A DELETION IN THE GENE ENCODING THE CD45 ANTIGEN IN A PATIENT WITH SCID


Purpose of the Study. Defects in genes required for the development of T cells often underlie the primary immunodeficiency known as severe combined immunodeficiency (SCID). Many gene defects have been identified in SCID patients although the most common is the X-linked form of SCID that is attributable to defects in the common cytokine receptor chain. This study examined the cause of a novel type of SCID that was associated with minimal surface expression of CD45. CD45 is an abundant cell surface protein with multiple isoforms. It is a protein tyrosine phosphatase that is critical for transmembrane signal transduction.

Methods. Peripheral blood mononuclear cells from the patient were examined for expression of CD45 using standard flow cytometry techniques. The CD45 gene was sequenced using polymerase chain reaction. To confirm the role of the mutation in the defective expression of CD45, the mutant cDNA was transfected into Chinese hamster ovary cells.

Results. The patient was found to have a homozygous mutation in CD45. The 6 bp deletion was located in the extracellular domain. The mutation did not affect transcript stability or translation, but protein was undetectable at the cell surface. This was true for 3 of the 8 isoforms examined and could be presumed to similarly affect all isoforms.

Conclusions. The homozygous mutation in CD45 was not found in any normal controls and was found to reproduce the defect in transfection experiments. The authors conclude that this 6 bp deletion in the extracellular domain was responsible for the reduced surface expression of CD45 and the patient’s SCID.

Reviewer’s Comments. This particular patient was the first identified as being CD45-deficient in 1997, although the mutation was not identified until this manuscript. It is apparently a rare type of SCID with only 2 patients known to be CD45-deficient. This study demonstrates the importance of the 2 deleted amino acids in the surface expression of CD45 and serves as a reminder of the many types of defects that can potentially be associated with SCID.

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MUTATION IN THE CLASS II TRANS-ACTIVATOR LEADING TO A MILD IMMUNODEFICIENCY


Purpose of the Study. Major histocompatibility complex (MHC) class II deficiency or the bare lymphocyte syndrome is an autosomal recessive congenital immunodeficiency which typically is associated with a severe combined immunodeficiency (SCID)-like picture. There are 4 gene defects that can cause this disorder: class II trans-activator (CIITA), RFX, RFX5, and RFX-associate protein defects. These are all transcription factors required for the coordinate transcriptional regulation of MHC class II genes. Approximately 70 patients with MHC class II deficiency have been described and the usual course is one of unrelenting infections and death by age 4 unless a bone marrow transplant is performed. This manuscript describes 3 adult siblings who had a mild infection history and were found to have CIITA deficiency.

Methods. Monocytes, B cells, and skin dendritic/macrophage cells were stained for MHC class II expression. B cell fusions were performed to identify the complementation group (putative gene defect) and ultimately the CIITA gene was sequenced. Transfection experiments were performed to confirm the functional defect was associated with the identified mutation.

Results. A single homozygous mutation was identified in all 3 siblings. This L469P substitution in CIITA results in an inability to translocate to the nucleus and markedly diminished activity of the transcription factor. Importantly, the activity was not abolished.

Conclusions. This is the first CIITA mutation to result in partial activity. All other mutations have been associated with an inability to translocate to the nucleus and none have been found to stimulate transcription. The mild phenotype in these patients could be attributable to the residual activity of the mutant protein.

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INTRAVENOUS GAMMA GLOBULIN THERAPY

ANTINFLAMMATORY ACTIVITY OF IVIG MEDIATED THROUGH THE INHIBITORY FC RECEPTOR


Purpose of the Study. High-dose intravenous gamma globulin (IVIG) has proven effective for the treatment of autoimmune diseases such as immune thrombocytopenia (ITP), but the mechanism for its beneficial effects have not been clearly defined. In this study, the molecular basis for the antinflammatory property of IVIG was investigated in a murine model of ITP.

Methods. ITP was induced in mice through the injection of an antiplatelet monoclonal antibody (mAb), and pretreatment with either IVIG or Fc antibody fragments (which bind to Fcy receptors on cells, but cannot bind antigens) could prevent the resulting thrombocytopenia. Through the use of specific blocking antibodies and transgenic mice, the authors tested whether IgG receptors (FcyRIIB, FcyRIIB) were involved in the protective effects of IVIG.

Results. The FcyRIIB receptor was required for protection, as demonstrated by genetic deletion or blocking with mAb. In addition, protection by IVIG was associated with the induction of FcyRIIB, which inhibits macrophage acti-
viation, and presumably also inhibits the phagocytosis of platelets in the spleen.

Conclusions. The authors concluded that IVIG inhibits autoantibody-mediated thrombocytopenia by inducing inhibitory FcγRIIB receptors on macrophages. The balance of inhibitory (FcγRIIB) and activating (FcγRIII) Fc receptors is likely to be a critical factor in the regulation of macrophage phagocytosis. These results suggest that autoantibody-triggered inflammatory diseases could be treated by new medications that inhibit macrophage phagocytosis.

Reviewer’s Comments. IVIG is an effective treatment for many diseases caused by autoantibodies, but its utility is limited by high cost, administration by prolonged intravenous infusion, and the occasional occurrence of side effects such as aseptic meningitis and renal insufficiency. This work suggests that new approaches could be developed that would utilize the same protective mechanism as IVIG, but be more easily administered and potentially have fewer side effects. This research also suggests that defects in the FcγRIIB inhibitory mechanism could underlie antibody-mediated autoimmunity. Although additional work is needed to determine whether the findings in this mouse model apply to human disease, these results are cause for optimism.

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HUMAN IMMUNODEFICIENCY VIRUS

LYPODYSTROPHY IN HIV-INFECTED CHILDREN IS ASSOCIATED WITH HIGH VIRAL LOAD AND LOW CD4+ -LYMPHOCYTE COUNT AND CD4+-LYMPHOCYTE PERCENTAGE AT BASELINE AND USE OF PROTEASE INHIBITORS AND STAVUDNE


Purpose of the Study. Maldistribution of body fat often associated with abnormalities in lipid and insulin metabolism (“lypodystrophy”) has been reported in human immunodeficiency virus (HIV)-infected adults. This study was initiated to determine whether similar abnormalities occur in children with HIV.

Methods. Twenty-eight prepubertal HIV-infected children were studied. Total and regional body fat mass was measured by dual energy x-ray absorptiometry (DEXA). Lypodystrophy was defined by both a decrease in arm and leg fat (extremity lypoatrophy) and an increase in truncal fat as measured by repeat DEXA. Baseline and follow-up characteristics of children with an without lypodystrophy were compared and factors associated with lypodystrophy were identified using odds ratios and appropriate statistical analyses.

Results. Eight of the twenty-eight children (29%) experienced lypodystrophy as defined. Children with lypodystrophy had significantly higher levels of HIV RNA, and lower CD4+ T-cell counts. Lypodystrophy was associated with the use of protease inhibitors and stavudine (d4T).

Conclusions. In this longitudinal observational study, 29% of children experienced morphologically defined lypodystrophy. This finding strongly suggests that children are also likely at risk for elevation in athrogenic lipid levels and insulin resistance as previously described in adults with HIV and lypodystrophy.

Reviewer’s Comments. Lypodystrophy is one of several emerging complications seen in HIV-infected children. These complications are likely related to the complex interplay of intrinsic host lipid metabolism, the presence of chronic HIV infection, and the specific drugs used to treat HIV. Lypodystrophy may be associated with significant cosmetic alterations in body habitus and consequently social and emotional disturbances. The long-term impact of the changes associated with lypodystrophy are yet to be defined in children but are likely to involve cardiovascular complications. The improved duration and quality of life of HIV patients is associated with significant long-term metabolic complications.

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POLIO VACCINE SAMPLES NOT LINKED TO AIDS

ANALYSIS OF ORAL POLIO VACCINE CHAT STOCKS

MOLECULAR ANALYSES OF ORAL POLIO VACCINE SAMPLES

Purpose of the Studies. The origin of human immunodeficiency virus (HIV) has been controversial. It is now generally accepted that HIV is a zoonosis, which occurred when simian immunodeficiency virus specific for chimpanzees (SIVcpz) was transmitted to humans. This likely occurred on several occasions in the past. It has been suggested in the lay literature that chimpanzee kidney cultures may have been used in the preparation of oral polio vaccine stocks used in Africa during the late 1950s and so could have introduced the virus into humans.

Methods. Molecular analysis of archived polio vaccines were studied independently by 3 groups.

Results. All 3 studies fail to find either chimpanzee components or HIV/SIV sequences in the polio vaccine stocks. Further, macaque monkey sequences were found, demonstrating that the technique for detection was appropriate, and that the source of the kidney cells used for vaccine development were macaque monkeys and not chimpanzees.

Conclusion. Polio vaccines did not transmit HIV to humans.

Reviewer’s Comments. Human vaccine development is complex, and the use of animal tissue cultures for vaccine production may allow contamination by microbes in the source material. The preparation of oral polio vaccines in the 1950s was done under conditions that would not meet current specifications for purity and safety. In 1999, Edward Hooper promulgated a theory about the transmission of HIV by early batches of oral polio vaccine supposedly grown in chimpanzee kidney cell cultures and tested in Africa. This theory had great social and political implications for the testing of new medical agents in developing countries. The articles reviewed demonstrate the vaccine stocks tested in Africa were not contaminated with HIV, were not prepared in chimpanzee cells, and were not responsible for the epidemic of HIV now ravaging the continent.

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Antiinflammatory Activity of IVIG Mediated through the Inhibitory FC Receptor

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Pediatrics 2002;110;467

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Antiinflammatory Activity of IVIG Mediated through the Inhibitory FC Receptor
James E. Gern
*Pediatrics* 2002;110:467

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