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Letter to the Editor

Interferon therapy: Mechanism of renal thrombotic microangiopathy in multiple sclerosis

Terapia con interferón: mecanismo de microangiopatía trombótica renal en la esclerosis multiple

Dear Editor,

Multiple sclerosis (MS) is a common and chronic autoimmune disorder in the central nervous system (CNS). It is an inflammatory and neurodegenerative disease, in which the myelin sheath on the neurons is targeted and destroyed. There are various treatment strategies for MS, including immune-suppressants, immune-modulators, and monoclonal antibodies. Immune-modulators such as Beta-interferons and glatiramer are among the primary therapies for the treatment and prevention of recurrence. Interferon beta-1 (IFN-β1) is a cytokine of the interferon family that is divided into two groups; 1a and 1b, depending on the culture medium used in the production of these drugs, which do not differ significantly in function.[1] The exact mechanism of these immune-modulators is unknown, but the current evidence suggests that they may affect the immune cells and cytokines that are involved in the pathogenesis of MS. Beta interferons can modulate the immune system by acting on cytokines released from T-helper lymphocytes and by affecting the migration of leukocytes from the brain blood barrier.[2] Common side effects of these cytokines include reaction at the injection site, flu-like symptoms such as fever, fatigue and muscle weakness, headache, and gastrointestinal disorders such as diarrhea and nausea. Common laboratory findings caused by the use of these cytokines include lymphopenia, neutropenia, and increased hepatic transaminases. One of the rare side effects of long-term use of interferons is the occurrence of Thrombotic Microangiopathy (TMA), which is rare, but due to the importance and possibility of irreversible damage, we will study it here in more details. It is hypothesized that interferons inhibit the proliferation and migration of epithelial cells and thus prevent angiogenesis, and so triggering thrombotic microangiopathy.[3,4] TMA is an obstructive and thrombotic disorder in small blood vessels characterized by systemic or local plaque aggregation, thrombocytopenia, and mechanical damage to erythrocytes and hemolytic anemia. The organ dysfunction that occurs in this complication is caused by blockage of small arteries with platelet and fibrin clots. Also, red blood cells collapse in contact with this fibrin net.[5] TMA generally includes hemolytic uremic syndrome (HUS) and Thrombotic thrombocytopenic Purpura (TTP). Complications in TTP are more likely to cause brain damage, and more kidney damage is expected in HUS. Etiologically, the manifestations of TMA are classified as follows: TTP, which occurs due to congenital or acquired deficiency of the enzyme ADAMTS 13, HUS caused by contamination with Shiga toxin released from *Escherichia coli* and atypical HUS. Atypical HUS, commonly known as secondary microangiopathy, depends on a variety of factors, including the complement system, coagulation cascade, medications, transplantation, pregnancy, etc., which can be treated by controlling the underlying factors if possible.[6,7] As mentioned, TMA has various underlying causes, but the side effects of drugs, including beta-interferons, have been suggested for several years as a possible cause of thrombotic microangiopathy. The microangiopathy induced by drugs, can caused by an acute disorder of immune system mediators or as a result of gradual and dose-dependent of the drug poisoning. During MS treatment the neurologic microangiopathy is more common and its complications include headache, seizures, and visual impairment, but microangiopathy has been reported rarely in the renal and gastrointestinal systems. Renal TMA induced by beta-interferon can be severe and very serious and even can lead to the kidney transplant. Complications of renal TMA include acute renal failure due to acute tubular necrosis, acute interstitial nephritis, uremic hemolytic syndrome, focal-segmental glomerulonephritis, and minimal change disease (MCD).[5] The patient's first clinical manifestation before hospitalization due to TMA caused by beta-interferon may include severe or malignant hypertension. Pathological changes due to kidney damage in malignant blood pressure are sometimes similar

to renal lesions caused by HUS and TTP, as would make the differentiation of the causes of the thrombotic microangiopathy difficult. Some hypotheses have been suggested about the mechanism that leads to renal thrombotic microangiopathy in the patients taking interferon beta. The pathogenesis of thrombotic microangiopathy may be due to inhibition of vascular endothelial cell growth factor activity (VEGF) in renal podocytes. The vascular endothelial growth factor stimulates signal transmission and transcription in the process of activating its second subtype receptor, which is essential for the angiogenesis process, while this process is stopped by alpha and beta interferon cytokines. So treatment with interferons due to its anti-angiogenesis effect has always been a significant cause of thrombotic microangiopathy.[5] The vascular endothelial growth factor is also a major factor in regulating the production of nitric oxide in epithelial cells, which plays a key role in dilating blood vessels and preventing thrombosis.[8] It should be noted that the duration of interferon treatment plays a role in vascular endothelial toxicity. According to a study of MS patients, microangiopathy caused by treatment with beta interferons may occur on average after 7 years. Although the role of vascular endothelial growth factor in renal physiology has not been fully explained, its role in the pathophysiology of several renal diseases has been reported, so the cumulative effect of interferon may be effective in the development of renal lesions.[5] A hypothesis of the role of antiphospholipid antibodies in the induction of uremic hemolytic syndrome by alpha-interferon has been suggested. Also in a study, anti-phospholipid antibodies were detected in patients with multiple sclerosis since they were treated with beta-interferon revealed that the beta-interferon therapy could also induce antiphospholipid antibodies and occurrence of microangiopathic presentations. In patients treated with interferon beta, anti-ADAMTS13 IgG synthesis has been reported rarely, and due to the role of this enzyme deficiency in thrombocytopenic purpura, it may be another mechanism for the occurrence of renal microangiopathic presentations in patients with MS.[5,9] TMA can occur in MS patients treated with beta-interferon even after years of appropriate response to the drug, so symptoms such as headaches and high blood pressure should be taken seriously and the patient should be monitored for renal problems. Any suspicious symptoms in these patients should be discontinued interferon treatment and other immunomodulators should be replaced to control the disease.

REFERENCES

1. Sirbu CA, Dantes E, Plesa CF, Axelerad AD, Ghinescu MC. Active pulmonary tuberculosis triggered by interferon beta-1b therapy of multiple sclerosis: four case reports and a literature review. Medicina. 2020;56:202, http://dx.doi.org/10.3390/medicina56040202.
2. Filippini G, Del Giovane C, Vacchi L, D'Amico R, Di Pietrantonj C, Beecher D, et al. Immunomodulators and immunosuppressants for multiple sclerosis: a network meta-analysis. Cochrane Database Syst Rev. 2013:CD008933, http://dx.doi.org/10.1002/14651858.CD008933.pub2.
3. Ozturk M, Basoglu F, Yilmaz M, Ozagari AA, Baybas S. Interferon β associated nephropathy in a Multiple Sclerosis patient: a case and review. Mult Scler Relat Disord. 2016;9:50–3, http://dx.doi.org/10.1016/j.msard.2016.06.012.
4. Malekzadeh MM, Alizadeh R, Aghsaeifard Z, Sahraian MA. Thrombotic microangiopathy in interferon-beta-treated multiple sclerosis patient. Clin Case Rep. 2020;8:1061–4, http://dx.doi.org/10.1002/ccr3.2808.
5. Mahe J, Meurette A, Moreau A, Vercel C, Jolliet P. Renal thrombotic microangiopathy caused by interferon beta-1a treatment for multiple sclerosis. Drug Des Devel Ther. 2013;7:723–8, http://dx.doi.org/10.2147/DDDT.S42138.
6. Nishio H, Tsukamoto T, Matsubara T, Okada Y, Takahashi R, Yanagita M. Thrombotic microangiopathy caused by interferon β-1b for multiple sclerosis: a case report. CEN Case Rep. 2016;5:179–83, http://dx.doi.org/10.1007/s13730-016-0220-7.
7. Abe T, Sasaki A, Ueda T, Miyakawa Y, Ochiai H. Complement-mediated thrombotic microangiopathy secondary to sepsis-induced disseminated intravascular coagulation successfully treated with eculizumab: a case report. Medicine (Baltimore). 2017;96:e6056, http://dx.doi.org/10.1097/MD.0000000000006056.
8. Omoto S, Utsumi T, Matsuno H, Terasawa Y, Iguchi Y. Thrombotic microangiopathy presenting with intestinal involvement following long-term interferon-β1b treatment for multiple sclerosis. Intern Med. 2018;57:741–4, http://dx.doi.org/10.2169/internalmedicine.9326-17.
9. Allinovi M, Cirami CL, Caroti L, Antognoli G, Farsetti S, Amato MP, et al. Thrombotic microangiopathy induced by interferon beta in patients with multiple sclerosis: three cases treated with eculizumab. Clin Kidney J. 2017;10:625–31, http://dx.doi.org/10.1093/ckj/sfw143.

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