

Leaders

Virus infections in primary immunodeficiency

A D Webster

Introduction

The human immune system limits the spread of viruses in tissues by a variety of specific (antibodies, cytotoxic T cells) and non-specific (interferons, natural killer cells) mechanisms. These have probably evolved to cope with some of the larger DNA viruses which have the genetic capacity to produce chemokine or cytokine inhibitors to neutralise individual defence mechanisms.¹ Specific antibody will prevent most viruses from infecting susceptible target cells, but it is T and natural killer cells which contain and eliminate an established infection. Specific T cell cytotoxicity depends on the proliferation of CD8+ lymphocytes which recognise viral encoded peptides on the surface of the target cell in the context of self major histocompatibility complex (MHC) class I antigens. This has been worked out in detail for influenza A which stimulates a brisk cytotoxic response in humans.² In general, cytotoxic CD8+ T cells alone are not sufficient for effective protection, because there is a good correlation between a predisposition to severe viral infection and the numbers of circulating CD4+ T cells in AIDS and some primary immunodeficiencies. The likely scenario is that CD4 T cells are specifically activated to produce cytokines, particularly interleukin-2 (IL2), which amplifies the cytotoxic response. In acute Epstein Barr virus (EBV) and varicella zoster infections circulating CD8+ cytotoxic T cell numbers increase. These express low levels of cytoplasmic BC1₂, a molecule which protects against apoptosis.³ This suggests that CD8+ cytotoxic T cells are end stage cells which probably die when they have delivered a lethal blow to the viral infected target cell.

The primary immunodeficiencies include a variety of defects in lymphocytes, complement, and phagocyte function, most being caused by inherited single gene disorders.⁴ Although complement and immune complexes may have an important role in defence against some viruses, only lymphocyte disorders are known to predispose to severe viral infections.

Primary T cell deficiency

Severe primary T cell deficiency is rare, occurring in about 1 in 100 000 live births in Europe. Most affected patients are infants or young children with inherited defects which affect both T and B lymphocyte function (severe combined immunodeficiency (SCID)).

The most common of these is adenosine deaminase (ADA) deficiency or defects in the γ chain of the IL2 receptor. Those affected are prone to a variety of opportunistic and pathogenic viruses, particularly herpes viruses such as cytomegalovirus (CMV), herpes simplex, varicella zoster, and enteroviruses.^{5,6} Chronic diarrhoea caused by adenovirus and rotavirus infection of the bowel also occurs, the former sometimes causing bone marrow aplasia. Most infants with SCID require bone marrow transplantation for long term survival, and it is now standard practice to give acyclovir as prophylaxis against herpes viruses in the interim. Blood transfusions are often needed for anaemia associated with severe infection in SCID, but it is important that the blood is irradiated otherwise donor white cells may induce graft versus host disease; this all too common mistake can only be avoided if paediatricians and pathologists become more aware of the possibility of SCID in infants with severe infection. The blood should also be seronegative for CMV to avoid severe primary infection. Patients with SCID with circulating B lymphocytes are at risk of fulminating EBV hepatitis, supporting the view that B cells are the only major reservoir of infection.⁵

Human papillomavirus (HPV) associated warts may be extensive, usually occurring in children with less severe SCID who have survived long enough to have been infected. The mechanism of protection against HPV is not understood, but probably involves Langerhans' cells in the epidermis which present viral antigens with HLA class II to CD4 T cells.⁷ These in turn, when activated, release cytokines, causing a non-specific local inflammatory response and ischaemia of the wart. Multifocal leucoencephalopathy caused by JC polyoma virus is very rare in infants with SCID who are usually too young to be exposed. This fatal complication mainly occurs in the severe secondary T cell deficiency associated with immunosuppressive drugs given after transplantation or for leukaemia or in AIDS.⁸ A close relative, BK polyoma virus, frequently reactivates in transplant recipients, but there is no good evidence that it causes disease.

Vaccination with live attenuated viruses should be avoided, although the risk of poliomyelitis and disseminated measles is small, probably because maternal IgG antibodies protect the infant; furthermore, most patients with SCID are given regular intravenous or

Department of
Clinical Immunology,
Royal Free Hospital
School of Medicine,
Rowland Hill Street,
London NW3 2PF
A D Webster

Correspondence to:
Dr A D B Webster

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subcutaneous immunoglobulin infusions which should protect against infection. Disseminated vaccinia virus infection used to be a common cause of death before routine vaccination was abandoned.

The prognosis for SCID has improved over the past decade, mainly due to better diagnosis and management of fungal and viral infections, and improved bone marrow transplantation techniques. CMV pneumonitis remains an important cause of death, although prophylaxis with acyclovir reduces the risk of infection. New polymerase chain (PCR) techniques to diagnose CMV, together with more powerful antiviral drugs, will improve the prognosis further.

The numbers and function of natural killer cells have not been routinely measured in patients with SCID, so we cannot assess whether natural killer cell deficiency contributes to viral infections in these syndromes. Complete deficiency of natural killer cells is probably very rare, but there have been a few reports of patients with an apparently inherited absence who have had severe herpes virus infections (EBV, CMV, and varicella). Patients with Chédiak-Higashi disease, in which there is a primary failure of leucocyte degranulation, have substantially reduced natural killer cell function because the cells cannot initiate lysis.⁹ Affected patients are not prone to severe viral infections, but do ultimately develop a lymphoproliferative disorder which may be virally induced.

EBV, immunodeficiency, and lymphomas

Non-Hodgkin's lymphoma, often presenting in the central nervous system and sometimes EBV related, is a complication of the Wiskott-Aldrich syndrome in which there is a deficiency of sialophorin on the lymphocyte surface. These patients have subtle functional defects in both T and B lymphocytes but do not usually have severe herpes virus infections.¹⁰ More dramatic EBV infection occurs in the X-linked lymphoproliferative syndrome (XLPS): men so affected may die from fulminant EBV hepatitis, or if they survive, may develop immunoglobulin deficiency or B cell lymphomas some years later.¹¹ A few female patients with similar features have been described. Although global deficiencies in T and natural killer cell function have been confirmed during acute infection in these patients, the underlying predisposing factor for severe EBV infection is not known; this may have to await the cloning of the relevant gene on the X chromosome.

Primary antibody deficiency

X-linked agammaglobulinaemia (XLA) and common variable immunodeficiency (CVID) are the most common disorders, the former being an important experiment of nature because affected patients have a selective defect in antibody production with normal T cell function and cellular immunity; conse-

quently, they recover normally from measles, mumps, and varicella infection. Patients with CVID also fail to make antibodies but often have additional moderate CD4+ T cell depletion, which probably explains why they differ from patients with XLA in being prone to varicella zoster reactivation. Enteroviruses are exceptional in requiring specific antibody to eliminate an established infection, as shown by the unequivocal predisposition of patients with XLA to chronic echovirus encephalitis.¹² Paralytic poliomyelitis following vaccination is also a potential risk, and prolonged excretion of virus without symptoms has been reported; all live vaccines are therefore contraindicated in these patients. It is surprising that there are so few cases of poliomyelitis in patients with XLA or CVID because many must be exposed to potentially pathogenic polio virus excreted by close relatives after routine vaccination. However, most patients receive regular prophylactic pooled IgG infusions which probably contain enough specific antibody to provide an adequate protective concentration in the saliva. Echoviruses seem to have a tropism for cortical neurones and small vessels in the meninges and peripheral limb muscles. Consequently, patients present with a variety of central nervous system features, particularly seizures, eighth nerve deafness, and slowly progressive dementia; chronic myositis is less common. Although virus was regularly cultured from the cerebrospinal fluid (CSF) of affected patients about 10 years ago, our recent experience shows that CSF cultures are frequently negative in patients with characteristic features of enteroviral disease. Furthermore, the CSF may show very little evidence of an inflammatory process, sometimes with a normal cell count, and only slightly raised protein. The best explanation for the failure to culture viruses is that most patients nowadays receive immunoglobulin prophylaxis which may contain enough specific antibody to neutralise enteroviruses partially, although this may not always be adequate to prevent infection. However, a rapid diagnosis can be made with a PCR technique which involves amplification of a conserved sequence in most enteroviral genomes.¹³ This technique cannot at present identify individual enteroviruses so we are not able to link particular clinical features with specific viruses. Once the central nervous system infection is diagnosed, regular high dose intravenous immunoglobulin may help, but usually there is a steady downhill course over the next two to 10 years. Regular infusions of immunoglobulin containing some specific antibody into a ventricular (Ommaya) reservoir can prevent progression of the disease in the short term, although the overall prognosis is still very poor. Enteroviral infection in hypogammaglobulinaemic subjects may be more prevalent than is generally recognised, and more work is needed to investigate a possible link with chronic inflammatory bowel disease and cardiomyopathy in these patients.

There is no evidence that patients with

XLA or CVID are more at risk from hepatitis C (HCV) and hepatitis B virus (HBV) infection transmitted in the community. However, they are at risk of exposure to HCV from contaminated immunoglobulin treatment and there have been four episodes in which a number of patients have been infected in the United Kingdom during the past decade.¹⁴ This risk should be much reduced with the recent introduction of immunoglobulin which has been pasteurised or treated with solvent and detergent to inactivate viruses. Patients with CVID seem to have a particularly poor prognosis following HCV infection, and four of nine of our patients infected in 1982 have died from cirrhosis within 10 years. Chronic T cell activation, which is part of the underlying pathology of CVID, may increase inflammation and liver cell necrosis. There is evidence that IgA deficiency can both predispose to and follow chronic HCV infection acquired in the community, but this survey was performed in Israel where the incidence of IgA deficiency in the general population is higher than in other parts of the world.¹⁵ Nevertheless, the finding supports the hypothesis that viruses can trigger immunodeficiency in genetically susceptible individuals.¹⁶

Patients with primary or secondary immunodeficiency might be expected to be at increased risk from infection with HIV, but there are no data from which to draw conclusions. A few patients with CVID have acquired HIV through sexual exposure, and interestingly, the virus has reversed the hypogammaglobulinaemia in some by polyclonally stimulating B cells to produce antibodies.¹⁷ However, the improvement in immunity is only temporary as all the patients have died from HIV related T cell deficiency and opportunistic infections within a few years.

In conclusion, clinical studies on patients with primary immunodeficiency have clearly shown the importance of T cells in protection against herpes viruses and of antibodies

against enteroviruses. We await the cloning of the XLPS gene which hopefully will throw light on the mechanism of controlling EBV infection.

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