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LETTER TO THE EDITOR

Intravenous immunoglobulin-induced aseptic meningitis in a patient with Miller Fisher syndrome

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Dear Editor,

Intravenous immunoglobulin (IVIG) is an established treatment for multiple conditions, including Miller Fisher syndrome (MFS). Although IVIG is considered safe, serious adverse effects may occur during or shortly after IVIG administration. Herein, we report a case of aseptic meningitis following IVIG treatment for MFS. To the best of our knowledge, no such association has been previously reported in a patient with MFS.

A 28-year old woman was admitted with a 3-day history of periorbital headache, vertigo, nausea, diplopia and impaired gait. Medical history included episodic migraine and recent flu-like symptoms. Clinical examination showed severe extrinsic ophthalmoplegia, bilateral cerebellar limb ataxia, diffuse areflexia and unsteady gait. Upon admission, laboratory workup, brain computed tomography and CSF studies were normal. Brain and spinal magnetic resonance imaging (MRI) were unremarkable. Electroneuromyography showed the absence of F-waves for the peroneal nerve. Autoimmune serologies revealed positive anti-GQ1b antibodies (titer superior to 1/100) and infectious workup was positive for influenza A IgG. Based on the clinical triad (ataxia, areflexia and ophthalmoplegia) and the laboratory results, Miller Fisher syndrome secondary to influenza A infection was diagnosed. Thus, the patient was promptly started on IVIG at a dose of 2 g/kg over 5 consecutive days.

Treatment onset was followed by improvement of ophthalmoplegia and ataxia. On the other hand, the patient complained of invalidating nausea and persistent headache. Nuchal rigidity and mental slowing were noted on clinical examination on the fourth day of therapy. Control CSF studies revealed pleocytosis (305 cells/µl; 56% lymphocytes), increased protein levels (76 mg/dl) with normal glucose and lactate levels. Multiplex polymerase chain reaction performed on CSF was negative. IVIG-induced aseptic meningitis was suspected and was further supported by the delayed appearance of drug-induced dyshidrosis on the patient's palms and soles in the days following the IVIG course. Symptomatic treatment was initiated. Complete neurological recovery was observed within 10 days of IVIG treatment. Follow-up CSF studies showed lower pleocytosis (56 total cells/µl; 97% lymphocytes) and higher protein levels (96 mg/dl). Follow-up electroneuromyography after clinical recovery showed a persisting aspecific reduction of F-waves persistence.

Intravenous immunoglobulin (IVIG) consists of intact IgG molecules derived from pooled plasma of healthy human donors. It is used in the treatment of hematological, inflammatory and auto-immune diseases, among which neurological disorders including Guillain–Barré syndrome, chronic inflammatory demyelinating polyneuropathy and myasthenia gravis. Despite a favorable safety profile, certain serious adverse events have been associated with IVIG infusions, such as anaphylaxis, Stevens–Johnson syndrome, thromboembolic events, acute encephalopathy, posterior reversible encephalopathy syndrome and aseptic meningitis. Drug-induced aseptic meningitis (DIAM) must be considered in case of fever or meningeal syndrome appearing after treatment onset. It typically appears within 48 h of IVIG infusion but may be observed up to four months after [1]. CSF studies show pleocytosis (as high as several thousands of cells/µl, with a mean of 300 cells/µl), with a frequent neutrophilic predominance (although mixed or lymphocytic pleocytosis are also encountered), and negative bacterial or viral investigations [1, 2]. CSF protein levels are often elevated, while glucose levels are generally normal [1]. Brain imaging is unremarkable. DIAM has also been associated with NSAIDs, antimicrobials, vaccines, monoclonal antibodies and antiepileptic drugs [2]. It is thought to occur in 0.6–1% of patients receiving IVIG, although this rate

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is probably underestimated because of study design variations and underreporting of adverse events [3]. Risk factors include female sex, high-dose IVIG infusion (i.e., 1–2 g/kg over 3–5 days), dehydration, first IVIG course, history of migraine or IVIG-induced DIAM, and underlying connective tissue disease (e.g. systemic lupus erythematosus) [3, 4]. The pathophysiological mechanism of DIAM remains unclear but is thought to originate either from direct leptomeningeal toxicity, either from hypersensitivity through complex immunological pathways involving complement activation and/or cytokine release [1].

In our case, the only predisposing condition for DIAM was a history of migraine. Extensive laboratory studies brought no argument for an underlying connective tissue disease. To the best of our knowledge, IVIG-induced DIAM in a patient with MFS patient has not been previously reported. Periorbital headache is a clinical variant of MFS and may precede gait abnormalities [5]. Its presence upon our patient's admission contributed to a somewhat delayed detection of IVIG-induced DIAM (i.e., on the fourth day of therapy). Bickerstaff encephalitis was also considered in our differential diagnosis, but it seemed less likely based on the patient's preserved consciousness, the reassuring brain MRI and the timing of symptoms relative to IVIG initiation.

DIAM is a self-limiting disorder that can be managed with symptomatic treatment. If IVIG discontinuation presents a health risk, infusion slowing, course fractioning or switch to subcutaneous injection may be considered [1]. Whether the administration of analgesics, antihistamines and hydration before treatment onset prevents DIAM remains debated.

As IVIG is increasingly used in the treatment of neurological disorders, clinicians should be aware of possible adverse events in order to avoid unnecessary explorations and treatments.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest related to this submission.

Informed consent Consent of the patient was obtained prior to submission.

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