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Cephalic/cardiac neural crest cell and moyamoya disease

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Abstract

Background: The neural crest is a transient structure present in early embryogenesis. Cephalic neural crest cells migrate into the pharyngeal arches and the frontonasal process that becomes the forehead and midfacial structures. They also contribute to forming the media of the arteries of the circle of Willis and their branches. The cardiac neural crest produces vascular smooth muscle cells in the ascending aorta, cardiac septum and coronary arteries.

Methods: In this review, we evaluate the role of the neural crest in moyamoya disease and the pathological implications from the concurrence of moyamoya disease and cardiovascular diseases from the point of view of neural crest cell distributions.

Results: Midline craniofacial and central nervous system anomalies with eye anomalies, morning glory disc anomaly in patients with moyamoya disease can both be explained as a subtype of cephalic neurocristopathy. Further, the association between moyamoya disease and cardiac manifestations (congenital cardiac defects and coronary artery disease) have also been reported. Both the cephalic neural crest and cardiac neural crest contribute to these concurrent arterial diseases, as cardio-cephalic neurocristopathy.

Conclusion: The concept of cephalic/cardio-cephalic neurocristopathy provides a new perspective to understanding the underlying aetiological associations and to developing future therapeutic approaches for concomitant moyamoya disease and cardiovascular diseases.

Keywords

Cephalic neural crest, cardiac neural crest, neurocristopathy, moyamoya disease, smooth muscle cell, embryology

Introduction

The neural crest (NC) is a transient structure dorsal to the neural tube early in embryogenesis, which develops from the most lateral part of the neural plate. Neural crest cells (NCCs) are pluripotent, and phylogenetically a characteristic of vertebrates. NCCs migrate extensively along the dorso-ventral axis and generate widely differentiated cell types, including pigment cells, adrenal medullary cells, bone and cartilage, connective tissues, glias and neurons of the peripheral nervous system, and smooth muscle cells (SMCs) of the cerebral, branchial and coronary arteries, and the aorta.[1] Moyamoya disease (MMD) is a progressive steno-occlusive arteriopathy of the intracranial artery, and extracranial involvement of MMD has been increasingly reported.[2–4] In this review, our aim was to describe the role of NC in MMD, and to discuss the pathological implications of concurrence diseases from the viewpoint of NCC distribution.

Neural crest cells

The NC can be divided into two groups: cephalic and trunk (Figure 1).[5] Each region has characteristic derivatives and functions. The cephalic NC produces the craniofacial mesenchyme and forms much of the craniofacial skeleton, including the skull, upper and lower jaws, hypobranchial skeleton, eye tissues, adenohypophysis and carotid body. Besides skeletal derivatives, cephalic NCCs give rise to SMCs and pericytes lining the facial and cerebral arteries in the prosencephalon (forebrain).[6] The cardiac NC is a subregion of the cephalic NC, extending from the otic (ear) placodes to the third somites,[5] which produces the entire muscular–connective tissue wall of the large arteries,[7] the aorticopulmonary septum[5] and coronary arteries.[8] The trunk NC contributes to neurons and glia of the dorsal root ganglia and the sympathetic ganglia, as well as Schwann cells. Finally, the sacral NC (a subregion

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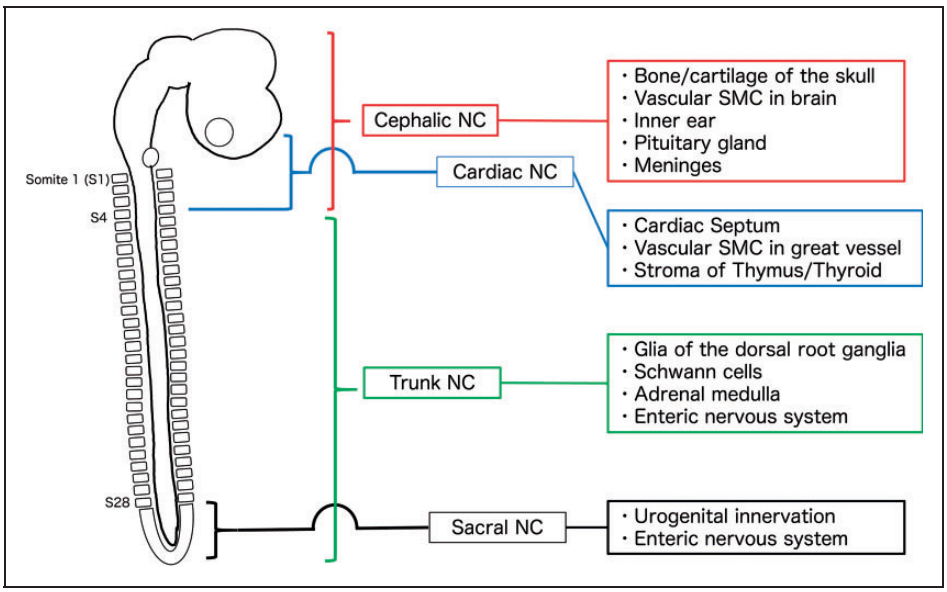

Figure 1. Diagram illustrating the location of the four parts of the neural crest (NC) and their derivatives. The NC can be divided into two regions: cephalic and trunk. The cardiac and sacral NC are subregions of the cephalic and trunk NC, respectively. Only the cephalic NC provides smooth muscle cells (SMCs).

of the trunk NC) generates the enteric and the sympathetic ganglia.

Anterior circulation/posterior circulation

There are two distinct populations that give rise to vascular SMCs. One is the mesoderm, which forms the descending aorta. The other is the NCC population, which generates SMCs in the beginning proximal portions of the aorta, extracranial arterial trunk and intracranial arteries.[6] In the brain, the prosencephalon (telencephalon, diencephalon and mesencephalon)[9] is supplied by vessels of cephalic NC origin, while the remaining caudal brain (rhombencephalon) is supplied by vessels of mesodermal origin.[6] The endothelium of all the vessels in the body, including the brain, is composed of the cells of mesodermal origin. Embryologically, the internal carotid artery (ICA) bifurcates into rostral and caudal divisions at the origin of the posterior communicating artery (PcomA). The posterior cerebral artery (PCA) is predominantly supplied by two patterns, the PcomA or the basilar artery (BA). Hence, it is not clearly defined whether the PCA territory belongs to the anterior or posterior circulation in a clinical setting. We hypothesised that the anterior/posterior circulation is defined embryologically. Only the cephalic NC contributes to formation of the media of the arteries of the circle of Willis and their branches.[6] Considering the area of the cephalic NCC distribution, the caudal division of the ICA comprises the PcomA and the entire PCA including P1.[10] As a result, PCA can be categorised in 'embryologically anterior circulation' (Figure 2).

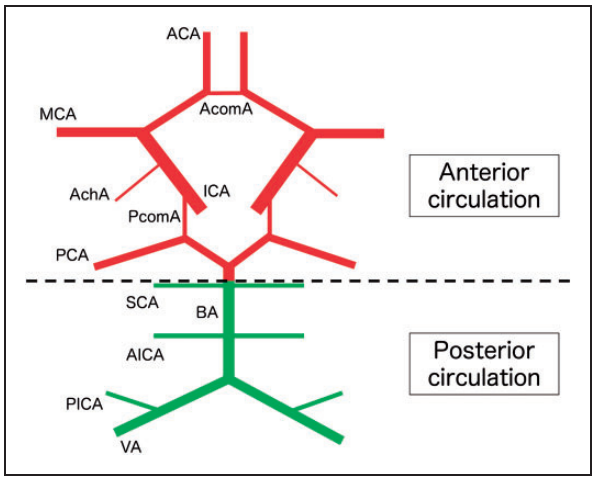

Figure 2. Origins of the media of the cerebral arteries. The media of the primitive internal carotid system is of neural crest (NC) origin (red), but that of the vertebro-basilar system is of mesodermal origin (green). The internal carotid system, including the entire circle of Willis and the posterior cerebral artery, can be categorised embryologically as the anterior circulation. The embryological border between the anterior and posterior circulations, which is determined by the presence of the NC cells in the media of the arteries, is located between the basilar tip and superior cerebellar artery. ACA: anterior cerebral artery; MCA: middle cerebral artery; AchA: anterior choroidal artery; PcomA: posterior communicating artery; PCA: posterior cerebral artery; ICA: internal cerebral artery; BA: basilar artery; SCA: superior cerebellar artery; AICA: anterior inferior cerebellar artery; PICA: posterior inferior cerebellar artery; VA: vertebral artery.

Neurocristopathy

In 1974, Bolande introduced the concept of 'neurocristopathy'.[11] Neurocristopathy is defined as a disease of NC origin. It originally meant failure of correct

migration or differentiation of NCCs, and was further classified into dysgenetic and neoplastic forms. Subsequently, another classification was proposed that grouped neurocristopathy according to the stage of NC development (NC induction and specification, NC migration and NC differentiation) that is affected during the onset of the disease. Recently, Vega-Lopez et al. proposed a new way for classifying neurocristopathy, based on the embryonic origin of the affected tissues.[12] According to their classification, some diseases arise from a developmental defect in only one NC population (e.g. cranial neurocristopathy, such as craniosynostosis), while other neurocristopathies arise from a defect in two or more NCC populations. Komiyama proposed additional forms of neurocristopathy, such as vascular neurocristopathy.[13,14] Vascular diseases concurrently involving vessels of the prosencephalon and cardiovascular regions, including the aorta, coronary arteries and outflow region of the heart, can be regarded as vascular neurocristopathy.

Cephalic neurocristopathy

Cephalic NCCs migrate into the pharyngeal arches and the frontonasal process that become the forehead, the middle of the nose and the primary palate. In some previous reports, the common pathomechanisms of multiple lesions were presumed to follow cephalic NCC distributions.

Midline craniofacial and central nervous system anomalies are commonly associated with eye anomalies. A basal encephalocele, a rare congenital malformation involving a cranial bone defect and cyst-like herniation through the defect, is often associated with hypothalamic pituitary dysfunction, congenital optic disc anomaly, midfacial anomalies and cerebral anomalies (e.g. agenesis of the corpus callosum).[15] Further, in terms of skeletal derivatives, congenital malformations of the nose can be associated with a variety of syndromes, including solitary median maxillary central incisor syndrome, CHARGE syndrome, median cleft face syndrome, PHACES syndrome, duplication of the pituitary gland-plus syndrome and syndromic craniosynostosis (e.g. Apert and Crouzon syndromes).[16]

The point worth noting here is the presence of vascular lesions in association with craniofacial mesenchyme derivatives. It has been suggested that there is an association between encephaloceles, congenital optic nerve anomalies and MMD.[17,18] Wang et al. reported morning glory disc anomaly (MGDA) in 15% of patients with MMD, which is significantly higher than that in the general population.[19] MGDA is a rare congenital deficiency of the optic disc characterised by an enlarged, funnel-shaped excavation of the posterior pole involving the hypogenetic optic disc, which resembles a morning glory flower. Among 13 cases with MMD-associated MGDA, three (23.1%) patients were found to have midline cranial defects, two (15.4%) had meningoencephalocele and one (7.7%) patient had duplication of the pituitary stalk. Involvement of the ICA was found in 10 (76.9%) patients.[19] The pathological changes involving the optic disc and intracranial arteries are suggestive of a similar deficiency during ectoderm development in both diseases.[19] Taking into account of the possibility of MMD as a vascular form of cephalic neurocristopathy,[13] the coexistence of MMD and these congenital abnormalities within the region of cephalic NCC distributions reflects the common underlying common pathomechanism, that is, a subtype of cephalic neurocristopathy.

Cardio-cephalic neurocristopathy

The caudal region of the cranial NC is called the cardiac NC because its cells (and only those particular NCCs) generate the vascular wall of the aortic arch arteries and the septum between the aorta and the pulmonary artery. Cardiac NCCs have also been shown to migrate into the ascending aorta and form SMCs.[6,8] Cardiac NCCs are not required for aortic arch artery formation, but are required for their repatterning[20] and for formation of the tunica media of SMCs of the arteries.[21]

Previous reports in an East Asian population suggested the association between MMD and cardiac manifestations.[2] Larson et al. reviewed 181 MMD patients (76.8% Caucasian) and 10 of whom had cardiac manifestations (5.5%), including aortic stenosis, pulmonary stenosis, atrial septal defect, patent ductus arteriosus and coarctation.[4] In addition, six MMD patients had congenital cardiac defects (3.3%), signifying a potentially higher prevalence in the MMD population.[4] Twenty-two patients with MMD were found to have concomitant coronary artery disease.[3,4] Overlapping pathology and their potential relationship, that is the defects or dysgenesis of the NC derivatives, may exist between these cardiac manifestations and MMD.[14]

Involvement of NCCs has not been discussed adequately in the past. In PHACE syndrome,[22] ACTA2 mutation syndrome,[23] MYH11 mutation syndrome[24] and MMD,[3] the primitive ICA and its branches (anterior, middle and posterior cerebral arteries, i.e. embryological anterior circulation), which are of cephalic NC origin, are preferentially involved, whereas the BA and vertebral arteries, which are of mesodermal origin, are mostly not involved. Interestingly, this distinct distribution of vascular pathologies is in accordance with that of cephalic NC. However, when this concurrence is considered in light of the novel concept of NC distribution and cardio-cephalic neurocristopathy, it is not surprising (Figure 3).[14]

NCCs and intracranial arteriopathy

NCCs provide an additional link between the head and the cardiovascular system. Syndromes linking the face,

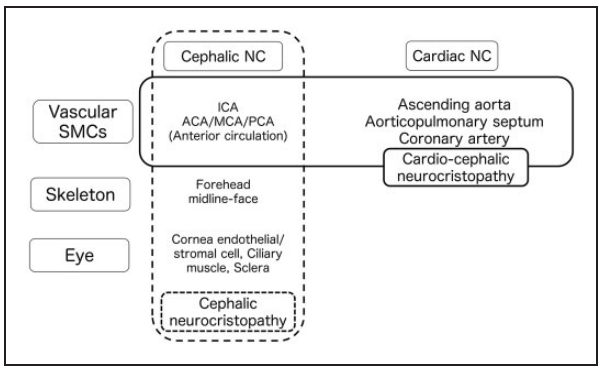

Figure 3. Concept of cephalic neurocristopathy and cardio-cephalic neurocristopathy. Derivatives of cephalic NC and cardiac NC are shown. Coexistence of intracranial artery disease (e.g. moyamoya disease) and some congenital abnormalities within the region of cephalic NCC distributions reflects the underlying common pathogenesis (cephalic neurocristopathy (dotted line)). In the same way, moyamoya disease with some cardiac manifestations can be considered as a cardio-cephalic neurocristopathy (black line). NC: neural crest; SMC: smooth muscle cell; ACA: anterior cerebral artery; MCA: middle cerebral artery; PCA: posterior cerebral artery.

intracranial artery disease and heart can best be understood when these regions are considered as a single developmental module.[25] The cephalic NC provides mesenchymal cells to the arteries in the cardio and cerebrovascular regions, while the endothelium of all the vessels in the body, including the brain, originates in the mesoderm.

NCCs are susceptible to subtle changes in the environment both during migration and on arrival at their destination. This means that small modifications in NCC migration and differentiation will become a causative factor for the development of neurocristopathy. So far, syndromes or diseases involving the head, intracranial artery and heart have been minimally discussed from the point of view of NCC distribution. Although the loss of NCCs or their dysfunction might not always directly cause abnormality in all patients and not at the same time, they may be involved secondarily because NCCs represent a major component in these complex tissue interactions.[25]

Limitations

A renal artery stenosis is reported as the most common site of extracranial vascular involvement of MMD, with an incidence of 5–8%.[26,27] This combination cannot be explained by a concept of neurocristopathy. Extracranial vascular involvement of MMD has unknown and multifactorial pathogenesis. Further exploration of these diseases is needed to elucidate the potential aetiological association between MMD and extracranial vascular disease. Contribution of NCCs to the SMCs in pathologies has not been directly proved so far. In the near future, the molecular biology and the construction of animal models for each neurocristopathy will be important not only to investigate the pathogenesis of these diseases, but also to identify potential therapies aimed at improving the symptoms.

Conclusion

There have been limited studies about MMD based on NC-derived SMCs. Concomitant MMD and cardiovascular disease is not uncommon. The concept of cephalic/cardio-cephalic neurocristopathy provides a new perspective to understanding the underlying aetiological association, and to develop future therapeutic approaches for these diseases.

Conflict of interest

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Informed consent

This review does not include patient data; consequently, no informed consent was necessary.

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