The steno-occlusive syndrome of the arterial circle of Willis

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Key words: moyamoya disease (MD), moyamoya disease mimics, neural crest, and RNF213 variant

Abbreviations: AIS: acute ischemic stroke, ICA: internal carotid artery, MCA: middle cerebral artery, MD: moyamoya disease, NC: neural crest, NCC: neural crest cell, PCA: posterior cerebral artery, Pcom: posterior communicating, VBA: vertebro-basilar artery

Introduction

Moyamoya disease (MD) is first reported in 1968 and 1969 by Kudo [1] and Suzuki et al [2], respectively. This disease is fairly common in Japan, Korea, and China whereas it is rare in European and North American countries. There have been many papers on incidence, etiology, symptomatology, diagnosis, treatment, and outcome of MD despite the unclear clinical definition of MD [3]. To my knowledge, however, there has been no paper why only the internal carotid artery (ICA) territory is involved and why the vertebro-basilar artery (VBA) territory is devoid of such an involvement.

MD is by definition not associated with any known diseases [3]. However, it is occasionally not easy to discriminate MD from MD mimics, such as unilateral MD, quasi-MD, occlusion of the proximal middle cerebral artery (MCA), dissection of the terminal portion of the ICA, and twig-like (aplastic) MCA. Differences between MD and MD mimics on the standpoint of pathogenesis are not clearly explained. The author tries to clarify the said two unanswered questions: selective involvement of ICA territory in MD, and differences between MD and MD mimics.

Definition of the anterior and posterior circulations of the brain

In our practice, we often use the term “anterior” and “posterior” circulations. The physicians who use them unfortunately vaguely define these because they mean different vascular territories. In the acute ischemic stroke (AIS) of the anterior circulation, the occlusion of the basilar artery is excluded. However, when the posterior cerebral artery (PCA) is predominantly supplied by the posterior communicating artery (Pcom artery, so-called fetal type, this should be called embryological type), AIS in the PCA territory is included in the anterior circulation ischemia. Contrary to this, when the PCA is predominantly supplied by the basilar artery (so-called adult type), AIS in this case is included in the posterior circulation ischemia. It is not clearly defined whether the ischemic PCA territory belongs to the anterior or posterior circulation.

Similarly, the locations of the cerebral aneurysms are roughly divided into the anterior and posterior circulations. The basilar bifurcation aneurysm is commonly classified as the posterior circulation aneurysm. P2-3 aneurysm is also classified as posterior circulation aneurysm even if the PCA is predominantly supplied by the Pcom artery.

In the clinical setting, there is no clear-cut definition of the anterior and posterior circulations. This is because there is no definition whether the PCA territory belongs to the anterior or posterior circulations. The author defines the anterior/posterior circulations by embryological basis. Figure 1. Distribution of the medial cells of the cerebral arteries migrated from the neural crest cells (NCCs) might contribute to such a classification because their distribution is unique to the anterior circulation.

Embryological distal annexation of the telencephalic branches of anterior choroidal artery

Embryology of the cerebral arteries helps to understand the vascular distribution of the anterior and posterior circulations. Figure 2. The third aortic arch contributes to the formation of the primitive ICA, which is a cranial continuation of the dorsal aorta. The dorsal aorta is distally divided into the cranial and caudal divisions at the origin of the Pcom artery. The cranial division of the primitive ICA is further divided into the primitive medial and lateral olfactory arteries. The former becomes future anterior cerebral artery while the latter becomes anterior choroidal artery, artery of the Heubner and later MCA. Primitive anterior choroidal artery has three branches: choroidal, diencephalic and telencephalic branches. Most telencephalic branches are transferred to the caudal division of the primitive ICA, which is called “distal annexation” [4]. After distal annexation, only small telencephalic branch such as an uncal branch remains as the branch of the anterior choroidal artery. The annexed (transferred) branches becomes the P2-4 portions of the PCA. Thus, the entire braches of the PCA as well as the Pcom artery belong to the primitive ICA, embryologically.

Neural Crest

Neural crest (NC) is characteristic to the vertebrates, and it is the structure formed between the cutaneous ectoderm and neural tube, the latter of which is formed by the fusion of bilateral neural folds, which develop from the most lateral part of the neural plate. NC appears when the neural tube is nearly closed at gestation of around 28 days. NC was first discovered by Swiss anatomist and physiologist at the university of Basal, Wilhelm His in 1868 and described as “Zwishenstrang” (the cord in-between). His name remains in the sulcus limitans of His for his discovery of this sulcus in 1893.

By the experiments by French biologist Nicole Le Douarin et al. in 1970s determined the fate map of the NCC by the experiments using a Japanese quail and chick. NCCs have pluripotent ability to become a various kinds of cells at the target organs after migration from the original position. Figure 3. For example, cranial NCC can be neurons and glia of the cranial ganglion, cartilage and bone, connective tissue while truncal NCC can be sympatho-adrenal cells, sensory neurons and glia, and pigment cells [5]. There is a distinct difference between the cranial NCC and truncal NCC. Only cranial NC can become connective tissue, i.e., mesenctoderm or ectomesenchyme. Echivers et al. of Le Dauran group showed that cephalic NC contributes to the media of the telencephalic and facial arteries, but not to the VBA [6]. Endothelium of all vessels in the body is originated from the mesoderm. In the paper of Etchevers et al. in 2001, the media of the P1s of the PCA are illustrated as mesodermal origin, but the present author believes they are actually of NC origin. In other words, the arterial circle of Willis is composed of the media of the NCC origin. Figure 4.

From the distribution of the NCC in the cranial arterial system, border between the anterior and posterior circulations might be between the basilar tip (P1 of the PCA) and superior cerebellar artery. This is contrary to the previously acknowledged border at the origin of the primitive trigeminal artery [7]. Cerebellum is embryologically the outgrowth of the first rhombomere (r1) [8]. The media of the superior cerebellar artery is found to be of mesodermal origin, and the artery supplying the cerebellum should be the artery of the rhombencephalic origin, i.e., basilar artery. Figure 5.

Neurocristopathy (= disease of the NC)

Disease of the NC is first named **neurocristopathy** by Canadian pediatric pathologist Robert Bolande in 1974 [9]. It includes dysgenetic neurocristopathy (Hirshspuring’s disease, Treacher Collins syndrome, facial clefting, etc.) and neoplastic one (neuroblastoma, carotid body tumor, paraganglioma, neurofibromatosis type 1, etc.). Because the media of the cerebral and facial arteries are composed of the cells migrated from the cephalic NC, the diseases of the cerebral and facial arteries (excluding the arteries in the vertebro-basilar system) can be called as vascular form of cephalic neurocristopathy.

Cephalic neurocristopathy

Cephalic neurocristopathy, i.e., diseases of the cephalic NC include agenesis or hypogenesis of the ICA, MD [10,11], PHACE syndrome [12], ACTA2 mutation related syndrome [13], neurofibromatosis type 1 related MCA occlusion [14]. PHACE syndrome is reported to present with MD. As is the case with ACTA2 mutation syndrome. Involved arteries among these cephalic neurocristopathy are all in the anterior circulation. Figure 6.

Cardio-cephalic neurocristopathy

NC can be divided into cephalic and truncal NCs along the anterior-posterior axis of the embryo. Cephalic NC extends from the diencephalon to the fifth somites. Cardiac NC extends from the otic placodes to the third somites. Thus, cardiac NC is located within cephalic NC.

Among above-mentioned cephalic neurocristopathy, concurrent occurrences of cardio- and cerebrovascular diseases have been reported in PHACE syndrome [12], ACTA2 mutation syndrome [13], and less frequently in MD [15,16]. Such concurrent occurrence could be considered in light of NC as a novel concept of **cardio-cephalic neurocristopathy** [17].

RNF 213 variant (R4810K) and cephalic neurocristopathy

Kyoto university group and Tohoku university group discovered RNF213 R4810K variant as a susceptibility gene in 2011, independently [18,19]. This variant is found 95% of familial and 73% of solitary MDs while the incidence among normal control in Japanese is 1.4%. Initially, this variant is thought to be specific to MD, but later it is proved that MD mimics also have this variant [20, 21]. Incidence of this variant in quasi-MD is reported 0-73.3% [14,22]. Interestingly, among the patients with atherosclerotic steno-occlusion of the intracranial major arteries, RNF 213 variant was found 23.8% in Japan [23] and 22.6-25.8% in Korea [24]. More interestingly, this variant was exclusively found 23.3% (10/43 patients) in the anterior circulation while it was not found in the posterior circulation (0%; 0/61 patients) [25]. As expected from embryological standpoints, significant difference of the incidence of RNF213 variants between the anterior and posterior circulations was observed.

It is not clear why such a distinct difference was observed between the anterior and posterior circulation. However, the author believes NC is more or less contributing to this difference. Embryological NCC may interact with the endothelium of the arteries in the anterior circulation. Consequently, steno-occlusive change is predominantly observed in the anterior circulation.

Steno-occlusive syndrome of the circle of Willis

Pathology of MD and atherosclerosis is essentially different. In atherosclerosis of coronary arteries, there are positive and negative remodelings. Negative remodeling results in diminished diameter of the vessel, which is quite similar to MD. In this situation, there is no clear-cut difference between atherosclerosis and MD.

MD is named for the resemblance that basal brain vessels have to a hazy puff of cigarette smoke on cerebral angiograms [2]. The development of moyamoya vessels is known to be variable. They are marked in some pediatric patients but are not well developed in other patients, especially adults. Of the 2 vascular structural changes, steno-occlusive changes are primary lesions of MD, and moyamoya vessels represent compensatory (responsive) angiogeneses, and are thus developed mostly from normal structures [10,26]. Basic pathology is the similar steno-occlusive changes both in MD and atherosclerosis in the anterior circulation.

Discovery of RN213 variant for MD, over 20% incidence of RNF213 variant in atherosclerotic steno-occlusion of the anterior circulation, and selective contribution of NCC to the media of the anterior circulation strongly favor the concept of steno-occlusive syndrome of the anterior circulation (the arterial circle of Willis), which includes MD, MD mimics, and atherosclerosis. Figure 7.

Comprehensive concepts of steno-occlusive changes in the anterior circulation provide more appropriate and rationale explanation of the MD and MD mimics [10,11]. However, further confirmation by the accumulation of the data is necessary.

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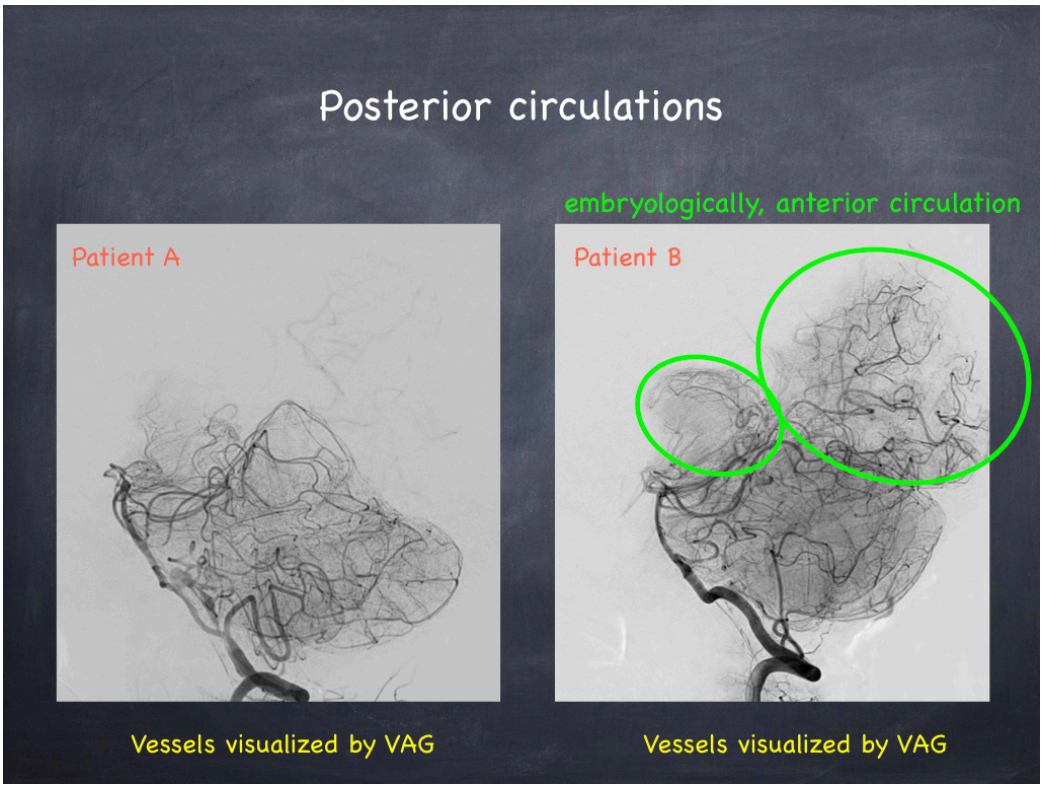

Figure 1.

Vague definition of the posterior circulation. The posterior circulation is commonly defined as the territory visualized by vertebral angiography. In this sense, two images (patients A and B) show both posterior circulations, but this is not the case.

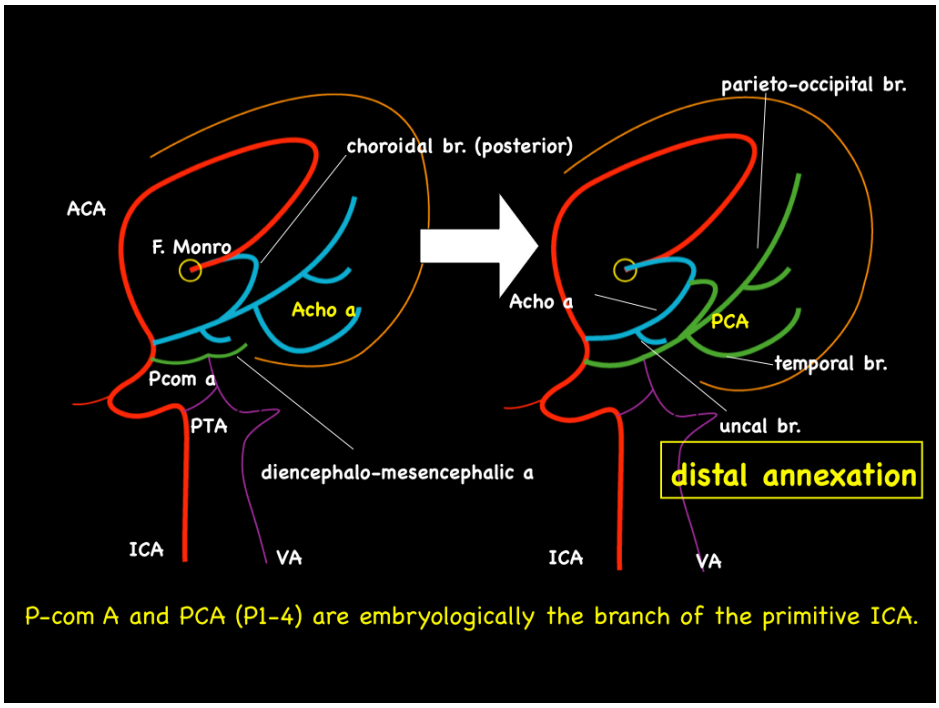

Figure 2.

Embryology of the anterior choroidal artery. Most telencephalic branches of the primitive anterior choroidal artery are transferred to the caudal division of the internal carotid artery, which is called “distal annexation”.

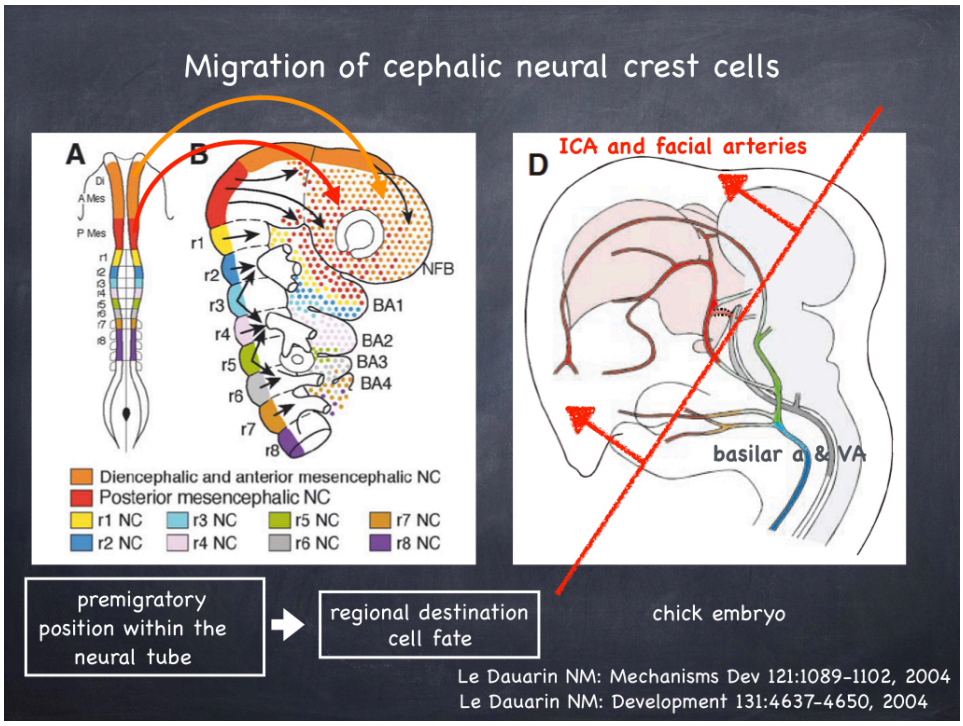

Figure 3.

Migration of the cephalic neural crest cells. Neural crest cells at the anterior and posterior mesencephalon migrate to the facial and telencephalic regions and contribute to the media of the telencephalic and facial arteries. However, Neural crest cells do not contribute to the media of the vertebra-basilar arteries.

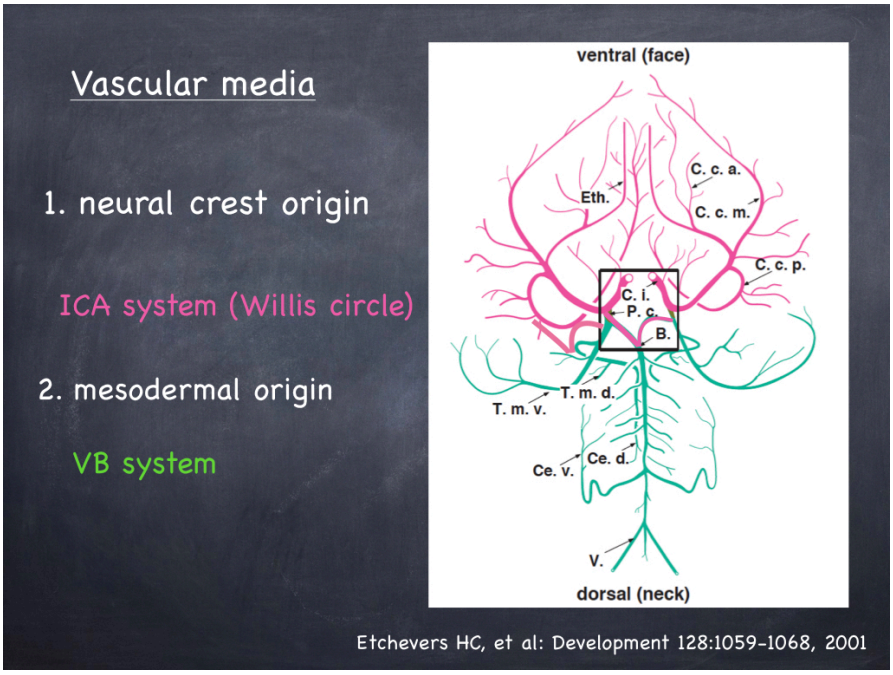

Figure 4.

Origins of the media of the cerebral arteries. The media of the internal carotid system is of neural crest origin, but that of the vertebra-basilar system is of mesodermal origin. Modified from the paper by Etchevers HC, et al.

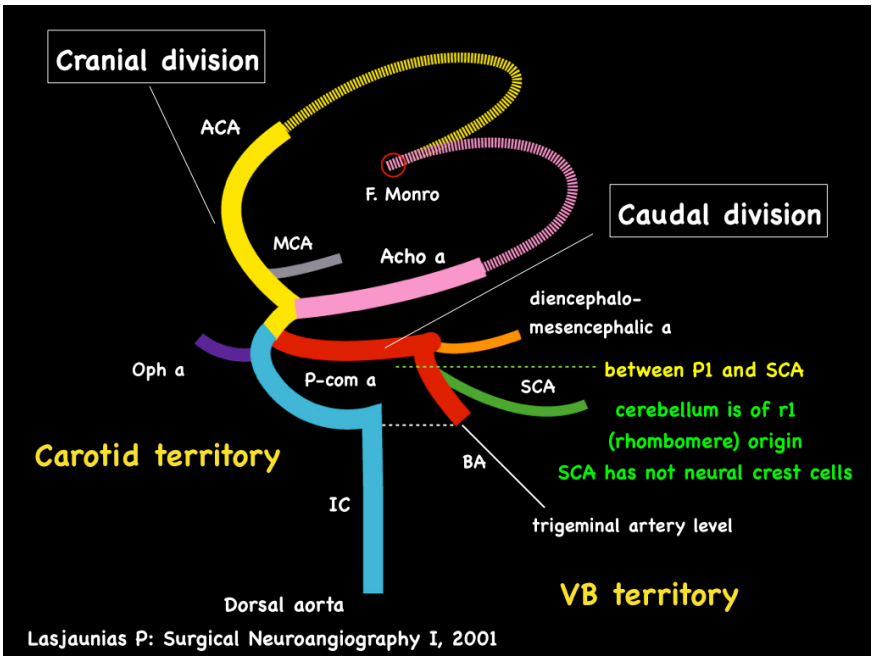

Figure 5.

Embryological border between the anterior and posterior circulations. This border is determined by the presence or absence of the neural crest cells in the media of the arteries. It is located between the basilar tip and superior cerebellar artery.

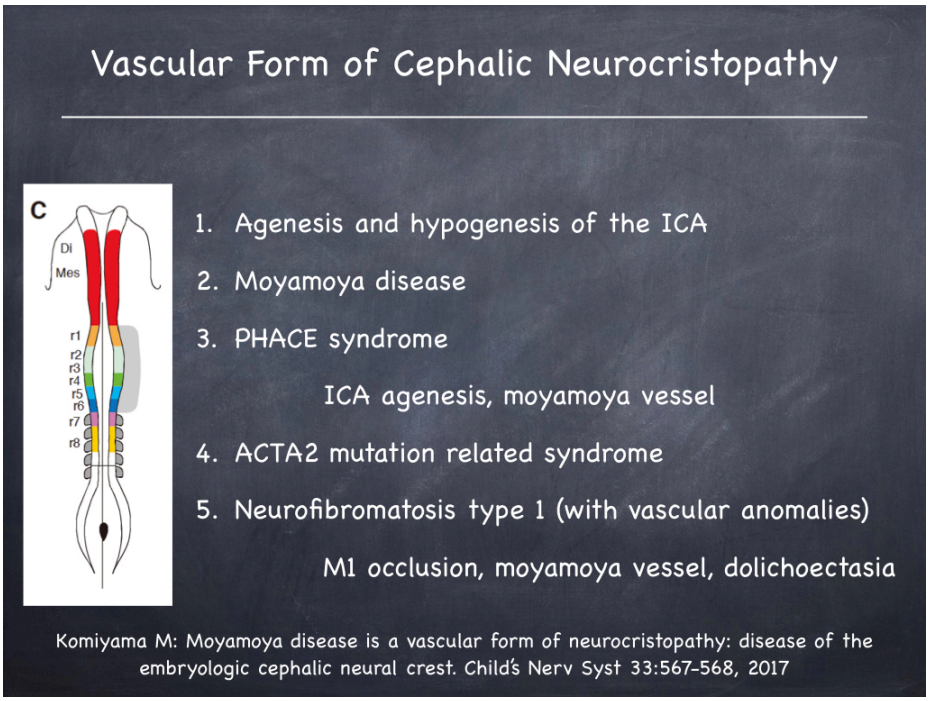

Figure 6.

Vascular form of the cephalic neurocristopathy. The involved abnormal vessels' media is of cephalic neural crest origin embryologically.

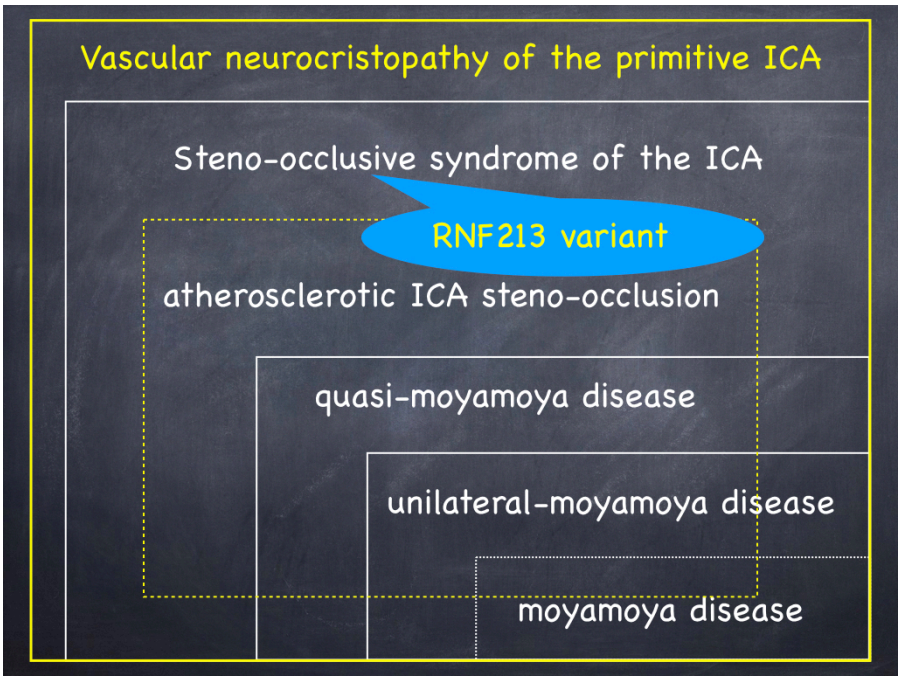

Figure 7.

Concept of steno-occlusive syndrome of the anterior circulation. Neural crest cells might be cryptic causes for this syndrome.