

Clinical Article

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Elastin Degradation and Collagen III Deficiency in the Superficial Temporal Arteries of Patients with Intracranial Aneurysms

Objective : We present the difference of histopathologic changes of the internal elastic lamina (IEL) and collagen III in the superficial temporal artery (STA) between aneurysmal patients and non-aneurysmal patients. Also, the pathologic data with clinical features by comparative methods to validate the risk factor of the intracranial aneurysm are presented.

Methods : Samples of the STA were harvested from 38 patients including aneurysmal and non-aneurysmal patients undergoing craniotomy. Paraffin-embedded sections were examined, using hematoxylin and eosin, van Gieson and mouse anti-collagen III staining techniques. Histopathological observations were analysed and correlated with clinical features such as presence of aneurysm, hypertension, age, and sex.

Results : Twenty-seven patients had the intracranial aneurysm. Of these 24 patients were 50 years old or older. Nineteen patients had a history of hypertension. Twenty patients were female. Histopathological study demonstrated the derangement of IEL and the deficiency of type III collagen were prominent in aneurysmal patients ($p < 0.05$). Fifty years old or older patients did not show correlation with the deficiency of type III collagen, but with the derangement of IEL ($p < 0.05$). The female sex was not correlated with the derangement of IEL but with the deficiency of type III collagen ($p < 0.05$). However, Hypertension was not correlated with these pathologic data.

Conclusion : Patients with intracranial aneurysms have severe histopathologic changes of the arterial wall showing the derangement of IEL and the deficiency of type III collagen. In the clinico-pathologic study, the advanced age and female sex were considered as risk factors of the intracranial aneurysm.

KEY WORDS : Elastin · Collagen III · Superficial temporal artery · Intracranial aneurysm.

INTRODUCTION

Subarachnoid hemorrhage (SAH) caused by the rupture of an intracranial aneurysm is a devastating disease with high morbidity and mortality^{10,31}. However, there is limited understanding to date, of the pathogenesis and risk factors predisposing to the formation and rupture of intracranial aneurysms. Several risk factors have been identified in playing a role in the formation and rupture of intracranial aneurysms; e.g. hypertension, cigarette smoking, alcohol consumption, aging processes of arterial walls, genetic factors, trauma, infection, sex, etc^{12,15,32}. In combination, these factors cause histologic arteriopathic changes of cerebral arteries followed by the formation and rupture of intracranial aneurysms^{4,32}. We believe that one component of arteriopathic changes for aneurysm formation is the weakness of the IEL, the layer most vital to the strength of the arterial wall and the deficiency of type III collagen which is the consequent structure of the extracellular matrix of vessels is another component of arteriopathic changes for intracranial aneurysms^{27,31,32}.

In this study, we harvested pericranial vascular tissues from samples of the STA of aneurysmal and non-aneurysmal patients undergoing craniotomy or craniectomy and used pathological methods to examine surgical specimens of the STA. Although this tissue admittedly is not an ideal specimen because its exact morphological structure is different from that of the circle of Willis, we believe it represents the best alternative option. Additionally, we evaluated these data from the pathological assessment with clinical features such as presence of aneurysm, hypertension, age, sex by the comparative method and tried to confirm the risk factor of formation and rupture of intracranial aneurysms through this comparative analysis.

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Fig. 1. Photomicrograph of elastin-stained superficial temporal arteries (van Giebson staining, $\times 100$). A : Completely intact internal elastic lamina. B : Moderately deranged internal elastic lamina. C : Severely deranged internal elastic lamina.

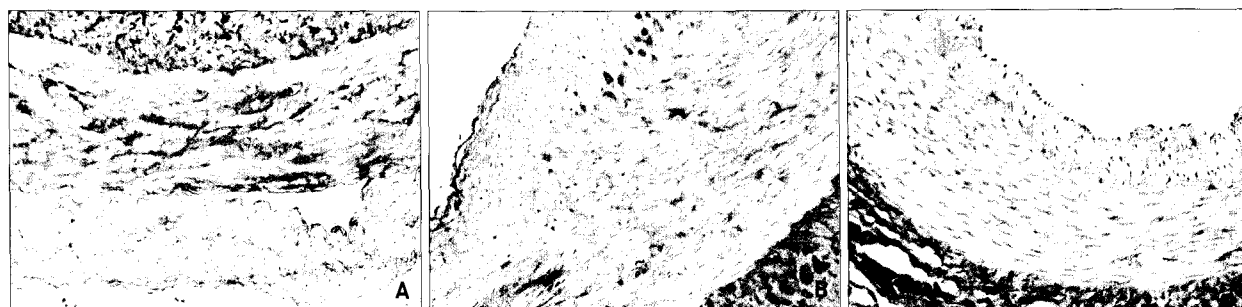


Fig. 2. Photomicrograph of collagen III-stained superficial temporal arteries (immunoperoxidase staining, $\times 200$). A : No deficiency of brownish collagen III fibers. B : Moderate deficiency. C : Severe deficiency.

MATERIALS AND METHODS

Study population

Thirty-eight subjects were enrolled in the study between December 2004 and July 2006. Inclusion criteria for aneurysmal patients included radiological documentation (computed tomographic angiography and three-dimensional digital subtraction angiography) of an intracranial aneurysm, surgically repaired aneurysm, a small sample of the STA being obtainable safely, no familial history of intracranial aneurysm and the patient or designate being able to give informed consent. Inclusion criteria for non-aneurysmal patients included no evidence of intracranial aneurysm based on noninvasive radiological study (computed tomographic angiography), craniotomy or craniectomy performed for any reason other than aneurysm repair, STA able to be safely isolated and sampled during the exposure for the above craniotomy and the patient or designate being able to give informed consent.

Tissue collection and immunohistochemistry

All surgical procedures were performed at single medical center. As a routine part of the craniotomy or craniectomy, the STA was exposed. A 2-cm segment of the exposed vessel was then transected, formalin fixed, embedded in paraffin, and sectioned. It was stained for elastin with van Giebson stain and was stained for collagen with immuno-

peroxidase staining using mouse anti-collagen III. The IEL was evaluated for the degree of disruption (degree of elastin degradation) and collagen III was also evaluated for the degree of deficiency by pathologists. The degree of elastin degradation and collagen III deficiency was divided into normal (N), moderate (M), and severe (S) group. Representative sections demonstrating different degrees of elastin degradation (disruption of internal elastic lamina) and collagen III deficiency were photographed (Fig. 1, 2).

Data acquisition

The following data were recorded for each subject : demographic (sex, age at time of current craniotomy), medical history (hypertension, family history of aneurysm or collagen vascular disease, self-reported current smoking and illegal drug use), and clinical data for aneurysmal patients (aneurysm location, ruptured or not, Hunt and Hess grade and Fisher grade on admission).

Statistical analysis

Histopathological observations were analysed and evaluated for correlation with clinical features such as presence of aneurysm, hypertension, age, and sex. Elastin degradation or collagen III deficiency rate ($[(M+S/N+M+S) \times 100\%]$ and severe rate of degradation or deficiency ($[(S/N+M+S) \times 100\%]$) were calculated in each feature. These data were analysed with independent-sample t-test and the chi-square

Table 1. Patients Characteristics : classification according to presence of aneurysm and hypertension, age and sex

	Aneurysm	Non-aneurysm	Total
Age			
≤49 yrs	9	5	14
≥50 yrs	18	6	24
Sex			
Male	10	8	18
Female	17	3	20
Hypertension (-)	13	6	19
Hypertension (+)	14	5	19
Total	27	11	38

Table 2. Elastin degradation and collagen III deficiency according to presence of aneurysm

Degree	Aneurysm		Non-aneurysm	
	Elastin	Collagen III	Elastin	Collagen III
Normal (N)	2	1	7	5
Moderate (M)	12	16	3	6
Severe (S)	13	10	1	0
Degradation or deficiency rate	92%*	96%†	36%*	55%†
Severe rate of degradation or deficiency	48%‡	37%§	9%‡	0%§

*, †, ‡, § $p < 0.05$ for comparison between aneurysm and non-aneurysm. Degradation or deficiency rate = $\frac{[M+S]}{[N+M+S]} \times 100\%$. Severe rate of degradation or deficiency = $\frac{[S]}{[N+M+S]} \times 100\%$.

test respectively. A p value of 0.05 or less was considered of statistical significance for all of the analyses.

RESULTS

Patients characteristics

We classified 38 patients according to four criteria : presence of aneurysm, hypertension, age, and sex. The averaged age of patients was 54 years and ranged from 31 to 72 years. We divided into two groups according to age. Fourteen patients were 49 years old or younger and 24 patients were 50 years old or older. This grouping was done facultatively by authors because we could find marked histopathologic change of STA in 50 years or older patients. Aneurysmal patients were 27, non-aneurysmal patients were 11. Nineteen patients were hypertensive, and 19 patients were non-hypertensive. Eighteen patients were male, 20 were female. For aneurysmal patients, older and female patients outnumbered younger and male patients (Table 1).

Elastin degradation and collagen III deficiency according to presence of aneurysm

With regards to elastin degradation, 2 patients had no degradation, 12 had moderate degradation and 13 had

Table 3. Elastin degradation and collagen III deficiency according to age

Degree	≤49yrs		≥50yrs	
	Elastin	Collagen III	Elastin	Collagen III
Normal (N)	6	4	3	2
Moderate (M)	7	9	8	13
Severe (S)	1	1	13	9
Degradation or deficiency rate	57%*	71%†	88%*	92%†
Severe rate of degradation or deficiency	7%‡	7%§	54%‡	38%§

*, † $p < 0.05$ for comparison between ≤49 yrs and ≥50 yrs. ‡, § $p > 0.05$ for comparison between ≤49 yrs and ≥50 yrs. Degradation or deficiency rate = $\frac{[M+S]}{[N+M+S]} \times 100\%$. Severe rate of degradation or deficiency = $\frac{[S]}{[N+M+S]} \times 100\%$.

severe degradation among 27 aneurysmal patients. Of 11 non-aneurysmal patients, 7 patients were intact, 3 were moderate, 1 was severe. Degradation rate for aneurysmal patients (92%) was statistically different from those for non-aneurysmal patients (36%, $p < 0.05$). Severe rate of degradation for aneurysmal patients (48%) was also significantly different from those for nonaneurysmal patients (9%, $p < 0.05$).

For collagen III deficiency, 1 had no deficiency, 16 had moderate deficiency, and 10 had severe deficiency for aneurysmal patients, whereas 5 were not deficient, 6 were moderate, none was severe for non-aneurysmal patients. Deficiency rate for aneurysmal patients (96%) was statistically different from those for non-aneurysmal patients (55%, $p < 0.05$). Severe rate of degradation for aneurysmal patients (37%) was also significantly different from those for nonaneurysmal patients (0%, $p < 0.05$) (Table 2).

Elastin degradation and collagen III deficiency according to age

In elastin degradation, 3 patients had no degradation, 8 had moderate degradation and 13 had severe degradation among 50 years old or older. Of 49 years old or younger, 6 patients were intact, 7 were moderate, and 1 was severe. Degradation rate for 50 years old or older patients (88%) was significantly different from those for younger patients (57%, $p < 0.05$). Severe rate of degradation for older patients (54%) was also significantly different from those for younger patients (7%, $p < 0.05$).

In collagen III deficiency, 2 had no deficiency, 13 had moderate deficiency, and 9 had severe deficiency for 50 years old or older patients, whereas 4 patients were intact, 9 were moderate, 1 was severe for 49 years old or younger patients. Deficiency rate was not statistically different between older patients (92%) and younger patients (71%, $p > 0.05$). Severe rate was also not significantly different between older (38%) and younger (7%, $p > 0.05$) (Table 3).

Table 4. Elastin degradation and collagen III deficiency according to presence of hypertension

Degree	Hypertension (-)		Hypertension (+)	
	Elastin	Collagen III	Elastin	Collagen III
Normal (N)	7	4	2	2
Moderate (M)	7	12	8	10
Severe (S)	5	3	9	7
Degradation or deficiency rate	63%*	79% [†]	89%*	89% [†]
Severe rate of degradation or deficiency	26% [†]	16% [§]	47% [†]	37% [§]

*, †, ‡, § $p > 0.05$ for comparison between hypertensive and non-hypertensive. Degradation or deficiency rate = $[M+S/N+M+S] \times 100\%$. Severe rate of degradation or deficiency = $[S/N+M+S] \times 100\%$.

Elastin degradation and collagen III deficiency according to presence of hypertension

In elastin degradation, 2 patients had no degradation, 8 had moderate degradation and 9 had severe degradation among patients who had a history of hypertension. Of patients who had no history of hypertension, 7 patients were intact, 7 were moderate, and 5 were severe. Degradation rate was not statistically significant between hypertensive patients (89%) and non-hypertensive patients (63%, $p > 0.05$). Severe rate was also not significantly different between the former (47%) and the latter (26%, $p > 0.05$).

In collagen III deficiency, 2 patients had no deficiency, 10 had moderate deficiency, and 7 had severe deficiency for hypertensive patients, whereas 4 patients were not deficient, 12 were moderate, 3 were severe for non-hypertensive patients. Deficiency rate was not statistically significant between hypertensive patients (89%) and non-hypertensive patients (79%, $p > 0.05$). Severe rate was also not significantly different between hypertensive (37%) and non-hypertensive (16%, $p > 0.05$) (Table 4).

Elastin degradation and collagen III deficiency according to sex

In elastin degradation, 3 patients had no degradation, 7 had moderate degradation and 10 had severe degradation among female patients. Of male patients, 6 patients were intact, 8 were moderate, 4 were severe. Degradation rate was not statistically significant between female patients (85%) and male patients (67%, $p > 0.05$). Severe rate was also not significantly different between female (50%) and male (22%, $p > 0.05$).

In collagen III deficiency, none had no deficiency, 13 had moderate deficiency, and 7 had severe deficiency for female, whereas 6 patients were not deficient, 9 were moderate, and 3 were severe for male. Deficiency rate for female (100%) was statistically different from those for male (67%, $p < 0.05$).

Table 5. Elastin degradation and collagen III deficiency according to sex

Degree	Male		Female	
	Elastin	Collagen III	Elastin	Collagen III
Normal (N)	6	6	3	0
Moderate (M)	8	9	7	13
Severe (S)	4	3	10	7
Degradation or deficiency rate	67%*	67% [†]	85%*	100% [†]
Severe rate of degradation or deficiency	22% [†]	17% [§]	50% [†]	35% [§]

*, †, § $p > 0.05$ for comparison between male and female. † $p < 0.05$ for comparison between male and female. Degradation or deficiency rate = $[M+S/N+M+S] \times 100\%$. Severe rate of degradation or deficiency = $[S/N+M+S] \times 100\%$.

However, severe rate was not significantly different between female (35%) and male (17%, $p > 0.05$) (Table 5).

DISCUSSION

Cerebral arteries comprise sequentially from the lumen : a monolayer of lining endothelial cells; an intima bounded by the IEL; a medial layer; an external elastic lamina; and adventitia³². The IEL which have a longitudinal arrangement of elastin fibers are the major constituents giving tensile strength to vascular walls and responsible for dilatation and recoil^{20,22}. The other major constituent of the arterial wall is the collagenous network. Collagens are extracellular matrix proteins that plays a dominant role in maintaining the structural integrity of various tissues¹¹. The main collagen types found in the human vascular wall are I, III, IV, V and VI²⁰. Together, type I and III collagens represent probably 80-90% of total arterial collagen. Among these, type III seems to be the main constituent in blood vessels. Type III collagen is specifically associated with vascular diseases whereas Type I is much more generally expressed³². Both structures of individual components, their interactions and turnover are equally important to the overall integrity of the arterial wall (arterial homeostasis)¹³.

While external elastic lamina is absent in cerebral arteries, IEL is the major structural support. Carmichael et al.³ reported that pathological examinations of intracranial aneurysms had pointed to defects of the IEL. Miskolczi et al.²¹ reported that elastin fibrin destruction by elastase or by β -aminopropionitrile which inhibits elastin cross-linking caused intracranial aneurysm formation in animal model. In our study, the derangement of IEL by elastin degradation was also prominent in aneurysmal patients.

Mutations in type III collagen have been identified in patients with the Ehlers-Danlos syndrome type IV, characterized by spontaneous arterial ruptures. Since the vascular

tree is particularly rich in type III collagen, it is thought to be very important for maintaining the structural integrity of the vascular wall. Some studies suggested that type III collagen deficiency is associated with cerebral aneurysm^{5,23,24}, while others dispute this relation^{18,31}. Mimata et al.²⁰ studied 15 cases of cerebral aneurysm immunohistochemically and reported that none had a complete deficiency of type III collagen in the aneurysmal wall, although the distribution patterns were different for type III collagen. In our study, type III collagen deficiency was prominent in the aneurysmal patients, although tissue specimens were not aneurysmal walls but arterial walls of the STA.

The majority of subarachnoid hemorrhage are due to the rupture of arteries and especially rupture of saccular aneurysms³². About 12-15% cases of saccular aneurysms are familial, often with an autosomal dominant pattern of inheritance^{6,27,32}. Some 85-90% of saccular aneurysms are sporadic with no obvious predisposing systemic factors. In the latter, the majority of aneurysms occur between the ages of 40 and 70 and this has highlighted the probability that most sporadic aneurysms are due to aging effects on the arteries^{8,28}. With aging, hemodynamic stress initially affects the endothelium, and changes in the endothelium induce atherosclerosis that in turn affects the strength of the aneurysmal wall and then layers of fibrous tissue develop between the endothelium and the internal elastic lamina^{14,30}. In atherosclerotic lesions, inflammatory cells such as macrophages and leukocytes affect the vascular pathology. They secrete many kinds of protease that destruct the extracellular matrix proteins like elastin and collagen III²⁹. This decreases the elasticity of the vessel wall and furthermore raises mounds or pads of fibrous tissue under the endothelium. Such pads are particularly prominent at vessel bifurcations thus gradually the sharp V-shaped bifurcation becomes rounded. This change in shape of the bifurcation may alter the direction of hemodynamic stress on the bifurcation resulting in pressure to form an outpouching at the bifurcation. In our study, elastin degradation increased significantly in 50 years old or older patients.

Hypertension is a well-known risk factor for SAH, but previous studies are contrary to each other with respect to the association between hypertension and SAH. In most studies, hypertension was found to increase the risk of SAH^{2,16,19}, whereas in two case-control studies hypertension was not associated with an increased risk^{11,18,26}. In our study, we observed no association between hypertension and arteriopathic changes of STA. We believe that the diminishing role of hypertension in aneurysm formation and enlargement in recent studies may be a result of early detection and treatment in a higher proportion of hypertensive patients²⁵.

Female patients outnumber male patients in many large series of ruptured intracranial aneurysms^{12,15}. Since female preponderance for SAH is not significant until the fifth decade, the cause of aneurysm formation in women is thought to be secondary to hormonal factors. It has been presumed that estrogen has an inhibitory effect on aneurysm formation^{14,15}. However, this relationship is controversial¹⁵.

The presumed effect of estrogen on inhibition of cerebral aneurysm formation is not well understood. However, several presumptions can be made. Collagen plays an important role in maintaining the strength of the vessel wall. Decreased estrogen activity associated with menopause results in a decrease in the amount of collagen present in other tissue such as skin and bone, contributing to skin atrophy and osteoporosis¹. With a similar manner, the collagen content of the cerebral arteries - especially collagen type III may also diminish after menopause. A decrease in the collagen content of the arterial wall could weaken the supporting connective tissue and predispose the artery to aneurysmal development^{12,15,24}. In our study, type III collagen deficiency rate for female was higher than those for male. We also speculate that collagen deficiency predispose the cerebral artery to aneurysmal formation.

The pathogenesis of intracranial aneurysm is unknown, but many researches indicate that it is due to multiple factors including sex, age, hypertension, cigarette smoking, alcohol consumption, and so on²⁵. Above all, cigarette smoking has been recognized as a high risk factor for the formation and rupture of aneurysm in recent years^{10,11,17}. Cigarette smoking causes or aggravates atherosclerosis, while changing shear stress of the wall of blood vessel. The thickened intimal layer of the arterial wall and increased fragility of the blood vessels speeds up breakdown of elastins on the wall, forming an intracranial aneurysm^{7,9}. However, the smoking factor was excluded in this study because most of patients were non-smoker except two non-aneurysmal patients who were male. So, a comparative study between non-smoker and smoker was impracticable.

The greatest limitation of this study was the use of STA. Admittedly, the circle of Willis and the STA are not exactly alike, and aneurysms of the latter are rare. For example, the degree and nature of the hemodynamic force that is experienced by the STA is very different than that seen by the constituents of the circle of Willis. This may be because the circle of Willis is subjected to greater turbulence and hemodynamic stress. Also, the geometry of the STA is very different, and it is not subject to the same abrupt changes in directions and bifurcations that are inherent to the circle of Willis.

Therefore, complete homeostatic failure may not occur

within the STA. Nevertheless, we believe that these intracranial and extracranial arteries have an ability to respond to hemodynamic factors to maintain arterial homeostasis. The degree to which they express such ability may vary based on the degree of exposure and the magnitude of the hemodynamic stress.

CONCLUSION

This study results demonstrate that a subgroup of patients with an cerebral aneurysm have severe histopathologic changes of the arterial wall consistent with the derangement of IEL and the deficiency of type III collagen. In the clinicopathologic study, the advanced age and female sex were considered as risk factors of the intracranial aneurysms. However, further epidermiological, clinical, and laboratory investigations will be needed to clarify the other risk factors for aneurysmal SAH.

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COMMENTARY

Intracranial aneurysms (IAs) are characterized by the occurrence of an abnormal bulging of one of the arteries in the brain. Even though significant recent progresses in the treatment of IAs especially through surgical approaches, the pathogenic mechanism of IAs is largely known. IAs are

a typical example of complex disease that is caused by multiple genetic and environmental determinants.

The Inoue group in The University of Tokyo made an impressive progress in elucidating the etiological mechanism of IAs through forward genetic approaches. They reported a genomewide linkage study of IAs in which positive evidence of linkage on chromosomes 5q22-31 (maximum LOD score [MLS] 2.24), 7q11 (MLS 3.22), and 14q22 (MLS 2.31). Among the loci showing suggestive evidence of location of the disease-causing genes of IAs in human whole genome, 7q11 locus are known to be the most promising locus since elastin gene is located in the region as well as the highest Lod score.

This work supports a hypothesis that the disease-causing

gene in 7q11 locus is actually elastin gene. However, the weakest problem of this work is that the patient samples are too small to be certain. I think that the author would show very interesting results on the etiological mechanism of IAs if they further investigate through forward genetic approaches after adding more samples.

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