

# Moyamoya syndrome following growth hormone-secreting pituitary adenoma

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## Abstract

We report a case of Moyamoya syndrome developing in association with growth hormone-secreting pituitary adenoma. A 31-year-old female presented with acromegalic features. Magnetic resonance imaging revealed a 1 × 2 cm tumor in the sella turcica and MR angiography demonstrated unremarkable findings. Blood growth hormone and insulin-like growth factor I levels were elevated to 74.1 ng/ml and over 1 575 ng/ml, respectively. The diagnosis was growth hormone-secreting pituitary adenoma, and the tumor was removed through a transsphenoidal approach. Four years after surgery, she visited the outpatient department due to left side weakness for 2 months. Magnetic resonance images showed acute and old infarcted lesions in the basal ganglia and subcortical area and residual small pituitary adenoma in the sellar area. MR angiography demonstrated stenosis of the bilateral distal internal carotid arteries with basal collateral vessels. Conventional cerebral angiography showed complete obstruction in the right internal carotid artery and severe stenosis of the left internal carotid artery, middle cerebral artery, and anterior cerebral artery with basal collateral vessels. Her blood growth hormone and insulin-like growth factor I levels were 15.3 ng/ml and 1 055 ng/ml, respectively. We believe that excess systemic exposures of growth hormone and insulin-like growth factor I may participate in the development of Moyamoya syndrome.

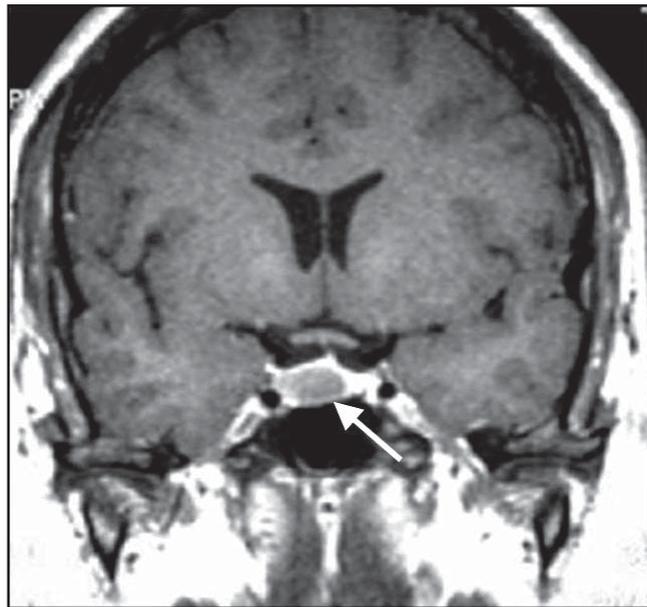
## INTRODUCTION

Moyamoya syndrome is a rare cerebrovascular disorder characterized by bilateral progressive supraclinoidal stenosis or occlusion of the internal carotid artery (ICA) and development of collateral vessels in the lenticulostriate region. The

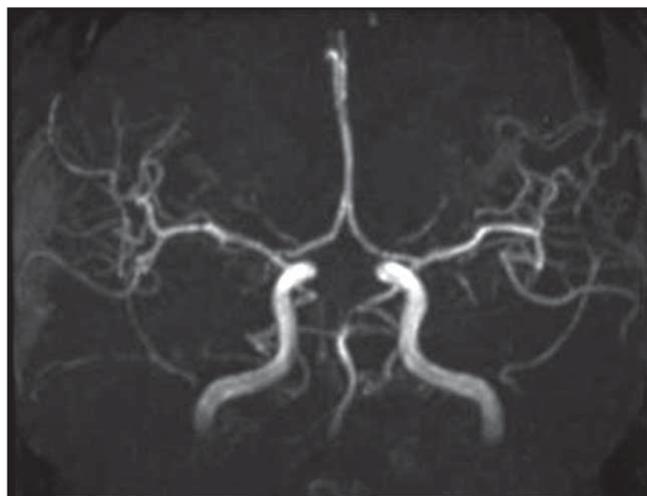
syndrome manifests itself in association with another disease or other clinical symptoms. We report a case of Moyamoya syndrome developing in association with growth hormone (GH)-secreting pituitary adenoma (PA), in which failure to maintain normal blood hormone levels by surgical treatment led to progression of the disease.

## CASE REPORT

A 31-year-old female presented with acromegalic features of the hands, feet, and face in the three months prior to admission. Her family and past history were noncontributory. Laboratory studies revealed that her blood hormone levels were elevated: GH 74.1 ng/ml (normal 0.28–8.70 ng/ml), insulin-like growth factor-I (IGF-I) 1575 ng/ml (121–436 ng/ml), adrenocorticotrophic hormone (ACTH) 23.5 pg/ml (8.2–54.8 pg/ml), thyroid-stimulating hormone (TSH) 0.86 mIU/L (0.35–3.73 mIU/L), T3 2.49 ng/ml (0.8–2.2 ng/ml), free T4 13.5 pmol/L (9.4–25 pmol/L), cortisol 10.65 ng/ml (5.3–24.53 ng/ml), luteinizing hormone (LH) 2.87 mIU/ml



**Fig. 1.** T-1 weighted gadolinium enhanced magnetic resonance image showed a 1 × 2 cm tumor in the sella turcica with surrounding enhancement by gadolinium but no invasion into the cavernous sinus.



**Fig. 2.** Preoperative MR angiography revealed unremarkable findings.

(0.6–53.2 mIU/ml), follicle-stimulating hormone (FSH) 2.97 mIU/ml (1.0–19.3 mIU/ml), and prolactin 7.5 ng/ml (3.7–44.8 ng/ml). Magnetic resonance imaging (MRI) showed a 1 × 2 cm sized tumor in the sella turcica with surrounding enhancement by gadolinium, but no invasion into the cavernous sinus (Figure 1). MR angiography demonstrated unremarkable findings (Figure 2). The diagnosis was GH-secreting PA and the tumor was removed through a transsphenoidal approach. The tumor was gray and soft, but a part of the adjacent cavernous sinus could not be removed completely. Histological examination showed that the GH-producing adenoma consisted of uniform cells forming a sinusoidal pattern with characteristic pseudorosettes in low density and medium to large non-polar cells with either uniform spherical nuclei or irregular, variable dense nuclei and large, granular, often acidophilic cytoplasm in a high density view (Figure 3). Postoperatively, her blood GH and IGF-I levels were 3.9 ng/ml and 606 ng/ml, respectively. She had not undergone any management including radiation therapy nor examination relating to the remnant PA for four years.

Four years after surgery, she visited the outpatient department due to left side weakness for 2 months. MRI showed cystic encephalomalacia in the right periventricular white matter and right basal ganglia and acute infarction in the right frontal area (Figure 4A). Also there was small residual PA in the sellar area (Figure 4B). MR angiography demonstrated stenosis of the bilateral distal internal carotid arteries (ICA) with basal collateral vessels. Digital subtraction angiography showed complete obstruction in the right ICA and severe stenosis of the left ICA, middle cerebral artery, and anterior cerebral artery with basal collateral vessels (Figure 5). Her blood GH and IGF-I levels were 15.3 ng/ml and 1055 ng/ml, respectively. An octreotide suppression test showed the decreased GH level from 14.8 ng/ml to 1.52 ng/ml after 60 minutes. She did not undergo bypass surgery because she had enough transdural collaterals via the external carotid artery and normal cerebral perfusion on single photon emission computed tomography. Two weeks later, her blood GH and IGF-I levels were normalized (1.7 ng/ml and 357 ng/ml) after oral octreotide treatment.

## DISCUSSION

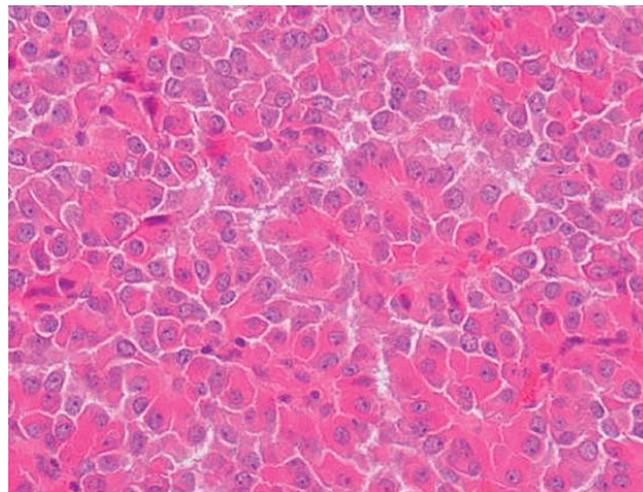
There are many cases about Moyamoya vessels associated with brain tumors (Aihara *et al.* 1992; Hardy *et al.* 1991; Kitano *et al.* 2000; Lau & Milligan 1986; Tsuji *et al.* 1984). However, only three cases of Moyamoya syndrome with pituitary adenoma have been reported, and the association was considered coincidental in all cases (Arita *et al.* 1992; Hardy *et al.* 1991). Additionally, one case of GH-secreting PA associated with secondary Moyamoya syndrome has been reported (Uchida *et al.* 2003).

The cerebrovascular changes were almost secondary, due to the compression of the bilateral internal carotid

arteries by the tumor, irradiation, or the presence of neurofibromatosis (Kitano *et al.* 2000; Levisohn *et al.* 1978; Mori *et al.* 1978). GH-secreting PA originates from somatotrophic cells in the anterior pituitary gland. We can remove the GH-secreting PA via transsphenoidal surgery. Because transsphenoidal surgery is restricted due to narrow operation field, complete extirpation of the tumor is sometimes difficult and remnant tumor can increase the blood GH and IGF-I levels.

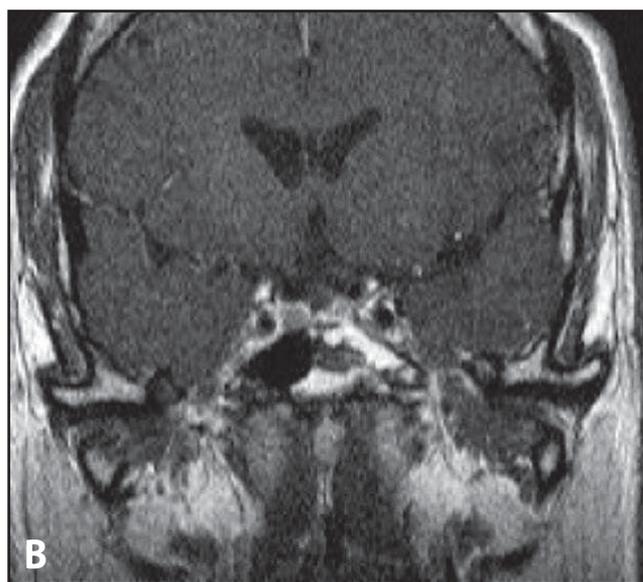
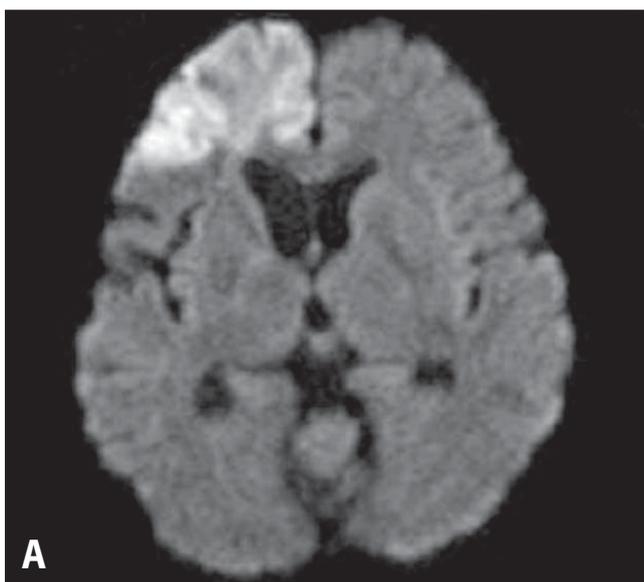
In our case, the adjacent cavernous sinus tumor could not be removed completely. The combination of transsphenoidal surgery and adjuvant gamma knife surgery (GKS) may be the optimal treatment for patients with GH-secreting PA (Ikeda *et al.* 2001). However, GKS was risky for the residual tumor in our case, because even low-dose radiation might cause stenotic or occlusive change of the internal carotid arteries. Octreotide is also useful for the treatment of elevated GH and IGF-I levels, and we choose octreotide because it temporarily decreased GH levels in a suppression test.

Excessive GH secretion constantly elevates systemic IGF-I levels, which is associated with increased mortality rates caused by cardiovascular, cerebrovascular, and respiratory diseases, as well as colon cancer (Orme *et al.* 1998). IGF-I has an important role in the development of vascular diseases. Most previous studies point to IGF-I as a mediator of atherosclerotic processes and diabetic vascular lesions. Shin-ichi *et al.* report that increased circulating IGF-1 and insulin-like growth factor binding protein-3 are associated with early carotid atherosclerosis (Shin-ichi 2005). An increase in carotid arterial intima-media thickness (IMT) was reported in patients with excessive GH. Colao *et al.* has demonstrated that in active acromegalic patients, IMT

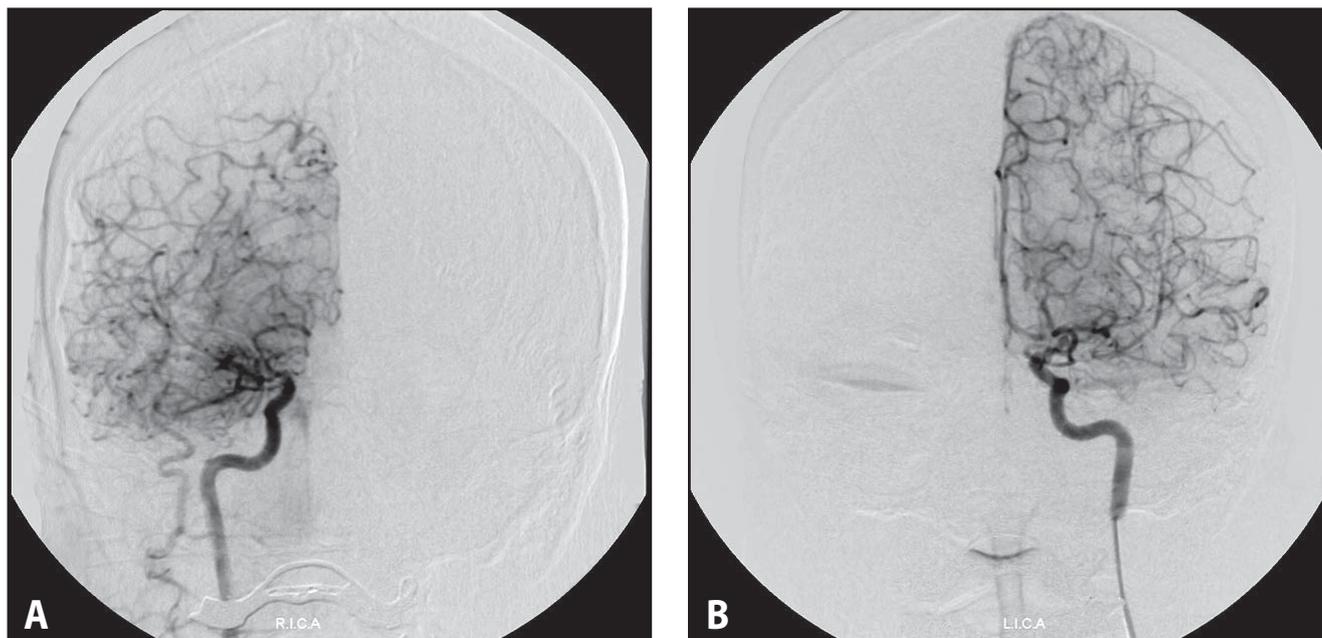


**Fig. 3.** The characteristic microscopic appearance of growth hormone-producing adenomas consists of medium to large non-polar cells with either uniform spherical nuclei or irregular, variable dense nuclei, and large, granular, often acidophilic cytoplasm on high density view.

of the carotid arteries is significantly higher than in sex and age matched controls (Colao *et al.* 2001). It has also been reported that GH deficiency increases arterial intima-media thickness, and it is reasonable to hypothesize that reduced nitric oxide (NO) synthesis might be implicated in the endothelial dysfunction of patients with GH deficiency. The central role of NO is to regulate endothelial function and inhibiting muscle cell proliferation (Capaldo *et al.* 1997). Barabutis *et al.* report that growth hormone releasing hormone (GHRH) induces the expression NO synthase (Barabutis *et al.* 2010). In our case, the PA was not completely removed, and



**Fig. 4. A:** An MR diffusion weighted image showed high signal intensity in the right frontal area due to acute cerebral infarction. **B:** The coronal view of the brain T-1 weighted gadolinium enhanced magnetic resonance image showed a small residual pituitary adenoma in the sellar area and a remnant tumor situated in the immediate vicinity of the cavernous sinus.



**Fig. 5. A, B:** Digital subtraction angiography showed complete obstruction in the right internal carotid artery and severe stenosis of the left internal carotid artery, middle cerebral artery, and anterior cerebral artery with basal collateral vessels.

the patient was not administered octreotide for 4 years after the surgery. We think that her GH and IGF-I levels remained high even though they were normal immediately after the operation. Thus, elevated GH down-regulates GHRH and the expression of NO synthase was reduced. Therefore, not only GH deficiency but also elevated GH and IGF-I levels may be involved in the progression of Moyamoya syndrome.

Four years after surgery, a brain MRI and a digital subtraction angiograph revealed progression of Moyamoya syndrome. These findings indicate that excess systemic GH and IGF-I may participate in the development of Moyamoya syndrome.

## CONCLUSION

This case suggests that excess systemic GH and IGF-I may play a significant role in the pathogenesis of Moyamoya syndrome. Also in the pituitary adenoma patients, it is important to check GH & IGF-I level periodically even though the tumor was removed.

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