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Review Article

# An Endocrine Perspective of Moyamoya Syndrome/Disease: A Literature Review

**Wasnaa Hadi Abdullah***

*Department of Pediatrics, College of Medicine, Al-Mustansiriyah University, Baghdad, Iraq*

## ABSTRACT

Moyamoya disease is a progressive rare type of cerebrovascular disease marked by stenosis and occlusion of the distal internal carotid arteries and circle of Willis branches, leading to development of a collateral network of blood vessels at the base of the brain. Growth hormone deficiency, hypothyroidism, hypogonadism, hypertriglyceridemia, and Graves' disease are all reported endocrinopathies those could occur in patients with moyamoya. Therefore, we would emphasize on the importance of regularly monitoring for these possible endocrinological disorders in patients diagnosed with Moyamoya disease in order to avoid any delay in diagnosis and thereafter the appropriate treatment.

**Keywords:** Moyamoya; Endocrine; Brain; Cerebral arteries

## INTRODUCTION

Moyamoya disease is a rare, progressive cerebrovascular disease marked by stenosis and occlusion of the distal internal carotid arteries and branches of circle of Willis, leading to creation of a collateral network of blood vessels at the base of the brain, giving a special appearance on the angiographic studies known as "moyamoya", which is a Japanese term meaning a "puff of smoke". Shimuzu and Takeuchi were the first who described this disorder in 1957 [1]. The highest incidence of this disease is during the first decade of life [2].

Moyamoya disease was found to be a significant cause of childhood stroke, especially in Asians who have mutations in the Ring Finger 213 gene (RNF213). RNF213 has been hypothesized as a potential genetic basis for familial types of Moyamoya syndrome [3]. Moyamoya Syndrome (MMS) is different from the Moyamoya Disease (MMD), where the syndrome has a similar radiographic appearance, but either the narrowing of blood vessels is caused by different mechanisms rather than a genetic cause as in the disease or the arteriopathy is associated with other systemic disorders such as systemic lupus erythromatosis, Sjogren syndrome, nodular polyarteritis, neurofibromatosis type 1, trisomy-21, sickle cell disease, and radiotherapy [3].

Moyamoya disease is also thought to be mediated by the immune system, especially when it has been associated with number of to autoimmune disorders such as Graves' disease, systemic lupus erythematosus, and diabetes mellitus. Hence it is of great value to analyze the different comorbidities as that could aid in defining the pathophysiology of Moyamoya disease [4]. Children typically get Moyamoya disease after the age of five years, and it progresses more quickly compared to adults [5].

The symptoms are caused by transient ischemic attacks, which result in focal neurological signs, seizures, and progressive cognitive impairment [6]. Headache (migraine) remains a common presenting symptom in Moyamoya. Hypertension is also a common finding, which could be a compensatory response to hypoperfusion or due to concomitant renovascular diseases [3].

## LITERATURE REVIEW

The anterior cerebral arteries and the internal carotid arteries supply the hypothalamic-pituitary areas with blood, these arterial branches are close to the stenosed carotid fork in Moyamoya disease [2]. Then through links to posterior cerebral and external cerebral artery branches, Moyamoya arteries provide collateral circulation to ischemic regions. The hypothalamus is perfused by reversed flow through these collaterals. Therefore, this defect can result in hypothalamic vascular insufficiency, leading to hypothalamic and pituitary dysfunction [2].

Endocrinopathies had been reported in conjunction with Moyamoya disease or syndrome [2]. Therefore, we aim from this

**Correspondence to:** Dr Wasnaa Hadi Abdullah, Department of Pediatrics, College of Medicine, Al-Mustansiriyah University, Baghdad, Iraq; E-mail: abdullah036@rediffmail.com

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review of the reported cases in literature to highlight the importance of regular monitoring for the clinical features of hypothalamic and pituitary dysfunction in patients with Moyamoya in order to diagnose and treat them early. The main reported endocrinological disorders are summarized as follow:

## Growth Hormone (GH) deficiency

Moyamoya disease can be associated with GH deficiency, which could be caused by chronic cerebrovascular insufficiency [7]. In 1990, the first case report of GH deficiency with Moyamoya disease was published, in which a 7-year-old boy with hypopituitarism presented with short stature. Then he had his first generalized convulsion six months after starting GH replacement therapy, which warranted further neuroradiological investigations to reveal the diagnosis of Moyamoya disease [8].

Another case report by Kalina M et al. [7], in which a 16-year-old boy referred because of headaches and short stature. The height was -4.3 SDS; and the bone age 11.5 years. No focal neurological deficits were observed. Isolated growth hormone deficiency was diagnosed based on baseline and stimulated growth hormone measurement. On brain Magnetic Resonance Imaging (MRI), a malformation of the cerebral vessels was suspected, and angio-computed tomography and pan-angiography revealed an image suggestive of Moyamoya disease. Daily doses of growth hormone were provided at a dose of 0.025 mg/kg/day, the first-year growth velocity was 12 cm per year and no side effects have been reported as a result of the treatment [7].

Mootha et al. [2] reported a 6-year-old child, presented with short stature (height of -3 SDS), with a bone age of 4.5 years. He failed two growth hormone provocation tests therefore it was decided to start him on GH therapy, however he developed transient left hemiparesis for which a brain MRI study was conducted revealing the ischemic changes in both hemispheres' white matter, with the right one showing more alterations. The Magnetic Resonance Angiogram (MRA) showed bilateral anterior and middle cerebral arteries narrowing, Moyamoya disease was recognized, and the child underwent a right-side revascularization operation. Growth hormone replacement was started a year later. A recurrence of neurological symptoms was reported for which he underwent a revascularization surgery on the left side, and GH continued. The patient remained stable after those surgeries and no side effects were reported from the GH therapy. He had exhibited an appropriate rise in his growth velocity [2].

Growth failure was also reported in number of families with BRCC3-related Moyamoya and majority of affected members had partial growth hormone deficiency [9].

Choi et al. reported the first patient with Noonan like syndrome 8-year-old patient found to have Moyamoya syndrome in 2015. The patient was started on GH for the severe short stature, 2 years later, she developed left hemiplegia, for which she underwent neuroimaging study to reveal the Moyamoya angiopathy [10].

Saying that, Yamashita had already reported the first patient of Noonan syndrome with antiphospholipid syndrome and moyamoya-like vascular lesions, who was treated with growth hormone without adverse effects [11].

A 13- year-old child known to have thalassemia since age of 15-month-old, was assessed for short stature, and found to have growth hormone deficiency for which, he was started on GH therapy. MRI was performed in view of GH deficiency and stenotic arteries were found suggestive of Moyamoya syndrome [12].

## Precocious puberty

Kazumata reported the first case of precocious puberty associated with Moyamoya disease in 1996 [13], in which an 8-year-old girl presented with menarche, advanced breast development (Tanner's stage III) and presence of pubic hair, on a medical background history of pustular psoriasis. Her pubertal precocity started at age of 7, which led to advancing in her bone age (11 years) at presentation. A normal neurological examination was reported, but a brain MRI revealed numerous flow voids in area of basal ganglia on both sides, indicating the existence of Moyamoya disease. The proximal segment of the anterior and middle cerebral arteries and the distal segment of the internal carotid arteries were all stenosed on cerebral angiograms. In the base of the brain, a network system of collateral vessels (Moyamoya vessels) also was found, confirming the presence of Moyamoya disease [13]. Precocious puberty is uncommon in Moyamoya disease, and severe hypothalamic damage is also uncommon. Ken Kazumata suggested that ischemic changes or a little destructive damage of the hypothalamus caused by dilated perforators was the cause of this patient's early puberty [13].

## Hypothyroidisim

Mootha et al. [2] reported a Caucasian female who was developing appropriately up the age of 7-month-old, when she experienced an ocular deviation and head tilt episode that lasted only a few seconds with restlessness. Similar attacks happened to her when she was 9 and 10-month-old. Later at the age of 17 months, she had another similar episode but associated with tonic-clonic convulsions, followed by persistent spastic hemiparesis and verbal and motor impairments. A cranial computed tomography with contrast revealed infarction in the posterior parietal and left occipital regions, The arteriogram revealed bilateral collaterals and occlusive constriction of both middle cerebral arteries, which was pathognomonic for Moyamoya disease, Her growth chart revealed a decline in growth velocity and short stature. Her height was -3 SDS at age of 3 years and dropped further down to -3.5 SDS by age of 9 years when her bone age was of 5 years and 9 months. Free T4 was 4.6 microgram/dl (normal value 5.5-12.8) and TSH was 3.3 mIU/ml (normal value 1.32-5) suggesting central hypothyroidism, Thyroxin was prescribed. The peak GH concentration after stimulation with Clonidine and Arginine was 1.6 ng/ml. The patient received GH therapy and experienced an appropriate improvement in growth velocity.

### Hypogonadism

Tien-Jen Lin et al. [14], reported a young man who suffers from Moyamoya disease, found to have empty sella leading to hypopituitarism and hypogonadism. The empty sella in this case could have been originated from an ischemic atrophy of the pituitary gland. However, high intracranial pressure and systemic hypertension point to pituitary injury due to a compressive mechanism and the creation of the empty sella [14].

In other unique association, a 14-year-old male who was surgically treated for cryptorchidism at a younger age, suffered from recurrent seizures and decline cognitive skills, presented with transient bilateral hemiparesis, found to have Moyamoya angiopathy. Further testing revealed Klinefelter syndrome [15]. The hypergonadotrophic hypogonadism was also reported in families with loss of BRCC3 loss-of-function mutations whom having Moyamoya angiopathy [16].

### Hypertriglyceridemia

Hyperlipidemia had been identified in individuals with Moyamoya disease/syndrome, with an incidence of 27.7% in a Mayo Clinic Minnesota research from 1979 to 2011 and 37.3 % in a Japanese study from 2001 to 2011 [17,18] .

Hyperlipidemia is one of the most common comorbidities in Moyamoya patients [19]. Documented patients in case reports and meta-analyses with Moyamoya and coexisting hyperlipidemia were all over 30 years old, and the causes for elevated levels of cholesterol were not clear [19]. Saying that, the first case report of pediatric patient to have Moyamoya disease and associated hypertriglyceridemia was reported by Chan et al. [19], a 9-year-old girl who was previously healthy; her family history is unknown because she was adopted at the age of three weeks. She had a history of gross motor delay, which was treated with physiotherapy, and she was well by the age of 3 years. She arrived at the emergency room with a sudden onset of weakness in the right arm. A stroke protocol brain MRI indicated a minor blockage of the distal internal carotid arteries, as well as several collateral vessels protruding from the circle of Willis, MRA was compatible with Moyamoya disease. Baseline fasting lipid profile was abnormal including elevated total cholesterol 427mg/dL (Normal is <200 mg/dL), raised fasting triglyceride 870 mg/dL (Normal is <150 mg/dL), normal HDL 48 mg/dL, Apolipoprotein B was of elevated at 219 mg/dL (55 mg/dL-125 mg/dL), and LDL not measurable owing to elevated triglycerides. Based on dietary recommendations, she was put on a pediatric low fat /low cholesterol diet. Pravastatin 20 mg was prescribed for her on a daily basis. After 14 days of Pravastatin medication, total cholesterol and triglyceride levels dropped to 267 mg/dL and 433 mg/dL, respectively [19].

### Graves' disease

In several studies assessing risk factors for Moyamoya disease progression, Graves' disease, is a well-known medical disorder that has been associated with rapid progression of Moyamoya disease [20,21].

78 cases of Moyamoya illness/Graves' disease had been reported in one study, the majority of which were female patients. Cerebral infarctions can occur in patients who are thyrotoxic [22]; Graves' disease may also increase nervous system activity, which is another probable mechanism [23]. Furthermore, in a prospective study, it has been noted that Moyamoya disease patients were more likely to have increased levels of thyroid autoantibodies compared with non-Moyamoya disease stroke patients, despite their euthyroid statuses [20].

## DISCUSSION

Previous research had demonstrated that vasculopathy can be prevented by suppressing thyrotoxicosis [24], as the clinical progression of Moyamoya disease patients with concurrent Graves' disease is quicker than that of Moyamoya disease patients without Graves' disease [25]. Appropriate antithyroid medication can reduce the risk of ischemic episodes or infarctions by reducing the hemodynamic load on the brain [21].

## CONCLUSION

Moyamoya disease associated with various endocrinological manifestations including Growth hormone deficiency, hypothyroidisim, hypogonadisim due to hypothalamic-pituitary dysfunction attributed to chronic cerebrovascular insufficiency. Moreover, an associated hypertriglyceridemia and Graves' disease have been reported in patients with Moyamoya disease. So, it does worth checking and regularly monitoring for those endocrinological manifestations in patients with Moyamoya disease aiming to early diagnosis and appropriate treatment.

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