A Hypertrophic Spinal Pachymeningitis Patient With Factor V Leiden (G1691A), MTHFR C677T, MTHFR A1298C, PAI-1 4G-5G, Glycoprotein IIIa L33P Gene Mutations

Serkan Civlan 1, Cemre Harvey 2, Duygu Herek 3, İbrahim Türkçüer 4, Ramazan Sabirli 5, Matteo Pellegrini 6, Aylin Koseler 7

Corresponding author: Aylin Koseler, aylinkoseler@gmail.com

Abstract

Hypertrophic pachymeningitis (HP) is a rare clinical entity of diverse etiology, characterized by a chronic inflammation that causes dura thickening. Reports of Idiopathic hypertrophic cranial pachymeningitis (IHCP) were related to infections, trauma, tumors, and rheumatologic conditions. It was first described by Charcot and Joffroy regarding spinal meninges in 1869. HP has three stages: progressive radicular symptoms begin first, then muscle weakness and atrophy start. Findings such as paraplegia, loss of bladder and bowel control, and respiratory distress caused by intercostal and diaphragmatic denervation are considered the third stage of the disease. Especially in the cranial form of the disease, nerve ischemia and various cranial neuropathic findings may occur.

Factor V Leiden (G1691A), MTHFR C677T, MTHFR A1298C, and PAI-1 4G-5G gene mutation analysis were measured with an ABI Prism. In this case report, the authors present a case of hypertrophic mutations pachymeningitis with Factor V Leiden (G1691A), MTHFR C677T, MTHFR A1298C, PAI-1 4G-5G, Glycoprotein IIa L33P gene.

In conclusion, we report a case of HP with Factor V Leiden (G1691A), MTHFR C677T, MTHFR A1298C, PAI-1 4G-5G, and Glycoprotein IIa L33P gene mutations. We emphasize that the identification of pachymeningitis can be easily bypassed with the application of limited laboratory techniques. As in this case report, we think that these mutations should be analyzed in patients diagnosed with pachymeningitis.

Introduction

Hypertrophic pachymeningitis (HP) is a rare clinical entity of diverse etiology, characterized by a chronic inflammation that causes dura thickening. Reports of Idiopathic hypertrophic cranial pachymeningitis (IHCP) were related to infections, trauma, tumors, and rheumatologic conditions [1]. Charcot and Joffroy described firstly regarding spinal meninges in 1869 [2]. HP has three stages - progressive radicular symptoms begin first, then muscle weakness and atrophy start. Findings such as paraplegia, loss of bladder and bowel control, and respiratory distress caused by intercostal and diaphragmatic denervation are considered the third stage of the disease. Especially in the cranial form of the disease, nerve ischemia and various cranial neuropathic findings may occur [3]. The authors present a case of hypertrophic mutations pachymeningitis with Factor V Leiden (G1691A), MTHFR C677T, MTHFR A1298C, PAI-1 4G-5G, Glycoprotein IIa L33P gene.

Case Presentation

A 62-year-old woman visited the clinic with back pain and bilateral numbness in her legs after a slipping fall. There are two traffic accidents and a couple of fractures in her femoral bones in her history. She stated that she has had pain and numbness in her lower extremities for years after the accident. In addition, she has had one abortion in her history.

A bilateral lower extremity physical examination consisted of normal vital findings and 5/5 muscle strength, intact and equal pulses, and equal bilateral diameters. She had neuropathic complaints in her bilateral lower extremities. Other parameters and findings were in the normal range (Tables 1, 2).

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| Laboratory Parameter | Level | Unit | Normal Range |
|----------------------|-------|------|--------------|
| GFR                  | 91    | mL/min | >90          |
| Glucose              | 97    | mg/dL | 82-115       |
| Urea                 | 51    | mg/dL | <50          |
| Creatinine           | 0.72  | mg/dL | 0.5-0.95     |
| Na⁺¹                | 143   | mmol/L | 136-145     |
| Cl⁻                  | 105   | mmol/L | 98-1,047   |
| K⁺                  | 5.27  | mmol/L | 3.5-5.1     |
| Total Protein        | 60.5  | g/L | 66-87       |
| Albumin              | 37.5  | g/L | 35-52      |
| AST                  | 28    | IU/L | <32         |
| ALT                  | 19    | IU/L | <33         |
| LDH                  | 214   | IU/L | 135-214    |
| Ca²⁺²               | 8.65  | mg/dL | 8.8-10.2   |
| CRP                  | 4.33  | mg/dL | 0.5-5      |
| Homocystein          | 16.45 | µmol/L | 5-12    |

**TABLE 1: Biochemical parameters of the patient**

GFR, glomerular filtration ratio; CRP, C-reactive protein; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase
For a DVT prediagnosis, rheumatism parameters and a thrombophilia genetic panel were collected in her previous visits. She has been administered Gabapentin, acetylsalicylic acid, metformin, and Vitamin B. Among the hematological and biochemical parameters of the patient, only the homocysteine level was high. (Tables 1, 2). Protein C, Protein S, and activated Protein C resistance levels and all rheumatologic parameters were found within the normal range (Table 3).
| Laboratory Parameter                              | Level       | Unit       | Normal Range |
|--------------------------------------------------|-------------|------------|--------------|
| Indirect Coombs                                  | Negative    |            |              |
| Indirect Coombs (with enzyme)                    | Negative    |            |              |
| Direct Coombs IgG                                | Negative    |            |              |
| Direct Coombs Complement (C3d)                   | Negative    |            |              |
| Anti Histone Antibody                            | Negative    |            |              |
| Nucleosome                                       | Negative    |            |              |
| Anti Ribosomal P Protein                         | Negative    |            |              |
| Anti-Sm/Rnp (Immonoblotting)                     | Negative    |            |              |
| Anti-Ssa                                         | Negative    |            |              |
| Anti -Jo 1 (Immunoblotting)                      | Negative    |            |              |
| Anti -Ssb                                        | Negative    |            |              |
| Anti -ScI 70                                     | Negative    |            |              |
| Anti -Sm (Immonoblotting)                        | Negative    |            |              |
| Anti Nuclear Antibody-Ana                        | Negative    |            |              |
| Anti Beta-2 Glycoprotein 1 IgG                   | 1.53 Negative | UI/MI       | 0-5          |
| Anti Beta-2 Glycoprotein 1 IgM                   | 0.79 Negative | UI/MI       | 0-5          |
| Anti Beta-2 Glycoprotein 1 IgA                   | 1.39 Negative | UI/MI       | 0-5          |
| Anti Phospholipid IgM                            | 1.46 Negative | Gpl Au/MI   | 0-10         |
| Anti Phospholipid IgG                            | 2.82 Negative | Gpl Au/MI   | 0-10         |
| Anti Cardiolipin IgG                             | 0.22 Negative | Gpl Au/MI   | 0-10         |
| Anti Cardiolipin IgM                             | 3.41 Negative | Mpl U/MI    | 0-10         |
| Protein C                                        | 130         | %          | 70-140       |
| Protein S                                        | 110.6       | %          | 54.7-123.7   |
| Activated protein resistance                     | 1.85        | %          |              |

**TABLE 3: Rheumatological and thrombophilia parameters of the patient**

Factor V Leiden (G1691A) and Glycoprotein IIIa L33P mutations were done with real-time PCR analysis. MTHFR C677T, MTHFR A1298C, and PAI-1 4G-5G gene mutation analysis were determined with the ABI prism DNA sequencing system (Figure 1).
The individual was found to be Factor V Leiden G1691A heterozygous, MTHFR C677T heterozygous, MTHFR A1298C heterozygous, PAI-1 4G-5G heterozygous, glycoprotein IIIa L33P heterozygous.

CT scans showed diffuse hyperdense thickening in the dura from the T1 level to the T12 level in the spinal cord. An MRI was obtained due to significant thoracic spinal cord suppression due to the thickening (Figures 2A, 2B).
Diffuse T1-2 hypointense thickening was observed in the dura starting from the T1 level and extending anteriorly to the T11 level and extending posteriorly from the T1 level to the L4-5 level (Figures 3A-3D). Thoracic dural thickening caused significant spinal cord compression. In some locations, myelomalacic signals in the spinal cord were observed. There was no contrast agent uptake in the thickening after intravenous contrast agent. However, intense contrast agent enhancement in the extradural area at the C2-3 level in the anterior and upper cervical left half of the spinal canal was seen (Figures 3E, 3F).

The patient was prediagnosed with IHCP. The patient was hospitalized and started Prednisolone treatment. Follow-up visits showed no neurologic deficits, and therefore the patient was discharged. MRI scans from a three-month follow-up showed no significant change.

Discussion
In this study, Factor V Leiden (G1691A), MTHFR C677T, MTHFR A1298C, PAI-1 4G-5G, and Glycoprotein IIIa L33P gene mutations were identified by DNA sequence analysis. To the best of our knowledge, our case is the first reported case of pachymeningitis which has multiple mutations in hematological genes. The incidence of hypertrophic spinal pachymeningitis was found to be higher in men than in women in a study (1:0.91) and this case is also important in terms of being an example of pachymeningitis in women [4]. Several proteases are involved in Factor V (FV) activation, including factor V, thrombin, factor Xa (FXa), and (transiently) plasmin. FXa and FVα form a prothrombinase complex, which increases the conversion rate of prothrombin to α-thrombin 300,000 times. Protein C (PC) inactivates FV, thereby regulating the amount of...
Homocysteine is a sulfurous amino acid that is formed by the removal of a methyl group from methionine and plays a regulatory role in remethylation and transsulfuration. Metabolic pathways. In the remethylation pathway, homocysteine is methylated and converted back to methionine in a reaction in which vitamin B12 (cobalamin) is used as a cofactor and 5-methyltetrahydrofolate (MTHF) is used as a substrate, and the enzyme methionine synthase functions. It is synthesized from methylenetetrahydrofolate (derived from dietary folate) by a reaction catalyzed by the enzyme 5-MTHF thermolabile methylenetetrahydrofolate reductase (MTHFR), which is the substrate of this metabolic pathway, and therefore it is used in folic acid deficiencies. The amount of substrate required for the remethylation pathway also decreases [7].

It has been shown that the C677T homozygous polymorphism (TT) of the MTHFR enzyme slows down the enzyme activity, thus the activity of the remethylation cycle, and is associated with significantly higher homocysteine levels [8]. It has been shown that the A1298C polymorphism of the MTHFR enzyme also affects total homocysteine concentrations and is a risk factor for neural tube defects [9].

Glycoprotein Ib/IIa receptors are proteins in the integrin class and are not found on the surface of circulating platelets but are presented on the surface by platelet activation. It is a calcium-dependent heterodimer and acts as a receptor for fibrinogen, fibronectin, vitronectin, VWF, and thrombospondin and governs platelet aggregation, tight adhesion, and scattering. There are studies on the glycoprotein Ib/IIa polymorphism. Platelet antigen polymorphism in the form of PL(A1) and PL(A2) of the gene encoding GpIIa is common and associated with vascular diseases [10]. Three polymorphisms of GPIIb/IIa have been identified. A1/A2 (Leu33Pro), a single nucleotide polymorphism (SNP) at position 196 in the beta 3 integrin gene, is most thoroughly investigated for its potential pathophysiological role in CAD.

Plasminogen activator inhibitor-1 (PAI-1) is the best known of the activator molecules. PAI-1 is a protein from the serpin family and exerts its effect through t-PA inhibition. PAI-1, together with t-PA, binds to fibrin and exerts its inhibitory effect. Since the source of PAI 1 and t-PA is endothelial and vascular smooth muscle cells, fibrinolysis is locally controlled [11]. A common polymorphism, known as 4G/5G, a deletion/insertion polymorphism of single guanine in the promoter region of the PAI-1 gene at base-pair -675, is found in homozygosity in approximately 25% of the general population [12].

Conclusions
In conclusion, we report a case of HP with Factor V Leiden (G1691A), MTHFR C677T, MTHFR A1298C, PAI-1 4G-5G, Glycoprotein IIa L33P gene mutations. We emphasize that genetic analysis may also be useful in the diagnosis of pachymeningitis and the determination of its cause, in addition to existing radiological examinations. As in this case report, we think that these mutations should be analyzed in patients diagnosed with pachymeningitis.

Additional Information
Disclosures
Human subjects: Consent was obtained or waived by all participants in this study.

Conflicts of interest: In compliance with the ICMJE uniform disclosure form, all authors declare the following:

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References
1. Naffziger HC, Stern WE: Chronic pachymeningitis; report of a case and review of the literature. Arch Neurol Psychiatry. 1949, 62:583-411.
2. Charcot JM, Joffroy A: Deux cas d'athrophie musculaire progressive avec lesions de la substance grise et des faisceaux antéro-latéraux de la meme epiniere. Arch Physiol Norm Pathol. 1869, 2:354-67.
3. Bosman T, Simonin C, Launay D, Caron S, Destée A, Defebvre L: Idiopathic hypertrophic cranial pachymeningitis treated by oral methotrexate: a case report and review of literature. Rheumatol Int. 2008, 28:715-8. 10.1007/s00296-007-0504-5
4. Yonekawa T, Murai H, Utsuki S, et al.: A nationwide survey of hypertrophic pachymeningitis in Japan. J Neurol Neurosurg Psychiatry. 2014, 85:732-9. 10.1136/jnnp-2013-306410
5. Van Cott EM, Khor B, Zehnder JL: Factor V Leiden. Am J Hematol. 2016, 91:46-9. 10.1002/ajh.24222
6. Beauchamp NJ, Daly ME, Hampton KK, Cooper PC, Preston FE, Peake IR: High prevalence of a mutation in the factor V gene within the U.K. population: relationship to activated protein C resistance and familial thrombosis. Br J Haematol. 1994, 88:219-22. 10.1111/j.1365-2141.1994.tb05005.x
7. Friedman AN, Bostom AG, Selhub J, Levey AS, Rosenberg IH: The kidney and homocysteine metabolism. J Am Soc Nephrol. 2001, 12:2181-9. 10.1681/ASN.V12102181
8. van Guldener C, Robinson K: Homocysteine and renal disease. Semin Thromb Hemost. 2000, 26:313-24. 10.1055/s-2000-8407
9. Sunder-Plassmann G, Födinger M, Buchmayer H, et al.: Effect of high dose folic acid therapy on hyperhomocysteinemia in hemodialysis patients: results of the Vienna multicenter study. J Am Soc Nephrol. 2000, 11:1106-16. 10.1681/ASN.V1161106
10. Di Castelnuovo A, de Gaetano G, Benedetta Donati M, Iacoviello L: Platelet glycoprotein IIb/IIIa polymorphism and coronary artery disease: implications for clinical practice. Am J Pharmacogenomics. 2005, 5:93-9. 10.2165/00129785-200505020-00002
11. van Leeuwen RT, Kol A, Andreotti F, Kluft C, Maseri A, Sperti G: Angiotensin II increases plasminogen activator inhibitor type 1 and tissue-type plasminogen activator messenger RNA in cultured rat aortic smooth muscle cells. Circulation. 1994, 90:562-8. 10.1161/01.cir.90.1.562
12. Burzotta F, Iacoviello L, Di Castelnuovo A, et al.: 4G/5G PAI-1 promoter polymorphism and acute-phase levels of PAI-1 following coronary bypass surgery: a prospective study. J Thromb Thrombolysis. 2005, 16:149-54. 10.1023/B:THRO.0000024052.79415.62