Human retroviruses and paediatric disease

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Retroviruses are a distinct group of RNA viruses which replicate via a double stranded DNA intermediate, synthesised from the virion by an RNA dependent DNA polymerase (reverse transcriptase). Thus unlike other viruses, exogenous RNA codes for DNA. The intermediate, known as the provirus, is integrated into host cell DNA and acts as a template for the production of viral genomic and messenger RNA by the host cell. Retroviruses are known to cause a wide range of diseases in numerous animals. (Table).

In spite of an intensive search for similar viruses in man the first human retrovirus was not reported until 1980. The human T cell leukaemia/lymphoma virus type I (HTLV-1) has since been shown to be the causal agent of the adult T cell leukaemia syndrome, and more recently to be closely linked to tropical spastic paraparesis.¹ A second human retrovirus HTLV-2 is similar to HTLV-1 but has yet to be associated with disease. The third human retrovirus previously known as lymphadenopathy virus (LAV-1), or human T cell lymphotropic virus type 3 (HTLV-3), and now collectively referred to as human immunodeficiency virus (HIV), is the causative agent of the acquired immune deficiency syndrome (AIDS) and its related disorders. All three viruses have animal counterparts. Retroviruses are divided into three groups: oncoviruses, lentiviruses, and spumaviruses. Oncoviruses are associated with transformation either by transporting an 'oncogene' into the host cell, or by inserting themselves next to cellular homologues of oncogenes and 'turning them on' by promoter activity. HTLV-1 and HTLV-II, although capable of causing transformation, do so by an alternative method by activating genes not necessarily next to them but at a

considerable distance. This is known as trans activation, and is similar to the function of bovine leukaemia viruses of cows. HIV is cytopathic and does not cause transformation in vitro, consequently. It is similar in structure to the lentiviruses such as the visna maedi virus of sheep. Spuma or foamy viruses have been recognised for some years, although with the possible exception of Quervain's thyroiditis, they have not been associated with human disease.

The HIV family of viruses share the same general structure as other retroviruses. The virion is 100 to 130 nm in diameter and contains two identical strands of RNA within a glycoprotein envelope. The Figure shows the genomic structure of the HIV provirus and its products. The Gag region codes for the core proteins, the Pol region codes for the magnesium dependent reverse transcriptase, and the Env region encodes the envelope glycoproteins. The Env region is highly polymorphic and may differ by 20% to 30% in different isolates of HIV. The sequences which encode the viral proteins are flanked by long terminal repeat sequences (LTRs). These regions contain promoter and enhancer elements for viral gene expression. The HIV virion contains an additional four open reading frames (sequences capable of encoding a protein)

Table Diseases caused by retroviruses in animals

Leukaemia (avian, mouse, cat, primates)
Lymphoma (avian, mouse, cat, primates, fish)
Carcinoma (mouse (mammary), chicken, (renal) cat, horse anaemia, aplasia)
Wasting and autoimmune disorders (cat, primates, mouse (system lupus erythematosus-like illness))
Arthritis (goats)
Nervous system (mouse, sheep, goat)
Osteopetrosis (chickens)

Figure The genes and proteins of HIV.

known as sor, tat III, 3'orf, and art. Tat III and art both produce proteins that enhance the expression of other HIV genes—in other words they are transactivators. The function of the sor and 3' orf has not yet been defined.

It is now clearly established that the T4 (CD4) molecule behaves as the receptor for HIV in human cells.² T4 is a non-polymorphic glycoprotein that defines a subset of lymphocytes known as helper/inducer cells which have antigen recognition and regulating function axial to the immune response. HIV binds directly to the T4 molecule via the envelope glycoprotein GP110³ and the introduction of T4 into any human cell renders it permissive for HIV replication.⁴ The T4 gene is expressed in the central nervous system⁴ and probably accounts for the dual lymphotropism and neurotropism of the virus. The profound immunodeficiency found in AIDS is principally due to deletion of the T4 lymphocytes, but a wide range of immunological abnormalities are associated with HIV infections. Dendritic cells and macrophages, both of which express T4, are also infected.⁵ The numbers of circulating cytotoxic suppressor cells, defined by the T8 (CD8) antigen, are increased and may regulate HIV expression.⁶ These abnormalities lead to a decreased blastogenic response of T lymphocytes to mitogens in vitro and cutaneous anergy to skin test antigens in vivo. Patients with AIDS characteristically have evidence of polyclonal B cell activation manifest by increased circulating immunoglobulins, detectable immunocomplexes, and enhanced spontaneous proliferation and responsiveness of B lymphocytes to B cell growth factors in vitro. HIV may be a direct polyclonal activator of these cells.⁷ The exaggerated B cell activity is, however, non-specific, and patients with AIDS produce a poor humoral response to new immunising antigens.

Whereas HIV seropositive adults become hypergammaglobulinaemic and children often become hypogammaglobulinaemic when infected with HIV, (which may in part account for the increased number of bacterial infections in vitro). HIV seems to be able to turn on or off gammaglobulin production. Indeed, a patient who had hypogammaglobulinaemia for many years became hypergammaglobulinaemic after HIV seroconversion (Webster ADB, Spickett G, unpublished observations). B cells are probably not infectable unless they express the CD4 antigen (Malkovsky M, Dalglish AG, unpublished observations).

The clinical spectrum of adult AIDS has been well reviewed⁸ and depends in part on the range of pathogens encountered by the immunocompromised subject. The centres for a disease control definition of paediatric AIDS differ only slightly

from that given for adult AIDS⁹ and accept the same diseases as indicative of underlying cellular immune deficiency in both groups, with the addition of childhood interstitial pneumonitis confirmed by biopsy. Children with AIDS, however, are much more likely than adults to have intercurrent bacterial infections and may have unique pulmonary and central nervous system manifestations.

AIDS in children most commonly presents with recurrent bacterial infections, often pneumonia or meningitis, persistent and recurrent oral candidiasis, and failure to thrive.⁹ Almost all will develop non-specific features, including generalised lymphadenopathy, hepatosplenomegaly, recurrent otitis media, persistent monilial 'nappy rash' and diarrhoea.¹⁰ These features are familiar to the general paediatrician, and a high index of suspicion is required to diagnose an acquired immunodeficiency syndrome. In particular, the distinction between AIDS and AIDS related complex is much less clear in children than in adults. Unilateral or bilateral parotid gland enlargement occurs in up to 20%, and in the context of non-specific features is highly suggestive of AIDS.

The major morbidity and mortality in paediatric AIDS is associated with lung disease. *Pneumocystis carinii* pneumonia occurs in 30% of paediatric cases and usually within the first 6 years of life; it carries a very poor prognosis, particularly when coexistent with bacterial infection. The most common lung disease, however, is chronic interstitial pneumonitis redefined by Rubenstein as pulmonary lymphoid hyperplasia.¹¹ This condition presents at the mean age of 14 months with radiological appearances of interstitial pneumonitis and characteristic findings on lung biopsy. It is often part of a spectrum of digital clubbing, parotid gland enlargement, and raised IgG values. Epstein Barr virus DNA is often found in the lung biopsy specimens.¹² The mortality from this condition is 15%, in comparison with a mortality of 60% in children with pneumocystis. The manifestations in the central nervous system, which are unique to paediatric AIDS, include microcephaly, developmental delay and regression with loss of achieved landmarks, and calcification of the basal ganglia.¹³ Children may also develop an encephalopathy with a combination of cortical and long track signs and ataxia, similar to the adult disease. Direct HIV infection of the central nervous system also probably occurs, although affected children often have antibodies to rubella, cytomegalovirus, and *Toxoplasma*. Hodgkin's and non Hodgkin's lymphomas have also been reported in paediatric AIDS. Kaposi's sarcoma occurs in less than 20% of children in most series.

More than 70% of all paediatric AIDS in the

United States of America has occurred in children born to mothers who are intravenous drug abusers (Centers for Disease Control, unpublished observations). In the United States New York, Miami, and Newark have the highest number of cases of paediatric AIDS cases and have reported an approximated 50% increase for each of the past six years. It is striking that almost one quarter of paediatric cases in America have been reported by a single hospital, and it is likely that the total prevalence of the condition is grossly underestimated. Maternal risk factors other than intravenous drug abuse are sexual promiscuity and regular contact with known HIV positive partners. Children may also contract AIDS from transfusion of infected blood or blood products, and more rarely from sexual abuse or needle stick injury. Medical injections may also be a risk factor in developing countries.¹⁴ HIV is transmitted in utero and has been isolated from a 15 week fetus;¹⁵ it may also cause a distinctive dysmorphic syndrome,¹⁶ suggesting infection in the first trimester. HIV is also likely to be spread by exchange of maternal and fetal blood at childbirth and may be transmitted by breast milk.¹⁷ The rate of spread from mother to child is uncertain and rates of between 50 and 90% have been reported for first and subsequent births.^{9 18} The mothers of HIV positive children may be asymptomatic and may subsequently have other HIV negative children.¹⁰ The diagnosis of AIDS in a child should therefore lead to screening of parents and siblings.

There is a single report of possible horizontal transmission of AIDS by biting.¹⁹ Several large studies have failed, however, to show the spread of AIDS from infected to non-infected children, even in circumstances of close contact and sharing of beds, toothbrushes, and eating materials.^{9 20} There is therefore no good evidence to support in any way the segregation of HIV positive children.

Laboratory diagnosis of AIDS in children is also more difficult than in adults. The profound lymphopenia of adult AIDS is absent in children. The earliest defect in cell mediated immunity is a decrease in circulating thymulin, a thymic hormone responsible for T cell maturation. B cell abnormalities are characteristically profound. Children do, however, develop antibodies to the major antigenic proteins of HIV and loss of anti-P24 may have the same predictive value for the development of AIDS as in the adult.²¹ Antibodies detectable in the first 6 months of life may be acquired from the mother, and in situ hybridisation has been used in the diagnosis of neonatal AIDS.²² AIDS must be differentiated from the primary immune deficiency syndrome, including severe combined immune de-

ficiency (SCID), Wiskott – Aldrich and Di Georges syndrome. SCID may be an important differential diagnosis, particularly as children with AIDS are often hypogammaglobulinaemic,¹⁰ but the distinctive clinical and laboratory features of the other syndromes should facilitate their identification.⁹

There is no effective specific antiviral drug for the treatment of AIDS. Antiviral strategy may be directed at the pathway by which the virus/T4 complex is endocytosed at the unique retroviral reverse transcriptase enzyme or at transcriptional and virus assembly control mechanisms.²³ Many *in vitro* inhibitors of reverse transcriptase exist. Azidothymidine, a thymidine analogue, crosses the blood brain barrier and has been tried in vivo. It is only moderately effective and its use has been limited by severe bone marrow toxicity.²⁴ Intravenous gammaglobulin treatment may prevent the high incidence of bacterial infection in children with AIDS.^{6 25} HIV positive children should never be given live viral vaccines or BCG; killed polio may be available and the triple of diphtheria/tetanus/killed polio is safe.

The development of vaccine has been based on the use of the envelope glycoproteins as immunogens. The envelope glycoprotein SP120 is highly polymorphic, and although serum from infected individuals can effectively cross neutralise different HIV isolates, no antibody raised to the envelope glycoproteins in vitro has shared this ability.²⁶ A vaccine using envelope glycoproteins from a combination of isolates may be more effective. Alternative approaches are therefore of interest. Antibodies raised to peptide sequences from gp41 the transmembrane glycoprotein seem to have some activity against all isolates so far tested (Dalglish *et al*, unpublished observations). Similarly, antibodies raised to monoclonal antibodies (anti-idiotypes) inhibited viral binding to T4 mol-

Provisional case definition of AIDS in children

- 1 A reliably diagnosed disease at least moderately indicative of underlying cellular immunodeficiency and
- 2 No known cause of underlying cellular immunodeficiency or any other reduced resistance reported to be associated with that disease. The diseases used as sufficiently indicative of underlying cellular immunodeficiency are the same as those used in defining AIDS in adults after the exclusion of congenital infections such as toxoplasmosis or herpes simplex virus infection in the first month after birth, or cytomegalovirus infection in the first six months after birth.

ecule and offer the exciting possibility of blocking a pathway used by every known HIV.²⁷

In the meantime counselling of HIV positive patients or at risk patients is the only means of preventing paediatric AIDS. Therapeutic abortion may be offered to asymptomatic HIV positive mothers, although further information on the outcome of such progress is urgently required. Mothers with AIDS should unquestionably be offered abortion, as pregnancy is likely to be fatal for both mother and child.

Two new human retroviruses have recently been isolated. HIV-2 is described in patients with AIDS from Cape Verde, Portugal, Central Africa, and most recently, France;²⁸ HTLV-IV has been isolated from asymptomatic patients in Senegal.²⁹ These viruses have not yet been directly compared but present data show that they are both more closely related to the simian retroviruses found in old world monkeys than to HIV-1. There is no reason to believe that children will be exempt from infection by these viruses.³⁰⁻³²

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