A Genetic Etiology of Pervasive Developmental Disorder Guides Treatment

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Children and adults with developmental delay frequently present with a mixture of clinically significant social, behavioral, attention, and mood problems. These individual symptoms often defy diagnostic categorization. This poses a major challenge for a psychiatrist, who then may struggle to arrive at a clear DSM-IV-based diagnosis and treatment algorithm. Increasingly, these children are diagnosed with pervasive developmental disorder not otherwise specified. In this clinical case conference, the authors discuss a patient who was seen with a previous diagnosis of pervasive developmental disorder not otherwise specified and a seemingly disparate pattern of symptoms. However, a thorough medical, neuropsychological, and genetic evaluation revealed a primary etiology for most of the symptoms and enabled the authors to devise a targeted treatment plan. Although pervasive developmental disorder not otherwise specified is viewed as a heterogeneous diagnostic category, genetic and neuropsychological studies support its inclusion as an autistic spectrum disorder. Thus, a psychiatrist can draw upon a developing literature on best practices for the care of individuals with autism spectrum disorders when devising recommendations for intervention. The importance of having complete genetic information for such patients is discussed.

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Autism spectrum disorders include classical autism, high-functioning autism (a label given to individuals with autism and an average or above cognitive level), Asperger's syndrome, Rett's disorder, and childhood disintegrative disorder. The diagnosis of pervasive developmental disorder not otherwise specified is used when deficits in social reciprocity and communication are not severe enough to warrant a diagnosis of autistic disorder or Asperger's syndrome. Given that the incidence of autistic spectrum disorders now is reported to be 1 in 166 children (1), it is not uncommon for psychiatrists to see these individuals in clinical practice and/or to reconsider diagnoses they have given previously to children who are now adults.

Biological evidence from twin studies, studies of extended family pedigrees, and studies of epidemiological cohorts suggests that individuals with pervasive developmental disorder not otherwise specified and autism share a common genetic profile (2). However, pervasive developmental disorder-like symptoms may be present in other psychiatric disorders. For example, although DSM precedence rules do not permit the diagnosis of attention deficit hyperactivity disorder (ADHD) once the criteria for autism spectrum disorder have been met, estimates of the presence of diagnosable ADHD in individuals with autistic spectrum disorder diagnoses range from 30% to 75% (3). A National Institute of Mental Health study of childhood-onset schizophrenia found that 21% of the probands had a lifetime diagnosis of pervasive developmental disorder not otherwise specified (4). It also is estimated that 30% of individuals with mental retardation meet criteria for pervasive developmental disorder not otherwise specified (2).

In sum, it is becoming increasingly important for psychiatrists to know about pervasive developmental disorders given their prevalence and the growing appreciation that many neurodevelopmental disorders are accompanied by symptoms of pervasive developmental disorder not otherwise specified. The case presented illustrates that in a substantial minority of cases, genetic screening can reveal more precise information about the etiology of symptoms and diagnosis. However, given the strong genetic relationship between pervasive developmental disorder not otherwise specified and autism, even if a more exact diagnosis cannot be made, a clinician can draw upon a literature on the best practices for treating persons with autism spectrum disorders (5). Although these practices, like the vast majority of interventions for children and adolescents, do not yet rise to the highest standards of empirical validation, they have been successfully implemented across individuals of a wide range of ages and developmental levels.

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Case Presentation

"Lisa" (her actual name has been changed) initially was referred to our clinic for a multidisciplinary evaluation when she was 9 years old. Her parents reported that she had longstanding socialization, learning, and behavior problems and anxiety. She was described as a bubbly girl; however, when faced with cognitive or social challenges, she exhibited tantrums, aggression, and self-injury. She had no true friends. Her academic performance was in the low-average range, and she had particular difficulties with mathematics. Interventions, including placement in special education and speech therapy, had been moderately effective. Her family was becoming increasingly worried as the gap in social and academic functioning between Lisa and her peers was widening.

Lisa was adopted at birth. Little was known about her biological mother or her prenatal history. She was born by use of vacuum extraction, weighing 7 lb 5 oz, after an otherwise uncomplicated delivery. Her adoptive mother described her as a challenging baby with colic. She sat at 5½ months and walked at 11 months. She spoke single words at 11 months and used phrased speech by 18 months. She was an only child.

Lisa started preschool at 3 years of age and adjusted reasonably well. In kindergarten, her play and socialization skills were delayed. In first grade, academic issues relating to inattention, difficulty following directions, and reading comprehension became evident. Her academic performance was well below average. She began to display behavioral problems, including talking out of turn, disturbing others, sulking when upset, difficulty transitioning between activities, a low tolerance for frustration, and poor impulse control. Her teachers also reported that Lisa was not able to make friends and exhibited autistic-like symptoms, including poor eye contact, solitary and limited imaginary play, difficulty expressing and understanding emotions, hand flapping, sensory hypo- and hypersensitivities, echolalia, and intolerance for change in routines.

At home Lisa was hyperactive, distractible, and impulsive and moved from activity to activity. When task demands exceeded her level of competence, she would shout and become highly agitated. Her mother also reported that Lisa did not initiate interactions with other children and became overwhelmed during group activities. Her leisure interests included reading, playing alone outdoors, and helping her father.

Given these symptoms, Lisa was referred for a neuropsychological evaluation by the school. Her expressive language, which was in the high average range, was significantly better than her receptive language, which was in the borderline normal range of intellectual functioning. On the WISC-III (6), Lisa obtained a full-scale IQ of 72, which is in the borderline range of intellectual functioning. She demonstrated significantly better performance on verbal measures (her verbal IQ was 83, low-average range) than on perceptual-organizational measures (her performance IQ was 65, intellectually deficient range). She demonstrated strengths on subtests reflecting a fund of knowledge (information, vocabulary). In contrast, her abstract verbal reasoning and arithmetic performance were relative weaknesses. Evaluation of her perceptual-motor integration skills suggested a developmental delay in the acquisition of eye-hand coordination. At this time, based on the school's assessment as well as a clinical interview with parents and teachers, Lisa was diagnosed with pervasive developmental disorder not otherwise specified by her neuropsychologist.

Lisa was deemed to meet her school's criteria for special education services. She continued in a mainstream class and began to receive speech and language therapy 1½ hours per week. The focus of this therapy was on semantic language concepts, pragmatic language skills, and auditory processing. She also received assistance through a resource specialist program daily for reading comprehension, written language, and math.

Her clinical mental status examination revealed that Lisa was a 9-year-old girl who appeared to be her stated age. She was well-developed, dressed, and groomed and had mild nonspecific dysmorphic features, including a long face and large ears. She made poor eye contact with the interviewer and mostly looked off to the side. She had no tics. She had difficulty sitting still during the interview and, at one point, got up and hit her mother. She reported her mood as good. Her affect was full and appropriate. Her speech was normal in volume and rate but had a singsong quality. Her thought process was mostly coherent, but she focused on certain topics, including her mother's recent surgery, without providing adequate context for the listener. Her mother reported no evidence of auditory, visual, olfactory, or tactile hallucinations, although Lisa was reported to engage in "self-talk" in which she recited lines from favorite videos, especially when alone. At these times, she did not appear to be responding to internal stimuli. Her thought content was generally appropriate for the interview. There was no evidence of suicidal or homicidal ideation. Her insight was developmentally appropriate for her cognitive age.

During her medical examination, Lisa appeared to be an attractive but somewhat overweight girl. Ear pinnas were prominent, with significant cupping, and macrocephaly and hyperextensible joints were noted. Based on her clinical presentation, the findings of her physical examination, her borderline intellectual functioning, and autism symptoms, Lisa was referred for high-resolution cytogenetic and fragile X syndrome DNA testing. These results documented a full mutation of the fragile X mental retardation 1 gene (>200 CGG repeats), and Lisa was subsequently diagnosed with fragile X syndrome. Fragile X syndrome is a "single-gene" disorder caused by a trinucleotide repeat expansion $(CGG)_n$ in the 5′ untranslated region of the fragile X mental retardation 1 gene located on the X chromosome. It is the most common form of inherited mental retardation, but in females, it usually causes learning disabilities. The full mutation, as in Lisa's case, occurs when individuals have more than 200 CGG repeats, leading to methylation, subsequent transcriptional silencing of the gene, and absence or deficiency of the fragile X mental retardation 1 gene protein. The behavioral phenotype of fragile X syndrome includes anxiety, hyperarousal, attention and executive functions problems, and pervasive developmental disorder symptoms (7).

Empirically based assessment of autistic spectrum disorders requires cognitive and academic achievement testing, evaluation of adaptive behavior, and autism assessment (8). Lisa's cognitive abilities were assessed with the Kaufman Assessment Battery for Children (9). She obtained a mental processing component of 69 (borderline

range of intellectual functioning), and scores on a nonverbal scale were significantly depressed relative to others. Lisa's academic achievement scores on the Woodcock-Johnson Psychoeducational Battery III (10) ranged from a high of 107 in basic reading (which assesses decoding and work attack as opposed to comprehension, on which she scored 90) to 81 in broad mathematics (which incorporates both calculation and mathematical reasoning). Scores on a developmental examination of visual motor integration revealed that Lisa's motor coordination and visual perception were well below average. The Vineland Adaptive Behaviors Scales (11) yielded an adaptive behavior composite of 54, corresponding to an age-equivalence of 5 years and 3 months. Assessment results were consistent with Lisa's academic profile, which included stronger reading fluency than comprehension, global deficiencies in math, and problems with penmanship as well as organization of expository writing.

To further assess autism symptoms, we completed the Autism Diagnostic Observation Schedule (12) module 3. Lisa engaged in imaginary play with the examiner and showed a wide range of affect and a good sense of humor. She was initially gaze avoidant, but over time, her eye contact improved. Her speech was rapid, repetitive, singsongy, and disorganized. She showed limited perspective taking and empathy. Her emotional insight and social relationships were lacking. Her scores of 3 in the communication domain and 4 in the reciprocal social interaction domain were within the range of an autism spectrum disorder but below the cutoff for full autism. The Social Communication Questionnaire (13) also was administered in an interview format to Lisa's parents. Her score of 20 was beyond the cutoff of 15, consistent with a pervasive developmental disorder but below the cutoff for full autism. We concurred with her prior diagnosis of pervasive developmental disorder not otherwise specified.

Given our new findings that Lisa had fragile X syndrome, we were able to devise a treatment plan that incorporated best practices for individuals with autism spectrum disorders but was tailored for an individual with fragile X syndrome. Starting with knowledge of the fragile X syndrome phenotype, we began our case formulation with the hypothesis that many of Lisa's behavioral and social problems stemmed from hyperarousal and anxiety.

Pharmacological Intervention

The use of psychotropic medication in children with pervasive developmental disorder is guided mainly by clinical experience and a limited number of research trials for stimulants (14) and selective serotonin reuptake inhibitors (SSRIs) (15). To help with anxiety symptoms manifesting as behavioral rigidity, Lisa was given sertraline, 25 mg each morning. She did quite well while taking this medication, with a reduction in her overt anxiety and an increase in her social interactions. Two months later, this dose was increased to 50 mg each morning, and she showed even greater improvement in these areas. Because of her attention symptoms, Lisa was given methylphenidate after she was stabilized with the SSRI. Dosing began at 18 mg/day, gradually increasing to 36 mg/day. This made a remarkable difference in her attention and concentration.

Psychosocial Intervention

The goal of intervention was to reduce Lisa's anxiety by accentuating her strengths and by increasing her self-esteem. Neuropsychological testing showed that Lisa exhibited aspects of a "nonverbal learning disability" profile (16), which is commonly seen in girls with fragile X syndrome. Test results indicative of this cognitive profile include relatively poorer performance on the Kaufman Assessment Battery for Children scales assessing nonverbal abilities, achievement test scores illustrating strong reading decoding with weak comprehension (but no hyperlexia), poor performance in math, and deficits in visual motor planning. Children with this cognitive profile exhibit excellent memories for facts and rote information, especially when it is delivered verbally, but display problems with abstract reasoning. They are concrete in their interpretations of language related to both academics and social situations. They benefit from teaching that capitalizes on their strengths in auditory memory and the consequent ability to develop a fund of knowledge. They require very deliberate and clear instructions to complete new activities. We consulted with Lisa's teachers to explain the nonverbal learning disability profile and fragile X syndrome and to provide suggestions about how to capitalize on her academic strengths. We counseled teachers to make no assumptions about Lisa's level of understanding of classroom materials, to use methods that were highly structured and sequential, and to use verbal instructions supplemented with visual cues.

We recommended that Lisa be provided with a written visual schedule that outlined the day's events to help in planning, sequencing activities, and preparing for changes in routine. Another important function of this visual schedule was to reduce Lisa's anxiety about upcoming transitions between activities. We also recommended that her parents and teachers use social stories—simple scripts about common situations written by the parent, teacher, and/or the child—to teach Lisa about what to expect in novel situations and to thereby reduce anxiety and behavioral dysregulation.

Lisa was referred for an occupational therapy evaluation. This form of therapy has been found to help individuals with fragile X syndrome, given their hyperarousal and sensory processing problems (7). Consistent with recommendations made for individuals with fragile X syndrome and individuals with autistic spectrum disorders, we also worked with her parents and her teachers to identify a system Lisa could use at school if she needed to calm down by taking a "time out" from the classroom.

Given her attention and concentration problems, it was recommended that her teachers and parents give Lisa clear, concise, single-step directions. The also were told to provide visual cues and reminders during instruction, to keep instructional materials as novel as possible, and to provide plenty of positive feedback. We also recommended seating Lisa close to the teacher and the front of the classroom and away from distracting influences such as windows or high-traffic corridors.

Finally, we recommended that Lisa participate in a social skills group. In this group, skills related to emotional understanding and awareness, perspective taking, stress and anger management, conversations, friendships, and problem solving would be taught. This form of intervention gave Lisa an opportunity to practice these skills with peers in a supportive and structured setting. Such groups have been shown to be effective in teaching skills and in reducing depression in children with pervasive developmental disorder of a similar cognitive level (17).

Lisa returned to our clinic when she was 12 and was experiencing increasing behavioral problems with moodiness and irritability. She was given aripiprazole at a dose of 5 mg at bedtime. Although risperidone is the only medication with an autism indication (18), her mother was concerned about its potential to cause weight gain and other side effects, such as increased prolactin. Aripiprazole was selected because the prescribing clinician believed it had a more favorable side effect profile. Her behavior improved remarkably, her mood stabilized, and she showed less irritability and aggression. She began menstruating 6 months later and concurrently developed significant problems with obsessive-compulsive behavior. Her sertraline dose was increased to 75 mg/day. This resulted in a reduction in this behavior. Given her strengths in expressive language and her developmental level, Lisa also was referred for cognitive behavior therapy for anxiety and depression.

Halfway through her sixth grade year, we also recommended that she be enrolled in a new intervention study about the efficacy of assistive technology for improving the expository writing skills of individuals with fragile X syndrome. In this protocol, she was instructed about how to use two computer programs, Write:OutLoud (for composition, revision, and editing) and Co:Writer (for word prediction), which help individuals to generate ideas and organize their thoughts with visual graphic templates (see www.donjohnston.com). After participating in this protocol, she again was tested with the Woodcock Johnson III Tests of Achievement (10). As reflected in her advancement to a grade equivalency of 10th grade—4 months on basic writing skills (spelling and grammar)—and 7th grade—1 month on broad written language (which also includes written expression)—Lisa appeared to benefit greatly from the assistive technology intervention.

Discussion

In summary, we describe the case of a 9-year-old girl with a prior diagnosis of pervasive developmental disorder not otherwise specified who was seen with mildly dysmorphic features; social, attention, and behavior problems; and academic weaknesses in mathematics, reading comprehension, and abstract reasoning. In this case, genetic testing was positive for the fragile X mental retardation 1 gene full mutation, and the patient was diagnosed with fragile X syndrome. Given the patient's diagnosis of pervasive developmental disorder, we were able to implement best practices for autism spectrum disorders built on a foundation of information related to the behavioral phenotype of fragile X syndrome.

Lisa's case clearly illustrates the importance of genetic testing for fragile X syndrome in girls who have borderline to normal IQ and autism spectrum symptoms. Fragile X syndrome is typically considered a mental retardation syndrome with a greater affect on males; however, because females have two X chromosomes, production of fragile X mental retardation 1 gene protein is maintained to varying degrees by the presence of the unaffected X chromosome, and they can appear with cognitive abilities ranging from the mental retardation range to normal or even higher-than-average IQ. The American College of Medical Genetics's policy statement on fragile X syndrome (FXS) states that "individuals of either sex with mental retardation, developmental delay, or autism especially when associated with other physical and behavioral characteristics of FXS, a family history of FXS, or a relative with undiagnosed mental retardation" should be tested for the fragile X mental retardation 1 gene mutation. Psychiatrists should be alerted that when they see females or males with a constellation of features described above, even without mental retardation, they should order fragile X syndrome and other genetic testing. Currently, it is estimated that approximately 15% of the cases of autism spectrum disorder may have a known genetic etiology (7). Psychiatrists also are urged to pay close attention to girls with pervasive developmental disorder symptoms because although four times as many boys are thought to be affected with autism spectrum disorders, some have cautioned that girls escape detection because of their milder symptom presentation and/or because of referral or teacher gender biases (19).

The difference in treatment planning for cases of pervasive developmental disorder with and without fragile X syndrome is subtle; however, we believe the identification of the genetic etiology of Lisa's clinical symptoms had important implications for her treatment. Anxiety and hyperarousal are more prominent features of fragile X syndrome than autism and almost universally modify symptom expression. For example, in boys with fragile X syndrome and autism, executive dysfunction generally manifests as disinhibition and emotion regulation problems, whereas girls typically do not manifest this symptom pattern (7). Mathematical reasoning, which is also associated with the fragile X mental retardation 1 gene protein, is not necessarily affected in individuals with autism alone. Furthermore, we know that individuals with fragile X syndrome have impaired sensory motor gating (highly correlated with symptoms of autistic spectrum disorder) and increased sympathetic responses to sensory stimuli. The evidence for sensory issues in idiopathic pervasive developmental disorder is mixed, whereas it is clear and consistent in fragile X syndrome. Another point of differentiation regards the nature of problems with social gaze. Although in autism without fragile X syndrome the cause of gaze abnormalities is poorly understood, in fragile X syndrome, it is most often anxiety and stress related.

Because anxiety and hyperarousal are phenotypic features of fragile X syndrome, treatment of these symptoms had been the first treatment goal. Lisa's has been successfully managed by focusing on psychopharmacological treatment of anxiety with an SSRI, ADHD symptoms with a psychostimulant, and mood instability with an atypical antipsychotic. Her academic environment has been adapted to capitalize on her cognitive strengths and mitigate her weaknesses. She also has been taught to use calming techniques in her social skills group, through her cognitive behavior therapy, and with the social stories technique.

The identification of fragile X syndrome in Lisa also has direct genetic counseling implications for her extended family. If it were possible, members of her family of origin would have been notified so that her siblings and other extended family members could be screened for fragile X syndrome or carrier status. In addition, the recent discovery of the fragile X-associated tremor ataxia syndrome (20), a neurodegenerative disorder occurring in elderly carriers of the fragile X mental regardation1 gene permutation, indicates that one of Lisa's grandparents is at risk for a late-onset disease that arises from an abnormality of the same gene but with completely different phenotypic expression.

Because fragile X syndrome is a disorder caused by a single gene, it provides a relatively clear model for studying the effects of secondary or tertiary modifying genes because the primary genetic deficit and phenotype are known. Understanding a single gene disorder, such as fragile X syndrome, illustrates how the development of new targeted psychopharmacological interventions may be possible. For example, it is known that the lack of a fragile X mental retardation 1 gene protein in fragile X syndrome leads to dramatic up-regulation of the metabotrobic glutamate 5 pathway, which affects synaptic plasticity, leading to long-term depression and subsequent development of weak and immature synaptic connections. The use of metabotrobic glutamate 5 antagonists has been helpful in improving cognition and in decreasing seizures in animal models of fragile X syndrome. Agents such as metabotrobic glutamate 5 antagonists (i.e., fenobam) may have very specific and targeted benefits to individuals with fragile X syndrome and hold promise for enhancing their cognitive functioning. Such advances in molecular genetics and psychopharmacology are another argument for knowing the precise etiology of symptoms.

Finally, this case highlights the need for increased funding to advance research about empirically validated treatments for children with developmental disorders. There have been few randomized, controlled trials for interventions in children with pervasive developmental disorder or fragile X syndrome. Although there are several empirically supported psychosocial interventions for children with lower functioning forms of autism, there have been no randomized, controlled trials of psychosocial interventions for higher functioning and older individuals, to our knowledge. Similarly, in fragile X syndrome, there is a wealth of information about how to approach the psychopharmacological treatment of anxiety, mood instability, and attention problems in children with fragile X syndrome based on open-label and case studies as well as extrapolation of the adult literature to children. There also is a clinical literature about psychosocial intervention strategies. However, the field still lacks true randomized, controlled trials.

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