Decreased Antiatherogenic Protein Levels are Associated with Aneurysm Structure Alterations in MR Vessel Wall Imaging

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Objective: Thickened intracranial aneurysm wall with atherosclerotic remodeling is a part of its degenerative scenario. Current magnetic resonance (MR)-vessel wall imaging enables the detection of atherosclerotic wall thickening as aneurysm wall enhancement. The purpose of this study was to examine the correlation between identified atherosclerotic remodeling in vessel wall imaging, and systemic atherosclerosis-related risk factors. *Methods:* A total of 39 aneurysms in 38 consecutive patients scheduled to undergo microsurgical clipping or endovascular coiling of intracranial aneurysms were prospectively evaluated. All patients underwent aneurysm MR-vessel wall imaging and the presence of aneurysm wall enhancement on contrast-enhanced vessel wall imaging was evaluated. The relationship between aneurysm wall enhancement and patient demographic data, aneurysm morphology and atherosclerosis-related risk factors including blood laboratory data were assessed. *Results:* Aneurysm wall enhancement was detected in 19 of 39 intracranial aneurysms (48.7%). The maximum diameter of the intracranial aneurysm ($P < .01$), apolipoprotein A2 ($P < .01$) and apolipoprotein C2 ($P = .01$) was significantly associated with the presence of aneurysm wall enhancement. In multivariate logistic regression analyses, the maximum diameter of the intracranial aneurysm (odds ratio: 1.67, 95% confidence interval: 1.17-3.05) and decreased apolipoprotein A2 (odds ratio: 0.62, 95% confidence interval: 0.34-0.97) was significantly correlated with aneurysm wall enhancement. *Conclusions:* Rather than atherosclerotic factors, antiatherogenic proteins reduction was associated with aneurysm wall enhancement in vessel wall imaging. To elucidate antiatherogenic factors might to help find out promoting factor of unruptured intracranial aneurysms instability.

Key Words: Atherosclerosis—dyslipidemia—intracranial aneurysm—vessel wall imaging—wall enhancement

Introduction

Intracranial aneurysm (IA) is a common vascular abnormality and detected in 0.5%-2% in imaging studies.[1,2] Recent biological studies clarified that inflammation of the IA wall is associated with a fragile vasa vasorum and atherosclerosis.[3,4] Since intracranial arteries lack a vasa vasorum at birth, atherosclerotic change may play an important role in IAs. As reported in previous pathological studies on IAs, atherosclerotic remodeling of the aneurysm wall is not a rare pathological feature in saccular IA.[5,6] Diffuse intimal thickening and inflammatory cells were observed in small aneurysms, whereas advanced atherosclerotic lesions were found in large aneurysms.[7] These studies suggested that the aneurysm wall thickens during its growth process with

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Received December 27, 2018; revision received April 22, 2019; accepted May 2, 2019.

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1052-3057/$ - see front matter

https://doi.org/10.1016/j.jstrokecerebrovasdis.2019.05.002

atherosclerotic remodeling. Previously, several studies reported the relationship between the serum levels of dyslipidemia-related proteins and IA, and showed elevated serum levels of lipoprotein(a) (Lp(a)) or low-density lipoprotein (LDL) was suspected factors with the presence of IAs.[8-11] However, the correlation between atherosclerotic change in IA wall and systemic atherosclerosis related factors, especially the serum levels of dyslipidemia-related proteins, has not been explored.

Current advanced imaging techniques, such as magnetic resonance (MR)-vessel wall imaging (VWI), enable visualization of the thickened aneurysm wall with thickened atherosclerosis, inflammation and neovascularization as aneurysm wall enhancement (AWE).[12,13] It is of interest hypothesis that AWE might be a novel imaging biomarker to be highly indicative of an unstable IA.[12,13] Unruptured IAs with AWE were found to be associated with the clinical scoring system as PHASES[14] for unstable IA.[15] The purpose of this study was to explore the correlation between atherosclerotic wall degeneration detected by VWI and atherosclerosis-related risk factors based on the hypothesis that dyslipidemia-related proteins are associated with atherosclerotic degeneration of IA walls.

Methods

Patients

This study was approved by the local university institutional review board and all patients provided written consent before the examination. Patients with one or more unruptured IAs scheduled to undergo microsurgical clipping or endovascular coiling between May 2017 and August 2018 were prospectively investigated. Patients who could not undergo magnetic resonance (MR) imaging or could not use contrast-material because of renal dysfunction or a history of allergy to contrast media were excluded in this study.

MR Acquisition

All patients underwent 3T-MRI (Vantage Titan, Canon Medical Systems, Tokyo, Japan or Ingenia CX, Philips Healthcare, Best, the Netherlands) before the surgery. The protocol for MRI included 3D time-of-flight MR angiography (MRA), and pre- and postcontrast T1-weighted 3D black-blood fast-spin-echo high resolution MR imaging (Multi Planar Voxel: MPV by Titan, a turbo spin-echo-based motion-sensitized driven-equilibrium sequence acquisition: motion-sensitized driven-equilibrium by Ingenia CX). 3D time-of-flight MRA was performed first for localization of subsequent scans. Images were generated using the maximum intensity projection. The parameters for the sequences for Titan were as follows: TR/TE 500/16.5 millisecondss, field of view (FOV) = 240 × 240 mm^2, acquired matrix = 256 × 192 and slice thickness = 0.9 mm. Those for Ingenia CX were as follows: TR/TE 400/13 milliseconds, FOV = 220 × 220 mm^2, acquired matrix = 224 × 175 and slice thickness = 1.0 mm. After an intravenous injection of Gd-BT-DO3A (Gadovist, Bayer Schering Pharma, Berlin, Germany) at 0.1 mmol/kg, scanning was performed in the sagittal plane. The total acquisition time was 5 minutes and 52 seconds per sequence for Titan, and 4 minutes and 42 seconds for Ingenia CX.

Image Analysis and Detection of AWE

Aneurysm maximum size, location, and irregularity such as a bleb formation were evaluated by digital subtraction angiography before treatment. Two blinded reviewers evaluated the VWI findings. The maximum intensity projection was constructed in axial, coronal, and sagittal views to identify the AWE. Aneurysm walls were evaluated with reference to the vessel anatomy shown by TOF MRA. The presence and pattern of AWE was evaluated as circumferentially or partially.

Risk Factors for Atherosclerosis

Patient history associated with the risk factors for atherosclerosis, such as hypertension, diabetes mellitus, dyslipidemia, and current smoking, were investigated. Current statin prescription was also evaluated.

Blood Examination Including Dyslipidemia-related Proteins

All patients had blood examinations within 3 days before the surgery under fasting conditions for over 10 hours. The serum levels of dyslipidemia-related proteins, such as total cholesterol, high-density lipoprotein (HDL), LDL, oxidized LDL, triglycerides, apolipoprotein (Apo) A1, A2, B, C2, C3, and E, remnant-like lipoprotein particle, Lp(a), dihomo-γ-linolenic acid, arachidonic acid (AA), eicosapentaenoic acid, and docosahexaenoic acid were measured, and LDL/HDL, non-HDL, Friedewald LDL and eicosapentaenoic acid/AA were calculated. In addition, the serum levels of fasting blood sugar, hemoglobin A1c, and uric acid were also measured.

Statistical Analyses

All statistical analyses were performed using JMP version 10.0 (SAS Institute, Cary, NC). Values are presented as the mean ± SD. Categorical variables were compared by the Fisher exact probability test. Continuous variables with normal distributions were analyzed by the Student's *t* test and those with non-normal distributions were analyzed by the Mann-Whitney *U* test. Univariate and multivariate logistic regression modeling analyses were utilized to investigate factors associated with VWI findings. All variables with a *P* value less than 0.10 in the univariate analyses were included in the multivariate logistic regression analysis to evaluate the independent factors for the detection of AWE. Intraclass correlation coefficient

was calculated to assess the inter-rater reliability of AWE. Significance was defined as a P value less than .05.

Results

Patient Demographics and Characteristics of IA

A total of 38 consecutive patients with 39 unruptured IAs were recruited. Nine patients with 9 unruptured IAs were excluded according to the criteria. VWI was performed for 8 aneurysms using Titan and 31 using Ingenia CX. Microsurgical clipping and endovascular coiling were performed for 7 and 32 aneurysms, respectively. All patients were examined and treated without any adverse events. Twenty aneurysms were located in the internal carotid artery, 7 in the anterior cerebral artery, 8 in the middle cerebral artery, and 4 in the posterior circulation. The mean maximum diameter was 7.7 ± 5.8 mm. Irregular morphology, such as a bleb formation, was detected in 15 aneurysms. Patient demographics and characteristics of IAs are summarized in Table 1.

Visualization of AWE

In total, AWE was detected in 19 (48.7%), of which it was visualized partially in 15 (78.9%) and circumferentially in 4 (21.1%). The intraclass correlation coefficient for the inter-rater reliability of AWE was excellent; 0.94. Representative case of AWE with the intraoperative findings was described in Figure 1.

Factors Associated with the Visualization of AWE

The relationships between the presence of AWE and morphological characteristics of IA, risk factors for atherosclerosis and blood examinations, including dyslipidemia-related proteins, are summarized in Table 2. The maximum diameter of the IA was significantly larger ($P < .01$), and the levels of Apo A2 and Apo C2 were significantly lower ($P < .01$ and = .01) for AWE. Moreover, the levels of Apo C3, Lp(a) and AA were slightly lower ($P = .07$, .06, and .05) for AWE. In the multivariate logistic regression analysis, using all these variables, the maximum diameter of the IA ($P < .01$) and Apo A2 ($P = .04$) were significantly correlated with AWE (Table 3). The cut-off values of the serum levels of Apo A2 using receiver operating characteristic curve analysis to maximize sensitivity and specificity was 29.5 (area under the curve, 0.771; 95% confidence interval, 0.57-0.89). The patients were divided into the 2 groups based on this cut-off value of Apo A2. The patients with lower levels of Apo A2 were also significantly correlated with the AWE ($P < .01$).

Table 1. *Patient demographics and IA characteristics*

Characteristics	Value
Patients	
Age ± SD (range), y	67.1 ± 10.0 (43-83)
Female Sex, n (%)	28 (71.8%)
Aneurysms	
ICA, n (%)	20 (51.3%)
ACA, n (%)	7 (17.9%)
MCA, n (%)	8 (20.5%)
Posterior circulation, n (%)	4 (10.3%)
Maximum diameter, mean ± SD (mm)	7.7 ± 5.8
Irregularity, n (%)	15 (38.5%)
AWE, n (%)	19 (48.7%)
Procedures	
Microsurgical clipping, n (%)	7 (17.9%)
Endovascular coiling, n (%)	32 (82.1%)

Abbreviations: ACA, anterior cerebral artery; AWE, aneurysm wall enhancement; IA, intracranial aneurysm; ICA, internal carotid artery; MCA, middle cerebral artery; SD, standard deviation

Discussion

This study demonstrated that the reduction of antiatherogenic proteins is associated with VWI findings representing atherosclerotic remodeling of the IA wall. Recent studies revealed that the inflammatory reaction in the IA wall reflects IA formation and rupture.[3,5,16,17] Furthermore, the progression of atherosclerosis within the aneurysmal sac correlated positively with aneurysmal growth and rupture.[7]

In the present study, the serum level of Apo A2 was significantly associated with AWE. The serum level of Apo A2 had positive correlation with those of HDL, Apo A1, C2, C3, and AA (Table 4). Recent studies suggested the correlation between HDL associated factors and aneurysmal rupture.[9,18] On the contrary, present study indicated the serum level of HDL had no significant correlation with AWE. On the one hand, the use of stains may have an effect on the values of dyslipidemia-related proteins. On the other hand, Apo A2 as a subpopulation of HDL may have higher sensitivity to AWE than HDL. However, further evaluation with a large number of sample size are needed to prove the correlation between these atherosclerotic factors and AWE. The difference of Apo A2 with or without AWE was relatively small, as well as both averages of them were within normal range between 25.9 and 35.7 mg/dL. In the presented study, 15 (38.5%) patients intake statins. The use of statin was not significantly associated with AWE; however, it may affect the values of dyslipidemia-related proteins.

Apo A1 and A2 are 2 main subpopulations of HDL.[19] The antiatherogenic properties of Apo A1 are well-known; however, whether Apo A2 has such properties is controversial. Previously, a prospective study reported a strong inverse relationship between serum Apo A2 levels and the risk of future cardiovascular disease events.[20] After adjustment for cardiovascular risk factors, including HDL cholesterol and Apo A1, increased Apo A2 levels remained associated with a lower risk of future

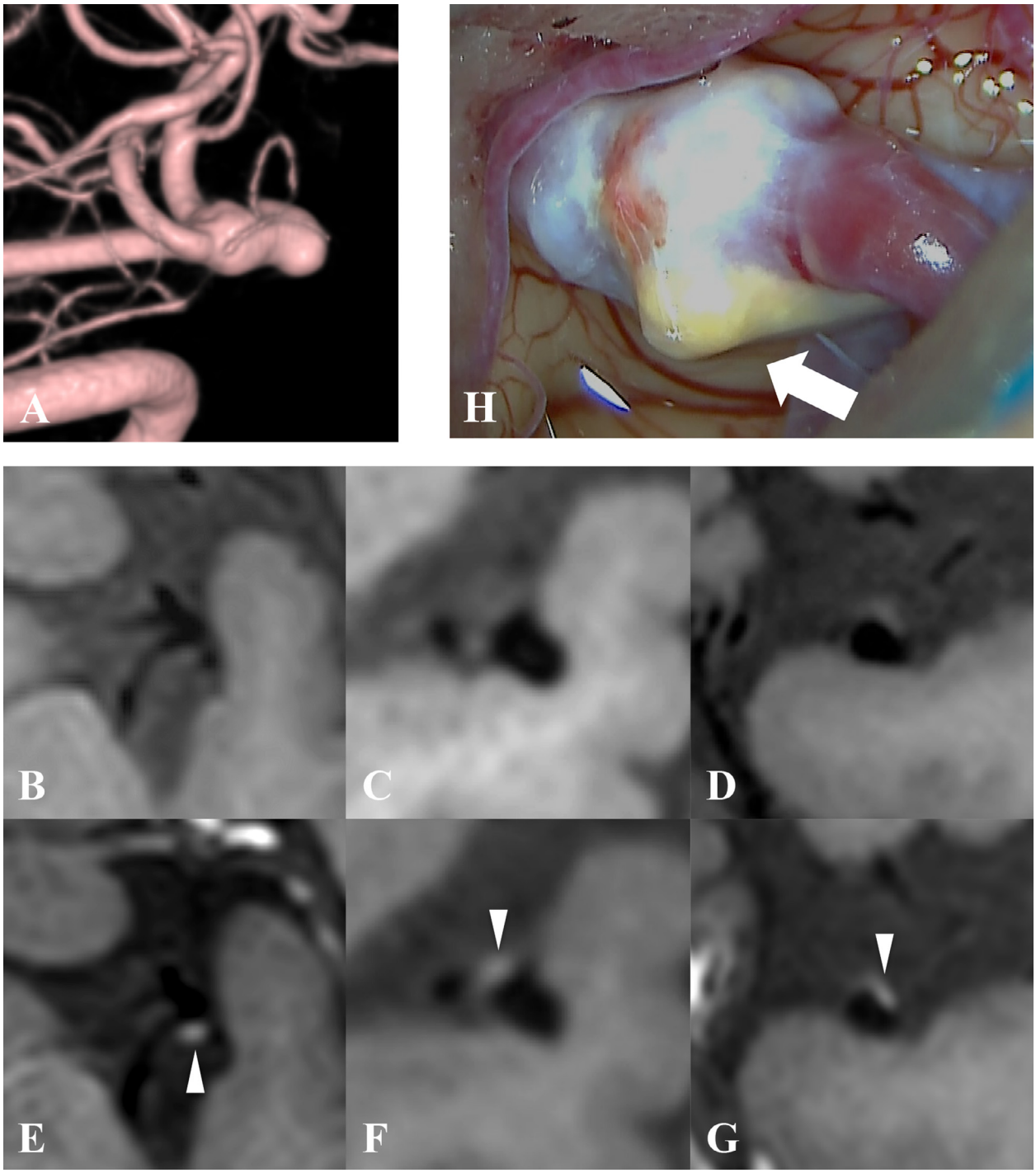

Figure 1. *Vessel wall imaging of an intracranial aneurysm. The 3D rotational left internal carotid angiogram indicated the left middle cerebral artery aneurysm (A). Native (B, C, D) and contrast-enhanced (E, F, G) vessel wall images were constructed in axial (B, E), coronal (C, F), and sagittal (D, G) views. Aneurysm wall enhancement was partially detected after injecting the contrast media (arrowhead). During the operation (H), an atherosclerotic change on the aneurysmal wall was detected (arrow).*

cardiovascular disease events.[20] In addition, human studies found that the incidence of cerebrovascular disease is higher in subjects with lower serum Apo A2 levels.[20,21] On the contrary, another recent study reported that Apo A2 may have both antiatherogenic and proatherogenic properties.[22] These studies suggested that the serum level of Apo A2 is inversely related with the extent of systemic atherosclerosis, and may be significantly associated with the risk of cardiovascular and cerebrovascular diseases. On the other hand, the plasma levels of total cholesterol, HDL, LDL, and triglycerides were not associated with immunohistochemical findings, inflammatory reactions,

Table 2. *Factors associated with AWE*

	AWE (+) (n = 19)	AWE (−) (n = 20)	*P* value
Demographic data			
Mean age, years	69.5 ± 10.0	64.9 ± 9.6	.13
Female sex, n (%)	15 (79.0%)	13 (65.0%)	.33
Risk factors			
Hypertension, n (%)	12 (63.2%)	10 (50.0%)	.41
Diabetes mellitus, n (%)	4 (21.1%)	2 (10.0%)	.34
Dyslipidemia, n (%)	6 (31.6%)	9 (45.0%)	.39
Statin, n (%)	8 (31.6%)	9 (45.0%)	.39
Current smoker, n (%)	5 (26.3%)	5 (25.0%)	.93
Aneurysm morphology			
Maximum diameter, mean ± SD (mm)	10.5 ± 7.1	5.1 ± 2.1	<.01*
Irregularity, n (%)	8 (42.1%)	7 (38.5%)	.65
Blood examinations, mean ± SD			
T-cho (mg/dL)	197.5 ± 30.7	217.5 ± 45.1	.11
HDL (mg/dL)	56.5 ± 13.7	62.1 ± 18.9	.29
LDL (mg/dL)	122.9 ± 26.3	132.0 ± 44.8	.44
oxLDL (U/L)	114.0 ± 37.4	109.1 ± 36.2	.67
LDL/HDL	2.3 ± 0.7	2.4 ± 1.1	.77
non-HDL (mg/dL)	141.0 ± 27.3	155.5 ± 52.1	.27
fLDL (mg/dL)	118.2 ± 26.6	126.5 ± 43.4	.47
TG (mg/dL)	113.9 ± 38.9	145.3 ± 91.9	.15
FBS (mg/dL)	105.9 ± 16.1	112.4 ± 53.9	.60
HgbA1c (%)	6.1 ± 0.8	6.0 ± 0.8	.68
UA (mg/dL)	5.0 ± 1.0	5.2 ± 1.4	.56
Apo A1 (mg/dL)	131.1 ± 18.7	139.5 ± 21.4	.19
Apo A2 (mg/dL)	26.8 ± 2.0	29.8 ± 3.4	<.01*
Apo B (mg/dL)	88.9 ± 16.0	90.9 ± 26.3	.77
Apo C2 (mg/dL)	3.9 ± 1.5	5.6 ± 2.5	.01*
Apo C3 (mg/dL)	8.9 ± 2.4	10.6 ± 3.6	.07
Apo E (mg/dL)	3.6 ± 0.9	3.6 ± 1.1	.96
RLP (mg/dL)	5.8 ± 2.4	7.9 ± 5.8	.14
LP(a) (mg/dL)	11.9 ±12.0	23.8 ± 26.5	.06
DHLA (μg/mL)	39.1 ± 9.9	39.6 ± 12.1	.91
AA (μg/mL)	180.7 ± 37.3	213.4 ± 63.7	.05
EPA (μg/mL)	76.9 ± 66.4	70.5 ± 58.3	.75
DHA (μg/mL)	137.6 ± 49.4	137.4 ± 40.5	.99
EPA/AA	0.4 ± 0.4	0.4 ± 0.3	.42

Abbreviations: AA, arachidonic acid; Apo, apolipoprotein; AWE, aneurysm wall enhancement; DHA, docosahexaenoic acid; DHLA, dihomo-γ-linolenic acid; EPA, eicosapentaenoic acid; FBS, fasting blood sugar; HgbA1c, hemoglobin A1c; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LP(a), lipoprotein(a); oxLDL, oxidized LDL; RLP, remnant-like lipoprotein particle; T-cho, total cholesterol; TG, triglycerides; UA, uric acid

*Significant.

or degradation of IA walls.[23] In the present study, the serum level of Apo A2 was one independent factor associated with AWE. However, the contribution of systemic atherosclerosis to local atherosclerotic remodeling of the aneurysm wall remains unclear because of the lack of histological examinations in this study. At this moment, the efficacy of antiatherogenic agents, such as statins to stabilize the IA remains controversial. Currently, anti-inflammatory agents, such as aspirin, are considered to reduce the incidence of IA rupture.[24]

In this study, the maximum diameter of the IA was significantly associated with visualization of AWE. There was no significant correlation between the serum level of Apo A2 and the maximum diameter of the IA. As for the pathological characteristics of IAs, the aneurysmal size paralleled the grade of the atherosclerotic lesion within the sac.[7] Advanced plaques with accumulation of alternating layers of mature smooth muscle cells and macrophages were found.[7] Furthermore, infiltrating leukocytes, mainly T-cells and macrophages, stimulated smooth muscle cell proliferation in areas of vascular wall thickening.[25] These studies suggested that the aneurysm wall is thickened and/or inflamed due to atherosclerotic remodeling with growth. This thickened and inflamed wall was

Table 3. *Multivariate analyses for factors associated with detectable AWE*

	AWE			
		95% CI		
Variable	OR	Lower	Upper	*P* value
Maximum diameter	1.67	1.17	3.05	<.01*
Apo A2	0.62	0.34	0.97	.04*
Apo C2	0.96	0.36	2.42	.93
Apo C3	1.11	0.55	2.42	.77
LP(a)	1.00	0.93	1.06	.96
AA	0.99	0.96	1.01	.27

Abbreviations: AA, arachnidonic acid; Apo, apolipoprotein; AWE, aneurysm wall enhancement; CI, confidence interval; Lp (a), lipoprotein(a); OR, odds ratio
*Significant.

detected as AWE on contrast-enhanced VWI. Thus, the maximum diameter of IA correlates with AWE.

Frösen et al[26] classified IA walls according to histological changes and found that mostly normal IA walls had the lowest rupture risk, and the rupture risk gradually increased for thickened walls with disorganized smooth muscle cells, hypocellular walls with either myointimal hyperplasia or organizing luminal thrombosis and extremely thin thrombosis-lined hypocellular walls. Recently, the association between unstable IA including ruptured one and AWE had been reported; however, most of them were devoid of histological examinations.[27-29] Recent histological examinations of unruptured IAs revealed that thickening vessel walls involving macrophages infiltration were commonly observed in IA-tissues with AWE.[30-32] On the contrary, histopathologic findings of aneurysm wall without AWE remains controversial; retained or losing mural cellularity.[30,31] Actually, IA wall thinning and hemodynamics have a potential effect on the progress of aneurysm expansion and rupture.[26,33] Therefore, interpretation of thin aneurysmal walls without AWE should be carefully discussed. Thickened wall structure could be detected by VWI; however, it remains controversy if AWE could work as potential imaging marker to identify prone to rupture aneurysms.[30,31,34,35]

Table 4. *Correlation between the serum level of Apo A2 and those of HDL, ApoA1, C2, C3, and AA*

Variable	R^2	*P* value
HDL	0.20	<.01*
Apo A1	0.32	<.01*
Apo C2	0.44	<.01*
Apo C3	0.30	<.01*
AA	0.24	<.01*

Abbreviations: AA, arachnidonic acid; Apo, apolipoprotein; HDL, high-density lipoprotein; R^2, coefficient of determination
*Significant.

This study has some limitations. First, the presented preliminary study was performed at a single center with a small sample size. Samples included only patients who underwent treatment, thus there was a bias that the majority of patients harboring small aneurysms were not included. This selection bias may have contributed to the detection of AWE. For further evaluation, a study involving a greater number of patients is needed. Second, VWI was performed using 2 different pieces of MR equipment. This bias also may have affected the assessment of the aneurysm status. Lastly, the assessment of blood examinations could be affected by fasting condition. Therefore, the blood sampling in this study was strictly performed under fasting conditions, as compared with recent studies[9,10] in which the timing of blood sampling was not uniform or not precisely described. Therefore, the present study has a high accuracy and uniformity for the assessment of blood examinations including dyslipidemia-related proteins.

Conclusion

Dyslipidemia-related proteins were found to be associated with the visualization of IAs, specifically the presence of AWE on VWI. In future studies, elucidation of the contribution of systemic atherosclerosis to the instability of IAs is warranted.

Conflict of Interest

The authors declare that they have no conflicts of interest.

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