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Case report

Hyperviscosity in HIV infected children – a potential hazard during intravenous immunoglobulin therapy

R. A. Hague[1], O. B. Eden[2], P. L. Yap[1], J. Y. Q. Mok[3], and P. Rae[1]

[1] Edinburgh and SE Scotland Blood Transfusion Service, [2] Royal Hospital for Sick Children, Edinburgh, and [3] City Hospital, Edinburgh, UK

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Summary. A four year old boy with symptoms of HIV infection and serum IgG of 53.2 g/l had been treated for 16 months with regular infusions of intravenous immunoglobulin (IV IgG). During one such infusion he developed temporary neurological symptoms and signs suggestive of the hyperviscosity syndrome. Serum relative viscosity was raised at 5.0 (normal range 0.42–2.78). Subsequent IV IgG infusions given at a slower rate have been without adverse reactions. In a study of eight HIV infected children including the index case, and 20 children not infected with HIV, serum relative viscosity was significantly raised in the HIV infected children ($p < 0.01$; students t-test). Viscosity correlated with total serum IgG, which was raised in all HIV infected children, and with serum IgM. In HIV infected children with very high levels of serum IgG a slow rate of IV IgG infusion should therefore be chosen due to the possibility of hyperviscosity.

Key words: HIV infected children – Hyperviscosity – IV IgG

Introduction

Intravenous immunoglobulin (IV IgG) is now used in the treatment of Human Immunodeficiency Virus (HIV) infected children with recurrent bacterial sepsis, suggestive of defective humoral immunity [3, 5, 9, 10]. Although such children have a pattern of infections resembling those experienced by patients suffering from primary hypogammaglobulinaemia, serum levels of IgG, IgA and IgM are typically raised [1], and can be 3 or 4 times the upper limit of the normal range. It has previously been reported that a polyclonal hypergammaglobulinaemia may be associated with a raised serum viscosity in very rare cases [reviewed in 7], and we report on a HIV infected child in whom infusion of IV IgG lead to serious symptoms suggestive of hyperviscosity.

Offprint requests to: P. L. Yap, Edinburgh and SE Scotland Blood Transfusion Service, Lauriston Place, Edinburgh EH3 9HB Scotland, UK

Case report

The patient (Case 1, Table 1) became infected with HIV after blood transfusions at the age of 4 months, before screening of blood for HIV antibody was available. He remained well until 14 months when he began to develop recurrent upper respiratory tract infections, and at 21 months of age developed an immune thrombocytopenic purpura (ITP) refractory to treatment with high dose IV IgG, and to prednisolone. At the age of 3 years 6 months, his platelet count had returned to normal but he continued to have recurrent respiratory infections, failed to thrive, and had generalized lymphadenopathy and hepatosplenomegaly. The serum IgG, IgA and IgM levels were respectively 34.8, 2 and 2.8 g/l (normal ranges were 5–13, 0.47–2.63 and 0.36–1.92 g/l respectively). HIV infection was then diagnosed, based on HIV antibody detection and he was commenced on regular infusions of IV IgG manufactured by the Scottish National Blood Transfusion Service [5, 6] at a dosage of 200 mg/kg every 3 weeks, infused at 2.4 ml/kg/h at a IgG concentration of 50 g/l. This IV IgG preparation consists almost entirely of IgG with a normal distribution of IgG subclasses.

Treatment with IV IgG was not associated with any adverse reactions until the age of 4 yrs 10 months, when, due to an infusion pump malfunction, the patient received the infusion 30% faster than usual. He suddenly became confused, distressed, and was unable to see. He was dysarthric before becoming totally aphasic, and a transient right facial palsy was noted. Pupils remained equal and reactive to light, eye movements remained full and no abnormality could be detected on ophthalmoscopy. Tone, power and reflexes remained equal and symmetrical. The IV IgG was immediately discontinued and a normal saline infusion set up. After 30 minutes, he fell asleep. Two and a half hours later there was no residual neurological symptoms or signs. In retrospect, his parents commented that he had very brief episodes of confusion and drowsiness during previous IV IgG infusions, on one occasion waking up after a sleep appearing unable to speak. The effect had lasted a matter of minutes.

On the day of his severe adverse reaction his serum IgG, IgA and IgM levels were 53.2 g/l, 1.3 g/l and 4.8 g/l respectively. No paraprotein bands were found on protein electropheresis. His serum relative viscosity measured by capillary viscometer was 5.0 before and after the infusion (normal range 0.42–2.78). A computerized tomography scan subsequently showed no abnormality, and the patient has had no recurrence of symptoms suggestive of hyperviscos-

Table 1. Serum viscosity and immunoglobulin levels of HIV infected children

Case number	CDC stage	Serum levels g/l IgG	IgA	IgM	Serum viscosity
1	P2C	53.2	1.3	4.8	5.0
2	P2F	29.6	3.3	2.4	3.5
3	P2C	46.8	0.3	2.3	3.5
4	P2A	14.8	1.6	1.1	3.0
5	P2A	17.2	1.2	0.9	3.2
6	P2A	18.8	0.7	1.2	3.6
7	P2A	24.0	0.7	2.2	2.0
8	P2D3	14.4	2.2	1.3	2.0

ity, continuing his 3 weekly infusions at a slower rate of 1.3 ml/kg per h. Subsequent viscosity measurements have varied between 3.0 and 5.0 (data not shown) and there was no difference in viscosity levels before and after IV IgG therapy. Immune complexes were also measured before and after IV IgG therapy and no change was observed.

Following this incident, we studied a further 7 children (Cases 2–8, Table 1) treated with IV IgG [8], who are described elsewhere [5], of whom none had suffered side-effects associated with IV IgG infusions. We also investigated 20 other children born to HIV seropositive mothers who were being followed in the Edinburgh perinatal transmission study [6]. These children were presumed uninfected, being over 18 months old, HIV antibody negative, and free from symptoms suggestive of HIV infection. Serum immunoglobulin levels were measured by laser nephelometry [6]. The mean (± SD) viscosity in the HIV infected group was significantly raised with a value of 3.2 ± 0.96 compared with the non-HIV infected group (2.3 ± 0.39; $p < 0.01$, student's t-test).

The relationship between serum IgG, IgA and IgM levels and the serum relative viscosity was investigated in the above samples and additional samples collected from the HIV infected children and the serum relative viscosity was found to correlate both with IgG levels ($r = 0.74$, $p < 0.001$) and with IgM levels ($r = 0.66$, $p < 0.001$). There was no significant correlation between serum viscosity and IgA levels (Table 1). In other HIV infected children, serum viscosity was measured on stored samples taken before and immediately following IV IgG infusions. No rise in viscosity could be demonstrated in any sample. Protein electropheresis revealed no oligoclonal or monoclonal bands in any of the specimens tested.

Discussion

Intravenous immunoglobulin has been used widely for the treatment of primary hypogammaglobulinaemia and ITP. Adverse reactions are rare and in most clinical situations serum immunoglobulin levels are low or normal in the recipients. In HIV infection, serum IgG levels prior to IV IgG infusion are usually high and problems with hyperviscosity have only once been previously described in an HIV infected adult [7].

The hyperviscosity syndrome has been described in adults with paraproteinaemias [4] and in patients with autoimmune and rheumatic diseases, when it is attributed to aggregates of intermediate size or to polyclonal IgG polymers [11]. Although we have shown that the serum viscosity is raised along with serum immunoglobulin levels in these children, there have been no previous reports of hyperviscosity symptoms occuring after IV IgG infusion. Clinical manifestations are rare in patients with viscosities less than 4 [12]. However, the 'symptomatic threshold' may be very variable, although remaining constant for any given patient. In this patient, the threshold was exceeded during one of the IV IgG infusions, and only the index patient developed symptoms during a rapid infusion of IV IgG.

Central nervous system (CNS) involvement by HIV as well as other infections (bacterial, viral or parasitic) have been documented [2]. We could not definitely exclude CNS infection in our patient as we did not have the opportunity to examine his cerebrospinal fluid. Nonetheless, it is possible that in a HIV infected patient with very high IgG levels, hyperviscosity might contribute to symptoms previously attributed to CNS infections and that methods of treatment which lower viscosity may be beneficial.

On the basis of our findings, we therefore recommend that in HIV infected children with very high serum immunoglobulin levels, the clinician is alerted to the problem of hyperviscosity. Caution should be exercised in these circumstances, and a slow rate of infusion of IV IgG chosen.

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