

# Moyamoya disease is a vascular form of neurocristopathy: disease of the embryologic cephalic neural crest

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Dear editor,

I would like to propose a new disease concept of moyamoya disease (MD), also referred to as “spontaneous occlusion of the circle of Willis,” of which the pathogenesis remains unknown. The recent discovery of the susceptibility gene, *RNF213*, for MD may provide new insights into its etiology but calls for a change in disease concept [1].

The neural crest (NC) is a transient, embryologic structure that was first found by a famous anatomist Wilhelm His in 1868 [2]. NC is called the fourth germ layer and is characteristic to the vertebrates phylogenetically. Neural crest cells (NCCs) are pluripotent and give rise to a variety of derivatives after migration in early embryogenesis, such as neurons, glias, cartilage, connective tissue, pigment cells, and adrenal cells. It was proposed to call the diseases of NC origin “neurocristopathy” (crista = crest, ridge), which is divided into dysgenetic and neoplastic forms [3, 4]. The typical dysgenetic form includes Hirschsprung disease, DiGeorge syndrome, coarctation of the aorta, and agenesis/hypogenesis of the internal carotid artery (ICA) [5], and the neoplastic form includes neuroblastoma, paraganglioma, and neurofibromatosis type 1 (NF1). Interestingly, it is reported that MD co-exists with Hirschsprung disease [6], coarctation of the aorta [7], and NF1 [8]. In addition, Phace syndrome may present with agenesis of the ICA, coarctation of the aorta, cardiac anomaly, and segmental facial hemangioma as well as MD [9]. Morning glory syndrome of the eye is also associated

with MD [10]. In these situations, MD is named “quasi-MD” because of the co-existence of systemic disease.

NC is classified by location along the neural axis into cephalic, vagal, trunk, and sacral NCs. Cephalic NC is unique to the vertebrates and yields many derivatives in the face and head, such as jaw, facial connective tissues, meninges, and the wall of the intracranial blood vessels except for endothelium. Intracranial arteries consisting of cephalic NCCs are confined to the arteries of the circle of Willis [11], that is, the branches of the primitive ICA supplying the forebrain (telencephalon and diencephalon). The vertebro-basilar arteries consist totally of mesoderm-derived cells. Cardiac NCCs located in vagal NC migrate to the third, fourth, and sixth branchial arches and the heart. Some congenital aortic and/or cardiac anomalies, including coarctation of the aorta and persistent truncus arteriosus, are associated with migrated NC cells of cardiac NC origin.

Embryologically, the cerebral arteries are initially composed of the cranial and caudal divisions of the primitive ICA, which is the cranial extension of the dorsal aorta. Cranial division supplies the forebrain while the caudal division supplies the mesencephalon. The hindbrain (rhombencephalon and myelencephalon) is essentially supplied by vertebro-basilar system after the establishment of the primitive ICA system [12]. Steno-occlusive changes in MD progress from anterior arteries to posterior ones during the course of MD. In this context, posterior arteries mean the posterior communicating artery and posterior cerebral artery (PCA) and do not include basilar artery and cerebellar arteries. Posterior communicating artery and P1 portion of PCA are the caudal division of the primitive ICA. In early embryogenesis, cortical (telencephalic) branches of the anterior choroidal artery are transferred to P2 portion of PCA. This means that the steno-occlusive changes occur exclusively to the primitive ICA and its branches.

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Histopathological changes in MD include thinning of the media due to degeneration of the vascular smooth muscle cells, marked tortuosity of internal elastic lamina, and fibrous intimal hyperplasia caused by proliferation of the vascular smooth muscle cells, which results in narrowing of the intravascular lumen [13]. These pathological changes in the arterial wall of the primitive ICA origin are strongly related to smooth muscle cells of NC origin, and not to the endothelium of mesodermal origin. However, there is a possibility that circulating smooth muscle progenitor cells that are discovered recently may contribute to the intimal hyperplasia in MD [14]. Further study is required to clarify the role of these smooth muscle progenitor cells in the pathogenesis of MD.

Now, it is obvious that the steno-occlusive changes of the cerebral arteries in both MD and quasi-MD occur only in the arteries of the NC origin [15]. Considering the roles of cephalic NC and its close relation to MD and quasi-MD, they can be regarded as a vascular form of neurocristopathy. Although most neurocristopathies are congenital, a vascular derivative of cephalic NCC may undergo pathological changes later in life caused by as yet undetermined genetic, epigenetic, and/or environmental factors in addition to *RNF213* gene mutation. This disease concept of MD, being deeply related to NC pathology, may enable us to understand the etiopathogenesis of MD and quasi-MD.

#### Compliance with ethical standards

**Conflict of interest** There is no conflict of interests.

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