Common variable immunodeficiency (hypogammaglobulinemia) with an autosomal recessive pattern of inheritance

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Summary

A 5 year-old boy presented with recurrent arthritis associated with fever first at 2 years and later at 3 and 5 years of age. He had an affected (hypogammaglobulinemic) elder sister with severe recurrent infections. His younger male sibling is normal. The parents are consanguineous but unaffected. His immunologic parameters indicated panhypogammaglobulinemia, normal absolute lymphocyte counts but low B cell counts and hyporesponsive proliferation to mitogen (PHA). He had an inverse T helper T suppressor ratio with increased T suppressor/cytotoxic phenotype. Complement studies and nitroblue tetralozium reduction test were normal. The clinical features, immunological parameters and pedigree pattern suggest a diagnosis of familial variable immunodeficiency with autosomal recessive pattern of inheritance.

Key words – Recurrent infections, panhypogammaglobulinemia, familial variable immunodeficiency.

Introduction

We report a case of panhypogammaglobulinemia in a family of two afflicted siblings of differing sexes sparing the younger male sibling. We have thus documented the existence of a common variable immunodeficiency in our local population. The underlying defect appears to be due to suppressor cell predominance. Autosomal recessive agammaglobulinemia could present in a similar manner as above except for absent immunoregulatory defect. We note an earlier report on selective IgA deficiency in a Punjabi girl,[1] but we are unaware of any report of primary hypogammaglobulinemia occurring locally previous to this. Our patient suffers from common variable immunodeficiency (predominant antibody defect) with predominant immunoregulatory disorder with probable increase in the population of activated suppressor T cells. The pattern of inheritance is autosomal recessive.

Case Report

KR is a 5 year-old boy of Indian origin who presented with recurrent arthritis since the age of 2 years when he suffered septic arthritis of the elbow. He was plagued by further episodes of febrile arthritis which included the left knee at age of 3, left knee and ankle at age 5 years. He was also troubled by frequent bouts of upper respiratory infections since 2 years of age. However, diarrhoea or rashes were absent, even in the neonatal period. Birth and neonatal period had been normal.

BCG had been given at birth with no untoward reaction. Three doses of triple antigen and oral polio vaccines were given with no complications. No immunising disease was noted. KR's elder sister was afflicted with arthritis of the hip at 2 years, *Haemophilus influenzae* meningitis at 4 years and died of pneumonia at the age of 5. She was diagnosed as having hypogammaglobulinemia. His younger brother age 3 years is unaffected. Their parents are first cousins.

Physical examination on admission to Paediatrics Unit, General Hospital, Kuala Lumpur, at 5 years, showed a febrile but otherwise normal-looking child with absent tonsils and scant small cervical lymph nodes. His height was 113 cm (– 1 SD below the mean) and weight was 15 kg (between – 2 SD and – 3 SD below the mean) based on National Council for Health Statistics Standards Chart. He did not have hepatosplenomegaly nor mucocutaneous candidiasis.

Except for inflamed swollen left ankle and knees, bilateral muscle wasting of calves and thigh, fixed felxion of left knees, there was no other significant findings.

No organisms were cultured from blood, synovial fluid or urine. The histopathological examination of biopsied synovium of the left knee showed non specific inflammation. Tuberculosis was excluded by guinea pig inoculation studies. Other data obtained in November 85 were as follows: TWDC 11.5 x 10^9/L, (segmented neutrophils 78%, lymphocytes 20%, eosinophils 2%), platelets 490 x 10^9/L and ESR 70 mm/h. Antinuclear antibody and rheumatoid factor were negative.

Management of child was as follows. During the acute episodes of septic arthritis at 5 years, th child was treated with six weeks of ampicillin and cloxacillin in addition to intramuscular gammaglobulin. There was clinical improvement following this. With subsequent regular four weekly intramuscular gammaglobulin injection (Gamma 16) at a dose ot 100 mg/kg and appropriate orthopaedic management, the child showed noticeable improvement in general health with marked decrease in frequency of upper respiratory infections, gain in weight and improvement in gait.

Immunological studies

Humoral and cellular immune functions were assessed. Serum immunoglobulins G, A and M and 3rd and 4th complement components (C3, C4) were assayed by single radial immunodiffusion using commercially available plates (Behringwerke-HG Marburg).

T and B cells enumeration was carried out using sheep red blood cell rossetting technique and direct immunofluorescence test respectively.

Cellular Immune studies

The Phytohemeagglutinin (PHA) lymphoblastic transformation assay was performed using peripheral blood lymphocytes in RPMI medium, cultured with varying dilutions of PHA, pulsed with H^3 Thymidine on day 3 and placed in scintillation counter 18 hours later. Using monoc-

clonal antibody OKT 3 (pan T cells), OKT 4 (T helper) and OKT 8 (T suppressor/cytoxic) (Ortho NJ), the T cell subsets were phenotyped and T helper/T suppressor ratio calculated.

Results

Mantoux test was negative. The nitroblue tetralozium reduction test and complement levels were normal.

Serum immunoglobulins: In both the patient and the affected sister, there was moderate reduction of the immunoglobulin of all classes (IgG, IgA, IgM) in the serum (Table I) Both the parents had normal levels.

Table I

Serum immunoglobulin level of patient, sibling and parents (mg/dl)

Serum	Patient at 14 months	Sister at 5 years	Father	Mother
IgG	303 (550–1000)**	357 (550–1100)**	1310 (550–1900)	2810
IgA	31 (35–75)	< 10 (60–150)	190 (60–330)	296
IgM	< 2 (40–80)	< 10 (40–95)	130 (45–145)	483

***Range of normal values from reference of Diagnostic test. Jacques Wallach. 2nd edition. 1974, 10-11.*

T and B cells enumeration: Proportion of B cells is moderately reduced in the patient; 5% as compared to 18% in the control. T cell numbers were normal (Table II).

Table II

T and B enumeration (%) (at age 5 years)

	T cell	B cell
Patient	75	5
Control	70	18
*(Normal values[11]) (1–4 years)	75 ± 5	14 ± 3

**The radioactive tritiated thymidine (H3 thymidine) uptake of peripheral blood lymphocytes cultured with PHA (a) is compared to thymidine uptake of peripheral blood lymphocytes in absence of PHA (b). Stimulation index = a/b.*

Phytohemeagglutinin (PHA) lymphoblastic transformation assay: The PHA lymphoblastic transformation of the patient was markedly reduced. The stimulation index* was less than 2 compared to 56 in the control (Table III).

Table III

PHLA lymphoblastic transformation assay of patient

	Patient	Control
Stimulation index	2	56

**values represent the ratio fo counts in stimulated cultures to counts in medium alone.*

T helper/T supressor ratio: The T cell subsets phenotype showed a T helper to T suppressor ratio of 1:2 (OKT 4 28%, OKT 8 58%). This implies an increased proportion of T suppressor cells with a reversal of T helper to T suppressor ratio. (Table IV). (The normal T helper to T suppressor ratio is $> 2 : 1$).

Table IV

Phenotype of T cell subsets of patient

	OKT 3	OKT 4	OKT 8
Control	69*	52	20
Patient	88	28	58

**Phenotype measured as percentage.*

Discussion

Hypogammaglobulinemia is a rare entity. Figures from Medical Research Council UK (1956 – 1968)[1 2] showed that the incidence is 1 per 1000,000 in the United Kingdom. We do not know the incidence in our community but this report, besides the selective IgA deficiency reported by Yadav et al,[1] indicates that primary immunodeficiency diseases exist but are under-reported in Malaysia.

Infantile X-linked hypogammaglobulinemia of Bruton could be excluded in this case since a female sibling is also affected. The disease in two siblings of differing sexes bears strong resemblance to autosomal recessive hypogammaglobulinemia counterpart to Bruton's X-linked hypogammaglobulinemia.[2] In autosomal recessive hypogammaglobulinemia, B cells are almost absent while T cell number and function are normal. The low B cell numbers (5%) and impaired T cell function (hyporesponsive PHA lymphoblastic transformation) but normal T cell numbers made us favour a diagnosis of common variable immunodeficiency. We excluded benign combined

immunodeficiency for although serum immunoglobulin was low, the T cell defect was only in function (PHA lymphoblastic transformation) and not in T cell numbers (T cell numbers were normal).

The features of this patient thus closely resemble the common variable immunodeficiency which is a heterogenous group of immunodeficiency diseases characterised by hypogammaglobulinemia, increased incidence of infections, but variable in onset, pattern of clinical manifestation, and cellular immune dysfunction (including hyporesponsive PHA lymphoblastic transformation).

In a pooled series of 40 patients[5], a quarter have normal or increased B cells, a quarter have a markedly decreased B cells (< 4%) and half have a moderately decreased B cells. In any of these patients, T helper T suppressor ratio may be reserved.[5] The presence of activated T suppressors may prevent normal B cell production of immunoglobulins.[5-8] The other underlying immunologic defect includes intrinsic B cell defect, presente of autoantibodies to T or B cells besides immunoregulatory T-cell imbalance.[4] Although we did not assess T suppressor function, the finding of predominant OKT 8 T suppressor phenotype (58%), a reduced OKT 4 T helper (28%) and a markedly depressed PHA lymphoblastic transformation does point towards an increased T cell suppressor or decreased T helper inducer activity.[5,8] Although the term 'Idiopathic late onset' or 'acquired hypogammaglobulinemia (common variable immunodeficiency)' is used, there are few documentations of its true acquisition. Many of the 'adult onset variable immunoglobulin deficiencies' are known to be genetically determined.[9]

We are proposing that the immunological defect of these siblings fits a pattern of a familial variable immunodeficiency (common variable immunodeficiency with predominant antibody defect) with an autosomal recessive inheritance as opposed to that of Feldman et al[9] which is autosomal dominant. Unlike the Feldman et al series of familial variable immunodeficiency with autosomal dominant pattern of inheritance, the parents of these hypogammaglobulinemic siblings did not show either clinical features of immunodeficiency disease nor hypogammaglobulinemia. The siblings of either parents are also asymptomatic as were their grandparents and grand uncles/aunties. Consanguinity of this affected male child's normal parents and the presence of another affected female sibling, therefore, strongly suggest an autosomal recessive mode of inheritance for this disease.

We have thus reported the first documented case of common variable immunodeficiency with an autosomal recessive pattern of inheritance in this country. This disorder is often familial but documentation of its inheritance is extremely scarce[4] in the literature.

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