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REVIEW

Thrombotic microangiopathy in Interferon Beta treated multiple sclerosis patients: Review of literature and report of two new cases

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Abstract
Beta interferons (IFN-β) were the first approved disease modifying therapies (DMTs) for relapsing-remitting multiple sclerosis (RRMS) and are still the most-widely prescribed medications for this disease. Despite good overall long-term safety data with prolonged use of this group of drugs, they can rarely cause serious and sometimes life threatening adverse effects. In this article we report two cases of thrombotic microangiopathy occurring during prolonged use of IFN-β and review the available literature on this topic.

Contents

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1. Introduction

Multiple sclerosis (MS) is a chronic and potentially disabling disease of the central nervous system and is the leading cause of non-traumatic neurological disability in young adults. Interferon β-1b (Betaseron/Betaferon®) was the first DMT to get regulatory approval in 1993 following publication of the initial phase III trial (The IFNB Multiple Sclerosis Study Group, 1993). Subsequently intramuscular (Avonex®) and subcutaneous (Rebif®) Interferon Beta-1a DMTs were also introduced (Rudick et al., 2001; PRISMS (Prevention of Relapses and Disability by Interferon Beta-1a Subcutaneously in Multiple Sclerosis) Study Group, 1998).

Common side effects of IFN-β include flulike symptoms including myalgia, fever, fatigue, headache, chills, nausea and vomiting and injection site reactions with the subcutaneous products. They can also result in worsening of spasticity (Bramanti et al., 1998). Regular monitoring of complete blood counts (CBC) and liver enzymes is recommended to screen for potential leukopenia, thrombocytopenia and hepatotoxicity. Despite these side-effects, serious complications are relatively rare and IFN-βs are generally considered to be safe. Nevertheless, as with all medications, rare serious and/or life-threatening side effects have been reported.

Thrombotic microangiopathy (TMA) describes a pathological process of microvascular thrombosis, consumptive thrombocytopenia and microangiopathic hemolytic anemia (MAHA), leading to end-organ ischemia and infarction affecting particularly the kidney and brain and patients may present with acute renal failure and/or cerebral dysfunction (Barbour et al., 2012).

It is a rare spectrum of disorders with a vast array of different causes (drugs, toxins, infections, pregnancy, and autoimmunity) that damage the endothelium via multiple and varied mechanisms (Radhi and Carpenter, 2012). TMA is common to hemolytic uremic syndrome (HUS), thrombotic thrombocytopenic purpura (TTP) and other disorders including malignant hypertension.

Although MS has association with other autoimmune disorders including idiopathic thrombocytopenic purpura (Sahraian and Eshaghi, 2010), there are no reports of TMA in treatment-naïve MS patients.

Microangiopathic complications of IFN-β therapy have been reported in hepatitis C (Ubara et al., 1998), and also in numerous patients treated with alpha interferons for various medical conditions (Rachmani et al., 1998; Al-Zahrani et al., 2003; Zuber et al., 2002). We present two new cases of thrombotic microangiopathy (TMA) during long-term treatment with IFN-β and will review other reported cases of similar condition in MS patients treated with IFN-β.

2. First case

A 52 year old right-handed Caucasian male with long standing history of RRMS diagnosed in 1990 had been on Betaseron since 1998.

Despite having significant gait and cognitive issues his disease had been relatively stable on DMT. Complete blood counts and liver enzyme testing every 6 months had been unremarkable since he first started on Betaseron. However, on routine blood work in February 2012 it was found that his hemoglobin has dropped from 134 to 114, and platelet count from 166,000 to 63,000/mm^3. He was feeling short of breath and wheezing and was advised to stop his Betaseron and seek immediate medical attention in the emergency room (ER). The patient elected to go to a Walk-in clinic where he was noticed to have a high systolic blood pressure of 190 and he was started on Nifedipine XL. Three days later he was brought to the ER after having a generalized tonic-clonic seizure. His blood pressure was 203/123 on admission and he was afebrile. Brain CT was normal. A chest X-ray showed pulmonary edema. His laboratory workup on admission is shown in Table 1.

Table 1 Laboratory findings in our cases at admission.

First case	Second case
• Urea: 27.9 mmol/L (2.7-8.1) • Creatinine: 297 μmol/L (44-106) • eGFR: 10 • AST: 61 (<40) • ALT: normal • Hb: 105 g/L • WBC: 14,100/mm^3 • Platelet: 22,000/mm^3 • Reticulocyte count: 105 (20-75) • INR, APTT: normal • LDH: 637 (120-230) • 24 h Urine metanephrine: normal (0.10), normetanephrine: 0.40 (normal<0.35) • UA was bland	• Mild elevation of liver enzymes • LDH: 631 (63-200) • Hb: 147 g/L • WBC: 17,500/mm^3 (80% neutrophils) • Platelet: 122,000/mm^3 • INR: 0.9, APTT: 29.4 • Urinanalysis: non-nephrotic range proteinuria, microscopic hematuria, occasional hyaline casts • Random sample of urinary metanephrine: normal • Normetanephrine was mildly elevated=0.58 (normal<0.40). • Creatinine: normal

The patient was diagnosed with renal failure and microangiopathy secondary to malignant hypertension (HTN) or thrombotic thrombocytopenic purpura (TTP). He received supportive treatment including plasma exchange and hemodialysis and was discharged after a prolonged admission. At follow-up 1 year later, he had not regained kidney function and remained on hemodialysis and was still taking a calcium channel blocker for hypertension.

3. Second case

A 41 year old right handed Caucasian female with history of RRMS since 1997 had been on Rebif 44 mcg since 2001 with good response and no major complications. In November 2012 she started to develop daily bilateral fronto-temporal headaches of moderate intensity. She presented to the ER in early January 2013 because of worsening headache. At triage she had two generalized tonic-clonic seizures. Her blood pressure was 231/150. Platelet count was 122,000/mm^3. The patient was admitted to the intensive care unit.