

Case Report

Acute aseptic meningitis due to intravenous immunoglobulin therapy in Guillain–Barré syndrome

Rajendra Singh Jain, Sunil Kumar*, Rakesh Aggarwal and Jagdeesh Chandra Kookna

Department of Neurology, Sawai Man Singh Medical College, Jaipur, Rajasthan, India

*Correspondence address. Department of Neurology, Sawai Man Singh Medical College, Jaipur, Rajasthan, India.
Tel: +919571414284; E-mail: doc.kumarsunil@hotmail.com

Received 21 August 2014; revised 29 September 2014; accepted 2 October 2014

The majority of adverse reactions of intravenous immunoglobulin (IVIG) therapy are mild, transient and self-limiting with potentially serious complications occurring in <5% of patients. IVIG-associated transient aseptic meningitis is one such rare adverse effect, which has been seldomly described in the literature. We report a case of aseptic meningitis due to IVIG therapy in a Guillain–Barré syndrome (GBS) patient. The cerebrospinal fluid analysis revealed high cell counts with predominance of lymphocytic cells, raised protein, normal glucose level and no growth of the organisms on culture. The patient improved with supportive care such as intravenous fluids and analgesics without neurological complications. This case emphasizes the importance of recognizing IVIG-associated complications like aseptic meningitis in GBS patients.

INTRODUCTION

Intravenous immunoglobulin (IVIG) therapy is the recommended treatment in Guillain–Barré syndrome (GBS) patients with well-documented efficacy. The majority of adverse reactions of IVIG therapy are mild, transient, self-limiting and commonly include headache, nausea, vomiting, myalgia, low backache, tachycardia, mild grade fever and flushing. However, potentially serious adverse effects are known to occur in <5% of patients receiving IVIG therapy [1]. These include thromboembolism, transverse venous sinus thrombosis, myocardial infarction, acute stroke, acute encephalopathy, posterior reversible encephalopathy syndrome, anaphylactic reaction, haemolytic anaemia, hepatitis, acute renal failure and serum sickness [2]. According to Kemmotsu *et al.* [3], IVIG-associated transient aseptic meningitis is an uncommon phenomenon occurring in ~1% of patients. We describe a case of aseptic meningitis following IVIG therapy for GBS, with the aim to apprise clinicians of this rare under recognized but potentially manageable adverse effect.

CASE REPORT

A 14-year-old boy presented with a 2-day history of acute onset pure motor, progressive, symmetric, areflexic, flaccid

quadriplegia without bladder/bowel, bulbar, respiratory involvement or autonomic dysfunction. There was no previous history of fever, diarrhoea, respiratory tract infection, any toxin exposure or dog bite. A clinical diagnosis of GBS was made with a Hughes disability scale of 4. Nerve conduction study on right ulnar, bilateral median, bilateral tibial and bilateral peroneal nerves showed a pure motor, predominantly demyelinating pattern. Electrocardiogram and serum potassium level were normal. Urinary porphobilinogen was negative. Clinical profile and electrophysiological parameters fulfilled the Asbury criteria of GBS. The patient was started on IVIG therapy according to the recommended dose of 0.4 g/kg/day. Since the patient's body weight was 45 kg, a total of 90 g IVIG was planned to be given over 5 days in divided doses.

On the fourth day, after receiving 72 g of IVIG infusion, the patient developed progressively worsening headache, neck pain and recurrent episodes of vomiting. There was no history of abnormal behaviour, loss of consciousness or visual symptoms. His temperature was normal and meningeal signs including neck rigidity, Kernig's and Brudzinski's signs were positive. Bilateral fundi were normal. There were no other focal neurological signs.

Haemogram (haemoglobin, total leukocyte counts, differential leukocyte counts, peripheral blood film examination

and erythrocyte sedimentation rate) and blood biochemistry including liver function tests, renal function tests, lipid profile and thyroid function tests were normal. Blood culture was sterile. X-ray chest was normal and Mantoux test was negative. Serum human immunodeficiency virus (HIV) ELISA tests were non-reactive and hepatitis viral markers including hepatitis B (HBV), hepatitis C (HCV) and hepatitis E (HEV) were negative. Lumbar puncture showed normal opening pressure (136 mmH₂O), and cerebrospinal fluid (CSF) analysis revealed pleocytosis (total cell counts: 180 cell/dl) with 85% lymphocytes and 15% polymorphs without any eosinophils. CSF protein was raised (110 mg/dl) with normal sugar (56 mg/dl) and chloride (111 mEq/l) levels. CSF gram stain, acid-fast bacillus stain (AFB) stain, KOH (potassium hydroxide) preparation, India ink and CSF culture for bacteria and fungi were negative. CSF polymerase chain reaction (PCR) for tuberculosis (TB), herpes simplex virus (HSV-1 and HSV-2), Epstein Barr virus (EBV), varicella and cytomegalovirus (CMV) were negative. Gadolinium contrast-enhanced magnetic resonance imaging (MRI) of brain showed no abnormality (Fig. 1).

The patient was managed symptomatically with hydration and analgesics without any specific antibiotic or antiviral therapy. A very slow infusion of IVIG was started under strict supervision and continued till completion of full dose. The patient's condition improved with disappearance of the signs of meningeal irritation (neck rigidity, Kernig's and Brudzinski's signs) over the next 2 days. The patient was finally discharged in stable condition with Hughes GBS disability scale of 1. He recovered completely without any neurological sequelae. He was asymptomatic at 4 months of follow-up.

DISCUSSION

The exact pathophysiology of IVIG-induced aseptic meningitis is not clear. The various postulated mechanisms include direct toxic effect, immunological drug hypersensitive reaction, allogenic immune reaction, hypersensitivity reaction to various stabilizing agents and cytokine release triggered by the therapy [4–6]. Wada *et al.* [7] showed the excitotoxic effect of IVIG in acute encephalopathy following IVIG therapy. Other possible explanation can be the leaking of small quantities of IVIG into the CSF, thereby causing inflammatory reaction and osmotic shifts. Anti-neutrophil antibodies in some IVIG brands may also play part in pathogenesis of IVIG-induced aseptic meningitis.

In our patient, the diagnosis of IVIG-associated aseptic meningitis was based on following points. First, there was a strong temporal relationship between onset of symptoms suggestive of aseptic meningitis and high-dose IVIG therapy. Secondly, no other cause of meningitis could be found even after extensive investigations and finally, there was spontaneous improvement of symptoms within few days. However, the possibility of viral meningitis could still be present, but the absence of prodromal symptoms and no identifiable viral markers ruled it out.

Most of the literature report appearance of symptoms within 48 h of initiation of IVIG therapy; however, in our case, aseptic meningitis developed after 72 h. According to Jarius *et al.* [8], IVIG-induced aseptic meningitis was frequently associated with polymorphic pleocytosis in the CSF examination, but in our patient lymphocytic pleocytosis was seen. The risk factors for IVIG-associated aseptic meningitis include rapid, high-dose infusion of IVIG and previous history of migraine. The likely mechanism in migraine is

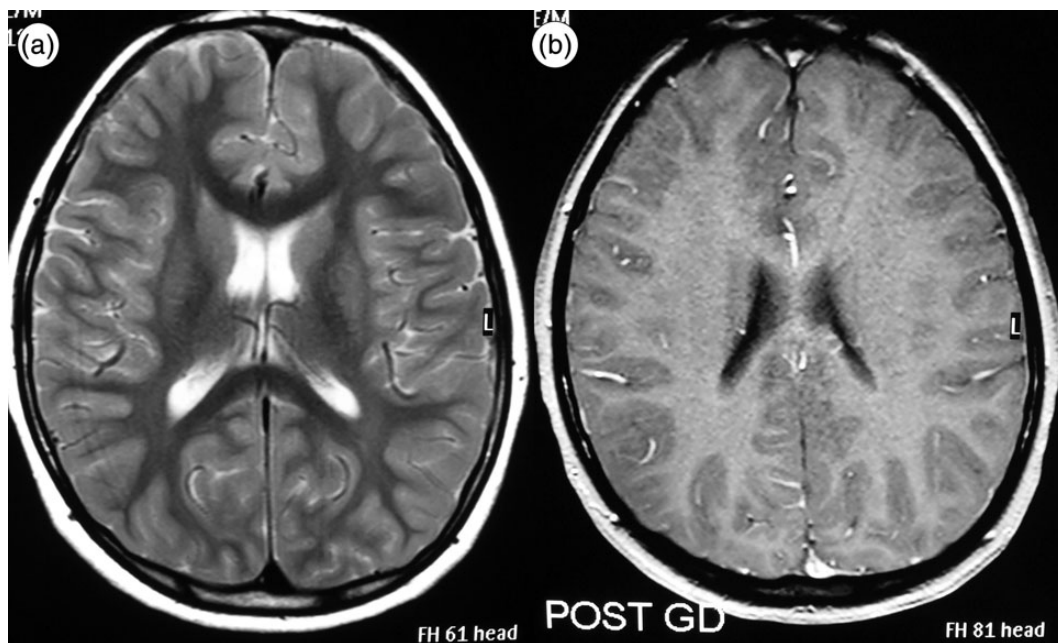


Figure 1: Gadolinium contrast-enhanced MRI brain was normal. There was no structural lesion or meningeal enhancement seen. T2W (a) and Gadolinium contrast-enhanced (b) MRI brain.

increased cerebrovascular sensitivity, although they lack signs of meningeal irritation (neck stiffness) [6]. Slower infusion rate, proper hydration and antihistamines may help to prevent mild adverse reactions to IVIG therapy. Systemic steroid may be required in severe cases [9]. Our patient improved without any neurological complications under strict supervision.

To conclude, headache and fever are well-recognized side effects of IVIG therapy, but patient can also present with transient, self-limiting, acute aseptic meningitis. Early recognition and management is important to prevent permanent neurological sequelae. Even if the patient develops IVIG-associated aseptic meningitis, IVIG therapy need not be withheld and should be continued at a slow infusion rate, with proper hydration, antihistamines and analgesics, as it is a life-saving drug for GBS. A high index of clinical suspicion should be kept for IVIG-induced aseptic meningitis and should be confirmed by careful neurological examination and CSF analysis as it is potentially manageable.

CONFLICT OF INTEREST STATEMENT

None declared.

REFERENCES

1. Duhem C, Dicato MA, Reis F. Side effects of intravenous immunoglobulins. *Clin Exp Immunol* 1994;**97**(Suppl 1):79–83.
2. Hamrock DJ. Adverse events associated with intravenous immunoglobulin therapy. *Int Immunopharmacol* 2006;**6**:535–42.
3. Kemmotsu Y, Nakayama T, Matsuura H, Saji T. Clinical characteristics of aseptic meningitis induced by intravenous immunoglobulin in patients with Kawasaki disease. *Pediatr Rheumatol* 2011;**9**:28.
4. Preminger-Shapiro R, Nussinovitch M, Soen G, Varsano I. Aseptic meningitis: a frequent side-effect of intravenous immunoglobulin? *Eur J Pediatr* 1995;**154**:866–7.
5. Incecik F, Hergüner MO, Altunbasak S, Yıldızdas D. Reversible posterior encephalopathy syndrome due to intravenous immunoglobulin in a child with Guillain-Barré syndrome. *J Pediatr Neurosci* 2011;**6**:138–40.
6. Sekul EA, Cupler EJ, Dalakas MC. Aseptic meningitis associated with high-dose intravenous immunoglobulin therapy: frequency and risk factors. *Ann Intern Med* 1994;**121**:259–62.
7. Wada A, Yoshida R, Oda K, Fukuba E, Uchida N, Kitagaki H. Acute encephalopathy associated with intravenous immunoglobulin therapy. *AJNR Am J Neuroradiol* 2005;**26**:2311–5.
8. Jarius S, Eichhorn P, Albert MH, Wagenpfeil S, Wick M, Belohradsky BH, et al. Intravenous immunoglobulins contain naturally occurring antibodies that mimic antineutrophil cytoplasmic antibodies and activate neutrophils in a TNF α -dependent and Fc-receptor-independent way. *Blood* 2007;**109**:4376–82.
9. Jayabose S, Mahmoud M, Levendoglu-Tuga O, Sandoval C, Ozkaynak F, Giamelli J Jr, et al. Corticosteroid prophylaxis for neurologic complications of intravenous immunoglobulin G therapy in childhood immune thrombocytopenic purpura. *J Pediatr Hematol Oncol* 1999;**21**:514–7.