Combined Choroidal Neovascularization and Hypopituitarism in a Paitent with Homozygous Mutation in Methylenetetrahydrofolate Reductase Gene

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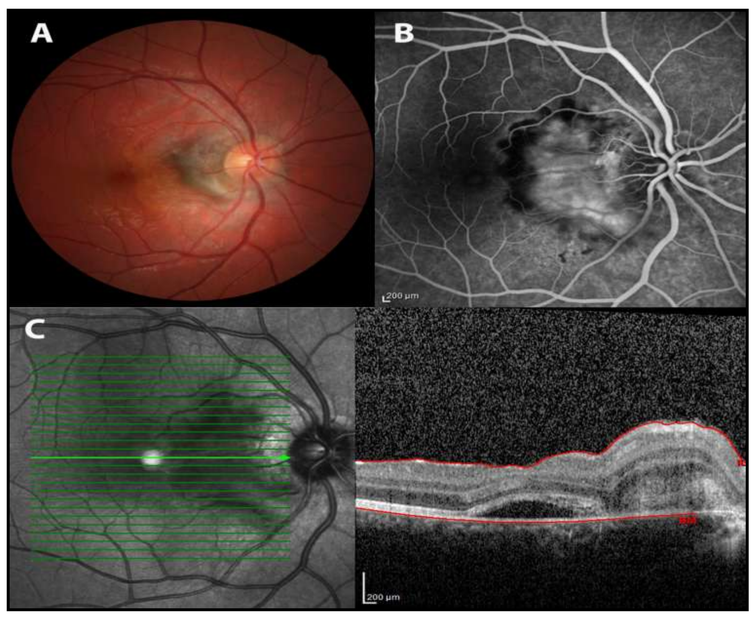
INTRODUCTION

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 underlying mechanisms of hemostatic dysfunctions in hypopituitarism are mostly unknown. Reduced enzymatic activity due to methylenetetrahydrofolate reductase (MTHFR) gene mutations are associated with hyperhomocysteinemia and have been linked to both arterial and venous thrombosis. Choroidal neovascularization (CNV) in the macular area is one of the major causes of severe visual loss and increased vascular endothelial growth factor (VEGF), which is mainly determined by hypoxic stimuli plays an integral role in the development of CNV and thus provide an important therapeutic target.

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

Figure 1. A: Choroidal neovascularisation 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 showed a peripapillary lesion with subretinal fluid elevating the neurosensory retina in the macular area.



CASE REPORT

A 20-year-old male was admitted to Gulhane School of Medicine, Department of Endocrinology and Metabolism outpatient clinic with the complaining of fatigue, anorexia, weakness and absence of penil 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 treatment for both hypothyroidism and GH deficiency. He defined that his complaining increased in the last three mounts. In physical examination, his blood pressure was 90/50 mmHg, and his pulse was 68 beats/minute. He was 164 cm tall and 58.5 kg. An 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. Laboratory results are shown in Table-1.

On the 5th day of hospitalization, the patient had rapid visual loss in the right eye. Best-corrected visual acuity 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 showed a hyperfluorescent lesion consistent with CNV (Figure 1_A) and optical coherence tomography (OCT) showed a peripapillary lesion with subretinal fluid elevating the neurosensory retina in the macular area (Figure 1_B). Magnetic resonance imaging 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 2_A: T1 Weighted, Figure 2_B: T2 Weighted). Because of his visual loss, department of ophthalmology did not allow insulin hypoglycemia test. Thyroid morphology was normal on ultrasonography. Because of his medical history, clinical and MRI findings, low thyroidal, adrenal, testicular, low GH, IGF-1 and low-normal other pituitary hormone levels (Table 1), he was diagnosed as hypopituitarism. First prednisolone 5 mg/day was started, one week later L-thyroxin 50µg/day was added to treatment. Since both hypopituitarism and CNV could be caused by hypoxia, conditions known to cause a hypercoagulable state were explored and a MTHFR C677T homozygous mutation was detected by polymerase chain reaction of genomic DNA. For the peripapillary CNV, 3 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 100 mg/day was also added to treatment. By the sixth month of follow-up, visual acuity 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.

Figure 3. OCT showed peripapillary scar formation and total resolution of the subretinal fluid at six month

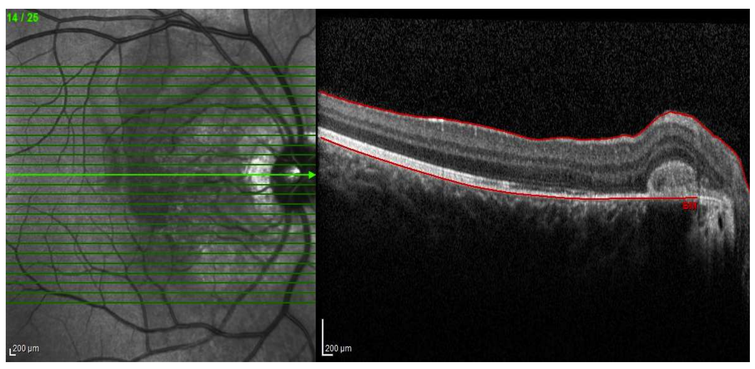
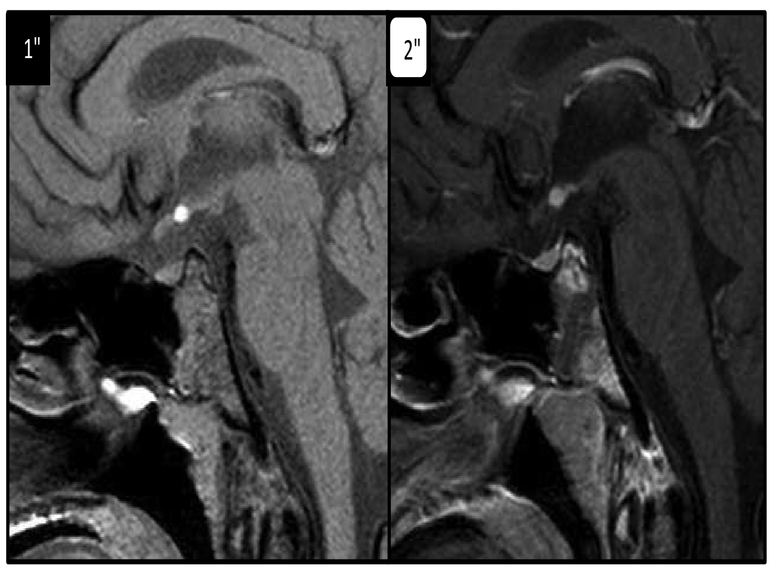


Table 1: Laboratory findings of the patient

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:	270000/ 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:	13.7µmol/L	PRL:	10.2 ng/mL (2.1-17.7)

WBC: Leucocyte, Hb: Hemoglobin, 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, Thyroid stimulating hormone, GH: Growth hormone, IGF1: Insulin-like growth factor 1, FSH: Follicle stimulating hormone, LH: Luteinizing hormone, Tot.test: Total testosterone, PRL: Prolactin

Figure 2. MRI of pituitary gland; hypoplastic adenohypophysis and pituitary stalk, ectopic neurohypophysis (1: T1 Weighted, 2: T2 Weighted)



CONCLUSION

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. CNV and hypopituitarism associated with a MTHFR gene mutation is highly unusual. Except for the Sheehan syndrome, any association of MTHFR mutation with hypopituitarism could not be identified to date. 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 a MTHFR gene mutation.

REFERENCES

1) Blondell RD: Hypopituitarism. Am Fam Physician 1991, 43: 2029-2036.
2) Targher G, Pichiri I, Zoppini G, Bonora E, Chonchol M: Hemostatic and fibrinolytic abnormalities in endocrine diseases: a narrative review. Semin Thromb Hemost 2009 35: 605-612.
3) Frosst P, Blom HJ, Milos R, Goyette P, Sheppard CA, Matthews RG, Boers GJ, den Heijer M, Kluijtmans LA, van den Heuvel LP, et al: A candidate genetic risk factor for vascular disease a common mutation in methylenetetrahydrofolate reductase. Nat Genet 1995, 10: 111-113.
4) Rosenfeld PJ, Brown DM, Heier JS, Boyer DS, Kaiser PK, Chung CY, Kim RY; MARINA Study Group Ranibizumab for neovascular age-related macular degeneration. N Engl J Med 2006, 355: 1419-1431.

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