Psychosis in a 12-Year-Old HIV-Positive Girl with an Increased Serum Concentration of Efavirenz

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Clearance and adverse effects of efavirenz are associated with CYP2B6-G516T polymorphism. Little is known about the prevalence of genotypes and implications for screening in children. We report (to our knowledge, for the first time in a child) the emergence of psychosis in a 12-year old white girl with an increased efavirenz concentration and heterozygous gene polymorphism of the CYP2B6-G516T.

HIV infection has been associated with mental illness in both adults and children. A review of data collected by the Pediatric AIDS Clinical Trials Group 219C revealed that children with HIV infection have an increased risk of psychiatric hospitalization, compared with age-specific healthy children, with no correlation with disease status [1]. The potential causes of psychiatric illness in HIV-infected children are multifactorial and may include biological predisposition for primary disease, psychosocial stress factors, HIV-related pathologic characteristics, or adverse effects of medication.

Efavirenz is a nonnucleoside reverse-transcriptase inhibitor that is metabolized through the cytochrome P450 system, primarily by hepatic CYP2B6 with limited involvement of CYP3A [2]. Several gene polymorphisms have been described at the CYP2B6 isoenzyme [3], the most significant genetic variant being a change at position 516 from G to T [4]. On the basis of several studies, with exact frequency depending on ethnicity, the wild-type genotype (CYP2B6-516-G/G) accounts for approximately one-half of the population, with a heterozygous variant (G/T) frequency of 40% and a homozygous variant (T/T) frequency of 10% [5–7].

Although efavirenz is known to be associated with neuro-psychiatric adverse effects in children, the literature contains few data regarding the association of psychosis with the use of efavirenz in this population. A review of psychiatric hospitalizations of HIV-positive children revealed no statistically significant relationship between exposure to a nonnucleoside reverse-transcriptase inhibitor and hospitalization [1]. This report describes the first known case of overt psychosis to develop in a child—a 12-year-old white girl who had a serum concentration of efavirenz that was 7–8 times higher than was expected in the context of heterozygous gene polymorphism encoding for the CYP2B6 isoenzyme.

Case report. The patient, a 12-year-old white girl with vertically acquired HIV infection, was admitted to a psychiatric hospital because of increasing psychotic symptoms occurring over the course of 1 year. Cognitive symptoms included social withdrawal, decreased concentration, delusions, and loss of daily skills. The patient’s outpatient therapist referred her for inpatient treatment after her family found writings containing delusional, suicidal, and homicidal statements.

On retrospective review with the patient’s parents and outpatient HIV treatment team, it was determined that the patient’s gradual change in the level of functioning began ~1 year prior to her hospital admission. At that time, the patient’s family disclosed her HIV-positive status to her, and her treatment team increased her dose of efavirenz. In addition, the patient had renewed contact with her biological father on his release from prison several months earlier. The patient and her family denied any ongoing or recent inappropriate dosing of her medication, including acute overdose, and the outpatient treatment team did not have concerns regarding abnormal prescription patterns over time or caregiver reliability.

The patient had a history of HIV infection that was well controlled with antiretroviral medications. Her regimen at presentation included the following oral treatments: 400 mg of lopinavir twice daily (18.2 mg/kg/day), 100 mg of ritonavir twice daily (4.6 mg/kg/day), 30 mg of stavudine twice daily (1.4 mg/kg/day), 250 mg of didanosine daily (5.7 mg/kg/day), and 600 mg of efavirenz daily (13.6 mg/kg/day). Changes of treatment over the previous several years had consisted only of an increase in the dosage of efavirenz from 350 mg to 400 mg daily in April 2003 and then to 600 mg daily in June 2004. The patient’s psychiatric history consisted of outpatient psy-
chotherapy starting in May 2005, with vague symptoms first documented in February 2005. The patient had never received pharmacotherapy or undergone hospitalization for psychiatric illness before the studied hospital admission. Her family history was notable for a biological father with a history of significant illicit drug and alcohol use, and both biological parents had a criminal history. The patient had lived with her paternal aunt and uncle, her adoptive parents, since the age of 6 years; prior to that, her maternal grandmother was her legal guardian. The patient had typically earned above-average grades at school and was beginning to attend a new school around the time of hospital admission.

Physical examination at hospital admission revealed normal findings, including a weight of 44 kg; vital signs within normal limits for her age; and normal neurological, head, neck, cardiopulmonary, abdominal, skin, extremity, and lymph node findings. The patient’s mental status examination was significant for a withdrawn and confused appearance, with blunted affect. She exhibited paucity of speech and psychomotor slowing. The patient’s ability to focus and sustain attention remained intact, with normal scores on the Mini-Mental Status Examination. Her thought process and content seemed impaired on the basis of written delusional beliefs, observed paranoid behaviors, and disorientation.

At hospital admission, laboratory findings, including complete blood cell count, liver function test results, lipid panel data, and thyroid function test results, were within normal limits, and an MRI with gadolinium enhancement revealed no cause for psychosis. The patient’s CD4+ T cell count was 1053 cells/mm³ (CD4 cell percentage, 35.1%), which is within the normal range for her age, and her HIV load was undetectable at <75 copies/mL. Most remarkable, however, was the patient’s serum efavirenz concentration of 19,013 ng/mL, which represented a 7–8-fold increase over the expected level (table 1).

Table 1. Antiretroviral drug concentrations for a 12-year-old girl with HIV infection.

<table>
<thead>
<tr>
<th>Antiretroviral drug</th>
<th>Dosage, mg/kg/day</th>
<th>Expected concentration, ng/mL</th>
<th>Observed concentration, ng/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>16 September 2005</td>
<td>4 November 2005</td>
</tr>
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<td>Lopinavir</td>
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</tr>
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a The lopinavir concentration was thought to be low because of the postdose timing of sample collection.
b The ritonavir concentration verifies that the patient was absorbing the drug.
c Less than the limit of quantification. Second value from 7 weeks after efavirenz therapy was discontinued.

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On the basis of both clinical evaluation and psychological test results, the patient received a diagnosis of an unspecified psychotic disorder. Her psychosis was presumed to have been related to her increased serum concentration of efavirenz—a hypothesis that was later supported by the gradual resolution of her symptoms after the discontinuation of efavirenz therapy. The patient’s delusional thoughts, paranoia, and disorientation had significantly improved by the time of discharge from the hospital. Antipsychotic drugs (initially, risperidone, which caused significant weight gain and was therefore changed to aripiprazole) were used to treat her symptoms but were later discontinued without the development of additional symptoms. The patient initially joined a self-contained classroom as a reintroduction to school and then successfully transitioned to a regular classroom. The patient’s socialization patterns normalized, and she became interested in making new friends and pursuing long-term relationships. One year after hospitalization, the patient, her family, and her outpatient treatment team agreed that she had returned to her baseline level of cognition and functioning.

Discussion. Implications of the CYP2B6-G516T polymorphism have been highlighted in HIV-infected patients receiving efavirenz therapy. Patients who are known to have the CYP2B6-G516T variants warrant close monitoring of efavirenz therapy to avoid potential development of high concentrations of the drug. As in the patient described here, in whom decreased efavirenz clearance most likely led to toxicity and, therefore, psychosis, patients with the heterozygous variant (G/T genotype) may also require therapeutic monitoring for both adverse effects involving the CNS and, possibly, drug concentrations. Given this patient’s normal MRI findings, absence of known family history of psychotic illness, and gradual resolution of symptoms after efavirenz treatment was discontinued, even without ongoing antipsychotic pharmacotherapy, medication toxicity represents the most likely etiology for her psychotic symptoms. It is impossible to determine for certain whether this toxicity developed gradually because of decreasing clearance over time or whether the patient tolerated toxic concen-
trations of efavirenz for a longer period of time with gradually worsening psychosis as a result. It seems likely, however, that the initial insidious onset of symptoms, coupled with multiple psychosocial factors in a developing and, therefore, sensitive physiologic state, contributed to the delayed resolution of the more subtle symptoms that the patient had exhibited.

CYP2B6-G516T was independently and significantly ($P < 0.001$) associated with efavirenz plasma clearance in the Adult AIDS Clinical Trials Group study, with a clearance of $<23\%$ in patients with the heterozygous variant (G/T) and $<54\%$ in patients with the homozygous variant (T/T) [5]. Subsequent studies have found increased plasma efavirenz concentrations in homozygous individuals [4, 6, 9] and in both homozygous and heterozygous patients, compared with those with wild-type genotypes (2.65 $\mu$g/mL vs. 1.71 $\mu$g/mL; $P < .01$) [10]. Homozygous individuals are also more likely to have an increased risk of efavirenz-related adverse effects [5, 9, 11]. Severe psychiatric symptoms, including depression, aggressive behavior, suicidal ideation and attempts, and paranoid or manic reactions, have in turn been associated with higher efavirenz plasma concentrations [5]. In a study involving HIV-positive adults [11], CNS symptoms were recorded in 32% of patients with at least 1 polymorphic CYP2B6-G516T allele, compared with only 4% of patients with wild-type genotypes ($P < .001$). Finally, severe psychosis associated with high plasma efavirenz concentrations in a previously described adult who was homozygous for the CYP2B6-G516T allele resolved after the dose of efavirenz was decreased [12].

One study found that the median clearance of oral efavirenz among 71 HIV-positive children receiving HAART was 3.04 L/h/m$^2$ in children with the T/T genotype, compared with 5.7 L/h/m$^2$ in those with the G/T genotype ($P = .02$) and 7.0 L/h/m$^2$ in those with the G/G genotype ($P = .003$). In addition, a multivariate analysis of efavirenz oral clearance revealed that age and CYP2B6-G516T variants were independently associated with oral efavirenz clearance [7].

Until further information becomes available, it may not be clinically useful or cost-effective to screen all patients initiating efavirenz therapy. More pharmacogenomic studies examining the relationships between genetic polymorphism, efavirenz drug clearance, and neuropsychiatric symptomatology are needed to determine the appropriate screening and monitoring of children receiving efavirenz therapy. In particular, it will be important to determine when to obtain drug concentration measurements, perform genotype testing for the CYP2B6-G516T, and analyze additional specific genotypes.

On the basis of current knowledge, however, patients receiving efavirenz therapy who develop significant and prolonged psychiatric symptoms, especially after the initiation of therapy or a dose increase, should have testing performed at least to determine drug concentrations (to rule out toxicity) and, possibly, for detection of the CYP2B6-G516T genotype. In addition, should genotyping become more widely practiced in the future, as is beginning in clinical psychiatry when determining antidepressant and antipsychotic metabolism [13], it could contribute significantly to the recommendations for pharmacotherapy by pediatricians treating children with HIV infection. Although the differential diagnosis in this population is extensive, drug toxicity must not be overlooked, and the treatment of drug toxicity may lead to resolution of symptoms, as in the case described here.

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References


