 Venous collagenosis and arteriolar tortuosity in leukoaraiosis

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Abstract

Leukoaraiosis (LA), an age-related white matter degeneration, is thought to be caused by chronic ischemia. To understand the pathogenesis of LA, we studied the pathology, particularly of the blood vessels, in 186 brains [84 of them with magnetic resonance imaging (MRI)] over the past 10 years. With normal aging, there is gradual thickening of the walls of periventricular veins and venules with collagen subtypes I and III. This venous collagenosis (VC) was increased in brains with LA. Occasionally, LA lesions are not periventricular, but nearer the cortex. In such cases, the most severe VC occurs in the LA lesion rather than near the ventricle. Therefore, LA and VC are not independent degenerative processes coincidentally found near the ventricles, and although damage to the ependyma could be a cause of VC, it cannot be the only cause. Whether VC precedes LA is unknown, but our experience suggests that severe VC is usually accompanied by LA. Arteriolar tortuosity, another age-related vascular pathology, is common in LA. Our thick celloidin sections show three-dimensional views of tortuous arterioles. The tortuosity is much more severe in the white matter and there is considerable loss of parenchyma around them. Staining for collagen IV in the basal lamina reveals tortuous vessels in an “empty bag” that represents the limits of the surrounding parenchyma. These enlarged perivascular spaces correspond to état criblé. The demyelination in LA lesions is accompanied by loss of cells, mostly oligodendrocytes. In studies of apoptosis in LA, we found increased apoptosis within the lesion compared to the surrounding white matter. In conclusion, our studies support the concept that LA results from chronic ischemia due to age-related vascular pathology.

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1. Leukoaraiosis

Leukoaraiosis (LA) is an age-related neurodegenerative condition, which appears as an area of hyperintense signal in the white matter on magnetic resonance imaging (MRI). It is characterized histologically by demyelination, loss of glial cells (predominately oligodendrocytes), and vacuolization (spongiosis) [1]. The pathogenesis of LA is not fully established, but it appears to result from white matter ischemia. This ischemia may be caused by cerebrovascular pathology and/or insufficient supply of nutrient-enriched blood from the heart. The deep white matter, the area where LA is found, receives its blood supply from arterioles originating from the pial border zone, a region with a perilous blood supply [2]. We believe that LA represents chronic white matter ischemia that is slow to develop, with cerebral dysfunction affecting motor functions such as gait, executive functions, and eventually progressing to dementia. If chronic ischemia is the cause of LA, one must be concerned about the role that aggressive antihypertensive therapy may play in the pathophysiology of this disease. Furthermore, carotid stenosis of moderate severity, in combination with age-related cerebrovascular pathology or diurnal swings of blood pressure, might result in poor irrigation of the deep white matter due to damping of the pulse pressure.

There are numerous pathological alterations of cerebral blood vessels which might contribute to LA including intimal hyperplasia and atherosclerosis; medial fibrinoid necrosis, hyaline degeneration, arteriolosclerosis, lipohyalinosis, amyloidosis, and dissection; and adventitial calcifications, siderosis, and Charcot–Bouchard microaneurysms. Restriction of blood flow or impairment of autoregulation is a feature of most of these lesions. In this article, we will focus on two less widely recognized cerebrovascular pathologies, tortuous arterioles in the white matter (Fig. 1) and periventricular venous collagenosis (Fig. 2).
2. Tortuous arterioles in the white matter

There is a general tendency to increasing tortuosity of arterioles in the brain with aging. It is not yet established whether or not there is a greater severity of arteriolar tortuosity in LA, but increasing severity of arteriolar tortuosity would surely cause increasing severity of chronic ischemia in the deep white matter. Our studies suggest that it would take hypertensive levels of pulsatile blood pressure to maintain flow in such tortuous blood vessels [3]. This is particularly significant because many of these tortuous arterioles arise from the leptomeningeal arterial border zone which already has a precarious blood supply.

In the more severe cases of arteriolar tortuosity, a considerable amount of brain parenchyma in the white matter around the tortuous vessels is lost, leaving an extensive perivascular space. In standard paraffin sections, such perivascular spaces may be seen as "état criblé". However, in thick celloidin sections (100 μm), these tortuous vessels can be seen in three dimensions and the extent of the vascular space can be better appreciated (Fig. 1). With immunohistochemical staining for collagen IV, a basement membrane component, the tortuous vessel can be seen in a cavity outlined by a collagen IV-stained membrane, which might correspond to a basal lamina at the brain parenchyma (Fig. 1). In these thick sections, it is readily apparent that considerable brain parenchyma is lost around these tortuous vessels. We consider this loss of white matter parenchyma to be a lesion, for which we propose the name "cavity". The severe arteriolar tortuosities within such cavities are, of course, also lesions, that is, age-related vascular defects that contribute to ischemia. Together, these lesions might be called "tortuosity lesions" and we define them as referring to areas of severe arteriolar tortuosity within a cavity in the brain parenchyma.

Only the very largest of these lesions might be detected on MRI scans, especially since much of the cavity is occupied by the tortuous vessel. Thus, in studies of vascular dementia in live patients, most of these lesions would likely be undetected on MRI. Specific neuropathological studies after autopsy would probably be required to establish the presence or absence of such lesions.

It is unknown how or why these vessels become tortuous. One finding related to this tortuosity is the fact that, with aging, the cerebral arterioles grow in such a manner that they twist around themselves in a clockwise direction as viewed from the proximal to distal direction of the blood vessels [4]. Why the vessels always twist one way is mysterious, but it may have something to do with the chirality of biological molecules, which are predominantly levorotatory (left-handed). As suggested by Akima et al. [4], "a torsion probably occurred on the trunk of the blood vessels causing the intertwining of the more peripheral branches". This torsion might be due to elongation of the peripheral vessels. The growing vessels push back and wrap around themselves and sometimes around the parent vessel. The vessel cannot grow forward, but it can push back to where there is more room in the Virchow–Robin space, which is larger around the parent vessel. This twisting produces some degree of tortuosity. In contemplating the images of tortuous vessels within cavities, we suggest the following hypothesis regarding the development of severe arteriolar tortuosity: With aging, the vessels become slightly longer and push back into the perivascular space, winding on themselves. At the same time or subsequently, there is a loss of brain parenchyma around the twisting vessel, leading to an enlarged perivascular space. This may be caused by age-related chronic ischemia immediately outside the vessel, perhaps by thickening or other alterations of the vessel wall, or perhaps due to inadequate perfusion. In any case, the increased perivascular space permits further growth and tortuosity of the blood vessel to fill the available space. The space continues to enlarge over time and the tortuosity of the enclosed vessel may itself contribute to the ischemia in the area of the developing cavity.

3. Periventricular venous collagenosis

We have identified and named a new type of cerebral vascular pathology, periventricular venous collagenosis [5]. This is one of the very few primary pathologies described in veins. In studies of brains of cases from newborns to 90 year-olds, we found a gradual increase in the thickness of the walls of veins and venules near the lateral ventricles. This increased thickness was only slight until after middle age, and then there was a variable degree of thickening from case to case. In cases with LA, we found a striking degree of vascular wall thickening, resulting in narrowed lumina and even occlusion (Fig. 2) [5]. In ordinary H&E sections, these vessels could be mistaken for hyalinized arterioles, but we have established that the affected vessels are exclusively venous and the material in the thickened walls is largely collagen. As revealed by staining for collagen IV, it can be seen that these vessels have an apparently normal basement membrane. The thickened vascular walls stain strongly for collagens I and III, and there is an outer membrane of collagen IV, possibly representing the glial basement membrane at the brain parenchyma.

It is unknown why the veins become thickened in this part of the brain and what this might have to do with leukoaraiosis. Is this collagenosis a cause or result of ischemia? We do not know, but we have found one case of LA where the lesion was some distance from the lateral ventricle and the venous collagenosis "followed" the lesion away from the lateral ventricle. This finding indicates that there is a mechanistic link between LA and venous collagenosis, rather than an incidental association, with both pathologies independently occurring near the ventricles. This coincidence of location is an important confirmation of the strong statistical association we have previously shown [5] between the degree of venous collagenosis and the severity of LA seen on MRI.
Fig. 1. Tortuous arterioles in cavities in the white matter. (A) Staining with antibody to collagen IV in a thick celloidin section shows two tortuous arterioles in cavities outlined by collagen IV-stained basement membranes. (B) Staining for alkaline phosphatase in a thick celloidin section shows several arterioles that become tortuous as they enter the white matter. Note the lighter background staining around the tortuosities, an indication of the extent of the cavities.

Fig. 2. Severe periventricular venous collagenosis in a case of leukoaraiosis. (A) Staining with trichrome in a paraffin section shows numerous affected veins (green) near the ventricle. (B) Staining with hematoxylin and eosin in a paraffin section shows a few thickened veins (arrows) at higher magnification.
Increased resistance to venous blood flow, resulting from the venous stenosis, might induce chronic ischemia and/or edema in the deep white matter, perhaps somehow leading to LA. There is not a typical lymphatic system in the brain, and the route of drainage of brain interstitial fluid is not yet fully understood. Some solutes and fluid may pass through the walls of venules and veins to be removed via the blood stream. This process could be impaired by the collagenous thickening of the venous walls.

Some believe that the interstitial fluid finds its way to the subarachnoid space, mingles with the CSF, and passes into the venous sinuses via the arachnoid villi (granulations). One theory of how the brain interstitial fluid reaches the subarachnoid space has been proposed by Rennels et al. [6], as follows: The interstitial fluid is returned to the subarachnoid space via perivenous channels. Rennels et al. proposed that subarachnoid CSF is pumped down into the brain in the periarteriolar spaces (Virchow–Robin spaces) by the pulsations of the arterioles. Tracers (horse-radish peroxidase) have been shown to flow down the arterioles (in the periarteriolar space), into the basement membrane around the capillaries, through the basement membrane around the postcapillary venules, into the perivenous space, and back out to the subarachnoid space and the CSF within a short period of time (5–10 min in cats and dogs). Collagenous thickening of the venous walls might or might not affect the flow proposed by Rennels et al. However, age-related arteriolar sclerosis might impede the pulsatile pumping. Rennels et al. also demonstrated that vasogenic edema in the brain can inhibit the flow of interstitial fluid. An alternative theory regarding the pathway of interstitial fluid has been proposed by Weller et al. [7]. He suggests that the interstitial fluid passes along the arteriolar system in a retrograde direction within a perivascular sleeve that surrounds the arterioles and arteries, all the way back to the carotids and emptying into lymph nodes there. There is some experimental support for the concept that lymphoid cells might utilize such a route; however, we do not favor such a route for the bulk of the interstitial fluid. Thus, the two main functions of the lymphatic system (i.e., drainage of interstitial fluid and trafficking of lymphoid cells) may be achieved in the brain by two different drainage systems. We have no suggestions regarding how venous collagenosis might impact the proposed mechanism of brain interstitial fluid flow by Weller et al.

It is conceivable, although there is no data to support this speculation, that some people have a genetic predisposition to develop excessive periventricular venous collagenosis, resulting in ischemia, and finally LA. On the other hand, in the specific case where the venous collagenosis developed some distance away from the ventricle, it appears that some ischemic event induced the development of an LA lesion. In this instance, it would appear that the venous collagenosis developed after the ischemia, and was not the cause of the ischemia. Therefore, we hypothesize that the venous collagenosis found in this LA lesion in an unusual location, as well as in those LA lesions that occur in the usual periventricular location, develop in response to ischemia (which is known to occur preferentially near the ventricle), and add to the ischemia by occluding the veins and inhibiting the return of interstitial fluid, that may be somewhat toxic to the cells bathed in it. Thus, the mechanism of the putative genetic predisposition to periventricular venous collagenosis may be primarily through an indirect effect that causes chronic periventricular ischemia with a reactive production of excessive collagen deposition in the walls of veins. There could also be a component of a direct predisposition to excessive venous collagenosis. These mechanisms need not be mutually exclusive. The most severe cases of venous collagenosis may be due to the additive or synergistic effects of both mechanisms.

4. Apoptosis in leukoaraiosis and blood vessel walls

In studies of apoptosis in leukoaraiosis, we found scattered TUNEL-labeled cells in the brain parenchyma, as well as many labeled cells in vessel walls. The apoptosis counts were greater in the lesions than in the nearby white matter, and by the appearance of the lesions, it seemed that oligodendrocytes were preferentially lost [8]. Vessels of all sizes had labeled cells; those with excessive collagen did not have more of them. TUNEL-positive cells in the walls of blood vessels in human brains have been previously reported [9–11], but their significance is unknown. The TUNEL-labeled cells in the vessel walls did not appear to be apoptotic in morphology.

5. Conclusions

Cerebral vascular pathology develops with aging, and certain aspects are pronounced in LA and perhaps in many cases of Alzheimer’s disease as well. LA appears to result from chronic ischemia and may involve the loss of oligodendrocytes by apoptosis. We have focused on two aspects of vascular pathology in LA that likely contribute to white matter ischemia and we believe are underappreciated, that is, tortuous arterioles and venous collagenosis. In this article, we have discussed several mechanisms of age-related cerebrovascular pathology that may conspire to cause LA: (a) failure of cardiac output and supply of nutrient-rich blood to the cerebral white matter, (b) tortuous arterioles causing decreased blood flow (and perhaps white matter cavities), (c) periventricular venous collagenosis causing reduced venous blood flow, (d) edema in the deep white matter inhibiting the flow of interstitial fluid out of the brain via perivenous channels, and (e) arteriolar sclerosis inhibiting pulsations that could drive interstitial fluid through the perivascular circulatory system envisaged by Rennels et al. [6].
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References
