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Case Report

Multiple Sclerosis Diagnosed in a Woman With Von-Willebrand Disease: A Case Report

Mohsen Farjoud Kouhanjani[1], Shirin Haghighat[2], Maryam Poursadeghfard[3*]

1. Student Research Committee, Shiraz University of Medical Sciences, Shiraz, Iran.
2. Department of Hematology and Medical Oncology, School of Medicine, Shiraz University of Medical Sciences, Shiraz, Iran.
3. Clinical Neurology Research Center, Shiraz University of Medical Sciences, Shiraz, Iran.

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ABSTRACT

Background: Von-Willebrand Disease (VWD) is the most common inherited bleeding disorder with an autosomal inheritance pattern. Multiple Sclerosis (MS) is a neurological disease, causing neurodegeneration and demyelination of the central nervous system through autoimmune mechanisms, and is a major cause of non-traumatic disabilities in youths. Some studies have shown the higher plasma activity of Von-Willebrand Factor in the active phase of MS. However, we could not find any study reporting co-occurrence of VWD and MS.

Case Presentation and Intervention: In this case report, we present a woman with VWD who had optic neuritis 8 years ago and a new onset right-side hemiparesis. She was finally diagnosed as a new case of MS.

Conclusion: There is a case of both VWD and MS; however, further investigation is needed regarding the association of VWD and MS.

Keywords: Von-Willebrand diseases, Multiple sclerosis, Von-Willebrand Factor

*** Corresponding Author:**
Maryam Poursadeghfard.
Address: *Clinical Neurology Research Center, Shiraz University of Medical Sciences, Shiraz, Iran.*
Tel: *+98 (71) 36121065,* ***Fax:*** *+98 (71) 36121065*
E-mail: *poursadegh@sums.ac.ir, poursadra@gmail.com*

Highlights

- Von-Willebrand disease is a common bleeding disorder.
- The role of coagulation system has been identified in neuro-degenerative diseases including multiple sclerosis.
- Here, we present a patient with Von-Willebrand disease who is diagnosed with multiple sclerosis.

Introduction

Von-Willebrand Disease (VWD) is the most common inherited bleeding disorder in humans which shows autosomal inheritance pattern [1]. This disorder includes two variants, quantitative (type 1 and type 3) and qualitative (type 2A, 2B, 2M, and 2N). Type 3 VWD is the least common and most severe form of VWD which is also associated with low level of factor VIII level [2]. Replacement of both Von-Willebrand Factor (VWF) and factor VIII is the mainstay of treatment for VWD, especially in patients with refractory desmopressin [3]. The goal of treatment in patients with VWD is not only correction of the primary hemostasis defect (VWF deficiency), but also the replacement of concomitant deficient factor VIII [1]. Humate-p is a purified, sterile concentrate of factor VIII, and VWF is one of these products used in the treatment of VWD [4].

Multiple Sclerosis (MS) is a neurological disease, causing demyelination and neurodegeneration of the central nervous system through autoimmune mechanisms, and is a major cause of non-traumatic disabilities which occur in youth. Symptoms of MS may vary based the site of lesions and their severity including sensory, motor, visual, cerebellar and cognitive dysfunctions [5]. Some studies have shown higher plasma activity of VWF in active phase of MS [6]. In a study by Roy et al., a coincidental rise of VWF, coagulation factor VIII, and its antigen were found in MS patients experienced a relapse or its peak of severity [7] To our knowledge, there is no study reporting co-occurrence of VWD and MS. In this case report, we present a woman with VWD who had optic neuritis many years ago and new onset right side hemiparesis which was finally diagnosed as MS.

Case Presentation

The case was a 30-year-old Iranian woman who diagnosed VWD type III referred to the neurologic clinic complaining of hemi-facial paresthesia. Her hematologic disorders were diagnosed after a fall causing facial trauma and an unstoppable episode of epistaxis at the age of 6 years. Coagulation studies were consistent with type III VWD and the results of assays were as follows: Factor VIII 2.08% (normal range: 50-150%) and VWF-Ag 3% (normal range: 61-127%). Family history revealed the same coagulation disorder in her brother and cousin. She had excessive vaginal bleeding for seven days after her menarche, and received prophylactic Humate-p for seven days monthly during her menstruations. In her past medical history, she had also experienced an episode of unilateral painless visual impairment about 8 years ago, causing problem in daily routines. Her symptom relieved within a few days and was completely recovered after one month.

She had no new complaint until her new symptoms appeared in the form of left hemi-facial (periorbital and perioral) paresthesia and paresis at the right upper and lower extremities one week prior to visiting the neurology clinic. On physical examinations, she had a normal mental status, along with a left-sided central facial palsy and left-sided weakness in the upper extremity with a strength score of 4 out of 5. When assessing the reflexes, we found that the deep tendon reflexes (2+/4 on the left and 2/4 on the right side) and plantar reflexes (mute on the left and downward on the right) were mildly asymmetric. The results of others neurological exams including sensory, cerebellum and gait all were normal.

Brain Magnetic Resonance Imaging (MRI) was requested to rule out cerebrovascular accidents secondary to her hematologic disorders. As shown in Figure 1, in the sagittal and axial planes of T2-weighted and Fluid-attenuated Inversion Recovery (FLAIR) images, there were typical oval-shaped, non-enhancing demyelinating MS plaques with Dawson's finger appearance in the periventricular and callosal area. Some of these plaques were perpendicular to the ventricle, and some abutting the ventricle. There were also one short-segment and peripherally located plaque in the cervical area (C2-3) which was not enhanced with Gadolinium. Immunoassay for IgG antibody against Aquaporin-4 receptors revealed a negative result. Finally, based on the revised

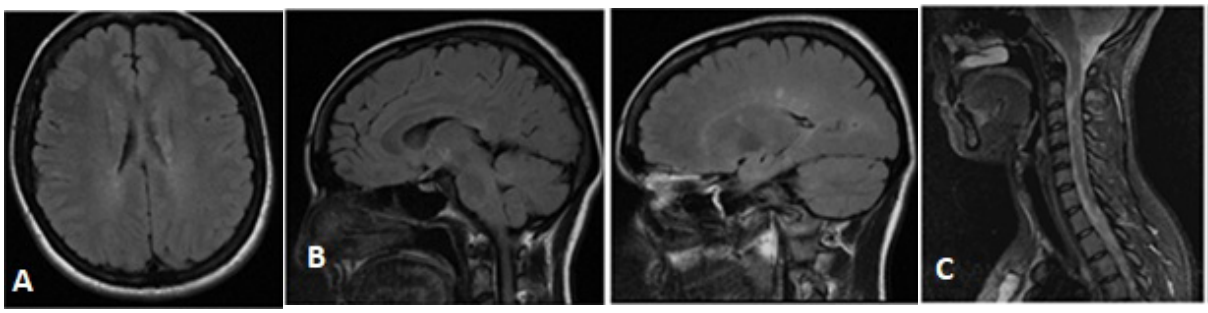

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Figure 1. FLAIR sequences of the brain MRI (A) and sagittal (B) views of the brain and sagittal view (C) of the cervical cord

They show typical demyelinating MS plaques in the periventricular, callosal and cervical (C2-3) areas, respectively.

2017 McDonald criteria [8], she was diagnosed as a new case of MS based on the dissemination on time (2 typical relapses) and dissemination in space (typical brain and cervical MRI findings).

Discussion

The MS is an autoimmune disease of the central nervous system associated with demyelination, multifocal inflammation, and axonal degeneration [9]. Certain coexisting conditions including depression, anxiety, and cerebrovascular, cardiovascular and autoimmune disorders have been reported to be more common in MS patients. These may influence the clinical course and treatment of MS [10]. In this case report study, we presented a woman with both MS and VWD. We did not find any similar case report to compare the results. Besides, it is not clear whether this coincidence is an accidental phenomenon or there is a real relationship between them.

Breakdown of Blood Brain Barrier (BBB) and transendothelial invasion of activated immune cells are proven mechanisms in the pathogenesis of MS [11]. The role of coagulation system has been identified in the pathophysiology of neurodegenerative disorders such as MS [12]. The essential roles of factor XII, thrombin and fibrinogen have been reported in the literature [13]. A study also suggested that coagulative factors can play a key role in mediating neuro-inflammation and could be used in future treatment strategies [14]. Nevertheless, the role of intrinsic pathway of coagulation is still unclear in modulation of the immune system and needs to be more clarified [15]. Several studies have demonstrated that VWF may play a natural regulatory role in cerebrovascular permeability [16, 17]. VWF is a multimeric glycoprotein which is synthesized in the endothelial cells and megakaryocytes or released by Weibel-Palade bodies in the endothelial cells and alpha granules of the platelet [18]. VWF plays two major roles in hemostasis: Platelet adhesion to sub-endothelial tissue at site of vascular injury, and protection of factor VIII from the proteolysis [18]. Kohriyama et al. evaluated the VWF and thrombomodulin in the blood of patients with MS. They revealed that VWF activity was significantly higher in patients with active disease compared to the control group which remarkably decreased following immunosuppressive therapy. They suggested that VWF can be used as a marker of BBB breakdown in MS [6].

Due to lack of strong supporting evidence on the association of MS and VWD, and the possibility of accidental coincidence between such diseases, further detailed case report studies are recommended in addition to further investigation on the molecular and cellular pathophysiological mechanisms.

Conclusion

Both type III VWD and MS were present in a woman who had been treated by Humate-p during her menstrual cycles for about seven days per month. Since there is no any report regarding the association of VWD and MS and relationship of Humate-p or VWF concentrate and development of MS, further investigations are necessary to confirm these possible associations.

Ethical Considerations

Compliance with ethical guidelines

All study procedures were in compliance with the ethical guidelines of the Declaration of Helsinki 2013. This study was approved by Ethics Committee of Shiraz University of Medical Sciences (SUMS) (Code: IR.SUMS.MED.REC.1400.175).

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Authors' contributions

Conceptualization, methodology, investigation, Writing-original draft, Writing-editing & review, and resources: All authors; Supervision: Maryam Poursadeghfard.

Conflict of interest

The authors declared no conflict of interest.

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