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The pattern of hypogammaglobulinaemia in Sri Lankan children

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Abstract

Objective To evaluate the prevalence of hypogammaglobulinaemia in Sri Lankan children who present with recurrent or severe bacterial infections.

Design A descriptive study.

Setting Medical Research Institute (MRI), Colombo.

Subjects 100 children between the ages of four months to twelve years referred to the Department of Immunology, MRI, for evaluation of immune status during four years from 1993 to 1997.

Measurements Immunoglobulin G, A and M levels were measured using radial immunodiffusion technique.

Results 22 out of 100 children had an underlying antibody deficiency, of whom IgA deficiency was the commonest (18 patients). Two patients had low IgG and A and elevated IgM levels, and they were diagnosed as having X linked-hyper-IgM syndrome. One patient had deficient IgA and IgM, and all three immunoglobulins were deficient in another.

Conclusions Results indicate that IgA deficiency is the commonest immunodeficiency in Sri Lanka, which is comparable with studies done in the West. This study also shows the need to improve the standard of care in patients with immunodeficiency.

Introduction

One of the primary functions of the immune system is the protection of the host against pathogenic microorganisms. The mechanisms include involvement of components of the innate immune system, such as the neutrophil and complement proteins, and the cells of the immune system, which include both T and B-lymphocytes. Dysfunction of the immune system gives rise to recurrent, severe or unresolving infections, and to infection with opportunistic organisms (1,2,3).

A defect in B-lymphocytes is associated with diminished production of antibodies, in particular IgA, IgG, and IgM, leading to recurrent infections with capsulate bacteria (4,5,6). Sinus and pulmonary infections are common in these patients, though infections of bone, gut and meninges may also occur. Selective IgA deficiency is the commonest

defect noted in the West, being present in one out of every 700 individuals. IgG deficiency is less common, and can be treated with parenteral preparations of immunoglobulin (7).

Children presenting with recurrent bacterial infection may have an underlying humoral deficiency. Specific diagnosis may provide treatment opportunities in some cases, whereas genetic counselling may be provided in inherited deficiencies.

Numerous studies have provided detailed information of the prevalence of immune deficiency in developed countries. However, no such information is available in Sri Lanka.

Material and methods

100 children between the ages of 4 months to 12 years consecutively referred by paediatricians to the Department of Immunology MRI, Colombo, for evaluation of the immune status were included in the study. Children who had four or more respiratory infections or diarrhoea episodes within a period of 6 months, and unresolving pneumonia or severe infections at other sites, were studied during 4 years from 1993 to 1997. The referring paediatrician clinically excluded the possibility of HIV infection, but this was not serologically confirmed.

A questionnaire was filled for every patient. 2 ml of blood was collected and serum was separated. Immunoglobulins G, A and M were measured using a radial immunodiffusion technique (8). Norpartigen plates (Behring) were used according to the manufacturer's instructions. Control sera were purchased from commercial sources.

In summary, 5 µl of serum from patients and the controls were placed in wells in each individual plate. The plates were incubated at room temperature in a moist chamber. The IgA and G plates were incubated for a period of 2 days, while the IgM plate was incubated for 3 days. The diameter of the precipitin ring was measured, and the individual immunoglobulin value was obtained by comparing with a standard curve provided by the manufacturer. The control sera were used to verify the results.

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Results

22 children had an underlying immunoglobulin deficiency (Table). The commonest deficiency, found in 18 children, was selective IgA deficiency. Most of them presented with respiratory tract infection; 10 had recurrent lower respiratory tract infections and 4 had unresolving pneumonia (Table). A deficiency of IgG and IgA, with a corresponding increase in IgM, was found in 2 boys.

They were diagnosed as having X-linked hyper-IgM syndrome (7). One patient had deficient IgA and IgM, and all three immunoglobulin levels were low in another.

Table

Presenting illness	Number
Recurrent lower respiratory tract infection	74
Unresolving pneumonia	13
Recurrent diarrhoea	8
Meningitis	4
Septicaemia	1
<i>Antibody deficiency</i>	
IgA	18
IgA & IgG	2
IgA & IgM	1
IgA & IgG & IgM	1
Total	22
<i>Features of IgA deficiency</i>	
Recurrent lower respiratory infection	10
Unresolving pneumonia	4
Generalised skin sepsis	2
Recurrent diarrhoea	1
Septicaemia	1

Discussion

Children with opportunistic infections and disseminated viral infections were not included in our study as they have an underlying cellular immune deficiency (4). As transplacental transfer of maternal antibodies protects newborn infants for about 4 months, children below this age group were also not included.

The results of our study indicate that in children IgA is the commonest humoral deficiency in Sri Lanka as it is in the West. As IgA is a secretory immunoglobulin present

in mucosal surfaces, it plays a major role in mucosal immunity, and accordingly, 14 out of 18 children with selective IgA deficiency in this study presented with severe recurrent infection of the respiratory tract, and one had recurrent diarrhoea. Though 2 children had generalised skin sepsis, this is unusual in IgA deficiency, as most people with IgA deficiency are clinically normal. However, they are at risk of severe and sometimes fatal anaphylactic reactions after blood transfusions, due to the presence of anti-IgA antibodies (7).

Of the 2 children who were diagnosed as X-linked hyper-IgM syndrome one presented with unresolving pneumonia. His IgG and IgA levels were reduced and IgM level was elevated. His B and T-lymphocyte counts and T cell function were normal. The other had recurrent lower respiratory tract infections (LRTI). The patient who was deficient in all three immunoglobulins had a story of recurrent LRTI. B-lymphocyte count was not performed in this case. Hence we were unable to make a diagnosis of Bruton's X-linked hypogammaglobulinaemia (7).

Patients with IgG deficiency may respond to pooled gammaglobulin given parenterally. Treatment has to be continued indefinitely. One patient with X-linked hyper-IgM syndrome was successfully treated with intravenous gammaglobulin. Since children may have sinopulmonary infections after waning of maternal antibodies, some of them may have transient hypogammaglobulinaemia of infancy. It is important to follow up such children some times up to two years, to exclude a permanent defect.

Patients with a clinically suggestive history should have a thorough immunological assessment. Patients with IgA deficiency may benefit from more intensive therapy eg. vigorous use of antibiotics during an infection, adequate physiotherapy and follow up after respiratory infections.

A majority (78%) of the children investigated in our study had normal immunoglobulin levels. There are several explanations for these results. Patients with IgG subclass deficiencies may have normal IgG levels, and IgG subclasses were not evaluated. Others are unable to produce specific antibodies against common pathogens in spite of having normal immunoglobulin levels. Such patients need to be identified by functional tests, such as evaluation of immune status after vaccination. Patients with complement deficiency, particularly of C₃, may have clinical picture resembling that of immunoglobulin deficiency, as will patients with neutrophil defects (3). Such patients have to be investigated by measuring serum complement component levels and by evaluating neutrophil function.

A larger study to evaluate other immunological variables, including complement levels, neutrophil function and T cell evaluation, is in progress. However, the present limited study indicates a need to improve the standard of

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care, including intravenous immunoglobulin therapy, in patients with immune deficiency. We also need to maintain a national registry for patients with immune deficiency disorders.

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The ultimate aphrodisiac

When informed that the firm Pfizer, having a marketing stall at the Labour Party conference, manufactured the anti-impotence drug Viagra, the Prime Minister's wife joked: "Don't worry – we don't need that".

Last Thursday, courtesy of a brief statement from Downing Street, the nation learnt that Mrs. Blair had been right, perhaps providing the final confirmation of Henry Kissinger's famous dictum that power is the ultimate aphrodisiac.

Andrew Alderson, *The Daily Telegraph* (London),
10 December 1999.