کارگاه‌های آموزشی مرکز اطلاعات علمی

مقاله نویسی علوم انسانی

اصول تنظیم قراردادها

آموزش مهارت های کاربردی در تدوین و چاپ مقاله
Combined choroidal neovascularization and hypopituitarism in a patient with homozygous mutation in methylenetetrahydrofolate reductase gene

Aydogan Aydogdu, Cem Haymana, Kamil Baskoy, Ali H. Durukan1, Gokhan Ozgur2, Omer Azal
Departments of Endocrinology and Metabolism, Ophthalmology, Hematology, Gulhane School of Medicine, Ankara, Turkey

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

INTRODUCTION

Hypopituitarism is defined as either partial or complete deficiency of anterior or posterior pituitary hormone secretion or both. Ischemic pituitary necrosis is one of the most common causes of hypopituitarism. 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. Reduced enzymatic activity due to MTHFR gene mutations is associated with hyperhomocysteinemia and has been linked to both arterial and venous thrombosis. In a recent study, genetic mutations of MTHFR were shown to increase the risk of hypopituitarism 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. 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.

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
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 funduscopic examination revealed a yellowish 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 neurohypophyis 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 μIU/ml by the 30th min. Because of his medical history, clinical and MRI findings, low thyroidal, (low T4) adrenal, (low cortizol) 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 1](https://example.com/figure1.png)

**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

![Figure 2](https://example.com/figure2.png)

**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/mm³ | Glu: 75 mg/dl | ACTH: 39.9 pg/ml (0-46) |
| Hb: 12.9 g/dl | Urea: 29 mg/dl | Cortisol: 2.29 μg/dl |
| Hct: 37.9% | Cre: 0.83 mg/dl | TSH: 3.0 μIU/ml (0.35-5.5) |
| Plt: 270,000/mm³ | 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 μmol/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 and CNV could be caused by hypoxia, conditions known to cause a hypercoagulable state were explored and an MTHFR C677T homozygous mutation was detected by polymerase chain reaction of genomic DNA. 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. 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. Methyltetrahydrofolate reductase (MTHFR) is a key enzyme in the folate metabolic pathway. It catalyzes the conversion of 5,10-methylenetetrahydrofolate (5,10-methylene-THF) to 5-methyltetrahydrofolate (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 due to increased plasma homocysteine level. Relationship between MTHFR and hypopituitarism in patients with Sheehan syndrome was also shown previously. 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, 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. This can easily explain the ectopy of the neurohypophysis without diabetes insipidus and the hypoplasia of the adenohypophysis.

Both hypopituitarism itself and testosterone replacement may increase the risk of embolism during hypopituitarism management. 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. High estradiol (E2) in men is also associated with an increased risk of stroke or embolism. 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 known human VEGF isoforms. In a large randomized,
to and potently neutralizes the biological activities of all VA deterioration in patients with CNV. Ranibizumab 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, levotrixin, 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.

REFERENCES

1. Prabhakar VK, Shalet SM. Etiology, diagnosis, and management of hypopituitarism in adult life. Postgrad Med J 2006;82:259-66.
2. Blondell RD. Hypopituitarism. Am Fam Physician 1991;43:2029-36.
3. Targher G, Pichi J, Zoppini G, Bonora E, Chonchol M. Hemostatic and fibrinolytic abnormalities in endocrine diseases: A narrative review. Semin Thromb Hemost 2009;35:605-12.
4. Günsoy G, Cimbek A, Acar Y, Erol B, Dal HC, Evrin N, et al. Combined portal, splenic and mesenteric venous thrombosis in inactive ulcerative colitis with heterogeneous mutation in MTHFR gene: A rare case of thrombophilia. J Res Med Sci 2011;16:1500-6.
5. Gokalp D, Tuzcu A, Bahceci M, Ayvildiz O, Yurt M, Celik Y, et al. Analysis of thrombogenic genetic mutations in patients with Sheehan’s syndrome: Is thrombophilia responsible for the pathogenesis of Sheehan’s syndrome? Pituitary 2011;14:168-73.
6. Hansworth DP, Smemerville DN, Ranson NT, Todd KC, GiganteLL, Wong SS. Spermatogenesis abnormalities in dome-shaped and mushroom-shaped choroidal melanomas. Ann Acad Med Singapore 2006;35:87-8.
7. Khairallah M, Kahloun R, Tugal-Tutkun I. Central serous chorioretinopathy, corticosteroids, and uveitis. Ocul Immunol Inflamm 2012;20:76-85.
8. Frosst P, Blom HJ, Milos R, Goyette P, Sheppard CA, Matthews RG, et al. A candidate genetic risk factor for vascular disease: A common mutation in methylenetetrahydrofolate reductase. Nat Genet 1995;10:111-3.
9. Austin RC, Lentz SR, Werstuch GH. Role of hyperhomocysteinemia in endothelial dysfunction and atherothrombotic disease. Cell Death Di 2004;11:556-64.
10. Chen Z, Karaplis AC, Ackerman SL, Pogribny IP, Melnyk S, Lussier-Cacan S, et al. Mice deficient in methylenetetrahydrofolate reductase exhibit hyperhomocysteinemia and decreased methylation capacity, with neuropathology and aortic lipid deposition. Hum Mol Genet 2001;10:433-43.
11. Sunil K, Menon R, Goel N, Sanghvi D, Bandgar T, Joshi SR, et al. Analysis of thrombophilic genetic mutations in patients with Sheehan’s syndrome: Is thrombophilia responsible for the pathogenesis of Sheehan’s syndrome? Pituitary 2011;14:168-73.
12. Fellner F, Triebe S, Hensen J, Baum U, Schmid J. Neuro-MR-findings in primary panhypopituitarism. Rontgenpraxis 1998;51:243-7.
13. Glueck CJ, Goldenberg N, Budhani S, Lotner D, Abuchaibe C, Gowda M, et al. Thrombotic events after starting exogenous testosterone in men with previously undiagnosed familial thrombophilia. Transl Res 2011;158:225-34.
14. Abbott RD, Launer LJ, Rodriguez BL, Ross GW, Wilson PW, Masaki KH, et al. Serum estradiol and risk of stroke in elderly men. Neurology 2007;68:563-8.
15. Swerdloff RS, Wang C, Cunningham G, Dobs A, Iranmanesh A, Matsumoto AM, et al. Long-term pharmacokinetics of transdermal testosterone gel in hypogonadal men. J Clin Endocrinol Metab 2000;85:4500-10.
16. Wang C, Cunningham G, Dobs A, Iranmanesh A, Matsumoto AM, Snyder PJ, et al. Long-term testosterone gel (AndroGel) treatment maintains beneficial effects on sexual function and mood, lean and fat mass, and bone mineral density in hypogonadal men. J Clin Endocrinol Metab 2004;89:2085-98.
17. Ferrara N. Vascular endothelial growth factor: Basic science and clinical progress. Endocr Rev 2004;25:581-611.
18. Nomura Y, Obata R, Yanagi Y. Intravitreal bevacizumab for iatrogenic choroidal neovascularization due to laser photocoagulation in central serous chorioretinopathy. Jpn J Ophthalmol 2012;56:245-9.
19. Rosenfeld PJ, Brown DM, Heier JS, Boyer DS, Kaiser PK, Chung CY, et al. Ranibizumab for neovascular age-related macular degeneration. N Engl J Med 2006;355:1419-31.
20. El Baba F, Jarrett WH 2nd, Harbin TS Jr, Fine SL, Michels RG, Schachat AP, et al. Massive hemorrhage complicating age-related macular degeneration. Clinicopathologic correlation and role of anticoagulants. Ophthalmology 1986;93:1581-92.

Source of Support: Nil. Conflict of Interest: None declared.
کارگاه‌های آموزشی مرکز اطلاعات علمی

مقاله نویسی علوم انسانی

اصول تنظیم قراردادها

آموزش مهارت های کاربردی در تدوین و چاپ مقاله