Activation Syndrome in a Patient With Attention-Deficit/Hyperactivity Disorder Treated With Atomoxetine: A Case Report

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Abstract: "Activation syndrome" represents a cluster of symptoms of excessive emotional arousal or behavioral activation, which emerges after the first few weeks of antidepressant treatment or a dose increase and resolves with dose reduction or cessation of treatment. It was reported after treatment with selective serotonin reuptake inhibitor and serotonin-norepinephrine reuptake inhibitor group of agents, but no case of activation syndrome has been reported with the norepinephrine reuptake inhibitor group. Atomoxetine is a norepinephrine reuptake inhibitor and nonstimulant and is used to manage symptoms of attention-deficit/hyperactivity disorder (ADHD). Atomoxetine-related symptoms of mania and hypomania were reported in literature previously. Here, we report a case of activation syndrome arising after atomoxetine (ATX) dose titration in a prepubertal male child with ADHD. Differentiation of activation symptoms from mania/hypomania symptoms after treatment with ATX may be important for the clinicians to manage the adverse effects and understand the risk factors behind activation syndrome with use of ATX in children and adolescents diagnosed with ADHD.

Key Words: atomoxetine, activation syndrome, mood dysregulation, attention-deficit/hyperactivity disorder

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"Activation syndrome" represents a cluster of symptoms of excessive emotional arousal or behavioral activation, which emerges after the first few weeks of antidepressant treatment or a dose increase and resolves with dose reduction or cessation of treatment.[1] Activation-related adverse effects mostly include restlessness, irritability, aggression, motor hyperactivity, insomnia, disinhibition, and impulsivity, although symptoms of anxiety, panic attacks, social withdrawal, bizarre behavior, and mania/hypomania-like behaviors were also reported.[2] The prevalence, clinical features, and acute versus chronic sequelae of activation syndrome among children and adolescents using antidepressants are not fully clarified. However, it was reported to be more common compared with adult patients and the rates increased with younger age.[3] Other risk factors of activation syndrome may include past or current symptoms of mood disorders in the patients and/or their families, elevated plasma concentrations of the therapeutic agents, temporal/developmental hypersensitivity to increased serotonin levels, increased amygdala reactivity, cumulative drug exposure, and allelic variations in the promoter region of the serotonin transporter.[2,3]

Previous studies reported similar rates of antidepressant-related activation symptoms among patients with depression and those with anxiety disorders, whereas no consensus exists for attention-deficit/hyperactivity disorder (ADHD) diagnosis on the emergence of activation syndrome.[4] Some authors suggest that treatment with stimulants and antidepressants among patients with ADHD may be related with activation.[3] Atomoxetine (ATX) is a selective inhibitor of the noradrenaline transporter leading to reduced noradrenaline and dopamine reuptake (serotonin-norepinephrine reuptake inhibitor [SNRI]) and is a frequently used nonstimulant agent for ADHD in the pediatric age group.[5] The most frequently reported adverse effects of treatment with ATX in clinical practice involve headache, reduced appetite, vomiting, sedation, irritability, fatigue, vertigo, and dyspepsia.[6] This article reports a case of activation syndrome in a prepubertal male patient with ADHD, which emerged after an increase in dose of ATX and resolved with cessation of treatment.

CASE

The patient was first brought to our department at the age of 7 years and 6 months with complaints of "hyperactivity, inattention, impulsivity, and negativism." The symptoms were pervasive across multiple settings, were age inappropriate, and impaired his functioning. He was diagnosed with ADHD at an another center a year ago and was started on methylphenidate treatment (MPH) immediate release 5 mg/d. Dose titration was suggested at that center for the ongoing symptoms of inattention and hyperactivity, which led the parents to apply to our department for a second opinion. Prenatal, natal, and postnatal history was normal, and developmental milestones were achieved within normal limits. He was being followed up at the department of pediatric endocrinology for idiopathic short stature for the past 2 years, although no treatment was commenced. Family history revealed no psychopathology.

Baseline mental status examination revealed inattention and hyperactivity symptoms with clinically normal intelligence and mild oppositional behaviors. Parent and teacher completed forms to evaluate *Diagnostic and Statistical Manual of Mental Disorders*, *Fourth Edition*,–Based Diagnostic and Screening Scales for Disruptive Behavior Disorders revealed that he fulfilled 7 and 8 criteria for inattention and 6 and 7 criteria for hyperactivity/impulsivity, respectively. Parents reported 2 oppositional symptoms, whereas the teacher reported none. He scored 12 (subthreshold anxiety) and 11 (subthreshold depressive symptoms), respectively, on the Screen for Anxiety and Related Disorders for Children and Children's Depression Inventory. According to history, mental status examination, and evaluations, he was diagnosed with ADHD-Combined Presentation, according to *Diagnostic and Statistical Manual of Mental Disorders*, *Fifth Edition,* Criteria (American Psychiatric Association 2013). Treatment with MPH extended 10 mg/d was initiated, and behavioral

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interventions to increase compliance were started. Follow-up at the fourth week of treatment revealed reduced appetite and insomnia along with negligible effects on attention and hyperactivity symptoms. Therefore, MPH treatment was stopped and ATX 10 mg/d (0.5 mg/kg per day) was started and gradually titrated at the eighth week to 25 mg/d (1.4 mg/kg per day). Five days after increasing the dose of ATX to 25 mg, parents contacted the department to report clinical worsening. Aggression, temper tantrums, irritability, odd behaviors such as licking his clothes and harming his peers with pencils emerged while previously manageable symptoms of noncompliance, hyperactivity, impulsivity, and inattention were aggravated. In his clinical assessment, mental status examination revealed irritability, restlessness, insomnia, and ADHD symptoms. However, no suicidal thoughts and none of the cardinal symptoms of mania/hypomania including pressured speech, racing thoughts, grandiosity, reduced need for sleep, increased goal-directed activity, and hypersexuality were observed. Evaluation with the Young Mania Rating Scale revealed a score of 6 (below threshold for mania), whereas evaluation with the Naranjo Adverse Drug Reaction Probability Scale revealed a score of 7 (probable).[7]

The patient was judged to display activation syndrome probably related to an increase in dose of ATX, and the treatment was stopped. Follow-up visit at the third day of treatment cessation demonstrated that aggression and odd behaviors were reduced, and they resolved completely at the seventh day. The patient was restarted on MPH immediate release and was still being followed up with the same treatment a year later. No symptoms of mania/hypomania or activation were observed through this period of follow-up.

DISCUSSION

Here, we presented a prepubertal boy with ADHD who was judged to develop activation syndrome probably because of ATX dose increase. In this case, irritability, aggression, odd behaviors like licking his clothes and harming peers emerged after dose titration, inattention, hyperactivity, and impulsivity symptoms increased in severity. The temporal relationship of those symptoms with increase in ATX dose, lack of cardinal symptoms of mania/hypomania, lack of alternative etiologies for symptoms, and their resolution with cessation of treatment led us to diagnose activation syndrome related with ATX.

Although activation symptoms may emerge anytime during treatment, they were mostly reported to arise in the first few weeks of treatment or an increase in treatment dose.[1] In addition, the rate of symptom resolution for activation syndrome may be related to the rate of activation symptom onset.[3] Supporting those views, the activation symptoms in our case emerged in the first week with the increased ATX dose and resolved in 1 week after cessation of treatment.

Symptoms of activation may include irritability, disinhibition, impulsivity, insomnia, restlessness, and motor hyperactivity, and those symptoms may be shadowed by symptoms of ADHD leading to complications in the assessment and measurement of activation.[3] The activation syndrome in our patient was also characterized by aggravation of preexisting symptoms of ADHD along with de novo symptoms of aggression, irritability, disinhibition, and insomnia. Studies on activation-related adverse effects were conducted mostly on ADHD patients with comorbid diagnoses of bipolar disorders and those with a history of treatment with stimulants and/or selective serotonin reuptake inhibitors.[3,8] In youth at risk for bipolar disorders, comorbidity and presence of ADHD may elevate risk for antidepressant-related adverse effects.[9] Risk factors for activation syndrome include mood symptoms before treatment, younger age, higher plasma concentration of drug, and mood disorder history in family. Immaturity of serotonergic/noradrenergic systems as well as polymorphisms in genes involved in those systems (eg, 5-HTR1Dβ) may also be important.[10,11] The only identifiable risk factor in our patient was his age and ADHD diagnosis and may be a high dose of ATX (1.4 mg/kg per day), although we could not rule out a polymorphism in CYP2D6, which may affect serum concentrations of ATX.

Several case reports of "mania- and hypomania-like symptoms," which emerged with ATX treatment, were found in the literature.[12–14] Agitation, hostility, aggression, psychomotor restlessness, and insomnia can be seen in activation as well as mania/hypomania. Unlike those case reports, lack of inflated self-esteem, grandiosity, pressured speech, reduced need of sleep, hypersexuality, and excessive goal-directed activity helped rule out mania/hypomania in our patient (Table 1).

Double-blind, placebo-controlled studies with ATX reported very low rates of irritability and mood lability as adverse effects.[5] On the other hand, the relationship between antidepressant-induced activation and bipolar disorder remains unclear. According to a study by Henderson and Hartman,[15] a history of mood disorder symptoms in the index patient as well as family history of mood disorders was found to be related with emergence of irritability, aggression, and symptoms of mania/hypomania among children with ADHD receiving ATX. However, they also indicated a nonnegligible ratio of the total sample (4.0%) developed "affective symptoms" without a personal/family history after ATX. Therefore, it may be prudent to screen patients with ADHD receiving ATX for changes in mood symptoms even when no personal/family history of mood disorders could be found as in our patient.

The main limitations in our case report are lack of evaluation of plasma concentration of ATX, polymorphisms in cytochrome enzymes (ie, 2D6), and allelic variations (ie, noradrenaline transporter, 5-HTR1Dβ). A specific instrument for treatment-related activation (ie, Treatment-Emergent Activation and Suicidality Assessment Profile) could not be used, although we used young mania rating score and Naranjo scales to overcome this limitation.[16] Regardless of those limitations, our case underlines the need to evaluate for treatment-related activation among children with ADHD receiving ATX and the importance of differentiating this syndrome from a mania/hypomania. There are still concerns about the uncertainty of the definition of activation syndrome and its impact on mood regulation and potential association with bipolar disorder. Therefore, understanding the prevalence of

TABLE 1. Activation Syndrome and Mania/Hypomania Differences

Activation Syndrome	Mania/Hypomania
Anxiety, panic attacks	Euphoria, inflated self-esteem, or grandiosity
Social withdrawal	More talkative than usual or pressure to keep talking
Hostility, aggression	Flight of ideas or subjective experience that thoughts are racing
Disinhibition	Increase in goal-directed activity (either socially, at work or school, or sexually)
Odd behavior	Excessive involvement in activities that have a high potential for painful consequences (eg, engaging in unrestrained buying sprees, sexual indiscretions, or foolish business investments).
Insomnia	Reduced need of sleep, increased energy

activation and clarifying the risk factors in children and adolescents diagnosed with ADHD represents an important area of research and may help us understand activation and other hyperarousal events and their relationships to the pathophysiology of mood dysregulation and bipolar disorder.[5]

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