Hereditary CD4+ T lymphocytopenia

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Accepted 13 November 1997

Abstract

Two siblings suffering from mental retardation, progressive bronchiectasis, extensive warts, and persistent hepatitis B are described. The propositus also had an unusual physiognomy and non-specific colitis. Both patients had a marked decrease in the population of CD4+ helper T cells.

(Arch Dis Child 1998;78:371-372)

Keywords: CD4+ lymphocytopenia; immunodeficiency; common variable immunodeficiency

We describe here two siblings with CD4+ lymphocytopenia in whom the aetiology seems to be hereditary.

Case reports

CASE 1

This boy was born in November 1981 to a Palestinian Arab family. His parents are first cousins. There are six siblings who are well and one sister who is similarly affected (case 2). A diminished appetite, failure to gain weight, and intermittent diarrhoea were first noticed at 6 months and have persisted to this day. He has severe learning difficulties, has control of his sphincters, possesses a very limited vocabulary, and can neither read nor write. He has an anxious appearance, microcephaly, dry hair, mild exophthalmos, micrognathus, a high arched palate, protuberant ears, and a short neck. There are no signs of puberty. Peripheral lymph nodes were palpable. The spleen was not enlarged. He has bilateral bronchiectasis and pansinusitis. He is clubbed and has extensive warts at the backs of both hands and lenticular opacities in both eyes.

Alkaline phosphatase, γ -glutamyltransferase, alanine aminotransferase, and aspartate amino-

transferase have been raised throughout 10 years of follow up. He was persistently positive for hepatitis B surface antigen. He is positive for hepatitis e antigen but has no corresponding antibodies. He had persistent intestinal infection with salmonella, campylobacter, shigella, and *Giardia lamblia* and evidence of chronic non-specific colitis.

CASE 2

The 18 year old sister of case 1 has minor learning difficulties. She can read and write with difficulty. She also has bronchiectasis, pansinusitis, warts at the backs of both hands, and is positive for hepatitis B surface antigen. There was no splenomegaly.

Immunological investigations

Both patients suffered from an absolute lymphocytopenia with lymphocyte counts frequently below 1200 cells/ μ l. Stimulation of T cells with phytohaemagglutinin, concanavalin A, and pokeweed mitogen varied from normal to low in patient 1 and was low in patient 2. Red blood cell adenosine deaminase and purine nucleoside phosphorylase were normal in patient 1. IgG, IgA, IgM, and IgG subclasses were normal in both patients. They also had antibodies to yersinia, pertussis, and streptolysin O and to numerous viruses. Antibodies to HIV were measured in both patients on three occasions during a three year period and found to be negative. Antinuclear factor speckled antibodies were found repeatedly in patient 1. Numerous other autoantibodies were absent.

The total number of T lymphocytes, assessed by their reactivity with anti-CD3 monoclonal antibody (MoAb) was below normal in patient 2 but normal in all other members of the family including patient 1 (table 1).

Results similar to those obtained with anti-CD3 MoAb were obtained when the sum of lymphocytes expressing either $\alpha\beta$ or $\gamma\delta$ cell receptors was calculated. The proportion of CD4+ cells was below normal in the two patients, but within the normal range in other members of the family. The CD4:CD8 ratio was markedly decreased in the two patients and somewhat reduced in the mother. The majority of the CD4+ cells displayed the "memory" phenotype (CD4+CD45RO+) in all members of the family. This was particularly pronounced in patient 1 in whom practically all of the CD4+ cells had the "memory" phenotype and none had the "naive" (CD4+CD45RA+) phenotype. In patient 2, in whom the level of T cells was markedly diminished, the population of natural killer cells was significantly increased. This was manifested by a marked

Table 1 Lymphocyte surface antigens (per cent of cells)

Cell	Normal	Patient 1	Patient 2	Healthy brother	Mother	Father
T cells						
CD3	68-82	74	33	73	69	69
$\alpha\beta$		59	30	67	63	69
$\gamma\delta$		10	3	4	4	
CD4	29-55	16	16	46	38	49
CD8	20-36	59	33	30	35	29
CD4:CD8	2:1	0.3	0.5	1.5	1	1.7
B cells						
CD19	5-15	75	7	9	7	
CD20		11.6	15.9	13.2	8	
Natural killer cells						
CD16	10-25	14	47	15	18	13
CD56	10-25	26	47	15	18	13
CD57		45	44.5	18	35	26
HLA-DR	7-20	32	23	13	23	19
CD4+CD45 RO+		98	87	59	73	86
CD4+						
CD4+CD45 RA+		0.04	13	24	13	7.5
CD4+						

increase of the proportion of CD16+ and CD56+CD3- cells. The proportion of B lymphocytes expressing the CD19 and CD20 markers was normal in all members of the family.

Discussion

Non-HIV related CD4+ lymphocytopenia has been recognised for the last 10 years, but as it probably is not a single nosological entity the exact classification of our patients' disease is a matter for discussion. The criteria for the diagnosis of CD4+ lymphocytopenia include: less than 300/ μ l of CD4+ T cells or less than 20% of the peripheral blood lymphocytes in at least two measurements, no evidence of HIV infection, or other immunodeficiency, and no history of administration of immunosuppressive drugs.¹ Both patients fulfilled these criteria.

Clinically, the manifestations of CD4+ lymphopenia range from no symptoms to mild or even opportunistic infections such as histoplasmosis and cytomegalovirus.¹ We have found no account of a familial incidence of CD4+ lymphopenia in the literature and suggest that the patients described here may represent a previously unnoticed symptom complex including mental retardation, pansinusitis, bronchiectasis, and warts. Immunologically, they had CD4+ lymphocytopenia, with increased markers of activation (DR;CD57) and "memory" (CD4+CD45RO+) and decreased function of cell mediated immunity. In addition, the male sibling had a peculiar physiognomy, non-specific colitis, persistent hepatitis B, and speckled antinuclear antibodies. It should be noted that our patients did not have opportunistic infections and, therefore, do not fulfill the criteria for primary CD4+ T cell deficiency as defined by the report of the World Health Organisation (WHO) Scientific Group on immunodeficiency diseases.²

Another condition which must be considered is common variable immunodeficiency (CVID). This is a heterogeneous group of conditions characterised by hypogammaglobulinaemia, recurrent bacterial infections, and various immunological abnormalities. Some

patients have a reduced CD4/CD8 ratio and thus may resemble the patients described by us. In CVID, however, serum IgG and IgA concentrations are usually decreased.^{2,3}

The immunoglobulin concentrations were normal on repeated investigations. Both our patients had antibodies to bacterial and viral antigens, yet these were not sufficient to ward off purulent, bacterial infections and bronchiectasis, as well as extensive warts on the extensor aspects of the hands presumably caused by papilloma virus.

There was no splenomegaly thus excluding the category of CVID with splenomegaly³ nor did the children have the facial anomalies described in the immunodeficiency, centromeric instability, and facial anomalies syndrome. Furthermore, CD4+ deficiency secondary to infection with hepatitis C has been excluded, as no hepatitis C antibodies were detected.⁴ CD4+ T cell deficiency is also a feature of the bare lymphocyte syndrome⁵ and of hereditary absence of the T4 epitope.⁶ Our patients do not fit the criteria of either of these syndromes. In the WHO report² allowance is made for the fact that new clinical forms of immunodeficiency and associated syndromes will be described in the course of time. We believe that we have described one such entity.

This study was supported by grants from the Miriam Coven-Fish Foundation and from the F Goldhirsch Foundation.

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