Primary immune deficiency among patients with recurrent infections

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Abstract

Objectives Primary immune deficiency is relatively rare. Patients present with recurrent or persistent infections or infections with opportunistic pathogens. We investigated patients who presented during the years 2005-7 with recurrent or persistent infections or infections with opportunistic organisms, for underlying immune deficiency.

Design Descriptive study.

Setting Department of Immunology, Medical Research Institute, Colombo.

Study population 257 patients referred to the Department of Immunology, Medical Research Institute, Colombo, with a history of recurrent infections, for evaluation of possible immune deficiency.

Measurements Appropriate evaluation of immunological competence of the humoral and cell mediated immune systems.

Results There were 8 patients with agammaglobulinaemia (X linked agammaglobulinaemia and autosomal recessive agammaglobulinaemia), 2 patients each with ataxia telangiectasia, IgA deficiency and hyper-IgE syndrome, 3 patients with common variable immune deficiency (CVID), and 1 patient each with Griscelli syndrome, hyper-IgM syndrome and X linked severe combined immune deficiency (SCID).

Conclusions Primary immune deficiency must be included in the evaluation of patients with recurrent infections, and timely intervention can prevent morbidity and mortality.

Introduction

Primary immune deficiencies (PID) are due to innate or genetic defects of the immune system [1]. They result in recurrent or severe infections, infections that do not respond to appropriate antibiotics, or infections due to opportunistic organisms. They may also present with autoimmune disease or malignancy.

PID may be due to defects in the innate or acquired immune system. Defects in the innate immune system include abnormalities in phagocytes such as neutrophils and macrophages, or in the complement system. Specific immune defects may be due to B lymphocyte dysfunction leading to disordered antibody production, or abnormalities in T lymphocytes [1, 2].

PIDs are rare. Studies in the West have noted IgA deficiency, the commonest PID, in 1 in 300 to 700 births [3], and other PIDs collectively in 1 in 10 000 births. In Sri Lanka the rates are unknown. However, IgA deficiency was the commonest humoral immune deficiency we detected [4].

So far no study has attempted to identify the entire range of immune deficiency in Sri Lanka. The present study aims to evaluate the immune status of patients suspected of having primary immune deficiency, and to identify the specific disease.

Material and methods

All patients with clinical features suggestive of immune deficiency, referred to the Department of Immunology, Medical Research Institute, Colombo from

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hospitals throughout the country during the years 2005-7 were included (table 1).

Table 1. **Study sample**

Clinical features	*Number*
Recurrent pneumonia	127
Unresolving pneumonia	55
Atypical pneumonia	1
Recurrent abscesses	32
Chronic diarrhoea	5
Recurrent meningitis	15
Septicaemia	12
Significant family history	10
Total	**257**

Following a detailed clinical examination, blood was taken for immunological investigations. These included full blood count, blood picture, erythrocyte sedimentation rate (ESR), C reactive protein (CRP), serum immunoglobulin IgG, IgA and IgM levels, and in some patients IgE. Functional antibodies were tested by determining isohaemagglutinin levels, and checking the level of antiVi polysaccharide after immunising with the typhoid Vi vaccine. The B lymphocyte count was performed using monoclonal antibodies against CD 19 and CD 20 using flowcytometry.

Complement C3 and C4 levels were done using a radial immune diffusion technique [5]. Neutrophils were assessed by obtaining the absolute count, and the oxidative function was assayed by the nitro blue tetrazolium assay (NBT test) as described elsewhere [6]. T lymphocyte count and subsets were assessed by flowcytometry (CD 3, CD 4 and CD 8 counts), while function in vivo was assessed by the Mantoux test. An in vitro T lymphocyte function test was performed (T cell proliferation test) as described elsewhere [7]. NK cells were assessed by flowcytometry. In one patient, the hair shaft was examined by light microscopy to diagnose Griscelli syndrome [8].

Secondary immune deficiency, including HIV/AIDS was excluded in all patients. Approval was obtained from the ethics committee of the Medical Research Institute, Colombo.

Results

Of 257 patients investigated, 20 patients were diagnosed with PID (table 2). Nineteen were in the paediatric age group. Eight patients had agammaglobulinaemia with B lymphocytes < 1% of the total lymphocyte population. These patients had either X linked agammaglobulinaemia, or autosomal recessive agammaglobulinaemia [9]. Of the 8 patients, there were two sets of siblings. Six patients with agammaglobulinaemia had pneumonia, in addition to other infections (table 3).

Table 2. **Primary immune deficiencies in Sri Lanka**

Primary immune deficiency	*Number*
Agammaglobulinaemia (XLA/AR)	8
IgA deficiency	2
Common variable immune deficiency (CVID)	3
Hyper IgM syndrome	1
X linked severe combined immune deficiency (SCID)	1
Ataxia telangiectasia	2
Hyper IgE syndrome	2
Griscelli syndrome	1
Total	**20**

Table 3. **Clinical features in patients with agammaglobulinaemia (XLA= X linked agammaglobulinaemia. AR = Autosomal recessive agammaglobulinaemia)**

Sex	*Age at presentation*	*Infections*	*Diagnosis*
Male	3 months	Septicaemia, empyema, pneumonia, multiple cerebral abscesses	? XLA
Male brother of above	2 years	Pneumonia	? XLA
Male	6 months	Septicaemia, meningitis, echthyema gangrenosum	? XLA ?? AR
Male	9 months	Recurrent pneumonia, recurrent otitis media	? XLA
Male brother of above	6 months	Otitis media	? XLA
Female	?	Recurrent respiratory infections	AR
Male	6 years	Meningitis, pneumonia	? XLA ? AR
Male	3 years	Pneumonia (×4) recurrent otitis media, arthritis	? XLA

Two patients had IgA deficiency, and 3 patients had common variable immune deficiency (CVID) [10]. The patient with X linked severe combined immune deficiency (X linked SCID) had probable γ chain deficiency [11]. Of the 2 patients with hyper IgE syndrome [12], one patient probably had pulmonary tuberculosis, and he responded well to anti-TB drugs.

Discussion

IgA deficiency is the commonest immune deficiency worldwide, including Sri Lanka [4]. However, we had only 2 patients, who presented with recurrent respiratory infection.

Common variable immune deficiency (CVID) is the commonest clinically significant PID. Most present in the third decade of life [10, 14]. In addition to recurrent infections, they are susceptible to autoimmune diseases and malignancy. Of the 3 patients diagnosed with CVID, one was clinically normal till the age of 29 years. She was diagnosed at the age of 42 years, by which time she had sufferred 2 attacks of meningitis, pneumonia and pulmonary tuberculosis (TB). Pulmonary TB is uncommon in CVID. TB was associated in one patient with an increase in double negative T cells (CD 3 + T cells) though we could not test the cells for the γδ T cell receptor [15].

One patient with severe combined immune deficiency (SCID) had X linked SCID. At present, the only genetic abnormality detected in patients with SCID with X linked inheritance is a deficiency of the common γ chain (cγ). Bone marrow transplantation is the only treatment available for these patients. Our patient had 6 male relations, including 2 siblings, who had all died in early infancy of severe infection.

There were 2 patients with ataxia telangiectasia, where the prognosis is bleak, as bone marrow transplantation is not effective. One patient with severe pneumonia presenting at the age of 5 months was diagnosed as having hyper-IgM syndrome. These patients have normal or increased IgM, with little or no IgG and IgA [16, 17]. One patient with Griscelli syndrome presented with a history of recurrent bronchopneumonia [18]. An elder sister had died at 4 months of an unspecified illness. He had silvery gray hair, as had his sister. His hair shaft revealed large, irregular clumps of melanin in the medulla.

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