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Factors Affecting Catecholamines in Caregivers of Patients with Dementia

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ARTICLE INFO

Article history

Received: 17th December 2020

Accepted: 26th January 2021

Published Online: 2nd April 2021

Keywords:

Age

BMI

Caregiver burden

Catecholamine

Dementia

ABSTRACT

Background: Caregivers of dementia patients have significantly higher levels of serum IL-6 and CRP compared to non-caregivers, and the accumulation of everyday stressors reportedly promotes the induction of inflammatory markers. However, few studies have identified factors that affect catecholamine levels in caregivers who experience a combination of physical and mental stress from caregiving.

Purpose: This study aimed to identify physical factors that impact catecholamine levels in caregivers of dementia patients. **Methods:** Participants were elderly caregivers living together with elderly Alzheimer's-type dementia patients. We performed logistic regression analysis, with levels of adrenaline, noradrenaline, and dopamine (indicators of catecholamine) as dependent variables. **Results:** Caregiver BMI had a significant impact on adrenaline levels (OR: 0.792; 95%CI: 0.654-0.960) and noradrenaline levels (OR: 1.210; 95%CI: 1.009-1.451), whereas age had a significant impact on dopamine levels (OR: 1.162; 95%CI: 1.019-1.324). **Discussion:** While caregiver BMI significantly impacted adrenaline and noradrenaline levels, the mechanism underlying these relationships is unclear. One possibility is that obesity (BMI) and a rise in sympathetic nerve activity contributed to hypertension. Our findings suggest that chronic stress in elderly caregivers may potentially impair the dopaminergic activation system in the brain. **Conclusion:** There is a need to identify factors which increase BMI in caregivers. Future studies aimed at gaining a better understanding of the lifestyle habits of caregivers and intervention studies aimed at reducing their BMI are warranted.

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1. Introduction

The mortality risk of caregivers has been reported to be 63% higher than that of non-caregivers^[1]. The chronic stress experienced by caregivers of dementia patients is thought to cause physiological changes in the body. Levels of D-dimer, a marker of fibrin formation and degradation, are reported to be significantly higher in caregivers than in non-caregivers^[2]. Similarly, caregivers of dementia patients have higher serum IL-6 and CRP levels relative to non-caregivers, and the accumulation of everyday stressors promotes an increase in inflammatory markers^[3].

Patients with probable Alzheimer's type dementia have a median survival period of 11.3 years from onset and 5.7 years from diagnosis^[4]. Caregivers of dementia patients are reported to experience a greater level of physical burden and mental distress than caregivers of patients with other disorders^[5]. One in three caregivers experiences depression, with depression occurring more frequently in caregivers of dementia patients compared to caregivers of patients with other chronic diseases^[6].

Aging and chronic stress can have a devastating impact on the vulnerable brain^[7]. The various emotions resulting from stress are caused by neurotransmitters such as noradrenaline and dopamine. Pathways triggered by these neurotransmitters have been studied in detail and are known to be closely related to emotions^[8]. Activation of sympathetic nerves results in the secretion of catecholamines (adrenaline, noradrenaline, and dopamine), leading to vasoconstriction, increased heart rate, and increased blood pressure, which can result in the onset of circulatory disorders. Moreover, mental stress is known to excite sympathetic nerves^[9]. Many organs are innervated by autonomic nerves. For instance, autonomic nerves innervate endocrine glands and regulate hormone secretion.

Only a few studies have examined factors which impact catecholamine levels when caregivers of dementia patients suffer from a combination of physical and mental stress due to caregiving. Therefore, the present study aimed to identify health-related factors which impact catecholamine levels in caregivers of dementia patients.

2. Methods

2.1 Participants

Participants were elderly caregivers living together with Alzheimer's-type dementia patients, and included caregivers who had good control of chronic diseases such as hypertension, diabetes, and dyslipidemia. Those with severe heart diseases and stroke were excluded.

2.2 Research Design

This was a cross-sectional study conducted to analyze factors which influence catecholamines in caregivers.

2.3 Caregiver Scales and Assessed Factors

To evaluate catecholamines, we assessed the levels of adrenaline, noradrenaline, and dopamine. Adrenaline has a heart-stimulating effect and is also involved in sugar and fat metabolism, noradrenaline has a hypertensive effect, and dopamine (a precursor of noradrenaline) has a specific effect on the central nervous system, renal system, circulatory system, and digestive system. The higher the levels of these catecholamines, the stronger their impact on the cardiovascular system.

The Japanese version of the Zarit Burden Interview (ZBI) was used to assess caregiver burden^[10]. We also assessed BMI by caregivers.

2.4 Ethical Considerations

This study was approved by the ethics committee of Nagoya University Graduate School of Medicine. Participants provided informed consent after they received a clear explanation that participation in the present study was voluntary.

2.5 Statistical Analysis

For logistic regression analysis, dichotomized (high or low) levels of adrenaline, noradrenaline, or dopamine based on median levels were entered into the models as dependent variables. Statistical analyses were performed using SPSS25. $P < 0.05$ was considered statistically significant.

3. Results

Of the participants, 23 were male and 29 were female. Levels of noradrenaline and dopamine were slightly higher than reference levels. Median systolic blood pressure values were 143.0 and 134.8 for males and females, respectively, with no significant difference between the two ($P = 0.574$; Table 1).

Table 2 shows the results of the bivariate correlation matrix. Noradrenaline levels were significantly correlated with dopamine levels ($r = 0.456$, $p < 0.05$), but no significant correlation was observed between adrenaline and noradrenaline levels.

Table 3 shows the results of the bivariate correlation matrix for hormone secretion and caregiver factors. Adrenaline levels showed a significant negative correla-

tion with BMI ($r=-0.345$, $P<0.05$), while noradrenaline levels showed a significant positive correlation with BMI ($r=0.297$, $P<0.05$). Dopamine levels showed a significant positive correlation with age ($r=0.354$, $P<0.05$).

Table 4 shows the results of a binomial logistic regression model with caregiver age, sex, total sense of care burden, BMI, and number of oral medications as independent variables. The high and low levels of each hormone were entered as dependent variables using the stepwise method. Hormone levels were dichotomized based on whether they were below or above the respective median level (0, 1) in order to extract factors that impact each hormone.

Caregiver BMI was extracted as a factor that significantly impacted adrenaline levels (OR: 0.792, 95%CI: 0.654-0.960) and noradrenaline levels (OR: 1.210, 95%CI: 1.009-1.451). Age was extracted as a factor that significantly impacted dopamine levels (OR: 1.162, 95%CI: 1.019-1.324). Binomial logistic regression analysis revealed that caregiver BMI significantly impacted.

4. Discussion

The present study identified age and BMI as health-related factors which impact catecholamine levels in caregivers of dementia patients.

Noradrenaline levels were found to be significantly correlated with dopamine levels. Stress is known to stimulate the hypothalamo-pituitary-adrenal system, as well as the sympathoadrenal system^[11-13]. Adrenaline is secreted into the blood from the adrenal medulla, noradrenaline is secreted from sympathetic nerve endings, and cortisol is secreted into the blood from the adrenal cortex^[14-16]. Both noradrenaline and dopamine are secreted from the adrenal medulla. Noradrenaline and adrenaline have been reported to inhibit the production of inflammatory cytokines by dendritic cells via β receptors^[17-18]. However, little is known about their other effects. In the present study, noradrenaline and dopamine levels were correlated with each other, suggesting that both catecholamines may be an objective indicator of stress response, which we surmise reflects stress from caregiving.

Mental stress tests markedly induce epinephrine release^[19]. Epinephrine (adrenaline) responses are negatively correlated with changes in BMI and waist circumference^[20]. Moreover, noradrenaline levels at rest have been shown to be a positive predictor of BMI^[21]. Although we identified caregiver BMI as a significant factor which impacts adrenaline and noradrenaline levels, how they are related mechanistically remains unknown. Some of the impairments in plasma glucose-insulin homeostasis noted

in visceral obesity may be related to an abnormal metabolic response to an adrenaline challenge^[22]. According to one study, only plasma norepinephrine and BMI were significant independent predictors of blood pressure, suggesting that obesity and heightened sympathetic nervous system activity contribute to blood pressure elevation^[23].

Age was identified as a factor which significantly impacts dopamine levels. Dopamine levels and dopamine transporter density have been reported to decrease with age^[24-25]. However, our results are inconsistent with the report that dopamine transporter density declines with age. Dopamine levels were heightened in our participants, despite them being elderly with a median age of 76 years. In fact, we found that dopamine levels tended to increase with age, with dopamine and age showing a positive correlation. This suggests that dopamine levels are increased in the elderly caregivers of the present study. One reason for this observation might be that caregiving activities stimulated the brain, which in turn led to the activation of dopamine receptors.

Our findings suggest that neurotransmission is likely to be highly active in elderly caregivers. Furthermore, given that dopaminergic neurons are reportedly more susceptible to neuroinflammation from chronic stress than other types of brain cells^[26-27], chronic stress in elderly caregivers might impair the dopaminergic activation system in the brain.

5. Conclusion

The present study identified factors which impact catecholamine secretion due to stress in caregivers of dementia patients. Specifically, age and BMI were found to impact catecholamine levels. In view of this finding, identifying factors which contribute to increased BMI will be important. Future studies aimed at gaining a better understanding of the lifestyle habits of caregivers and interventional studies aimed at reducing BMI are needed. Furthermore, the small sample size was another limitation of this study. Accordingly, future studies should follow and observe these blood biochemical factors in the long term.

Acknowledgements

We thank all participants for their cooperation with the study.

Disclosure statement

The authors declare no conflict of interest.

Table 1. Participant characteristics

	Median	IQR (25-75%)
Caregiver Age	76	72-79
Adrenaline (Ref: ≤100) (pg/mL)	39.5	22.3-56
Noradrenaline (Ref: 100-450) (pg/mL)	610	471-718.3
Dopamine (Ref: ≤20) (pg/mL)	21.0	14-31.3
BMI	23.4	20.7-25.2
SBP	142	125.5-147.8
DBP	78	72.8-87.5

BMI: Body mass Index, SBP: systolic blood pressure, DBP: diastolic blood pressure

Table 2. Associations of outcome measures

		1	2	3
1. Adrenaline	r	1.000		
	p (two-tailed)			
2. Noradrenaline	r	.137	1.000	
	p (two-tailed)	.333		
3. Dopamine	r	.188	.456*	1.000
	p (two-tailed)	.183	.001	

r: Spearman's correlation coefficient; p: significance level, *p < 0.05

Table 3. Correlations between catecholamines and caregiver factors

		Age	SBP	BMI
Adrenaline	r	.099	-.002	-.345*
	P	.487	.988	.012
Noradrenaline	r	.002	.030	.297*
	P	.991	.832	.032
Dopamine	r	.354*	-.066	-.069
	P	.010	.640	.625

r: Spearman's correlation coefficient; p: significance level, p < 0.1, *p < 0.05, **p < 0.01

Table 4. Logistic regression analysis with catecholamines as the dependent variable

Dependent variable	Variable (covariate)	B	P	OR	95% CI	
					Lower limit	Upper limit
Adrenaline	BMI	-.233	.017	.792	.654	.960
Noradrenaline	BMI	.191	.040	1.210	1.009	1.451
Dopamine	Caregiver age	.150	.025	1.162	1.019	1.324

Two groups for each catecholamines based on median values were created, as follows: adrenaline (<39.5=0; ≥39.5=1), noradrenaline (<610=0; ≥610=1), dopamine (<21=0; ≥21=1). B: partial regression coefficient, P: level of significance, 95%CI: 95% confidence interval, BMI: Body Mass Index.

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Author's contributions

Akemi Hirano conceived the idea and designed the study. Akemi Hirano carried out the data analysis and interpretation. Akemi Hirano wrote the first draft of the

manuscript and Yusuke Suzuki, Koichiro Ina, Joji Onishi critically discussed all versions of the manuscript. Yusuke Suzuki, Koichiro Ina, and Toshio Hayashi recruited the participants, and Akemi Hirano contributed to the overall supervision of the study.