

Three-Dimensional Pathological Analysis of Cerebral Aneurysm Initiation

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Abstract. Cerebral aneurysm is known to initiate at the cerebral artery bifurcation. The pathological mechanism of cerebral aneurysm awaits further understanding especially on its initiation. This study sought to elucidate the three-dimensional structure of cerebral vascular bifurcations with and without aneurysms using human cadavers. The two cases had aneurysmal initiations out of total 7 cases. The studied structure was intimal hyperplasia, tunica media and internal elastic lamina, which were recognized by elastica masson staining. The results showed that the non-existence of tunica media and internal elastic lamina was found in the lesion without aneurysm. The non-existence of intimal hyperplasia was only found in the lesion with aneurysm. These data suggest that the formation of intimal hyperplasia may be related with the initiation of aneurysm. We regarded the boundary of existence arteriosclerosis as the position for new arteriosclerosis occurs and thought the direction of new arteriosclerosis grows would influence whether the cerebral aneurysm initiates or not.

Keywords: Cerebral aneurysm · Initiation · Intimal hyperplasia · Tunica media · Internal elastic lamina

1 Background and Purpose

The rupture of cerebral aneurysm is a major cause of subarachnoid hemorrhage. Cerebral arterial bifurcations are known to be its common sites. The aneurysm initiation is generally believed to occur as the mechanical strength is weakened. Although there are numerous studies of the mechanism of cerebral aneurysm, full understanding of initiation, growth and rupture is still unknown.

Currently, there is no treatment that can cure cerebral aneurysm completely, and no preventative therapy of cerebral aneurysm is developed. The rupture of cerebral aneurysm causes 2/3 of the patients death or after effect [1] so that it is impossible to rehabilitate them in society. Therefore, it is necessary to develop a new treatment to prevent the initiation of cerebral aneurysm to reduce the number of patients suffering

from the cerebral aneurysm. For reaching this purpose, full understanding of initiation of cerebral aneurysm is required.

The human cadavers and animal models were used to study the initiation of cerebral aneurysm traditionally. The human cadavers were first used for pathological analysis to study about the initiation of cerebral aneurysm in the early years. The data showed the non-existence of tunica media [2], internal elastic lamina [3] and the existence of intimal hyperplasia [4] was recognized as a phenomenon of aneurysm initiation. Actually, the non-existence of the tunica media and the internal elastic lamina was recognized as the factors of aneurysm initiation still nowadays [5]. However, the reason why this phenomenon was caused is still unknown. Later, hemodynamics of cerebral arteries was thought to influence the initiation of cerebral aneurysm, and animal experiments were occurred for this kind of study. As a result, hemodynamics seems to have something to do with initiation of cerebral aneurysm [6, 7], but still the cause of effect relationship between hemodynamics and cerebral aneurysm did not clear. Considering the differences of body condition between animals and human beings. It is still necessary to use human cadavers for this study. In order to approach to elucidating the mechanism of initiation of cerebral aneurysm, we developed a new idea of studying human cadavers. Both of the human cerebral arteries with an aneurysm and with no aneurysm should be elucidated in 3D so that the temporal and spatial pathological changes of the cadavers might be clear. Therefore, the purpose of this study is to elucidate the vascular structure of human bifurcations before and after initiation in 3D pathologically.

2 Method

2.1 Sections Cutting

The pathological analysis method used in this research was cutting subcontinuous tissue sections and occurring pathology staining. Then, the optical microscope was used to observe and extract the pathological characteristics of the tissue. The details of analysis objects were shown in Table 1.

Table 1. Detailed information of the analysis objects.

ID	Age/sex	Location	With an aneurysm or not
Case 1	Unavailable	BA	With an aneurysm
Case 2	Unavailable	BA	With an aneurysm
Case 3	74/M	Lt IC-PC	With no aneurysm
Case 4	74/M	Rt IC-PC	With no aneurysm
Case 5	74/M	BA	With no aneurysm
Case 6	78/F	BA	With no aneurysm
Case 7	33/M	BA	With no aneurysm

2.2 Observing and Analyzing

In order to analyze accurately and on basis, we used qualitative analysis and quantification method. Explaining in detail, as shown in Fig. 1A, we took the part of cerebral arteries which the lumen appeared as the analysis area, and took the Sects. 300 μm intervals as measurement objects. Then, as shown in Fig. 1B, 3 mm from the apexes of bifurcation of cerebral arteries regarded as the localization that the aneurysms initiate easily was dealt with examining areas. The apex of the bifurcation was set to zero point, left direction was set to minus distance, right direction was set to plus distance. Measurement was occurred from zero point to both directions. The measure points were 11 points in total and were set to zero point and the points 600 μm intervals from zero point to each direction. Finally, in order to elucidate the distribution of tunica media and intimal hyperplasia, it is necessary to measure the thickness of tunica media and intimal hyperplasia. However, as shown in Fig. 1C1, depending on the situation, internal elastic lamina might be meandering so that we had to add imaginary lines for measuring. Therefore, as shown in Fig. 1C2, while measuring the thickness of tunica media or intimal hyperplasia, we defined the length of the vertical direction of internal elastic lamina as the thickness. In this research, we defined non-existence of the intimal hyperplasia or the tunica media, while the thickness was 0 μm .

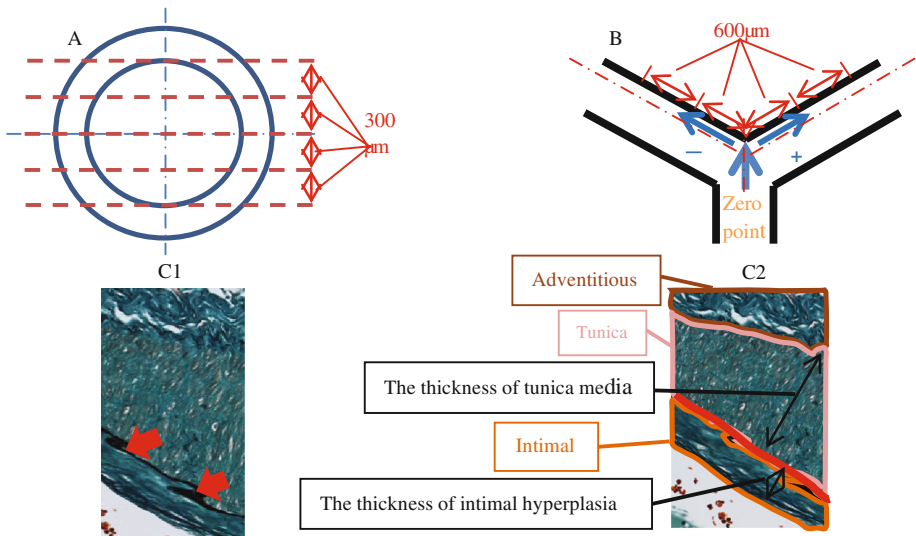


Fig. 1. Image of the cross section of the vessel lumen (A). The tissue sections were expected to be taken as 300 μm intervals for measuring. Also, image of the longitudinal section of the vessel lumen (B). Each section was measured the pathological characteristics 600 μm intervals from zero point to each direction. Because of the internal elastic lamina meandering (C1), imaginary lines were added for the measurement of the thickness of intimal hyperplasia or tunica media (C2).

3 Results

Results of the pathological characteristics of cerebral arteries with an aneurysm and cerebral arteries with no aneurysm were showed below in details.

3.1 Cerebral Arteries with An Aneurysm

The subcontinuous partial images located on the bifurcation of tissue sections of the typical example were shown as Fig. 2A. As a result, the non-existence of internal elastic lamina, tunica media and intimal hyperplasia was found in aneurysmal parts. Here indicates the intimal hyperplasia by yellow.

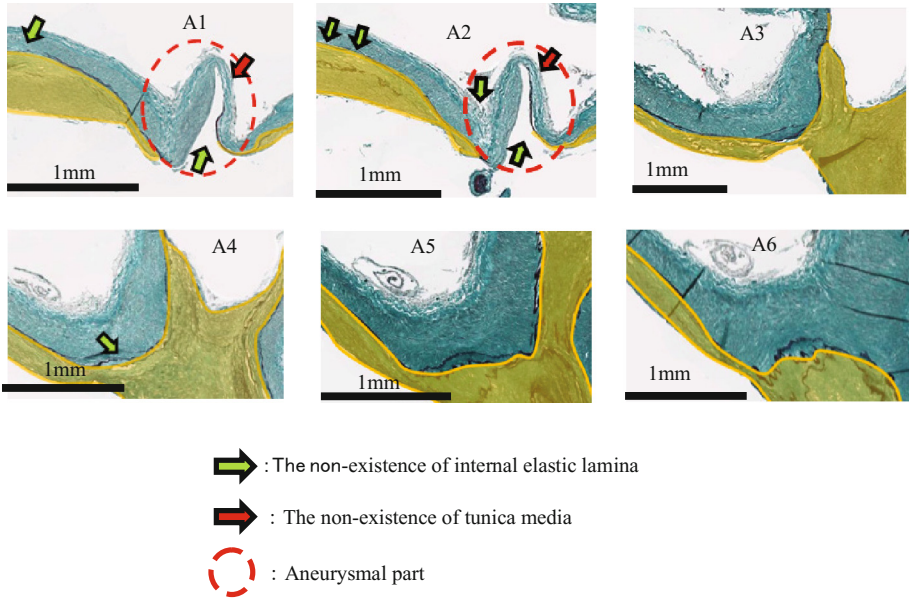


Fig. 2. The subcontinuous partial images of the typical case with an cerebral aneurysm (A). The existed only in two of the all partial images (A1) (A2). The non-existence of intimal hyperplasia, tunica media and intimal hyperplasia was found only in the aneurysmal part (A1) (A2). (Color figure online)

3.2 Cerebral Arteries with No Aneurysm

The subcontinuous partial images located on the bifurcation of tissue sections of the typical example were shown as Fig. 3A. As a result, the non-existence of internal elastic lamina and the non-existence of tunica media was found in the non-aneurysmal part. However, the non-existence of intimal hyperplasia were not found in the non-aneurysmal part. Here indicates the intimal hyperplasia by yellow.

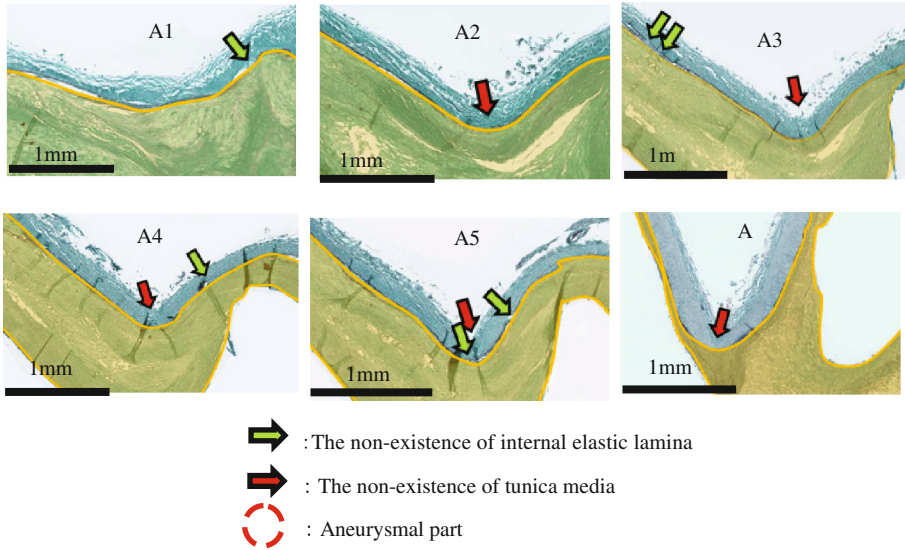


Fig. 3. The subcontinuous partial images of the typical case with no cerebral aneurysm (A). The non-existence of internal elastic lamina was found in some of the non-aneurysmal part (A1) (A3) (A4) (A5). Also, the non-existence of tunica media was found in some of the non-aneurysmal part (A2) (A3) (A4) (A5) (A6). However, the non-existence of intimal hyperplasia was not found in the non-aneurysmal part. (Color figure online)

3.3 Summary of the Results

We quantified these results and made a summary of the results of all of these cases. Both of aneurysm cases and non-aneurysm cases had the pathological characteristic of the

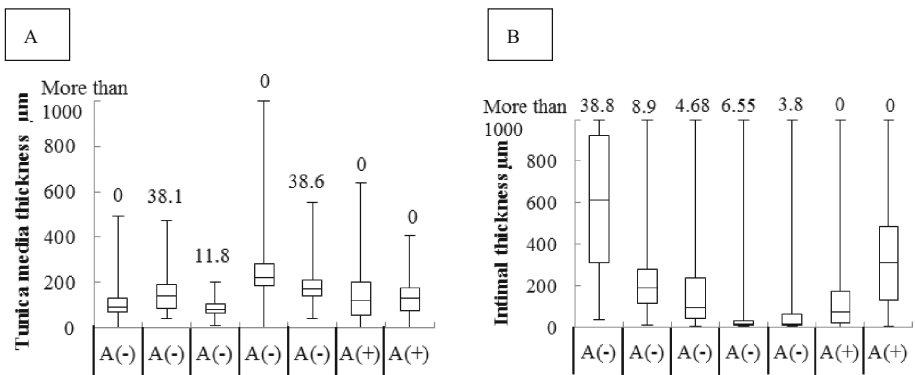


Fig. 4. The thickness of tunica media of all the cases (A) showed the non-existence of tunica media occurred in both of the aneurysm cases and the non-aneurysm cases. On the other hand, the thickness of intimal hyperplasia of cases (B) showed the non-existence of intimal hyperplasia occurred only in the aneurysm cases

non-existence of internal elastic lamina. Here we expressed the aneurysm cases as the mark “A(+)” and the non-aneurysm cases as the mark “A(-)”. In order to show the minimum of the thickness, the numbers were wrote over the error bars of each sections. In addition, while the minimum showed “0”, it meant non-existence. Also, the pathological characteristic of tunica media was shown in Fig. 4A. It indicated that both of aneurysm cases and non-aneurysm cases had the pathological characteristic of the non-existence of tunica media. Finally, the pathological characteristics of intimal hyperplasia were shown in Fig. 4B. It indicated that only aneurysm cases had the pathological characteristic of the non-existence of intimal hyperplasia.

4 Discussion

4.1 Discussion on the Relationship Between Aneurysm Initiation and the Distribution of Internal Elastic Lamina or Tunica Media

It is said that the non-existence of internal elastic lamina, the non-existence of tunica media and the existence of intimal hyperplasia are the reason why cerebral aneurysm initiate through previous studies [2, 3]. However, as shown in Fig. 5, compared the aneurysm cases with the non-aneurysm cases, the phenomenon of the non-existence of internal elastic lamina and the non-existence of tunica media were found in both of the cases. Therefore, we thought that the non-existence of internal elastic lamina or the non-existence of tunica media may be some kinds of phenomenon but not be the original factor of the cerebral aneurysm initiation.

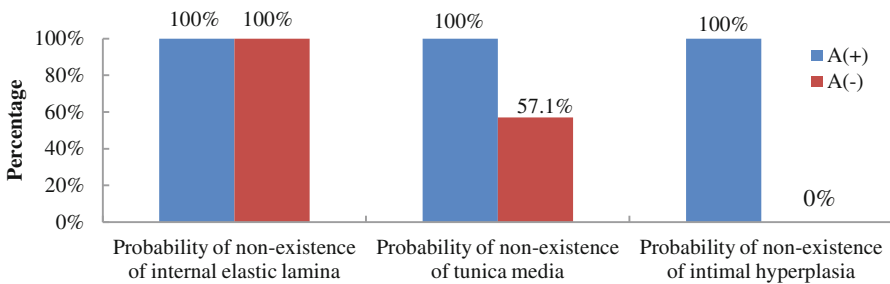


Fig. 5. The condition of pathological characteristics of all the cases showed the non-existence of internal elastic lamina and tunica media was possibly found in both of aneurysm cases and non-aneurysm cases non-existence of intimal hyperplasia was possibly found only in aneurysm cases. This indicated that the formation of intimal hyperplasia may be concerned with aneurysm initiation.

4.2 Discussion on the Relationship Between Aneurysm Initiation and the Distribution of Intimal Hyperplasia

The non-existence of intimal hyperplasia was found only in the aneurysm cases. Therefore, we thought that it is possible that the formation of intimal hyperplasia may be

concerned with the cerebral aneurysm initiation. In order to surmise the relationship between the distribution of intimal hyperplasia and mechanism of initiation of cerebral aneurysm, we used the heatmap to show the thickness of intimal hyperplasia in detail. As shown in Fig. 6, all the two cases with an aneurysm have the common characteristic that the aneurysm parts (the parts of where the intimal hyperplasia loss) located at the boundary of where the thickness of intimal hyperplasia changed distinctively (so called the bottom of intimal hyperplasia).

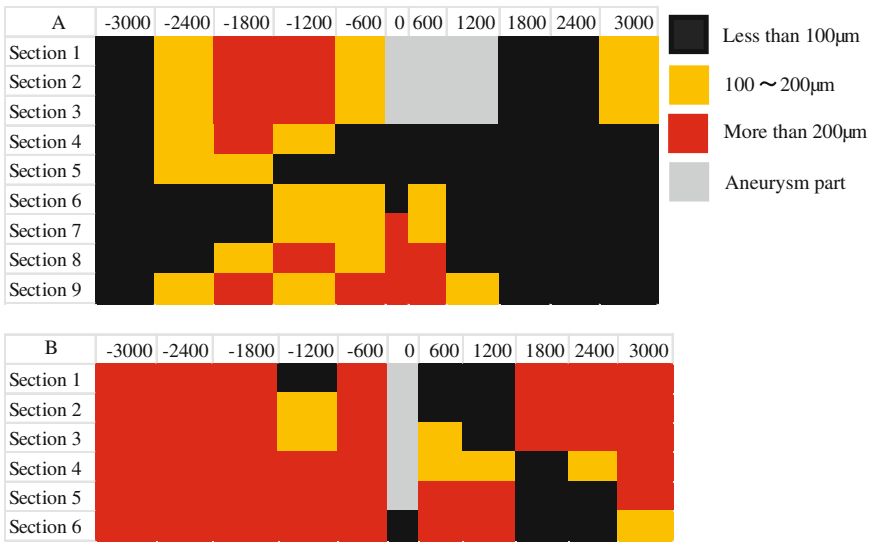


Fig. 6. The distribution of thickness of intimal hyperplasia of case 1 with an aneurysm (A) and case 2 with an aneurysm (B). The common characteristic of the aneurysmal parts (the parts of where the intimal hyperplasia loss) located at the boundary of where the thickness of intimal hyperplasia changed distinctively.

4.3 Discussion on the Mechanism of Aneurysm Initiation Based on the Results

Previous studies showed that some factors such as hemodynamics may cause the migration of cells [8] and the intimal hyperplasia occurs because of the migration of smooth muscle cells, and the condition of endothelial cells decides whether the smooth muscle cells migrate or not [9]. Here we thought the boundary of where the thickness of intimal hyperplasia changed distinctively as the location that the intimal hyperplasia would occur in near future. As shown in Fig. 7, based on these evidence, we thought that the smooth muscle cells of boundary migrated to the location that arteriosclerosis occurred because the topical migrated factors only existed at where the intimal hyperplasia occurred. As a result, the vessel wall of boundary of where the thickness of intimal hyperplasia changed distinctively became thinner and thinner and finally a cerebral aneurysm initiated there. On the other hand, we thought that the smooth muscle cells of boundary of where the thickness of intimal hyperplasia changed distinctively migrated

to the location no matter whether arteriosclerosis occurred or not because the migrated factors existed at all the locations. As a result, the vessel wall of boundary of where the thickness of intimal hyperplasia changed distinctively did not become thin because of the neogenetic intimal hyperplasia and the cerebral aneurysm initiation did not occur.

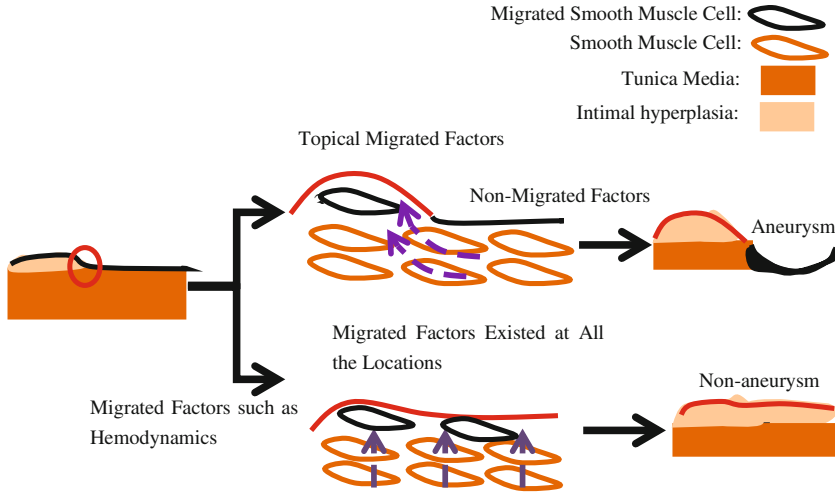


Fig. 7. The mechanism of the cerebral aneurysm initiation. The location where migrated factors distributed may influence the direction of smooth muscle cells migrated and decided whether an aneurysm initiates or not.

5 Summary

5.1 Finding of This Research

We studied the pathological characteristics of cerebral vascular bifurcations with and without aneurysm for elucidating the cerebral aneurysm initiation. Here we would like to summarize the findings of this research.

- (1) The non-existence of internal elastic lamina and the non-existence of tunica media were found in both cases, whereas the non-existence of intimal hyperplasia was found only in the case with an aneurysm.
- (2) Not the non-existence of internal elastic lamina or tunica media but the non-existence of intimal hyperplasia may be the reason of initiating cerebral aneurysm.

5.2 Contribution of This Research

These results make a new view of point for elucidating cerebral aneurysm initiation, and might be useful for developing a new kind of treatment for preventing the initiation of cerebral aneurysm. We also expect this research to be useful for the development of a new system of prediction of the cerebral aneurysm initiation.

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