Case Report

Moyamoya Angiopathy with Growth Hormone Deficiency in 13 Years and 10 Years Old Boys Brothers in Iraq: A Case Report

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Abstract

Moyamoya disease is a rare, progressive cerebrovascular disease marked by stenosis and occlusion of the distal internal carotid arteries and branches of the circle of Willis, leading to creation of a collateral network of blood vessels at the base of the brain. It has been found to be a significant cause of childhood stroke. We would like to present two cases of moyamoya angiopathy with a growth hormone deficiency, in 13-year-old and 10-year-old brothers in Iraq. Hypothalamic-pituitary dysfunction may complicate Moyamoya angiopathy, which is attributed to chronic cerebrovascular insufficiency. Therefore, it is worth checking and regularly monitoring for this problem, especially in growing children and adolescents, to achieve normal growth and development.

Keywords: Growth hormone, moyamoya disease, short stature

Introduction

Moyamoya disease (MMD) is a rare, progressive cerebrovascular disease marked by stenosis and occlusion of the distal internal carotid arteries and branches of the circle of Willis, leading to the 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."[1] The highest incidence of this disease is during the first decade of life.[2] It has been 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 (MMS). MMS has a similar radiographic appearance to MMD, but it is associated with other systemic disorders such as systemic lupus erythematosus, neurofibromatosis type 1, trisomy-21, sickle cell disease, and radiotherapy.[3] Children typically get MMD after the age of 5 years, and it progresses more quickly compared to adults.[4] The symptoms are caused by transient ischemic attacks, which result in focal neurological signs, seizures, and progressive cognitive impairment.[5] Headache remains a common presenting symptom in Moyamoya angiopathy (MMD and MMS). Hypertension is also a common finding, which could be a compensatory response to hypoperfusion or due to concomitant renovascular diseases.[3]

Here we would like to present two cases of Moyamoya angiopathy with growth hormone (GH) deficiency, which, to our best knowledge, represent the first reported cases in Iraq.

Case Presentation

Case 1

A 13-year-old boy, a product of non-consanguineous marriage, who was well until the age of 11 years when he started to develop abnormal body movements as a form of sustained contractions of the left upper limb with brief episodes of eye deviations followed by loss of awareness to the surrounding, lasting nearly 15 min, followed by regaining consciousness. He was admitted to Child Welfare Teaching Hospital in Baghdad/Iraq where the complete

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clinical evaluation was done, and the diagnosis of MMD was made depending on brain magnetic resonance imaging (MRI) (bilateral foci of abnormal signal intensity involving the deep white matter in addition to multiple areas of abnormal signal in the cortical/subcortical regions of both cerebral hemispheres consistent with old ischemic insults), and magnetic resonance angiography (MRA) (severely attenuated middle cerebral arteries and anterior cerebral arteries bilaterally, with an extensive network of collateral vessels in the basal ganglia and hypothalamus). After he completed his treatment in the hospital, he was discharged home well on Aspirin tab, Carbamazepine syrup, and physiotherapy. In the following year, the patient developed recurrent neurological symptoms including convulsive attacks of similar nature to the first one (2–4 attacks per month), in association with headache and left side weakness. These symptoms made a revascularization surgery necessary, so the patient underwent it at age of 12.5 years (catheter angiography then Encephalo-Duro-Arterio-Myo-Synangiosis [EDAMS] of both sides without complications). He has been neurologically stable since that procedure without any medication. At that time, his mother noticed poor height gain especially in the last 2 years, but physicians advised the mother to just follow up at the current time. At the age of 13 years, a pediatric endocrinologist was consulted for the growth problem. Apart from poor school performance with more deterioration in the last 2 years, and the same disease in his brother (Case 2), other parts of the history were not relevant.

Case 2

A 10-year-old boy, the first case's younger brother, with a history of recurrent convulsion at the age of 8.5 years for which the diagnosis of MMD was made depending on MRI (bilateral anterior subcortical abnormal signal intensity involving both frontal and upper parietal lobes, picture of acute infarction with multiple bilateral small tortuous hyperintense foci seen mainly on the medial aspect of temporal basal ganglia and parietal white matter tract) and MRA (a tangle of vessel–puff of smoke appearance) and underwent catheter angiography and then EDAMS of both sides without complications at age 9 years with the same history of short stature as his older brother.

Clinical Examination

Case 1

Conscious, active, looks well, with dysmorphic facies (hypertelorism, saddle nose, broad forehead, and low set ears) [Figure 1A]. Weight (42 kg, –0.65 standard deviation [SD]), height (141 cm, –2 SD), mid parental height (171.5 cm, –0.7 SD), SMR G4P3 according to Tanner staging, heart rate (110 beat/min), respiratory rate (20 cycle/min), temperature (36.8°C), and blood pressure (100\60 mm Hg). System examination was normal except for grade 3 power in both upper and lower limbs. Reviewing of his height measurements revealed low growth velocity with deterioration of height *z* score in the last 1.5 year: the height at the age of 11.5 years was 139 cm (–1 SD), 12 years was 140 cm (–1.3 SD), 12.5 years was 141 cm (–1.5 SD), and 13 years was 141 cm (–2 SD).

Case 2

Same facies as his older brother [Figure 1B], weight (31.5 kg, –0.27 SD), height (130 cm, –1.4 SD), SMR G1P1 according to Tanner staging, heart rate (94 beats/min), respiratory rate (18 cycles/min), temperature (37°C), and blood pressure (95\60 mm Hg). System examination was normal except for grade 3 power in both upper and lower limbs. Reviewing of his height measurements revealed low growth velocity with deterioration of height *z* score in the last year: the height at the age of 9 years was 130 cm (–0.6 SD), 9.5 years was 130 cm (–1 SD), and 10 years 130 cm (–1.4 SD).

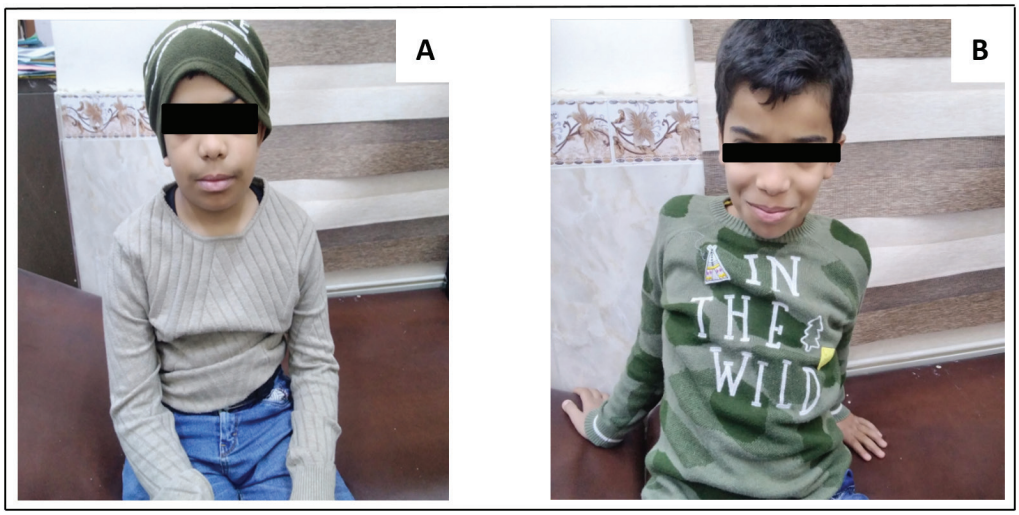

Figure 1: (A) Case 1. (B) Case 2. The photos were taken with the consent of the patients' family

Investigations and Follow-up

Case 1

Bone age was 11 years. Complete blood count, renal function test, serum calcium and phosphorus, and general urine examination were normal. Free T4: 1.5 mg/dL (0.8–1.7), thyroid stimulating hormone (TSH): 4.18 mIU/mL (0.4–4.2), and antitissue transglutaminase antibodies IgA and IgG were negative. IGF-1 was 38 ng/mL and peak GH after stimulation with clonidine was 0.77 ng/mL. Recombinant growth hormone (rGH) had been commenced at a dose of 0.035 mg /kg/ day, and he gained 4 cm height within 6 months of rGH therapy.

Case 2

Bone age was 8 years. Complete blood count, renal function test, serum calcium and phosphorus, and general urine examination were normal. Free T4: 1.47 mg/dL (0.8–1.7), TSH: 3.38 mIU/mL (0.4–4.2), and antitissue transglutaminase antibodies IgA and IgG were negative. IGF-1 94 ng/mL and peak GH after stimulation with clonidine was 0.55 ng/mL. rGH had been commenced at a dose of 0.025 mg /kg/ day, and he gained 3.5 cm height within 6 months of therapy.

Discussion

MMD refers to primary Moyamoya angiopathy, usually bilateral, whereas MMS correspond to Moyamoya angiopathy associated with well-known underlying inherited or acquired condition, and cerebral angiopathy may be unilateral or bilateral.[3] In our cases, as cerebral angiopathy was associated with dysmorphic facies, it is most likely to be a MMS rather than MMD. Hereditary MMS constitutes a heterogeneous group with various clinical presentations, various modes of inheritance (autosomal dominant inheritance with incomplete penetrance, autosomal-recessive, X-linked-recessive, or multifactorial inheritance), in addition to variable penetrance of the cerebrovascular phenotype.[3] These different patterns of inheritance and variable penetrance may explain the presence of two affected sons for apparently not affected parents. A genetic study was not done for these patients as it is unavailable in Iraq, and it is considered cost to be done outside. The shared dysmorphic facies may suggest syndromic entity such as Noonan syndrome. Choi *et al.*[6] reported the first patient with Noonan-like syndrome and MMS. The patient was initially diagnosed as a case of Noonan syndrome and rGH was started for the severe short stature. Two years later, she developed left hemiplegia, for which she underwent neuroimaging study to reveal the Moyamoya angiopathy.

MMD can be associated with GH deficiency, which could be caused by chronic cerebrovascular insufficiency.[7] 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 angiopathy. 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]

In 1990, the first case report of GH deficiency with MMD was published, in which a 7-year-old boy with hypopituitarism presented with short stature. Then he had his first generalized convulsion 6 months after starting GH replacement therapy, which warranted further neuroradiological investigations to reveal the diagnosis of MMD.[8] Another similar case report by Maria Kalina in which a 16-year-old boy was referred because of headaches and short stature. Isolated GH deficiency was diagnosed based on baseline and stimulated GH measurement. MRI and MRA were suggestive of MMD. Daily doses of rGH 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.* reported a 6 years old child, who presented with short stature. He failed two GH provocation tests; therefore, rGH therapy was started. However, he developed transient left hemiparesis for which a brain MRI study was done, and MMD was recognized. For which he underwent a revascularization surgery, and rGH continued. The patient remained stable after those surgeries and no side effects were reported from the rGH therapy. He had exhibited an appropriate rise in his growth velocity.[2] Growth failure was also reported in a number of families with BRCC3-related Moyamoya and the majority of affected members had partial GH deficiency.[9]

Conclusions

GH deficiency related to hypothalamic-pituitary dysfunction may complicate Moyamoya angiopathy and is attributed to chronic cerebrovascular insufficiency. Therefore, it is worth checking and regularly monitoring for this problem, especially in growing children and adolescents, to achieve normal growth and development.

Ethical approval

The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki. It was carried out with patients verbal and analytical approval before sample was taken. The study protocol and the subject information and consent form were reviewed and approved by a local ethics committee according to the document number 5 on January 2, 2022 to get this approval.

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Conflicts of interest

There are no conflicts of interest.

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