Onset of Abnormal Movements and Cardiovascular Symptoms after Acute Change in Complex Polypharmacy in a Child with Attention-Deficit/Hyperactivity Disorder and Mood Symptoms

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Chief Complaint and Presenting Problem

T. IS AN 8-YEAR, 1-MONTH-OLD MIXED-RACE (Latino and African American) boy who presented to the emergency department (ED) after complaining of chest pain and abnormal movements that had started following an acute change in medication.

History of Present Illness

T. was being treated in the community for diagnoses of attention-deficit/hyperactivity disorder (ADHD) and bipolar disorder, not otherwise specified (BD-NOS). T.'s mother reported that T. had had many ADHD symptoms present since kindergarten, including difficulty with concentration and completion of tasks, inattention, restlessness, impulsivity, frequent interruption of conversations, and need for constant redirection. T. also was reported to have other behavioral problems, including refusal to follow directions and aggressive behavior toward family members, including slamming or punching objects. In the previous few months, he was reported to have become more oppositional and more disrespectful, and he had attempted to set fires and been cruel to animals.

T.'s mother also reported that T. had experienced difficulty with emotional regulation, and had threatened to hurt himself in the past when angry. He also reportedly had had brief crying spells when he was upset. His mood was reported to be irritable when he did not have his desires fulfilled; T. himself reported his mood as "sad and mad" most of the time. His mother reported that he had experienced difficulty sleeping, typically going to bed at 1:30 a.m. and waking up at 6:30 a.m. T. was reported to have nightmares at times, but he was not able to recall the content. His mother denied that he had demonstrated grandiosity, elevated mood, racing thoughts, or pressured speech. There was no history of suicidal ideation, suicide attempts, or psychotic symptoms. There was no history of abuse, trauma, tics, obsessive compulsive and anxiety symptoms, or use of substances.

T. had been treated for his aggressive behavior by an outpatient child and adolescent psychiatrist with aripiprazole 5mg by mouth (p.o.) daily for a total of 1.5 years. Two months prior to his ED presentation, aripiprazole had been discontinued because of reported weight gain (1.81 kg in 1.5 years) and ineffectiveness at

decreasing aggressive episodes. Lithium CR 300 mg p.o. daily was subsequently started to address the continued aggressive behavior to self and others. One month prior to the ED presentation, guanfacine extended release 2 mg p.o. daily was started.

Four days prior to his ED presentation, T.'s psychiatrist had recommended several changes in his medication regimen to target what his mother called "spasm attacks." These attacks were described by mother as T. hitting and slamming objects, punching holes into walls, attempting to physically harm family members with knives and shovels, and attempting to harm himself by placing his head outside or attempting to get out of a moving car. These symptoms had been escalating over the past few months. Recommended medication changes included discontinuation of guanfacine extended release 2 mg, an increase in lithium CR to 450 mg from 300 mg, and initiation of risperidone 1 mg and lisdexamfetamine (LDX) 50 mg. T.'s mother reportedly did not feel comfortable with the multiple medication changes recommended, so she only stopped the guanfacine extended release and increased the lithium CR.

In the 2 days following the lithium CR increase and guanfacine extended release discontinuation, T. reportedly experienced no adverse effects. On the day of his ED presentation, his mother had started the LDX 50 mg in the a.m.; 45 minutes after starting the medication, T.'s mother reported that T. was rubbing his chest and complaining of chest pain. He would not eat, which was very unusual for him, and he reportedly started to gasp for air. T. was taken to a nearby family practice clinic for evaluation. There had been no past history of abnormal movements, shortness of breath, or chest pain.

Past Psychiatric History

T. had been diagnosed with ADHD, combined type, in kindergarten and medication treatment had been initiated. He had been treated by two child and adolescent psychiatrists in the past; he had been under the care of his current child psychiatrist for the past 1.5 years, and during that time the psychiatrist had also diagnosed BD-NOS.

T. had never been hospitalized in a psychiatric facility or been in out-of-home placements. He had never attempted suicide. At the

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time of the ED evaluation, he was receiving intensive in-home health services, which included transportation to monthly outpatient psychotherapy appointments.

Developmental History

Mother had taken paroxetine during the pregnancy and smoked cigarettes. T. was a twin, born at 31 weeks (Twin B) and delivered via caesarean section. He weighed 1500 g, and his APGAR scores were 6 and 7 at 1 and 5 minutes. Delivery was complicated by difficulty breathing. He was initially given oxygen and then placed on a continuous positive airway pressure (CPAP) device. He spent 1 week in the neonatal intensive care unit (NICU), then 4 weeks in the step-down unit, and was reportedly discharged with full recovery.

Mother described him as being “easily sick” as an infant, despite sleeping and eating well, and having an easy temperament. As a toddler, T. was very active and reported to be a climber; his mother reportedly needed to supervise him at all times.

Developmental milestones were achieved at an appropriate age per mother’s recollection. During T.’s participations in a Head Start program, his mother and teachers reportedly noted “something different” in his behavior and activity level.

Educational History

T. is enrolled in a small, exceptional children class for his behavioral problems in a local primary school. He has received an individualized educational program since kindergarten; however, T. is reported to be currently failing most of his subjects except math. Last year he was suspended from the bus for many months because of multiple fights, and this year he has had multiple bus suspensions for failing to follow the rules, talking, and switching seats.

Social History

T. was raised by both biological parents, and lives with them, his twin sister, and a half-brother in rural North Carolina. He is reported to have a good relationship with his family members despite his behavioral problems. The Department of Social Services was involved with the family 4 months before the ED presentation because of concerns of physical abuse and domestic violence by the father. The father was not allowed to be at home until the investigation was completed 5 weeks later. The allegations were not substantiated, per the mother’s report.

T. denied any history of abuse or of witnessing domestic violence. Parents reportedly did not have an established mode of discipline. T. likes to watch television, play video games, and talk to his friends.

Family History

T.’s mother is a 34-year-old Latina who is attending community college. She has been diagnosed with asthma and anxiety disorder, NOS and is taking paroxetine. Father is a 45-year-old African American who works in construction. He has been diagnosed with diabetes mellitus. Siblings include a twin sister and a 16-year-old half-brother; both are reported to be healthy.

Family history, per the mother’s report, is significant for depressive illness in the mother and anxiety disorder in both parents. There is no other reported family history of psychiatric illness.

Medical History

T. was diagnosed with asthma and obesity. He is not on any routine medications for asthma. T. had an incarcerated left inguinal

herniorrhaphy at 3 months of age and a past myringotomy for multiple ear infections. When he was ~5 years of age, T. had been hit in the head by a bat while playing baseball. Emergency evaluation was notable for a laceration requiring stitches, but no loss of consciousness or concussion was reported.

T.’s mother denied that T. had any history of cardiac problems, thyroid dysfunction, hematological problems, or seizure disorder. He had no medication allergies.

Medication History

It is unclear what medication was initiated first, as T.’s mother gave a sketchy history that was not consistent with the medical record reviewed. Records indicated that 1 year prior to the ED presentation, T. had been prescribed a combination of aripiprazole 5 mg and mixed amphetamine salts (MAS) prescribed as 20mg by mouth once a day (p.o. q.) a.m. and 10 mg p.o. q. 11 a.m.. The MAS was discontinued because of perceived lack of effectiveness, and aripiprazole was continued. Records indicate a recommendation for the addition of LDX 40 mg, but the mother did not adhere to this. Two months prior to the ED presentation, aripiprazole was discontinued because of lack of benefit in control of aggressive behavior and a report of a 1.81 kg weight gain. Lithium CR 300 mg was then added to target aggressive episodes, but this was not perceived as helpful; therefore, extended release guanfacine 2 mg was added 1 month later to target impulsivity and aggressive behavior.

Mental Status Examination

T. is an 8-year-old Latino/African American boy who appeared his stated age; he was of average height but overweight. He had a scar on his left forehead from a previous head injury. He was wearing a hospital gown and had a body odor possibly secondary to excessive movement. He was alert and oriented to person, place, time (except for year), and situation. He was very friendly and talkative. His constant pacing interrupted what would have been otherwise very good eye contact. He was very restless, climbing out of the bed, trying to turn his gown around on his body, playing with the hospital bed, interrupting his mother, fidgeting, and exiting the room multiple times. T. reported a constant need to move. He made it clear that having to pace was uncomfortable.

Abnormal jaw movements, which were visible only when he spoke, made his speech somewhat slurred. He appeared short of breath, and facial grimaces were noted when he inhaled sharply. Speech was forceful, pressured, and elaborated, but volume and tone were normal. Thought process was tangential most of the time, but there were times that he was circumstantial. There was no flight of ideas or loose associations. T. reported that his mood was “happy;” affect was anxious. He denied suicidal ideation, homicidal ideation, or visual and auditory hallucinations, and did not appear to be responding to internal stimuli. His insight was fair, as he was able to recognize that there was something abnormal about his speech and his subjective discomfort; he was also able to recognize the impropriety of his behavior at home. Judgment was fair for age, and he was cooperative with treatment.

Clinical Course

Upon T.’s presentation to the family practice clinic, an electrocardiogram (ECG) was performed and reported to be abnormal, and T. was transported to a university ED. During the ambulance ride, T. was given oxygen, which relieved his chest pain. Upon arrival at the ED, he was noted to be stuttering, anxious,

short of breath, and tremulous, and was exhibiting abnormal mouth movements and “jittery hands.” He was reported to be more talkative than usual, pacing and making facial grimaces. He was moving his jaw from side to side when he spoke, protruding his tongue, and licking his lips. T. reported the need to move around frequently.

In the ED, a repeat ECG was reported as normal. Initial pulse was 102, respiration rate was 16, and blood pressure was 140/92 mm Hg. Laboratory testing was notable for a lithium level of 0.10 mEq/L (normal range 0.50–1.50 mEq/L), microcytic cell volume (MCV) 65 fL (normal range 77–91 fL), mean corpuscular hemoglobin (MCH) 21.1 pg (normal range 25–33 pg), red blood cells (RBC) 5.45 M/uL (normal range 4.0–5.2 M/uL), and RD 16.8% (normal range <14.5%), suggesting a microcytic anemia. T. was given diazepam 5 mg and diphenhydramine 25 mg intravenously, which were reported to reduce his excessive talking, overactivity, and lip licking. After sleeping for 3 hours, he awoke with mild symptoms of jaw movements, pacing, and talkativeness. He was still fidgety, and had slightly rapid speech, mild shortness of breath, and lateral jaw movements with speech. However, he appeared to be less anxious, and he was no longer protruding his tongue. Later that day, his pulse was 89, respiratory rate 20, and blood pressure 129/65 mm Hg. After observation, T. was discharged later that day with instructions to stop all his medications and follow up with a child and adolescent psychiatrist at the university outpatient clinic.

Outpatient Follow-up

T. was reevaluated by a child and adolescent psychiatrist at the university outpatient clinic 2 weeks after his ED visit. He was on no medication. There were no interim reports of additional sequelae or further abnormal movements. Diagnoses of ADHD, combined type and oppositional defiant disorder (ODD) were confirmed. He was started on 20 mg methylphenidate (MPH) extended release p.o. daily to target his ADHD symptoms, and clonidine 0.1 mg for sleep. The MPH extended release was gradually increased to 50 mg before a switch was made to a different MPH extended release preparation titrated to 54 mg (last known dose). At the last report, T. tolerated this medication adequately and had no further recurrence of cardiovascular symptoms, abnormal movements, or other adverse effects.

Brief Formulation

T. is an 8-year, 1-month-old mixed Latino/African American boy referred to the ED for chest pain and abnormal movements after an acute change in medication treatment, characterized by the addition of LDX to recently increased lithium and discontinued extended release guanfacine. T. has a complicated clinical picture notable for prenatal exposure to nicotine and paroxetine, and complications of prematurity at birth. Clinical phenomenology is consistent with ADHD, combined type, and ODD. Although the mother's current historical reports do not endorse BP symptoms, mood symptoms and aggressive behavior have also been targets of pharmacological intervention.

From a biological perspective, T. has a diathesis for mood and anxiety symptoms, given a significant family history. In addition, a previous history of asthma and a possible iron deficiency anemia may be contributing to his current cardiovascular symptomatology. It is unlikely that a past head injury played a role, as there had been no loss of consciousness. From a psychosocial perspective, this child's symptoms must be viewed in the context of his ongoing educational and social vulnerabilities and intrafamily conflicts. In an attempt to address an increase in aggressive behavior, T. was

prescribed an acute change in several medications in his complex polypharmacy regimen. The onset of cardiovascular complaints and abnormal movements appeared to coincide temporally most acutely with initiation of a high dose stimulant following a recent discontinuation of extended release guanfacine and an increase in lithium.

Multi-Axial Diagnoses

Axis I:	Medication-induced movement disorder, NOS ADHD, combined type ODD Rule out mood disorder, NOS
Axis II:	None
Axis III:	Obesity Asthma Microcytic anemia Hypertension, most likely secondary to stimulant
Axis IV:	Psychosocial stressors: academic failure, family conflicts
Axis V:	Global Assessment of Functioning Score: 45

Discussion

This case illustrates a phenomenon all too familiar to child and adolescent psychiatrists: the development of acute, distressing, and functionally impairing adverse effects of a complex medication regimen in the context of a complicated diagnostic picture. Given the fact that multiple medication changes were recommended simultaneously rather than systematically and sequentially, it is not surprising that untoward results occurred. Whereas targeted combined pharmacotherapy (vs. “polypharmacy”) tends to be the rule rather than the exception in pediatric psychiatry, systematic, carefully thought out changes in one medication at a time are generally recommended in outpatient practice (Wilens et al. 1995). There is a small evidence base supporting the efficacy of medication combinations, in contrast to what is known about monotherapy, but combinations are frequently used in practice to address complex comorbid presentations, without adequate scientific evidence (Walkup et al. 2009).

T. developed acute cardiovascular signs and symptoms of chest pain, tachycardia, and hypertension, and neurological signs and symptoms of akathisia, dyskinesia, jitteriness, and agitation following a single, rather high starting dose of LDX. These symptoms are all consistent with adverse effects associated with stimulant medications. LDX is the most recent United States Food and Drug Administration (FDA)-approved stimulant for treatment of ADHD, and acts as an inactive amphetamine pro-drug. A year after LDX was released, multiple adverse effects were reported including agitation, tachycardia, dystonia, chest pain, jitters, tremors, fasciculations, abdominal pain, and insomnia, which have also been reported with other stimulants (Spiller et al. 2008). Not surprisingly, the most frequently reported adverse effects of LDX in youth randomized to receive 50 mg and 70 mg doses titrated weekly were decreased appetite, insomnia, upper abdominal pain, headache, irritability, vomiting, and nausea within the first week (Biederman et al. 2007).

Abnormal movements, including dyskinesia, have also been reported frequently with stimulants (Lipkin et al. 1994; Senecky et al. 2002; Rodnitzky 2003).

Withdrawal dyskinesia and other abnormal movements may be observed in children receiving polypharmacy in the context of

complicated clinical pictures of comorbidity (Teoh et al. 2001; Hollis 2007; Sabuncuoglu 2007; McLaren et al. 2010). Recent studies suggest that positive response to stimulants in ADHD corresponds to downregulation of postsynaptic dopamine receptors. As antipsychotics upregulate dopamine receptors, combining them with stimulants potentially may lead to untoward reactions. It has been shown that withdrawal dyskinesia symptoms can appear anywhere from 2 days to 2 months after discontinuation of an antipsychotic; if a stimulant is started during this time, an increase in abnormal movements could result (Hollis 2007). This is unlikely to have been the case with T., as his aripiprazole had been discontinued several months before starting the stimulant. Fortunately, the abnormal movements were transient and resolved in < 24 hours. It is interesting that his ADHD diagnosis would have placed him at somewhat increased risk for the development of tics as well, but fortunately that appeared not to be the case, at least in the short run (Spencer et al. 2001).

T. also presented with akathisia, the unpleasant state of motor restlessness characterized as an inability to sit still. The pathophysiology of akathisia is not completely understood, but likely arises from interactions in subcortical and possible spinal dopamine/norepinephrine systems (Blaisdell 1994). Akathisia may range in intensity from a sense of disquiet or anxiety to severe discomfort, and can be classified as acute, tardive, and/or withdrawal subtype (Blaisdell 1994). In children, akathisia may be difficult to differentiate from agitation/activation in association with stimulant treatment or even ADHD-associated hyperactivity. T. clearly described an uncomfortable feeling and an urge to move of acute onset, which was new to him and therefore unlikely to have been related to his ADHD.

Other factors may be associated with akathisia, including non-neuroleptic drugs, and the presence of iron deficiency anemia. T. was found to have a microcytic anemia that could have been associated with an undiagnosed medical problem such as thalassemia or iron deficiency anemia. Iron status may play a putative pivotal role in the pathophysiology and development of acute akathisia as a result of interactions of iron with D2 receptors (Sachdev 1995). Iron deficiency has also been implicated in the pathophysiology and severity of ADHD symptoms, and movement disorders such as restless leg syndrome are related to the role of iron in the production of dopamine and norepinephrine.

Other factors may have contributed to T.'s acute abnormal movements. His high starting dose of 50 mg LDX may have rendered him unusually vulnerable, and, notably, he had no reported adverse effects with low-dose methylphenidate stimulant 2 weeks later.

In addition, T.'s concomitant and past treatment with other medications may have contributed to his acute symptoms. Guanfacine extended release, although indicated for treatment of ADHD in children, has also been reported to reduce tics and abnormal movements in the short acting form (Scahill et al. 2001). It is possible that abrupt discontinuation of guanfacine may have been associated with transient rebound hypertension and a susceptibility to abnormal movements. The increase in lithium may have also rendered T. more likely to experience abnormal movements, as lithium has been described as reducing the effect of LDX (Wayne 2007).

Fortunately, T.'s acute abnormal movements and cardiovascular symptoms resolved quickly with a combination of a benzodiazepine and antihistamine; short-term follow-up revealed that he could tolerate combination treatment with only low-dose methylphenidate and clonidine. Longer-term follow-up results are not yet available, but it is very likely that this child will continue to need carefully titrated, systematically monitored, targeted combined pharmacotherapy and psychosocial treatments.

Conclusion

In conclusion, over the past two decades, there has been a steady increase in the diagnosis of ADHD and in the use of stimulants, particularly in the United States. Increased use of stimulants, particularly in combination with other medications, requires increased awareness and vigilance regarding potential adverse effects (Pliszka et al. 2007). Caution is advised when combining multiple agents, and systematic titration of one medication at a time, starting with low doses, is recommended.

Disclosures

Dr. Potter and Dr. John have no conflicts of interest or financial ties to disclose.

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