Progressive Multifocal Leukoencephalopathy in a Patient with Hypogammaglobulinemia

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We describe a child with congenital hypogammaglobulinemia that was diagnosed at 13 months of age. When he was 4 years old, gait disturbances began. The main neurological manifestations were progressive spastic tetraparesis and intellectual and speech deterioration. No infectious agent was identified. A magnetic resonance imaging scan of the central nervous system revealed periventricular demyelinating areas in the frontal, temporal, and parietal lobes with cortical atrophy. Stereotactic brain biopsy confirmed the diagnosis of progressive multifocal leukoencephalopathy caused by JC virus. He was treated with intravenous and intraventricular cytarabine and interferon-α, and there was clinical improvement. We emphasize the need for brain biopsy as soon as a neurological complication is suspected in patients with congenital hypogammaglobulinemia for whom cerebrospinal cultures or polymerase chain reaction analyses are negative.

Hypogammaglobulinemias are characterized by a production defect in one or all immunoglobulins [1, 2]. They differ in terms of inheritance patterns, genetic disorders, pathogenesis, age at presentation, and involvement of cellular immune responses [1–4]. Encephalitis in patients with hypogamaglobulinemias has been reported; its incidence has decreased during the last few years because of the use of intravenous γ-globulin [1, 5]. In most cases, it has been associated with a viral etiology; enterovirus and coxsackievirus (types 1 and 3) are the most frequently recognized organisms [6–8]. Recently, encephalopathies due to measles virus and papovavirus have been described in immunoglobulin-deficient patients. Neurological manifestations are often heterogeneous, varying from a dermatomyositis-like syndrome to generalized involvement of the CNS; in patients with a subacute or chronic course, these manifestations may resemble chronic encephalopathy caused by HIV and human T cell leukemia virus type 1 (HTLV-1) [9–11].

In this report, we describe a child with congenital hypogammaglobulinemia who developed a subacute neurological disorder; his clinical outcome and response to treatment are also reported.

Case Report

A 5-year-old boy with congenital hypogammaglobulinemia that was diagnosed at 13 months of age presented to our institution. He was his mother’s only child, and his parents were nonconsanguineous. At the time of diagnosis of hypogammaglobulinemia, the IgG level in serum was 80 mg/dL (normal value, 762 ± 209 mg/dL); no CD20 cells were found (table 1). In vivo cellular response to eight antigens was positive in four antigens; in vitro cellular stimulation to nonspecific mitogens was normal. Replacement treatment with intravenous γ-globulin (400 mg/kg) was started.

When the patient was 4 years old, he was in good general condition and had no history of infectious diseases; gait disturbances began at this age. Six months later, he developed spastic paraparesis, hypertonia, and hyperactive tendon reflexes in the lower limbs as well as Achilles tendon and hamstring shortness, bilateral reducible pes equinus, and speech and cognitive disorders; muscular atrophy was maintained. Muscular tone, reflexes, and active and passive movements in the upper limbs were preserved. Cranial nerves, taxis, sensibility, and sphincter control were normal. A CT scan of the brain showed mild signs of frontal lobe atrophy.

At the time of presentation, the WBC count, erythrocyte sedimentation rate, and muscular enzyme levels were within normal ranges. CSF analysis showed a mild increase in the protein level (0.64 g/L) and a lymphocyte count of 100/mm³; the myelin basic protein level was normal. Investigations for common organisms, fungi, parasites, and mycobacteria in serum and CSF were negative, as were those for viruses (herpesvirus, measles virus, and enterovirus).

Since the patient had received a blood transfusion, viral culture and PCR analysis of blood and CSF were performed for HIV and HTLV-1; the results were negative. Flow cytometry ruled out the presence of activated CD4⁺/CD25⁺ cell subsets, which is typical of HTLV-1 infection. Results of electrophysiological studies (electromyography, testing for evoked responses, and electroencephalography) were normal. MRI of the brain showed periventricular demyelinating areas in the frontal, parietal, and temporal lobes with cortical atrophy (figure 1); no spine alterations were demonstrated.
Table 1. Results of immunologic testing for a 5-year-old boy with congenital hypogammaglobulinemia and progressive multifocal leukoencephalopathy.

<table>
<thead>
<tr>
<th>Serum Ig levels (mg/dL)</th>
<th>Immunophenotypes* (%)</th>
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<tbody>
<tr>
<td>IgG, 80 (normal value, 762 ± 209)</td>
<td>CD3 cells, 73 (normal value, 60–80)</td>
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<tr>
<td>IgA, not measurable (normal value, 37 ± 18)</td>
<td>CD4 cells, 46 (normal value, 36–46)</td>
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<tr>
<td>IgM, 170 (normal value, 54 ± 23)</td>
<td>CD8 cells, 25 (normal value, 19–30)</td>
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<tr>
<td></td>
<td>CD20 cells, 1 (normal value, 6–23)</td>
</tr>
<tr>
<td></td>
<td>Surface Ig, 0</td>
</tr>
<tr>
<td></td>
<td>Antibody response to tetanus toxoid, negative</td>
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<tr>
<td></td>
<td>Antibodies to nuclear antigens, negative</td>
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<tr>
<td></td>
<td>Multitest,² positive in four antigens</td>
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* Determined by flow cytometry.
² In vivo cellular response to eight antigens.

Stereotactic brain biopsy of the periventricular lesion was performed with hematoxylin-eosin, periodic acid–Schiff total inclusion, Luxol Fast Blue (GURR-BDH Chemical Ltd, Poole, England), immunolabeled with papovavirus, measles virus, and herpesvirus, and inclusion in EPON. This study revealed preserved cerebral parenchyma, mild edema with diffuse extension, oligodendrocyte nuclei with homogeneous chromatin, and ultrastructural ground-glass images (figure 2). Immunolabeling for herpesvirus, measles virus, and papovavirus was negative. Myelin testing showed focal demyelinization.

In situ hybridization was performed as follows. Biopsy specimens were formalin fixed and paraffin embedded. Hematoxylin-eosin-stained tissue sections were prepared from paraffin blocks. Other tissue sections on slides were deparaffinized and rehydrated by sequential immersion into xylene and graded alcohols. Endogenous peroxidase was inhibited with 3% perox-

de in PBS. Proteinase K was applied to the tissue sections. After rinsing, 20 μg of the hybridization mixture (JC virus bioprobe; Enzo Diagnostics, New York) was applied to each specimen, and the slides were covered with coverslips. The slides were placed on a heating block for ~2–3 minutes to denature the DNA.

Hybridization was performed in a humid chamber at 37°C for 60 minutes. The posthybridization agent (kit, Enzo Diagnostics) was applied at 37°C. The slides were immersed in the developing solution (Vector Laboratories, Burlingham, CA) for 60 minutes at 37°C, stained with hematoxylin, dehydrated, and covered with a coverslip (figure 3).

Progressive multifocal leukoencephalopathy due to JC virus, a member of the Papovaviridae family, was diagnosed. The patient was treated with cytosine arabinoside (60 mg/m² of body surface intravenously and 10 mg/m² of body surface intrathecally) daily, followed by subcutaneous IFN-α (Bioferon A 3,000,000 U/d; Sidus Institute, Buenos Aires, Argentina) every other day for 3 months. After the first course of treatment, a partial improvement in gait and speech was observed, but there were no changes on the brain images. One month after this treatment course was completed the patient had a relapse, and a second course of treatment was administered. At the time of this writing, the patient had partial favorable motor and cognitive responses.

Discussion

CNS involvement due to viral infections in immunocompromised patients occurs frequently. Leukoencephalitis is a well-documented complication in patients with hypogam-
performed for the mother did not detect nonrandom inactivation rule out the diagnosis. The authors thank Dr. Jorge Correale (University of Southern of the X chromosome; however, this result does not definitively

globulinemia and progressive multifocal leukoencephalopathy. The arrow shows oligodendrocyte nuclei. The tissue section on a slide was stained with hematoxylin, dehydrated, and covered with a coverslip (original magnification, ×400).

maglobulinemia; enteroviruses are the most common pathogens, although it is not always possible to detect them in all patients because isolation of the viruses from the CSF is difficult [2, 7, 8]. The highest incidence of leukoencephalitis is among patients with sex-linked agammaglobulinemia during treatment with intramuscular γ-globulin, because serum titers are not sufficiently protective; the incidence is lower among those being treated with intravenous γ-globulin [1, 3, 5, 12].

Other viruses act as opportunistic pathogens in individuals with immunologic disorders, especially when there is an alteration in the cell-mediated immune response [13]. As described in this report, JC virus, a member of the Papovaviridae family, acts as one of these pathogens. These viruses cause progressive multifocal leukoencephalopathy, a demyelinating disease of the CNS. Primary infection due to JC papovavirus occurs in the first decade of life [14]. When cellular immune function is altered, infection is reactivated, producing neurological disease.

Several investigators have described progressive multifocal leukoencephalopathy in patients with primary deficiencies (hyperimmunoglobulinemia M) [15] or secondary deficiencies (HIV infection or immunosuppressive therapies) [16, 17]. It rarely occurs in previously healthy individuals [18]. We were not able to establish the basal immunologic diagnosis for our patient. We considered a diagnosis of sex-linked agammaglobulinemia because of the absence of ganglionic tissue and B lymphocytes in peripheral blood and bone marrow and a good cellular response. We were not able to confirm this condition because restriction fragment length polymorphism analysis performed for the mother did not detect nonrandom inactivation of the X chromosome; however, this result does not definitively rule out the diagnosis.

Since the IgM level in serum at the time of diagnosis of hypogammaglobulinemia in our patient was 170 mg/dL, we suspected possible hypergammaglobulinemia M, but it was excluded by the presence of CD40 ligand. Other types of hypogammaglobulinemia (e.g., common variable immunodeficiency) may involve immunity in a way (clinical and laboratory) that is similar to sex-linked agammaglobulinemia; however, in patients with hypergammaglobulinemia, there may be progressive cellular involvement, which could explain an infection (as in our patient). It is not clear what the pathogenic mechanism was in our patient because we did not confirm an alteration in cellular immunity before and during the development of the neurological condition or previous infectious diseases (we ruled out HIV and HTLV-1 infections).

Studies performed in the United States showed that 65% of serum specimens from patients older than 10 years of age had antibodies to JC virus [14]. Therefore, it is believed that pooled γ-globulin for intravenous use might have titers of such antibodies. Considering that our patient received appropriate treatment with intravenous γ-globulin, we wonder if the antibodies have a protective value.

Treatment of patients with chronic leukoencephalitis has been empirical. IFN-α, cytosine arabinoside, and γ-globulin are used in different routes of administration alone or in combination [19–22]. In most previously reported cases, temporary clinical improvement occurred, and relapses were observed when treatment was discontinued; therefore, several treatment courses are employed, although the disease is slowly progressive and fatal [12, 19]. The average duration of survival ranges from 6 to 12 months; it is shorter for patients with HIV infection because of the association with other complications. In our case, we used the combination of intrathecal and intravenous cytosine arabinoside and subcutaneous IFN-α in two treatment courses. There was evident clinical improvement with greater motor and cognitive activities, although there were no changes on the brain images. We believe that the therapeutic combination was effective at stopping the progression of the disease; at the time of this writing, he had survived 3 years in a stable clinical state.

To our knowledge, this is the first reported case of progressive multifocal leukoencephalopathy due to JC virus in association with humoral immunodeficiency in Latin America in which the duration of survival was greater than generally described and the clinical condition was stable. We emphasize the significance of early diagnosis for patients with primary immunologic deficiencies who have neurological signs and symptoms. It should be considered that negative cultures do not rule out a possible viral encephalic infection and that brain biopsy should be performed early when there is no diagnosis. Early treatment is one of the few ways to improve the quality of life for these patients.

Acknowledgment

The authors thank Dr. Jorge Correale (University of Southern California, Los Angeles) for his counsel in the management of our patient.
References