Mini Review

Stem Cell Research and Regenerative Medicine

Cardiomyocytes increase in Transmitting Tissue due to Congenital Arteritis

Kim Gyun*

Department of Stem Cell and Research, Cyprus

*Author for correspondence: gyunkim@edu.co

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Abstract

The etiology of MMA is still unknown. The onset of disease in a large number of pediatric cases raises the question of the role of genetic factors in disease etiology. The clinical course or progression of MMA is largely unknown in these patients. By building comprehensive molecular and cellular profiles of pediatric MMA patients' plasma and CSF, respectively, our study provides insight into the levels of circulating endothelial progenitor cells (cEPCs) and the pathogenesis of MMA and the selection of early stages of the disease. The aim is to elucidate the release of proteins that have been induced-progression. Cytofluorometry and immunoassays were used in pediatric MMA patients and compared to controls by age and sex. Elevated cEPC levels in peripheral blood and upregulation of angiogenic markers (ie, angiopoietin-2 and VEGF-A) in CSF were detected. This finding is likely related to deregulation of angiogenesis, as indicated by moderate collateral network development (Suzuki III-IV). The lack of significant modulation of neurofilament light in cerebrospinal fluid led us to rule out the presence of significant neuronal damage in children with MMA. Despite our limited cohort of pediatric patients, we found several unique cellular and molecular characteristics in their blood and CSF samples. Our results are supported by a more comprehensive and prospective study to identify predictive or prognostic circulating biomarkers and potential therapeutic targets for personalized care in pediatric MMA patients.

Keywords: cEPC • ANG-2• VEFG-A • Cerebrospinal fluid • Plasma

Introduction

Moyamoya arteriopathy (MMA) is a rare brain disorder characterized by progressive stenotic occlusive lesions of the terminal segments of the internal carotid artery (ICA) and the development of compensatory, unstable collateral vessels called moyamoya vessels vascular disease [1]. It leads to hemorrhagic stroke, neurological morbidity and even mortality in affected patients, often young adults and children. MMA is common in East Asian countries but rarely reported in Caucasians. The first peak appears in children aged 5-9 and the second peak appears in children aged 45-49 [2].

Although the etiology and etiology of MMA are still unknown, its association with a genetic disorder, high familial prevalence, and strong linkage to ring finger protein 213 (RNF213)/ mysterin-encoding gene variants in East Asian patients has been reported, reinforces the role of genetic factors in MMA. In addition, there are several reports implicating RNF213 as a sensor for mitochondrial dysfunction, hypoxia, and inflammation, and has recently been implicated in antibacterial activity and lipid metabolism [3]. An emerging important role of genetic background, yet to be outlined, is supported by a large number of pediatric cases [4].

MMA is a complex mechanism by which acquired infectious, inflammatory, and flow dynamic conditions can lead to disease in genetically susceptible individuals through abnormalities in angiogenic and angiogenic pathways is strongly believed to be due to Surprisingly, the stenotic changes observed in MMA are not characterized by lipid accumulation, inflammatory cells, or macrophage infiltration into the subintimal layer, as is typical in atherosclerosis [5]. yeah. Furthermore, as luminal narrowing progresses in

atherosclerosis, outward vascular remodeling occurs, increasing outer diameter, in contrast to the decrease in outer diameter that occurs in MMA. Pediatric MMA patients with headaches and certain symptoms can be misdiagnosed. A child's inability to accurately report his or her symptoms can hamper a timely diagnosis and increase the likelihood that the stroke will be completed. Frequent childhood behaviors such as hyperventilating and crying can cause a stroke or her TIA. Fully dilated cortical vasculature during chronic ischemia constricts in response to the reduction in carbon dioxide partial pressure due to prolonged hyperventilation, ultimately leading to reduced cerebral perfusion [6]. However, the pathophysiology of MMA in children is still not fully understood, and few studies of pediatric populations with MMA have been reported due to ethical concerns and small sample sizes due to the rarity of the disease. Nevertheless, MMA accounts for one-fifth of identifiable cerebral artery lesions in childhood stroke and is also known to be the leading cause of cerebrovascular disease in children in East Asia [7]. In contrast to adults with MMA who have both intracranial hemorrhage and ischemic stroke, pediatric MMA patients mainly suffer from transient ischemic attack (TIA) or arterial ischemic stroke. Although stroke is the leading cause of severe long-term disability and death worldwide, childhood stroke is a rare condition. A recent study defined MMA as the third most common underlying etiology of childhood stroke, accounting for 14% of all cases. Lee and his colleagues reported his 8% of arterial strokes in MMA children. Drug therapy remains unable to halt the progression of arterial disease, and revascularization remains the most effective treatment for childhood MMA. Due to the current lack of knowledge about pathophysiology, several studies have reported different types of biomarkers (proteins, circulating cells, etc.) in various biological matrices (peripheral blood, CSF, plasma, urine, etc [8].

EPCs play important roles in physiological and pathological angiogenesis. Notably, a marked reduction in cEPC was evident in a homogenous cohort of non-surgical Caucasian adult MMA patients. However, little is known about their role in the early onset of disease [9]. Despite conflicting data on modulation of her EPC numbers in children with MMA, there is consensus about their defective function observed both in vitro and in vivo. Altered levels of EPCs, cytokines, chemokines, and growth factors were detected in body fluids of MMA patients, suggesting angiogenesis and impaired angiogenesis as possible disease mechanisms. Since vascular endothelial growth factor-A (VEGF-A) plays a central role in angiogenesis and the angiogenesis of new blood vessels, VEGF-A regulation may influence the effects of angiogenic stimuli in damaged brain regions of MMA patients. may represent The VEGF pathway overlaps with many other signaling pathways, including: B. Angiopoietin/Thailand. The secreted glycoprotein angiopoietin 2 (ANG-2) is a pro-angiogenic factor involved in new blood vessel formation, but also promotes pathological angiogenesis, vascular permeability, and inflammation [10]. Indeed, ANG-2 is overexpressed in several inflammatory diseases and is involved in both direct regulation of inflammation-associated signaling pathways and inflammatory cell recruitment. Thus, upregulation of ANG-2, already expressed in ECs as a vasodilatory cytokine, increases angiogenesis but can cause defective angiogenesis and a prolonged general inflammatory state. Interestingly, autocrine release of ANG-2 mediates cerebral vascular collapse in MMA, and elevated serum ANG-2 levels contribute to pathologic aberrant angiogenesis and/or instability of vascular structure and function. and can cause cerebral hemorrhage in adult MMA patients. Matrix metalloproteinase 9 (MMP-9) plays a key role in regulating extracellular matrix remodeling and angiogenesis and is a key enzyme in the degradation of extracellular matrix proteins. It has already been described as a key component of MMA [11].

Results

Recruitment of pediatric MMA patients

Sixteen pediatric MMA patients for whom whole blood and/or CSF samples could be collected from the original cohort of over 150 patients in the GEN-O-MA project were included in this study [12]. The full research methodology has already been reported elsewhere. The mean age of the selected patients was her 9.2 years (range 3–16 years)

and 50% were female [13]. Of these patients, 75% developed an ischemic cerebrovascular event (43.8% ischemic stroke, 31.3% transient ischemic attack, TIA), but he had no hemorrhagic stroke. did not. These clinical features are consistent with those reported in the literature. Patients with presumed IV Suzuki grade accounted for 56.25% of the study population and those with III Suzuki grade accounted for 43.75%. Of the entire cohort, 87.5% (total) had stenotic occlusive lesions affecting both hemispheres (bilateral stenosis) and the remaining 12.5% had unilateral lesions. Of 16 patients he had 12 of his MCA-STA (superficial temporal artery) bypasses. Five of the 16 cases were classified as syndromes, 2 with neurofibromatosis type I, 1 with trisomy 21, distal trisomy 4q, and 1 with an as yet undiscovered syndrome. Her 14 unrelated pediatric subjects (43 male subjects) with a mean age of 7 years (range 1–14 years) were selected as controls [14]. There were no significant differences in age or sex between MMA patients and unrelated controls (UNR), which included patients with a variety of diseases not closely related to MMA (e.g., hemodynamic mechanisms primary epilepsy; multiple sclerosis; intracranial hypertension). All relevant clinical features of MMA patients are summarized [15].

Discussion

This study seeks to fill current gaps in knowledge about the pathophysiology of MMA by identifying comprehensive molecular and cellular profiles of plasma and CSF in children with MMA. The ultimate aim is to define putative, non-invasive new biomarkers that can be harnessed to elucidate disease etiology and serve as potential therapeutic targets from a translational perspective. The mean age of the 16 European pediatric patients enrolled in the GEN-O-MA project he was 9.2 years (range 3–16 years). As expected, no patients were characterized by hemorrhagic stroke, but the majority of patients presented with ischemic events, including ischemic stroke and transient ischemic attacks, and MMA reported elsewhere. There were also common clinical features in children with The entire cohort of patients investigated was Suzuki grade III and IV, indicating progressive stenosis of her ICA or severity of moyamoya vascular network, respectively, or development of collateral vessels from the ECA (external carotid artery). increase. All patients had symptoms of ischemic cerebrovascular events. No children in our series were diagnosed with early or late stages of neuroradiological disease (I-II or V-VI). In most cases in our institution, the diagnosis of symptomatic MMA in the pediatric population leads to early surgical management that explains some specific findings in the current cohort of patients. showed a stenotic-occlusive lesion affecting both hemispheres, leading to an established diagnosis of MMA. No prevalence was found in the proportion of boys and girls in pediatric MMA patients. This finding differed from adult MMA cohorts characterized by prevalence in female patients and from previous well-established data from the literature. Such issues could be explained by the release of hormones associated with secondary sex characteristics and could provide clues to investigate other pathways that may be involved in this obscure disease. As such, the incidence of MMA exhibits a bimodal age distribution. Sex hormones may play a special role in her second peak (ages 45–49), which coincides with the age range of physiological menopause in Western countries. However, the specific impact of sex characteristics in MMA, especially in pediatric patients, has not yet been fully elucidated. The importance of gender differences in MMA has also been reported in her profiling of her ICA transcriptome in adult patients. In this study, RNA sequencing analysis (RNAseq) identified 133 and 439 sex differentially expressed genes (DEGs) in males and females. Another of his RNAseq studies identified a total of 533 DEGs in the peripheral blood of MMA patients, further highlighting the importance of the transcriptomic approach in multifactorial disease.

A considerable amount of evidence in the literature supports the involvement of cEPC in the pathogenesis and development of MMA. However, little is known about their role in the early onset of disease. By examining the role of cEPCs in a pediatric MMA cohort, the present study demonstrated elevated levels of circulating CD45dimCD34+CD133+ mononuclear cells in patients' peripheral blood. The reported elevated levels may be associated with higher rates of cEPC recruitment, possibly due to the presence of stenotic lesions leading to the formation

of specific networks of collateral vessels. Sprouting and new vessel formation may have required the recruitment of cEPCs that migrated from the bone marrow to cerebral regions. No statistically significant difference was found in his cEPC between his two subgroups of MMA patients (before and after neurosurgery), suggesting that neurosurgery did not affect his percentage of cEPC. doing. Notably, a marked reduction in cEPC was evident in a homogenous cohort of non-surgical Caucasian adult MMA patients. Other groups have suggested that cEPCs are decreased in pediatric MMA patients, but the age disparity between the groups analyzed may represent the bias underlying these results.

Conclusions

Pediatric MMA patients displayed several unique cellular and molecular characteristics in both blood and CSF compared with age- and sex-matched controls. Furthermore, we highlighted differences in cEPC between pediatric and adult patients with MMA. Despite a limited patient cohort, our results support the ultimate goal of identifying predictive and prognostic circulating biomarkers and potential therapeutic targets for personalized care of pediatric MMA patients. It may suggest some areas of investigation that need to be confirmed by more comprehensive and prospective studies.

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