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ORIGINAL COMMUNICATION

Histopathology of Moyamoya angiopathy in a European patient

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Abstract

Background and purpose Moyamoya angiopathy (MMA) is rare outside Asia. Little is known about pathophysiology in European patients. This study aims to elucidate the histopathology of non-Asian MMA and its similarities and differences to those cases from Asia.

Methods Here, we present a 57-year-old European woman with MMA and describe the post-mortem examination results of the brain and cerebral arteries.

Results Histopathological findings in cerebral blood vessels were identical to those found in Asians. This included thickening and undulation of the internal elastic lamina as well as fibrocellular thickening and proliferation of smooth muscle cells of the intima in the distal segments of the internal carotid arteries and in proximal and middle segments of the anterior and middle cerebral arteries. Collateral vessels showed fragmented internal elastic lamina and thinning of the media with isolated microaneurysms.

Conclusions Histopathological changes found in this European patient are identical with those described in Asians. Despite suspected different genetic triggers and unknown pathophysiological cascades, MMA in Europeans seems to result in a common final pathway compared with the disease in Asians.

Keywords Moyamoya angiopathy · Autopsy · Histopathology · Europeans

Introduction

While in Asia Moyamoya angiopathy (MMA) is a relatively common cerebral vasculopathy, it is extremely rare in other parts of the world, in particular in Europe [1]. It is characterized by progressive stenosis and ultimately occlusion of the intracranial portions of the internal carotid artery and the anterior portions of the circle of Willis [2]. The disorder is particularly well researched in Japan and Korea. In these countries, numerous descriptions especially of the clinical presentation and the histopathological features of the condition have been published. Recently, the R4810K variant of the RNF213 gene as a founder mutation has been identified as a triggering factor in Asian patients. Interestingly, this mutation is also associated with incomplete moyamoya-like vasculopathies and with premature arteriosclerosis [3]. However, the underlying pathophysiological processes leading to MMA are widely unknown [4, 5]. Outside of Asia the available literature is scarce; especially there is an obvious shortcoming of reports about European patients. There exist a few case series reports, some from our own patients' collective [6, 7], but most of these reports are afflicted with insufficient clinical, demographic and epidemiologic information [8, 9]. It is argued that in European patients, the condition manifests later in life and consequently fragile collateral vessels are exposed to hemodynamic shear stress for a shorter time period [6]. This assumption is based on the notion that the prevalence of intracerebral hemorrhage is lower in the European patient population compared to the Asian patient population [1, 6, 9, 10]. Nonetheless, precise knowledge on the histopathological presentation of MMA in non-Asian patients in comparison to those from Asia is widely lacking [1, 8]. There is—to the best of our

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knowledge—only one case report mentioning post-mortem pathology findings of a 29-year-old Caucasian patient in the United States [11].

In the following, a new case of a 57-year-old female patient will be described. The patient succumbed to intracerebral hemorrhage after bypass surgery, even though the prognosis of bypass surgery is reportedly excellent in European patients [12, 13].

Methods

Clinical and autopsy findings of a European patient suffering from Moyamoya angiopathy are described. Written consent of the family members were obtained for autopsy, post-mortem examination of the brain and publication. The brain, including all intracranial/intradural vessels as well as both extradural internal carotid arteries (ICA) within the canalis caroticus were removed during autopsy. After fixation in 10% buffered formaldehyde for 2 weeks, the circle of Willis, i.e., bilateral anterior cerebral artery up to A2, middle cerebral artery (MCA) up to M2, posterior cerebral artery up to P3, the basilar artery, both vertebral arteries, the intradural segments of ICA, an 8-cm-long segment of both extradural ICAs within the carotid canal as well as bypass vessels connecting left superficial temporal artery to the left MCA were carefully removed, cut into transversal slices and separately embedded in paraffin. Furthermore, a total of 26 different brain regions were cut and paraffin-embedded. Histological sections were stained with hematoxylin and eosin, Berlin blue, Elastica van Gieson stains, and immunohistochemically with antibodies against smooth muscle actin.

Results

A female patient of German origin, born in 1961, experienced a left frontal intracerebral hemorrhage in 1990. In 1999, the patient suffered an infarction of the left middle cerebral artery (MCA) with subsequent neurological deficits, including right-sided hemiparesis, motor-sensory aphasia, apraxia, and encephalopathy. Perfusion MRI, conventional angiography and special Doppler sonography to detect vasomotor reactivity demonstrated hemodynamic insufficiency on both hemispheres. In view of the continuing risk of stroke with hemodynamic insufficiency, in May 2017 a bypass was performed between the superficial temporal artery and a peripheral branch of the right MCA, complicated by postoperative subdural hematoma and the need for borehole trepanation. In January 2018, a bypass between the left superficial temporal artery and the left MCA was created. As an unusual adverse event, the patient again developed a large subdural hematoma, requiring borehole trepanation. Two weeks after the evacuation of the hematoma, the patient experienced another secondary hemorrhage and 3 months later a massive hemorrhage in the left thalamus and basal ganglia region (Fig. 1a) at considerable distance from the surgical site, most likely due to a hypertensive crisis and a until then unknown deficiency of factor 13. Despite all therapeutic efforts, the patient suffered a subsequent infarction in the right MCA territory end of March 2018 and died on April 19, 2018 at the age of 57 years.

A post-mortem examination of the brain was performed, yielding the following findings.

Apart from hemorrhagic and ischemic changes of the brain tissue, arteriosclerotic changes of the vertebral arteries (bilateral), basilar artery and internal carotid artery were observed (Fig. 1b). In addition, however, high-degree Moyamoya changes (Fig. 1c), including thickening and undulation of the internal elastic lamina as well as fibrocellular thickening and proliferation of smooth muscle cells of the intima (Fig. 1d), were identified in the distal segments of the internal carotid arteries (ICA, bilateral) and in proximal and middle segments of the anterior and middle cerebral arteries. Furthermore, arteriosclerotic changes, in the form of cholesterol crystal deposits in the intima, were detected in the ICA (Fig. 1e). In the collateral vessels with fragmented internal elastic lamina and thinning of the media, isolated microaneurysms were found (Fig. 1f).

Discussion

To the best of our knowledge, this is the second of only two post-mortem case reports [11] describing the cerebrovascular histologic changes of a non-Asian patient with idiopathic MMA. In Asia, these changes have been repeatedly described [14, 15]. Typical histopathological findings in Asian patients include eccentric fibrocellular thickening of the intima resulting from abnormal smooth muscle cell proliferation, thinning of the media and prominently tortuous and often duplicated internal elastic lamina. In addition, there are no inflammatory and typically, no atheromatous changes. In Asian cases, it is well established that the abnormal proliferation of intimal cells results in vascular occlusion and thrombosis with consecutive hypoxia, which in turn stimulates the development of collateral vessels through the formation of dilated and tortuous perforating arteries [5, 16]. The Moyamoya collateral vessels with thin media and fibrin deposits in the vessel wall, fragmented elastic lamina, attenuated media, and microaneurysms are fragile. Therefore, they represent the pathophysiological correlate of the susceptibility to bleeding associated with MMA, while the narrowed blood vessels are the cause of embolic and hemodynamic infarctions [17–19]. The only case of a Caucasian patient ever published before is the case of the autopsy of

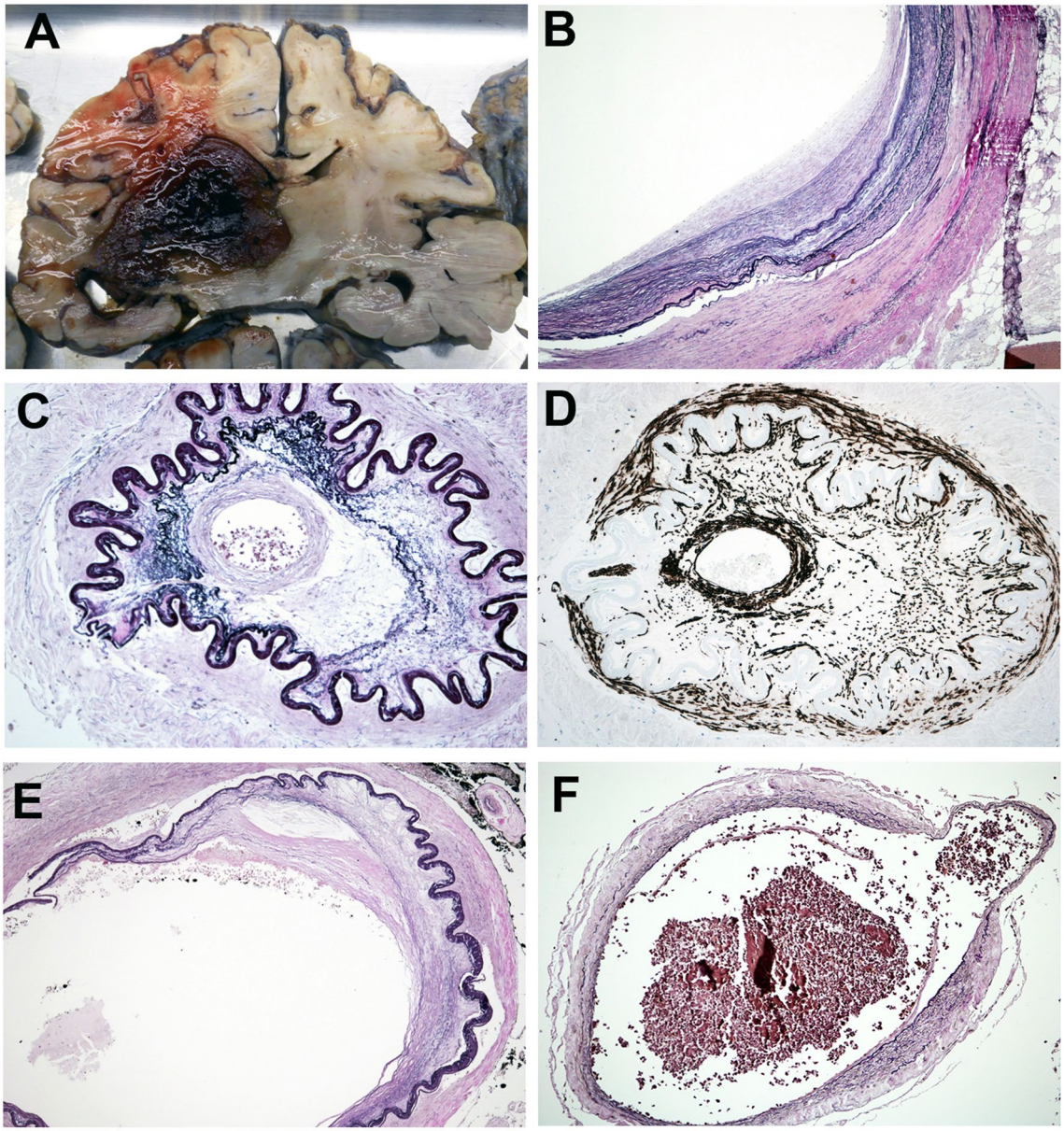

Fig. 1 Post-mortem analysis of the brain

a female patient of European origin in the United States, which showed intimal proliferation of the intracranial ICA as well as the anterior and middle cerebral arteries with medial thickening [11]. Furthermore, the authors describe an undulating intact internal elastic lamina which was focally thickened or splitted [11]. Neltner et al. did not discuss the similarity or dissimilarity with Japanese or Korean cases [11]. The histological changes reported here in this new case are impressive as they show, on one hand, that the histological–pathophysiological presentation of MMA is identical in this European patient as in Asian patients, and, on the other hand, that changes characteristic of MMA can occur in conjunction with arteriosclerotic changes. Given the identical histopathological picture, it seems unlikely that the clinical presentation differs between European and Asian patients [1, 6–8, 20]. Differences in the age at onset and consequently a later manifestation are conceivable [6, 7, 21, 22]. A more benign course in non-Asian patients as recently mentioned for a Finnish cohort has to be scrutinized based on this data [23]. Furthermore, it can be assumed that the number of unreported cases and the rate of misdiagnosis are higher in Europe compared to Japan and Korea where the condition is well known [9]. In contrast to the earlier strict diagnosis by exclusion of patients with comorbid arteriosclerosis, the degree of arteriosclerotic changes in extracranial vessels should be taken into account, because a patient may have

mild arteriosclerosis and typical MMA [9]. In our patient, the susceptibility to bleeding was found to be caused by a previously unknown factor 13 deficiency. The pathologic findings highlight that in Europeans, there is a risk of similar pathophysiological consequences as seen in Japan, i.e., hemodynamic and embolic infarction and intracerebral hemorrhage [24]. Based on pathophysiological reasoning, revascularization surgery appears to be a plausible approach also in European patients [12, 13], despite the tragic outcome after surgery in the case reported here.

Compliance with ethical standards

Conflicts of interest There is no conflict of interest.

Ethical standards As this was a single case study no ethical approval was necessary.

Informed consent The family members of the deceased patient gave their consent of post-mortem analysis and publication.

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