1 Autism Spectrum Disorders: Phenotype and Diagnosis

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CONTENTS

THE SPECTRUM OF AUTISTIC DISORDERS

Autism is a syndrome that emerges in the first three years of life and is defined by a pattern of qualitative abnormalities in reciprocal social interaction, communication, and repetitive interests and behaviors. The *Diagnostic and Statistical Manual* (DSM-IV)

of the American Psychiatric Association includes five different disorders under an umbrella term of pervasive developmental disorders (PDDs). These include autistic disorder, Asperger's disorder, pervasive development disorder not otherwise specified (PDDNOS), Rett syndrome, and childhood disintegrative disorder (CDD). Because there is great diversity in the severity of these features in affected individuals, an umbrella term of autism spectrum disorders (ASD) has been suggested to include autism, atypical autism or PDDNOS, and Asperger's syndrome (see Volkmar et al., 2005). Disorders within the spectrum are discriminated from each other primarily by milder and less comprehensive difficulties (PDDNOS and atypical autism) or by the absence of language delay and mental retardation (Asperger's syndrome). Family history and twin studies suggest that, at least in some cases, these disorders share genetic roots, but the degree to which different etiologies and genetic patterns account for individual differences within ASD is an open question (Piven et al., 1997).

The last two disorders in the PDD umbrella are more rare and have more specific diagnostic features. Rett syndrome is included because of the phenotypic overlap with autism, at least in the preschool age group. Rett syndrome is characterized by a period of normal development followed by a regression in language and social skills usually between 6 and 18 months as well as the onset of hand stereotypies such as hand wringing (Hagberg and Witt-Engerstrom, 1986; Mount et al., 2003). It occurs mostly in girls. The presence of abnormal physical features seen in Rett syndrome, e.g., head growth deceleration, loss of purposeful hand movements, ataxia and gait abnormalities, scoliosis, and hyperventilation and breath holding (Tanguay, 2000), and the nature of the regression are the keys to differentiating this rare disorder from ASD.

By definition, children with CDD must have normal development until age two and then experience a regression that affects not only social communication, but also other areas such as gross and fine motor skills (Volkmar and Rutter, 1995). Most often these regressions occur after age three. It is important to note that most researchers do not include individuals with Rett and CDD in samples of autism or ASD.

Because of the lack of a clear neurobiological marker, ASDs are necessarily defined by behavior, which is both intriguing and frustrating for researchers. Nevertheless, there have been major advances in the last 20 years in the ability to reliably define and quantify the behaviors that differentiate autism and other ASDs from other disorders and from typical development (Lord and Corsello, 2005). In some ways, the field of autism is at a crossroads where categorical diagnoses, such as Asperger's syndrome, or even not quite categorical diagnoses, such as PDDNOS, do not seem sufficient. However, reliable and valid measures of independent dimensions in ASD are not yet easily accessible. The next 10 years may see substantial progress in these areas as large and carefully documented samples become available for study.

The purpose of this chapter is to provide background concerning phenotype and diagnosis for the interested neuroscientist. Having initially defined terms, various aspects of the phenotype of ASDs are discussed and general issues in diagnosis are considered.

THE PHENOTYPE

Core Features

Social and Communication Deficits in ASD

In the last 20 years, our understanding of the aspects of communication and social interaction specific to children with ASD, compared to children with various developmental disabilities, has become increasingly refined. For example, deficits in communication in ASD go beyond language delay to include a social failure to compensate for this delay, which other children (e.g., children who are deaf) do through gesture, eye contact, and increased attention to facial expressions. Other common deficits in communication associated with autism include stereotyped language, such as delayed echolalia, reciting passages from favorite videos or commercials, pronoun reversal, and use of stereotyped phrases (such as a child who says, "Can I call you right back, sweetie?" when he does not want to answer a question). Most individuals with autism are delayed in their acquisition of both receptive and expressive language. Delays in receptive language have been proposed to be particularly associated with autism in preschool children (Philofsky et al., 2004). Formerly, it was expected that half of all individuals with autism would not use speech as their primary mode of communication. Nevertheless, in a recent study, the proportion of 9-year-olds with ASD who spoke fluently was about 40% in two independent samples, and the proportion who were nonverbal (i.e., who used fewer than five words on a daily basis) was less than 15% (Lord et al., in press), perhaps because of better intervention and also the broadening of the diagnostic criteria (see Chapter 2).

Individuals with autism have difficulty with imitation, imaginative play, and nonverbal communication — three categories of behavior that are sometimes considered examples of communication deficits and sometimes social deficits (APA, 2000; WHO, 1992). The most prototypical examples of social deficits have to do with reciprocity, such as seeking to share enjoyment (e.g., coming to get a parent to see a new Lego construction), feeling genuine concern and offering comfort to another person, and forming caring friendships that go beyond classroom or parent-arranged interactions. Several recent studies have suggested that, rather than considering social and communication deficits as separate, it is more parsimonious and valid to think of a single social communication factor that includes nonverbal communication and reciprocal conversation. Separate consideration would still be given to whether an individual is delayed in basic dimensions of vocabulary, syntax, and phonology in either or both receptive and expressive language (Charman et al., 2005).

Many of the examples of social communication deficits in ASD involve behaviors that typical infants master in the first year or two of life, such as following another person's shift in gaze and other aspects of joint attention, vocalizing "back" to someone who is talking to them, and smiling at someone who smiles and vocalizes to them in a positive way (Baranek, 1999). In fact, difficulties with joint attention are probably considered the most clear "schema" marking autism as different from other developmental disorders (Mundy and Sigman, 1989). Lack of social reciprocity

at a higher level of abstraction also fills that role, particularly for older children and adults who may have learned the importance of attending to gaze but still may not be able to have a conversation in which they spontaneously ask about and listen to how someone else feels about a particular event. Children and adults with ASD are different from all but very young babies in basic social behaviors. On the other hand, some of the deficits in autism occur in areas that are associated with developmental change such as gestures, more complex imaginative play, and cooperative play in a group, thus representing delays as much as deviance.

Repetitive and Restricted Behaviors and Interests

The next defining area, restricted and repetitive behaviors and interests, contains the largest proportion of examples that represent deviance. Here we see the presence of behaviors that would be abnormal at any age (e.g., stereotyped hand and finger movements, odd ways of visually inspecting objects, and unusual intonation). There are also unusual preoccupations (e.g., with drainpipes, flags, TV show credits) and circumscribed interests so intense that they interfere with social interactions and other behaviors (e.g., a child who has to carry Disney figurines with him and will not put them down even in order to play with a new toy or pick up a cookie). They also include preoccupations with a part of an object, such as the wheels on toy vehicles, and unusual sensory responses, such as smelling toys or people, as well as repetitive behaviors such as lining up toys or spinning objects, flicking light switches, or opening and closing cupboard doors. Unusual motor behaviors, most often involving rapid movements of the hands and fingers, often in peripheral vision, or whole body movements, such as spinning or running and flapping or repetitive hopping and posturing are also common (LeCouter et al., 1989). Repetitive behaviors and interests differ from the abnormalities in social communicative behaviors in their variety across individuals with ASD, and variability within individuals across time (Charman et al., 2005). They also appear to have somewhat different trajectories, at least from early childhood to adolescence (Lord et al., in press; Richler, Bishop, and Lord, in press).

ASD is also characterized by insistence on sameness which includes both the development of unusual rituals (such as lining toes up with a crack in the sidewalk on the way to school) and substantial distress when everyday routines are violated (such as having a bath earlier or later than usual), although it should be noted that these behaviors occur in substantial numbers of children and adults with other disabilities as well (Shao et al., 2003; Lord et al., 1994). There are subtle differences in the behaviors shown by children with ASD and those by children and adults with obsessive-compulsive disorder (OCD). In ASD, repetitive behaviors are often enjoyable to the child or adult and involve intense interests such as dinosaurs or flags or Japanese animé; whereas with OCD the individual is typically uncomfortable when carrying out the behavior, and the behaviors are most often common compulsive behaviors such as checking and counting (Leckman et al., 1997).

There are a number of theoretical issues frequently raised in ASD that occur in consideration of a number of psychiatric disorders. Space is too limited to discuss

them here, but they include the idea of a spectrum of disorders, how delay is separated from deviance, how "core" difficulties affect experience and in turn affect learning and development, and how co-occurring conditions should be taken into account. Active research programs are currently addressing these issues.

Sex Differences

Autism and all other ASDs except Rett Syndrome are much more common in males than females, with ratios of 3 or 4 to 1, found in most epidemiological studies, and ratios of up to 10 to 1 for many research samples (Lord et al., 1982; Fombonne, in press). Sex ratios move closer to 1:1 for children with autism who are profoundly retarded. When differences in IQ are controlled for, it is not clear if females with ASD are different from males in terms of their behavioral presentation (Lord et al., 1982), but there are some suggestions from genetic-linkage studies that multiplex families with all affected males may differ genetically from families with males and females affected (Cantor et al., 2005; Lamb et al., 2005; Stone et al., 2004). Because of the rarity of females with autism and the need to control for IQ, small sample sizes have been a major limitation to many studies.

Other Associated Features

ASD and Cognitive Impairments

ASDs are associated with various degrees of mental retardation, which are often, though not always, related to the severity of autistic symptoms. As described in Chapter 2 of this volume, earlier it was believed that more than 75% of children with autism were also mildly to severely retarded. However, most recent epidemiological studies have indicated that the proportion of children with ASDs with nonverbal IQs below 70 (e.g., mildly to severely retarded) may be less than 50%. In part, this may be due to society and medicine's increasing recognition of individuals with milder ASDs (Gernsbacher et al., 2005). It may also be due to better understanding of appropriate ways to separate nonverbal problem-solving skills from language skills in the assessment of children with limited receptive and functional expressive language skills. If carried out by an experienced clinician with appropriate tests, nonverbal IQs appear to be quite stable from age two to later school age in most children with ASDs and, if anything, they may increase up to about 20 points over time (Lord et al., 1982; Charman et al., 2005; McGovern and Sigman, 2005).

There is much more variation in verbal IQ scores than nonverbal IQs in ASD. Separate measures of nonverbal intelligence and verbal ability are important in interpreting specific behaviors in ASD that are often linked to neurobiological factors, and these are also significant in selecting proper control groups. Consequently, it is critical that these assessments are done systematically and by experienced clinicians. There have also been several interesting, though not yet replicated, neurobiological findings (e.g., differences in head circumference) related to children with autism with very marked differences between nonverbal and verbal IQ (Joseph et al., 2002). Larger differences between performance IQ and adaptive scores are

also one of the distinguishing characteristics of ASD compared to mental retardation without ASD.

Comprehensive theories explaining the neuropsychological aspects of autism continue to be proposed but have not been able to easily address the range of findings with regard to phenotype, history and prognosis, and neurobiological factors. Various theories have attempted to account for social cognitive deficits through concepts such as a lack of central coherence (Frith, 2004), a lack of theory of mind (Baron-Cohen and Howlin, 1994; Lord and Richler, in press), and deficits in executive functioning (Ozonoff, 1995). A lack of central coherence is described as the inability to integrate information when a whole represents more than the sum of its parts (e.g., a picture of a face made up of typed "x's"). Executive functioning refers to the ability to plan and organize action, including inhibiting simple responses and anticipating a progression of events.

Specific deficits in joint attention, implicit learning, imitation, memory, and other aspects of information processing have all been proposed (Mundy and Sigman, 1989; Renner et al., 2000; Rogers and Pennington, 1991; Stone et al., 1997; Boucher, 1981; Ozonoff et al., 1994). When general intellectual level is taken into account, it has been difficult to show strong associations between specific cognitive deficits and the core social deficits of ASD except for joint attention. Nevertheless, the theories provide insight and working hypotheses for potentially important phenotypic characteristics and for behavioral treatments.

Relationship to Sensory and Motor Impairments

While not part of the diagnostic criteria, parents often report abnormal sensory behaviors in children with ASD. Both increased and decreased responsiveness to sensory stimuli in all domains have been reported (Rogers et al., 2003). Some individuals with ASD are described as tactilely defensive. They appear to not want to be touched, or they do not want to touch certain textures or surfaces. Common complaints include the inability to wear socks or shoes, an intolerance of clothes made of certain fabrics or tags in clothing, or extreme disturbance caused by brushing, washing, or cutting the child's hair. Some individuals seek proprioceptive input by crawling under furniture or into small, cramped spaces, or seek vestibular input by spinning, swinging, or bouncing repetitively. In the auditory domain, severe behavioral reactions can be triggered by loud or unusual noises, or sometimes by common sounds such as coughing or singing. Other individuals may visually inspect objects (e.g., peering out of the corners of their eyes or examining things at very close range). Others have reported an increased pain threshold (Charman and Baird, 2002; Filipek et al., 2000).

There are some data suggesting an underlying motor impairment in children with ASD. Motor milestones are delayed in up to 33% of cases (Mayes and Calhoun, 2003). Gait disturbances such as tiptoeing (Kielinen et al., 2004; Vilensky et al., 1981) and problems with balance and coordination (Ghaziuddin and Butler, 1998; Jones and Prior, 1985) have been documented. In a more detailed analysis, Minshew et al. showed the presence of significant postural abnormalities in children with ASD (Minshew et al., 2004).

A higher incidence of autism and autism-like behaviors has also been reported in individuals with primary sensory impairments, e.g., those with visual or auditory loss. It has long been recognized that congenital blindness is associated with an autism-like presentation (Carvill, 2001). Children blind from birth frequently show repetitive motor behaviors similar to the hand and finger stereotypies exhibited in autism, the so-called "blindisms." Beyond that, others have reported impaired social and communication skills in blind children, as well (Brown et al., 1997; Hobson and Bishop, 2003). However, factors such as the etiology of the blindness, as well as methodological problems with differing diagnostic criteria and behavioral observation scales, make this a complex association (Carvill, 2001). There are fewer reports on the association between hearing loss and autism, but one study examining a large sample of hearing-impaired children found an autism rate of 4% (Jure et al., 1991).

Relationship to Epilepsy

The occurrence of epilepsy in individuals with autism has long been recognized; however, the reported prevalence varies widely from 5 to 44% (Tuchman and Rapin, 2002). Critical review of the literature reveals that heterogeneity in samples may play a role in this variability (see Ballaban-Gil and Tuchman, 2000 for review). Factors as simple as differences in recruitment and nonuniformity in epilepsy determination and autism diagnosis likely contributed. The age of participants in the sample may also play a role because of the bimodal age of seizure onset in autism (early childhood and adolescence). Rates may also be inflated by inclusion of nonidiopathic autism cases (e.g., those with gross brain malformations, cerebral palsy, tuberous sclerosis, or other neurogenetic disorders), which themselves have a higher rate of associated epilepsy. Finally, because some studies have found an association between lower IQ and increased risk of epilepsy (Pavone et al., 2004; Tuchman et al., 1991), differing IQ levels in the sample may impact reported rates. Epileptiform EEGs (e.g., spikes, spike wave, or sharp waves) are also reported in ASD patients with rates varying from 18 to 60% in those with seizures (Kawasaki et al., 1997; Rossi et al., 1995) and from 8 to 46% of those without seizures (Kawasaki et al., 1997; Tuchman et al., 1997; Tuchman et al., 1991).

The increased risk for epilepsy and EEG abnormalities in individuals with ASD may provide an important clue to the underlying neuropathology in at least a subset of cases. Few studies have directly investigated the relationship of epilepsy and the common deficits in language, cognition, and behavior seen in this population. Over 10 years ago, Tuchman (1994) raised a series of fundamental questions regarding this relationship, including whether the occurrence of epilepsy or epileptiform EEGs together with the cognitive, language, and behavioral deficits seen in ASD were all just an epiphenomenon of the underlying neural dysfunction or were causally related to these deficits. So far these questions have gone unanswered.

Macrocephaly in ASD

Beginning with Kanner's initial report (Kanner, 1943), increased incidence of large head size (macrocephaly) has been reported in autism. Postmortem studies (Bailey et al., 1998; Kemper and Bauman, 1993) as well as structural imaging studies

(Piven et al., 1996; Piven et al., 1995) suggest that brain volume is increased in autism. Studies using strict definitions of macrocephaly (>97% or 2 SD or more above the mean) have confirmed this phenomenon (Fombonne et al., 1999; Lainhart et al., 1997; Stevenson et al., 1997) but report variable rates from as low as 12% (Fidler, Bailey, and Smalley, 2000) to as high as 30% of cases with autism or ASD (Woodhouse et al., 1996). In a meta-analysis of over 500 patients, a rate of 20.6% for macrocephaly in autism was calculated (Fombonne et al., 1999). The association between head circumference and gender is not well understood. One study showed significantly more females with macrocephaly (Lainhart et al., 1997); another showed the opposite (Davidovitch et al., 1996), and still others have found no association (Fombonne et al., 1999).

There is also controversy regarding the age at which the head growth occurs. It is generally agreed that larger head size is common in younger children with ASD, but adult data has yielded more conflicting results. This may be a function of the fact that head growth better reflects brain growth at earlier ages. Lainhart and colleagues (Lainhart et al., 1997) found a greater percentage of older subjects with macrocephaly, suggesting that brain growth is occurring later. However, Aylward and colleagues found no overall difference in measurements of head size as a function of age, but did report significantly larger brain volumes in younger vs. older ASD children compared to controls (Aylward et al., 2002). Others have also reported the normalization of brain volume with age (Courchesne et al., 2001). These findings could be interpreted as suggesting that the earlier brain growth is associated with macrocephaly, which persists as the children age despite normalization of the brain size.

Yet even the age at which the abnormal brain growth starts is unclear. Infantile macrocephaly has been associated with an increased risk of developing an autism spectrum disorder (Bolton et al., 2001). However, in a small retrospective analysis, Courchesne and colleagues reported the head circumferences of autism subjects were actually smaller at birth compared to a reference sample, and then a pattern of very early rapid head growth emerged (e.g., between birth and 14 months of age) in the autistic subjects. They further suggested that this may even be a marker for development of autism (Courchesne et al., 2003).

Macrocephaly is also more common in nonautistic family members of autistic individuals (Fidler et al., 2000; Miles et al., 2000) and therefore may represent part of the broader phenotype in autism. On the other hand, it is not specific to ASD. High rates also occur in ADHD (Ghaziuddin et al., 1999) and possibly other developmental disorders.

Comorbid Psychiatric Diagnoses

Many symptoms present in psychiatric diagnoses can also be seen in individuals with ASD including attentional deficits and hyperactivity, anxiety, obsessive-compulsive behaviors, depression, and even psychosis. However, with the complexity of the behavioral phenotype in ASD, it is often difficult to determine the extent to which a given behavior is indicative of a separate psychiatric diagnosis or simply a manifestation of the autism. This phenomenon of comorbidity is of interest to

researchers because it may indicate important neuroanatomical, neurochemical, or genetic overlaps between the ASDs and these other disorders.

Probably the most commonly recognized co-occurring symptom complex is that of attentional deficits and hyperactivity. By definition according to the DSM-IV, an ASD is an exclusionary criterion for making an attention deficit hyperactivity disorder (ADHD) diagnosis. However, studies have found that the symptomatology that would qualify for diagnosis is present in approximately one third of ASD individuals (Goldstein and Schwebach, 2004).

There are many studies showing a higher prevalence of depression in individuals with ASD (for review, see Ghaziuddin et al., 2002). Depression might be more common in higher functioning patients (Ghaziuddin et al., 1998). Although this area of research is more controversial, there is also some evidence that there is an increased risk of bipolar disorder in individuals with ASD as well (Stahlberg et al., 2004; Wozniak et al., Kim et al., 1997)

Anxiety (Muris et al., 1998), obsessive-compulsive symptoms (Russell et al., 2005), and even Tourette syndrome (Baron-Cohen et al., 1999) are also present in individuals with ASD. Schizophrenia has been reported in autism, but rates are extremely variable (Volkmar and Cohen, 1991; Konstantareas and Hewitt, 2001). Formal thought disorder has also been shown in individuals with autism at higher rates than those with other psychiatric diagnoses (van der Gaag, Caplan, van Engeland, Loman, and Buitelaar, 2005).

Developmental Trajectories

There are a number of trajectories of development that are associated with ASDs. Most parents of children with ASD, with hindsight, describe ways in which their children's development was not quite right prior to 18 months (Rogers and DiLalla, 1990). Analyses of videotapes from the first year of life of children who were later diagnosed with autism revealed differences from typical children in response to name and in a number of different sensory behaviors even then. Differences between children later diagnosed with autism and children with other developmental disorders have been found but are less clear (Baranek, 1999; Osterling and Dawson, 1994). For example, difficulties with gaze were found to be more common in very young children who were later shown to have a developmental delay and not autism than those who received autism diagnoses. Before 12 months of age, differences between children with autism and those with typical development tend to be subtle and not clearly discriminative, whereas differences in social responsiveness are much clearer at or after age 1 (Zwaigenbaum et al., 2005).

About one quarter to one third of children with ASD experience a clear loss of social and communication skills in the second year of life (Lord et al., 2004). Most often these children had already begun to fall behind in subtle ways before the regression. However, compared to children with ASD without losses, they had more frequent and more sophisticated social and communication behaviors until the time of regression, at which point they usually stopped talking and lost some if not all skills such as waving, playing peek-a-boo, and imitating sounds (Luyster et al., 2005). Children with ASDs who have had regressions do not seem to represent a

discrete subgroup within ASD in terms of later symptoms or outcomes, but do show slightly lower verbal IQ scores, more gastrointestinal symptoms, and a more frequent family history of autoimmune disorders, compared to ASD children without regression (Richler et al., in press; Molloy et al., in press). As mentioned previously, regression is also a core feature of the developmental trajectory of Rett syndrome and CDD.

Prognoses for ASD

Prognoses for ASD are quite variable, though children with severe autism in early childhood seldom fall outside the spectrum of autism-related disorders as older children and adults (Lord et al., in press). Nevertheless, it is quite common for specific behavioral characteristics to change in many ways, including variation over time in the number and extent of repetitive behaviors (Moore and Goodson, 2003; Bishop and Norbury, 2002) and changes from social withdrawal or passivity to more active but odd interactions (Wing, 2005). Most children with early diagnoses of autism will not be completely independent as adults; many will need support in employment and residential living (Howlin, 2000). Nevertheless, a significant minority, especially of cases with less clear manifestations of the disorder in early years and with fluent language by age 5, will be able to take responsibility for many of their activities of daily living and will complete high school and even postgraduate education (Szatmari et al., 2003).

The number of adults with autism who can drive, live on their own, and hold some kind of partially supported or independent employment has grown significantly in the last 10 years (Howlin et al., 2004). Social motivation and social skills frequently, though not always, improve in later childhood and adolescence and early adulthood. Nonverbal intelligence scores in the early years, particularly if a good assessment of early language skills is not available, are predictors of later prognosis, as are repetitive behaviors and the severity of social–communication deficits as measured through parent report or direct observation in younger children (Howlin et al., 2004; Lord et al., in press). Comorbid depression and generalized anxiety disorder become increasingly frequent as children with ASD enter adolescence and adulthood (Ghaziuddin and Greden, 1998). Szatmari and colleagues (2003) have suggested that overall functioning for individuals with ASDs is best characterized by two factors: one that describes the severity of autism-specific difficulties in social and repetitive behaviors, and the other that describes general level of functioning, including receptive and expressive language, nonverbal intelligence and adaptive skills, as well as the presence of comorbid disorders (Mahoney et al., 1998).

As discussed in Chapter 2 of this volume, both CDD and Rett syndrome are very rare and are associated with more uniformly poor prognoses than autism and other ASDs. For many years, there have been case reports of individuals with autism who have marked deterioration in behavior and sometimes in other skills during adolescence (Rutter et al., 1994), but this is rarely reported in follow-up studies.

RELATIONSHIP TO DISORDERS WITH KNOWN ETIOLOGY

Because autism is a clinical syndrome, it can and does coexist with other medical disorders. Current estimates are that 10 to 15% of ASD cases may be etiologically related to some known neurological or genetic disorder (Barton and Volkmar, 1998; Rutter et al., 1994) and 3 to 9% are thought to have detectable cytogenetic abnormalities (Fombonne et al., 1997; Wassink et al., 2001). Studying syndromes with high prevalence of autism may provide clues into the neuropathological and genetic underpinnings of autism spectrum disorders.

Neurogenetic Syndromes

The most well-known associated medical conditions are Fragile X (FRAX) and tuberous sclerosis complex (TSC). A high percentage of patients with both of these disorders will show autistic features; although the occurrence of these disorders in samples ascertained for ASD is relatively small. Autism has been reported in up to 44% of patients with Fragile X syndrome (Philofksy et al., 2004), but fewer than 5% of autism patients have Fragile X (Bailey et al., 1993; Brown et al., 2002; Klauck et al., 1997; Piven et al., 1991; Wassink et al., 2001). Similarly, autism has been reported in 17 to 61% of individuals with TSC (Curatolo et al., 2004) but fewer than 3% of individuals with autism actually have TSC (Gillberg et al., 1994; Smalley, 1998) although this may be higher (8 to 14%) in autism patients with epilepsy (Smalley, 1998).

Two preliminary screening studies suggested that MECP2 mutation rates (the mutation associated with Rett syndrome) may be as high as 3 to 5% in female autism samples (Carney et al., 2003; Lam et al., 2000) although other studies have not found the mutation (Lobo-Menendez et al., 2003; Vourc'h et al., 2001).

A more recently described syndrome involving a maternally derived duplication of chromosome 15q overlapping the region deleted in Prader-Willi and Angelman syndromes has been reported to occur in 1 to 3% of autism cases (Cook et al., 1998; Cook et al., 1997; Schroer et al., 1998; Weidmer-Mikhail et al., 1998; Wolpert et al., 2000). Although these children frequently meet diagnostic criteria for ASD, they also exhibit significant cognitive impairment, gross motor delays, hypotonia, epilepsy, and facial dysmorphisms (C. Schanen, personal communication).

There are also case reports and small case series of autism co-occurring with many other genetic disorders including neurofibromatosis (Gillberg and Forsell, 1984; Williams and Hersh, 1998), hypomelanosis of Ito (Zappella, 1993), Moebius syndrome (Gillberg and Steffenburg, 1989), Prader-Willi and Angelman syndromes (Steffenburg et al., 1996), Joubert syndrome (Ozonoff et al., 1999), Down syndrome (Fombonne et al., 1997; Kent et al., 1999), Williams syndrome (Reiss et al., 1985), Sotos syndrome (Morrow et al., 1990), muscular dystrophy (Komoto et al., 1984; Zwaigenbaum and Tarnopolsky, 2003), Cowden syndrome (Goffin et al., 2001), phenylketonuria (PKU; Baieli et al., 2003); Smith–Lemli–Opitz syndrome (SLO; Tierney et al., 2001). Autistic symptomatology has also been reported in association with chromosomal anomalies (deletions, translocations, and duplications) on the sex

chromosomes and almost every autosome (see Gillberg; 1998, Lauritsen et al., 1999; Miles et al., 2005; and also Chapter 3 of this volume for reviews).

These associations can be important for a variety of reasons: single gene disorders and anomalies may point to autism susceptibility genes; many genetic disorders have implications for genetic counseling in the families; knowledge of the comorbid condition may influence prognosis; and rarely, as in the case of the metabolic disorders, they point to a treatment that could impact the course of the autistic symptomatology.

DIAGNOSIS AND ASSESSMENT

An experienced clinician, using standardized methods, can reliably diagnose autism starting at age 2, and sometimes even younger. However, diagnoses, especially of PDDNOS and atypical autism, at age 2 are significantly less stable than they will be at age three. Most children with less certain diagnoses at 2 will go on to have more obvious autistic features, including repetitive behaviors by age 3, but a significant minority seem to truly "grow out of ASD," and another group may remain just in or outside ASD for many years, as measured by standard instruments or judged by experienced clinicians (Bishop and Norbury, 2002; Lord et al., in press).

It has been common wisdom that the symptoms of autism are most clearly recognizable between about 4 and 5 years (Le Couter et al., 1989), but it is not clear if this is still the case when many children, at least in North America and Western Europe, receive diagnoses and begin intervention several years before this. In general, the few intervention studies indicating "recovery" from autism in a significant number of cases have not been replicated (see Dawson and Osterling, 1997; Rogers, 2000). More typical have been gains in IQ, made primarily by the children with the highest IQs at the start (Smith, 1999; Sheinkopf and Siegel, 1998). Specific behavioral interventions have been shown to result in clear improvements in specific behaviors (e.g., Goldstein, 2002; Stahmer et al., 2003; Lord and McGee, 2001), but to date there have not been sufficiently well-controlled studies of comprehensive interventions to compare their effectiveness, determine the "active ingredients" in the treatments that account for improvements, or to look at individual differences in responses to behavioral treatments (see Tsai, 1999 and McDougle, 1997 for a discussion of psychopharmacological treatments).

Less classic cases of ASD tend to receive later diagnoses than children with autism (Szatmari et al., 1989). This may not reflect later onset of symptoms as much as delayed recognition that the child has core social communication deficits. Many of these children receive other psychiatric diagnoses such as ADHD or oppositional behavior or emotional disturbance either in preschool or the early school years. Although these children experience considerable difficulty in social situations and in school, their fluent language and sometimes their socially directed but odd behavior confuse diagnosticians and clinicians. From a developmental perspective, their early experiences may be very different from a more cognitively impaired child with autism. The more able child with ASD today will have had much greater opportunities for learning in ordinary school and through exposure to same-age peers and age-appropriate expectations than most children with autism in the past.

However, they also may have been teased and rejected in ways that a child with autism in specialized educational settings and who is less aware of social feedback would not have experienced. Even now, despite improved awareness and recognition of ASDs, there are some individuals who do not receive an ASD diagnosis until their teenage or even adult years. Usually these individuals were identified as having other disorders such as ADHD or anxiety disorders as children, but because of relatively strong verbal skills, the possibility of ASD was never raised.

Standardized Diagnoses

One of the major changes in the field of ASD in the last 20 years has been international adoption of standard measures used for assignment of diagnostic status. These include a caregiver interview, the Autism Diagnostic Interview-Revised (ADI-R: Le Couteur et al., 2003), which provides information about social reciprocity, communication and repetitive behaviors and interests both currently and in the past, and the Autism Diagnostic Observation Schedule (ADOS: Lord et al., 1999), which offers structured observation in standardized contexts, and codings of social and communicative behavior, carried out by a clinician in a 30- to 45-minute office visit (Lord et al., 2000).

The ADOS and ADI-R both use additive models within the three domains (social reciprocity, communication, and repetitive behaviors) to create a diagnostic algorithm. The ADI-R was intended to distinguish between autism and nonspectrum disorders, though recently an algorithm for atypical autism and PDDNOS has been proposed (Risi et al., submitted). Different cutoffs are used in the communication domain for verbal and nonverbal individuals so that these scores must be considered separately.

The ADOS is a structured observation that consists of four modules with different sets of materials, tasks, and algorithms. Use of a specific module is determined by the child's or adult's expressive language level and chronological age. Algorithms offer classifications of autism or ASD, though many children with clinical diagnoses of ASD will fall in the autism range and *vice versa*. Neither the ADI-R or ADOS is intended to be used as a simple measure of severity because codes for individual items are ordinal and do not represent equal intervals. Traditionally, scores on both instruments are related in nonlinear ways to chronological age and IQ. Nevertheless, in samples of individuals with ASD who fall within relatively narrow age and IQ ranges, ADOS scores have been shown to be related to several neurobiological features (see Chapter 15 of this volume), including eye-tracking and activation of the fusiform gyrus during face processing (Klin et al., 2002; Schultz et al., 2000).

When used together, the ADI-R and ADOS offer sensitivity of 82% and specificity of 86% for autism and 60% sensitivity and 88% specificity for non-autism ASD in children from age 4 through 12, excluding children with profound mental retardation. Using the ADI-R and ADOS, better sensitivity for children who had ASD but did not meet criteria for autism could only be achieved if specificity was sacrificed. It seems likely that a combination of direct observation by a clinician and a caregiver interview results in the most reliable diagnoses (Risi et al., submitted).

Because of the required training and the length of time involved in the administration of the ADI-R, there have been attempts at using alternative instruments. However, replacing the ADI-R with the Social Communication Questionnaire (SCQ; see Rutter et al., 2003), a parent screening questionnaire developed using questions from an earlier form of the ADI-R, resulted in significantly less sensitivity than using the full interview (Corsello et al., submitted). It may be that other combinations of parent report and clinician observation based instruments including the Social Responsiveness Scale (SRS: Constantino et al., 2000), the Communicative Competence Checklist (CCC: Bishop, 2003), and even the Vineland Adaptive Behavior Scales (VABS: Sparrow et al., 2005), may work equally well and be more efficient than the current system; however, these have not yet been well researched. It should also be noted that with briefer scales, opportunities for more detailed phenotypic analyses may be limited or less focused on the core features of autism.

SUMMARY AND CONCLUSIONS

Altogether, autism spectrum disorders are one of the most reliably diagnosable of childhood onset psychiatric disorders (Volkmar and Rutter, 1995). They are of interest to neuroscientists on many levels, from the quest to find effective treatments or methods of prevention to the search for biological bases of social behavior and early communication. Despite the reliability of the diagnosis, there is still remarkable heterogeneity in clinical presentation. As yet, there are no pathognomonic signs, symptoms, or biomarkers that are universal or specific to autism. Poor social use of eye contact is probably the most frequently identified single behavior in ASD, and it is not always present, nor does it only occur in individuals with ASD. Because there seem likely to be a number of neurobiological pathways leading to ASD, there has been interest in identifying more homogeneous subtypes that may be associated with genetic or other patterns. This approach is far less straightforward than one might think because of the interrelatedness of various aspects of the disorder — for example: mental retardation, language level, social skills, ordinary maturity, and experience. Studies of very young children offer the purest opportunity to observe the disorder "unfolding," but are limited by the kind of neurobiological and specific cognitive measures appropriate at young ages. Studies of siblings of children with autism offer the opportunity to identify children at younger ages and earlier points in development but may not be representative of other children with ASDs (Szatmari et al., 2000).

Adaptations of neuropsychological measures, such as eye tracking and event-related potentials (ERPs) (see Chapter 17 of this volume), are also a potential source of information. Older, higher functioning children and adults are more easily studied using traditional neuropsychological and neurophysiological measures, but are more complicated diagnostically. These measures in older children and adults also seem more likely to have been affected by different life experiences in terms of time and quality of social interactions than they would be in very young children (Schultz et al., 2000). Thus, interpreting what is the cause or the result of unusual behaviors and preferences becomes more difficult to assess. Larger samples are now available, allowing researchers to look more closely at individual differences in phenotype and to provide more specific conceptualizations of the nature of social deficits and repetitive

behaviors and interests. Developing psychometrically valid continuous measures of severity in ASD that are not confounded by age and IQ will also provide the opportunity for more interesting studies of links between genotype and phenotype.

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