Turkish Journal of Endocrinology and Metabolism, (2000) 1 : 33-35 **ORIGINAL ARTICLE**

Factor V Leiden Mutation - an Unusual Cause of Hypopituitarism?

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Hypopituitarism is a disorder of diverse etiology that results in partial or total loss of pituitary functions. Here we report a 49-year-old female patient presenting with absence of peripheral pulses of the right upper extremity and anterior pituitary failure. She was initially diagnosed as Sheehan's syndrome in 1974 and Takayasu arteritis in 1990. But she was found to be positive for factor V Leiden mutation in 1990. We suggest that this mutation, which causes resistance to activated protein C and is an established risk factor for thrombosis, also is the cause for both the ischemic necrosis of the pituitary and subclavian artery occlusion in our case.

Key words: Hypopituitarism, factor V Leiden mutation

Introduction

Hypopituitarism is a disorder of diverse etiology that results in partial or total loss of pituitary hormone function. Although ischemic necrosis is somewhat a common cause of hypopituitarism, it is rarely attributed to thrombotic and vasculitic syndromes. We report here a case of panhypopituitarism, presenting with absence of peripheral pulses of the right upper extremity and anterior pituitary failure. She was initially diagnosed as Sheehan's syndrome and Takayasu arteritis, but later found to be positive for factor V Leiden mutation.

Case Report

NA, a 49-year-old female patient, presented with headache and foot and heel pain. In her history, she told us that after her last delivery in 1967, she lactated only for about two months and then symptoms like failure to resume menses, hypotension, cold intolerance and slowing in hair growth developed. Although there was only minimal hemorrhage during her delivery and a lactation period for about two months, she was diagnosed as Sheehan's syndrome and began to take anterior pituitary replacement therapy (prednisolon plus L-thyroxin plus estrogen) since then.

In 1990, she presented with malaise, fever and headache. On physical examination peripheral pulses on the right upper extremity were not palpable. With arteriography, an occlusion on the right subclavian artery was shown and the patient was diagnosed as Takayasu arteritis. Prednisolon therapy was given in pharmacological doses and her complaints regressed.

On her last admission she was 49 years old and found to be hypertensive during her routine control. With Doppler study the occlusion on the right subclavian artery persisted and increased collateral circulation was observed, but the renal arteries were intact. An empty sella was diagnosed with

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magnetic resonance imaging. Her serum prolactin was 8.8 ng/ml, which is thought to be higher than that found in Sheehan's syndrome (1). Although she was diagnosed as Takayasu arteritis as the cause of the thrombotic phenomena, we investigated other factors that may increase the thrombotic risk. Anti-cardiolipin antibodies IgM and IgG were normal and the lupus anticoagulant was found to be negative, but the patient was positive for factor V Leiden mutation.

Discussion

Hypopituitarism is a disorder of diverse etiology that results in a partial or total loss of anterior or posterior pituitary hormone function. Ischemic necrosis is somewhat a common cause of hypopituitarism, and it was first Sheehan that demonstrated the relationship between postpartum ischemic pituitary necrosis and hypopituitarism. Although postpartum hemorrhage is the most common cause of ischemic pituitary necrosis, diabetes mellitus and other systemic diseases such as temporal arteritis, sickle cell disease and trait, arteriosclerosis and eclampsia are all considered among other less common causes. Vasculitic syndromes such as Takayasu disease are reported as the cause of panhypopituitarism in rare cases (2). Thrombotic phenomena causing cavernous sinus thrombosis is an other rare cause of panhypopituitarism (3).

There are several genetic defects that have been established as risk factors for venous thrombosis. Among these are protein C, protein S and antithrombin deficiencies, resistance to activated protein C associated with the factor V Leiden mutation, and increased prothrombin associated with the prothrombin 20210 A allele (4).

Resistance to activated protein C (APC) is the most common inherited risk factor for venous thrombosis (5). Most cases of APC resistance are caused by the point mutation in factor V gene (G to A transition at nucleotide position 1691), which predicts replacement of Arg 506 in the APC- cleavage site with a Gln and referred to as factor V Leiden mutation. After activation, mutated factor V, FV: Q506, is less effectively degraded by APC than normal factor V, which results in increased thrombin generation and a hypercoagulable state. This mutation is highly prevalent in the general population (%5-10). Heterozygosity is associated with a 5-10-fold increased risk of thrombosis, whereas homozygous cases have 50-100-fold increased risk of thrombosis (6).

The factor V mutation is a common cause of venous thromboses, but may also be associated with arterial thrombotic events, such as myocardial infarction (7), stroke (8) and small bowel infarction (9). Smoking (7), post-partum state (10), the use of oral contraceptives (11) and surgery are reported as predisposing factors for thrombosis in these patients (12). Factor V Leiden mutation is also associated with an increased risk of venous thromboembolism during pregnancy and the puerperium (13).

In our case, Sheehan's syndrome was the presumed diagnosis for panhypopituitarism, although her last pregnancy's outcome did not support the classical obstetrical history of Sheehan's syndrome. Subclavian arterial occlusion which developed years after the initial diagnosis of Sheehan's syndrome could be explained by the most suitable vasculitic syndrome for this patient-i.e. Takayasu arteritis. The presence of factor V Leiden mutation in this patient made us to conclude that both hypopituitarism and subclavian arterial occlusion could be caused by this special situation which increases risk for venous, but also arterial thrombosis.

The severity of a postpartum hemorrhage does not always correlate with the presence of Sheehan's syndrome. In some cases, locally released factors or increased thrombotic tendency may mediate thrombosis, vascular spasm or constriction of the arterial blood supply to the pituitary. In our opinion genetic defects which poses increased tendency for arterial and venous thrombosis should be investigated in patients previously diagnosed as Sheehan's syndrome or patients presenting with hypopituitarism and no identifiable cause.

References

1. Özbey N, İnanç S, Aral F, Azezli A, Orhan Y, Sencer E, Molvalılar S. Clinical and laboratory evaluation of 40 patients with Sheehan's syndrome. *Isr J Med Sci* **30:** 826-829, 1994.
2. Toth M, Szabo P, Racz K, Szende B, Balogh I, CzirJak S, Slowik F, Glaz E. Granulomatous hypophysitis associated with Takayasu's disease. *Clin Endocrinol (Oxf)* **45:** 499-503, 1996.

3. Frohman LA. Diseases of the anterior pituitary. In: Felig P, Baxter JD, Frohman LA (eds), Endocrinology and Metabolism. *McGraw-Hill* p: 289-383, 1995.

4. Bertina RM. Factor V Leiden and other coagulation factor mutations affecting thrombotic risk. *Clin Chem* **43:** 1678-83, 1997.

5. Herrmann F.H., Koesling M, Schroder W, Altman R, Jimenez Bonilla R, Lopaciuk S, Perez-Requejo JL, Singh JR. Prevalence of factor V Leiden mutation in various populations. *Genet Epidemiol* **14:** 403-11, 1997 (Abstract).

6. Dahlback B. New molecular insights into the genetics of thrombophilia. Resistance to activated protein C caused by Arg506 to Gln mutation in factor V as a pathogenic risk factor for venous thrombosis. *Thromb Haemost* **74:** 139-48, 1995.

7. Rosendaal FR, Siscovick DS, Schwartz SM, Beverly RK, Psaty BM, Longstreth WT Jr, Raghunathan TE, Koepsell TD, Reitsma PH. Factor V Leiden (resistance to activated protein C) increases the risk of myocardial infarction in young women. *Blood* **89:** 2817-21, 1997.

8. Bontempo FA, Hassett AC, Faruki H, Steed DL, Webster MW, Makaroun MS. The factor V Leiden mutation: spectrum of thrombotic events and laboratory evaluation. *J Vasc Surg* **25:** 271-5, 1997 (Abstract).

9. Heresbach D, Pagenault M, Gueret P, Crenn P, Heresbach-Lr Berre N, Malledant Y, Fauchet R, Horellou MH, Silver J, Messing B, Bretagne JF. Leiden factor V mutation in four patients with small bowel infarctions. *Gastroenterology* **113:** 322-5, 1997.

10. Zuber M, Toulon P, Marnet L, Mas JL. Factor V Leiden mutation in cerebral venous thrombosis. *Stroke* **27:** 1721-3, 1996.

11. Vandenbroucke JP, Koster T, Briet E, Reitsma PH, Bertina RM, Rosendaal FR. Increased risk of venous thrombosis in oral-contraceptive users who are carriers of factor V Leiden mutation. *Lancet* **344:** 1453-7, 1994.

12. Emmerich J, Alhenc-Gelas M, Aillaud MF, Juhan-Vague I, Jude B, Garcin JM, Dreyfus M, de Moerloose P, Le Querrec A, Priollet P, Berruyer M, Vallantin X, Wolf M, Aiach M, Fiessinger JN. Clinical features in 36 patients homozygous for the ARG 506-- > GLN factor V mutation. *Thromb Haemost* **77:** 620-3, 1997.

13. Gerhardt A, Scharf RE, Beckmann MW, Struve S, Bender HG, Pillny M, Sandmann W, Zotz RB Prothrombin and factor V mutations in women with a history of thrombosis during pregnancy and the puerperium. *N Engl J Med* **342** (6): 374-80, 2000.