Immune Deficiency Disease of Undetermined Aetiology in Infancy

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SUMMARY

Immunodeficiency diseases in infancy may be genetic or may result from an infection acquired during intrauterine life. A precise aetiological diagnosis is important for genetic counselling purposes, prognosis and treatment. The case of a young female child with a combined immunodeficiency disease and thrombocytopenia is presented. The difficulties of establishing a precise aetiological diagnosis are illustrated.

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Immune deficiency diseases in infancy are best known as a number of well-defined inherited disorders. Among these disorders are diseases that affect antibody production, cell-mediated immunity, and a combination of both (combined deficiency). There have been recent reports of an acquired immune deficiency disease resulting from congenital rubella infections, involving both humoral and cell-mediated immunity.[1,2] It is possible that other congenitally acquired infections, e.g. syphilis, cytomegalovirus and toxoplasmosis may produce a similar syndrome.[3] It is important to determine the cause of an immune deficiency disease in order to facilitate sound genetic counselling and effective teatment. Without an accurate diagnosis it is impossible to give a prognosis.

This report describes a female infant who presented with recurrent infections and thrombocytopenia. Investigation revealed a combined immunodeficiency disease associated with increased peripheral destruction of platelets. The difficulties encountered in determining whether the disorder is an inherited condition or an acquired immune deficiency disease resulting from a congenital infection, are clearly illustrated.

CASE PRESENTATION

A 3½-year-old White girl with repeated upper respiratory tract infections, purulent otitis media and frequent epistaxes was referred to our Immunology Unit.

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Past History

The child was born full-term in October 1968 after a normal pregnancy and delivery. During labour there was a delayed second stage, but no immediate postnatal complications were reported. The infant's developmental milestones in the first year of life were noted to be delayed, and mental retardation was suspected. Physical examination at the age of 10 months confirmed the mental retardation, and on further examination generalised lymphadenopathy and hepatosplenomegaly were found. Examination of other organ systems was non-contributory. Triple vaccine consisting of diphtheria, whooping cough and tetanus (DWT) was administered during infancy at the recommended ages, and a 'booster' was given at 1½ years. Measles vaccination was carried out at 1 year of age. Smallpox vaccination was not given as the child was ill at the time the vaccination was due. Repeated upper respiratory tract infections and otitis media occurred and were treated successfully.

Laboratory investigations in August 1971, when the child was aged 2 years 10 months, showed a haemoglobin level of 10,4 g/100 ml, leucocytes 2 300/μlitre with neutrophils 28%, monocytes 7%, lymphocytes 54%, eosinophils 11%, and the blood film was noted to exhibit reduced numbers of platelets. A bone marrow aspirate showed moderate hypercellularity, normoblastic erythropoiesis, active myelopoiesis with an eosinophilia of 14%, normal numbers of megakaryocytes and scanty free-lying platelets. The findings were interpreted as suggesting 'hypersplenism'. Further investigations showed normal thyroid function, and the serum calcium, phosphorus, cholesterol, glutamic oxaloacetic transaminase (SGOT), glutamic pyruvate transaminase (SGPT) and VDRL tests were all normal. X-ray studies of the chest and bones were normal. A lymph node biopsy showed reactive follicular hyperplasia, suggesting hyperactivity of the B cell system. Clusters of pale abnormal histiocytic cells were present in some areas. The paracortical areas appeared well-preserved.

Present Examination (April 1972)

A small, irritable girl of 3½ years, hirsute, microcephalic and mentally retarded, was seen. Webbing of the neck was present, but no other stigmata of Turner's syndrome were noted. Generalised lymphadenopathy and a 2-finger hepatosplenomegaly were found. There was a purulent discharge from drainage tubes placed in both middle ears.

Laboratory tests: The haemoglobin value was 11,0 g/100 ml, leucocytes 5 700/μlitre, with neutrophils 65%, monocytes 5%, lymphocytes 21%, eosinophils 9%, platelets 100 000/μlitre and reticulocytes 5%. A bone marrow aspirate revealed adequate to increased numbers of megakaryocytes, without obvious budding, findings suggestive of increased peripheral destruction of platelets. A smear from the buccal mucosa showed chromatin-positive material in over 15% of cells, indicating an XX female. Peripheral blood samples taken on repeated occasions for chromosome cultures all failed to yield an adequate number of metaphases for analysis. Rubella virus and cytomegalovirus were not cultured from repeated urine samples. An adenovirus type III was isolated from the urine on one occasion during an upper respiratory tract infection.

Immunological Studies

Humoral immunity: The results are detailed in Table I. The immunoglobulin levels and complement titres were estimated on two occasions. The IgM concentration was elevated, IgA decreased, and IgG normal. Complement levels were low. The Coombs test was negative. The child was found to be blood group A, with no demonstrable anti-B agglutinins. Antibody titres to diphtheria, measles and poliomyelitis were all less than expected for the immunised child. The antibody titre to cytomegalovirus was 1/8, and no antibodies to rubella virus could be detected. Rheumatoid factor was not detected, and the toxoplasma complement fixation and dye tests were negative.

Cell-mediated immunity: Cutaneous delayed hypersensitivity reactions to both *Candida* antigen and diphtheria toxoid were negative. Lymphocyte transformation to both phytohaemagglutinin (PHA) and *Candida* antigen was impaired. Circulating lymphocytoxins were not detected.

Giblett *et al.*[4] recently reported 2 female children suffering from a combined immune deficiency disease and in both of whom there was a complete absence of the red cell enzyme adenosine deaminase (ADA). Because of the similarity between these 2 cases and our patient, a sample of blood was examined for the presence of ADA by means of starch gel electrophoresis. The enzyme appeared to be present in normal concentration and conformed to the common 1 - 1 genetic type.

Studies on the Parents

Mother: The haemoglobin value was 13,7 g/100 ml, leucocytes 8 200/μlitre (neutrophils 77%, monocytes 5%, lymphocytes 18%) and platelets 208 000/μlitre. The serum immunoglobulins were normal and the total complement was 1/31, with the β_1C 1/31. The toxoplasma indirect fluorescent antibody test and Sabin-Feldman dye test were negative. Antibody titres were: cytomegalovirus 1/8,

TABLE I. RESULTS OF TESTS OF IMMUNOLOGICAL FUNCTION

	Patient	Normal
Humoral immunity		
1. Immunoglobulins		
IgG	840 mg/100 ml	500 - 1 360
	700 mg/100 ml	
IgA	30 mg/100 ml	45 - 135
	4 mg/100 ml	
IgM	320 mg/100 ml	46 - 190
	250 mg/100 ml	
2. Complement titres		
Total	1:15	1:37 - 1:64
	1:25	
β_1C	1:15	1:23 - 1:65
	1:25	
3. Blood group iso-antibodies	Group A — no anti-B agglutinins	Anti-B agglutinins should be present
4. Antibody titres		
Diphtheria	0,01 - 0,02	0,1 - 1,0
Measles	1:100	1: 50 - 1:10 000
Poliomyelitis:		
Type I	1:10	1:100 - 1: 1 000
Type II	1:10±	1: 10 - 1: 1 000
Type III	Negative	1: 0 - 1: 1 000
Cell-mediated immunity		
1. Delayed hypersensitivity reactions		
Candida antigen	Negative	Positive
Diphtheria toxoid	Negative	Positive
2. Lymphocyte transformation index		
Candida antigen	1:1	3:1
Phytohaemagglutinin	2:1	10:1

rubella virus 1/512, with no detectable neutralising IgM antibody to rubella virus; a repeat test 2 weeks later did not show a rise in titre. H^3-thymidine incorporation by lymphocyte cultures with *Candida* antigen and PHA were normal.

Father: Blood count and serum immunoglobulins were normal, as was lymphocyte transformation to *Candida* and PHA.

Progress

The patient is attending a special school. Repeated upper respiratory tract infections persist and prophylactic erythromycin is administered during the winter, decreasing the frequency of infection. The recurrent purulent otitis media requires frequent insertions of grommets into the drums of both ears to provide adequate drainage of the middle ear and in addition co-trimoxazole drug therapy is successfully used. The mother is again pregnant and has now presented for genetic counselling.

DISCUSSION

The child appears to suffer from a combined immunodeficiency disease. Humoral antibody responses to childhood inoculations were suboptimal and dysgammaglobulinaemia exists. Cell-mediated immunity was impaired as evidenced by absent cutaneous delayed hypersensitivity responses to *Candida* and diphtheria skin tests, and failure of both *Candida* and PHA to stimulate lymphocyte transformation *in vitro*. Apart from the management of the child there is an urgent need for a definitive diagnosis, so that genetic counselling may be given to the mother who is 3 months pregnant. The possible aetiology includes both non-hereditary and hereditary disorders.

Non-Hereditary Disorders

Congenital rubella: In 1945 Norman Gregg[5] reported congenital heart defects, central nervous system damage, deafness and eye defects in neonates of mothers who had contracted rubella infection during the first trimester of pregnancy. Later work[6] established the expanded rubella syndrome that included failure to thrive, hepatosplenomegaly, thrombocytopenia and bony lesions. In these neonates rubella virus has been isolated from the urine, throat washings and blood, and from biopsy specimens of lymphoid organs or postmortem culture of tissue from various organs. More recently Good *et al.*[1,7] have drawn attention to the immunological aspects of congenital rubella, in which cell-mediated immune responses may be defective. The lymphocytes of infants with congenital rubella infections are unresponsive to PHA stimulation, though skin tests to *Candida*, DNCB and SS antigen may be normal. Antibody responses to *Salmonella* antigens were normal in 6 of 7 cases tested. The authors[7] suggest that the persistence of the virus in the lymphocytes results in inability of these cells to undergo the metabolic changes requisite to their recruitment for immunological function. In addition to cell-mediated immune deficiency Michaels[2] described patients with impaired antibody response to measles, poliomyelitis, diphtheria toxoid and blood group substances, suggesting an immune paresis resulting from the rubella infection. The responses to these antigens became normal when rubella virus excretion ceased. The IgM-neutralising antibodies to the rubella virus were initially high, decreasing as the virus was excreted and the infection terminated. Congenital rubella virus infection is the commonest cause of an acquired immunodeficiency disorder; in our patient evidence of rubella infection was not found. However, it is possible that the investigations were carried out at a time when the patient was recovering from the infection, at which stage the rubella virus cannot often be isolated from the urine.

Other infectious diseases: It is possible that an acquired combined immunodeficiency disease may result from congenital infection with syphilis, cytomegalovirus or toxoplasma. There was no laboratory evidence of any such infection in our patient.

Lymphocytotoxin: A combined immunodeficiency disease may result from lymphocyte destruction by a circulating lymphocytotoxin. No lymphocytotoxin was detected in serum from our patient.

Hereditary Disorders

Wiskott-Aldrich syndrome: This is a syndrome characterised by eczema, recurrent infections and thrombocytopenia. The neonate is born with an intact immune system[8] and the immune deficiency disorder usually develops during the first year of life. There are low levels of IgM and dysfunction of the afferent limb of the cell-mediated immune response. This syndrome is a sex-linked recessive transmitted disease, and has not been reported in females. In our patient, an XX female, the Wiskott-Aldrich syndrome is an extremely unlikely diagnosis, although it is theoretically possible that, due to random X-chromosomal inactivation (the Lyon hypothesis), the disease could occur in a female.

The presence of webbing of the neck in this child caused us to consider Turner's syndrome as a possible diagnosis which would have been another way in which the Wiskott-Aldrich syndrome diagnosis in a female could be supported. Chromosome analysis of fibroblasts has not been carried out so we have not excluded, with certainty, a mosaic state.

Thymus aplasia or dysplasia: In the Nezeloff and Di-George's syndromes there is aplasia of the thymus gland and defective cell-mediated immunity. In the Di-George's syndrome there is an associated aplasia of the hypoparathyroid glands resulting in hypocalcaemic tetany at birth. Hereditary thymic dysplasia (lymphopenic agammaglobulinaemia) is a disorder of the bone marrow lymphocyte resulting in a combined immunodeficiency disorder. Genetic transmission is either X-linked or autosomal recessive. Patients with these thymic aplasia and dysplasia syndromes are very severely immunosuppressed and die at a young age from recurrent infections.

The features of our patient do not fit in with any of the presently recognised inherited immunodeficiency syn-

dromes. Although the patient may represent a *forme fruste* of such an inherited disorder, it appears that the immune disorder described is more likely to be the result of an acquired intra-uterine infection. We have advised against amniocentesis and interference with the present pregnancy. Follow-up studies may permit an aetiological diagnosis to be established, since immune deficiency states associated with congenital infections usually improve with time.

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