

Anti-sulfatide antibodies in HIV-infected individuals with sensory neuropathy

Abstract—We used ELISA to estimate the prevalence of anti-sulfatide antibodies in HIV-infected individuals with distal sensory neuropathy (DSP) and compared the results with the prevalence in HIV-infected individuals without DSP and in individuals with neuropathy who are not infected with HIV. We found that 36% of HIV+/DSP+ individuals had immunoglobulin (Ig) G anti-sulfatide antibody titers greater than 1,500, whereas IgG anti-sulfatide antibodies were rarely found in HIV+/DSP− or HIV−/DSP+ patients.

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G. Lopate, MD; A. Pestronk, MD; S. Evans, PhD; L. Li, BS; and D. Clifford, MD

Anti-sulfatide antibodies are present in some patients with peripheral neuropathy, including Guillain-Barré syndrome, and in a distal symmetric autoimmune neuropathy.^{1,2} Polyclonal immunoglobulin (Ig) M anti-sulfatide antibodies are most often present in patients with a primarily small-fiber neuropathy. Monoclonal IgM anti-sulfatide antibodies are usually present in patients with a sensory > motor demyelinating polyneuropathy.¹ IgG anti-sulfatide antibodies are rarely found in patients with neuropathy. IgG and IgM anti-sulfatide antibodies have been reported in patients with HIV infection, including patients with and without neuropathy.^{3,4}

Neuropathy is present in 30 to 95% of individuals with HIV infection, depending on the method of detection.⁵ The most common form of neuropathy, a distal sensory polyneuropathy (DSP) is present in 30 to 60% of patients with AIDS.⁵ The principal symptoms of DSP, paresthesias and dysesthesias, underlie the fact that it is a predominant small-fiber neuropathy. The role of anti-sulfatide antibodies in the neuropathy associated with HIV infection has not been established. However, sulfatide is present on CD4⁺ and CD4[−] cells from HIV-infected individuals and the HIV proteins gp120 and gp160 can bind to sulfatide in vitro as well to monocytes expressing sulfatide in an in vivo assay.^{6,7}

Because of inconclusive data, we evaluated the prevalence of anti-sulfatide antibodies in HIV-infected individuals with and without DSP. We also correlated the presence of anti-sulfatide antibodies with clinical features of the neuropathy and HIV infection.

From the Department of Neurology (Drs. Lopate Pestronk, and Clifford), Washington University, St. Louis, MO; and Department of Biostatistics (Dr. Evans and L. Li), Harvard University, Boston, MA.

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Address correspondence and reprint requests to Dr. Glenn Lopate, Department of Neurology, Washington University School of Medicine, Box 8111, 660 South Euclid Avenue, St. Louis, MO 63110; e-mail: lopateg@neuro.wustl.edu

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Methods. Serum was obtained at baseline before treatment from patients enrolled in the AIDS Clinical Trial Group phase II study⁸ of recombinant human nerve growth factor (NGF) for the treatment of HIV-associated DSP (HIV+/DSP+). Control serum from adult patients with HIV infection but no DSP (HIV+/DSP−) was obtained from individuals who were seen at the AIDS Clinical Trial Unit at Washington University. Consecutively eligible patients who were being evaluated for other studies were screened for the absence of signs and symptoms of neuropathy. These patients also had to be without active opportunistic infection; not on any medications known to be neurotoxic including didanosine, zalcitabine, and stavudine; and by history to have no other diseases associated with neuropathy including but not limited to diabetes mellitus, hereditary neuropathy, autoimmune neuropathy, B₁₂ deficiency, or malignancy.

Control serum was also obtained by analyzing 55 consecutive samples sent to the Washington University Neuromuscular Laboratory for evaluation of neuropathy (HIV−/DSP+).

Serum was assayed by ELISA for IgM and IgG binding to purified sulfatide and to control antigens GM1 and other gangliosides and histone H3 and for IgM binding to myelin-associated glycoprotein (MAG) as previously described.¹ Titers greater than 1,500 were considered abnormal based on previous results from neuropathy patient and control serums.

The presence of anti-sulfatide antibodies in HIV+/DSP+ patients from the AIDS Clinical Trial Group phase II study of NGF was correlated with CD4 counts, HIV-1 RNA, age, average and worst pain as measured by the Gracely Pain Scale, global assessments of pain by the subjects and investigators, quantitative sensory testing for cool detection threshold, intraepidermal skin biopsy, and neurologic findings using a modification of the Neuropathy Impairment Score for Lower Limb.⁸

Fisher's exact test was used to assess associations between groups and the presence of anti-sulfatide antibodies. Exact CIs were used to estimate the prevalence of these antibodies. The Mann-Whitney rank sum test was used to compare the distributions of antibody titers between groups. Within the HIV+/DSP+ group, exact tests were used to assess associations between the presence or absence of anti-sulfatide titers with categorical variables and the Kruskal-Wallis test was used for continuous variables.

Results. Ninety-seven serum samples were available from individuals enrolled in the AIDS Clinical Trial Group phase II study of recombinant human NGF for treatment of HIV-associated DSP. Thirty-five (36%; 95% CI: 26.57% to 46.48%) of these serums (HIV+/DSP+) had high IgG anti-sulfatide antibody titers greater than 1,500 (figure), whereas only two of the 20 control serums (10%; 95% CI: 1.23% to 31.7%) from HIV+/DSP− individuals ($p = 0.032$) and none of the 55 control serums (0%; 95% CI: 0.0% to 6.46%) from HIV−/DSP+ individuals ($p < 0.001$) had high IgG anti-sulfatide titers.

No serum from HIV+/DSP+ or HIV+/DSP− patients had specific high-titer IgM binding to sulfatide or MAG or IgM or IgG binding to gangliosides. Two serums from

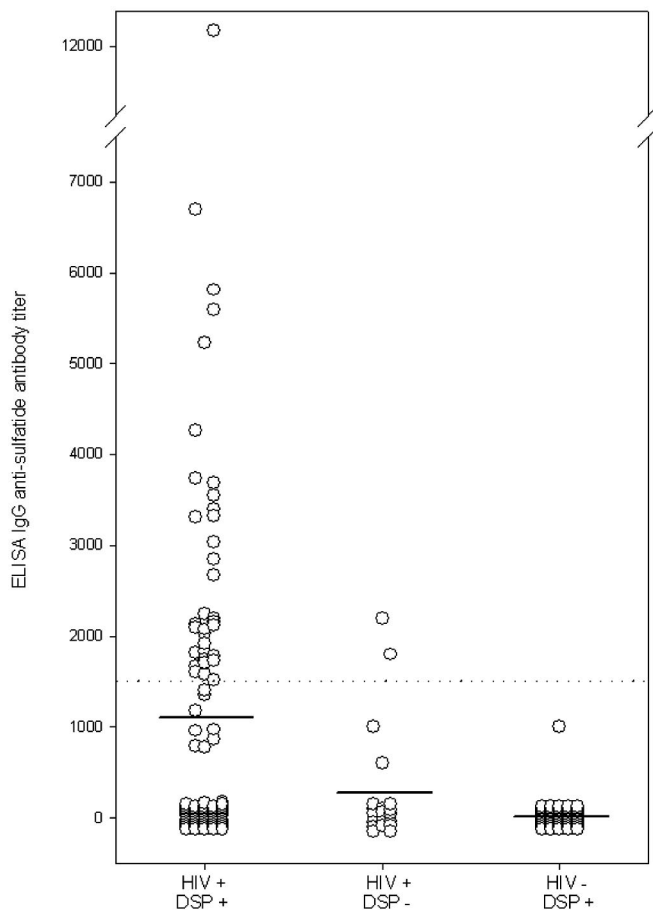


Figure. IgG anti-sulfatide antibody titers in HIV-infected patients with and without neuropathy and in uninfected patients with neuropathy. Immunoglobulin G anti-sulfatide antibodies with titers >1,500 are common in HIV+ /distal sensory polyneuropathy (DSP)+ individuals (36%) but not in HIV+ /DSP- individuals (10%), $p = 0.032$ or in HIV- /DSP+ individuals (0%), $p < 0.001$. The bars represent the mean anti-sulfatide antibody titer.

HIV- /DSP+ individuals had high titer (>1,500) IgM anti-sulfatide antibodies.

Within the HIV+ /DSP+ group, no significant associations were found between anti-sulfatide antibody titers and CD4 counts, HIV-1 RNA, age, average and worst pain as measured by the Gracely Pain Scale, global assessments of pain by the subjects and investigators, quantitative sensory testing for cool detection threshold, intraepidermal skin biopsy, and neurologic findings using a modification of the Neuropathy Impairment Score for Lower Limb.⁸

Discussion. Autoantibodies are common in HIV-infected individuals,⁹ and include anti-phospholipid, anti-snRNP, and anti- α -myosin antibodies. The increased prevalence of autoantibodies in HIV-infected patients may be related to an altered immune system or to cross-reactivity between viral and self-antigens.⁹ Anti-sulfatide antibodies could be related to sulfatide, which is expressed on CD4⁺ cells from HIV-infected individuals.⁶ Sulfatide might also provoke an immune response if it is presented after incorporation into the viral coat during budding.¹⁰

Most studies have not found correlations between the presence of autoantibodies and clinical manifestations of HIV.⁴ Our study showed that HIV-infected individuals with DSP (HIV+ /DSP+) have an increased prevalence of high-titer serum IgG anti-sulfatide antibodies. IgG anti-sulfatide antibodies were found in significantly more HIV+ /DSP+ individuals than HIV+ /DSP- or HIV- /DSP+ individuals. However, we found no association between the presence of anti-sulfatide antibodies and any clinical measures in the HIV+ /DSP+ group. This suggests, as with other neuropathy-related autoantibodies, that although IgG anti-sulfatide antibodies are associated with the presence of a DSP in patients with HIV, and not with HIV infection or neuropathies unrelated to HIV infection, their clinical and pathogenic importance remains to be determined.

Previous studies, in contrast to our results, have found anti-sulfatide antibodies in HIV-infected individuals both with and without neuropathy.^{3,4} One area of caution in the interpretation of our study involves recruitment of our patient population. We recruited the HIV+ /DSP+ group at an earlier time point than the HIV+ /DSP- group. There may be a source of bias because antiretroviral or other therapies have changed over the past few years. We were also not able to match the HIV+ /DSP+ individuals to HIV+ /DSP- for variables such as CD4 count and viral load. Anti-sulfatide antibodies could be a marker of more advanced disease, which was likely present in the NGF (HIV+ /DSP+) study population. However, controls for such variables were also not clearly included in previous studies of anti-sulfatide antibodies.

A more likely reason for variations in results between our study and previous ones is differences in controls used in the ELISA methodology. We rigorously exclude polyspecific antibodies by comparing IgG binding to sulfatide with binding in both blank control wells and in wells containing other control antigens. When wells with control antigens are also positive, this suggests polyspecific antibody binding that has few specific clinical correlations.¹ Elimination of polyspecific antibodies from results reduces the apparent frequency of serum anti-sulfatide antibodies in control groups to the low levels found in this study. When polyspecific antibodies are eliminated, as in our study, we find that high-titer IgG anti-sulfatide antibodies are relatively common in HIV+ /DSP+ individuals and occur more frequently than in HIV-infected individuals without neuropathy or in individuals with neuropathy who are not infected with HIV.

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NeuroImages

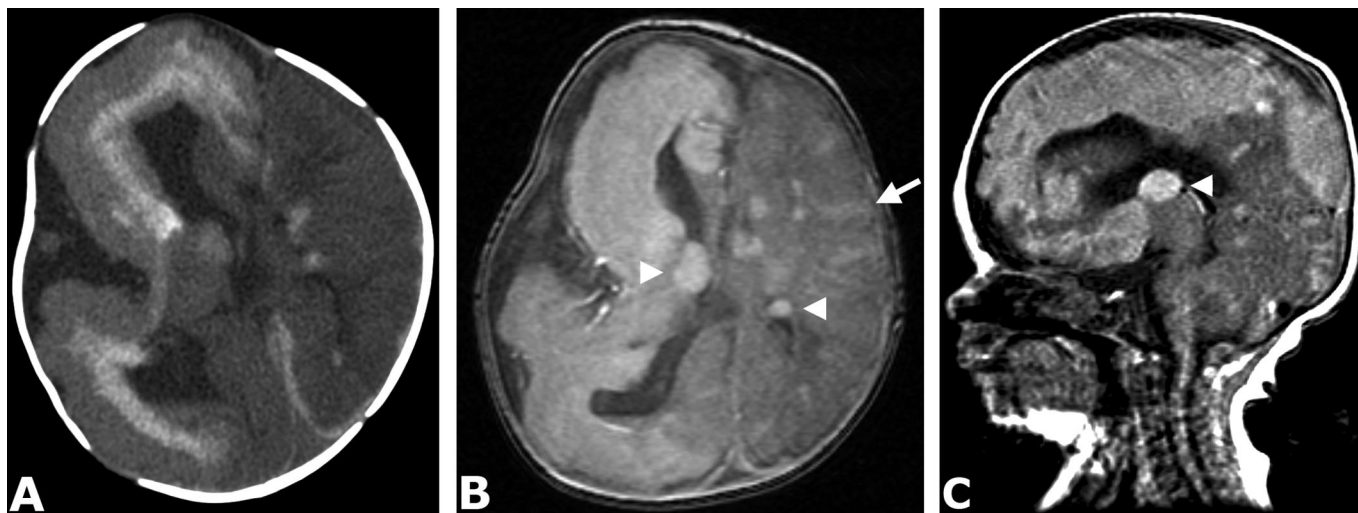


Figure. CT without contrast (A) shows hemimegalencephaly and calcified heterotopia outlining the right lateral ventricle. Axial T1-weighted MRI with contrast (B) and sagittal T1-weighted MRI without contrast (C) demonstrate cortical dysplasia in the left hemisphere (arrow) and subependymal nodules (arrowheads).

Hemimegalencephaly and tuberous sclerosis complex

Michael S. Cartwright, MD; Sean C. McCarthy, BA; and E. Steve Roach, MD, Winston-Salem, NC

A 1-day-old boy was transferred to the neonatal intensive care unit secondary to tachypnea. He had macrocephaly and full fontanelles. Imaging demonstrated hemimegalencephaly and subependymal nodules (figure). Further evaluation revealed cardiac rhabdomyomas and renal angiomyolipomas. Definite tuberous

sclerosis complex was diagnosed on the basis of the presence of two major features.¹

Hemimegalencephaly and tuberous sclerosis complex are distinct and rare conditions that are characterized by cortical malformations. While they are currently thought to be unrelated, there are similar cases in the literature² and it is conceivable that an abnormality early in cortical development could lead to both conditions in an individual.

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Address correspondence and reprint requests to Dr. Michael S. Cartwright, Wake Forest University School of Medicine, Department of Neurology, Medical Center Blvd., Winston-Salem, NC 27157; e-mail: mcartwri@wfbmc.edu

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