

Combined choroidal neovascularization and hypopituitarism in a patient with homozygous mutation in methylenetetrahydrofolate reductase gene

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We report a case of choroidal neovascularization (CNV) secondary to methylenetetrahydrofolate reductase (*MTHFR*) gene mutation in a 20-year-old male patient with hypopituitarism. Treatment with three consecutive injections of intravitreal ranibizumab (anti-vascular endothelial growth factor) resulted in significant improvement of the patient's vision and the appearance of the macula. A search of the literature produced no previously reported case of *MTHFR* gene mutation associated both CNV and possibly hypopituitarism. With hormone replacement therapy of hypopituitarism, acetyl salicylic acid 100 mg/day also was started. The patient was clinically stable both for CNV and other thromboembolic disorders over a 6-month follow-up and also 1-year follow-up period.

Key words: Choroidal neovascularization, drug therapy, hypopituitarism, intravitreal injections, methylenetetrahydrofolate reductase deficiency, *MTHFR*, ranibizumab, vascular endothelial growth factor

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INTRODUCTION

Hypopituitarism is defined as either partial or complete deficiency of anterior or posterior pituitary hormone secretion or both.^[1] Ischemic pituitary necrosis is one of the most common causes of hypopituitarism.^[2] On the other hand, hypopituitarism itself may increase the risk of thromboembolism/hypercoagulopathy, and the underlying mechanisms of hemostatic dysfunctions in hypopituitarism are mostly unknown.^[3] Reduced enzymatic activity due to *MTHFR* gene mutations is associated with hyperhomocysteinemia and has been linked to both arterial and venous thrombosis.^[4] In a recent study, genetic mutations of *MTHFR* were shown to increase the risk of hypopituitarism^[5] in patients with Sheehan syndrome.

Choroidal neovascularization (CNV) is an exhibition of the diseases affecting choroid, Bruch's membrane, and retinal pigment epithelium (RPE). CNV characterizes the growth of new blood vessels from the choroid into the subretinal pigment epithelium, which, in several patients, reach the retina. Virtually any pathologic process that engages the RPE and damages Bruch's membrane can be complicated by CNV. The most

frequent causes of CNV are age-related macular degeneration (AMD) and high myopia.^[6] CNV in the macular area is one of the major causes of severe visual loss. Increased vascular endothelial growth factor (VEGF), which is mainly determined by hypoxic stimuli, plays an integral role in the development of CNV, and thus provides an important therapeutic target.^[7]

Here we report a case of CNV secondary to *MTHFR* gene mutation in a young patient with hypopituitarism and his good clinical outcome after treatment with intravitreal ranibizumab injection.

CASE REPORT

A 20-year-old male was admitted to Gulhane School of Medicine, Department of Endocrinology and Metabolism outpatient clinic, with the complaints of fatigue, anorexia, weakness, and absence of penile erection. A detailed medical history taking revealed that the patient had been diagnosed with hypothyroidism and growth hormone (GH) deficiency at the age of 10 and was subsequently started with treatment for both hypothyroidism and GH deficiency. After a 3-year

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levothyroxine and GH therapy, he himself had stopped the medication and was free of any drug for the past 7 years. He defined that his complaints increased in the last 3 months. He was hospitalized for further evaluation. On physical examination, his blood pressure was 90/50 mmHg and his pulse was 68 beats/min. He was 164 cm tall and weighed 58.5 kg. A eunuchoid appearance with an arm span that was more than 5 cm longer than height, and no facial and minimal axillary hairy were noted. Tanner score of the pubis was 2 and penis length was 5 cm. Right and left testicular volumes were 3.4 ml and 2.5 ml, respectively, on ultrasonography. He had no hyperpigmentation on his skin or oral mucosa. Other physical findings were unremarkable. Laboratory results are shown in Table 1.

On the 5th day of hospitalization while waiting for magnetic resonance imaging (MRI) appointment, the patient had rapid visual loss in the right eye. Best-corrected visual acuity (VA) was 20/50 in the right eye and 20/20 in the left eye. Dilated funduscopy examination revealed a yellowish

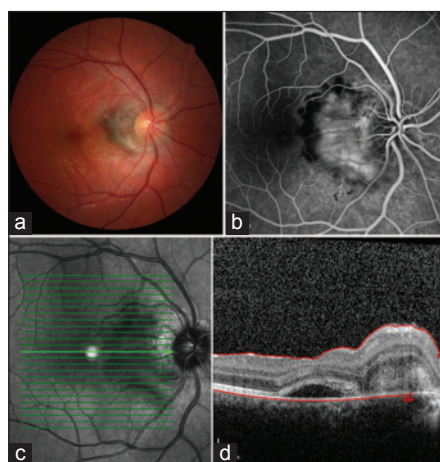


Figure 1: (a) Choroidal neovascularization is observed next to the temporal side of the optic disc in the right eye in color fundus photograph. (b) FA demonstrates hyperfluorescence due to fluorescein leakage. (c) OCT shows a peripapillary lesion with subretinal fluid elevating the neurosensory retina in the macular area

elevated lesion near the optic disc, with macular edema and hemorrhage next to the temporal side of the optic disc in the right eye. Fluorescein angiography (FA) showed a hyperfluorescent lesion consistent with CNV [Figure 1a], and optical coherence tomography (OCT) showed a peripapillary lesion with subretinal fluid elevating the neurosensory retina in the macular area [Figure 1b]. MRI of the brain revealed a hypoplastic adenohypophysis and a hypoplastic pituitary stalk. An ectopic neurohypophysis was found located in the area of the hypothalamus [Figure 2a, T1 weighted; Figure 2b, T2 weighted]. Because of his visual loss, Department of Ophthalmology did not allow insulin hypoglycemia test. Thyroid morphology was normal on ultrasonography. Thyrotropin releasing hormone stimulation test resulted in a maximum thyroid stimulating hormone (TSH) level of 7.6 μ IU/ml by the 30th min. Because of his medical history, clinical and MRI findings, low thyroidal, (free T4) adrenal, (low cortisol) testicular, (low total testosterone) low GH, insulin-like growth factor 1 (IGF-1), and low-normal other pituitary hormone levels [Table 1], he was diagnosed as having hypopituitarism.



Figure 2: MRI of pituitary gland: hypoplastic adenohypophysis and pituitary stalk, ectopic neurohypophysis (a, T1 weighted; b, T2 weighted)

Table 1: Laboratory findings of the patient

Hematological analysis	Biochemical analysis	Hormone analysis
WBC: 6300/mm ³	Glu: 75 mg/dl	ACTH: 39.9 pg/ml (0-46)
Hb: 12.9 g/dl	Urea: 29 mg/dl	Cortisol: 2.29 μ g/dl
Hct: 37.9%	Cre: 0.83 mg/dl	TSH: 3.0 μ IU/ml (0.35-5.5)
Plt: 270,000/mm ³	AST: 15 U/l	FT4: 0.85 ng/dl (0.89-1.76)
	ALT: 9 U/l	GH: 0.066 ng/ml (0-1)
	Total-C: 156 mg/dl	IGF-1: 30.9 ng/ml (116-358)
	LDL-C: 84 mg/dl	FSH: 1.37 IU/l (1.4-18.1)
	HDL-K: 58 mg/dl	LH: 2.04 IU/l (1.24-8.62)
	TG: 68 mg/dl	Tot. test.: 103.66 ng/dl (241-877)
	Homocys: 13.7 μ mol/l (5-14)	PRL: 10.2 ng/ml (2.1-17.7)

WBC = Leukocyte; Hb = Hemoglobin; Hct = Hematocrit; Plt = Thrombocyte; Glu = Glucose; Cre = Creatinine; AST = Aspartate aminotransferase; ALT = Alanine aminotransferase; C = Cholesterol; LDL = Low-density lipoprotein; HDL = High-density lipoprotein; TG = Triglyceride; Homocys = Homocysteine; ACTH = Adrenocorticotropic hormone; TSH = Thyroid stimulating hormone; FT4 = Free T4; GH = Growth hormone; IGF-1 = Insulin-like growth factor 1; FSH = Follicle stimulating hormone; LH = Luteinizing hormone; Tot. test = Total testosterone; PRL = Prolactin

First, prednisolone 5 mg/day was started; 1 week later, l-thyroxin 50 mg/day was added to the treatment. Since both hypopituitarism^[2] and CNV could be caused by hypoxia,^[8] conditions known to cause a hypercoagulable state were explored and an *MTHFR* C677T homozygous mutation was detected by polymerase chain reaction of genomic DNA.^[9] For the peripapillary CNV, three intravitreal injections of anti-VEGF antibody (ranibizumab) were administered for persistent fluid collection. Before the start of testosterone gel 50 mg/day treatment, acetyl salicylic acid (ASA) 100 mg/day was also added to the treatment. By the 6th month of follow-up, VA increased to 20/20 and OCT showed peripapillary scar formation and total resolution of the subretinal fluid [Figure 3]. No subsequent thromboembolic event was determined. On the annual control, 1 year after the event, he was still taking L-thyroxin, testosterone gel, prednisolone, and ASA. His vision on the right eye was stable with 20/20 and no thromboembolic event was determined.

DISCUSSION

In this report, we described a clinical combination of hypopituitarism and CNV, possibly related to a genetic mutation of *MTHFR* C677T gene, and a successful treatment course for CNV after ranibizumab treatment. *MTHFR* gene mutations have been linked to both arterial and venous thrombosis.^[4] Methylene tetrahydrofolate reductase (*MTHFR*) is a key enzyme in the folate metabolic pathway. It catalyzes the conversion of 5,10-methylene tetrahydrofolate (5,10-methylene-THF) to 5-methyl tetrahydrofolate (5-methyl-THF). Mutations in genes of the homocysteine metabolic pathway may confer an increased risk for ischemia. Several authors reported significant associations between *MTHFR* gene polymorphism and cardiac diseases, stroke, and recurrent abortion^[9,10] due to increased plasma homocysteine level. Relationship between *MTHFR* and hypopituitarism in patients with Sheehan syndrome was also shown previously.^[5] Except for the Sheehan syndrome, any association of *MTHFR*

mutation with hypopituitarism could not be identified to date. The present patient had anterior hypopituitarism, but the functions of posterior hypophysis were found to be normal. History and physical examination findings showed that hypopituitarism existed for a long period. The other reasons of hypopituitarism were examined. There was no adenoma or other intracranial tumors affecting the pituitary gland. Since radiologically pituitary tuberculomas mimic adenomas,^[11] we excluded tuberculosis after finding no adenoma with the pituitary gland. MRI findings showed no lesions suitable for hypophysitis, tuberculomas, or sarcoidosis. There was no history of pituitary surgery, radiotherapy, cranial trauma, pituitary apoplexy, subarachnoid hemorrhage, or ischemic stroke. Finally, no primary cause of hypopituitarism could be found except an *MTHFR* gene mutation. MRI showed hypoplasia of anterior hypophysis and ectopic posterior hypophysis. A potential reason could be the interruption of the pituitary stalk due to ischemia, leading to blockage of the axonal transport of antidiuretic hormone (ADH) and oxytocin, as well as hypothalamic releasing hormones.^[12] This can easily explain the ectopy of the neurohypophysis without diabetes insipidus and the hypoplasia of the adenohypophysis.

Both hypopituitarism itself^[3] and testosterone replacement may increase the risk of embolism during hypopituitarism management.^[3,13] If there is a potential risk factor for thromboembolism, such as *MTHFR* gene mutation, the risk may increase further. In a previous study, new thrombotic events were identified in patients with familial thrombophilia after initiating testosterone replacement, and the authors suggested that men on testosterone therapy experiencing thrombosis should be screened for familial thrombophilias.^[13] High estradiol (E2) in men is also associated with an increased risk of stroke or embolism.^[14] The major source of E2 in men comes from the aromatization of testosterone (endogenous and/or exogenous) to E2. In a study on hypogonadal men, mean E2

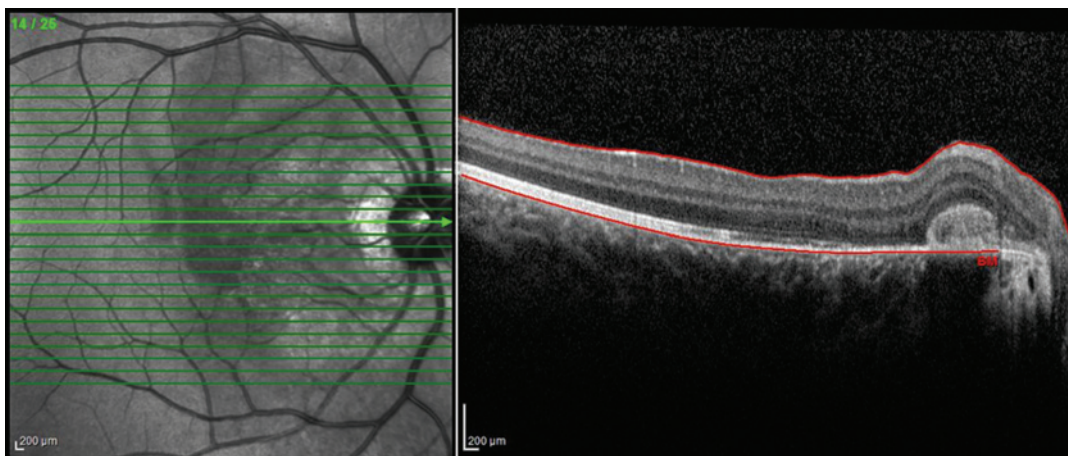


Figure 3: OCT showing peripapillary scar formation and total resolution of the subretinal fluid at 6 months

levels were in the low-to-normal range before testosterone gel (AndroGel, Abbott, Abbott Park, IL, USA) treatment, while serum E2 levels increased by an average of 30.9% and 45.5% after a 30-day treatment.^[15] In another study, serum E2 concentration increased progressively from 6 to 24 months on testosterone gel (50-100 mg/day testosterone), with levels rising to the upper limit of the male reference range.^[16] In our patient, testosterone treatment was coupled with ASA to prevent new thromboembolic events.

CNV is one of the leading causes of severe visual loss.^[17] Most common reasons of CNV are age-related macular degeneration and myopia. There was no myopia in the patient, and he was 20 years old. CNV is also well recognized as a complication of laser photocoagulation for central serous chorioretinopathy (CSC).^[18] Any patient with a diagnosis of central serous chorioretinopathy (CSCR) should be questioned to determine any recent corticosteroid use.^[19] But our patient did not take any treatment with corticosteroid or no laser photocoagulation treatment was applied just before CNV occurrence. Experimental and clinical evidences indicate a central role for VEGF in the pathogenesis of CNV. The increased local VEGF production which is mainly determined by hypoxic stimuli, could be augmented by an *MTHFR* gene mutation related thrombosis. No retinal vascular pathologies were detected on ophthalmic exam such as branch or central retinal vein or artery occlusion. The available anti-VEGF medications can block choroidal angiogenesis, but they may also reduce vascular hyperpermeability that is often the main cause of VA deterioration in patients with CNV. Ranibizumab is a recombinant, humanized antibody fragment that binds to and potently neutralizes the biological activities of all known human VEGF isoforms. In a large randomized, multicenter, sham-controlled phase III study (MARINA trial) that included only patients with minimally classic or occult CNVs, at the 12-month visit, 95% of ranibizumab-treated eyes maintained stable vision. After 24 months, 90% of eyes in the ranibizumab group versus 53% in the control group demonstrated stable vision.^[19] VA and CNV findings recovered successfully also in our patient. Moreover, no recurrence was seen in the following 6 months. Hemorrhage is a rare but serious complication of choroidal neovascular membrane (CNVM) and is attributed to use of anticoagulant or antiplatelet drugs.^[20] However, no ASA-associated increased risk of hemorrhage was observed in patients with CNV, which was also valid for our patient.

CONCLUSION

CNV and hypopituitarism associated with an *MTHFR* gene mutation is highly unusual. Although there are no recommendations in this regard, the observations in the present patient indicate that antiangiogenic therapy can be

useful and safe for the treatment of CNV in such a condition. Along with corticosteroids, levotroxin, and testosterone replacement for the hypopituitarism, ASA treatment to prevent recurrent embolic events could be a reasonable approach when thrombotic ophthalmic complications occur in subjects with an *MTHFR* gene mutation.

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