

Clinical Features and Diagnosis of Autism and Other Pervasive Developmental Disorders

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ABSTRACT

Pervasive developmental disorders (PDDs), or autism spectrum disorders, are neurodevelopmental disorders resulting in impaired social interaction, verbal and nonverbal communication deficits, and repetitive, stereotyped behaviors and restricted interests. This article reviews the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision criteria for the PDDs, which include autistic disorder, Asperger's disorder, Rett's disorder, childhood disintegrative disorder, and PDD not otherwise specified, with a focus on autistic disorder, which is most characteristic of the PDDs. In addition, associated clinical and epidemiologic features of the PDDs and comorbidities are discussed. Principal components of the diagnostic evaluation are presented with an emphasis on early identification of these disorders.

INTRODUCTION

Pervasive developmental disorders (PDDs), as defined in the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision*,¹ are characterized by dysfunction in three core areas of early childhood development, namely, social interaction; communication and language skills; and behavior, specifically by the presence of stereotyped, repetitive behaviors and restricted activities and interests. Autistic disorder, or autism, which is the most representative type of PDD² and the most researched to date,³ was first described by Leo Kanner in 1943, who reported

FOCUS POINTS

- Pervasive developmental disorders (PDDs) affect social interaction and communication and are associated with repetitive, stereotyped behaviors.
- Autistic disorder is the most characteristic PDD which involves deficits in these three developmental domains.
- Early identification of PDDs is essential as early intervention improves prognosis.

many of the principal diagnostic features of children with the disorder.⁴ These include an “inability to relate” socially or “to convey meaning to others” through language and an “insistence on sameness” in daily routines.⁴ Kanner posited that these symptoms were “innate,”⁴ and in fact, our current conceptualization of autism and other PDDs is that these are “complex neurodevelopmental disorders”⁵ which are highly heritable⁶ and most likely involve early dysfunction in central nervous system development.³

PDD was introduced as a diagnostic category in the *DSM-III*⁷ and has come to be synonymous with autism spectrum disorder (ASD), as both terms refer to disorders affecting a child's social, communicative, emotional, and cognitive development.² The terms PDD and ASD are used interchangeably in this article depending on which term was utilized by the referenced study (eg, the *DSM-IV-TR* utilizes “PDD” while some current research studies prefer “ASD”). In addition to autism, there are four other disorders that are currently classified as PDDs by both the *DSM-IV-TR* and the *International Statistical Classification of Diseases and Health Related Problems, Tenth Revision*,⁸ namely, Asperger's disorder.

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der, Rett's disorder, childhood disintegrative disorder (CDD), and PDD-not otherwise specified (NOS).^{1,3} While each involves deficits in the same core developmental domains as autism, they are distinguished by the ways in which these domains are affected, along with differences in age of onset, gender distribution, course, and prognosis (Table).^{1,3,5,6,9-14}

This article reviews the diagnostic criteria and associated clinical features of PDDs, with an emphasis on autism itself, as it is the most characteristic of the PDDs² and the focus of increased research efforts in recent years; this research has led to a greater understanding of the genetics and neurobiology of these disorders.^{15,16} Both greater public awareness of autism and PDDs and reports of their increasing prevalence (the most recent estimate is one in 166 for all PDDs)⁹ have contributed to the growing interest in these disorders. While the increased prevalence is likely due in large part to new diagnostic categories and broadening of the diagnostic criteria over the past 50 years,⁹ these developmental disorders are not uncommon and the importance of early diagnosis and referral for educational and behavioral interventions cannot be over-emphasized.^{3,17} That is, understanding the clinical features, associated medical and genetic aspects, and comorbidities of PDDs, reviewed here, is critical for early identification and intervention, which improve long-term prognosis.^{5,17}

AUTISTIC DISORDER

The *DSM-IV-TR*¹ criteria for the diagnosis of autistic disorder include manifestations of dysfunction in social interaction and communication as well as the presence of repetitive, stereotyped behavior. Specifically, there must be a total of at least six impairments in these three areas, and at least two of the six must be deficits in social interaction (Criterion A).¹ In addition, delays or dysfunction in either social interaction, language (used in social communication), or symbolic play had to begin before 3 years of age (Criterion B).¹ Also, Rett's disorder or CDD must not be more appropriate diagnoses (Criterion C).¹ The Table summarizes the principal clinical features of autism as well as the other PDDs, which are discussed below.

Impairments in social interaction (Criterion A1) may include pronounced deficits in non-verbal social behaviors (eg, lack of eye contact, facial expressions, body posturing, and gesturing), lack of age-appropriate peer relationships, absence of spontaneous attempts to share interests or pleasure with others (eg, not pointing or showing things to others), or "lack of social or emotional reciprocity."¹ That is, children with autism primarily lack joint attention in that they fail to share actively in others' activities or interests.⁵ They may

behave as if they are unaware of the presence of others, select solitary over social activities, and possibly only interact with parts of people (eg, someone else's hand, using them "as tools or 'mechanical' aids,"¹ or as Kanner⁴ observed, "as if they are objects." For these reasons, children with autism are sometimes described as being in their "own little world."⁵

Deficits in communication (Criterion A2) encompass both verbal and nonverbal disabilities, and thus are closely aligned with social impairments.¹ More specifically, these deficits may include delay or absence in spoken language (which is not compensated for by attempts to communicate through gestures or other means); inability to converse appropriately with others, despite the presence of speech; odd, stereotyped, or repetitive uses of language; or the absence of imaginative or pretend play.¹ There may be a great deal of variability in the area of communication, ranging from no expressive or receptive language to fluent speech but with semantic or inappropriate social uses of language.⁵ For example, speech may be monotonous in its tone or involve abnormal pitch, rate, rhythm, or emphasis.¹ Language may involve meaningless, stereotyped repetitions of phrases or peculiar uses of words,¹ and children may refer to themselves in the second or third person, instead of as "I."^{3,4} Echolalia, which can be immediate (repetition of a phrase one has just heard) or delayed (repetition of a phrase heard in the past),¹⁸ occurs in up to 75% of individuals with an ASD who are verbal,¹⁹ and is a cardinal feature of autism.⁵ However, not all children with autism demonstrate echolalia. In addition, echolalia can be present in other disorders,^{18,19} such as dementia, other childhood language disorders, and blindness in children as well as in normal development.¹⁸ Additionally, receptive language is marked by difficulties in understanding abstractions (eg, irony, sarcasm), which further impairs social communication.^{1,5} The hallmark of these deficits in speech and language in autism is that neither is used to perform a social function; that is, as Kanner⁴ described, in children with autism, "speech is rarely communicative." Not only communication in the form of receptive and expressive language, but communication via gesturing (eg, pointing, showing) or imitating is also substantially impaired,^{1,5} underscoring the primacy of social dysfunction in this disorder.

Restricted and stereotyped behavioral patterns (Criterion A3) may include restricted interests that are abnormally intense, rigid adherence to routines or rituals, repetitive motor mannerisms, or preoccupation with the parts of objects.¹ Restricted interests are often variable, ranging from cars and trains to numbers and letters, for example, but they are by definition inappropriately intense or odd in their

TABLE
CLINICAL CHARACTERISTICS OF THE *DSM-IV-TR* PERSISTENT DEVELOPMENTAL DISORDERS (REVISED VERSION)^{1,3,5,6,9-14}

<i>Disorder</i>	<i>Prevalence</i>	<i>Gender Ratio (M:F)</i>	<i>Age of Onset</i>	<i>Developmental Domains</i>				<i>Associated Medical/Genetic Features</i>	<i>Course/Prognosis</i>
				<i>Social</i>	<i>Communication</i>	<i>Behavior</i>	<i>Cognitive</i>		
Autistic disorder (Autism)	13:10,000 ⁹	~4:1 ¹	Delays must be present before 3 years of age; ¹ signs often present in first year of life. ³ 20% to 25% may have developmental regression. ³	Poor eye contact; lack of gesturing or facial expressions. ¹ No age-appropriate peer relationships. ¹ No spontaneous sharing of interests with others; not pointing. ¹ No social reciprocity.	Speech delay or absence. ¹ When speech present, inappropriate social uses of language; difficulty understanding abstractions. ^{1,5} Odd, stereotyped language; echolalia. ^{1,5} No imaginative play. ¹	Intense restricted interests. ¹ Rigid adherence to routines. ¹ Repetitive motor mannerisms, eg, hand-flapping. ¹ Preoccupation with parts of objects. ¹ Nonspecific motor abnormalities, eg, toe-walking. ¹	MR common, ranging from mild to profound. ^{1,3} Nonverbal skills superior to verbal; irregular distribution of abilities. ^{1,3} Some may have above-average cognitive skills, eg, calculating calendar dates. ^{1,3}	Epilepsy, EEG abnormalities common. ⁵ More likely to have macrocephaly, poor motor coordination, mild hypotonia. ⁵ Abnormal responses to sensory stimuli. ^{1,5} Complex genetics; highly heritable. ⁶	Continuous course. ¹ School-age children may show some improvement in social functioning. ¹ Higher language and cognitive abilities are positive prognostic factors. ¹
Asperger's disorder	3:10,000 ⁹	>5:1–9:1 ^{1,10}	Often not recognized until school age when child has difficulties with peers. ^{1,11}	Same as autistic disorder. ¹ Interested in social interactions but inappropriate, odd in relating to others. ^{10,11}	No speech or language delay. ¹ May have precocious vocabulary, speak as if giving a lecture: "little professors." ^{10,11} Odd prosody, tone, rate; speech may be tangential or circumstantial. ^{10,11}	Same as autistic disorder. ¹ Focus on circumscribed interests to exclusion of social knowledge; speak about interests in formal, "one-sided" way. ^{10,11}	Occasional cases of mild MR, though uncommon. ¹	Motor difficulties, poor coordination, clumsiness. ^{1,11} Evidence for heritability but limited studies. ¹¹	Continuous course. ¹ Social interests, adaptation may improve in adolescence. ¹ Better prognosis than autism. ¹
Rett's disorder	1:22,800 (live female births) ¹²	Almost exclusively female (classical form). ¹²	Regression begins at 5–18 months of age. ^{1,12} Head growth deceleration (5–48 months of age). ¹	Loss of social skills at ~1–4 years of age, with later improvement. ¹² Maintain eye contact. ¹²	Loss of speech. ¹² Severe expressive and receptive language impairments. ¹	Loss of hand use; stereotyped hand movements (hand-wringing, washing). ^{1,12} Ataxia, later spasticity, scoliosis, rigidity. ¹²	Severe or profound MR. ¹	Seizures common; EEG abnormalities in almost all patients, beginning in period of regression. ¹² Breathing, sleep problems. ¹² Mutations in MECP2 gene in most cases. ¹²	Progressive regression; some improvement in social interaction in childhood and adolescence. ¹
Childhood disintegrative disorder	0.2:10,000 ⁹	4:1 ^{1,3}	Regression begins after 2 years of age and prior to 10 years of age, ¹ typically between ages 3–5 years. ¹³	Same as autistic disorder. ¹ Loss of social skills. ¹	Same as autistic disorder. ¹ Loss of receptive and expressive language skills. ¹	Same as autistic disorder. ¹ Loss of bowel and bladder control. ¹ Loss of motor skills. ¹	Severe MR. ¹	Seizures and EEG abnormalities common. ¹³ Associated with medical disorders in some cases. ^{1,13} Limited genetic data; appears to be "sporadic." ¹³	Continuous course. ¹ Deterioration reaches plateau with minimal improvement, "limited recovery" in most cases. ¹³
PDD-NOS	20.8:10,000 ⁹	M>F ³	Deficits begin within first few years after birth. ¹⁴	Social deficits are the primary disturbance. ^{1,14}	Verbal/nonverbal communication deficits may be associated with social impairment. ¹	Stereotyped behavior, interests, activities may be associated with social impairment. ¹	Not defined. ¹	Not defined. ¹ Genetically associated with autism. ¹⁴	Better prognosis than autism. ¹⁴

DSM-IV-TR=*Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition–Text Revision; M=male; F=female; MR=mental retardation; EEG=electroencephalograph; MECP2=methyl-CpG binding protein-2; PDD-NOS=pervasive developmental disorder-not otherwise specified.

content.⁵ Children with autism may engage in compulsive behaviors, such as repeatedly lining up objects in a specific way.^{1,5} They may become overly interested in the moving parts of objects, or engage in repetitive acts such as opening and closing doors.^{1,5} In addition, slight changes in daily routines can lead to behavioral outbursts.¹ Kanner⁴ described this obsessive rigidity affecting both interests and behavior as an “insistence on sameness.” Motor stereotypes may include hand or finger-flapping, rocking, and spinning,^{1,5} or there may be nonspecific motor abnormalities such as toe-walking or unusual hand movements or body postures.¹ The course of autism is “continuous,”¹ though school-age children may show some improvement in social, play, and communicative functioning, which may improve with appropriate intervention.¹⁹ Positive prognostic factors include greater language and cognitive abilities.^{1,20}

Although cognitive abnormalities are not part of the *DSM-IV-TR* criteria for autistic disorder, most children with autism have mental retardation, which can range from mild to profound.^{1,3} Typically, nonverbal skills are superior to verbal skills, and there tends to be an irregular distribution of cognitive abilities.^{1,3} Some children with autism, however, may have above-average cognitive skills, such as being able to calculate calendar dates.^{1,3} At the same time, autism may be associated with conditions that cause mental retardation, such as fragile X syndrome and tuberous sclerosis.^{3,21} While autism is ~4 times more common in boys than in girls, this varies based on level of cognitive functioning; the male:female ratio is greatest in children with normal cognitive functioning and lowest for children with profound mental retardation.^{22,23} That is, females with autism are more likely to have more severe mental retardation.^{1,22,23} Epilepsy and electroencephalograph (EEG) abnormalities without seizures are common in autism and PDDs,^{1,5,24} and will be discussed further in the “Diagnostic Evaluation and Comorbidities” section of this article. With respect to neurologic abnormalities, macrocephaly, poor motor coordination, and mild hypotonia are more likely in children with ASDs.⁵ There is evidence that head circumferences are normal at birth, but increase abnormally from 6–12 months, resulting in macrocephaly.^{5,25} Children with autism may display abnormal responses to sensory stimuli, ranging from hypersensitivity to noise to decreased sensitivity to pain.^{1,5} In addition, the heritability of autism is >90%, with greater concordance rates in monozygotic versus dizygotic twins, though autism is likely polygenic and involves complex genetics.⁶

While the *DSM-IV-TR* specifies that dysfunction must be present prior to 3 years of age for autism to be diagnosed,¹ questions have been raised as to how early the diagnosis can

be made accurately and to what extent the current diagnostic criteria are applicable to very young children.²⁵ ASDs can be diagnosed at 14 months, but the diagnoses are less stable at early ages.²⁵ In particular, one study of 48 children diagnosed with autism or an ASD by 2 years of age found that diagnostic stability was 68% for autism and 63% for ASDs.²⁶ Diagnosis prior to 30 months of age, lower symptom severity (notably in the area of social functioning), and better cognitive skills predicted less diagnostic stability by 4 years of age.²⁶ Many parents (~80%) observe abnormalities in their child’s development by 2 years of age, most often due to speech and language delays,²⁵ and some parents become aware of problems in the child’s social relatedness from around the time of birth.¹ Signs of dysfunction in children 6–12 months of age may include poor eye contact, lack of facial expression, delayed babbling, poor coordination, and hypotonia.²⁵ From 9–14 months of age, children with ASDs may demonstrate delayed receptive and expressive language. They may not point or gesture often or respond to their names being called. They may have repetitive behaviors.²⁵ However, motor mannerisms typically emerge in the preschool years⁵ and some young children may meet criteria for autism but not the full criteria for repetitive behaviors until around 3 years of age.³ During 20–24 months, children with ASDs may not show interest in other children; they have limited facial expressions, “abnormal prosody” in their speech, and restricted interests in addition to repetitive behaviors.²⁵ Early identification of ASDs is critical, as studies have shown that early interventions led to improvement in social functioning, language, and cognitive abilities.²⁵ (Landa²⁵ provides a comprehensive list of early signs of ASDs from 6–24 months of age.)

While there are early signs of dysfunction within the first year of life in most children with autism, there is evidence of developmental regression in ~20% to 25%,³ with even greater percentages reported.²⁷ That is, following a period of normal or mildly delayed development during the first 1–2 years, these children lose social and communication skills.^{1,27} Initially, this phenomenon was questioned, as it was based on parental reports,³ though retrospective studies have demonstrated that a subgroup of children with autism experience regression in social and language development.²⁷ In a recent prospective, longitudinal study, Landa and colleagues²⁷ assessed 125 infants between 14 and 36 months of age, most of whom were at high risk for developing autism, as they had siblings with the disorder. The developmental trajectories of toddlers who received an early diagnosis of an ASD (at 14 months of age) were clearly distinct from those of toddlers who were diagnosed later, with respect to sharing positive

affect, joint attention, and gesturing (though almost all of the toddlers who were not given an ASD diagnosis at 14 months of age did have signs of “developmental disruption” at that time). Specifically, this study found that the “later-diagnosis” group regressed from being almost indistinguishable from the non-ASD group at 14 months (except that children in the later diagnosis group shifted gaze less frequently from an object to another’s eyes and to the object again [or vice versa] compared to a non-“broader autism phenotype” group), to displaying similar social and communication deficits as the “early-diagnosis” group by 24 months of age (following a period in the later-diagnosis group of slowed language growth, lack of gains in joint attention, and losses in shared positive affect and gesturing).²⁷ Other investigations of early signs of autism, including prospective studies of the high-risk infant siblings of children with ASDs,^{28,29} indicated that infants and toddlers who are later diagnosed with ASDs demonstrate delays in communication, affect sharing, joint attention, and repetitive behaviors early on, but that signs of autism may not be clinically identifiable or present from birth.^{16,30}

Recent research has focused on characterizing and understanding the mechanisms underlying the social dysfunction in ASDs.³¹ For example, Klin and colleagues³¹ utilized eye-tracking technology to compare how individuals with autism view movie scenes involving social situations. These studies showed that adolescents and young adults with autism spent more time looking at others’ mouths and bodies or objects and less time looking at eyes compared to control subjects, and thus they miss social cues.³¹ Similar findings of a preference for focusing on mouth over eye regions were observed in 2-year-old children with autism compared to children who were either typically developing or developmentally delayed but did not have autism.³² In this study,³² less time spent looking at eyes was associated with greater social impairment. There is also evidence that individuals with ASDs have difficulties in facial recognition and have been found to show decreased activation of the fusiform region and amygdala when perceiving faces.³³ In addition, one theory proposed by Baron-Cohen³⁴ is that ASDs may represent a “hyper-systemising” approach to the environment, which may account for resistance to change and poor social functioning in these disorders.¹⁶

ASPERGER’S DISORDER

Asperger’s disorder is defined in the *DSM-IV-TR* as involving the same deficits in social interaction (Criterion A) and stereotyped behavior and restricted interests (Criterion B) as in autistic disorder, but without any language or cognitive

delays (Criteria D and E).¹ These deficits, particularly in social relatedness, significantly impair the individual’s daily functioning (Criterion C).¹ In addition, the *DSM-IV-TR* specifies that criteria cannot be met for another PDD or schizophrenia (Criterion F).¹ Although Asperger’s disorder and autism share diagnostic criteria, there are qualitative differences in the nature of the social dysfunction and repetitive behaviors in the two disorders.¹¹ Unlike autism, individuals with Asperger’s disorder are not necessarily socially withdrawn and are usually interested in interacting with others, but their socially inappropriate or odd style of relating to others (eg, speaking in a formal way as if giving a “monologue”) and difficulty reading social cues cause them to become isolated.^{10,11} In Asperger’s disorder, restricted interests and rigidity in adhering to rituals are more common than motor mannerisms.¹⁰ Individuals with Asperger’s disorder will become experts in a particular circumscribed area of interest, learning a great deal of factual information on this topic often to the exclusion of other types of experience, eg, social activities.^{10,11} This furthers their social isolation, as they attempt to talk to others about these singular interests as if they are giving a lecture, and for this reason, individuals with Asperger’s disorder are sometimes described as “little professors.”^{10,11}

In contrast to autism, there are no delays in language or cognition early in life in Asperger’s disorder.¹¹ However, speech in individuals with the disorder may be characterized by abnormal prosody, tone, or rate, and may be tangential, circumstantial, or overly verbose, consistent with a lack of attunement to the social uses of language and a focus on the individual’s own interests.^{10,11} While mental retardation is not common in Asperger’s disorder, there have been cases of mild mental retardation.¹ Usually, verbal skills (eg, vocabulary, verbal memory) are superior to non-verbal (eg, fine and gross motor, visual-spatial, visual-motor abilities), as individuals with Asperger’s disorder frequently have motor difficulties such as poor coordination, odd gait, and “clumsiness.”¹¹ Asperger’s disorder is often not recognized until a child reaches school age and begins to experience social difficulties with peers, particularly as there is no language delay, the child’s vocabulary can be precocious, and social problems do not emerge at home where their interactions are primarily mediated by adults.¹¹

Asperger’s disorder is much more common in males (with male:female ratios estimated at 5:1 to at least 9:1).^{1,10} While there are few genetic studies of Asperger’s disorder specifically, there is evidence for a family history of the disorder in first-degree relatives.¹⁰ In his original description of the disorder, pediatrician Hans Asperger noted that family members of those affected demonstrated similar features.¹¹ Other traits

that Asperger reported included decreased facial expressions and gestures, peculiarities in communication, lack of empathy and intellectualization of feelings, and school behavioral problems such as aggression stemming from their social deficits.¹¹ The question of distinguishing Asperger's disorder and autism diagnostically continues to be a challenge, yet it is clear that social dysfunction in this disorder leads to significant functional impairment.^{1,11}

RETT'S DISORDER

Rett's disorder is characterized by a defined pattern of regression, with respect to social, language, motor, and cognitive development, beginning at ~5–18 months of age.^{1,12} The *DSM-IV-TR* diagnostic criteria specify that from birth to 5 months of age, children with Rett's disorder appear to demonstrate typical development (Criterion A), in that prenatal, perinatal, and psychomotor development seems to be unremarkable and head circumference is normal at birth.¹ Retrospectively, however, subtle abnormalities, such as mild hypotonia and atypical or excessive hand movements, have been described during this period.¹² A period of developmental regression follows (Criterion B), characterized by deceleration of head growth (between 5–48 months of age); loss of hand skills (between 5–30 months of age) and development of stereotypical hand movements; early loss of social skills, though this improves later; poor coordination of gait or truncal movements; and severe impairment in expressive and receptive language with marked psychomotor retardation.¹ Severe or profound mental retardation is often also found in Rett's disorder.¹ Deceleration in head growth may not occur in all children with Rett's disorder, and regression may not begin until ~18 months of age in some cases.¹² Classically defined Rett's disorder is found only in females, as the disorder has been linked to a gene on the X chromosome that encodes methyl-CpG binding protein-2 (MECP2), which is involved in regulating the expression of other genes during development.¹² Mutations in MECP2, which have been reported in 87% of females with classical Rett's disorder, and 50% of girls with a variant form of the disorder, occur more often on the paternal X chromosome and are thought to be lethal in males, accounting for the predominantly female distribution of the disorder.¹² As autistic symptoms occur less often in very young females than in males, Rett's disorder should be considered diagnostically in females with these symptoms.¹² In addition, Rett's disorder is second to Down's syndrome as a cause of mental retardation in females.¹² Molecular genetic analysis for mutations in MECP2 should be included in the diagnostic evaluation.¹²

It is important to underscore how the progression of motor and social abnormalities in Rett's disorder, initially described by physician Andreas Rett in 1966, distinguishes it from other PDDs. Specifically, following the initial period of generally unremarkable development up to ~6 months of age, motor development seems to plateau. Significant developmental delays and neurologic symptoms are present by 15 months of age in ~50% of girls. Ages 1–4 are characterized by rapid loss of social and cognitive abilities, along with speech and hand use. Stereotyped hand movements, consisting of hand-wringing, washing or clasping, and hand-to-mouth movements, are characteristic of Rett's disorder, and occur almost continuously during the day, interfering with purposeful use of the hands. Ataxia and loss of motor function affect ambulation, such that girls may lose or not develop the ability to walk. Social skills, including interest in others, are also lost during this stage, though in contrast to autism, eye contact is not affected. However, social interaction improves from 2–10 years of age. For this reason, many girls with Rett's disorder may not demonstrate signs of autism at particular stages of the disorder, notably when they are <6 months of age or >3–5 years of age. Motor symptoms progress to involve spasticity, scoliosis, and rigidity at older ages. Additional features of Rett's disorder include seizures, which are common, and EEG abnormalities, which are present in almost all cases beginning during the period of regression. Respiratory and sleep problems and bruxism have also been described. There is limited research on the long-term course of Rett's disorder, and many cases are undiagnosed due to lack of familiarity with this disorder.¹²

CHILDHOOD DISINTEGRATIVE DISORDER

CDD is characterized in the *DSM-IV-TR* by developmental regression that begins after at least 2 years of what appears to be normal development in the areas of social interaction, communication, play, and adaptive behavior (Criterion A). This is followed by loss of skills prior to 10 years of age in the following areas: receptive and expressive language, social abilities, bowel and bladder control, play, and motor skills (Criterion B). In addition, there is similar dysfunction as that described in autistic disorder in social interaction, communication, or restrictive, repetitive behaviors (at least two of these areas are affected; Criterion C). Another PDD and schizophrenia must not be more appropriate diagnoses (Criterion D). Severe mental retardation is often found in CDD.¹

CDD, which is also known as Heller's syndrome, as it was first described by educator Theodore Heller in 1908, is rare and research on the disorder is limited.^{1,13} Onset of regression

is typically at ~3–5 years of age, and may be rapid (within days to weeks) or gradual (within weeks to months), and occasionally is associated with behavioral changes (eg, agitation, anxiety, irritability).^{1,13} While CDD may be associated with medical conditions in some cases, such as tuberous sclerosis, metachromatic leukodystrophy, neurolipidoses, and others, this has not been found in most, though a thorough medical and neurologic work-up is recommended.^{1,13} CDD is characterized by a marked loss of language, social, and even self-help skills, such as toileting, and appears similar to autism following the regression.¹³ In addition, occurrence of seizures and EEG abnormalities are similar to autism.¹³ The course is continuous, and in most cases, deterioration reaches a plateau with minimal gains and “a limited recovery”; in a minority of cases, deterioration is progressive.¹³ CDD appears to be “sporadic,” as cases of the disorder occurring in families have not been identified, though genetic studies are limited and there may be genetic or gene-environment etiologies that have yet to be identified.¹³

PERVASIVE DEVELOPMENTAL DISORDER-NOT OTHERWISE SPECIFIED

The *DSM-IV-TR* describes PDD-NOS as “a severe and pervasive impairment in the development of reciprocal social interaction” that is associated with nonverbal or verbal communication deficits or stereotyped behaviors and interests, but the specific criteria for another PDD are not met.¹ The disorder cannot be due to schizophrenia or schizotypal or avoidant personality disorders.¹ In addition, the *DSM-IV-TR* includes “atypical autism” in this category, which refers to cases that do not meet full diagnostic criteria for autistic disorder, as symptoms are “atypical” or “subthreshold,” or age of onset may be delayed.^{1,14} That is, PDD-NOS refers to cases primarily involving social deficits^{1,5,14} where symptoms are fewer or less severe than in autistic or Asperger’s disorders and do not meet criteria for Rett’s disorder or CDD,¹⁴ though the criteria for PDD-NOS are vaguely defined.^{5,14} As Towbin¹⁴ states, it “is likely that PDD-NOS is not just one condition.” Genetics and family studies indicate that there is an association between PDD-NOS and autism, as siblings of individuals with autism are equally likely to be diagnosed with either PDD-NOS or autism.¹⁴ At the same time, ~33% of the first-degree relatives of individuals with an ASD may be part of what has been called the “broader autism phenotype,” which describes individuals who may have similar features to ASDs but are not impaired functionally and do not meet the criteria for an ASD.³⁵ The concept of functional impairment distinguishes PDD-NOS from the broader phenotype, yet further research is required to

make the diagnostic criteria more specific and to characterize further “endophenotypes” such as differences in cognitive abilities, face recognition, or eye tracking, within this category.¹⁴

DIAGNOSTIC EVALUATION AND COMORBIDITIES

Early identification of ASD symptoms and signs (eg, lack of social smile; poor eye contact; no babbling, pointing, or gesturing by 12 months of age; no spoken words by 16–18 months of age or two-word phrases by 2 years of age; atypical play behavior; loss of language or social skills) by primary care physicians (PCPs) and early referral to a multidisciplinary team (including a child psychiatrist and psychologist, pediatric neurologist, neuropsychologist, and developmental pediatrician) are critical in the diagnosis of ASDs, as recent evidence has shown that early intervention improves prognosis.^{5,17} For this reason, in 2007, the American Academy of Pediatrics published a “Surveillance and Screening Algorithm” for ASDs that recommends universal surveillance (ie, obtaining a developmental history, addressing parental concerns, assessing risk factors) and screening at preventive visits.¹⁷ While there is no conclusive test or biologic marker for ASDs, there are numerous screening and diagnostic tools that may be utilized to assist in the evaluation of children who may have an ASD.^{5,17} Among the available screening tools are the “level 1” tests, which can be administered at primary care visits, including the Checklist for Autism in Toddlers (CHAT; parent report/clinician observation; 18–24+ months of age),^{36–38} which is characterized by low sensitivity but high specificity, and the modified CHAT (parent report; 16–48 months of age),³⁹ which is more sensitive.^{5,17,22} “Level 2” screening tools, which aid in distinguishing between ASDs and other developmental disabilities, include the Autism Behavior Checklist (interviewer completes; ≥18 months of age)⁴⁰ and the Childhood Autism Rating Scale (trained interviewer completes; >2 years of age).^{17,41} The “gold standard” diagnostic tests for ASDs are the Autism Diagnostic Interview-Revised,⁴² which is a semi-structured, standardized interview for parents, and the Autism Diagnostic Observation Schedule,⁴³ which is a “structured observation” of the patient, both of which require formal training to administer.⁵ PCPs are advised to refer children for a comprehensive evaluation as early as possible when there are concerns regarding the child’s development or if there is a positive result on a screening test, and to be particularly “vigilant” in monitoring at-risk siblings of children with ASDs,¹⁷ as the risk of a younger sibling of a child with autism having the disorder has been reported as >15%.⁴⁴

The initial evaluation of any child who may have an ASD should include vision and hearing exams, as disabilities in these areas may mimic characteristics of ASDs.^{5,17} That is, while lack of eye contact or response to one's name being called may occur in autism, these signs may instead be indicative of impairments in vision or hearing, respectively.¹⁷ In addition, lead testing is recommended due to pica.¹⁷ It is also important to be aware that autism is associated with numerous genetic syndromes, which occur in individuals with autism at various rates, including fragile X syndrome (~2%), tuberous sclerosis (0% to 4%; 8% to 14% of patients with autism and epilepsy), Down syndrome (0% to ~17%), and Angelman syndrome (~1%), among others.²¹ For this reason, high-resolution karyotype and fragile X testing is recommended in children with an ASD and mental retardation; dysmorphic features; or a family history of fragile X, mental retardation, or dysmorphic features.^{5,17} Testing for MECP2 mutations (Rett's disorder) and fluorescence in situ hybridization for chromosome 15q (Angelman and Prader-Willi syndromes) should also be considered.⁵ In addition, epilepsy is common in ASDs, with prevalence ranging from 5% to 40%,^{5,24} and all seizure types have been described, though seizures are more likely to occur in individuals with ASDs and mental retardation.²⁴ EEGs are clearly indicated in children with clinical signs of seizures and in children who have language regression (as Landau-Kleffner syndrome is characterized by language regression between 4–7 years of age and EEG abnormalities),^{5,17,24} though some clinicians recommend performing EEGs in all children with autism.⁵ Metabolic and imaging studies are recommended when there is a specific clinical indication.^{5,17} Other medical problems that have been reported to occur often in or to be associated with autism include disturbances in sleep, gastrointestinal symptoms, dietary restrictions, and allergies and immunologic abnormalities.^{5,45}

Behavioral and affective symptoms that may also occur in patients with ASDs include attentional difficulties, hyperactivity, obsessive-compulsive symptoms, tics, mood lability, anxiety, and depression.³ For this reason, it is important to consider other psychiatric conditions that may co-occur with ASDs. Although the *DSM-IV-TR* states that attention-deficit/hyperactivity disorder (ADHD) and autistic disorder cannot be co-diagnosed, Reiersen and Todd⁴⁶ reported that there is evidence that some patients with autism may meet criteria for ADHD, which is associated with greater behavioral and social impairment, and that in less severe ASD cases the ADHD symptoms may be the chief complaint that leads to the clinical presentation. Forty-one percent to 78% of children with an ASD have ADHD symptoms in clinic studies.⁴⁶ At the same time, attentional difficulties may be due to the developmental and cognitive deficits in autism, and may not indicate the presence of ADHD as a

distinct disorder.³ Nonetheless, Reiersen and Todd⁴⁶ argued that there are instances where the two disorders co-occur, and that evaluation should include assessment of both ASD and ADHD symptomatology when present. In addition, a recent study⁴⁷ found that 70% of 11–14-year-old children with an ASD in a population-derived sample, most of whom were boys, met criteria for at least one other psychiatric disorder, based on parent interviews, including anxiety disorders (~42%, which included a high rate of “social anxiety disorder”; the authors note that this may be due to the social deficits of ASDs, or may represent social anxiety in these individuals), ADHD (~28%), and oppositional-defiant disorder (~28%). These studies underscore the importance of evaluating the full range of psychiatric symptoms that may occur in patients with ASDs.

CONCLUSION

The PDDs, as described in the *DSM-IV-TR*, are disorders that affect the core developmental domains of social interaction and verbal and nonverbal communication, and involve repetitive, stereotyped behaviors and restricted interests. These disorders, which are also referred to as the ASDs, include autistic disorder (which is the most paradigmatic of the PDDs), Asperger's disorder, Rett's disorder, CDD, and PDD-NOS. In addition, cognitive development is often affected in these disorders, although there is a range across disorders, and there may be associated neurologic signs (eg, motor symptoms, EEG abnormalities). Some of the disorders (Rett's disorder, CDD, the regressive type of autistic disorder) are characterized by developmental regression, that is, loss of acquired skills. While the etiology of these disorders is unknown, there is evidence of heritability in most of these disorders. Given that the PDDs as a group are not uncommon, early identification and referral of patients with these disorders cannot be overemphasized, as early intervention improves long-term prognosis. **PP**

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