

SHORT REPORT

Transverse sinus thrombosis and IVIg treatment: a case report and discussion of risk–benefit assessment for immunoglobulin treatment

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A 54 year old woman presented with symptoms resulting from a thrombosis of the lateral transverse and sagittal sinuses the day after an infusion of intravenous immunoglobulin (IVIg) replacement treatment. She had previously suffered a milder episode after IVIg. Following recurrent bacterial chest infections and sinusitis for more than 40 years, a diagnosis of IgG1 deficiency had been made two years earlier, after exclusion of other causes. She made a good recovery from the thrombosis but high platelet counts were investigated and primary thrombocythaemia was diagnosed. Investigation of humoral immunity revealed protective amounts of IgG antibodies to pathogens, and because the previous IgG1 deficiency had resolved IVIg infusions were not restarted. She made a good response to treatment with hydroxyurea, with improvement of the headaches and lowering of the platelet counts. Prophylactic antibiotics reduced the number of bacterial chest infections and nasal corticosteroids improved the chronic sinusitis. This case is presented to highlight the need to look for other contributing factors for severe recurrent headaches after IVIg treatment, and to consider the risk of thrombosis even when replacement doses of IVIg are used. It is also important to emphasise the need to ensure that an isolated IgG subclass deficiency is not transient; that failure to produce specific IgG antibodies to immunisation and/or exposure antigens is confirmed, thus meeting the criteria for the diagnosis of primary antibody deficiency. A thorough risk–benefit assessment is essential before blood product treatment is started.

The indications for the therapeutic use of immunoglobulin preparations continue to expand. The use of these products should always involve a risk–benefit assessment, to be sure that not only are the indications met but that the likelihood of serious complications has been considered. A risk–benefit assessment details the therapeutic benefit of such treatment in the patient and this is balanced against the particular level of risk of adverse effects of the treatment.

“The risks involved fall into two main categories: those associated with the infusion of intravenous immunoglobulin and the longer term risks of blood borne viruses or currently unknown organisms”

Indications for intravenous immunoglobulin (IVIg) treatment include replacement treatment in patients with confirmed antibody deficiencies^{1,2} and those autoimmune diseases for which there is good evidence of the efficacy of IVIg.

The risks involved fall into two main categories: those associated with the infusion of IVIg and the longer term risks

of blood borne viruses or currently unknown organisms.³ This case report describes the use of such a blood product for an IgG subclass deficiency, which turned out to be transient.

This case is an unusual combination of primary thrombocythaemia, recurrent bacterial chest infections, and transient IgG1 deficiency. It is reported to highlight the need for risk–benefit assessment for each patient before IVIg treatment is begun.

CASE REPORT

A 54 year old woman with an acute, severe headache, nausea, and difficulty in speech the day after an infusion of IVIg (21 g) was admitted to the neurosurgical unit. She had suffered a previous episode of headache, vomiting, and photophobia five months earlier, also after IVIg, and had recently experienced an increase in the frequency of “migraines” during and immediately after IVIg infusions. She had been receiving IVIg every three weeks following a diagnosis of an isolated IgG1 deficiency two years earlier, having presented with recurrent bacterial chest infections and sinusitis for over 40 years. Computed tomography scans then had revealed chronic sinusitis and bronchiectasis; causes other than an isolated IgG deficiency had been eliminated.

Before admission to the neurosurgical unit she had suffered from a fit and magnetic resonance imaging had shown bilateral transverse and sagittal sinus thrombosis with secondary haemorrhage. There was no evidence of acute infection. Management included anticonvulsant treatment, anticoagulation with heparin and then warfarin for three months, and discontinuation of hormone replacement treatment. The serum immunoglobulin concentrations were normal, including IgG subclasses (table 1¹), and protective amounts of IgG antibodies to pathogens were detected; these were performed 16 weeks after the last IVIg infusion; IVIg infusions were not restarted.

The speech problems and headache resolved quickly and she was discharged within five days. During the stay it was noted that she had a high platelet count ($> 600 \times 10^9/\text{litre}$) on two occasions without evidence of infection; previously high platelet counts ($> 1000 \times 10^9/\text{litre}$) had been attributed to chronic infection. A bone marrow aspirate was performed and showed a hypercellular marrow with very active megakaryocytopoiesis. The trephine confirmed vastly increased numbers of pleomorphic megakaryocytes, confirming thrombocythaemia, and a diagnosis of primary thrombocythaemia was made. Treatment was started with hydroxyurea. She made a good response to treatment, with a decrease in frequency and severity of the headaches, which eventually stopped. Prophylactic antibiotics have reduced the number of bacterial chest infections and nasal corticosteroids improved the chronic sinusitis.

Table 1 Serum immunoglobulin values, including IgG subclasses and protective IgG antibodies to pathogens, 16 weeks since the last intravenous immunoglobulin infusion

Serum immunoglobulins	Concentration (g/l)	Normal range
IgG1	8.4	6.0–12.0 g/l
IgG2	3.8	3.2–10.2 g/l
IgG3	3.6	1.2–6.6 g/l
IgG3	0.7	0.2–1.9 g/l
IgG4	0.3	0.1–10.3 g/l
IgA	2.0	0.8–5.0 g/l
IgM	1.0	0.5–2.0 g/l
Specific antibodies		
Tetanus	0.13	>0.1 IU/ml
Diphtheria	>1	>0.5 IU/ml
Pneumococci	>100	>45 IU/ml

DISCUSSION

The widespread use of IVIg preparations has resulted in a worldwide shortage of these expensive products and they should only be used when the criteria for a diagnosis of primary antibody deficiency have been met.⁴ These criteria include a reduction of IgG and one other major immunoglobulin isotype in the serum, in conjunction with failure to respond to immunisation and/or exposure antigens, and documented recurrent bacterial infections.

Adverse reactions to high dose treatment are known to include severe headaches and aseptic meningism, but are unusual in patients receiving replacement immunoglobulin doses.

Thrombosis after IVIg treatment is rare,^{5–7} especially after replacement doses. The mechanisms that contribute to this are unknown, although contamination of IVIg preparations by coagulation factor XI has been postulated.⁸

“All patients should have a thorough risk–benefit assessment done before starting treatment with intravenous immunoglobulin, especially if this is to be life long”

The patient suffered a thrombosis of the transverse sinus, originally thought to be an intracerebral tumour. The transverse sinus thrombosis was originally considered to be an apparent complication of increased viscosity associated with the IVIg replacement treatment but in fact she had primary thrombocythaemia (probably long standing), and lateral sinus thrombosis is a known risk in this disease.⁹ Thrombocythaemia is also known to cause headaches⁹; in this case, the combination of those two factors may have contributed to the presentation, although primary thrombocythaemia alone is a sufficient cause of central nervous system thrombosis.

The main lesson to be learnt from this case was not to dismiss severe recurrent headaches following IVIg treatment, despite a previous history of migraine, and even though mild headaches are a common adverse event. In such a situation, consider thrombosis in cerebral vessels. Other contributing factors should be sought, such as a raised platelet count, together with reasons for raised serum viscosity, including paraproteinaemia or coagulopathy.

The criteria for a diagnosis of primary antibody deficiency, including failure to produce specific IgG antibodies to immunisation and/or exposure antigens, should always be followed

Take home messages

- Beware severe, recurrent headaches following intravenous immunoglobulin (IVIg) treatment
- Do not assume that a high platelet count is solely the result of intercurrent infection
- Ensure that an isolated IgG subclass deficiency is not transient and use the diagnostic criteria for primary antibody deficiencies, which include failure of specific IgG antibody production
- Do a thorough risk–benefit assessment before starting IVIg

and the finding of low serum immunoglobulins checked on several occasions to ensure that an isolated IgG subclass deficiency is not transient. All patients should have a thorough risk–benefit assessment done before starting treatment with IVIg, especially if this is to be life long.

CONCLUSION

It is uncommon for headaches after IVIg to be severe, recurrent, and complicated by nausea and photophobia. In such a situation it is necessary to consider sinus thrombosis and look for additional risk factors.

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