PROTOCOL
PROSPECTIVE STUDY OF PATIENTS WITH CONGENITAL ANEMIAS

BACKGROUND AND RATIONALE

General Overview

One of the populations in which acquired immune deficiency syndrome (AIDS) was seen early in the present epidemic was hemophiliacs treated with commercially prepared clotting factor concentrates. This occurrence was recognized as consistent with the hypothesis that the disease is caused by a transmissible agent which is capable of sustaining itself as a prolonged or chronic infection, and which is present in the blood of at least some infected persons. Commercial preparations of factor VIII and IX are almost certain to expose hemophiliacs to any virus that may be present in the blood of any of the tens of thousands of plasmapheresis donations pooled to make each lot of these biologically active proteins. It is not surprising, therefore, that a newly introduced agent with the indicated characteristics would soon appear among hemophiliacs.

From the occurrence of AIDS among hemophiliacs, it seemed predictable that as the etiologic agent became increasingly prevalent in the United States, transfusion of whole blood and unpooled components would also become a mechanism of transmission. The first case in which transfusion was suspected as the source of AIDS was reported in 1982, and the number of transfusion-associated incidents is now sufficiently large that there is no doubt that the disease is a potential consequence of administration of blood and blood components.

Publicity about transfusion-associated AIDS resulted in great concern in the medical community, especially among blood collection services. With no specific etiologic agent identified, however, there were few measures that could be effectively applied. One approach was to ask persons aware of epidemiologic circumstances that could have exposed them to the risk of infection to refrain from giving blood. In addition, serious consideration was given to use of laboratory screening procedures known to be non-specific but that nonetheless might identify enough infections to improve the safety of the blood supply.

A major change in the situation was brought about by the identification of the infectious agent underlying the immunologic defects responsible for AIDS. Since 1983, materials from patients with persistent generalized lymphadenopathy or with AIDS have yielded isolates of retroviral strains with essentially identical characteristics. Although the designation of the virus as "LAV" may have a claim to priority, the more widely used and evocative name is "HTLV-III". In addition to the fact that the same virus has been isolated from appropriate patients by several laboratories, the frequency of antibodies to components of HTLV-III among persons in various groups with an increased risk of clinical disease has been approximately proportional to the extent of that risk. On the basis of this evidence, HTLV-III is now generally accepted as the etiologic basis of AIDS. Whether other factors contribute to the frequency with which HTLV-III infection leads to clinical disease or immune changes is not yet established.

Study of Persons with Congenital Anemias

Thus far, few cases of transfusion-associated AIDS have been seen in persons with congenital anemia treated with blood or blood products. However, occasional cases with lymphadenopathy and/or other findings consistent with milder expressions of HTLV- III infection have been seen.

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The present study was proposed by the National Heart, Lung, and Blood Institute when it became apparent that transfusion of blood and blood components was a mechanism of transmission of the etiologic agent of AIDS. Patients with congenital Anemias were selected for study because, unlike hemophiliacs (whose transfusional requirement is met in most instances with pooled products), they receive whole blood and unpooled components, enabling investigation of immunologic and virologic changes associated with these products, including those related to AIDS. The subsequent identification of HTLV-III as the etiologic agent of AIDS offers the opportunity to investigate the extent to which these changes may be attributable to infection with this virus.

For purposes of this study, persons with any congenital anemia will be considered as possible study subjects. This includes, but is not limited to, sickle cell anemia (SS), other sickle cell disease (e.g. SC, S thal, and S thal), thalassemia major and intermedia, and Blackfan-Diamond anemia.

OBJECTIVES

1. To determine the sero-reactivity rate for HTLV-III in patients with congenital anemias.

2. To assess the natural history of HTLV-III infection in the following clinical subgroups:

    a) Patients with no symptoms potentially related to HTLV-III infection

    b) Patients with generalized lymphadenopathy, weight loss, unusual fatigability, or other manifestations that may precede AIDS, or that may represent a less severe expression of HTLV-III infection.

    c) Patients with diagnosed AIDS.

3. To determine the frequency and severity of immunologic changes in patients receiving blood products in relation to the following factors:

    a) Characteristics of the blood products received, including type (whole blood, packed red cells, buffy coat-poor or frozen red cells, or other unpooled components), amount, frequency, and the interval from last administration to the time of observation.

    b) Host characteristics, including sex, age, ethnicity, the presence of chronic or recurrent transfusion-transmitted infections, other complications of the anemia, other medical conditions, and clinical status as defined in (2) above.

4. When immunologic changes are found, especially in intermittently or newly transfused patients, to evaluate the extent to which they may be attributable to one or more of the following:

    a) Allogeneic stimulation.

    b) Red cell destruction and the resulting iron overload.

    c) Acute infection with cytomegalovirus (CMV) and/or Epstein-Barr virus (EBV), or reinfection or reactivation of latent infection with either/both.

d) Acute or chronic infection with HBV, the agent of delta hepatitis, and/or the agents of NANB hepatitis, or reactivation of the latter.

e) HTLV-III infection.

5. To determine whether the putative immunosuppressive effects of transfusion influence the severity of manifestations or the tendency to chronicity of any infections (CMV, EBV, HBV, NANB hepatitis, HTLV-III) that are acquired from transfusion.

6. To collect for long-term storage in a TSS-NHLBI repository plasma and cells at the time of each observation from each person entered into the study. This will serve as a source of specimens in future years for evaluating agents to which persons with congenital anemias may have been exposed.

7. To assess the potential for transmission of transfusion- associated viral infections to household members of treated congenital anemia patients, and to evaluate the role of such transmission in further amplification of the reservoirs of infection.

STUDY POPULATIONS

1. Persons with any congenital anemia who have been treated with at least ten (10) units of blood or blood products since January 1, 1979.

2. Persons who have not received blood or blood products since January 1, 1979, and who fall into one of the two following categories:

   a) Patients with any congenital anemia.

   b) Parents, siblings, spouses, children (including those born during the study period), and other household members of the treated patients in Group (1) above.

ELIGIBILITY

The living situation of the patient and household members should be such that follow-up for three to four years is likely to be possible. The place of residence should be such that the patient and members of his household can be expected to keep clinic appointments regularly, or can be visited at home by one of the study's patient managers without undue cost in time and/or money.

SELECTION

The number of persons to be selected for each of the three study populations listed above will be specified in the Manual of Operations. Scheduling of appointments for recruitment will be balanced with respect to:

a) Age, diagnosis, and amount of blood or blood products, for Group (1).

b) Age and diagnosis, for Group (2a).

c) Age, relationship to index case, and anti-HTLV-III status of the index case, for Group (2b).

PROCEDURE

Enrollment

The patient manager assigned to each clinical center's hematology clinic(s) will become acquainted with the staff, learn scheduling procedures and other routines, and become familiar with record-keeping and charts. The clinic's patient roster will be reviewed for eligibility of the individuals. After identifying eligible subjects, further selection may be necessary in terms of the quotas for the groups described under Study Populations above.

All clinic patients will be informed that a transfusion safety study will be conducted, and that the cooperation of those whose participation is solicited will be appreciated. In addition, support may be sought through scheduled or special meetings with patients and members of their families.

Patients already scheduled for visits during the first year of patient entry can be seen as planned, although some adjustments may be needed if the number on any given day would exceed the load that could be enrolled. It is anticipated, however, that persons with mild disease may not be routinely scheduled for annual appointments, or may fail to keep them when scheduled. These patients will need to be identified, and an effort made to recruit them into the study.

The patient manager will describe the study and procedures to be followed to the patient and family. After obtaining informed consent, the patient manager will conduct the entry interview, which will include questions about medical history and present health. Patients over age 12 will be questioned about patterns of behavior, including sexual practices (specifically homosexual contacts) and recreational intravenous drug use.

The patient manager will then conduct a partial physical examination. To be included are: height, weight, temperature, and examination of the mouth, exposed skin, and lymph nodes in the head and neck. If any abnormalities are found, a physician on the study staff will conduct a more complete physical examination, which will include checking for hepatosplenomegaly and a more extensive examination of the skin and lymph nodes, including axillary and inguinal nodes.

The patient manager will also draw a sample of blood. The blood collection procedure, including the amount of blood to be drawn, is specified in the Manual of Operations.

A household roster will be obtained at entry into the study. The patient manager, with the support of the senior clinical staff, will then determine the willingness of household members to participate in the study.

Follow-up

All patients entered into the study will be placed into one of three categories based on the presence of symptoms related to AIDS: asymptomatic, symptomatic, or AIDS. These categories will be defined in the Manual of Operations and will be consistent with CDC criteria. Patients who are asymptomatic will be followed at six-month intervals. Patients who are symptomatic or diagnosed to have AIDS at entry will be followed every three months. Patients who are asymptomatic at entry into the study but who subsequently present with symptoms which require that their category be changed to either symptomatic or AIDS will be followed at three-month intervals, beginning when the patient's category is changed. Symptoms other than those related to AIDS may also make patients eligible for special follow-up.

Each follow-up visit will include a shorter version of the entry interview, a physical examination, and drawing a sample of blood, as described above. The household roster will also be updated.

Subjects will be told as soon as possible if their test results indicate the presence of HTLV-III antibodies. The results of all other laboratory tests must be available at that time.