Neurodevelopmental/Neuroradiologic Recovery of a Child Infected With HIV After Treatment With Combination Antiretroviral Therapy Using the HIV-Specific Protease Inhibitor Ritonavir

ABSTRACT. Background. Neurodevelopmental impairment has been identified in children infected with human immunodeficiency virus (HIV). The frequency and spectrum of neurologic impairment are greater in children than those reported for adults. In children, HIV is known to enter the central nervous system early in the course of the disease. The presentation of pediatric neuro-acquired immune deficiency syndrome ranges from static (eg, nonprogressive developmental delay) to progressive encephalopathy (eg, acquired microcephaly, pyramidal tract signs, and spasticity).

It has been demonstrated that antiretroviral agents can improve or even reverse the course of neurologic impairment in children. These changes have been attributed to various degrees of central nervous system drug penetration. Increasingly, protease inhibitors and combination antiretroviral therapy using reverse transcriptase inhibitors are being used in the treatment of children infected with HIV. The addition of a protease inhibitor to nucleoside analogue therapy has been reported to delay disease progression and prolong life in adults with moderate to advanced HIV disease. No data currently exist on the impact of combination therapy using two nucleoside analogues and a protease inhibitor on neurodevelopmental and neurologic function in children with HIV infection. The following case report presents the effects of combination therapy using ritonavir in a child infected with HIV.

Case Report. An 8-year, 2-month-old African-American boy was infected with HIV through vertical transmission. Regular monitoring of the patient's neurodevelopmental status has been conducted as part of his participation in longitudinal research protocols. For the first 5½ years of life, his neurodevelopmental status was normal, with cognitive functioning as measured by standardized psychometric tools solidly in the average range. Speech and language skills were age-appropriate. Tests of gross and fine motor functioning as well as evaluation of overall neurodevelopmental status suggested normal development. Magnetic resonance imaging (MRI) of the brain was consistently normal. His family reported that adaptive functioning, peer and family relationships, and behavior were all within normal limits. School reports indicated consistently that the patient was performing at age and grade level, with respect to both academic achievement and behavior.

Initial concerns regarding the patient's development were expressed by both his family and school at age 6 years, 6 months. These concerns included difficulty with classroom work, decreased attention, word-finding problems, fatigue, staring spells, and loss of strength. His family and school reported a marked loss of skills acquired previously. Results of formal psychological and speech and language evaluation reflected statistically significant drops in test scores from baseline, with both delayed and atypical skills evident.

The patient's condition worsened rapidly. Within a few months, he was no longer able to use sentences to communicate. Cognitive testing was attempted, but he was unable to participate because of significant fatigue, limited attention, and inability to communicate verbally. His family described periods of disorientation and confusion, lethargy, and disinterest in age-appropriate activities. He became agitated and overstimulated easily both in small group settings and in crowds. He demonstrated both fine and gross motor impairments. When frustrated, he displayed infantile and autistic-like behavior.

MRI with contrast showed diffuse atrophy as well as mild prominence of the ventricles and sulci compared with baseline assessment. In addition to fatigue and neurologic symptoms, wasting syndrome was diagnosed, with loss of percentiles in both weight and height by age 7½ years. Low-grade elevation of liver function tests and amylase was noted. Blood cultures for mycobacteria were negative, as were serologic tests for hepatitis.

Previous antiviral treatment had included zidovudine monotherapy begun at age 20 months through AIDS Clinical Trials Group protocol 128. This was changed to dideoxyinosine monotherapy through AIDS Clinical Trials Group protocol 144 at 4 years of age, which was discontinued at age 6.5 years because of pancreatitis. A brief course of stavudine monotherapy was associated with recurrence of pancreatitis. Zidovudine monotherapy was reinstated at age 7 years. With the availability of new medications, at age 7 years, 9 months, the patient began combination therapy with ritonavir (350 mg/m² per dose twice a day), zidovudine (120 mg/m² per dose every 8 hours), and 3TC (4 mg/kg per dose twice a day).

In the 6 months since the initiation of combination therapy, we have observed significant changes in the patient's neurodevelopmental functioning. Substantial improvements have occurred in both his cognitive and his language functioning. Improvements in laboratory measures were noted, as well as a three-log reduction in viral load and a significant increase in CD4+ T-lymphyocyte percents and total counts. Repeat MRI of the brain was performed that demonstrated normal size of the ventricular system and cerebral volume, compared with the earlier study, which had shown diffuse atrophic changes. Signal intensity of the white matter was normal on all sequences, and no mass lesions were noted. These
changes were consistent with the resolution of all previous abnormal findings.

Discussion. In a short time, we have observed and documented a dramatic recovery in our patient’s virologic, hematologic, and neurodevelopmental functioning as shown in neuroradiographic imaging after initiation of combination therapy. These positive changes suggest that the use of combination therapy not only significantly suppresses HIV replication, but can also lessen or even reverse some of the neurologic and neurodevelopmental sequelae of neuro-acquired immune deficiency syndrome. If these findings are replicated in other HIV-infected children using combination therapy, it will reinforce the importance of aggressive, combination treatment for children. Pediatrics 1998;101(3). URL: http://www.pediatrics.org/cgi/content/full/101/3/e7; HIV/AIDS, antiretroviral combination therapy, neurodevelopment, protease inhibitors.

ABBRéVIATIONS. HIV, human immunodeficiency virus; CNS, central nervous system; AIDS, acquired immune deficiency syndrome; ddI, dideoxyninosine; ACTG, AIDS Clinical Trials Group; MRI, magnetic resonance imaging; CSF, cerebrospinal fluid.

Neurodevelopmental impairment has been identified in children infected with human immunodeficiency virus (HIV). The frequency and spectrum of neurologic impairment are greater in children than those reported for adults. In children, HIV is known to enter the central nervous system (CNS) early in the course of the disease. It is estimated that between 30% and 65% of HIV-infected children may develop neurologic impairment (neuro-acquired immune deficiency syndrome [neuro-AIDS]) because of HIV infection. The presentation of neuro-AIDS ranges from static (eg, nonprogressive developmental delay) to progressive encephalopathy (eg, acquired microcephaly, pyramidal tract signs, and spasticity). It has been demonstrated that antiretroviral agents can improve or even reverse the course of neurologic impairment in children. Changes in ventricular size have been demonstrated in response to continuous zidovudine treatment. Brouwers et al reported improvements in neurocognitive functioning as a result of antiretroviral therapy, whether zidovudine was administered through continuous infusion or by mouth intermittently. Neurocognitive changes also have been reported with oral dideoxycytidine and continuous infusion soluble recombinant CD4 or with oral dideoxinosine (ddI) alone. Although no overall change was observed in computed tomographic brain scan severity ratings, a significant improvement was noted in both neurocognitive function and ventricular size after treatment. These changes have been attributed to various degrees of CNS drug penetration.

The US Food and Drug Administration has approved the use of a class of drugs called HIV-specific protease inhibitors for the treatment of HIV infection. In March 1997, ritonavir (Norvir) was one of the first two protease inhibitors to include in the package insert information regarding safety, pharmacokinetics, and dosing recommendations for children with HIV/AIDS (Kim Struble, personal communication). Increasingly, protease inhibitors and combination antiretroviral therapy using reverse transcriptase inhibitors are used in the treatment of children infected with HIV. This class of drugs has created new opportunities in the management of HIV disease. Protease inhibitors have been shown to reduce plasma HIV RNA levels and increase CD4+ cell levels in adults. The addition of ritonavir to nucleoside analogue therapy has been reported to delay disease progression and prolong life in adults with moderate to advanced HIV disease. Furthermore, Nabulsi and colleagues found that adding ritonavir to ongoing noninvestigation antiretroviral medication significantly improved the quality of life of patients infected with HIV (eg, increased self-care and mobility and reduced pain and depression) compared with a group of patients receiving a placebo. Mueller and coworkers assessed the safety and tolerance of ritonavir for use with HIV-infected children, suggesting that children can tolerate ritonavir. Preliminary results suggest a significant antiviral effect.

Currently no data exist on the impact of combination therapy using two nucleoside analogues and a protease inhibitor on neurodevelopmental and neurologic function in children with HIV infection. The following case report presents the effects of combination therapy using ritonavir in an HIV-infected child.

CASE REPORT

An 8-year, 2-month-old African-American boy was infected with HIV through vertical transmission. He was born at full term by cesarean section to a 22-year-old HIV-positive woman with no apparent history of substance abuse but who had received a blood transfusion in 1980 (8 years before the patient’s birth). The patient’s birth weight was 3380 g, length 50 cm, and head circumference 34 cm (all growth parameters at the 50th percentile), with Apgar scores of 8 at 1 minute and 9 at 5 minutes. At the time of delivery, the mother’s only HIV-related reported symptom was generalized lymphadenopathy. The patient was diagnosed as HIV-infected at 4 months of age by positive culture performed as part of a prospective research protocol. He has resided in a stable, nurturing environment with his paternal grandmother since 9 months of age. His mother died when he was 3 years old; he had had very little contact with her during the 18 months before her death.

During the first year of life, the patient’s only HIV-related symptoms were hepatosplenomegaly and generalized lymphoadenopathy. CD4+ T-lymphocyte counts were consistently >2000/mm³. At 20 months of age, he began treatment with zidovudine monotherapy through AIDS Clinical Trials Group (ACTG) protocol 128. At that time, his CD4+ T-lymphocyte counts were in the range of 1000/mm³. He was begun on Pneumocystis prophylaxis, with both trimethoprim/sulfamethoxazole and then dapsone, ultimately requiring intravenous pentamidine because of erythema multiforme. Between the second and third year of life, findings consistent with lymphoid interstitial pneumonitis were noted on chest radiography, and the patient experienced episodes of recurrent sinusitis. By age 4, his CD4+ T-lymphocyte counts had dropped into the 200/mm³ range, and he was changed to ddI monotherapy through ACTG protocol 144. At age 6, he developed pancreatitis and, as a result, ddI was discontinued. Antiretroviral therapy was reinitiated briefly at age 6 years, 6 months with stavudine (d4T) monotherapy, but this was discontinued after a recurrence of pancreatitis. At 7 years of age, the patient developed Pneumocystis carinii pneumonia, which was treated successfully with intravenous pentamidine. Zidovudine monotherapy also was reinstated at that time. The patient’s CD4+ T-lymphocyte counts had fallen to <50/mm³.

Regular monitoring of the patient’s neurodevelopment has
been conducted as part of his participation in ACTG research protocols. For the first 5 1/2 years of life, his neurodevelopmental status was normal, with cognitive functioning as measured by standardized psychometric tools solidly within the average range (Table 1). Speech and language skills were age-appropriate (Table 2). Tests of gross and fine motor functioning as well as evaluation of overall neurodevelopmental status suggested normal development. Magnetic resonance imaging (MRI) of the brain was consistently normal. His family reported that his adaptive functioning, peer and family relationships, and behavior were all within normal limits. School reports consistently indicated that the patient was performing at age and grade level, with respect to both academic achievement and behavior.

NEUROLOGIC DISEASE PROGRESSION

Initial concerns regarding the patient’s development were expressed by both his family and his school at age 6 years, 6 months. These concerns included difficulty with classroom work, decreased attention, word-finding problems, fatigue, staring spells, and loss of strength. His family and school reported a marked loss of skills acquired previously. Formal evaluation was conducted at age 7 years, 3 months to document his cognitive and language functioning. Results of standardized cognitive assessment with the Wechsler Intelligence Scale for Children, Revised reflected statistically significant drops in test scores from baseline (Table 1). On standardized tests of language functioning, the patient evidenced a pattern of both delayed and atypical skills (Table 2). Atypical features in expressive language development included decreased speech intelligibility and word-retrieval problems. Vocal weakness and hoarseness also were present.

Because of continued loss of skills and the development of staring spells, the patient was referred for neurologic assessment and neuroradiologic studies. Neurologic examination showed minimal abnormalities. Motor strength and tone were within normal limits. Deep tendon reflexes were 2+. Magnetic resonance imaging (MRI) of the brain was consistently normal. His family reported that his adaptive functioning, peer and family relationships, and behavior were all within normal limits. School reports consistently indicated that the patient was performing at age and grade level, with respect to both academic achievement and behavior.

TABLE 1. Cognitive Assessment Data

<table>
<thead>
<tr>
<th>Cognitive Measure</th>
<th>3 Years, 1 Month</th>
<th>4 Years, 5 Months</th>
<th>5 Years, 7 Months</th>
<th>5 Years, 11 Months</th>
<th>7 Years, 3 Months</th>
<th>8 Years, 3 Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>MSCA Verbal</td>
<td>50</td>
<td>48</td>
<td>54</td>
<td>47</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perceptual/Performance</td>
<td>52</td>
<td>48</td>
<td>40</td>
<td>32</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quantitative</td>
<td>50</td>
<td>40</td>
<td>48</td>
<td>20</td>
<td></td>
<td></td>
</tr>
<tr>
<td>General cognitive index</td>
<td>101</td>
<td>93</td>
<td>96</td>
<td>79</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WISC–R Verbal</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Performance</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>78</td>
<td></td>
</tr>
<tr>
<td>Full scale IQ</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>60</td>
<td></td>
</tr>
<tr>
<td>WISC–III Verbal</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>83</td>
</tr>
<tr>
<td>Performance</td>
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<td>Full scale IQ</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>67</td>
</tr>
</tbody>
</table>

MSCA indicates McCarthy Scales of Children’s Abilities; WISC–R, Wechsler Intelligence Scale for Children–Revised; WISC–III, Wechsler Intelligence Scale for Children–3rd Ed. 

* Mean, 50; SD, 10; * Mean, 100; SD, 16; † Mean, 100; SD, 15.

TABLE 2. Speech and Language Data

<table>
<thead>
<tr>
<th>Speech/Language Measures</th>
<th>5 Years, 0 Months</th>
<th>6 Years, 2 Months</th>
<th>7 Years, 3 Months</th>
<th>8 Years, 4 Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPVT-R</td>
<td>89‡</td>
<td></td>
<td>71‡</td>
<td>96‡</td>
</tr>
<tr>
<td>PLS-3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Auditory comprehension</td>
<td>92‡/6 years, 1 month</td>
<td>5 years, 8 months</td>
<td>6 years, 5 months</td>
<td></td>
</tr>
<tr>
<td>Expressive communication</td>
<td>88‡/5 years, 11 months</td>
<td>5 years, 6 months</td>
<td>6 years, 10 months</td>
<td></td>
</tr>
<tr>
<td>TWF</td>
<td>&lt;71‡</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

PPVT-R indicates Peabody Picture Vocabulary Test–Revised, Form L; PLS-3, Preschool Language Scale–3; TWF, Test of Word Finding.

* Mean, 100; SD, 15.

‡ Age-equivalent scores.
RESULTS

Posttreatment

We have observed significant changes in the patient’s neurodevelopmental functioning in the 6 months since the initiation of combination therapy. He has demonstrated substantial improvement in his cognitive and language functioning. On the Wechsler Intelligence Scale for Children, 3rd ed, an individually administered measure of intellectual functioning given at age 8 years, 3 months, he demonstrated significant improvement in verbal comprehension (Table 1). Although overall cognitive measures did not improve significantly, no additional loss of cognitive functioning was noted. Difficulties persist on tasks of perceptual organization and visual–motor integration.

Striking improvements were observed simultaneously in the patient’s speech and language skills. His performance was characterized by significant gains in vocabulary development and overall communication skills. Standard scores on the Peabody Picture Vocabulary Test–Revised, the Preschool Language Scales–3, and the Test of Word Finding reflected a return to baseline functioning (Table 2). Continued deficits were noted in auditory processing, development of syntax, and word retrieval. This pattern is consistent with a specific language impairment.

Improvements in laboratory measures were noted, as were a three-log reduction in viral load and a significant increase in CD4+ T-lymphocyte percents and total counts (Table 3). Repeat MRI of the brain was performed at age 8 years, 2 months and compared with the previous examination performed 10 months earlier (Figure 1). The posttreatment study demonstrated normal size of the ventricular system and cerebral volume, compared with that from the earlier study, which had shown diffuse atrophic

**TABLE 3.** Hematologic/Virologic Data

<table>
<thead>
<tr>
<th></th>
<th>6 Years, 3 Months</th>
<th>7 Years, 6 Months</th>
<th>7 Years, 9 Months</th>
<th>8 Years, 1 Month</th>
<th>8 Years, 2 Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD4* (%):</td>
<td>8</td>
<td>1</td>
<td>4</td>
<td>NM</td>
<td>17.4</td>
</tr>
<tr>
<td>Total CD6</td>
<td>6/mm³</td>
<td>7/mm³</td>
<td>1/mm³</td>
<td>NM</td>
<td>564/mm³</td>
</tr>
<tr>
<td>Viral load7</td>
<td>NM</td>
<td>701 ± 613 copies/mL</td>
<td>432 copies/mL</td>
<td>&lt;400 copies/mL</td>
<td></td>
</tr>
</tbody>
</table>

* Percent CD4+ T-lymphocyte count.

† Total CD4+ T-lymphocyte count.

‡ Amplicor HIV-1 Monitor Test (Roche Diagnostic Systems Inc, Branchburg, NJ).

§ Combination therapy initiated.

NM indicates not measured.
changes. Signal intensity of the white matter was normal on all sequences, and no mass lesions were noted. These changes were consistent with the resolution of all previous abnormal findings.

Follow-up neurologic examination performed when the patient was 8 years, 3 months revealed a normal gait. He remained unable to skip or to walk on his heels or toes. Strength was diminished slightly on the left in both the upper and lower extremities, although motor tone was normal to passive movement. Cranial nerves, deep tendon reflexes, and Babinski responses all were within normal limits. The patient could not perform a finger-to-finger sequential opposition task accurately, and mild mirroring in the contralateral hand was observed. He also was unable to perform a graphesthesia task.

Over the course of combination therapy, the patient has demonstrated progressive, positive improvements in his behavioral functioning. Social withdrawal and other autistic-like behaviors have been eliminated. He demonstrates an interest in the activities of others and is able to initiate and sustain social interactions. Most significantly, he no longer experiences periods of confusion or lethargy. He is well oriented and engaged in his environment. His family reports that his daily living and adaptive skills are returning to baseline levels.

DISCUSSION

The resolution of atrophic changes seen in HIV-infected patients on imaging studies has not been reported previously with protease inhibitors. The restitution of normal ventricular and cerebral volumes was surprising. Other causes of mass effect were excluded because no structural lesions or discrete mass-like areas of abnormal signal intensity or contrast enhancement were seen. Alternative etiologies of reversible atrophy, such as nutritional depletion, dehydration, or exogenous steroid administration, were excluded on a clinical basis. An explanation for resolution of the patient’s staring spells is unclear, because their etiology was never firmly established. However, because the diagnosis of partial complex epilepsy is not excluded by a normal electroencephalogram, the patient was treated for partial complex epilepsy with phenobarbital and, subsequently, with gabapentin.

The neurodevelopmental improvement and resolution of cerebral atrophy associated with combination therapy are more dramatic than previous reports involving nucleoside analogue therapy alone for HIV-infected children with neuro-AIDS. This is unexpected, because drug levels of ritonavir in the cerebrospinal fluid (CSF) have been measured in a small number of patients and have been demonstrated to be <1% of the corresponding plasma levels (Ann Hsu, personal communication). Because ritonavir is highly protein-bound, it is generally accepted that free drug is responsible for the observed pharmacologic activity. Because CSF protein levels are low, ritonavir could possibly have significant pharmacologic effects in the CSF.

The impact of combination therapy on the CNS may result from an overall reduction in viral burden that, in turn, results in lower levels of endogenous or exogenous neurotoxins present in the CSF. Furthermore, it is possible that some neuronal injury may be reversed if there is a reduction in levels of viral elaborated toxic products. It remains to be determined whether there is a threshold for viral product-mediated injury. An alternative hypothesis is that CNS structures are differentially sensitive to injury during the developmental period, with some time-sensitive periods for injury reversal.

In a short time, we have observed and documented a dramatic recovery in our patient’s virologic, hematologic, and neurodevelopmental functioning, as shown by neuroradiographic imaging after initiation of combination therapy. These changes suggest that the use of combination therapy not only significantly suppresses HIV replication, but also can lessen or even reverse some of the neurologic and neurodevelopmental sequelae of neuro-AIDS. If these findings are replicated in other HIV-infected children using combination therapy, it will reinforce the importance of aggressive, combination treatment for children.

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