

Antibody deficiency with hyper IgM - a case report

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Abstract

A 20-month-old Indian boy presented with recurrent pyogenic infections and failure to thrive. His IgG and IgA levels were low, but his IgM was elevated. He also had undetectable isohaemagglutinin titre and neutropenia, both parameters being poor prognostic indicators in this very rare primary immunodeficiency state - antibody deficiency with hyper IgM. Our patient subsequently succumbed to *Pseudomonas aeruginosa* septicaemia and meningitis in spite of aggressive antibiotic and intravenous gammaglobulin therapy. To the best of our knowledge, this is the first such case to be documented in Malaysia.

Key words: Antibody deficiency, hyper IgM, primary immunodeficiency, recurrent infections.

INTRODUCTION

Antibody deficiency with hyper IgM is extremely rare. It is characterized by very low or absent IgG and IgA levels with normal or elevated IgM levels. Such patients usually present with recurrent pyogenic infections and failure to thrive. We present here a case of antibody deficiency with hyper IgM which, to the best of our knowledge, is the first such case to be documented in Malaysia.

CASE REPORT

Clinical history

A 20-month-old Indian boy, the youngest of three siblings in a family of consanguineous parents, was admitted in July 1988 with an abscess of the left thigh and a previous history of multiple abscesses elsewhere on his body. Since the age of 5 months, he had been troubled by frequent upper respiratory tract infections. At the age of 9 months, he was hospitalized for pneumonia and, by the age of 1 year, he had developed chronic otitis media.

Physical examination

On admission, he was febrile, weighed 6.7 kg and had a height of 72.0 cm [both at -3SD below median on the National Council of Health Statistics (NCHS) chart]. He had reddish hair and fair skin (both parents were of dark complexion) normal facies, but his right eye was swollen

with periorbital cellulitis and conjunctivitis. He also had bilateral chronic otitis media. There were scars from pyoderma on his thighs and the rest of his lower limbs. Besides signs of consolidation in the respiratory examination, the rest of the systemic examination was normal.

Laboratory findings

Results of laboratory investigations were as follows: Hb 8.8 g/dL, total white cells $10.6 \times 10^9/L$, neutrophils 7.0% (742/microL), lymphocyte 81.0%, eosinophils 5.0%, platelets $242 \times 10^9/L$; serum protein 71.0 g/L, albumin 36.0 g/L.

Serum immunoglobulins: IgG <2.5 g/L (normal 3.1 - 13.9), IgA not detectable (normal 0.3 - 1.3 g/L) and IgM 3.09 g/L (normal 0.45 - 2.0); complement levels were normal. Blood group: O, isohaemagglutinin anti-A and anti-B were not detectable.

Cellular immune studies: B lymphocytes 20.0% (normal 6.0 - 25.0)*, T lymphocytes (CD3 cells) 76.0% (normal 52.0-80.0)*. Cellular proliferation to phytohaemagglutinin (PHA) and Mantoux test did not show any abnormality. Nitroblue tetrazolium dye test (NBT) was also normal. Chest x-ray showed bilateral multiple opacities. Initial culture from a cutaneous abscess on the thigh grew *Staphylococcus aureus*;

* Values of 5 normal children age 1 - 4 years using the peroxidase method of immunophenotyping with monoclonal antibodies. (Ortho. Raritan, NJ).

later cultures from the ear swab, blood and cerebrospinal fluid grew *Pseudomonas aeruginosa*.

Course of disease

In spite of aggressive antibiotic therapy including cefuroxime, netilmicin and cotrimoxazole, and the administration of intravenous immunoglobulin, the patient succumbed to the illness after 3 weeks in the hospital.

DISCUSSION

Primary immunodeficiency is a rare disorder. The incidence has been stated to be 1 per 100,000 population (MRC UK, 1969). Antibody deficiency with hyper IgM (first reported in 1966) is rarer still, such that little is known of the prognosis of this disorder.²

These children present typically with recurrent infections. However, if all children with recurrent infections were to be investigated, a majority will be found to be non-immunodeficient.³ To overcome this, Hosking and Robertson has devised guidelines based on infectious and non-infectious parameters to determine the population of children with recurrent infections who are more likely to be immunodeficient and thus require immunological investigations.³ Using these guidelines, our patient had a score of 42 (a score of 20 or more is an indication for immunological work-up). As a result, we further investigated the child and reached a diagnosis of immunodeficiency with hyper IgM. Antibody deficiency with hyper IgM is a primary immunodeficiency characterized by very low or absent IgG and IgA levels with normal or elevated IgM levels. Patients with this disorder have a high incidence of recurrent pyogenic infections including otitis media, pneumonia and septicaemia.⁴ In addition to the above infections at the various anatomical sites, our patient also had recurrent abscesses, periorbital cellulitis and conjunctivitis.

Patients with this condition differ from those with congenital X-linked agammaglobulinaemia in that they produce IgM, have B lymphocytes in the blood and IgM-secreting plasma cells in the lymph nodes, gut and marrow. In most cases, the IgM does not have useful antibody activity, as assessed by isohaemagglutinins, primary response to bacteriophage X174 or natural antibody to *E. coli*. Patients who develop meningitis are those with the lowest isohaemagglutinin titres, irrespective of their serum IgM concentrations,¹ as is the case in our

patient whose isohaemagglutinin titre was not detectable.

Although the symptoms in patients with antibody deficiency with hyper IgM resemble those with panhypogammaglobulinaemia, there are two differences. One is that haematological complications are more frequently seen in this condition. Usually these take the form of neutropenia with counts in the 200–800/micro L range and little or no elevation with infections.⁵ This is also seen in our patient (neutrophil count of 742/micro L). In general, neutropenia makes the prognosis very much worse.⁵

Our patient had a normal platelet count. However, thrombocytopenia is known to occur occasionally in antibody deficiency with hyper IgM. Its cause is unknown, but possibilities include diminished production and increased sequestration in the spleen.⁵

The other difference is that patients with antibody deficiency with hyper IgM are very much more susceptible to infection by opportunistic organisms than those with congenital X-linked panhypogammaglobulinaemia. Examples of these infections are pneumonia due to *Pneumocystis Carinii* and *Candida oesophagitis*.⁵ Our patient had *Pseudomonas aeruginosa* septicaemia and meningitis.

The immunopathogenesis of this condition has not been fully elucidated. There appear to be a defect of the isotypic switching mechanism in the development of B lymphocytes, permitting the formation of IgM producing but not IgG or IgA forming B lymphocytes.^{6,7} This mechanism appears to be regulated by T lymphocytes and a report of it being a T cell-mediated suppression of IgG and IgA synthesis but not IgM has come to the fore.^{8,9}

The exact mode of inheritance in this condition is difficult to determine in our patient. However, antibody deficiency with hyper IgM is known to be predominantly X-linked, although autosomal recessive inheritance has been reported.

Delay in diagnosis of this disorder can be avoided if the Hosking and Robertson criteria are applied to children with recurrent infections. This would lead to earlier referral to centres with facilities to assess immune functions. Early administration of intravenous immunoglobulin to the affected child is imperative.

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