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Use of skin advanced glycation end product levels measured using a simple noninvasive method as a biological marker for the diagnosis of neuropsychiatric diseases

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Abstract

Objectives: The accumulation of advanced glycation end products (AGEs) may be involved in the pathophysiology of several neuropsychiatric diseases. In this study, the skin AGEs level of several neuropsychiatric diseases was assessed with a simple noninvasive method. Moreover, whether skin AGE level can be used as a biomarker for the diagnosis of these diseases was evaluated.

Methods: A total of 27 patients with schizophrenia, 26 with major depressive disorder, and 10 with major neurocognitive disorders (MNDs), such as Alzheimer's disease or dementia with Lewy body, as well as 26 healthy controls were enrolled in this study. The skin AGE levels of the patients were assessed with an AGE scanner, a fluorometric method used to assay skin AGE levels.

Results: One-way analysis of covariance was performed after adjusting for significant covariates, including age. Although the group with MNDs had higher skin AGE levels than the other groups, the main effect of diagnosis did not significantly affect the skin AGE levels of the groups.

Conclusions: Skin AGE levels in neuropsychiatric diseases with mild symptoms did not significantly differ. Further large-scale studies using a simple noninvasive method for the early detection and treatment of MNDs must be conducted.

KEYWORDS

advanced glycation end products, carbonyl stress, neuropsychiatric disease, skin AGEs

1 | INTRODUCTION

Several peripheral biomarkers have been considered as diagnostic, therapeutic, and/or prognostic markers of neuropsychiatric diseases, such as schizophrenia (SZ) (Ohnuma et al., 2008, 2018; Ohnuma & Arai, 2011; Sannohe et al., 2017; Takeda et al., 2015; Tani et al., 2019) and major depressive disorder (MDD) (Baba et al., 2012; Caroleo et al., 2019; Kraus, Kadriu, Lanzenberger, Zarate, & Kasper, 2019; Lambert & Gressier, 2019; Satomura et al., 2011), and major neurocognitive disorders (MNDs), including Alzheimer's disease (AD) (El Kadmiri, Said, Slassi, El Moutawakil, & Nadifi, 2018; Olsson et al., 2016) and dementia with Lewy body (DLB) (Atik, Stewart, & Zhang, 2016; Jellinger, 2018; McKeith et al., 2017; Schade & Mollenhauer, 2014). These studies were performed based on the pathophysiological mechanisms underlying each disease,

such as disturbed homeostasis of neurotransmitters, including peripheral monoamine and amino acid, neurodevelopmental problems, impaired immune response, and complex mental health problems. Recently, studies have focused on the importance of early intervention in individuals with AD because the disease can progress to a certain degree with inflammation caused by the accumulation of amyloid beta (Aβ) peptides and neurofibrillary tangles (NFTs) in hyperphosphorylated tau protein and because no anti-dementia drugs can improve the symptoms of this condition. Recently, the following nuclear molecular imaging techniques, which are effective tools for the diagnosis of diseases at an earlier stage, have been developed (Valotassiou et al., 2018): single-photon emission computed tomography using radioisotopes, such as technetium-99m or iodine-123 with high-spatial resolution and positron emission tomography using radiopharmaceuticals labeled with an isotope to visualize the accumulation of Aβ peptides and NFTs in hyperphosphorylated tau protein. However, these neuroimaging modalities are expensive and invasive (Oukoloff et al., 2015; Valotassiou et al., 2018). Thus, the use of biomarkers measured using a simple noninvasive and cost-effective technique is preferred.

Recently, several peripheral biomarker studies have shown that molecules associated with micro-inflammation can be involved in the pathophysiology of neuropsychiatric diseases (Ohnuma et al., 2019; Ohnuma & Arai, 2011). Recently, the association between carbonyl stress and advanced glycation end products (AGEs) in MND associated with aging, such as AD (Takeuchi & Yamagishi, 2009; Yamagishi, Nakamura, Inoue, Kikuchi, & Takeuchi, 2005) and DLB (Castellani, Smith, Richey, & Perry, 1996; Munch et al., 2000; Munch, Gerlach, Sian, Wong, & Riederer, 1998) has been the focus of research. Moreover, recent studies have found high serum levels of pentosidine and glyceraldehyde-derived AGEs and lower levels of soluble receptors that can inhibit the effects of AGEs, which are markers of carbonyl stress, and their related molecules in patients with SZ (Arai et al., 2010; Emanuele et al., 2011; Katsuta et al., 2014; Kouidrat et al., 2013; Miyashita et al., 2014a, 2014b; Steiner et al., 2009; Takeda et al., 2015). Furthermore, carbonyl stress and micro-inflammation-related molecules can be used as therapeutic or prognostic biomarkers in patients with SZ (Ohnuma et al., 2018).

As previously mentioned, a noninvasive method for measuring skin AGE levels must be developed (Hagen et al., 2017; Kouidrat et al., 2013; Tani et al., 2019). Some studies have shown positive correlation between skin AGE levels in some tissues such as blood, kidney, blood vessels, bone, and urine (Kida, Saito, Shinohara, Soshi, & Marumo, 2019; Mulder et al., 2006; Yamagishi, Fukami, & Matsui, 2015). Furthermore, it was reported by skin biopsy study that skin autofluorescence levels reflect the same position AGE levels such as collagen-linked fluorescence, pentosidine, carboxymethyl-lysine, and carboxyethyl lysine (Meerwaldt et al., 2004). These studies measuring skin AGE levels were also performed in neuropsychiatric diseases and the results showed alterations in the levels in patients with MDD (van Dooren et al., 2017), SZ (Kouidrat et al., 2013), and MNDs (Igase et al., 2017). Thus, the present study aimed to investigate whether skin AGE levels measured using a simple noninvasive method can be a used as a biomarker for the diagnosis of patients with SZ, MDD, and MNDs.

2 | METHODS

2.1 | Study population

The study was carried out in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of Juntendo Hospital (17-074). All participants provided a written informed consent prior to participation. All Japanese patients with SZ, MDD, and MNDs (AD and DLB) were enrolled at the Department of Psychiatry, Juntendo University Hospital, Tokyo, Japan. Moreover, the patients met the criteria of the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) for each disease. All MNDs, including AD, were diagnosed according to the NINCDS-ADRDA criteria (McKhann et al., 1984), and none of the patients had a family history of AD. Patients with DLB were diagnosed according to the diagnostic criteria by McKeith et al. (2005). Healthy controls (HC) without current or previous history of psychosis and neurocognitive disorders according to the Structured Clinical Interview for DSM-5 (SCID-5) were recruited from the Juntendo Hospital website. The inclusion criteria of this study were as follows: (a) patients aged between 20 and 75 years; (b) those without history of diabetes, kidney dysfunction, and chronic inflammatory disease (e.g., collagen disease), (c) those with body mass index (BMI) <30 kg/m^2 (indicative of moderate obesity); and (d) those without any history of smoking or alcoholism. The severity of clinical symptoms was assessed using the Brief Psychiatric Rating Scale (BPRS) for SZ, with each item rated on a 7-point scale, as previously described (Katsuta et al., 2014). The severity of MND and MMD were evaluated using the Mini-Mental State Examination (MMSE) (Folstein, Folstein, & McHugh, 1975) and Hamilton depression scale (HAM-D) (Hamilton, 1960), respectively.

2.2 | Measurements of skin AGE levels

Skin AGE levels were assessed with a TrūAge Scanner (Morinda Worldwide Inc.), a fluorometric method used to assay AGE levels in the skin, as previously reported (Tani et al., 2019). In brief, the forearm of the patient's dominant arm was placed on the TrūAge Scanner. The skin in the area that is assessed should be healthy, homogeneous, free of birthmarks, tattoos, or excessive hair growth and must not have recent exposure to skin creams or any other substances that may contain fluorescent properties. The measurement takes ~15 s. Each measurement was performed in triplicate, and the median value was used for statistical analysis.

2.3 | Statistical analysis

All statistical analyses were conducted using the Statistical Package for the Social Sciences software version 22 (IBM Corp., Armonk, NY). Fisher's exact test was used to analyze the difference between groups in terms of sex. A p value <.05 was considered statistically significant. Differences skin AGE levels are examined with one-way analysis of

TABLE 1 Clinical variables and skin AGEs levels in present participants

	Patients with				Fisher's exact test		Post hoc test	
	SZ $n = 27$	MDD $n = 26$	MND $n = 10$	HC $n = 24$	*p* value	χ^2	*p* value	*Z*
Sex, M/F	8/19	13/13	5/5	3/21	**.021**	**9.354**	**.005 (MDD vs. HC)**	**−2.811**
					Kruskal–Wallis test			
Age, mean ± *SD* (years)	53.7 ± 8.9	53.1 ± 7.4	61.3 ± 8.3	53.0 ± 6.5	.067	7.157	NA	
BMI, mean ± *SD* (kg/m^2)	23.0 ± 3.9	22.0 ± 1.9	22.2 ± 3.0	21.2 ± 2.1	.252	4.086	NA	
Clinical symptoms	34.2 ± 14.7 (BPRS)	7.3 ± 6.8 (HAM-D)	23.9 ± 5.8 (MMSE)	NA	NA			
					ANCOVA*			
					p value	*F*		
Skin AGE levels, mean ± *SD* (A.U.)	230.2 ± 40.5	238.5 ± 46.9	257.0 ± 39.9	234.6 ± 45.1	.91	0.181	NA	

Note: Patients with schizophrenia (SZ, $n = 27$), major depressive disorder (MDD, $n = 26$), major neurocognitive disorder (MND, $n = 10$), and healthy controls (HCs, $n = 24$).

Abbreviations: AGEs, advanced glycation end products; BMI, body mass index; NA, not applicable.

[a]Detailed statistical values for ANCOVA are provided in the Section 3 of the text. *p* values with statistical significance are in bold.

covariance (ANCOVA) to assess the association between SZ, MDD, MND, and HC as well as relevant covariates, including age, sex, and BMI.

3 | RESULTS

Finally, 87 participants were enrolled in the study. Among the participants, 27 presented with SZ, 26 with MDD, 10 with MND ($n = 8$, AD; $n = 2$, LB), and 26 with HC (Table 1). The groups significantly differed in terms of sex, and post hoc test showed that the number of female patients with HC was significantly higher than that of female patients with MDD. However, no significant differences were found in terms of BMI and age between the groups (Table 1).

To ensure whether there are changes in skin AGE levels among the groups, one-way ANCOVA was performed using skin AGE levels as dependent variables and age and BMI as covariates because age and obesity (as reflected by BMI) can increase skin and peripheral AGE levels based our previous studies (Sannohe et al., 2017; Takeda et al., 2015; Tani et al., 2019). Sex was also used as a covariate (dummy variable) because its distribution was significantly different between the groups (Table 1). For skin AGE levels, the relationship between SZ, MDD, MND, and HC as well as age ($F = 2.52$, $df = 3$, $p = .06$), sex ($F = 1.51$, $df = 3$, $p = .22$), and BMI ($F = 0.55$, $df = 3$, $p = .65$) did not significantly differ. Although age showed significant regression ($\beta = 1.99$, $p = .001$), sex and BMI did not ($\beta = -1.32$, $p = .90$/$\beta = -2.74$, $p = .09$). Thus, age was used as a covariate. No significant difference was observed in skin AGE levels between the groups, despite the ages that were thought to affect AGE levels. The main effect of diagnosis did not show significant difference in skin AGEs levels among the groups (Table 1).

4 | DISCUSSION

In the present study, we investigated whether skin AGE levels measured using a simple noninvasive method could be used as a biomarker for the diagnosis of several neuropsychiatric diseases, such as SZ, MDD, and HC, and MNDs. One-way ANCOVA was performed after adjusting for significant covariates, including age. Patients with MND had a higher skin AGE level than patients with SZ, MDD, and HC. However, the main effect of diagnosis failed to show the statistically significant difference in skin AGEs levels among the groups. In a recent study, patients with SZ had significantly higher levels of peripheral carbonyl stress markers, such as pentosidine (Katsuta et al., 2014; Sannohe et al., 2017) and glycer-AGEs (Takeda et al., 2015), than those with HC. These studies included a large number of participants but failed to show whether AGE levels can be used as diagnostic markers because discriminant analysis did not obtain statistically significant results (Takeda et al., 2015). However, micro-inflammation markers, particularly soluble tumor necrosis factor receptor 1, can be used to identify some patients with SZ and HC who are resistant to treatment (Nishimon et al., 2017; Ohnuma et al., 2018). Thus, the markers of micro-inflammation can be used as prognostic biomarkers of treatment resistance, but not as diagnostic markers. In the present study, the relationship between skin AGE levels and severity of clinical status was not analyzed because only a small number of participants were included in each group in the regression analysis, and the participants from the outpatient department only presented with mild symptoms. Indeed, as shown in Table 1, the SZ group in the current study had milder symptoms (BPRS: mean ± *SD* = 34.2 ± 14.7) than the group in a previous study in which increased levels of peripheral carbonyl stress markers were observed in 274 participants with SZ (BPRS: mean ± *SD* = 59.3 ± 13.9) (Sannohe et al., 2017). The MDD group in

the current study had mild symptoms based on the HAM-D scores (7.3 ± 6.8, cut off score: <7), and the MND group also had mild cognitive symptoms (MMSE score, mean ± *SD*: 23.9 ± 5.8). That is, patients with mild AD had an MMSE score between 17 and 23. Thus, further studies must investigate the relationship between skin AGE levels and severity of symptoms, particularly those of MND, because diabetes mellitus and its associated carbonyl stress may be involved in the pathophysiology of AD (Sato et al., 2006; Takeuchi & Yamagishi, 2009) and in the early detection of AD using invasive methods that measure AGE levels in the cerebrospinal fluid or serum (Yamagishi et al., 2005). Recently, early clinical interventions were recommended for the prevention of the onset and progression of MND because numerous drugs used in clinical trials, including the beta-secretase inhibitor clinical trials for AD, were found to be ineffective (Anderson, Hadjichrysanthou, Evans, & Wong, 2017).

The present study had some limitations. That is, the number of participants was relatively small, and the severity of clinical symptoms was not assessed because all participants from the outpatient department presented with mild symptoms.

In conclusion, the skin AGE levels of patients with SZ, MDD, MND, and HC did not significantly differ. Thus, using skin AGE-level measurement as a diagnostic biomarker in neuropsychiatric diseases is "premature" for better clarity. However, this method might be useful for detecting the early state of well-known disease complications of neuropsychiatric diseases such as diabetes mellitus and cardiovascular diseases (Hoffman, 2017; Pugazhenthi, Qin, & Reddy, 2017) and for the prevention of onset and progression of these comorbidities. From this point of view, cohort-studies using skin AGEs measurements as predictive marker for these comorbidities would be worthy and should be conducted in each disease.

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CONFLICT OF INTEREST

The authors declare no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

All authors contributed to the conception, design, and writing of this manuscript.

DATA AVAILABILITY STATEMENT

The data used in this study are available from the corresponding author upon reasonable request.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The Ethics Committee of Juntendo University School of Medicine approved this study (17-074). All participants provided a written informed consent prior to participation.

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