An Adolescent with Suicidal Behavior After Liver Transplant

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The patient was a 14-year-old sixth-grade girl who had been born in Sweden and now lived with her mother. The patient was taken to the Psychiatric Emergency Department because she was aggressive toward her mother, who reported that the patient had frequent periods of uncontrollable rage, during which the patient would scream and spit at her mother.

The patient had undergone cadaveric left lateral segment orthotopic liver transplantation (OLT) for extrahepatic biliary atresia at 10 months of age and had developed hepatitis B from the donor. She had been treated with tacrolimus anhydrous (current dose 1mg q12h) since the transplant. She first manifested anxiety symptoms and violent tantrums at age 6 years, following surgery for a bile duct stricture. She developed nonsuicidal self-injurious behavior at age 12 years, including hitting herself with belts and an attempt to cut herself a few months before presentation to the PED.

The patient had experienced worsening depressive symptoms over the previous 6 months, including sadness, crying, poor sleep, poor concentration, poor appetite, excessive guilt about her aggressive behavior, transitory auditory hallucinations, and thoughts of suicide. She was evaluated in the emergency department of another institution 3 months ago, after she was prevented from jumping from a window to commit suicide. Since then, she had been treated with psychotherapy without psychiatric medication. She was hospitalized for PTC replacement for biliary obstruction with elevated liver enzymes and cirrhotic liver changes 3 weeks before presenting to the PED. During that hospitalization, psychiatric consultation was required to manage disruptive behavior.

The patient was close to her father and brother, who remained in Sweden; she found the separation painful. Adjusting to New York City also had been difficult; she had no friends and did not participate in extracurricular activities. There was no history of physical or sexual abuse, or substance use. Family history of psychiatric disease was negative.
Although the patient presented with a clear history of depression, she was diagnosed with Mood Disorder Not Otherwise Specified (NOS) because of the uncertain etiologic contributions from liver disease, transplantation-associated complications, and the effects of immunosuppression. Depression appears to be the most prevalent psychiatric complication of OLT in adults, whereas problems with important relationships is the most frequent psychological reaction in pediatric patients; however, anxiety and depressive feelings are also common among children and adolescents.

To our knowledge, this case is the first report of suicidal behavior in a pediatric OLT patient. A report somewhat similar to the case described an 11-year-old girl with worsening dependency problems and emotional instability following liver transplantation for biliary atresia. Although she became severely dysphoric during brief separations from her parents (ie, their leaving her bedside), she never manifested suicidal behavior or ideation. A study that followed 104 adolescent recipients of liver, heart, or kidney transplants for at least a year after transplant surgery found that 16% developed posttraumatic stress disorder (PTSD) but did not report any cases with suicidal behavior. Studies of psychiatric complications of OLT in adult patients likewise do not describe suicidal behavior, but a study of child and adolescent renal transplant patients reported that 39% of the sample had either suicidal ideation or attempted suicide but did not distinguish between the two.

Our case contains previously identified risk factors for suicidal behavior in adolescents, including depression, anxiety, disruptive behavior, and conflict with family members. The prevalence of suicide attempts in girls has been reported to increase significantly at age 13 years. School problems, family conflicts, and puberty have been associated with mood symptoms in young transplant patients. Suicidal ideation and attempts are more frequent in adolescents with chronic illnesses and physical disabilities and among those who are dissatisfied with their health. In pediatric OLT patients, length of hospitalization and postoperative complications are associated with severity of mood symptoms, but not with suicidal behavior.

Adverse central nervous system effects of immunosuppressant treatment also could be a potential contributor to the symptoms of depression and anxiety in our patient. Depression and aggressive behaviors that reversed with dosage reduction were reported in two (5%) of 40 pediatric patients who had received tacrolimus for brief periods following OLT. Kemper and colleagues reported neuropsychological and behavioral disturbances as significant and frequent adverse effects of tacrolimus treatment in children, occurring at drug levels within the therapeutic range, as in our patient. Neuropsychiatric complications attributable to tacrolimus also were found in an adult sample (n = 101) receiving immunosuppressive therapy shortly after OLT. As with children, neuropsychiatric effects occur in adults at therapeutic tacrolimus levels. Additional literature has noted that the symptoms of tacrolimus-associated neurotoxicity may be reversed in most patients by reducing or discontinuing these drugs. However, some patients have experienced permanent or fatal neurological damage after dose reduction or discontinuation.

The mechanisms underlying the neuropsychiatric side effects of tacrolimus are not clear. However, it is possible that depressive and anxiogenic effects of this compound may involve alterations in signal transduction pathways. Tacrolimus, also known as FK 506, exerts immunosuppressive effects in T-lymphocytes by forming complexes with specific binding proteins (FKBPs) that are part of a larger class of immunosuppressant binding proteins, termed immunophylins. The FK506/FKBPs...
complexes inhibit calcineurin-dependent nuclear translocation of transcription factors, essential to cytokine gene expression.17

Binder has recently reviewed evidence that specific FKBP 51 polymorphisms may be associated with glucocorticoid receptor GR resistance in major depressive disorder and with GR supersensitivity in PTSD, concluding that results are more consistent in PTSD than in depression.18

It is possible that effects of tacrolimus on GR function may have contributed to our patient’s dysphoric symptoms. Tatro and colleagues reported that tacrolimus reduced nuclear localization of the GR and inhibited expression of GR-responsive genes including FKBP51 in neuronal cell cultures.19 Evidence from non-neuronal cell lines also suggest that tacrolimus acts on GR to influence gene expression but the direction of these effects is inconsistent.

For example, tacrolimus was reported to block the transcriptional effects of aldosterone,20 whereas a number of other studies from the University of Ohio found that tacrolimus enhanced the effects of glucocorticoids on gene expression. Another study found tacrolimus-associated increases in GR hormone-binding affinity accompanying the replacement of FKBP51 with PP5. However that lab also reported decreases in number of GR.21 An earlier study from the same laboratory also reported increased GR affinity with tacrolimus.22

In our case, it is possible that perturbations in GR function may have resulted from prolonged tacrolimus and contributed to her heightened vulnerability to stress and maladaptive behavioral response to stressors.

CONCLUSION
OLT is an effective treatment for advanced hepatic diseases refractory to current medical approaches.23 OLT has been associated with a variety of psychiatric disorders, one of the most common being mood disorder.1,2,24,25 Other neuropsychiatric symptoms, including anxiety, psychosis, and adjustment disorder also have been described.1,26 Surprisingly, few reports are available of psychiatric disorders in children following OLT.

Adolescent liver transplant patients are at higher risk for depressions that can lead to suicide attempts. Multiple psychosocial stressors, complicated medical conditions, impaired liver function, as well as long-term immunosuppressant treatment, significantly contribute to these clinical manifestations. Mental health providers should be integrated with transplant teams to assess psychiatric comorbidity and to evaluate the risk of suicidal behavior.

REFERENCES
case challenges