1980–1981, participants reported 15% stress. A higher age was associated with higher levels of CSF VILIP-1 ($p = 0.015$) and CSF MBP ($p = 0.018$), but not with levels of CSF NF-L ($p = 0.093$) or MMSE performance ($p = 0.803$). The 3 CSF biomarkers were significantly associated with each other, that is, VILIP-1 and MBP ($p = 0.000$), VILIP-1 and NF-L ($p = 0.038$), and MBP and NF-L ($p = 0.000$).

In age-adjusted linear regression models it was found that psychological stress at baseline was related to higher levels of late-life CSF VILIP-1 ($\beta = 0.113$, $p = 0.017$) and CSF MBP ($\beta = 0.060$, $p = .030$) (Table 2). There was also a trend observed for higher levels of CSF NF-L ($\beta = 0.133$, $p = 0.056$). The findings remained after further adjustments (Table 2). Reports of stress in the other 2 follow-up examinations, that is, in 1974–1975 and 1980–1981, were not significantly associated with levels of CSF biomarkers (data not shown).

Among the 79 women who participated in all 3 midlife examinations, 48 (59%) never reported stress, 20 (25%) reported stress at 1 examination, and 11 (14%) reported stress at 2–3 examinations. Those who never reported stress had lower levels of CSF VILIP-1 (mean 12.2 ng/L) than those who reported stress at 1 (mean 12.6 ng/L) and 2–3 examinations (mean 15.5 ng/L). In a linear regression model, it was found that higher CSF VILIP-1 was associated with number of examinations when stress was reported (age adjusted $\beta = 0.059$, $p = 0.036$). There was no such dose-response relationship for CSF MBP or CSF NF-L (Table 3).

4. Discussion

We found that longstanding stress in midlife was associated with higher levels of the neurodegenerative CSF biomarkers VILIP-1 and MBP in late-life in a sample of women followed up for more than 25 years. There was also a trend observed for higher levels of CSF NF-L. In addition, there was a positive association between levels of CSF VILIP-1 and number of examinations when stress was reported. The findings suggest that longstanding psychological stress can be related to neural atrophy and demyelination processes in brain.

VILIP-1 plays a functional role in integrating the cytosolic calcium concentration and the oxidative status of the cell (Liebl et al., 2014). The protein has been demonstrated as a marker of neuronal injury and is excessively released during neuronal degradation (Lee et al., 2008). High levels of CSF VILIP-1 thus reflect the end result of several brain diseases with extensive neuronal cell death (Lee et al., 2008) and correlate well with ischemic stroke (Laterza et al., 2006), AD pathology (Fagan et al., 2014; Tarawneh et al., 2012), and whole-brain atrophy (Tarawneh et al., 2015). Psychological stress in midlife was also associated with higher levels of CSF MBP, which is a main component of the myelin membrane and important for the myelination process of neurons (Zhan et al., 2018). Increased concentrations of CSF MBP are seen in white matter degeneration (Omlin et al., 1980), subcortical vascular disease (Bjerke et al., 2011; Brouns et al., 2010), and other demyelinating diseases (Romme Christensen et al., 2013). During chronic demyelinating conditions, MBP can precipitate and aggregate outside the cell membrane and cause damaging effects on the neighboring neurons (Zhan et al., 2018). Myelin degradation can also result in retrograde degeneration, that is, that part of the axon, distal to the injury, relapse (Bjerke et al., 2011). In an earlier study from this population we found that midlife stress was related to late-life white matter lesions

Table 2
Associations between stress at baseline (1968–1969) and late-life CSF biomarkers of neurodegeneration (1993–1994) in linear regression models ($n = 81$)

Characteristics	No report of stress $n = 61$ (75.3%) mean ± SD	Psychological stress $n = 20$ (24.7%) mean ± SD	Model 1			Model 2		
			β-Coefficient	95% CI	*p* Value	β-Coefficient	95% CI	*p* Value
VILIP-1 (ng/L)	12.3 ± 4.7	16.5 ± 6.3	0.113	0.021, 0.204	**0.017**	0.112	0.019, 0.204	**0.025**
MBP (ng/mL)	0.95 ± 0.25	1.12 ± 0.32	0.060	0.001, 0.115	**0.030**	0.060	0.002, 0.117	**0.042**
NF-L (ng/L)	291.8 ± 213.4	425.1 ± 304.2	0.133	−0.04, 0.269	0.056	0.134	−0.003, 0.271	0.055

Model 1: adjusted for age. Model 2: adjusted for age, depression, and cardiovascular factors.
Significant at the level of $p < 0.05$ (5% significance) are shown in bold.
Key: CI, confidence interval; CSF, cerebrospinal fluid; MBP, myelin basic protein; NF-L, neurofilament light; SD, standard deviation; VILIP-1, visinin-like protein-1.

Table 3
Associations between longstanding stress in 3 midlife examinations[a] and late-life CSF biomarkers of neurodegeneration measured in linear regression models ($n = 79$)

Characteristics	No report of stress $n = 48$ (59.3%) mean ± SD	Stress report in 1 examination $n = 20$ (24.7%) mean ± SD	Stress report in 2–3 examinations $n = 11$ (13.6%) mean ± SD	Model 1			Model 2		
				β-Coefficient	95% CI	p Value	β-Coefficient	95% CI	p Value
VILIP-1 (ng/L)	12.2 ± 4.9	12.6 ± 5.4	15.5 ± 6.8	0.060	0.004, 0.116	**0.036**	0.059	0.002, 0.115	**0.042**
MBP (ng/mL)	0.97 ± 0.26	1.03 ± 0.35	0.99 ± 0.23	0.008	−0.027, 0.043	0.647	0.008	−0.027, 0.044	0.641
NF-L (ng/L)	312.0 ± 229.8	349.8 ± 285.2	337.1 ± 253.1	0.016	−0.067, 0.099	0.704	0.017	−0.066, 0.101	0.680

CSF biomarkers measured in 1993–1994. Model 1: adjusted for age. Model 2: adjusted for age, depression, and cardiovascular factors.
Significant at the level of $p < 0.05$ (5% significance) are shown in bold.
Key: CI, confidence interval; CSF, cerebrospinal fluid; MBP, myelin basic protein; NF-L, neurofilament light; SD, standard deviation; VILIP-1, visinin-like protein-1.
[a] Psychological stress measured in 1968–1969, 1974–1975, and 1980–1981.

(Johansson et al., 2012), which partly can support the association between midlife stress and higher levels of CSF MBP.

Late-life CSF NF-L was not significantly related to midlife stress in our study, but there was a trend in that direction ($p = 0.056$). Neurofilaments are major structural proteins in the cytoskeleton and play a central role in the control and maturation of regenerating myelinated axons and growth of dendrites (Zetterberg et al., 2016). Increased CSF NF-L is thus a marker of large-caliber axonal damage and can be used to monitor general neurodegeneration (Zetterberg et al., 2016).Increased levels of CSF NF-L are seen in a wide range of cerebral disorders, such as white matter lesions (Sjogren et al., 2001), subcortical vascular disease (Bjerke et al., 2011), and dementia (Zetterberg et al., 2016), but do not correlate very well with the presence of amyloidal plaque (Zetterberg et al., 2016).

The neurodegenerative process is characterized by a progressive and irreversible loss of neurons in specific brain areas and is accompanied by several alterations in the cellular processes, for example, protein aggregation, neurotoxicity, oxidative stress, and cytoskeletal alterations (Jellinger, 2009). Longstanding stress may have a profound effect on the brain by inducing neurochemical changes (Jellinger, 2009) and have earlier been associated with increased risk for dementia (Greenberg et al., 2014; Johansson et al., 2010) and structural brain changes (Johansson et al., 2012; McEwen, 2000). In a previous Prospective Population Study of Women, we found that midlife stress was associated with higher levels of CSF tau (Johansson et al., 2018). The tau pathology has a key role in synaptic dysfunction and neuronal death, because of altered cytoskeleton in AD and other neurodegenerative disorders (Iqbal et al., 2010). One clinicopathologic study also showed that chronic stress was associated with a higher amount of neurofibrillary tangles in brain (Terracciano et al., 2013).

In an earlier study we found that psychological stress had no associations with the levels of CSF Aβ42, the main proteinopathies recognized in AD (Johansson et al., 2018), which suggests that other biomarkers mediate the association between stress and dementia. According to the Jack et al. hypothesis, the typical AD progression starts with the amyloidal pathology, that is, aggregation of amyloid plaque in the brain and lower levels of Aβ42 in CSF, which is later followed by neurofibrillary tangles in the brain and increased tau levels in CSF (Jack et al., 2013). Stress might contribute to neurodegeneration and cognitive brain disorders through other pathways. Perhaps several neurophysiological mechanisms can be involved in the molecular pathology in the aging brain and contribute to interindividual variations in the expression of the clinical disease. It may also be that stress makes neurons more vulnerable to the influence of amyloidosis. In addition, a number of CSF studies have found no associations between levels of Aβ and levels of VILIP-1, MBP, and NF-L (Höglund et al., 2017; Kester et al., 2015), suggesting that these markers have no central part of the Aβ aggregation process.

Report of stress in the 2 follow-up examinations, in 1974–1975 and 1980–1981, was not associated with the late-life CSF biomarkers in this study. The reason for this is unclear. One explanation could be that significance was lost because of limited statistical power, that is, smaller sample sizes and fewer reports of stress. For example, only 15% ($n = 12$) of the women reported stress in the 1980–1981 examination. Another explanation could be that stress in later midlife has other characteristics, or other causes, than stress in younger ages.

Among the strengths of the study are the long follow-up, the population-based sample, and the comprehensive examinations. There are also methodological issues that need to be considered. First, psychological stress was based on a subjective personal response to a single question. This stress question has, however, been used in several previous studies and has been associated with number of life-stressors (Johansson et al., 2013), high neuroticism (Johansson et al., 2014), psychosomatic diseases (Hange et al., 2007), hypertension (Eriksson et al., 1989), and myocardial infarction (Bengtsson, 1973). Second, the sample was relatively small, which resulted in low statistical power. The results may therefore be underpowered to detect small differences between groups. Third, multiple comparisons were made in this study (i.e., 3 tests), which may lead to false-positive findings. On the other hand, to use, for example, the Bonferroni method to correct this may give rise to false-negative results. The new findings should be considered only suggestive until further confirmed. Fourth, cumulative attrition is a problem in long follow-up studies and the participation in the LP study was only 10% of the eligible sample. However, participants and nonparticipants were similar in a number of variables. Compared with nonparticipants, participants in the LP study in 1992–1994 were younger, had a lower rate of dementia and mortality, and reported less stress in midlife. They may thus be healthier and have less neurodegenerations than the general population. This might likely have underestimated our findings. Fourth, as CSF biomarkers were measured in late-life, we cannot exclude the possibility of survival effects. Finally, the study was conducted in a population of women from Western Europe and the results cannot be generalized to men or other groups.

5. Conclusion

Stress has been suggested to be a risk factor for neurodegenerative disorders, such as AD. There is a lack of knowledge about the underlying molecular mechanisms. In this study, we found that longstanding midlife stress was associated with late-life neurodegenerative biomarkers in CSF, that is, VILIP-1 and MBP. The findings suggest that stress might be involved in neural damaging processes in brain. CSF VILIP-1 is an unspecific marker for neuronal injury and CSF MBP reflects neuroaxonal demyelination. To the best of our knowledge, this is the first study to examine these associations and we hope that the result can be replicated in larger samples in forthcoming studies.

Disclosure

The authors L.J., S.S., S.K., X.G., A.Z., and I.S. declare no competing financial interests. H.Z. and K.B. are cofounders of Brain Biomarker Solutions in Gothenburg AB, a GU Ventures-based platform company at the University of Gothenburg. H.Z. has served at scientific advisory boards for Eli Lilly, Roche Diagnostics, and Wave, and has received travel support from Teva.

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