Letter to the Editor

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Response to "Familial Intracranial Aneurysm Requires Not Only Whole-Exome Sequencing, But Also Mitochondrial DNA Sequencing"

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Dr. Finsterer [1] mentioned the necessity of mitochondrial gene studies for familial intracranial aneurysms (FIAs) addressed in our study [2]. However, we want to discuss several different points in our study to which Dr. Finsterer's comments cannot be directly applied.

First, aneurysms in a patient with late-onset mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS) do not seem to be diagnosed as true saccular intracranial aneurysms because a diameter of approximately 0.4 mm is located in the clinoid segment of the left internal carotid artery and dilation and dissection at the distal cervical segment of the bilateral internal carotid arteries [3]. Therefore, it is difficult to agree that an intracranial aneurysm, which is a small uncertain aneurysm (with a size of less than 1 mm), is associated with the mitochondrial disease even though large-vessel vasculopathy, such as aortic aneurysm leading to rupture, was reported as a rare finding in MELAS [4].

Second, it would be difficult to suggest any association of mitochondrial DNA with the occurrence of intracranial aneurysm, even though there are some reports regarding the association of abdominal aortic aneurysm (AAA) with mitochondrial DNA defects, and such an AAA was also associated with intracranial aneurysms. In addition, our study patients (all three families used in our study) neither revealed any stigmata of mitochondrial disease nor any evidence in family pedigrees of maternal inheritance through which mitochondrial gene defects are transmitted. Therefore, it is unlikely that mitochondrial gene defects were involved in the genetic pathogenesis of FIAs in our study patients. Any possibility of such an association cannot be suggested without any further genetic study because familial aggregation of aneurysms is rare in genetically associated vascular disease [5].

Third, the authors suggested three possible mechanisms for aneurysm formation in mitochondrial disorders: reduction of the muscular tone due to reduced nitric oxide production, inflammation of the vessel walls due to increased proinflammatory cytokines (IL-6 or IL-10), and mitochondrial apoptosis involving activation of ceramide synthase-6 [2]. However, the genes (eNOS, IL-6, IL-10, ceramide synthase-6 gene) involved in these possible mechanisms were not selected as possible causative genes in our study patients. Furthermore, the authors also mentioned other causative gene mutations for FIAs in PPIL4, RBF213, ANGPTL6, SMAD3, COL22A1, PCNT, ARHGEF17, LOXL2, STAT1, THSD1, ELN, PKD1, PCNT, COL4A1, ANIB4, ACE, endoglin polymorphisms, apolipoprotein-E genotype, myeloperoxidase pathways, and the balance of regional matrix metalloproteinase family [2]. However, none of these genes was identified as causative candidates in our study patients. This result suggests that mitochondrial defects did not play a role in our study patients.

Fourth, although thoracic aortic aneurysms (TAAs) and AAAs have similarities in terms of structure and appearance, they have two distinct pathophysiological disease entities. An aortic aneurysm is defined as a permanent localized dilatation with a diameter of ≥ 3.0 cm [6]. Being separated at the ligamentum arteriosum, the aneurysm proximal to the ligamentum is non-arteriosclerotic, whereas arteriosclerosis is abundant in the aneurysm distal to it [7]. This difference

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may be attributed to the embryologic origins of vascular smooth muscle cells (VSMCs) between the ascending and descending aorta, with the ascending aorta VSMCs originating from the neural crest from which the dura mater and some components of the intracranial vasculature develop [8], while those in the descending thoracic and abdominal aorta originating from the paraxial mesoderm.

It should be emphasized that TAA and AAA have different prevalence, genetic predisposition, and patterns of inheritance [6]. An autosomal dominant inheritance pattern is seen in approximately 20% of individuals with TAA or dissections, combined and named as thoracic aortic disease (TAD), whereas such a pattern of inheritance is not seen in AAA. More than 16 causative genes closely associated with heritable TAAs have been identified, and evidence shows that these genes do not contribute to the pathophysiology of AAAs. Non-syndromic TAD individuals have similarly affected first-degree relatives in 21.5% of patients, with variable penetrance and expressivity, illustrating that many individuals with TAA might have an underlying mutation in the absence of a genetic syndrome [9]. The majority of families with hereditary TAD with the presence of systemic features of Marfan syndrome and Loeys–Dietz syndrome have mutations in one or more of these genes, whereas mutations in these genes are only found in 30% of families with non-syndromic hereditary TAD, indicating that more research is still required to discover other genes linked to TAD.

Several studies have reported an association between AAAs and genetic polymorphisms. After extensive meta-analysis and GWAS, 10 genetic loci were identified to have a genome-wide level of significance ($p = 5 \times 10^{-8}$) when validated within independent cohorts [6]. Identifying all genes and pathological variants that contribute to aortic aneurysms is challenging, owing to the genetic heterogeneity of this disease.

Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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