Treating a Child With Asperger's Disorder and Comorbid Bipolar Disorder

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Children and adolescents with pervasive developmental disorders, including Asperger's disorder, often are seen by pediatricians, pediatric neurologists, child psychiatrists, and other professionals as having a variety of behavioral and emotional disturbances (1–3). Aggression and self-injury are among the most common problematic behaviors that come to the attention of clinicians. In some of these children and adolescents, these disturbing behaviors are symptoms of a comorbid psychiatric condition. However, many clinicians continue to view them as part of the underlying developmental disorder. In consideration of the long-term disability associated with the pervasive developmental disorders and the absence of specific pharmacological treatments for the core deficits of this disorder, it is of paramount importance to recognize and treat comorbid psychiatric conditions in these children, which can substantially improve functioning (2, 3).

"The most consistent historical diagnosis given to Abraham was pervasive developmental disorders not otherwise specified or Asperger's disorder."

This report summarizes a clinical case conference presented at McLean Hospital in Belmont, Mass. The presentation was used to inform clinicians about the occurrence of psychiatric disorders among developmentally disabled children, with an emphasis on those with pervasive developmental disorders. It also serves as an illustration of how aggression and self-injury can be symptoms of comorbid psychiatric disorders and underscores the necessity of proper diagnostic formulation in these children. For this child, the proper diagnosis was not recognized for years. Once he was diagnosed with comorbid bipolar disorder, appropriate treatment led to a decrease in problematic behaviors, an improvement in quality of life for the child, and a decrease in family burden.

Case Presentation

Abraham (not his real name) first came to the McLean outpatient department at the age of 13.5 years. He had just been discharged from inpatient hospitalization and required ongoing outpatient pharmacologic management. His mother stated that he had been diagnosed with Asperger's disorder and despite numerous placements in therapeutic schools, hospitalizations, and medication trials, he continued to be violent and aggressive. None of the medications that he had tried had been effective, except thioridazine. Abraham had been treated with thioridazine, 125 mg/day, for an extended period. Both parents, who were well educated, felt that their son did not simply have Asperger's disorder, and they wanted to know what other diagnoses could be made. In addition, Abraham's parents were concerned about his current medication regimen because he had recently developed an unusual tongue movement, which was most prominent when he missed a dose of thioridazine.

At the initial evaluation, Abraham had ongoing sleep disturbances, obsessions, sadness, irritability, and racing thoughts. He spoke in a loud, anxious manner. He washed all the clothes in the house in a frenzied and intense manner late into the night, even if the items were clean. Abraham obsessed about a girlfriend who he reported was enrolled at a local public high school, although the girlfriend did not, in fact, exist. Abraham also felt that God could transfer thoughts from one person to another and that God and other people could read his mind. Abraham stated that something was "haywire" and that he felt like he was "unraveling." He could not follow his own thoughts and felt disorganized. Abraham also stated that he felt he could see his dead uncle. He admitted to biting himself when he was upset.

His mother said that Abraham had become more aggressive over the past few months. Without provocation, he had hit his younger siblings and struck out at people. In addition, his mother described him as being more perseverative than usual. He was extremely intrusive physically and engaged in some inappropriate touching. His mother stated that Abraham's whole family was gravely affected by his behavior. His siblings were afraid of him. His mother, who was a graduate student at the time, had missed many classes, and his father often had to leave work early in order to help with Abraham.

His parents described him as quite silly and anxious at age 2.5 years. At age 4, Abraham had become aggressive and had engaged in bizarre talk using repetitive nonsensical words. Abraham was first hospitalized when he was 8 years old. Psychological testing at that time showed that he had some looseness of association and some breaks with reality. Psychotherapy notes at that time stated that he had "manic-like behaviors."

Since the age of 8, he had undergone numerous evaluations. He had a history of being fidgety, having grandiose and racing thoughts, exhibiting disorganized behav-

ior, and being aggressive. Abraham showed mood lability and had discrete episodes of hypomania, evidenced by silliness, hypersexuality, poor sleep, and perseverative and pressured obsessive ritualistic behaviors, such as washing clothes all night. He had received numerous diagnoses in the past, including conduct disorder, attention deficit hyperactivity disorder (ADHD), social learning disability, anxiety disorder, pervasive developmental disorders not otherwise specified, and Asperger's disorder. The most consistent historical diagnosis given to Abraham was pervasive developmental disorders not otherwise specified or Asperger's disorder. However, none of the historical diagnoses had captured his symptom complex completely. One treating psychiatrist had entertained the possibility that Abraham might have mood dysregulation and tried lithium to treat his symptoms, but no formal diagnosis of bipolar or affective disorder had been made.

The results of past neurologic evaluations, including an EEG and magnetic resonance imaging, had all been within normal limits. A test for fragile X syndrome had been negative. At 6 years old, Abraham had psychological testing; his verbal IQ was 111, and his performance IQ was 97. He had difficulty grasping a pencil and was noted to have trouble placing pegs in a Peg-Board with only one hand. He had difficulty "reading" the emotional content in pictures in the Children's Apperception Test (which contains drawings of familiar social situations, such as a father sitting in a chair with a boy next to him). Abraham routinely had difficulty labeling the feelings shown in the pictures accurately and had difficulty perceiving the social interactions that were taking place. The examiner felt that his inability to identify the feelings of others was causing Abraham to misperceive what was going on socially in his environment. In addition, Abraham was highly anxious and inattentive and had difficulty with self-control. He was seen as managing his anxiety by trying to control social situations in an effort to counter some of the social rejection he faced. The examiner concluded that Abraham had a "social learning disability." At numerous subsequent psychological evaluations, Abraham was noted to have disorganized thinking.

He had been prescribed a number of medications over the years. He was initially given imipramine but developed a glazed look and stomach aches, so it was discontinued. He had tried four selective serotonin reuptake inhibitors (SSRIs)—fluoxetine, clomipramine, sertraline, and paroxetine—all of which led to an increase in sleep disturbances, agitation, aggression, and, at times, homicidal ideation. In addition, he was given a low dose of methylphenidate (10 mg/day), which increased his agitation. A trial of perphenazine, up to 9 mg/day, caused side effects but no improvement. The psychiatrist who suspected an underlying mood disorder tried lithium, up to 600 mg/day. Lithium decreased Abraham's impulsivity and motor agitation; however, it was discontinued because it caused diarrhea.

Abraham had been hospitalized just before his outpatient visit at McLean Hospital because of his worsening depressive symptoms and suicidal ideation. He was sad, could not concentrate, and did not want to attend his new school. Abraham was intermittently suicidal and preoccupied with skunks and washing all the clothes in the house. In addition, he began experimenting with electrical appliances, and just before his last hospitalization, he had stuck a knife in an electrical socket.

While in the hospital, he had to be placed in the quiet room frequently because of his aggressive, inappropriately intrusive, and oppositional behaviors. At times Abraham had to be placed in six-point restraints because he slammed his body repeatedly against the door of the quiet room. He underwent a short trial of paroxetine during this stay to address his depression and obsessiveness, but he became increasingly irritable, sad, sleepless, and aggressive on this regimen. Abraham was discharged from the facility with a diagnosis of Asperger's disorder and "rule out intermittent explosive disorder." His medications included clonidine, 0.25 mg/day, and thioridazine, 125 mg/day.

At the time of his initial evaluation, Abraham lived with his supportive family. His mother and father, married for 16 years, were both in their late 30s at the time. His three siblings were all younger than Abraham. His father had experienced episodes of major depression, which responded to pharmacologic treatment. An uncle had been diagnosed with ADHD, and a maternal grandfather had alcoholism. There was no family history of anxiety disorder, obsessive-compulsive disorder (OCD), developmental disorders, psychosis, or bipolar disorder. There was also no family history of neurological disorders.

Abraham's mother's pregnancy was uncomplicated and went to full term; his birth weight was 7 lb, 10 oz. His mother did not use alcohol, illicit drugs, or prescription medications during pregnancy. He was slightly jaundiced at birth but did not require phototherapy. His mother breast-fed him for 15 months, and he gained weight normally. His mother described Abraham as an infant as calm and cuddly and liking to be held. His sleep patterns were irregular from an early age. As an infant, Abraham seemed to visually track objects in his crib, even if there was nothing there. As a toddler, Abraham had only fair eye contact. He never had stereotypic movements. Abraham had a tendency to be preoccupied with objects, particularly mechanical things, at times to the exclusion of people.

Abraham's parents noticed that Abraham was different from other children when he was 2 years of age. For example, although his speech development was timely, he tended to speak in a loud voice, with odd prosody. Although he was very bright and often had precocious speech, Abraham spoke with pronominal reversals, repeated nonsensical words, and engaged in lengthy pedantic monologues regarding his circumscribed topics of interest. His motor development was timely. In addition, Abraham had difficulty with fine motor skills and was noted at age 6 to have an awkward pencil grip while writing. He had little capacity for reciprocal interaction. Abraham did not seem to have the capacity to understand other people's feelings and had little capacity to empathize with others. He had difficulty making friends because he was controlling and bossy and wanted all the other children to engage in his activity of choice while adhering strictly to his rules. He also had difficulty sharing and taking turns in a socially appropriate manner. Abraham often preferred to be in the company of adults and related to adults better than to his peers. He had an odd preservative way of seeking comfort during times of distress, during which he would intrusively ask questions repeatedly.

Over the years, his focus of interest shifted. For example, as a preschooler, he was preoccupied with his stuffed animals and needed to line them up in a certain way; as a preadolescent, he was preoccupied with trains and collected all the train schedules that he could acquire; and as an adolescent, he focused more on mechanical items, such as electrical sockets and washing machines, with an intense inquisitiveness as to how they worked. In addition, he was very good with numbers as a young child and was able to do multiplication at age 6. He had extreme difficulty adjusting to changes in his routine and was very rigid in his insistence on adhering to his daily schedule.

Upon initial examination in our clinic, Abraham appeared well dressed, well groomed, and eager to converse. He made brief eye contact but more often he looked around the room with darting eyes. He was quite fidgety. His speech was somewhat pedantic in style, pressured, and loud. He described his mood as "fine." His affect was irritable and labile, ranging from anger to sadness. His thought content was notable for grandiosity; he thought that he had the capacity to understand everyone in the world. He asserted that he had a girlfriend (who did not exist). Abraham believed that he could read other people's minds, that other people could take thoughts out of his head, and that other people could then turn his own thoughts against him. He felt that his younger siblings were intentionally trying to hurt him. He was not suicidal or homicidal at the time. His thought process was overly inclusive, perseverative, and, at times, circumstantial. There was no evidence for current auditory, visual, tactile, or olfactory hallucinations, although he stated that he had been conversing with a dead person just before his recent hospitalization. He did not have the capacity for reciprocal conversation. He also did not seem to understand that other people might have feelings separate from his.

Abraham was given the following diagnoses: bipolar disorder (mixed, with psychotic features) and Asperger's disorder, with features of OCD. Shortly after his initial outpatient evaluation, Abraham was hospitalized at McLean because of ongoing agitation and unsafe behavior. His thioridazine and clonidine doses were slowly tapered, and he was given other medications, including valproate and propranolol. Both trials were of short duration and limited efficacy owing to side effects. Eventually, a combination of 1 mg b.i.d. of oral clonazepam, 2100 mg/day of lithium (1.0 mM), and 3 mg/day of risperidone led to a marked reduction in his behavioral symptoms. Over the next few months his mood normalized and his aggressive, extreme compulsive and disruptive behaviors stopped.

Follow-Up

Abraham has not been hospitalized for several years now. In the intervening years, his risperidone has been slowly tapered to 1.5 mg/day, and his lithium dose has remained at 2100 mg/day. He has continued to do well with his medication regimen, with minor adjustments for occasional episodes of mild hypomania. During these hypomanic periods, Abraham's obsessiveness also increases, and it has become clear over the years that his obsessiveness cycles with his mood and is more of a manic preoccupation than the type of obsessiveness typically seen in children with pervasive developmental disorders.

Abraham currently attends a therapeutic day school that specializes in educating individuals with autistic spectrum disorders, where he receives psychotherapy, group therapy, behavioral and social pragmatic intervention, and vocational preparation. The professional staff at the school and at McLean Hospital are in regular contact regarding his progress.

His mother states that Abraham is more responsible, he is helping appropriately around the house, he is trying to be a good big brother to his siblings, and he is an excellent driver. His siblings look up to him now and are not afraid of him. In addition, once Abraham's condition was stable, his mother was able to finish her graduate program and went back to work.

Although Abraham's impaired mood symptoms are currently under control, he continues to have difficulty in a number of areas: in peer relationships (he prefers the company of adults to peers), in his ongoing preservative way of seeking comfort when distressed, in his ongoing interest in circumscribed topics (although it is not as intense and pressured as when he is manic; Abraham now has the capacity to be redirected from his obsessions), in his pedantic speech (although he is no longer pressured and disorganized), in the monotonous quality to his speech, in his ongoing difficulty understanding the feelings of others, in his awkward gross motor movements, and in his difficulty adjusting to change in his routine. Aside from these ongoing symptoms of underlying Asperger's disorder, the only remaining issues are those that his mother feels are typically seen in adolescent boys, as he struggles to individuate from his parents. Abraham was able to personally describe his other successes in an interview.

Interview With Abraham

Abraham: [Immediately after he was introduced, Abraham eagerly went to the front of the room and began addressing the people attending the conference without any questions having been asked of him.] First of all, I started high school in August of [deleted]. I am going to get my high school diploma in [deleted]. So far, I'm doing very, very well, and when I get my diploma, I am probably going to go on to college or something like that, but I would like to share some of my improvements with you: I started this high school program, which does not end until [deleted]. I also now have a driver's license [applause]. Thank you very much. This license says I can drive. [Abraham held up his license for all to see.]

Also, I would like to share that despite walking out a couple of times, I now have a job as a cashier in a food grocery store. I had a job before this, but I quit in the middle of the day the first time. I had the job, then I called them later and said, "May I please come back?" and they said, "Sure," after a few days of thinking. I quit in the middle of the day a second time too and did not go back to that site. Now I have a different job at another

food store; the old job was a food store job as well. At this job, I am the cashier making $6.40 an hour, for those that are interested.

I also want to say I am a very religious person, I'm very strong with God; I'm not going to get deeply into it, as it's not very appropriate at this time. I just want to say I am very religious; I always have been.

Also, I have had no accidents since I got my license, and that shows a lot of ability to drive well.

Regarding this high school program issue, I have my hard times in this high school program in regards to making friends, but in general I have done well over all, and I thank God and I thank all for your help.

Dr. Coyle: Now, tell me when you had this job and you quit it on two occasions. The first job at the first grocery store did not go well?

Abraham: Actually work-wise, I did a good job. I'm very good at being polite to customers and helping them out, but I had this one day when something went wrong. I said, "Good-bye, I'm leaving," and I left without any notice.

Dr. Coyle: So, it sounds like you are really doing well with your new job.

Abraham: I like it a lot.

Dr. Coyle: You said you had some problems with making friends at work and at school?

Abraham: Friendships have never been completely easy for me, but at my house, I have a lot of neighborhood friends because the kids in my school are obviously like me in some ways. They are not going to be happy and cannot offer the perfect friendship.

Dr. Coyle: Could you tell me about some of your friends in your neighborhood?

Abraham: Well, I have this one friend. He is more my brother's friend than mine, but he really helps me a lot because he said that I have a nice personality, and I do. I have a very nice personality. I'm very helpful and caring, every single day. For example, now I walk my dog to be helpful to the dog and to the family. Although, some days I might get off because I have something important, but most days I give my dog a very quick 3-mile walk.

Dr. Coyle: Do you have any hobbies?

Abraham: I like to read the Bible, I like to go to church, I like to drive, and I like to work.

Dr. Coyle: How long have you been seeing Dr. Frazier?

Abraham: I met Dr. Frazier for the first time….

This was weird, because I actually announced to my mom that I needed to go back in the hospital; she didn't say I had to go back, I announced it. She said, "Well, if you say so, let's go." So I went and that was my first time as an inpatient here and when I met Dr. Frazier.

I am too upset to think about that [the hospitalization]. But…do you want my honesty?

Dr. Coyle: Yes.

Abraham: Well, the reason I wanted to go to the hospital was to visit all the people that I met the first time I was in the hospital.

Dr. Coyle: It also sounds like you were still having a difficult time.

Abraham: I was still having a hard time, but I basically liked my first time in the hospital. About a month after I left the hospital, I said to myself, "I miss those people there…the staff. I would love to go back to see them." I knew that one way that was possible was to be hospitalized again, because you can't go back to visit. So, I went back—I said, "Mom I need the hospital again. I'm going nuts" (even though I was really fine, and I wasn't really that upset). I just thought I had to say something to convince her. I went back to the hospital, and I was only there for a day, then I was transferred here and started working with Dr. Frazier. That's how I'm with her. When I was hospitalized here, I just wouldn't stop running around.

Dr. Coyle: Do you remember what the hospital stay here was like?

Abraham: Yes, I mean, like, I'm bipolar, and until I got on to this lithium, which protects me from it, I was really not doing well because sometimes, when I was really feeling low, I'd run into my mother and jump on her lap and start crying like my little brother. Once I met Dr. Frazier, she put me on lithium and I was fine, depression-wise. I still get depressed sometimes but not like before, and even when I am depressed…I can drive just fine.

Dr. Coyle: Mrs. [deleted], what changes have you observed since Abraham was hospitalized 3 years ago?

Mrs. [deleted]: Before the hospitalization, we were at the end of our rope. Abraham's problems were dominating the family, frightening his siblings. Safety issues were a constant concern. My husband and I were looking into a residential placement. Now, Abraham is a different person—responsible, hardworking, and a conscientious big brother.

Discussion

Asperger's disorder is a developmental disorder that is on a diagnostic continuum with autism and falls under the category of pervasive developmental disorders. The American Psychiatric Association included this diagnosis in DSM-IV. The disorder is characterized by a paucity of empathy, naive and inappropriate interactions, a limited ability to form friendships with peers, pedantic and poorly intonated speech, egocentrism, poor nonverbal communication, intense absorption in circumscribed topics, and, at least in some patients, ill-coordinated movements. Although Asperger's disorder is similar to autism in many respects, the distinguishing feature in individuals with the disorder is their relatively normal speech development. In

addition, individuals with Asperger's disorder are less likely to have stereotypical behaviors and tend to have normal intelligence. In fact, a delayed onset of language may be the only developmental variable that predicts diagnosis when children with high-functioning autism and Asperger's disorder are compared (4). The long-term outcome for individuals with Asperger's disorder is generally more positive than for those with autism. For example, many individuals with Asperger's disorder go on to college and start their own families. The disorder may have a later age at onset (>24 months) than autism. Before the publication of DSM-IV, Asperger's disorder was often described as high-functioning form of pervasive developmental disorder and was coded as pervasive developmental disorders not otherwise specified.

Diagnosis

An English study by Howlin and Asgharian (5) found that the diagnosis of Asperger's disorder is often delayed in affected individuals, despite parents' concerns about their children's abnormal social development, beginning around age 30 months. Children with autism tended to be diagnosed around age 5.5 years on average, whereas those with Asperger's disorder tended to be diagnosed around age 11 (5). Earlier diagnosis and appropriate intervention can optimize a child's functioning. The American Academy of Child and Adolescent Psychiatry published practice parameters for the assessment and treatment of individuals with autism spectrum disorders (6). In addition, the Child Neurology Society and the American Academy of Neurology proposed a method for diagnosing and assessing autism that entails a dual-level approach: 1) routine developmental surveillance and 2) diagnosis and evaluation of autism. (Specific recommendations for each of these two levels are described in reference 7.)

Prevalence and Genetics

Estimates of the prevalence rate for autism have varied somewhat over the past decade. Autism was thought to occur in 1 out of 2,000 children and more recently has been estimated to occur in 1 out of 500 children (1, 7). In a recent English survey of 15,500 children (aged 2.5–6.5 years) (8), the prevalence rate for autism was found to be 16.8 per 10,000 children and 45.8 per 10,000 children for other pervasive developmental disorders.

The concordance rate for autism in monozygotic twins is 60%; the concordance rate for a broader autism phenotype is 90% (9, 10). In one study (11), the risk of recurrence for autism (i.e., the frequency of autism in subsequent siblings) was estimated at 6%–8%, or up to 200 times the risk in the general population. However, a more complicated analysis of the same data using a mixed-model method (i.e., a major gene model, a polygenic model, a sibling-effect model, and a mixed-model consisting of major-gene and shared-sibling effects) (12) estimated that the relative risk of recurrence of autism is only 4.5%, which is 65 times greater than the risk in the general population. The difference in concordance between monozygotic twins and dizygotic twins or first-degree relatives is consistent with the requirement for multiple interacting genes; a combination of three separate risk genes provides the most plausible model (13). Current genetic research in autistic spectrum disorders is directed at identifying genetic loci that may be associated with components of the disorder, such as social impairments, cognitive deficits, and obsessional traits (14).

As a component of autistic spectrum disorders, Asperger's disorder has been estimated to occur in 8.4–10 of 10,000 children in one study (1, 8). Asperger's disorder may be highly heritable. For example, a recent familial aggregation study (15) demonstrated that in families of children with pervasive developmental disorders (34 with two affected children, 44 with one affected child, and 14 with an adopted child with pervasive developmental disorders), all components of the lesser variant of pervasive developmental disorders (or with traits like those in pervasive developmental disorders) were more common in biological relatives than nonbiological relatives, which confirmed the familial aggregation of the traits. Children who had a greater risk of family members being affected were those with a higher level of functioning who came from families in which two children were affected with pervasive developmental disorders (15). However, the genetics of Asperger's disorder, in particular among the pervasive developmental disorders, have not been well studied. Future research needs to focus on the genetics specific to this disorder.

Comorbidity of Asperger's and Bipolar Disorders

Several investigators have described children with mood lability who satisfy many of the diagnostic criteria for bipolar disorder in their prepubertal years (16–19). Children with presumptive bipolar disorder exhibit mixed mood states, chronic irritability, rapid cycling, suicidality, and oppositionality. Children with developmental disabilities have a two-to-six-times greater risk of experiencing comorbid psychiatric conditions than their developmentally normal peers (3, 20–22). The presence of comorbid affective disorders in these children may more severely impair an individual with already limited cognitive functions and social skills (23). However, individuals with Asperger's disorder and other developmental disabilities can suffer from treatable comorbid mood disorders for years, despite frequent medical assessments and developmental and psychiatric evaluations. The reasons for this delay in diagnosis of a comorbid mood disorder are complex and multiple. The symptoms of mood disorders can be masked by other symptoms or behaviors in the population with autistic spectrum disorders; for example, behaviors that are characteristic of or associated with autistic spectrum disorders (i.e., obsessiveness, stereotypies, hyperactivity, inattention, social intrusiveness, social withdrawal, aggression, and self-injurious behaviors) may become more pronounced, intense, or exaggerated during manic or depressive phases. The changes in these behaviors in individuals with both Asperger's and bipolar disorders are usually episodic and occur within the context of a mood state and are

responsive to effective treatments for mood disorders. Individuals with autistic spectrum disorder or Asperger's disorders have a limited ability for abstract thinking, restricted or odd expression of emotions in their faces, voices, or words, and limited capacity to understand the mental states and feelings of themselves or others. Most individuals with autistic spectrum disorders are very sensitive to changes in their environment, and their moods and behaviors shift in response to these changes (24).

Diagnosing Comorbid Bipolar Disorder

Bipolar disorder should be entertained as a possible diagnosis when there is deterioration in cognition, language, behavior, or activity; when there is a clear pattern of fluctuation or cyclicity in activity, behavior, and interests (with "good times" and "bad times"); and when observed behavior indicates a mood problem. (As examples of the latter, an increase in crying, self-injury, sleep disturbances, and social withdrawal, a decrease in activity, and a loss of interest in activities of daily living may indicate depression; an increase in silliness, distractibility, poor judgment, intrusiveness, laughing, aggression, pressured speech, noncompliance, and agitation may represent symptoms of mania [24–26].)

Although more research needs to be done to delineate the similarities and differences in mood states between individuals with Asperger's disorder and developmentally normal individuals, Sovner (25) (and with Parry [26]) proposed some criteria as a starting point. Sovner noted that there are four specific domains of functioning in individuals with developmental disorders that can be further affected by a comorbid affective illness, making the task of diagnostic formulation difficult. These four domains are intellectual distortion, psychosocial masking, cognitive disintegration, and baseline exaggeration (25).

Rates of the prevalence of comorbid pervasive developmental disorders, specifically Asperger's and bipolar disorders, are difficult to ascertain as Asperger's disorder is a relatively new diagnostic category that first appeared in DSM-IV, and the actual prevalence of pediatric bipolar disorder will be difficult to fully ascertain until the definition of bipolarity in children is more fully agreed upon. However, in a population of children evaluated by a pediatric psychopharmacology clinic, Wozniak and colleagues (27) reported that out of 727 children, 52 met criteria for pervasive developmental disorders, 114 met criteria for mania, and 14 of 52 children with pervasive developmental disorders met criteria for both pervasive developmental and bipolar disorders (which represented 2% of all referrals, 12% of the children with bipolar disorder, and 27% of the children with pervasive developmental disorders). Clearly, these data suggest that there was an overrepresentation of children with pervasive developmental disorders in the overall group with bipolar disorder and an overrepresentation of children with bipolar disorder in the group with pervasive developmental disorders. However, the study did not specifically represent individuals with Asperger's disorder, and it is not clear how generalizable these data were to the group with general pervasive developmental disorders because they represented children who were evaluated in a pediatric psychopharmacology clinic. To date, there is little known about the prevalence of mood disorders in a group of children with Asperger's disorder who were not specifically referred for treatment of serious behavioral problems.

There are a number of published case reports and studies that suggest an association between autistic spectrum disorders and bipolar disorder (27–31), although not all of these reports are explicit regarding the number of children that actually had Asperger's disorder because they predate DSM-IV. For example, Komoto and colleagues (28) described three autistic children who also had an affective disorder and a positive family history of depression or bipolar disorder. Gillberg (29) described a patient with Asperger's disorder and recurrent psychosis who had a family history of bipolar disorder. Lainhart and Folstein (24) reviewed all of the current published case reports regarding children with autistic spectrum disorders and comorbid affective disorders (N=17). In a study of a group of patients with Asperger's disorder who were followed into adolescence, Wing (30) found that nearly one-half of the patients developed affective disorders. In another study (31), children with autistic spectrum disorders who had a family history of bipolar disorder were compared with children with autistic spectrum disorders who had no a family history of bipolar disorder; clear differences in symptom profiles were seen in the two groups. The children without a family history of bipolar disorder did not have marked cyclic variations in behavior, showed less florid agitation, fearfulness, and aggression, and were of lower functioning, whereas the children with a family history of bipolar disorder showed extremes of affect, cyclicity, intense obsessive interests, neurovegetative disturbances, and regression after a period of normal or precocious development.

There is an accumulating body of literature that suggests that autism spectrum disorders may be associated with a family history of affective disorders (28–36); several of the studies indicate that there is a greater risk of bipolar disorder in family members of individuals with Asperger's disorder, in particular. For example, a higher prevalence of affective disorders, especially bipolar affective disorder, was found in the families of about one-third of the individuals who were diagnosed with autism spectrum disorders (31, 32, 35). DeLong and Dwyer (33) found that relatives of probands with pervasive developmental disorders had a 4.2% prevalence of bipolar disorder (nearly five times greater than that expected in the general population) and that the prevalence was highest among relatives of probands with Asperger's disorder (6.1% versus 3.3% for relatives of probands with autism). On the other hand, Gillberg (34) found rates of affective disorder in this group that were similar to those found in the general population. He found that four (17%) of 23 children with Asperger's disorder and three (13%) of 23 with autism had family histories of major affective disorders. On the other hand,

Piven and colleagues (35) found that although major depression had a higher lifetime prevalence in the parents of autistic probands (27%) than in the normal population, bipolar disorder did not. Finally, DeLong and Nohria (36) studied 40 children with autistic spectrum disorder, 20 of whom had no identifiable neurological disorder that could account for their autism. A family history of affective disorders enriched by sevenfold the risk of autistic spectrum disorders in the group compared with those who did have an underlying neurological disorder, such as tuberous sclerosis or congenital rubella.

Neurobiology

In 1978 Damasio and Maurer proposed a mesolimbic model of autism (37). More recently, Bachevalier (38) demonstrated deficits in social reciprocity and an increase in circumscribed behaviors in nonhuman primates who had had their amygdalo-hippocampal complexes lesioned during infancy. The amygdala is a critical component of the limbic or affective loop in the brain and has been implicated in both neuropathological and neuroimaging studies of Asperger's disorder, autism, and bipolar disorder. The involvement of the amygdala and the limbic system and the apparent involvement of the right side of the brain in Asperger's disorder suggest areas of overlap with bipolar disorder, which also has been described as involving dysfunction of the right hemisphere (39).

Treatment

Unfortunately, despite the fact that there are medications that can help children with mood disorders in the autistic spectrum, many children are never diagnosed properly, nor do they come to the attention of mental health professionals. For example, in an epidemiological study (40), at least 41% of the children who were developmentally disabled were affected by comorbid psychiatric disorders, but less than 10% of the children with comorbid psychiatric disorders had seen a specialist.

There are numerous system biases and multiple issues that contribute to the lack of proper psychiatric diagnoses and treatment for children with autistic spectrum disorders. These children may suffer from two disorders, both carrying with them a societal prejudice. This prejudice partly influences medical professionals to the degree that psychiatric evaluation and treatment are often overlooked in these children, which results in the phenomenon known as "diagnostic overshadowing," in which changes in mood and behavior are wrongly attributed to the individual's developmental disorder rather than to a comorbid psychiatric condition (23). Owing to the individual's poor communication and social skills, the expression of psychopathology (e.g., self-injurious behavior, aggression, and rocking) may be different from that of a cognitively and developmentally normal individual. Understanding the etiology of a disturbing behavior is extremely important.

The selection of medications for treating problematic behaviors requires careful observation of the child with an autistic spectrum disorder over a period of time, owing to the patient's limited ability to express problems verbally and poor insight. In general, targeting symptoms of a psychiatric disorder, and not of an individual behavior, should be the basis of treatment with psychopharmacologic agents. For example, the individual behavior of self-injury may be a symptom of numerous psychiatric disorders. Proper formulation needs to occur before treatment is initiated.

It is important to emphasize that there are a limited number of controlled trials regarding the use of psychopharmacological interventions in this population. Therefore, pharmacological intervention should be chosen judiciously, and patients should be closely monitored for symptom improvement and side effects. Given that these patients are often treated with psychotropic medications, there is a crucial need for systematic controlled trials to establish both the safety and efficacy of pharmacological agents in children with Asperger's disorder and with developmental disabilities in general.

Historically, children with developmental disabilities have been reported to have a higher rate of dyskinesias (29.7%) when treated with neuroleptics (41). However, when 16 neuroleptic-naive autistic children were assessed at baseline for stereotypies, mannerisms, and dyskinetic movements, 25% were found to have abnormal movements (42). In addition, the raters in this study were unable to distinguish these abnormal baseline movements from the dyskinesias that other autistic children had developed during treatment with neuroleptics. Nonetheless, tardive dyskinesia is a concern to clinicians, especially when they are considering use of typical antipsychotics in this population. Therefore, the atypical agents, with their lower (but not yet fully determined) risk of tardive dyskinesia, offer much promise for the pharmacotherapy of these children and other pediatric populations (43–45).

Thioridazine is a typical antipsychotic agent that has been used historically in child psychiatry with relative frequency. Like the atypical agents, thioridazine has lower acute extrapyramidal side effects and some serotonin 5-HT_2 receptor antagonism, which has made it an attractive agent for use in youth. However, thioridazine has recently been given a "black box" warning because of its tendency to cause prolongation of the QT interval on ECGs.

Risperidone, when used in children with autistic spectrum disorders, leads to significant reduction of repetitive behaviors, aggression, impulsivity, and some elements of social relatedness (43). The effectiveness of risperidone was evaluated in a retrospective chart review of the treatment of children with bipolar disorder who did not have pervasive developmental disorders. In this study (45), risperidone was extremely helpful in decreasing mania, psychosis, and aggression. In addition, studies using other atypical agents for the treatment of childhood bipolar disorder are beginning to appear in the literature (44).

Although pharmacological studies of lithium are few among developmentally disabled individuals, case reports indicate that lithium can be quite helpful in the treatment of bipolar symptoms in children with pervasive develop-

mental disorders (28, 31, 46). In addition, DeLong and Dwyer (33) reported that four out of seven children with Asperger's disorder and comorbid bipolar disorder and a family history of bipolar disorder had a good response to lithium treatment (33).

Children with Asperger's disorder generally require ongoing multimodal intervention to achieve optimal functioning; psychotherapy, social skills training, speech and language intervention at times, occupational and physical therapy, vocational training, and psychopharmacologic intervention can treat the severely impairing symptoms of comorbid psychiatric disorders (1, 6). Coordination of services and communication between various providers is essential. Our patient, Abraham, was ultimately placed in a special school for individuals with Asperger's disorder that provided psychotherapy, social pragmatics, group therapy, and some vocational training.

Conclusions

Abraham's story illustrates a number of important points regarding the comorbidity of bipolar and Asperger's disorders. From an early age, Abraham clearly had characteristics that are seen in children with Asperger's disorder. Furthermore, the hallmarks of Asperger's disorder remained with Abraham, even after his comorbid bipolar disorder was appropriately treated. Although Abraham was impaired by his developmental disorder, it is quite clear that the symptoms of Abraham's bipolar disorder led to severe disruption of functioning. Abraham had symptoms of an affective illness beginning at an early age. For him, delayed diagnosis and treatment led to 5.5 years of progressive dysfunction and a worsening of symptoms. His affective disorder exacerbated the underlying symptoms of Asperger's disorder. For example, when he was manic, Abraham became more intrusive and engaged in more socially inappropriate behaviors; his pedantic speech became more pressured, he engaged in lengthy monologues, and his obsessionality became intense. Once comorbid bipolar disorder was diagnosed and appropriate treatment occurred, Abraham gradually began to recover and his self-injury, aggression, and intense pressured obsessiveness disappeared. Abraham's father has a history of depression, which is consistent with the findings of a higher rate of affective illness in the first-degree relatives of children with Asperger's disorder.

Abraham has a history of treatment with a typical antipsychotics, during which he developed oral dyskinesia. Some literature has suggested that children with autistic spectrum disorders may have a slightly higher incidence of dyskinesias or withdrawal dyskinesias (41). Of note, Abraham's tongue movements disappeared when he was switched to risperidone. In addition, Abraham responded well to the combination of lithium and risperidone. Both medications (lithium and risperidone) have been described in the literature as being helpful and well tolerated in individuals with autistic spectrum disorders (31, 32, 43).

Educating pediatricians, pediatric neurologists, child psychiatrists, and other mental health professionals about the high prevalence of comorbid psychiatric conditions in individuals with autistic spectrum disorders is crucial so that these children receive appropriate treatment. Appropriate treatment can greatly enhance a child's ability to optimize his or her developmental trajectory (6, 7), as shown in this case conference.

Finally, since children with autistic spectrum disorders and other developmental disorders have historically been excluded from treatment trials, the existing psychopharmacological literature is sparse. More rigorous research is needed on the use of psychopharmacological agents in this population to assess more fully the risks and benefits of treatment for comorbid affective disorders and other psychiatric conditions.

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