Intravenous immunoglobulin in virus associated haemophagocytic syndrome

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Abstract

A 1 year old boy with virus associated haemophagocytic syndrome caused by cytomegalovirus infection is described. Persistent severe thrombocytopenia responded to repeated intravenous infusions of immunoglobulin.

Virus associated haemophagocytic syndrome is known to occur in association with herpes virus infections. Although the mortality is high, complete recovery has been reported. Immunoglobulin infusions have been shown to increase platelet counts in chronic immune thrombocytopenia. This treatment was effective in a child with severe persistent thrombocytopenia complicating virus associated haemophagocytic syndrome.

Case report

A boy aged 1 year presented with a one month history of intermittent fever and rash. Two days before presentation, he developed periorbital cellulitis, epistaxis, and a petechial rash. He was the only child of healthy, unrelated parents. He had previously been well, had received no transfusions, and had been immunised with the full course of triple vaccine and oral polio. He was taking no medications.

On admission, he was febrile (39-1°C) with a diffuse petechial rash. There was generalised lymphadenopathy and appreciable hepatosplenomegaly. Examination of the nervous and respiratory systems was normal.

An initial peripheral blood count showed a haemoglobin concentration of 120 g/l, platelets $5 \times 10^9$/l, and a white cell count of $8.3 \times 10^9$/l, with an absolute neutrophil count of $0.08 \times 10^9$/l. Within 18 hours the haemoglobin was 83 g/l, the platelet count $4 \times 10^9$/l, and the total white count $2.7 \times 10^9$/l. Red cells were hypochromic and microcytic, and occasional reactive lymphocytes were visible. Clotting function was normal.

A bone marrow aspirate showed increased cellularity with active erythropoiesis, increased granulopoiesis, and plentiful megakaryocytes. Haemophagocytosis was present. There was no evidence of malignancy. A repeat bone marrow examination one month later was unchanged. An inguinal lymph node biopsy specimen showed reactive hyperplasia: the architecture...

Days of intravenous immunoglobulin

Days

Platelets

V(X) x 10^12

Discussion

The term 'virus associated haemophagocytic syndrome' (VAHS) was introduced to describe a disorder characterised by benign histiocytic hyperplasia and prominent haemophagocytosis associated with a systemic virus infection.1 Herpes viruses, in particular cytomegalovirus, have been most commonly implicated, although since the original description the syndrome has been expanded to accommodate associations with non-viral infections and with other underlying illness including immune deficiency states, and has been termed 'haematophagic histiocytosis'.2

The clinical and histopathological features of this patient were consistent with the diagnosis of VAHS. Haemophagocytosis, histiocytic hyperplasia, and active cytomegalovirus infection were documented. There was no evidence of malignant proliferation of histiocytes, and serum lipids were not raised as may be found in other haemophagocytic syndromes, such as malignant histiocytosis and familial erythrophic lymphohistiocytosis respectively.

There is no specific treatment for VAHS at present. Specific antimicrobial therapy has been used with success against bacteria associated with haemophagocytic syndrome and acyclovir in two patients with VAHS associated with Epstein-Barr virus.3 There are no reports of the use of ganciclovir in the treatment of VAHS associated with cytomegalovirus.

Other approaches to treatment of VAHS have included immunosuppression. Both splenectomy and the use of steroids or vinca alkaloids have met with temporary success at best, however, and some authors have advocated reduction in immunosuppression as critical in the management of such patients. Etoposide has been successful in controlling haemophagocytosis in both familial erythrophic lymphohistiocytosis and VAHS associated with Epstein-Barr virus, but did not affect the outcome in the latter patient.4 Cyclosporin has been used in the long term treatment of haematophagic histiocytosis associated with Weber-Christian disease.5

There are no published reports of the use of intravenous immunoglobulin in this condition. A trial of this treatment was initiated in view of potentially life threatening severe thrombocytopenia.

The mechanism by which immunoglobulin caused an increase in platelet count in this patient is uncertain. The precise immunoregulatory disturbance that occurs in VAHS is uncertain, but the platelet count response to immunoglobulin suggests that the mechanism of platelet destruction has features in common with that in idiopathic thrombocytopenic purpura.6 Low platelet counts precluded measurement of platelet associated immunoglobulin in this patient.

In conclusion, intermittent intravenous immunoglobulin has proved safe and effective was preserved, prominent secondary follicles were present in an expanded paracortex, and there was some associated sinus histiocytosis. There was no evidence of associated haemophagocytosis nor any morphologic evidence of cytomegalovirus infection.

Virological investigations provided evidence of cytomegalovirus infection: cytomegalovirus IgM was present, cytomegalovirus was cultured from the urine on two occasions, and cytomegalovirus DNA hybridisation was strongly positive in buffy coat specimens. There was no evidence of infection with other herpes viruses, but an adenovirus type 2 was cultured from urine seven weeks after the initial presentation. An eye swab grew Staphylococcus aureus.

Tests of immune function showed no deficiency other than neutropenia. Serum immunoglobulin concentrations were normal. Total numbers of circulating lymphocytes, total T cells, and populations of CD4 and CD8 T cells were within the normal range. Increased numbers of activated B cells and natural killer cells were present, consistent with active viral infection. A direct Coombs' test was weakly positive.

Liver function tests were normal. Serum cholesterol and triglyceride concentrations were both within the normal range.

He was initially treated with intravenous antibiotics, platelet transfusions, and a transfusion of packed red cells. In view of persistent severe thrombocytopenia and bleeding manifestations, he was started on daily intravenous infusions of immunoglobulin at a dose of 0·4 g/kg/day for five days. A rise in platelet count was apparent on the fourth day of this course. Although the rise in platelet count was not sustained, the response to subsequent courses of immunoglobulin infusions was maintained (figure). This response was less noticeable with shorter courses of one or two days' immunoglobulin at the same dose.

His subsequent course has been uneventful, despite persistent severe neutrophils and recurrent thrombocytopenia associated with petechiae. A Hickman line was inserted to allow venous access. No measurable effect of the immunoglobulin infusions was apparent on haemoglobin concentration, total white cell count, or absolute neutrophil count. No side effects attributable to the immunoglobulin infusions were observed.

Discussion

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In conclusion, intermittent intravenous immunoglobulin has proved safe and effective
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in the treatment of severe persistent thrombocytopenia complicating VAHS.

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Do children need anticonvulsant treatment after a first fit?
The specious argument runs 'Epilepsy means recurrent fits. A single fit is therefore not epilepsy and does not require antiepileptic treatment'. The sensible argument depends on an assessment of the pros and cons of treatment. Estimates of recurrence risk after a first unprovoked seizure have varied from about 30% to 70%. A prospective study of 283 children in New York (Shinnat et al, Pediatrics 1990;85:1076-85) has given useful information. The overall risk of recurrence was 26% after one year, 36% after two years, 40% after three years, and 42% after four years. Factors increasing the risk were previous known cerebral pathology, abnormal electroencephalogram (EEG), and seizures of focal origin. Age at first seizure and duration of seizure did not influence the risk. Of 101 recurrences only two were status epilepticus and neither child suffered neurological sequelae.
The authors conclude that first unprovoked seizures should not lead to anticonvulsant treatment irrespective of risk factors.

The following table summarises the recurrence risks found in this study:

<table>
<thead>
<tr>
<th>% Recurrence risk (years)</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
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<tbody>
<tr>
<td>Overall</td>
<td>26</td>
<td>36</td>
<td>40</td>
<td>42</td>
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<tr>
<td>Previous known brain pathology</td>
<td>37</td>
<td>53</td>
<td>60</td>
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<tr>
<td>Idiopathic</td>
<td>24</td>
<td>33</td>
<td>36</td>
<td></td>
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<tr>
<td>Idiopathic: Normal EEG</td>
<td>15</td>
<td>23</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td>Abnormal EEG</td>
<td>41</td>
<td>54</td>
<td>56</td>
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