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ORIGINAL RESEARCH

Age Related Cognitive Function Was Positively Associated with Diastolic Pressure and Negatively Associated with Antibody Expression in Chinese Oldest-Old and Centenarian Adults

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Purpose: Age related cognitive function (ARCF) is of increasing concern in an aging population. Few studies have examined the relationships between ARCF and antibody expression or blood pressure, particularly in older populations. Large sample sizes are needed to elucidate these relationships to inform better strategies for identification and prevention of cognitive decline. The present study was designed to investigate these relationships in Chinese oldest-old and centenarian adults.

Patients and Methods: A household survey was performed that included 436 centenarians and 520 oldest-old adults (80–99 years) residing in 16 cities and counties of Hainan province, China. ARCF was assessed using the mini-mental state examination.

Results: The median age of participants in this study was 92 years, with a range of 80 to 116 years. Females accounted for 68.5% (655) of the participant pool. Multivariate linear regression analysis showed that age [Exp(B): −0.220, 95% confidence interval (CI): −0.270–-0.169], female gender [Exp(B): −3.459, 95% CI:-4.458–-2.460], Han ethnicity [Exp(B): −1.732, 95% CI: −2.693–-0.772], serum creatinine [Exp(B): −0.019, 95% CI: −0.037–-0.001], immunoglobulin light chain KAP [Exp(B): −0.008, 95% CI: −0.015–0.000], and anti-ribonucleoprotein antibody [Exp(B): −6.393, 95% CI: −10.898–-1.887] were negatively associated with ARCF ($P < 0.05$). Coronary artery disease [Exp(B): 1.957, 95% CI: 0.170–3.744] and diastolic pressure [Exp(B): 0.041, 95% CI: 0.002–0.079] were positively associated with ARCF ($P < 0.05$).

Conclusion: ARCF was positively associated with diastolic pressure and negatively associated with antibody expression in Chinese oldest-old and centenarian adults.

Keywords: age related cognitive function, antibody expression, centenarian, diastolic pressure, oldest-old

Introduction

Age related cognitive function (ARCF) is of increasing concern in an aging population. The brain is an immune privileged organ, and many immune factors expressed in the brain are essential for removing pathogens, misfolded proteins, and dead cells.[1] Recent studies have suggested that immune factors are closely related to neurodegenerative disease, and can be directly activated by fibrillar Aβ and neurofibrillary tangles.[2,3] Understanding the role of immune

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factors such as expressed antibodies in modulation of ARCF in older populations is critical.[3,4] Recent studies have shown that abnormal blood pressure may also contribute to ARCF, and patients with abnormal blood pressure were at significantly higher risk of cognitive decline.[5,6]

Few studies have evaluated the relationships between ARCF and antibody expression or blood pressure, particularly in older populations. Moreover, these studies primarily included adults that would not be considered "oldest-old" or centenarians, or included older adults in Western countries.[3–7] Age and region may be associated with ARCF, and the factors that contribute to ARCF remain unclear.[8] Therefore, large sample sizes are needed to elucidate these relationships in Chinese oldest-old and centenarian adults to aid in development of strategies to identify and prevent cognitive decline. Hainan has the highest density of oldest-old and centenarian adults in China, and the China Hainan Centenarian Cohort Study (CHCCS) is a data source for a large population-based sample of oldest-old and centenarian adults. The present study was designed to investigate the relationships between ARCF and antibody expression or blood pressure in Chinese oldest-old and centenarian adults. In other words, the hypothesis of the present study was that ARCF may be related to antibody expression and blood pressure in Chinese oldest-old and centenarian adults.

Materials and Methods

Using the list of oldest-old and centenarian adults provided by the Department of Civil Affairs of Hainan Province, China, a household survey was conducted on all centenarians (100 years or older) and oldest-old adults (80–99 years) residing in 16 cities and counties of Hainan province from June 2014 to June 2016 (Figure 1).[9,10] The survey sample of 1863 cases included 966 centenarians and 897 oldest-old adults. The inclusion criteria were: 1) aged ≥ 80 years; 2) residing in Hainan province. The exclusion criteria were: 1) missing data; 2) autoimmune diseases. Following application of the inclusion and exclusion criteria, 436 centenarians and 520 oldest-old adults were included in this study. This study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Chinese People's Liberation Army General Hospital (301HNLL-2016-01). All participants provided written informed consent before participating in the study.

A household survey method was used to collect basic information using interview questionnaires, physical examinations, and blood tests conducted by systematically trained local doctors and nurses who could communicate in the local language. Data collected in this study included age, sex, ethnicity, education level (illiteracy, elementary school level, and junior high school level), stroke, diabetes, coronary artery disease (CAD), body mass index (BMI), systolic pressure, diastolic pressure, alanine aminotransferase (ALT), aspartate aminotransferase, serum creatinine (Scr), urea nitrogen, uric acid (UA), triglyceride, high density lipid cholesterol and low density lipid cholesterol, immunoglobulin A, immunoglobulin G, immunoglobulin M, immunoglobulin E, complement C3, complement C4, immunoglobulin light chain KAP,

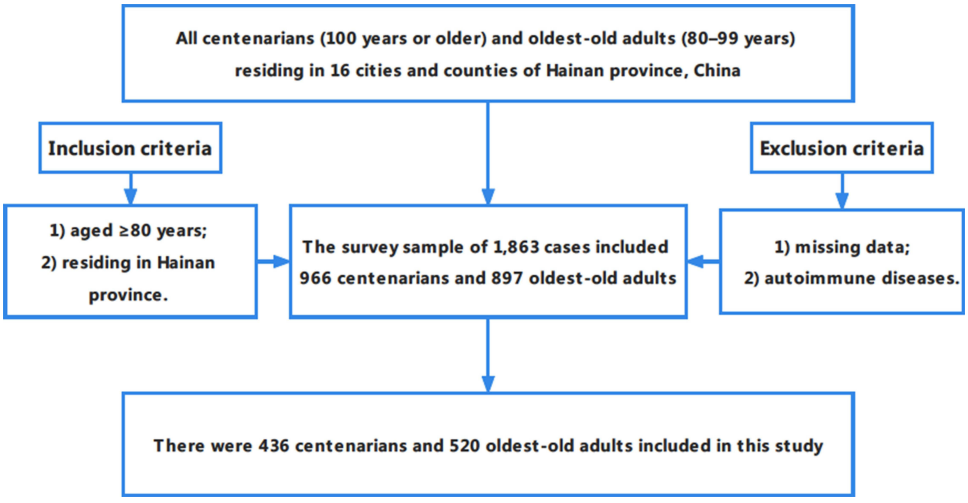

Figure 1 Flow chart of the participant selection process.

immunoglobulin light chain LAM, anti-cardiolipin antibody, anti-β2 glycoprotein I antibody, anti-ribonucleoprotein antibody, anti-Sm antibody, anti-Sjogren syndrome antigen A antibody, anti-Sjogren syndrome antigen B antibody, anti-scleroderma-70 antibody, anti-mitochondrial antibody, proliferating-cell nuclear antigen antibody, anti-Jo-1 antibody, anti-centromere antibody, anti-double-stranded deoxyribonucleic acid antibody, anti-nucleosome antibody, anti-histone antibody, anti-ribosomal P-protein antibody, and anti-pm-scl antibody.

The mini-mental state examination (MMSE) was administered by specialized neurologists to evaluate ARCF during the same visit in which interview questionnaires were investigated, and physical examinations and blood tests were performed.[11] The Georgia Centenarian Study has previously showed that age and education could significantly affect performance of MMSE.[12] Identification of age related cognitive decline (ARCD) using the MMSE based on education level were as follows: illiteracy, 17 points; elementary school level, 20 points; and junior high school level, 24 points.[13,14]

Statistical Analysis

Statistical analysis was performed using Statistic Package for Social Science 19.0 software package (Chicago, IL, USA). Data were presented as means and standard deviations (continuous variables with normal distributions), medians and interquartile ranges (continuous variables with skewed distributions), and numbers and percentages (categorical variables). Comparisons were performed between participants with and without ARCD using Student's t-tests for continuous variables with normal distributions, Mann–Whitney *U*-tests for continuous variables with skewed distributions, and Chi-squared tests for categorical variables. All variables evaluated in the study were included in the multivariate linear regression analysis, which was used to analyze the variables associated with ARCF. $P < 0.05$ (two-sided) was considered statistically significant.

Results

The median age of participants in this study was 92 years, with a range of 80 to 116 years. Females accounted for 68.5% (655) of the participant pool. As shown in Table 1, participants with ARCD were older, more likely to be female and classified as "other ethnicity", had a lower proportion of CAD, had lower levels of BMI, diastolic pressure, ALT, and UA, and higher levels of immunoglobulin light chain KAP and anti-β2 glycoprotein I antibody. In addition, participants with ARCD had a higher proportion of illiteracy, and had anti-scleroderma-70 antibody than those without ARCD ($P < 0.05$).

Multivariate linear regression analysis showed that age [Exp(B): −0.220, 95% confidence interval (CI): −0.270–-0.169], female gender [Exp(B): −3.459, 95% CI: −4.458–-2.460], other ethnicity [Exp(B): −1.732, 95% CI: −2.693–-0.772], Scr [Exp(B): −0.019, 95% CI: −0.037–-0.001], immunoglobulin light chain KAP [Exp(B): −0.008, 95% CI: −0.015–0.000], and anti-ribonucleoprotein antibody [Exp(B): −6.393, 95% CI: −10.898–-1.887] were negatively associated with ARCF ($P < 0.05$; Table 2). CAD [Exp(B):1.957, 95% CI: 0.170–3.744] and diastolic pressure [Exp(B): 0.041, 95% CI: 0.002–0.079] were positively associated with ARCF ($P < 0.05$).

Discussion

The present study found a positive association between diastolic pressure and ARCF in Chinese oldest-old and centenarian adults. This result was consistent with that in a study in which the incidence of cognitive decline was associated with reduced blood pressure at follow-up.[15] Furthermore, hypotension and stroke are strong risk factors for development of cognitive decline.[16] Lower diastolic pressure and orthostatic hypotension in older populations have been shown to be strongly correlated with increased risk of cognitive decline.[17] Reduced diastolic pressure can limit blood supply to the brain, resulting in reduced blood perfusion of the brain, and exacerbation of cognitive decline.[18] Reduced blood pressure may be related to small vessel disease (lacunar infarction, leukoaraiosis, subcortical white matter lesion, or micro-bleed) or large vessel disease (stroke).[19] Older populations can exhibit varying degrees of vascular disease, hypotension, and cognitive decline. In addition to vascular changes, pathological changes in brain regions responsible for blood pressure regulation may promote reduced blood pressure, resulting in cognitive decline.[20] Adequate control of blood pressure to prevent hypotension may help to preserve cognitive function in older populations.

Older populations with chronic kidney disease are at increased risk of cognitive decline. The prevalence of cognitive decline in patients undergoing dialysis is particularly high, with a range of 30% to 87%.[21,22] Furthermore, chronic kidney

Table 1 Demographic and Blood Analysis Data for Individuals with and without ARCD

Characteristic	With ARCD (n=740)	Without ARCD (n=216)	P
Age (year)	100 (85, 102)	85 (82, 100)	<0.001
Sex, n (%)			<0.001
Male	197 (26.6)	104 (48.1)	
Female	543 (73.4)	112 (51.9)	
Ethnicity, n (%)			0.035
Han	651 (88.0)	201 (93.1)	
Other	89 (12.0)	15 (6.9)	
Education level, n (%)			<0.001
Illiteracy	633 (85.5)	151 (69.9)	
Elementary school level	72 (9.7)	47 (21.7)	
Junior high school level	35 (4.8)	18 (8.4)	
Stroke, n (%)	14 (1.9)	1 (0.5)	0.137
Diabetes, n (%)	46 (6.2)	15 (6.9)	0.700
Coronary artery disease, n (%)	34 (4.6)	18 (8.3)	0.033
BMI (Kg/m^2)	19 (17, 22)	20 (18, 22)	0.001
MMSE	10 (6, 13)	23 (20, 26)	<0.001
Systolic pressure (mmHg)	150 (133, 169)	148 (133, 170)	0.796
Diastolic pressure (mmHg)	77 (70, 86)	79 (72, 90)	0.017
ALT (U/L)	10.7 (8.4, 14.4)	12.1 (9.6, 15.9)	<0.001
AST (U/L)	21.5 (18.5, 25.5)	21.7 (18.9, 26.3)	0.355
Scr (umol/L)	80 (66, 98)	84 (64, 99)	0.528
UN (mmol/L)	5.5 (4.4, 7.0)	5.6 (4.7, 6.8)	0.790
UA (umol/L)	328.5 (266.0, 389.0)	348.5 (293.1, 404.8)	0.008
Triglyceride (mmol/L)	1.05 (0.83, 1.50)	1.06 (0.78, 1.47)	0.406
HDL-C (mmol/L)	1.40 (1.14, 1.69)	1.39 (1.18, 1.64)	0.775
LDL-C (mmol/L)	2.88 (2.37, 3.48)	2.90 (2.41, 3.57)	0.430
Immunoglobulin A (mg/dl)	330 (254, 414)	334 (246, 426)	0.757
Immunoglobulin G (mg/dl)	1535 (1343, 1770)	1515 (1310, 1740)	0.227
Immunoglobulin M (mg/dl)	106 (74, 145)	97 (69, 137)	0.130
Immunoglobulin E (IU/mL)	220 (71, 784)	222 (63, 597)	0.713
Complement C3 (mg/dl)	105 (90, 120)	105 (92, 119)	0.881
Complement C4 (mg/dl)	25 (20, 31)	24 (20, 31)	0.477
Immunoglobulin light chain KAP (mg/dl)	399 (336, 459)	370 (321, 438)	0.004
Immunoglobulin light chain LAM (mg/dl)	206 (174, 244)	204 (178, 229)	0.529
Anti-cardiolipin antibody (RU/mL)	2.30 (2.00, 3.44)	2.00 (2.00, 3.79)	0.184
Anti-β2 glycoprotein I antibody (RU/mL)	4.10 (2.00, 6.78)	3.29 (2.00, 6.29)	0.019
Anti-ribonucleoprotein antibody, n (%)	731 (98.8)	216 (100)	0.103
Anti-Sm antibody, n (%)	735 (99.3)	214 (99.1)	0.704
Anti-Sjogren syndrome antigen A antibody, n (%)	680 (91.9)	204 (94.4)	0.211
Anti-Sjogren syndrome antigen B antibody, n (%)	733 (99.1)	214 (99.1)	0.979
Anti-scleroderma-70 antibody, n (%)	736 (99.5)	211 (97.7)	0.018
Anti-mitochondrial antibody, n (%)	721 (97.4)	212 (98.1)	0.546
Proliferating-cell nuclear antigen antibody, n (%)	727 (98.2)	210 (97.2)	0.344
Anti-Jo-1 antibody, n (%)	731 (98.8)	214 (99.1)	0.725
Anti-centromere antibody, n (%)	728 (98.4)	211 (97.7)	0.498
Anti-double-stranded deoxyribonucleic acid antibody, n (%)	709 (95.8)	204 (94.4)	0.394
Anti-nucleosome antibody, n (%)	738 (99.7)	215 (99.5)	0.656
Anti-histone antibody, n (%)	726 (98.1)	212 (98.1)	0.970
Anti-ribosomal P-protein antibody, n (%)	729 (98.5)	214 (99.1)	0.531
Anti-pm-scl antibody, n (%)	738 (99.7)	214 (99.1)	0.189

Abbreviations: ARCD, age related cognitive decline; BMI, body mass index; MMSE, mini-mental state examination; ALT, alanine aminotransferase; AST, aspartate aminotransferase; Scr, serum creatinine; UN, urea nitrogen, UA, uric acid; HDL-C, high density lipid cholesterol; LDL-C, low density lipid cholesterol.

Table 2 Factors Associated with ARCF in Multivariate Linear Regression Analysis of Oldest-Old and Centenarian Adults

Factor	Exp (B)	95% CI	P
Age (years)	−0.220	−0.270–−0.169	<0.001
Female, n (%)	−3.459	−4.458–−2.460	<0.001
Other ethnicity, n (%)	−1.732	−2.693–−0.772	<0.001
Stroke, n (%)	−1.924	−5.182–1.333	0.247
Diabetes, n (%)	1.164	−0.510–2.837	0.173
Coronary artery disease, n (%)	1.957	0.170–3.744	0.032
BMI (Kg/m^2)	0.017	−0.107–0.141	0.785
Systolic pressure (mmHg)	0.000	−0.020–0.021	0.990
Diastolic pressure (mmHg)	0.041	0.002–0.079	0.040
ALT (U/L)	0.067	−0.011–0.144	0.091
AST (U/L)	−0.034	−0.105–0.038	0.355
Scr (umol/L)	−0.019	−0.037–−0.001	0.036
UN (mmol/L)	0.105	−0.072–0.281	0.246
UA (umol/L)	0.005	0.000–0.010	0.060
Triglyceride (mmol/L)	−0.413	−1.116–0.290	0.250
HDL-C (mmol/L)	0.384	0.654–1.422	0.468
LDL-C (mmol/L)	0.231	−0.272–0.735	0.368
Immunoglobulin A (mg/dl)	0.001	−0.002–0.004	0.422
Immunoglobulin G (mg/dl)	0.000	−0.002–0.003	0.739
Immunoglobulin M (mg/dl)	−0.001	−0.008–0.005	0.700
Immunoglobulin E (IU/mL)	−2.3390E-5	0.000–0.000	0.792
Complement C3 (mg/dl)	−0.003	−0.023–0.018	0.805
Complement C4 (mg/dl)	−0.030	−0.080–0.019	0.232
Immunoglobulin light chain KAP (mg/dl)	−0.008	−0.015–0.000	0.040
Immunoglobulin light chain LAM (mg/dl)	0.002	−0.009–0.012	0.758
Anti-cardiolipin antibody (RU/mL)	−0.051	−0.111–0.009	0.097
Anti-β2 glycoprotein I antibody (RU/mL)	0.009	−0.036–0.053	0.695
Anti-ribonucleoprotein antibody, n (%)	−6.393	−10.898–−1.887	0.005
Anti-Sm antibody, n (%)	4.099	−1.163–9.362	0.127
Anti-Sjogren syndrome antigen A antibody, n (%)	0.649	−0.905–2.202	0.413
Anti-Sjogren syndrome antigen B antibody, n (%)	−0.670	−4.911–3.572	0.757
Anti-scleroderma-70 antibody, n (%)	1.530	−2.636–5.695	0.471
Anti-mitochondrial antibody, n (%)	0.006	−2.627–2.639	0.996
Proliferating-cell nuclear antigen antibody, n (%)	0.288	−2.645–3.220	0.847
Anti-Jo-1 antibody, n (%)	0.438	−3.358–4.235	0.821
Anti-centromere antibody, n (%)	0.153	−2.862–3.167	0.921
Anti-double-stranded deoxyribonucleic acid antibody, n (%)	0.991	−0.968–2.950	0.321
Anti-nucleosome antibody, n (%)	0.855	−6.270–7.980	0.814
Anti-histone antibody, n (%)	0.302	−2.630–3.234	0.840
Anti-ribosomal P-protein antibody, n (%)	−1.314	−4.771–2.143	0.456
Anti-pm-scl antibody, n (%)	2.669	−3.496–8.835	0.396

Abbreviations: ARCF, age related cognitive function; CI, confidence interval; BMI, body mass index; ALT, alanine aminotransferase; AST, aspartate aminotransferase; Scr, serum creatinine; UN, urea nitrogen, UA, uric acid; HDL-C, high density lipid cholesterol; LDL-C, low density lipid cholesterol.

disease has been shown to be closely associated with development of dementia and cognitive decline.[23–25] Scr is a marker of reduced kidney function and was previously associated with cognitive decline.[26] In our study, Scr was negatively associated with ARCF in Chinese oldest-old and centenarian adults. Reduced kidney function results in an inability to eliminate metabolites and toxins, which can accumulate in the body and negatively impact cognitive function.

We also found that anti-ribonucleoprotein antibody and immunoglobulin light chain KAP were negatively correlated with ARCF in Chinese oldest-old and centenarian adults. Immunoglobulin light chains are small protein molecules formed by plasma cells.[27–29] Previous studies have shown that accumulation of immunoglobulin light chains in the brain may contribute to reduced cognitive function.[30,31] In addition, other studies have shown that older patients positive for anti-ribonucleoprotein antibody had reduced cognitive function, and this reduction was mitigated by steroid treatment.[32,33] Therefore, reduction in anti-ribonucleoprotein antibody through steroid treatment may be a strategy to protect cognitive function in older populations.

Our study was subject to several limitations. First, this was a survey of Chinese oldest-old and centenarian adults, and the results may not be generalizable to all populations. Second, this was a cross-sectional study, and the findings need to be confirmed in studies with large sample sizes that include follow-up data collection.

Conclusions

ARCF was positively associated with diastolic pressure and negatively associated with antibody expression in Chinese oldest-old and centenarian adults.

Ethics Approval and Consent to Participate

This study was approved by the ethics committee of Hainan Hospital of Chinese People's Liberation Army General Hospital (301HNLL-2016-01). Informed consent was obtained from all participants and/or their legal guardians.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no conflicts of interest.

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