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Case report

Posterior Reversible Encephalopathy Syndrome, Multiple Sclerosis and interferon therapy: Association, coincidence or convoluted interplay?

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ABSTRACT

Background: Posterior reversible encephalopathy syndrome (PRES) has only rarely been reported in patients with multiple sclerosis (MS).

Methods: Case report of a patient with relapsing remitting (RR) MS patient on interferon (INF) treatment, who developed posterior fossa PRES.

Results: A 46-year-old male diagnosed with RR MS in 2010 was placed on INF beta-1a therapy. He remained in clinical remission for seven years. He then presented with headache of one month duration and worsening upper extremity ataxia. Cranial MRI revealed two new enhancing cerebellar lesions (one with tumefactive features). Within the next 10 days the patient developed severe holocephalic headache, vomiting, altered consciousness and gait instability. Urgent brain MRI revealed diffuse hyperintense lesions in T2WI and FLAIR sequences in bilateral cerebellar hemispheres and the right thalamus, with marked swelling, increased diffusivity indicative of vasogenic edema and patchy-nodular enhancement, while smaller lesions were also found in posterior temporal, parietal and occipital lobes. Severely elevated blood pressure was noted. Treatment with hypertonic agents, esmolol drip and IV steroids was instituted, resulting in remarkable improvement within the next several days. Repeat MRI showed almost complete resolution of the cerebellar lesions. Interferon beta was discontinued and blood pressure remained well controlled.

Conclusions: Patients with RR MS on IFN beta therapy can develop PRES via the combination of hypertension and endothelial dysfunction by IFN, even when stable on this treatment. Neurologists should be keen to differentiate the appearance of PRES lesions from those of fulminant MS relapse, opportunistic infections or malignancy.

1. Introduction

Posterior reversible encephalopathy syndrome (PRES) refers to a neurological disorder of (sub)acute onset characterized clinically by a variety of symptoms, quite distinctive brain imaging findings most likely reflecting vasogenic edema and generally favourable prognosis (Fugate and Rabinstein, 2015). The causes of PRES are numerous and diverse, with a number of them being iatrogenic. The pathophysiology of PRES is still the focus of debate. One of the main hypotheses presumes impaired cerebral autoregulation leading to disruption of the blood–brain barrier (BBB), while the other indicates that development of PRES is precipitated by arginine vasopressin (AVP) axis overstimulation leading to vasopressin V1a receptor activation and consequent cerebral vasoconstriction, endothelial dysfunction, and brain edema (Largeau et al., 2019). Here, we describe the case of an MS patient who developed PRES, following long-term use of interferon beta-1a.

2. Case report

A 46-year-old male was diagnosed with RR MS in 2010, at which point treatment with interferon (IFN) beta-1a three times weekly was initiated. The patient experienced sustained clinical remission. He was an active smoker and had underlying depression treated with...
bupropion and venlafaxine. He had no history of hypertension, diabetes mellitus, renal or hepatic disease, organ transplantation, treatment with immunosuppressive agents, use of vasoactive substances, endocrinopathies or other major co-morbidities.

In January 2017 he presented with headache of one month duration and worsening ataxia of the upper extremities. Cranial MRI revealed two new enhancing cerebellar lesions (one with tumefactive features).

Ten days later the patient developed severe holoccephalic headache, vomiting, altered consciousness and gait instability. In the emergency department, he was found to be drowsy, but not confused or disoriented. Arterial blood pressure was 210/140 mmHg. Fundoscopy revealed no papilledema. On neurologic examination, relatively mild clinical signs were elicited (mild vertical nystagmus, gait instability and upper limb ataxia).

Urgent brain MRI revealed diffuse hyperintense lesions in T2WI and FLAIR sequences in bilateral cerebellar hemispheres, with marked swelling, increased diffusivity and patchy-nodular enhancement, leading to effacement of the fourth ventricle and dilatation of the third and lateral ventricles. Similar lesions were seen in the juxtacortical and deep white matter of the posterior temporal, occipital and posterior parietal lobes, as well as the right thalamus (Fig. 1).

Routine admission laboratory tests were unremarkable. No renal or hepatic disorder were found.

Treatment with hypertonic saline (3%), mannitol and IV steroids (methylprednisolone) was instituted. Hypertension was initially controlled with esmolol continuous intravenous infusion with amiodipine, metoprolol, spironolactone and perindopril added later. A remarkable clinical improvement was observed within the next ten days. On discharge, the patient returned to his previous neurological status with only minor neurological signs remaining related to baseline MS deficits. Blood pressure was maintained under 140/85 mm Hg with amiodipine 10 mg twice daily, spironolactone 50 mg daily and beta-blocker (metoprolol 50 mg twice daily). Interferon beta 1a was discontinued.

Repeat MRI undertaken at 6 weeks, showed almost complete resolution of the cerebellar, thalamus and temporoparietooccipital lesions, with normal size of the ventricular system (Fig. 2). Lumbar puncture revealed an opening pressure of 21 cm of water and yielded 10 white blood cells per mm$^3$, normal values of glucose and protein, normal IgG Index, presence of pattern III oligoclonal bands and negative bacterial and viral cultures thus ruling out infectious causes. After 12 weeks, treatment with teriflunomide 14 mg was initiated, whereas antihypertensive therapy was changed to 40 mg olmesartan, 5 mg nebivolol and 10 mg amiodipine daily. Follow-up MRI studies at 12 and 24 months showed only lesions attributed to multiple sclerosis, whereas the Expanded Disability Status Scale (EDSS) score has remained stable at 2.00. At that time blood pressure was efficiently controlled with a combination 20 mg olmesartan and 5 mg amiodipine daily.
3. Discussion

IFN beta (1a or 1b) has been used as a first line therapy for RR MS for over 20 years. All interferon products are generally considered safe and well-tolerated with an acceptable side-effect profile. Serious adverse events such as thrombotic microangiopathy (TMA) (Vsoughi and Marriott, 2014) or pulmonary hypertension (Fok et al., 2016) have been reported very rarely. For the former, a causal association with INF use has been demonstrated recently, since it was shown that type I interferons have dose-dependent toxic effect on the microvasculature through endothelial dysfunction (Kavanagh et al., 2016). The potential mechanism of action in the latter is that of IFN beta stimulating the vasocostriction cascade causing fibromuscular intimal proliferation of arterioles and arteries. This resembles the postulated mechanism of IFN beta induced vasocostriction causing Raynaud’s phenomenon and livedo reticularis. As such it may explain a case of IFN beta-1b-related arterial hypertension (Modrego and Gazzola, 2012) and could be a contributing factor for the development of hypertension in our patient. Chronic IFN beta-1a treatment could also have led to endothelial dysfunction and disruption of BBB integrity, resulting thus in the development of PRES either in isolation or by making our patient much more susceptible to the effect of blood pressure elevations.

PRES is a clinicoradiological syndrome characterized by acute cerebral endotheliopathy with consecutive disruption of the BBB and vasogenic edema. PRES is most often associated with medical conditions such as hypertensive crisis, organ transplant, malignancy, infection, autoimmune, endocrine or renal disorders, eclampsia and medications such as immunosuppressive, chemotherapeutic, cytotoxic and stimulant agents (Fugate and Rabinstein, 2015). In our patient either by history or after an extensive diagnostic work up most of the aforementioned conditions had been ruled out.

PRES only rarely has been reported in MS patients and usually as a secondary manifestation of thrombotic microangiopathy (Vsoughi and Marriott, 2014). Morrow et al. described a PRES case secondary to high dose corticosteroid use for an MS relapse in a patient without a history of hypertension and with no other secondary cause of hypertension identified (Morrow et al., 2015). With the exception of fingolimod, none of the other new MS disease modifying therapies have been linked to PRES. Linda et al. described occurrence of PRES in association with fingolimod treatment (Linda and von Heijne, 2015), with a total of 30 cases of PRES having been reported from post-marketing data sources by the manufacturing company (Novartis Data on File).

PRES diagnosis is not always straightforward and the differential diagnosis may be quite extensive especially in atypical cases or in immunosuppressed patients. Infectious, autoimmune or paraneoplastic encephalitis, malignancies (lymphoma, gliomatosis cerebri, metastatic disease), Progressive Multifocal Leukoencephalopathy (PML), CNS vasculitis, toxic leukoencephalopathy, osmotic demyelination syndrome and Acute Demyelinating Encephalomyelitis (ADEM) should be considered among other entities in the differential diagnosis (Fugate and Rabinstein, 2015). The symptoms and signs are nonspecific in isolation, and the brain imaging findings, though characteristic, are not pathognomonic and do not exclude alternative diagnoses. It should also be kept in mind that the diagnosis of PRES does not mainly depend on the imaging findings, but both the clinical context and the judgment of the clinician are crucial for making the correct diagnosis.

In our patient, IFN beta-1a treatment and hypertension, and perhaps their interplay, were the only risk factors found to be potentially linked with PRES. The absence of other major organ target involvement implies that hypertension was not long standing. Also after INF beta therapy cessation hypertension was relatively easily controlled, which argues against the fact that previously undetected essential hypertension had triggered PRES.

In conclusion, it is plausible that in our patient chronic interferon use may have contributed to the development of hypertension, which resulted in PRES. Another possibility is that endothelial dysfunction and microvascular toxicity induced by chronic interferon beta therapy may facilitated PRES development. In such patients, the appearance of new subcortical, cortical or posterior fossa lesions with atypical features should always raise suspicion for the presence of PRES, but also should be thoroughly investigated to be differentiated from those of fulminant MS relapse, opportunistic infections (such as PML) or malignancy.

References