Hyper IgM syndrome in an infant

T M R Gunasekera[1], R de Silva[2], M A M Faizal[3], D H Karunatilake[4] and S de Silva[5]

Introduction

Hyper IgM syndrome (HIGM) is a primary immunological disorder characterised by the defective immunoglobulin (Ig) class switching and impaired communication between components of the system. These patients have normal or elevated levels of serum IgM and markedly decreased levels of IgG and IgA. We report an infant with HIGM syndrome who had persistent pneumonia.

Case history

A 6-month old infant was transferred to the Intensive Care Unit (ICU) of the Lady Ridgeway Hospital with severe bronchopneumonia.

He was the first child of healthy, non-consanguineous parents. The family history was unremarkable. He was well until he developed respiratory symptoms with fever at the age of 5 months. His condition deteriorated over a fortnight despite therapy, later developing arterial blood desaturation needing ventilation. Examination showed a lean non-dysmorphic infant. There was no lymphadenopathy, and a faint BCG scar was seen. Evidence of bronchopneumonia was present.

The white cell count was 10500/microlitre, with 54% neutrophils and 44% lymphocytes. The acute inflammatory markers were elevated and the blood picture showed evidence of bacterial sepsis. Bacterial blood cultures were repeatedly sterile, but fungal cultures revealed growth of *Candida guillermonde* on 2 occasions. Tracheal aspirates were sterile and *Pneumocystic carinii* was not detected. Mycoplasma antibodies, HIV screen and mantoux tests were negative. High resolution CT scan showed homogeneous hyperdense areas within alveoli with air bronchogram and cystic areas in the right lower lobe compatible with *Pneumocystic carinii* pneumonia, *Alveolar proteinosis* or severe bronchiolitis obliterans. Serum IgM level was 87.6 (range10-85) mg/dl with undetectable IgG and IgA. Flowcytometry revealed normal lymphocyte subsets.

He was ventilated for 12 weeks during which he had several exacerbations of bronchopneumonia needing combinations of IV antibiotics including cotrimoxazole, and IV fluconazole for fungal septicaemia, and 2 episodes of mucoid diarrhoea. He was diagnosed as HIGM syndrome and 3 weekly IVIG therapies and cotrimoxazole prophylaxis was started. During subsequent 7 months he had 2 episodes of mild lower respiratory tract infections, but was otherwise well.

Discussion

HIGM syndrome comprises a heterogeneous group of disorders characterised by normal or elevated serum IgM, and markedly decreased IgG and IgA.

The normal immune response involves interactions between helper T cells, B cells and other components of the immune system. Professional antigen presenting cells (APC), such as dendritic cells, macrophages and B cells internalise antigen, process and present the derived peptides on the surface in conjunction with MHC class II molecules. CD 4+ T lymphocytes recognise the peptide-MHC complex via the T cell receptor. In addition, co-stimulatory molecules on the APC deliver a "second signal" to the T cell.

Mutations of 5 different genes responsible for HIGM have been identified. X- linked HIGM 1 (30% of patients) is due to absent CD 154 on T cells [1]. CD 40 is absent on B cells and macrophages in autosomal recessive HIGM 3 (<1%) [2]. 70% are due to intrinsic B cells defects and are mainly autosomal recessive. They include defects due to mutations in the activation induced cytidine deaminase gene (HIGM 2) [3] and uracil DNA glycosylase gene [4]. Anhidrotic ectodermal dysplasia with associated immune deficiency is a rare cause of X-linked HIGM [5].

The clinical presentation depends on the molecular defect. All patients get infections with encapsulated bacteria, as in patients with other antibody deficiencies. These include sino-pulmonary infections caused by *Haemophilus influenzae, Streptococcus pneumoniae, S. pyogenes and Staphylococcus aureus*. Recurrent diarrhoeal infections with *Giardia, Campylobacter, Rotavirus* and *Cryptosporidium* may cause growth faltering and malabsorption.

Patients with intrinsic B cell defects have antibody deficiency. However, patients with HIGM 1 and HIGM 3,

Senior Registrars in [1]Paediatrics and [3]Paediatric Intensive Care; and [4]Paediatrician, and [5]Paediatrician (Intensive Care Unit), Lady Ridgeway Children's Hospital, Colombo 8. [2]Consultant Immunologist, Department of Immunology, Medical Research Institute, Colombo 8.

Correspondence: TMRG, *e-mail <sanjika@kodak.lk> Telephone 0777 579 656.* *Received 10 May and revised version accepted 7 July 2007. Conflicts of interest: none declared.*

with absent CD 154 and CD 40 respectively, are prone to opportunistic infections such as *Pneumocystis carinii*, *Cryptosporidia* and *Toxoplasma* indicating an associated defect in cellular immunity [6].

Diagnosis is mainly by laboratory tests. Common variable immune deficiency, X- linked agammaglobulinemia, severe combined immune deficiency and transient hypogammaglobulinemia of infancy warrant exclusion. Flowcytometric assays are available to confirm the diagnosis in HIGM 1 and 3. Gene analysis identifies specific mutations, and is important in family screening. Prenatal diagnosis is possible [7].

The main treatment modality is IVIG, which is sufficient in patients with intrinsic B cell defects. For patients prone to defects in cellular immunity, prophylactic cotrimoxozole therapy against *Pneumocystic carinii* is given, but adequate data are lacking. Absolute neutropaenia responds to G-CSF. Bone marrow transplantation has been successful only in a minority. Even with appropriate therapy, survival at 25 years is only 20%.

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