14. Gordon D.O.Lowe, Haemophilia, Blood Products and HIV Infection, Scot Med J Vol. 32:109- 111, 1987

Prevalence of viral and HIV infection in haemophilia

Twenty years ago, the life expectancy of a severe haemophiliac was only half that of a non-haemophiliac. From 1967, the therapeutic use of cryoprecipitate, a plasma concentrate rich in factor VIII (antihaemophilic factor), allowed control of such bleeding and greatly reduced the premature mortality.

From the mid-1970s, the therapeutic use of lyophilised clotting factor concentrates allowed more predictable correction of the coagulation defect; the performance of major surgery; and self-administration of home treatment, which prevented serious joint bleeds and hospitalisation, and reduced disability and time off work. Factor VIII concentrates were used for the 80% of congenital bleeders who have classical haemophilia, and factor IX concentrates for the 10% who have congenital factor IX deficiency of Christmas Disease. Cryoprecipitate remained the treatment of choice for the other 10% of congenital bleeders with von Willebrand's disease, since it is rich in von WAillebrand factor.

Whereas one therapeutic or prophylactic infusion of cryoprecipitate comes from about 20 blood donors, one infusion of lyophilised clotting factor concentrate (factor VIII or factor IX) originates from several thousand blood donors. It follows that exposure to bloodborne viruses which are reasonably prevalent in the population is inevitable. This was first apparent for viral hepatitis : a spate of clinical hepatitis (usually non-A, non-B) followed the introduction of clotting factor concentrates in the mid-1970s, and thereafter the majority of concentrate-treated haemophiliacs were noted to have intermittently or continuously elevated serum transaminases (again their viral status was usually non-A, non-B.

An increased incidence of AIDS was noted in haemophiliacs in the USA shortly after the recognition of the AIDS epidemic, in 1982. Subsequently, HIV-antibody testing of sera from haemophiliacs in the Western world showed a high incidence of positive results.

Immunosuppression by blood products in haemophilia

The high prevalence of HIV infection in haemophiliacs may reflect not only the 'seed' (transfusion of HIV-contaminated blood products) but also the 'soil' (prior immunosuppression by regular infusion of non- HIV-infected blood products). Several studies have reported immune disturbances in treated haemophiliacs, in the absence of HIV- antibodies these findings may reflect the effects of plasma proteins, or possibly of other viruses, on the immune system. We have shown that concentrate-treated severe haemophiliacs had reduced skin test responses to a new antigen (DNCB), which was unrelated to their HIV- antibody status, but which correlated with the amount of factor VIII replacement therapy in recent years. Further-more, factor VIII concentrate and immunosuppressive effects on lymphocytes in vitro.

In Edinburgh haemophiliacs exposed to the HIV-contaminated batch of factor VIII concentrate, Ludlam and colleagues reported that the probability of seroconversion was related to the severity of previous T-lymphocyte changes, and to the extent of total transfusion with factor VIII. The immunosuppressive effects of replacement therapy in haemophiliacs may therefore predispose to HIV-infection, and possibly to its progression.

Progression of HIV infection in haemophilia

It has been suggested that positive HIV antibody tests in haemophiliacs may sometimes represent an antibody response to 'dead' viral proteins in plasma concentrates. However several pieces of evidence suggest that positive antibody tests usually represent active proliferation of the virus in vivo. Firstly, progressive increases in HIV-antibody titre are invariably seen in serial studies of seropositive haemophiliacs attending this centre (E.A.C. Follet, 1987, personal communication). Secondly, progressive decreases in lymphocyte counts or T4-lymphocyte counts have been observed in seropositive haaemophiliacs attending this centre or the Edinburgh centre. Thirdly, HIV has been isolated from the T-lymphocytes of some seropositive haemophiliacs. Finally, the rate of progression of HIV- infection to AIDS in haemophiliacs appears similar to that in other high risk groups.

Kaposi's sarcoma appears to be rare in haemophilia compared to other risk groups : it may be due to another agent, which is inactivated in clotting factor concentrates.

Preventive measures against new HIV infection of haemophiliacs

Following the recognition of HIV-infection from blood transfusion, especially from large-donor-pool clotting factor concentrates, several preventive measures were instituted. Firstly, blood donors were selected, by asking members of high risk groups and their sexual partners to refrain from donation, and by screening of donations for HIV antibody. In the future, screening may be extended to include HIV-antigen (which would narrow the 'window' between donor infection and the production of detectable HIV-antibody), and possibly tests for the recently-recognised HIV-2 virus.

Secondly, clotting factor concentrates have been heat-treated since 1985: heat treatment would be expected to destroy this rather fragile virus.

A third means of reducing the risk of HIV infection in haemophilia is to use lower-risk treatments. Low-risk treatments include cryoprecipitate, fresh frozen plasma, the synthetic drug desmopressin which increases endogenous factor VIII levels and eventually genetically-engineered factor VIII.