JAMDA xxx (2017) 1.e1–1.e6

JAMDA

journal homepage: www.jamda.com

Original Study

Advanced Glycation End-Products Are Associated With the Presence and Severity of Paratonia in Early Stage Alzheimer Disease

Hans Drenth MPT[a,b,*], Sytse U. Zuidema PhD[c], Wim P. Krijnen PhD[a], Ivan Bautmans PhD[d], Cees van der Schans PhD[a,e], Hans Hobbelen PhD[a,c]

[a] Research Group Healthy Aging, Allied Healthcare and Nursing, Hanze University of Applied Sciences, Groningen, The Netherlands
[b] Zuid Oost Zorg, Organization for Elderly Care, Drachten, The Netherlands
[c] Department of General Practice and Elderly Care Medicine, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands
[d] Frailty in Aging Research Group and Gerontology Department, Vrije Universiteit Brussel, Brussels, Belgium
[e] Department of Rehabilitation Medicine, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands

Keywords:
Advanced glycation end-products
dementia
motor function
biomarker

A B S T R A C T

Objective: Paratonia, a distinctive form of hypertonia in patients with dementia, causes loss of functional mobility in early stage dementia to severe contractures and pain in the late stages. The pathogenesis of paratonia is not well understood. Patients in early stage dementia with diabetes mellitus showed a significantly higher risk for the development of paratonia. Both Alzheimer disease and diabetes mellitus are related to higher concentrations of advanced glycation end-products (AGEs). The purpose of this study is to explore the association of AGEs with the prevalence and severity of paratonia in patients with Alzheimer disease.
Design: Observational longitudinal, 1-year follow-up cohort study with 3 assessments.
Setting: Day care centers for patients with dementia.
Participants: A total of 144 community-dwelling patients with early stage Alzheimer or Alzheimer/vascular disease were recruited from 24 dementia day care centers in The Netherlands.
Measurements: The presence of paratonia (Paratonia Assessment Instrument), the severity of paratonia (Modified Ashworth Scale for paratonia), and AGE levels (AGE-reader).
Results: From the 144 participants (56.3% female and 43.7% male, with a mean [standard deviation] age of 80.7 [7.7] years), 118 participants were available for final follow-up. A significant association between AGE levels and the presence of paratonia (odds ratio 3.47, 95% confidence interval [CI] 1.87–6.44, $P < .001$) and paratonia severity ($\beta = 0.17$, 95% CI 0.11–0.23, $P < .001$) was determined. In participants who developed paratonia and those with persistent paratonia throughout the study the AGE levels (95% CI −0.38 to −0.13, $P < .001$ and 95% CI −0.46 to −0.06, $P = .012$, respectively) and the severity of paratonia (95% CI −0.60 to −0.35, $P < .001$ and 95% CI −0.38 to −0.12, $P < .001$, respectively) significantly increased, whereas the AGE levels remained stable in those participants without paratonia. Notwithstanding, change in AGE levels was not significantly ($P = .062$) related to change in paratonia severity, mixed model analyses provided evidence for both a significant time and between participant effect of AGEs on paratonia severity.
Conclusions: This study suggests that elevated AGE levels are a contributing factor to paratonia and its severity and could be the result of peripheral biomechanical changes reducing elasticity and increasing stiffness. These results provide a new perspective on paratonia and gives rise to further research whether paratonia could be postponed or movement stiffness can be improved by reducing AGE levels.

This work was supported by the Dutch Alzheimer organization (grant number: WE.03-2012-09) and by regular funds of the Research Group Healthy Aging, Allied Healthcare and Nursing, Hanze University Groningen, the Department of General Practice and Elderly Care Medicine, University Medical Center Groningen, the Frailty in Aging Research Group, and Gerontology Department, Vrije Universiteit Brussels and ZuidOostZorg, Organization for Elderly Care, Drachten.

* Address correspondence to Hans Drenth, MPT, Research Group Healthy Aging, Allied Healthcare and Nursing, Hanze University of Applied Sciences, PO Box 3109, Groningen 9701 DC, The Netherlands.
E-mail address: j.c.drenth@pl.hanze.nl (H. Drenth).

http://dx.doi.org/10.1016/j.jamda.2017.04.004
1525-8610/

A wide variety of movement disorders are reported in patients with dementia. Paratonia, a distinctive form of hypertonia, is one of these movement disorders and is characterized by an active unintentional resistance against passive movement.[1] Paratonia has a prevalence of 10% in the early/mild stages, and up to 90%–100% in later/severe stages of dementia. As dementia progresses, the severity of paratonia increases from actively assisting the passive movement (because of an inability to relax) and mild resistance toward severe high resistance and muscle tone that causes loss of mobility, severe contractures, and pain in the last stage of dementia.[2,3] Resistance in paratonia is variable, in particular in the very early stages of dementia paratonia can fluctuate between no resistance, actively assisting, and active resistance against passive movement.[2–4] In early-stage dementia, paratonia hampers functional mobility such as raising from a chair, walking, and turning.[2] The pathogenesis of paratonia is not well understood, and no effective interventions are available to prevent, postpone, or combat paratonia.

It has been shown that patients in early stage dementia with diabetes mellitus (DM) have a significantly higher risk for the development of paratonia in comparison with those with dementia but without DM.[1] Previous research also reported that DM is a risk factor for muscle rigidity in patients without dementia.[5] Interestingly, both Alzheimer disease (AD) and DM are related to higher concentrations of advanced glycation end- products (AGEs), suggesting that AGEs could possibly be involved in the development of paratonia. The occurrence of AGEs is mediated by nonenzymatic condensation of a reducing sugar with an amino group.[6–8] With aging, there is an imbalance between the formation and natural clearance of AGEs, which results in an incremental accumulation in tissues.[6–9]

As stated before, the pathogenesis of paratonia is not well understood. Obviously with dementia, central nervous system pathology plays a role; yet, peripheral biomechanical changes are also suggested. In this perspective, it is of interest to know that the cross-linking processes by AGEs are responsible for an increasing proportion of insoluble extracellular matrix and thickening of the tissues, thereby increasing mechanical stiffness and loss of elasticity.[6,10,11] Noncross-linking effects occur through the binding of AGEs to the receptor for AGEs (RAGE). RAGE is a multiligand member of the immunoglobulin superfamily of cell surface molecules that is widely localized in a variety of cell lines, including endothelial, neuronal, smooth muscle, mesangial, and monocytes.[12] AGE/RAGE binding subsequently incites activation of intracellular signaling, gene expression, and production of proinflammatory cytokines and free radicals. At the peripheral (tissue) level, these inflammatory processes exhibit strong proteolytic activity by which the collagen becomes more vulnerable and tissue elasticity decreases.[12,13] At the central level (central nervous system), AGE/RAGE interaction appears to affect neuronal function.[7,13]

The role of AGEs in the development of paratonia is currently unknown. The purpose of this study is to explore the association of AGEs with the prevalence and severity of paratonia in patients with AD.

Methods

Study Design and Ethical Consideration

This study was a multicenter, longitudinal, 1-year follow-up cohort study with 3 assessments; at baseline, after 6 months, and after 12 months. The medical ethical committee of the University Medical Center Groningen approved the study (NL43641.042.13).

Study Population

Participants, recruited from 24 dementia day care centers in The Netherlands, were considered to be eligible for inclusion in the study when they satisfied the following criteria: (1) an established diagnosis of AD or Alzheimer/vascular dementia (AD/VaD) according to DSM-IV criteria[14]; (2) Early stage dementia; a score of stage 5 or lower on the global deterioration scale[15]; and (3) having a light colored (Caucasian) skin (skin pigmentation influence AGE measurements[16]). Written informed consent was obtained from patients or their legal representatives. Participants were excluded if they had an established diagnosis of dementia other than type AD or AD/VaD or were using first generation psychotropic drugs because these drugs can possibly mimic paratonic rigidity.

Outcome Measures

Paratonia

The presence of paratonia was assessed by trained and experienced physiotherapists by employing the Paratonia Assessment Instrument (PAI), a reliable and valid measurement based on a successively passive mobilization of both shoulders toward anteflexion/retro-flexion, elbows toward flexion/extension, and combined hips/knees toward extension/flexion.[17] With the participant in a sitting position, the examiner began with a slow movement of the limb, after which the movement was accelerated. Paratonia was diagnosed as being present when the following 5 criteria are all met: (1) an involuntary variable resistance; (2) a degree of resistance that varied depending on the speed of the movement (eg, a low resistance to slow movements and a high resistance to fast movement); (3) resistance to passive movement in any direction; (4) no clasp-knife phenomenon; and (5) resistance in 2 movement directions in the same limb or 2 different limbs.

We used a Modified Ashworth Scale, validated to assess paratonia severity (MAS-P) as described by Waardenburg et al.[18] In the MAS-P, each category contains a tone and passive movement feature, thereby creating a more consistent scale for paratonia.[18] During the PAI assessment, the assessor quantified the muscle tone based on the resistance induced by the passive movements of the limbs into a total of 12 MAS-P scores (the corresponding movement directions from the PAI). The MAS-P is based on a 5-point scale ranging from 0 to 4, meaning 0 = no increase in muscle tone or no resistance during passive movement, 1 = slight increase in muscle tone or slight resistance during passive movement, 2 = more marked increase in muscle tone or more marked resistance during passive movement, 3 = considerable increase in muscle tone or considerable resistance during passive movement, and 4 = severe resistance such that passive movement is impossible. A score of 0.5 was assigned in the event of active assistance. For further analyses, the 12 scores were summarized as the average MAS-P value. The MAS-P shows acceptable reliability.[18]

AGE levels

AGE levels were assessed by the main researcher through skin auto fluorescence (SAF) by using an AGE Reader device (Diagnoptics, Groningen, The Netherlands). The AGE reader measures fluorescent skin tissue AGEs, which correlate with nonfluorescent AGEs.[19,20] The AGE reader is a desktop device that has a light source that illuminates the skin of the forearm and uses the fluorescent properties of AGEs to measure tissue accumulation of AGEs.[19] SAF is calculated (by the AGE reader software) as the ratio between the emission light and the excitation light, multiplied by 100 and expressed in arbitrary units. An elevated SAF (arbitrary units) score corresponds to a high tissue AGEs level.[19] All AGE reader measurements were performed at room temperature in a standardized semi-dark environment with the participants in a seated position and the volar side of the right forearm placed on top of the AGE reader. The measurements were performed on the skin without sweat, skin lotions, or visible skin abnormalities and with the assessor being blinded for PAI/MAS-P scores. The mean of 3 consecutive measurements was used. The AGE reader is reported