Psychiatric Assessment of Severe Presentations in Autism Spectrum Disorders and Intellectual Disability

Bryan H. King, MD[a,b,*], Nina de Lacy, MD[b], Matthew Siegel, MD[c,d,e]

KEYWORDS

• Autism • Intellectual disability • Self-injury • Aggression • Hyperactivity • Psychiatric evaluation

KEY POINTS

- Psychiatric illnesses are common in autism spectrum disorder (ASD)/intellectual disability (ID).
- Externalizing behaviors are common presenting symptoms but are etiologically nonspecific.
- Genetic conditions associated with ASD/ID may inform medical surveillance as well as potential therapeutics.
- Co-occurring medical conditions are common in ASD/ID and may contribute to symptom presentation.
- Environmental factors, for example, change in caregiver or experience of trauma, may be particularly significant in the setting of ASD/ID.

INTRODUCTION

Decades ago, Sovner and Hurley[1] somewhat rhetorically debated whether individuals with ID experience affective illness. Although the answer then as now is an unequivocal yes, uncertainty does remain as to how the presentation of psychiatric

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[a] Department of Psychiatry and Behavioral Medicine, Seattle Children's Autism Center, Seattle Children's Hospital, Seattle, WA, USA; [b] Department of Psychiatry and Behavioral Sciences, University of Washington, Seattle, WA, USA; [c] Developmental Disorders Program, Spring Harbor Hospital, ME, USA; [d] Tufts University School of Medicine, Boston, MA, USA; [e] Maine Medical Center Research Institute, ME, USA
* Corresponding author.
E-mail address: bhking@u.washington.edu

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disorders may be altered in the setting of atypical intellectual development. Moreover, as the genetic underpinnings of neuropsychiatric illness are revealed and certain behavioral phenotypes elaborated in association with particular genetic abnormalities, questions have been raised about the appropriateness of applying nonspecific illness labels to behaviors that occur in specific contexts. In cases of hyperphagia and restricted interests in Prader-Willi syndrome, for example, is value added by superimposing the psychiatric diagnoses of impulse control disorder or obsessive-compulsive disorder?

Conversely, there is every bit as much heterogeneity in symptom expression in the context of genetic syndromes as for the general population. Not everyone with Prader-Willi syndrome has significant skin-picking behavior nor does Lesch-Nyhan syndrome guarantee aggression, although these are common symptom-syndrome correlations. Taking a step back, the same can be said for persons with idiopathic ID: not everyone with severe ID is aggressive, self-injurious, or hyperactive. These problems occur only in a minority of this population.

Howe[2] observed that "there are some among the lowest class of idiots who seem to have a superabundance of innervation, who are consequently very active. They appear like insane persons in a state of excitement, and yet they have no speech, and no reasoning faculties."[2] Hurd,[3] who was superintendent of the Eastern Michigan Asylum, wrote that irritability, violence, and impulsivity alone are insufficient grounds for the diagnosis of insanity in this "lowest grade of imbeciles," but impulsive acts, "morbid propensities," and "acts of suicidal intent" (eg, "attempting to dash one's brains"), "occurring in higher grades of imbecility" are symptoms consistent with "actual insanity," even in the absence of delusions.

The recognition that even severe ID neither protects nor precludes an individual from experiencing psychiatric illness is thus one of the earliest observations from clinicians working in this field. Modern studies generally estimate that having ID increases the risk of psychiatric illness at least 3-fold or 4-fold relative to the general population,[4,5] thereby underscoring the importance of careful psychiatric assessment in this population.

PREVALENCE OF PSYCHIATRIC ILLNESS

Estimates of the overall prevalence of psychiatric disorders in individuals with ID range from 10% to 39%.[6,7] In children and adolescents, emotional and behavioral problems occur up to 7 times more frequently than in typically developing youth.[8]

Specific factors that place individuals with ID at increased risk for developing comorbid psychopathology include severity of disability, lower adaptive behavior, language impairments, poor socialization, low socioeconomic status, and families with only 1 biologic parent.[9] In general, developmental and genetic disorders are associated with elevated rates of depression and anxiety. Specific genetic syndromes are also associated with increased rates of particular disorders, such as higher rates of depression in Down syndrome (DS),[10] anxiety, and ADHD in individuals with Williams syndrome and increased rates of schizophrenia in velocardiofacial syndrome (22q11.2 deletion syndrome).[11,12]

Psychiatric illness is also clearly more prevalent in the ASD population than in the general population. Prevalence estimates vary based on the type of measure used. When diagnostic instruments developed for the neurotypical population are used for individuals with ASD, high rates of comorbid psychiatric illness are found. Using the Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS) for School-Age Children,[13] in a psychiatrically referred population, produced an estimate of

6.4 comorbid psychiatric diagnoses in each child with ASD.[14] Similarly, using the Structured Clinical Interview for DSM-IVTR (SCID)[15] in adults with ASD resulted in diagnosing 60% to 70% of subjects with depression and anxiety.[16] Instruments adapted for the ASD population produce lower estimates, such as rates of anxiety and depression of 10% to 44% in children with ASD.[17]

REASONS FOR REFERRAL FOR PSYCHIATRIC ASSESSMENT

Although psychiatric illnesses are common in the setting of ID, it is the presence of severe behavioral problems that typically prompt referral for psychiatric evaluation. King and colleagues[18] analyzed the chief complaints from 251 consecutive psychiatric referrals in an institutionalized population with mostly severe to profound ID. Behavioral disturbances accounted for upwards of 80% of reasons for referral, with the remainder representing a collection of medical concerns (eg, rule out tardive dyskinesia and assess current medication regimen). As can be seen in **Fig. 1**, self-injurious behavior, aggression, hyperactivity, and impulsivity top the list.

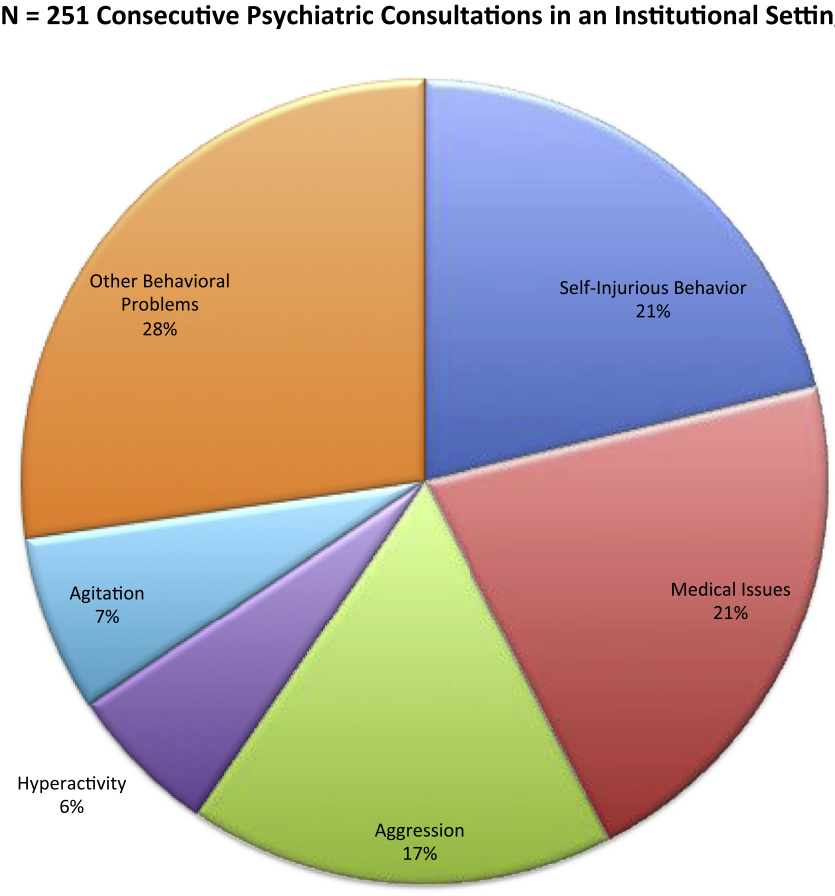

Fig. 1. Reasons for psychiatric referral. (*Data from* King BH, De Antonio C, McCracken JT, et al. Psychiatric consultation in severe and profound mental retardation. Am J Psychiatry 1994;151(12):1802–8.)

More recently, Siegel and colleagues[19] examined the reasons for psychiatric admission to a specialized inpatient service for children and adolescents with autism and related conditions. In this population requiring acute stabilization for severe behavioral disturbance, aggression and self-injurious behavior predominated.

These severe behavioral presentations are heterogeneous from the standpoint of their diagnostic etiology, and comorbidity among them is common. The approach to the assessment for each of these behavior targets is not exclusive but must clearly be comprehensive. Siegel and Gabriels highlight the variety of potential contributing factors to symptom presentation in the setting of ASD/ID. (See the article by Siegel and Gabriels elsewhere in this issue for further exploration of this topic.)

GENERAL ASSESSMENT ISSUES

Assessment of psychiatric disorders in children and adolescents typically involves several variables, including a child's own description of symptoms and experiences; descriptions from parents, teachers, or other care providers; and direct observations of behavior.

Language Skills and Communication Development

Because of often limited language development and communication skills and symptom presentation that may differ from that observed in the absence of intellectual impairments, interviews with family, teachers, and other caregivers regarding their observations and assessment of nonverbal aspects of behavior take on a more critical role in evaluating mental disorders in this population. It is also of particular importance to clinicians to construct a picture of a child's baseline level of cognitive and executive functioning, emotional expressivity, and language development. With respect to the latter, it is important to distinguish between receptive and expressive language skills, because these may be different. It is not unheard of, for example, to be astounded that a minimally verbal youngster takes a ride on the Internet like a professional, navigating text menus and entering search terms with ease. Many parents are appropriately sensitive to the possibility that discussing all of the problems that brought a child in to the hospital or clinic within earshot of the child may, at a minimum, be uncomfortable for many patients—and, on occasion, agitate the child and prompt or elicit behavioral disturbances like those being discussed.

Accommodations Made by Caregivers

Interviews of children with ASD/ID and their caregivers may need to be adapted to capture relevant information. Similar to cases of obsessive-compulsive disorder, family systems frequently accommodate behaviors and symptoms of a child in order to minimize disruption and maintain homeostasis within the family unit. It is, thus, sometimes necessary to identify and subtract out accommodation to gain an appreciation for the true level of dysfunction. Questions, such as "What would happen if you insisted John get off the computer?" and "How would John react if you did bring him into the store?" may provide a more full picture.

Clinician Questions

Questions asked in an interview of a patient should be short, simple, and to the point and asked one at a time with ample time allotted for processing of the information. Whenever possible, the clinician should attempt to verify the comprehension of the question in order to avoid successive "yes" or "no" answers. Similarly, echolalic responses can be checked by switching the order of the variables: "Are you happy or

sad?" and then "Are you sad or happy?" Clinicians should be aware that some individuals with developmental delay might seek to please and thus answer in the affirmative if they do not understand the question or know the answer.[20] In addition, clinicians should avoid leading questions. For example, if a child with ID is asked whether he/she hears voices, most positive responses refer to normal internal self-talk. Instead children could be asked if they hear things others people in the room do not hear. In particular, self-report questionnaires have been found frequently unreliable in the ID population due to problems with question content, question phrasing, and response format.[21]

Comorbidities

Comorbid medical and neurologic conditions are also germane to psychiatrists, in particular, the presence of epilepsy, metabolic/mitochondrial disorders, and autoimmune, gastrointestinal, and endocrine illness.

A comprehensive assessment thus encompasses several potential etiologic dimensions, including

Diagnostic
Medical
Developmental
Environmental

In the following sections, these dimensions are reviewed, including case vignettes focusing on some of the most common presenting behavioral symptoms to child psychiatrists.

DIAGNOSTIC CONSIDERATIONS

As discussed previously, knowledge of the underlying cause of an ID or ASD may be helpful in informing the psychiatric work-up and ongoing management. ASD and ID are increasingly understood as common or shared neurobehavioral outcomes of hundreds of underlying genetic conditions[22] disrupting molecular pathways involved in organogenesis and organ function, including, but not necessarily limited to, the brain. ASD and ID may be associated with single gene variants or copy number variants that might have an impact on any 1 of dozens of relevant genes with an array of neurobehavioral and somatic consequences. These genetic events can have complex neuropsychiatric implications. For example, a clinician caring for DS patient wants to place early-onset Alzheimer dementia on the differential for an individual with disruptive behavior and likewise check thyroid, visual, and hearing function in the presence of mood disturbance, because DS carries well-established risks for such problems.[23] More subtle effects are also potentially important in this population. For example, patients with genetic syndromes have higher rates of perinatal birth complications and those with congenital cardiac or other defects may undergo multiple early surgeries, incurring the concomitant neurobehavioral risks of repeated anesthesia.[24]

More recently, as genes are identified and the pathophysiology associated with genetic disruption is elaborated and understood, potential targets for intervention and rational pharmacologic treatment are also revealed. Genetic and molecular diagnosis ultimately assist in parsing diagnostic options with more specificity.

As a case in point, fragile X syndrome (FXS) and tuberous sclerosis complex (TSC) are both disorders that significantly increase the risk for ASDs. FXS is a trinucleotide repeat disease affecting the *FMR1* gene, which, in its full expression, may account

for approximately 5% of ASD cases[25] and is the most common heritable cause of ID.[26] Symptoms of autism appear in 20% to 50% of individuals with FXS.[27,28] ADHD symptoms and executive function deficits are also common,[29,30] and the developmental trajectory of attention and working memory more broadly is significantly delayed compared with typically developing individuals.[31] Increasingly, it is understood that premutation carriers under 200 repeats may also manifest with ASD and other psychiatric disorders.[22] The gene defect in FXS is associated with an excitatory/inhibitory imbalance in the synapse,[32] likely resulting from upregulation of glutamatergic spine formation and a concomitant hyperexcitable state.

The gene defect in TSC affecting hamartin or tuberin also results in an excitatory inhibitory imbalance, and up to 60% of patients have ASD.[33–35] The imbalance is in the opposite direction, however, likely resulting from activation of the PI3K/mTOR pathway. The disorders associated with TSC are similar to those in FXS, including ADHD, aggression, and epilepsy,[36,37] neatly illustrating how similar neurobehavioral outcomes can be produced by opposed microstructural mechanisms. Mouse models seem to confirm this opposition.[38]

Although still preliminary, these findings suggest the presence of a Goldilocks phenomenon in which the balance of excitation and inhibition needs to be "just right." The imbalances created in certain genetic syndromes, which may present with similar behavioral symptoms, may actually require different, even opposite approaches, as when the problem is "too cold" or "too hot." Emerging, specific treatments for ASD in the context of FXS may actually exacerbate ASD symptoms in disorders like TSC and vice versa.

Thus, newer research is targeting the specific pathways involved in TSC and FXS,[39–41] offering the prospect of more rationally defined therapies and underlining the importance of accurate diagnosis at the genetic-molecular level. More broadly, a similar phenomenon is found in other monogenic conditions and polygenic copy number variants, where loss or gain of function mutations and deletions or duplications can produce similar phenotypes. Increasingly, therefore, the identification of the genetic condition underlying ID or ASD informs treatment selection given behavioral phenotype alone cannot discriminate molecular mechanism.

In patients with an identified genetic diagnosis, consultation of the literature can be helpful to psychiatrists in suggesting treatment. Many genetic syndromes have a neuropsychiatric signature, although phenotypic severity and presentation also often vary widely for reasons that are incompletely understood. Furthermore, it is common to see the neurobehavioral presentation in neurogenetic disorders evolve over time, sometimes changing radically over the neurodevelopmental arc through early adulthood. Clinicians want to continue reassessment, adjusting behavioral interventions, medications, and dosages accordingly.

In patients without a diagnosis, genetic assessment is a first-line recommendation[42] in both ASD and ID. In the authors' institution, the Comparative Genomic Array Hybridization (CGH) + Single Nucleotide Polymorphisms (SNP) array is the most common first line general assay. FXS testing is often added for ID and ASD. Where there is high suspicion based on phenotype for a particular disorder, Fluorescence In Situ Hybridization testing may be substituted where available given its ease and affordability.

MEDICAL CONSIDERATIONS

The importance of considering potential medical contributions to the expression of severe behavioral disturbance cannot be overstated where behavioral change is

often the canary in the coal mine of an underlying medical condition. Studies have repeatedly demonstrated that co-occurring medical conditions are common, perhaps even to be expected, as a result of the condition that underlies the neurodevelopmental disorder. For example, Charlot and colleagues[43] observed that 60% of individuals with ID admitted to their specialized inpatient service for severe behavior disorders had constipation, and 38% had gastroesophageal reflux. With respect to risks associated with particular syndromes, the craniofacial abnormalities and immune system deficits forming part of the common phenotype of 22q.11 deletion/velocardiofacial syndrome (the most common survivable genetic deletion syndrome) frequently lead to recurrent otitis media.[44]

In cases of idiopathic ID and ASD, medical problems as commonplace in childhood as constipation, tooth pain, or ear infection can initially present as severe behavioral exacerbations.[45] Furthermore, chronic comorbidities, such as autoimmune, endocrinologic, cardiac, or gastrointestinal disorders, are common in those with genetic syndromes. The specific genetic deficit underlying an ASD or ID may involve basic physiologic pathways involved in homeostasis, basic metabolism, stress response, and immune and inflammatory mechanisms: many mechanisms could account for behavioral exacerbations during illness or stress flares. For example, the deleterious neuropsychiatric effects of physiologic stress on children with mitochondrial or metabolic disorders (associated with ID and ASD in some cases)[46] are well known in clinical practice and may require buffering with sick day management. Clinicians should also be alert to the possibility for anticipating medication or dosage adjustment during puberty, growth spurts, or weight changes.

Many individuals with moderate to severe ID and ASD are nonverbal or have highly impaired expressive language and may have extreme baseline sensory sensitivity or insensitivity. Thus, clinicians are presented with both the challenges of engaging such individuals in regular physical examinations (eg, it can be challenging to look in the ear of someone with extreme sensory sensitivity) and the fact that many individuals have limited or no ability to tell care providers that they are in pain or to help localize the site of their discomfort. Thus, psychiatrists must be vigilant for possible medical problems presenting as behavioral problems in this population. Opportunities should be sought to package assessments (eg, during required anesthesia or conscious sedation) and maintain excellent preventative medical care hand in hand with psychiatric care optimization. It is encouraging to see that several initiatives are under way to support general health maintenance for the population with ID.[47,48]

Another important factor to consider is the potential behavioral toxicity of medications used to treat co-occurring conditions. Many individuals with ASD and related conditions also have epilepsy for example, and the potential adverse impact of an anticonvulsant in terms of increasing irritability, adversely affecting mood, or diminishing impulse control and contributing to behavioral activation is well established.[49] Children with comorbid conditions requiring the use of medications for pulmonary, cardiac, or gastroenterologic symptoms, such as calcium channel blockers, phosphodiesterase inhibitors, and centrally acting antiemetics or muscle relaxants, are also at high risk of neurobehavioral side effects.

In this context, virtually any psychotropic drug can contribute to behavioral disturbance in some individuals, and it is important to consider possible alternative medical strategies as potentially more helpful than parallel and competing approaches with psychiatric drugs. Close coordination with providers, particularly the prescribing neurologist, is clearly of benefit.

Case Vignette: Agitation/Impulsivity

Presentation: A 12-year-old girl with Smith-Lemli-Opitz syndrome is brought in for an emergent appointment by her parents because she is becoming increasingly dysregulated and agitated, including attempts to dart away from her parents in public places. She has low expressive verbal ability and cannot explain what is wrong but does appear agitated and labile.

Work-up

Diagnostic: molecular testing previously performed

Medical: Complete blood count + differential, electrolytes, urinalysis, lipid panel

Developmental: long history of developmental delay and ASD but no recent changes

Environmental: no changes in caregivers, history of abuse, or other recent disruption

Results: urinalysis shows greater than 100,000 colony-forming units of Escherichia coli and many white cells; complete blood count shows white blood cell count of 19.

Management: in consultation with her primary care physician and the biochemical genetics department, as her primary inpatient psychiatrist you decide to pursue hospital admission. After several days of antibiotics, a steroid burst and optimization of her cholesterol dietary supplements her agitation is much improved. Psychiatric medications are left unchanged, but note is made to avoid haldoperidol because it exacerbates cholesterol abnormalities in Smith-Lemli-Opitz syndrome.[50]

DEVELOPMENTAL CONSIDERATIONS

Human development is a path-dependent process with every future state affected by past state. From conception onwards, genome and environment interact in a continuous bidirectional process mediated by the brain. Individuated patterns of genetic expression progressively unfold over the long human neurodevelopmental arc into young adulthood, reflecting unique combinations of genomic variation (and mutation) with environmental experience. Over time, these patterns specify the sequential construction and growth of brain structures from which behaviors emerge, also in temporally patterned sequences recognizable as characteristic developmental periods and milestones. Long-term synaptic potentiation and the creation of brain internetworks serve to stabilize mature skills and memories and inhibit juvenile or unneeded behaviors.

Cognition (defined here as learning and memory) and behavioral development are, therefore, inextricably intertwined throughout development. Individuals' general intellectual ability modifies their ability to learn, remember, and reproduce new behaviors and knowledge. Furthermore, humans learn most importantly through social learning; thus, those individuals with impaired social cognition as occurs in ASD experience problems in acquiring new behaviors associated with these deficits. There is well-validated support for the notions that ID is associated with or increases risk for neurodevelopmental disorders, including ASD, attention-deficit/hyperactivity disorder (ADHD), and schizophrenia[51] and, conversely, that higher general cognitive function is a predictor of better psychiatric outcomes in these disorders. Petersen and colleagues[52] have shown that language ability, independent of other measures of cognitive function, uniquely contributes to the risk for behavior problems in children.

Thus, there are perhaps 2 major dimensions that might be encompassed under developmental dimensions of assessment. One is to consider where a given patient is on a developmental continuum, that is, what is reasonable to expect in terms of learning and behavior. Do individuals' IDs place them on a different trajectory, where what might be a concerning symptom in a typically developing child—for example, the

persistence of rigidity or hitting into the kindergarten years—merely reflects a slower timetable? A second, related question to ask is to what degree is the problem behavior or symptom expression a reflection of what has been learned?

Psychiatric diagnoses may, therefore, be somewhat malleable in light of what is expected for developmental level given the degree of ID. This is the essential idea of developmental delay as distinct from ID. It is the same principle that underlies the qualifiers in *Diagnostic and Statistical Manual of Mental Disorders* criteria for certain disorders (eg, that the symptoms being manifest are in excess of, or atypical, in light of the individuals developmental age).

ADHD is a paradigmatic example of a neurobehavioral disorder that must be viewed in a developmental context. It is the most commonly diagnosed neuropsychiatric disorder among persons with ID.[53,54] Cardinal symptoms of course include inattention, impulsivity, and hyperactivity with onset before age 12, reflecting the expectation that in a typically developing child these behaviors are increasingly suppressed during the early school years as the prefrontal cortex matures, supporting the development of stronger executive function. ADHD has its own developmental course in typically developing children, with hyperactivity dominating earlier and inattention more prominent in the preteen years.[55] Lower cognitive function appears likely to exacerbate and lengthen symptoms and there is evidence that the presence of ID increases the risk for ADHD.[56]

Perhaps similar to Sovner and Hurley's rhetorical running of affective disorders up the flagpole in ID, historically, it has occasionally been considered superfluous to diagnose ADHD in the presence of ID. Over the years, some investigators[57–59] have argued that ADHD symptoms in this population are merely outgrowths of restricted cognition. Recent studies by Neece and colleagues,[53,56] however, compared ADHD in children and adolescents with ID and typical development and found that ADHD was a clinically and functionally valid diagnosis as a distinct comorbidity of ID. Individuals with ID experienced a similar developmental course with respect to symptoms of hyperactivity but, unlike typically developing children, who exhibited an increase and then decrease in inattentive symptoms in the teen years, persons with ID had no change in these symptoms, supporting the idea that lower cognitive function is at least correlated with persistent inattentive ADHD.

ENVIRONMENTAL CONSIDERATIONS

Changes to environment or social setting can be important triggers to acute behavioral crisis and decompensation in persons with ASD and ID. Individuals with ASD and ID may be particularly sensitive to changes in their environments, given common issues, such as behavioral rigidity, stereotyped interests and routines, difficulty with transitions, sensory sensitivity, and impulsivity. Acute decompensation may be precipitated by a change in routine or setting, loss of a caregiver or friend, or even dietary or housing changes. Lower levels of general cognitive function can make adaptation to change and learning challenging or more prolonged. In a study that explored precipitating events associated with crisis visits to an emergency department, Lunsky and Elserafi[60] found 6 stressful life events that were significant predictors of a likely emergency visit. These events were move of house or residence; a serious problem with family, friend or caregiver; problems with police or other authorities; sustained unemployment; recent trauma/abuse; and drug or alcohol problem. Other studies have shown that the risk for trauma in ID is elevated throughout the lifespan.[61]

Inasmuch as ID is a risk factor for psychiatric illness, the importance of environmental factors on trajectory and outcome cannot be overstated. Many studies have

examined various contributors to quality of life in persons with ID. Factors like independence, self-determination, interpersonal relation,s and social inclusion all importantly influence quality of life.[62]

A robust literature highlights the importance of environmental factors on the development and maintenance of behaviors that can be maladaptive.[63] Hitting or biting may be an effective way to gain or keep something of importance, and these behaviors play out in preschools all over the world. As these and related behaviors are reinforced in the environment, they may become particularly problematic over time. Systematic and detailed assessment of the potential functions that behaviors serve is a critical part of the assessment of these symptoms in the setting of ASD/ID. Behavioral analysis and related interventions are highlighted elsewhere in this issue by Doehring and colleagues.

Case Vignette: Aggression

Presentation: a 17 year-old nonverbal adolescent with autism is brought in by his mother and older sister (who happened to be visiting from out of state) for evaluation of aggressive behavior. He has been hospitalized on 3 occasions for attempting to stab the care providers in his group home. During each hospitalization he is described as calm; there is virtually no aggression evident in the hospital setting.

Work-up

Diagnostic: molecular testing previously performed and noncontributory

Medical: recent routine laboratory testing was normal but a weight gain of 20 lb was noted at last outpatient visit attributed to a change in appetite associated with receipt of olanzapine initiated during previous hospital stay.

Developmental: patient seems to have better receptive than expressive language and was diagnosed with ASD early in life. He has a history of significant aggressive and self-injurious behavior, which eventually prompted his out-of-home placement.

Environmental: he has been relatively stable until approximately 2 years ago, however, when his group home changed.

A detailed history of the events that had resulted in hospitalization, all of which seemed to happen entirely out of the blue and when the patient seemed to be in particularly good spirits, prompted his sister to remember a childhood game she and her brother played in the home. The game, monsters, involved one of the kids taking a table knife from the kitchen and chasing the other through the house until caught and then everyone falling down and switching roles. This information resulted in a significant reconceptualization of the knife wielding behavior that had resulted in emergency hospitalizations and a successful behavioral intervention strategy.

SUMMARY AND FUTURE DIRECTIONS IN ASD/ID

Children with ASD/ID present myriad challenges to diagnosticians with respect to the complexity of psychiatric presentation and the seemingly innumerable potential factors that might contribute to symptom expression. Furthermore, the unraveling of these issues is often complicated by communication impairments, developmental variation, and co-occurring medical problems.

This article approaches this complexity by focusing on 4 broad dimensions that inform the approach to evaluation and treatment in ASD/ID. Through the consideration of known genetic factors, medical conditions, developmental influences, and environmental factors, clinicians will be well positioned to move forward with the ongoing assessment and treatment of these challenging conditions.

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