

SHORT REPORT

Aseptic meningitis associated with high dose intravenous immunoglobulin therapy

J D G Watson, J Gibson, D E Joshua, H Kronenberg

Abstract

Two cases of aseptic meningitis occurred in temporal association with high dose intravenous immunoglobulin therapy to treat thrombocytopenia. In neither case was any other aetiological agent identified and both patients completely recovered within a few days. This phenomenon has been reported in only one previous paediatric case.

High dose intravenous immunoglobulin (IVIg) therapy has been used with increasing frequency for a range of indications, notably immune thrombocytopenic purpura (ITP).¹ Side effects include fever, vomiting, transient headache and serum sickness like reactions.^{2,3} Two adult patients with thrombocytopenia developed transient aseptic meningitis in association with a course of high dose IVIg therapy.

Case 1

The first patient was a 25 year old female university student who was diagnosed in Yugoslavia as having ITP at the age of 22. At that time her platelet count was $14 \times 10^9/l$ and there were plentiful megakaryocytes on bone marrow examination. She was initially reluctant to accept treatment but in 1988 (aged 24) was treated unsuccessfully with both prednisone (50 mg/d for five weeks) and intravenous immunoglobulin (IVIg). No details of the formulation and dose of the IVIg are available.

Later in 1988 the patient came to Australia and was re-evaluated. Her platelet count was $14 \times 10^9/l$ and the bone marrow findings were again consistent with ITP. She was anti-nuclear antibody negative and unresponsive to another trial of prednisone (50 mg/d for 15 days). Splenectomy was recommended and the patient was admitted to hospital in March 1989 for a pre-operative course of high dose IVIg, which in view of her previous lack of response, was started at a dose of 1 g/kg/d.⁵ The IVIg preparation used was Intragam (CSL, Australia) which is a low pH formulation prepared with ethylene glycol⁶ and was given over eight to 12 hours. Before treatment the platelet count was $9 \times 10^9/l$ and by day three it had risen to $251 \times 10^9/l$. The treatment was then stopped. Late on day three the patient developed a progressively worsening

frontal headache and on day four rigors, sweating, nausea, myalgia, photophobia and neck stiffness were reported. Her temperature was 37.5°C, Kernig's sign was absent and there were no focal neurological signs.

The next day a non-contrast CT scan of the brain was normal and a lumbar puncture demonstrated clear cerebrospinal fluid (CSF) with a pressure of 230 mm H₂O. The CSF cell count was $2 \times 10^6/l$ red cells and $22 \times 10^6/l$ white cells. The white cell differential was 64% lymphocytes, 3% monocytes and 33% neutrophils. The CSF protein was 0.48 g/l (normal 0.15-0.45) and the glucose 2.9 mM (blood glucose 5.2 mM). A gram stain and a direct examination for Cryptococci were negative as was a CSF cryptococcal antigen test. Blood cultures and subsequent serum viral titres were negative.

The patient was treated with analgesics but no antibiotics. A repeat lumbar puncture on day nine revealed clear fluid with a pressure of 210 mm H₂O. Red and white cell counts were each $1 \times 10^6/l$, protein was 0.44 g/l and the glucose was 2.2 mM (blood glucose 4.1 mM). The neurological symptoms slowly resolved over the next few days and on day 15, when the platelet count was $297 \times 10^9/l$, a splenectomy was successfully performed. There were no post-operative complications and the patient remained neurologically normal. Two months later her platelet count was $438 \times 10^9/l$.

Case 2

The second patient was a 26 year old male who was born in the Lebanon, and migrated to Australia at the age of 10 years. From about that time he suffered multiple episodes of easy bruising, purpura and epistaxis and had bled profusely from a head laceration sustained in a car accident. His platelet count was consistently low, ranging from 14 to $28 \times 10^9/l$. When first seen at our hospital in 1980 the platelet half life was 50-60 hours and bone marrow examination showed numerous megakaryocytes. Records elsewhere revealed that his two male siblings also had thrombocytopenia but a female sibling was normal. There was no consanguinity. On at least one occasion the platelet count responded modestly to prednisone but the exact diagnosis remained obscure.

Nevertheless, when he was admitted in July

Royal Prince Alfred Hospital,
Camperdown,
New South Wales,
Australia
Department of
Neurology
J D G Watson
Department of
Haematology
J Gibson
D E Joshua
H Kronenberg

Correspondence to:
Dr Gibson,
Haematology Department,
Royal Prince Alfred
Hospital,
Missenden Road,
Camperdown, NSW,
Australia 2050

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1989 to have a scalp lesion removed, it was decided to try a five day course of IVIg. The platelet count on admission was $16 \times 10^9/l$ and he was given 0.4 g/kg/d of Intragam. On day three of treatment he experienced frontal headaches, nausea and vomiting, and on the next day neck stiffness, photophobia and a temperature of $37.3^\circ\text{--}38.0^\circ\text{C}$. The infusion was ceased. There were no focal neurological signs and a CT head scan without contrast was normal. A lumbar puncture, carried out after a platelet transfusion, showed slightly turbid fluid with a pressure of 230 mm H₂O. There were 83×10^6 red cells and 131×10^6 white cells per litre. The white cell differential count was 72% polymorphs, 26% lymphocytes and 2% monocytes. Protein was 0.56 g/l and glucose 3.3 mM (blood glucose eight hours earlier was 7.4 mM).

No organisms were seen on Gram stain, or grown on culture. Direct examination and antigen test for Cryptococci were negative as was culture including cultures for Mycobacteria. Viral studies were not carried out and blood cultures were negative. Intravenous ampicillin, 2 g four hourly, was prescribed empirically after the lumbar puncture, but stopped after three days because of rapid symptomatic improvement and the negative bacteriological results. By day seven he was neurologically normal but the platelet count was only $28 \times 10^9/l$. Surgery was postponed but subsequently performed under platelet cover two months later. When last reviewed in November 1989 he was still thrombocytopenic but otherwise well.

Discussion

The complications of high dose IVIg include a number of neurological symptoms such as transient headaches, vomiting and altered consciousness associated with fevers and rigors in a small percentage of patients.^{2,3} To our knowledge, however, aseptic meningitis has been reported on only one previous occasion. Kato *et al* described a two year old child with ITP who developed this complication following the use of two different immunoglobulin preparations; immunoglobulin prepared with polyethylene glycol and a sulphonated preparation.⁴ A co-existent significant peripheral blood eosinophilia suggested a possible allergic reaction. Neither of our cases, however, showed an eosinophilia during the episode of meningitis.

It is conceivable that our cases may have had coincidental viral aseptic meningitis. Arguing against this possibility were the absence of

prodromal features, absence of a history of recent contact with others suffering from viral illnesses, no relevant recent travel and no identifiable rise in serum viral titres (case 1). Given the strong temporal association of meningitis with the high dose IVIg infusions and the rapid resolution with cessation of this therapy, we feel that they were aetiologically related.

With such small numbers of reported cases, very few conclusions can be drawn regarding the importance of dose and formulation and the possible mechanisms of the aseptic meningitis. In Kato's patient⁴ and case 2, a dose of 0.4 g/kg/d was used whilst in case 1 we used two and a half times this dose. At least three separate preparations of HDIg have now been implicated in this phenomena. Aseptic meningitis associated with drug therapy has been reported infrequently, although well documented cases attributed to cotrimoxazole and azathioprine have been described.^{7,8}

In conclusion, although headache and fever are a well recognised side effects of high dose IVIg, aseptic meningitis has only been reported in one previous patient, a paediatric case. With the increasing use of this therapy for a range of disorders including an expanding number of neurological disorders,⁹ this phenomenon may be of considerable clinical significance.

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