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A Case Report of Moyamoya Syndrome and Achalasia in an 11-Year-Old Boy with a Family History

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Abstract

Background and Objective: Moyamoya disease is a condition caused by the obstruction of intracranial vessels, which can lead to ischemic or hemorrhagic vascular events. Most patients have underlying risk factors that contribute to the development of this vascular disease. This article presents a case of Moyamoya disease associated with esophageal achalasia in an 11-year-old boy with a family history of the condition. Comprehensive examinations of this patient did not reveal any complications other than achalasia as a risk factor.

Key Words: Achalasia , Clinical features, Epidemiology , Moyamoya disease.

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1- INTRODUCTION

Achalasia is the most well-known motility disorder of the esophagus, having been diagnosed approximately 300 years ago. In 1937, Landau identified its cause as the incomplete relaxation of the lower esophageal sphincter and named it achalasia. The incidence of achalasia is higher in Caucasians, with an equal ratio of occurrence between both genders. Familial prevalence has been observed in children. Genetic and autoimmune factors have also been proposed in this disease, with antibodies against the myenteric plexus and HLA-DQB1 and HLA-DQA1 found to be more prevalent in these patients compared to control groups. The dysfunction of muscles is secondary to neurological disorders caused by a decrease in non-adrenergic, non-cholinergic inhibitory ganglion cells in the smooth muscles at the distal end of the esophagus. Damage to the inhibitory neurons leads to the failure of the lower esophageal sphincter to relax (1).

The term "moyamoya," which translates to "puff of smoke" in Japanese, was first introduced by Takahashi and Shimizu in 1957 to describe the distinctive angiographic appearance of this condition (2). Since its initial discovery, the characteristics of moyamoya disease have been well understood; however, the exact cause remains unknown. The prevalence of this condition is particularly high among Japanese and Korean populations, while it is significantly less common in Caucasians.

The likelihood of occurrence in the parents and siblings of those affected is 30 to 40 times higher than that in the general population. Most of these patients also present with well-established associated conditions that serve as risk factors, such as radiation therapy to the head and neck, Down syndrome, neurofibromatosis type 1 (with or without hypothalamic-optic pathway tumors), and sickle cell disease. Moreover, there are certain uncommon associated conditions, including congenital heart defects, renal artery stenosis, giant cervical and facial hemangiomas, and hyperthyroidism (3, 4).

Moyamoya disease is a disorder characterized by stenosis of the intracranial vessels that can lead to ischemic or hemorrhagic vascular events. Most patients have complications as underlying risk factors for the above vascular disease (5). In this article, we present a case of a Moyamoya patient who experienced an ischemic stroke. Comprehensive evaluations of this patient did not indicate any associated complications as risk factors.

Familial instances typically follow a multigenic inheritance pattern or an autosomal dominant pattern with incomplete penetrance. A recent study indicated that the primary genetic source for Moyamoya disease (MMD) is autosomal and is located on chromosome q25.17 (6). Cytokines involved in angiogenesis may play a role in the progression of stenotic changes. The primary clinical manifestations include cerebral infarction, transient ischemic attacks (TIAs), intracerebral hemorrhage, and seizure activity (7). In children, ischemic symptoms are the most common. Alongside clear instances of stroke or transient ischemic attacks (TIA), there can be a gradual deterioration in cognitive abilities linked to chronic cerebral hypoperfusion. These episodes may arise during hyperventilation events, such as crying, which can result in the constriction of cerebral arteries. Hemorrhages—whether intracerebral, intraventricular, or subarachnoid—are more prevalent in adults compared to children. The clinical diagnosis relies on cerebral angiography.Moyamoya vessels appear as multiple small, round, and twisted regions of low intensity that extend from the suprasellar cisterns. There are obstructive

changes noted in the distal segments of the internal carotid artery, anterior cerebral artery, and middle cerebral artery, accompanied by ischemic brain lesions and collateral circulation observable within the basal ganglia (8).

The diagnostic criteria encompass stenosis or occlusion in the distal segments of the internal carotid arteries, as well as the proximal segments of the anterior and/or middle cerebral arteries (1). Abnormal vascular networks were noted in the arterial phase near the site of artery occlusion. This condition is classified as either definite or probable, based on whether it affects one side or both sides. In pediatric cases classified as probable, there is a possibility of progression to bilateral lesions within 2.2 years, whereas lesions in adults generally remain stable (9).The natural progression of Moyamoya disease varies among individuals. In some cases, the disease may advance slowly, characterized by rare events and intermittent occurrences, while in others, there may be explosive episodes leading to a rapid decline in neurological function. Although the clinical course can be quite aggressive, the outcomes are diverse, and certain patients experience only minimal impact (10).Various therapeutic strategies have been explored to prevent the recurrence of cerebral ischemia. However, medical treatments, including vasodilators, low molecular weight dextrans, and steroids, have proven to be ineffective (11). A variety of surgical methods have been devised to enhance blood circulation to the brain in instances of chronic hypoperfusion, focusing on the revascularization of ischemic cortical vessels.Direct bypass procedures, like the superficial temporal artery to middle cerebral artery bypass, as well as indirect bypass techniques (which involve placing a vascularized soft tissue flap on the brain's surface), have the potential to enhance clinical symptoms.The latter option is favored for young children (12); however, the indications and timing for surgical revascularization in children with Moyamoya disease remain a topic of debate, especially considering the highly variable natural history of the condition (11).

1-1.Etiology

Inherited Conditions:

• Sickle cell disease or trait

• Down syndrome

• Neurofibromatosis type 1

Acquired Conditions:

• Radiation to the head or neck

• Chronic meningitis

• Skull base tumors

• Atherosclerosis of the basal cerebral arteries

• Arteriosclerosis

• Cerebral vasculitis (2)

1-2.Epidemiology

The onset of symptomatic moyamoya disease shows two distinct age peaks: one occurring between 5 and 9 years and another between 45 and 49 years. While this condition is predominantly found in East Asian nations, especially Japan and Korea, there has also been a reported rise in the incidence of moyamoya disease in Western countries.A study carried out in California and Washington involving 298 patients reported an incidence of MMD of 100 cases per 100,000 individuals. Additionally, a recent study conducted in East Asian countries found that 10 to 15 percent of patients had a family history of MMD, based on data collected from 2000 to 2011.The research also observed a greater prevalence of MMD in females, with a female-to-male ratio of 2.2. Furthermore, a more recent analysis utilizing a national inpatient sample

database indicated that MMD is distributed among various racial groups in accordance with their relative proportions within the U.S. population.The prevalence of MMD is notably higher among Caucasians, followed by Asian Americans. The primary reason for hospital admission due to ischemic stroke associated with MMD exhibits a bimodal age distribution, with the initial peak occurring in early childhood and the second peak emerging in the fourth decade of life (2).

1-3. Pathophysiology

The exact pathophysiology of MMD is not fully understood, but a genetic predisposition is suspected, particularly in East Asian populations. Variations in the BRCC3/MTCP1 and GUCY1A3 genes have been associated with Moyamoya syndrome. Individuals with moyamoya disease display both concentric and eccentric fibrous thickening of the intima in the intracranial internal carotid artery (ICA). A study conducted on a population from the Midwestern United States revealed a notably high prevalence of type 1 diabetes, thyroid autoimmune disorders, and various other autoimmune conditions among those with moyamoya disease, indicating a potential autoimmune link. Chronic brain ischemia caused by stenosis is thought to result in the overproduction of pro-angiogenic factors, including fibroblast growth factor and hepatocyte growth factor. This overexpression subsequently leads to the development of a delicate network of collateral blood vessels (2).

Subtypes of MMD (with involved chromosomes) described in the literature include:

• MYMY1 - chromosome p3

• MYMY2 - RNF213 gene on chromosome q2517

• MYMY3 - chromosome q238

• MYMY4 - X-linked recessive condition characterized by MMD, short stature, hypergonadotropic hypogonadism, and facial dysmorphism.

• MYMY5 - ACTA2 on chromosome q2310

• MYMY6 with achalasia - GUCY1A3 gene on chromosome q324

1-4. Stages of Moyamoya Disease

The Suzuki stages outline the progression that begins with the initial stenosis at the distal end of the ICA. This is followed by the emergence of a deep yet delicate network of Moyamoya vessels, which subsequently decreases in size while simultaneously giving rise to branches from the external carotid artery. The nagile plexus is mainly composed of the perforating arteries originating from the thalamus and the lenticulostriate area. The Suzuki stages of Moyamoya disease are detailed below:

• **Stage 1:** There is a narrowing at the bifurcation of the carotid artery. Angiographic imaging indicates that the constriction is limited to the distal segment of the internal carotid artery.

• **Stage 2:** This stage marks the "onset and appearance of basal Moyamoya." Angiographic examination reveals stenosis affecting all terminal branches of the internal carotid artery, including the anterior cerebral artery (ACA) and middle cerebral artery (MCA), as well as the deep Moyamoya vessels.

• **Stage 3:** "Worsening of basal Moyamoya." Angiographic assessment demonstrates an aggravation of the deep Moyamoya vessels. Magnetic resonance angiography (MRA) performed at this stage exhibits a "smoky puff" appearance. There is also an observed deviation of the ACA and MCA.

• **Stage 4:** "Reduction of basal Moyamoya." Angiographic evaluation

reveals a regression of the deep Moyamoya vessels, accompanied by the emergence of transdural collateral vessels. Additionally, a deviation in the posterior cerebral artery (PCA) is observed.

• **Stage 5:** "Diminution of Moyamoya." Angiographic assessment indicates a progressive reduction of the deep Moyamoya vessels, along with the development of transdural collateral vessels.

• **Stage 6:** "Resolution of Moyamoya." Angiographic evaluation shows that the deep Moyamoya vessels are no longer present, and there is total occlusion of the ICA . The blood supply to the ACA and MCA regions is mainly sourced from the external carotid artery (2).

This study aims to investigate a patient with Moyamoya syndrome in association with achalasia and a family history.

2- CASE REPORT

The patient is an 11-year-old child with a known case of achalasia. The patient's issues began in infancy, presenting as non-bilious and projectile vomiting, which gradually increased in frequency throughout the day and was resistant to oral treatments. Due to the evaluation of the cause of this treatment-resistant vomiting, the patient was admitted to the hospital, where an endoscopy was performed. The findings indicated a stricture at the distal esophagus, which was also confirmed by a chest X-ray with a barium swallow, leading to the diagnosis of achalasia. This diagnosis had been considered since infancy, and the patient has undergone multiple endoscopies for dilation of the lower esophagus, with symptoms being well-controlled.

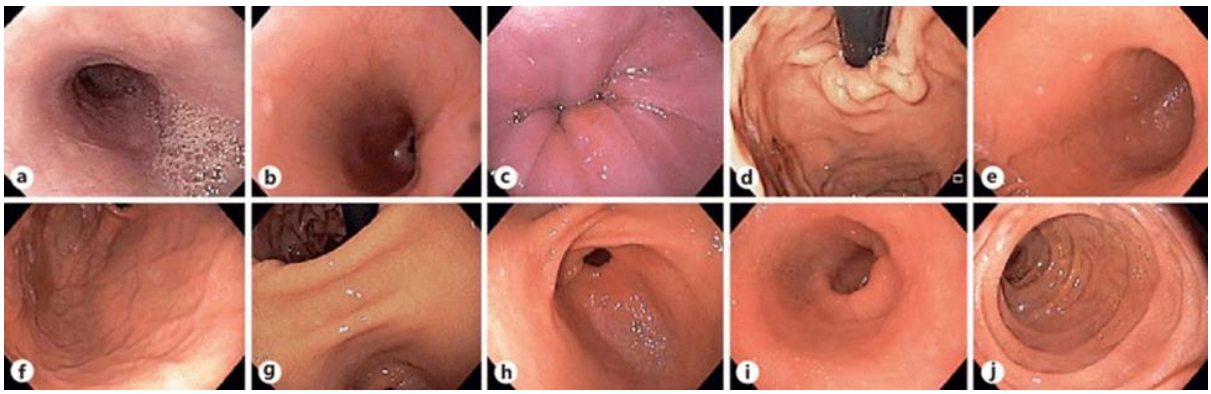

Figure-1: Endoscopic report for dilatation. **A:** Esophaus (upper third), **B:** Esophaus (middle third), **C:** Esophaus (Lower third), **D:** Body, **E:** Fundun, **F:** Antrum, **G:** Duodenal, **H:** Duodenum (second part), **I:** EG Junction, **J:** EG Junction

2-1.Diagnostic Laboratory Tests

Routine laboratory tests, including CBC, ESR, electrolytes, PT, PTT, urinalysis, and ABG, were all normal. Additionally panel tests for hypercoagulable vascular disorders and collagen also showed normal results.

2-2.Family History of the Disease

The patient's younger brother was diagnosed with achalasia in infancy with similar symptoms. He received treatment and showed improvement; however, after some time, he experienced cyanosis of the lips and altered levels of consciousness during the day. Cardiac evaluation revealed elevated pulmonary artery pressure and right heart failure, for which he received cardiac medication. But unfortunately, he died 3 months ago due to cardiac arrest. A brain evaluation (CT angiography) was also performed for the

brother, which was normal. Given the recurrence of achalasia in both children of this family at a young age, genetic testing was requested for the patient, his brother, and their parents. The results indicated Moyamoya syndrome type 6 in both brothers.

Doppler ultrasound of both common carotid arteries and their branches showed normal results. Cardiac and brain evaluations for the patient (Figure 2) and MRA with and without contrast (Figure 3) were performed, which are currently normal; however, continuous follow-up has been recommended.

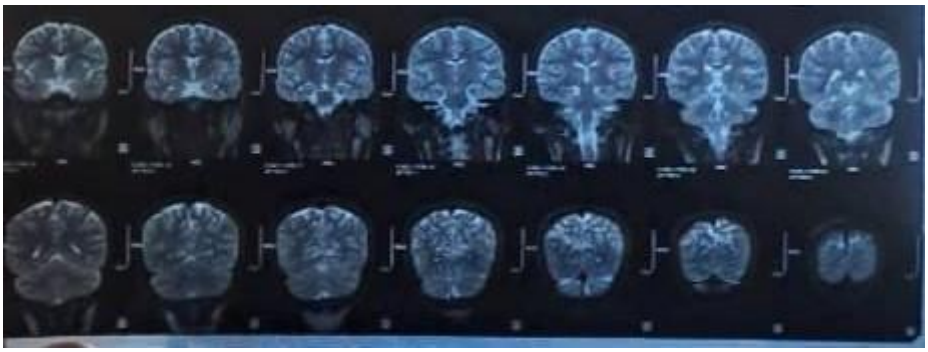

Figure-2: Genetic evaluation of the patient and diagnosis of Moyamoya syndrome with GUCY1A3 gene mutation.

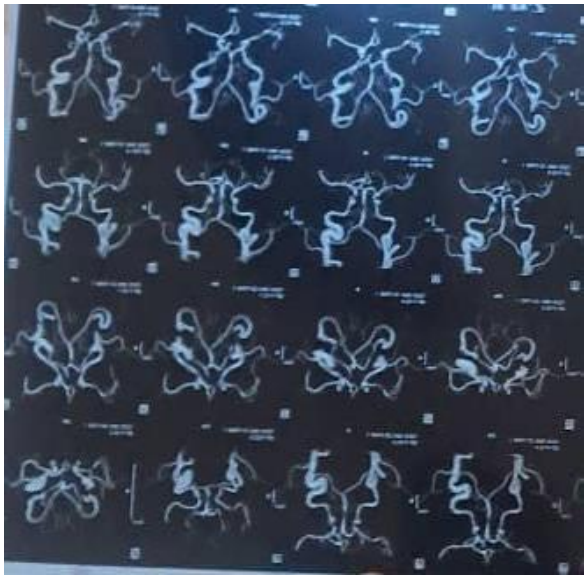

Figure-3: MRA with and without contrast.

3- DISCUSSION

Comprehensive studies have shown that MMD is a rare neurological condition that is most effectively treated by a collaborative team of pediatric neurologists and neurosurgeons. It is crucial to understand that there is currently no definitive cure for Moyamoya disease. Early identification of Moyamoya disease, combined with prompt surgical intervention, is crucial, as medical treatments primarily serve as secondary prevention and do not stop the disease's progression. The goals of both medical and surgical therapies are to improve cerebral blood flow. Advanced treatment for stroke or intracranial hemorrhage is carried out according to standard protocols (4).

Comprehensive evaluations have revealed that our case does not present any of the known risk factors for the disease. This suggests that it is likely a case of Moyamoya disease rather than a syndrome.

A study found that platelet activation and endothelial cell activation are present in all condition associated with immune-mediated thrombocytopenia, such as Thrombotic Thrombocytopenic purpura (TTP),Heparin-induced Thrombocytopenia (HIT) , and Antiphospholipid Syndrome (APS) ,except for immune Thrombocytopenic Purpura (ITP).This leads to a prothrombotic state and an increased risk of thrombosis (13).

A case report exists regarding Moyamoya disease linked to TTP, which can be clarified. However, ITP should not be considered a related risk factor. While hypercoagulable disorders have been documented in some instances of ITP, these occurrences have only been observed shortly after splenectomy (14). The distribution between genders for pediatric and adult cases of CA3s was comparable for both male and female patients (15).

In adult cases, cognitive impairment was recognized as a significant predictor of poor performance in activities of daily living (ADL) three years after the initial presentation.

Previous studies have confirmed a link between cognitive dysfunction and reduced cerebral blood flow. However, these studies have also indicated that conventional imaging techniques do not reveal the association between cognitive dysfunction and ischemic microstructural changes in the brain (16).

While long-term follow-up studies of untreated patients have indicated that 50 to 66% experience progressive neurological deficits and unfavorable outcomes (10), our patient showed no signs of vascular deterioration over four years of follow-up without undergoing any surgical intervention. This may suggest a better prognosis for our patient compared to cases from East Asia. However, it is essential that more patients are followed for a minimum of five years due to the rarity of this disease. Further research in this area is recommended.

4- CONCLUSION

Cardiac evaluations and MRA conducted for the patient are currently normal. However, due to the death of his brother from cardiac issues, continuous monitoring has been advised.

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