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References

Immune Complex Deposition in the Choroid Plexus of Patients with Acquired Immunodeficiency Syndrome

M. F. Falangola, MD,* B. G. Castro-Filho, MD,† and C. K. Petito, MD*

We identified immune complex deposits in the choroid plexus of approximately 75% of patients with acquired immunodeficiency syndrome (AIDS) who had either normal brains or human immunodeficiency virus encephalitis. Since circulating immune complexes are common in AIDS patients, and since local choroid plexus pathology usually was absent, their likely origin is from the bloodstream. Choroid plexus deposits of immune complexes have been implicated in altering the function of this structure or in enhancing its vulnerability to infection. Therefore, immune complex deposition in the choroid plexus of AIDS patients may be responsible for some of the common alterations in the cerebrospinal fluid and for the frequency of opportunistic infections in this region.


Circulating immune complexes (ICs) are found in more than 80% of both adults and children with the acquired immunodeficiency syndrome (AIDS) [1, 2] and in chil-

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### Patient Data

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Sex</th>
<th>Age (yr)</th>
<th>Risk Factors</th>
<th>Duration of AIDS&lt;sup&gt;a&lt;/sup&gt; (mo)</th>
<th>AIDS-related Systemic Diseases&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Brain Disease</th>
<th>Choroid Plexus IC Deposits</th>
<th>Choroid Plexus Inflammation</th>
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<td>2</td>
<td>M</td>
<td>34</td>
<td>IVDA</td>
<td>36</td>
<td>PCP/CMV</td>
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<td>+</td>
<td>-</td>
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<td>3</td>
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<td>-</td>
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<td>-</td>
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<td>M</td>
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<td>2</td>
<td>PCP/Kaposi's sarcoma</td>
<td>-</td>
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</tbody>
</table>

<sup>a</sup>Interval between initial presentation with AIDS-defining illness and death.

<sup>b</sup>Includes those diagnosed during life and at autopsy.

IC = immune complex; HIVE = HIV encephalitis; PCP = Pneumocystis carinii pneumonia; CMV = cytomegalovirus; HS = herpes simplex; ITP = idiopathic thrombocytopenic purpura; Tb = Mycobacterium tuberculosis; NA = information not available; IVDA = intravenous drug abuse.

...dren, the levels of ICs generally correlate with a more severe disease course [2]. These ICs contain specific immunoglobulin isotypes, complement, and antigens of human immunodeficiency virus (HIV) and other infectious agents [3]. Deposition of ICs into tissue may damage systemic organs such as lung or kidney but the brain usually is protected by the blood-brain barrier, which prevents circulating macromolecules, including ICs, from entering.

The choroid plexus, however, is vulnerable to IC deposition since its capillaries have open or "gap" junctions that allow free passage of macromolecules. In addition, choroid plexus receptors for immunoglobulins and complement [4, 5] may increase its vulnerability to IC deposition. Accordingly, we examined postmortem choroid plexus of patients with AIDS for the presence of IC deposition. In order to rule out local IC formation, patients with opportunistic infections and lymphomas of the central nervous system (CNS) were excluded, as the choroid plexus frequently is involved [6] (personal observations, 1994). A preliminary report of this study was published previously [7].

### Materials and Methods

Formalin-fixed choroid plexus specimens from 19 AIDS patients, 12 of whom had HIV encephalitis (HIVE), were examined. Material for frozen sections or electron microscopy was unavailable. Paraffin-embedded sections cut 5 to 7-μm thick were stained with hematoxylin and eosin (H&E), periodic acid–Schiff (PAS), and Heidenhain's azan. Immunohistochemical studies were performed by the avidin-biotin method using overnight incubation with monoclonal antibody to HIV gp41 (1:500 dilution; Genetics Systems, Seattle, WA), polyclonal antibody to IgG-Fc fragment (1:1,000 dilution; Dako, Carpinteria, CA), and polyclonal antibody to C3d complement (α2D) (1:2,000; Dako). Following incubation with the primary antisera, sections were washed and...
Subepithelial immune complex deposits (arrows) in the choroid plexus are stained with periodic acid-Schiff (A) and azan (B) and are immunoreactive for IgG (C) and complement (D). (x 600)

Sequentially incubated with biotinylated secondary antibody, the avidin-biotin complex (Vector Labs, Burlingame, CA), and hydrogen peroxide with 3,3′-diaminobenzidine. A positive control was a sample from a patient previously diagnosed with HIVE (for anti-HIV gp41) and the identification of intravascular serum immunoreactivity (for anti-IgG and anti-C3d) in each slide examined. Saline solution was substituted for all primary antibody as a negative control. The choroid plexus was blindly evaluated for the presence or absence of inflammation, endothelial cell hypertrophy, and mesenchymal cell proliferation—each graded as negative, focal, moderate, and intense—and for the presence of IC deposition (PAS and IgG/C3d deposits).

**Results**

Fifteen patients were men and four were women; their average age was 40 years. Risk factors for HIV infection included homosexuality (in 8), intravenous drug abuse (in 6), heterosexual contact (in 2), and promiscuity (in 1), and were unknown in 2 patients (Table). Neither age, sex, HIV risk factors, duration of AIDS, AIDS-related infections or tumors in systemic organs, nor HIVE correlated with the presence of inflammation or IC deposits in the choroid plexus. None of the patients had detectable infectious agents in the choroid plexus as determined by routine microscopic examination.

Inflammation was present in 6 (31%) of the 19 patients and consisted of focal infiltrates of lymphocytes and plasma cells in the connective tissue, predominantly in the perivascular areas. It was more frequent with HIVE (41%) than without HIVE (14%). Similarly, marked endothelial hypertrophy, characterized by enlarged vesicular nuclei, and mesenchymal cell proliferation of the choroid villi stroma were seen more frequently with HIVE than without HIVE (67 and 58% vs 43 and 29%). The relatively small number of patients (n = 19) did not allow for adequate statistical analyses and thus the significance of these comparisons is not clear.

Fourteen of the 19 patients had IC deposits located immediately beneath the basement membrane of the choroid plexus epithelium. In 12 patients, homogeneous, acidophilic, PAS-positive deposits were seen (Fig A) and were azan positive (Fig B) in 3 and immunoreactive for IgG and C3d in 10 (Figs C, D). The choroid plexus in an additional 2 patients (Patients 13...
Discussion

Circulating ICs develop from the interaction between antigen-antibody complex and fractions of complement, and thus are found with a large number of infectious, neoplastic, and autoimmune diseases. Their deposition may lead to tissue injury, which has been associated with systemic vasculitis and glomerulonephritis. Tissues that are highly vascularized and have capillaries with gap junctions such as the kidney and the choroid plexus are at increased risk for IC deposition. Not surprisingly, ICs in choroid plexus have been found with autoimmune nephritis, systemic lupus erythematosus, hepatosplenic schistosomiasis, and cirrhosis [8–11] but not with diseases such as cancer, atherosclerosis, or bronchopneumonia [5].

IC disease is a known complication of AIDS. In addition to the high incidence of circulating ICs, IgA-related IC-mediated renal disease [12] and IC-related vasculitis in peripheral nerve and muscle of HIV-positive patients [13] have been described. The present demonstration of frequent IC deposition in the choroid plexus of AIDS patients is additional evidence that HIV infection has a component of IC disease. The deposits were associated with endothelial hypertrophy and mesenchymal proliferation but not with local inflammation. It is likely that they were deposited from circulating ICs, as local choroid plexus inflammation was not required for their formation. The incidence of IC deposition of approximately 75% was similar in patients with otherwise normal brains and choroid plexus as well as in patients with HIV and choroid plexus inflammation.

IC deposition in the choroid plexus in AIDS patients may have at least two important functions. First, it could damage the blood–cerebrospinal fluid (CSF) barrier and alter the selective permeability of the choroid plexus and composition of the CSF. Indeed, the CSF of AIDS patients frequently has elevated protein levels, IgG, and pleocytosis, for which choroid plexus abnormalities could be responsible [14]. Second, IC deposition could render the choroid plexus vulnerable to blood-borne infections including opportunistic infections such as toxoplasmosis (6) and HIV infection. Precedent for this hypothesis is seen in an experimental model of serum sickness in which IC deposition in the choroid plexus renders the animal more vulnerable to CNS infections [15].

References


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