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Autism and Related Disorders

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Abstract

The Pervasive Developmental Disorders are a group of neurodevelopmental disorders that include Autistic Disorder, Asperger's Disorder, Pervasive Developmental Disorder - Not Otherwise Specified (PDD-NOS), Childhood Disintegrative Disorder (CDD), and Rett's Disorder. All feature childhood onset with a constellation of symptoms spanning social interaction and communication and including atypical behavior patterns. The first three disorders (Autistic Disorder, Asperger's Disorder, and PDD-NOS) are currently referred to as Autism Spectrum Disorders, reflecting divergent phenotypic and etiologic characteristics compared to Rett's Disorder and CDD. This chapter reviews relevant research and clinical information relevant to appropriate medical diagnosis and treatment.

Keywords

Autistic Disorder; Autism; Asperger's Disorder; Rett's Disorder; Childhood Disintegrative Disorder; Pervasive Developmental Disorder – Not Otherwise Specified

Autism and the pervasive developmental disorders (PDDs) are conditions characterized by significant difficulties in social interaction, communication and unusual behaviors. These conditions and their features are summarized in Table 1. More recently, a subgroup of these disorders, Autistic Disorder, Asperger's Disorder, and Pervasive Developmental Disorder – Not Otherwise Specified, have been referred to as , also referred to as Autism Spectrum Disorders (ASDs). Of these conditions, autistic disorder has been the most extensively studied.

1. Diagnostic Concept

1.1. History

Infantile Autism was first described in 1943 by Leo Kanner (Kanner, 1943). He reported on 11 children who exhibited an inability to relate to others from very early in life but who were overly concerned with change in the non-social environment. Many of the children never talked. Those who did had language that was unusual in various ways, such as echolalia, pronoun reversal, idiosyncratic language, and difficulties with social language. Kanner also observed atypical behaviors, including ostensibly purposeful repetitive motor movements like hand flapping or body rocking). For some time after Kanner's initial description, autism was thought to be an early onset form of schizophrenia. In the 1970s, several converging lines of data suggested that autism was a brain based disorder with a strong genetic component.

The year following Kanner's report, Hans Asperger published a paper in German about a cohort of children with good verbal skills but major problems in social interaction and motor function (Asperger, 1944). They exhibited highly developed circumscribed interests that interfered with acquisition of other skills. Fathers often had similar problems. He used the word autism in describing this condition, unaware of Kanner's work the previous year. The condition received little attention in the English literature until an influential review by Wing introduced the concept to a broader audience (Wing, 1981).

Two of the presently recognized PDDs are associated with significant regression in skills. In Rett's disorder birth and early development are normal but head growth slows and development then deteriorates (VanAcker et al., 2005). Unusual hand washing stereotyped mannerisms develop and purposeful hand movements are lost. Rett initially believed the condition might be a form of autism, but social difficulties become much less prominent as children, almost all girls, enter the school years. The disorder is now known to be due to a defect in the MECP-2 gene. In Childhood Disintegrative disorder, early development, through (at least) the first 24 months, is normal. A period of relatively acute regression then occurs with onset of a clinical picture similar to that seen in autism (Volkmar et al., 2005). The condition, first described in 1908, is rare and was referred to as disintegrative psychosis in the past. Extensive medical investigations have failed to reveal a specific common etiology. Unlike progressive neuropathological processes, the child loses skills but stabilizes with no further deterioration or progress. The outcome is considered worse than for autism.

The most common, and somewhat paradoxically least studied, of the PDDs is the 'subthreshold' form (PDD-NOS, or atypical autism). In these cases, some features suggestive of autism are present but full criteria for autism or another specified PDD condition are not met (Towbin, 2005). Interest in this diagnostic construct has grown with awareness of the relevance of genetic factors to autism and the 'broader autism phenotype' (Piven et al., 1997).

1.2. Diagnostic Criteria

Criteria for Autistic Disorder, as used in the International Classification of Diseases and Related Health Problems (ICD-10 (World Health Organization, 1992), are provided in Table 2. These are essentially the same as in the Diagnostic and Statistical Manual of Mental Disorders – Text Revision (DSM-IV-TR (American Psychiatric Association, 2000). Problems focus upon in the traditional "triad" of impairments in social development, communication/play, and restricted interests and repetitive behaviors, with the social features weighted most heavily. This definition, based on the results of a large, international field trial, has been shown to have a good balance of sensitivity and specificity across the IQ range and to increase the diagnostic reliability of less experienced clinicians (Volkmar et al., 1994).

For Asperger's disorder, the social and atypical behavior criteria are met without clinically significant language delay; these criteria have been criticized as insufficiently precise, and as a result the diagnosis remains somewhat controversial (Miller and Ozonoff, 1997; Woodbury-Smith et al., 2005). For PDD-NOS, social criteria with additional symptoms in communication *or* repetitive behaviours *or* in both but of reduced severity. For CDD a period of two years normal development is required before clinically significant loss of skills in multiple areas (e.g., social, communication, play, motor, toileting skills) and the onset of characteristic autism symptoms (Volkmar, Koenig, and State, 2005). For Rett's disorder early development is normal followed by a period of decelerated head growth, loss of purposeful hand movement, poor trunk stability and gait problems, and impaired language and psychomotor retardation. These features develop between 5 and 48 months;

social engagement is most impaired in younger children but gains in this area are made later (Van Acker et al., 2005).

1.3. Clinical Features

The onset of autism is definitively before age 3 years; in most cases parents are worried in the first year of life (Volkmar et al., 1994). Occasionally a period of normal or near normal development is noted, although there is some evidence suggesting that marked regression in the absence of prior indications of atypical development is relatively uncommon. The social problems of children with autism are severe and persistent. Some children with autism never talk and those who do often have speech remarkable for echoed language (echolalia), problems with pronouns and social language use, idiosyncratic use of words, and marked problems with prosody and speech modulation (Paul and Wilson, 2009). Stereotyped behaviors and unusual responses to the environment are frequent and can interfere with provision of educational programs. Cognitive abilities are typically very scattered with areas of strength in nonverbal skills. Approximately 10 percent of individuals with autism display islets of unusual ability, or savant skills. These abilities significantly exceed overall intellectual ability of the affected individual and, more generally, of the typical range of skill. Examples of common domains of savant skills include musicianship, drawing ability, extraordinary memory, or calendrical calculation, i.e. the ability to name days of the week corresponding to dates (Hermelin, 2001). The neural basis of these special skills is incompletely understood, but acquired savant skills in non-autistic individuals have been associated with damage to left fronto-temporal regions. Like the broader syndrome of ASD, savant skills have been theoretically linked to decreased long range connectivity and enhanced local connectivity (Hughes, 2010). Many individuals with autism display outstanding facility in decoding letters and numbers, or *hyperlexia* (Newman et al. 2006).

In Asperger's disorder, overt verbal skills are preserved, though communication, especially the social facets, is often affected. Asperger referred to these children as "little professors," noting a characteristic pedantic style and a tendency to fixate on topics of special interest (Klin, Pauls et al., 2005). Gross motor and fine motor delays are frequently noted. In contrast to autism, verbal cognitive skills are often an area of strength, and the individual may exhibit the profile of nonverbal learning disability (Volkmar and Klin, 1998). As per Asperger's original impression, some studies have observed recurrence risk in family members higher than that in autism (Klin, Pauls et al., 2005).

In Rett's disorder the development of the clinical picture described above typically takes place in the first years of life. Psychomotor retardation is severe, as are movement problems, and seizures are frequent. In CDD the onset of the condition may be heralded by a period of nonspecific agitation or anxiety. Once the condition has had its onset subsequent gains tend to be minimal.

In PDD-NOS the clinical presentation is highly variable. Given the nature of the 'subthreshold' definition it is not surprising that various attempts have been made to identify potential subtypes, subgroups, e.g., those in which either attentional or affective symptoms are more prominent (Towbin, 2005). Advances in genetics may help to clarify issues of subtypes in relation to specific genes that contribute to autism (Gupta and State, 2007).

1.4. Differential Diagnosis

Autism and related conditions must be differentiated from each other as well as from other developmental disorders. Both history and clinical examination are helpful in this process. Features relevant to differential diagnosis within this group of conditions are presented in Table 1. In intellectual deficiency/mental retardation not associated with autism, social and

communication problems are typically impaired on par with overall cognitive level; in contrast, children with ASD display social skills lagging behind their overall developmental level. Children with language disorders typically have preserved social skills and attempt to communicate using compensatory strategies, rather than the dramatically reduced communication characteristic of autism. Children who are blind and deaf may show some behaviors suggestive of autism (e.g., stereotyped movements) without the broader constellation of impairments associated with autism.

2. Epidemiology

2.1. Prevalence and incidence

In the recent past, autism was considered a relatively rare disorder with a prevalence rate of 4.5 in 10,000 individuals (Lotter, 1966). More recent studies have provided successively higher prevalence rates. A thorough review conducted in 2005 estimated the prevalence of autism spectrum disorders to be 60 per 10,000 (Fombonne, 2005). The Center for Disease Control reported a prevalence rate of 1 in 150 children in 2007 (Autism and Developmental Disabilities Monitoring Network Principal Investigators, 2007) and 1 in 110 in 2009 (Autism and Developmental Disabilities Monitoring Network 2006 Principal Investigators, 2009). A recent and highly publicized study reported a rate of 1 in 90, but this estimate was based on unverified parent report in the context of a phone interview (Kogan et al., 2009). Despite this observed increase in prevalence and public outcry regarding an autism “epidemic”, it remains unclear that rising prevalence reflects more cases of the disorder rather than increased diagnosis of a consistent base rate in the population. Factors speculated to contribute to this increase in prevalence include increased awareness, more accurate recognition of higher- and lower-functioning ends of the autism spectrum, diagnostic substitution, and the influence of cultural and politico-legal factors, such as public perception and access to services (King and Bearman, 2009).

2.2. Gender

ASDs occur more frequently in boys than girls. This ratio has traditionally been estimated at 3-4:1 ratio, though recent studies have reported ranges both more and less pronounced (Fombonne, 2005; Autism and Developmental Disabilities Monitoring Network Principal Investigators, 2007; Autism and Developmental Disabilities Monitoring Network 2006 Principal Investigators, 2009). Intellectual functioning interacts with gender such that, among higher functioning individuals the ratio of boys: girls is higher (~6:1) than in lower functioning samples (~1.5:1). Asperger’s disorder tends to have an even more pronounced gender bias of 9 to 1 (Fombonne and Tidmarsh, 2003).

2.3. Culture and socioeconomic status

Kanner’s initial impression that autism occurs at a higher frequency among children of higher socioeconomic status has not been supported by subsequent research. Prevalence does not vary across racial and socioeconomic groups (Yeargin-Allsopp et al., 2003), though parents of higher socioeconomic status and with greater pecuniary resources may more effectively obtain diagnostic evaluations and thus be reflected disproportionately in community samples (Autism and Developmental Disabilities Monitoring Network 2006 Principal Investigators, 2009). Increased public awareness, through governmental and private initiatives, and greater insurance coverage for autism-related clinical services facilitate recognition and service provision for children from diverse socioeconomic backgrounds.

3. Etiology and pathophysiology

3.1. Genetic and Environmental factors

Though genetic contributions were mentioned in original accounts of ASDs, subsequent theories of the causes focused on parenting, specifically suggesting that emotionally aloof “refrigerator” mothers caused children to retreat from the social world. In the 1970s, mounting evidence indicating genetic and biological factors led to the justified rejection of speculation regarding a psychogenic etiology. Autism spectrum disorders are currently recognized to be the most heritable of childhood psychiatric disorders, with shared genetic mechanisms common to all ASDs (Frith, 2004). The initial approach to genetic analysis of autism focused on comparison of concordance rates among monozygotic and dizygotic twins. These studies and a number of follow-up studies indicated significantly higher concordance rates for both ASD and a broader autism phenotype (e.g., language or social difficulties without meeting clinical criteria for ASD) in monozygotic compared to dizygotic sibling pairs (Bailey et al., 1995). Evidence for a genetic contribution also comes from recurrence in siblings of children with ASD much higher than the general prevalence (Jones and Szatmari, 1988; Ritvo et al., 1989). Though much attention has been devoted to the genetics of ASD in the 30 years following initial twin studies, a clear genetic etiology has not emerged; heritability is inferred to be complex, with multiple genes involved in assumedly diverse genetic pathways culminating in the disorder (Risch et al., 1999). Despite the lack of a clear or universal genetic mechanism, research has revealed specific genetic causes for isolated cases as well as a number of candidate genes and chromosomal regions indicated as relevant across multiple studies, including 2q, 7q, 15q, 17q, 11 (Freitag, 2007; Szatmari et al., 2007; Gupta and State, 2007).

Because concordance among monozygotic twins is not 100 percent, environmental or experiential factors are presumed to contribute to the development of ASD. Obstetric and pre- and peri-natal complications have been explored, but no consistent correlate has emerged; moreover, increased observation of such difficulties may reflect a consequence, rather than cause of the condition. Immunological factors (e.g., fetal vulnerability to maternal antibodies) and viral infections during pregnancy have been explored without a clear connection emerging. Vaccines have recently received public scrutiny as a cause of autism, both in terms of mercury-based chemicals used as preservatives or the weakened virus itself. Extensive epidemiologic research suggests the absence of a correlation between vaccine administration and development of ASD (DeStefano, 2002). A major thrust of current research is to understand interactions among genetic or metabolic vulnerabilities, such as mitochondrial dysfunction, and environmental factors.

3.2 Psychological theories of ASD

Two prevailing classes of theories attribute autistic impairments to (a) core impairment in social functioning and dysfunction in corresponding brain systems (Dawson et al., 2005) and (b) dysfunctional processing of information that is complex or requires perception or manipulation at the gestalt level. Social accounts of ASD posit that specific human brain systems exist to process information pertaining to other humans (Brothers, 1990), and autistic dysfunction originates in these brain systems, exerting secondary, peripheral impacts through developmental effects. For example, the social motivation hypothesis posits that that reduced social drive leads to inattention to people and consequent failure of developmental specialization in experience-driven brain systems, such as the face perception system (Dawson, Webb, and McPartland, 2005). Within the class of social brain theories, the “theory of mind” account suggests specific difficulty with attribution of mental states to others; a criticism of this conceptualization has been that it fails to account for the earliest emerging and most developmentally basic symptoms of ASD.

Interconnectivity theories of ASD have taken several forms. The “weak central coherence” account posits a lack of a central drive for coherence, with the consequent focus on dissociated fragments rather than integrated “wholes”, leading to a fragmentary and overly concrete experience of the world. Another hypothesis posits deficits in “executive functioning”, i.e., in the capacity to abstract rules, inhibit irrelevant responses, shift attention, and, generally speaking, to “multitask.” A commonality among these theories is that, in contrast to social information processing theories, they generally cite non-specific brain processes in which the nature of the information processed is relevant only insofar as it requires distributed brain function (Horwitz et al., 1988; Just et al., 2004). For example, it has been posited that, due to poor long range connectivity, simple, local processing is intact while complex, distributed information processing is impaired in ASD (Minshew and Williams, 2007). Because social interaction tends to be complex, these theories suggest that it is particularly vulnerable to disruption.

3.3 Neurobiological accounts

ASDs are recognized to be brain-based neurodevelopmental disorders, with differences emerging early in childhood. However, as is the case for genes, no universal neuro-functional or neuroanatomical abnormality has been discovered; as is also the case for genes, this, in part, likely reflects heterogeneity in etiologic and developmental course. Cytological studies of brain structure have revealed reduced neuronal size and increased cell packing density in the hippocampus, amygdala, mammillary body, anterior cingulate cortex, and septum. Furthermore, decreased numbers of Purkinje cells and granule cells in the cerebellum have been described (Minshew et al., 2005). Multiple structural brain studies have also revealed abnormalities in cerebellar regions, but specific areas affected have varied between studies. Several studies have also indicated reduction in the connective tract of the corpus callosum (Minshew et al., 2005). A combination of early childhood pediatric data and subsequently collected magnetic resonance imaging data suggest that a significant portion of children with ASD exhibit increased atypical development of brain volume, with temporal lobe white matter showing overgrowth during the second year of life despite typical size at birth (Hazlett et al., 2005; Courchesne et al., 2001). Studies of neurochemistry have revealed various atypicalities in individuals with ASD, though elevated blood serotonin levels have been reported with the greatest frequency. Other findings have included abnormal peptide excretion, neuroendocrine/HPA function, amino acid levels, uric acid excretion, and central cholinergic and gabaergic receptors (Anderson and Hoshino, 2005). A current topic of great interest is the role of oxytocin and vasopressin in autistic neuropathology. Because of their role in prosocial behavior and social bonding (Lim and Young 2006), these neuropeptides have long been speculated to be involved in autistic social dysfunction (Modahl et al. 1992). Oxytocin has been shown to increase eye gaze in typical individuals (Guastella, Mitchell, and Dadds 2008), and a recent study found that administration of intranasal oxytocin administration improved emotion recognition in adolescents with ASD (Guastella et al.). Variation in the oxytocin receptor gene has been associated with ASD in some populations (Wermter et al. 2010), but current evidence suggests this is not true for all groups (Tansey et al. 2010).

Functional brain imaging studies have also revealed a variety of atypicalities without an emergent universal pattern. Rates of seizures are increased in children with ASD, and electroencephalographic recordings (EEGs) reveal increased incidence of anomalous EEG in children with ASD, even among those without seizure disorder, most notably among individuals with significant cognitive impairment (Minshew et al., 2005). Following from the aforementioned social brain theories of ASD, numerous functional magnetic resonance imaging and event-related potentials studies of hemodynamic and electrophysiological brain responses suggest anomalous functioning of brain regions subserving the processing of

social information (Dawson, Webb, and McPartland, 2005; Schultz, 2005). Affected brain systems have been posited to include: face perception, linked to the fusiform gyrus (Kanwisher et al., 1997; Puce et al., 1996); biological motion perception, linked to the superior temporal sulcus (Pelphrey et al., 2003); the action-perception system, linked to the inferior frontal gyrus and inferior parietal lobe (Iacoboni et al., 1999; Rizzolatti and Craighero, 2004); perception of emotional states and emotional experience, linked to the amygdala and limbic system (Adolphs et al., 1995; LeDoux, 1994); visual perception of the human body, linked to the extrastriate body area in lateral occipitotemporal cortex (Downing et al., 2001); social reward and reinforcement, linked to the orbitofrontal cortex (Bechara et al., 1994; Cools et al., 2002); and theory of mind, linked to the ventromedial prefrontal cortex (Castelli et al., 2002).

An additional body of research, paralleling psychological theories of impaired processing of complex or global information, has investigated connectivity in the brains of individuals with autism. Several studies have directly measured connectivity through imaging of white matter tracts connecting different brain regions, demonstrating atypical patterns of connective tissue in ASD (Barnea-Goraly et al., 2004; Herbert et al., 2004; Keller et al., 2007); however, most evidence for atypical interconnectivity in ASD has relied on fMRI to examine covariation in activity in distal brain regions. This approach has demonstrated atypical connectivity at rest (Di Martino et al., 2009; Cherkassky et al., 2006) and during a wide range of tasks, including face perception (Bird et al., 2006; Welchew et al., 2005; Koshino et al., 2008; Kleinhans et al., 2008), attribution of mental states during viewing of animations (Kana et al., 2008; Castelli et al., 2002), language processing (Kana et al., 2006; Just et al., 2004), executive function (Koshino et al., 2005; Just et al., 2007), visual-motor action (Mizuno et al., 2006; Turner et al., 2006; Villalobos et al., 2005), and response inhibition (Kana et al., 2007). This body of research reveals inconsistent patterns of results across studies, including underconnectivity, overconnectivity, and typical patterns of connectivity, suggesting that connectivity problems may not be a universal feature of ASD (Kleinhans et al., 2008).

4. Assessment

4.1. Diagnostic assessment

Diagnostic assessment of ASD is made according to clinical assessment of the presence of ICD-10 or DSM-IV-TR criteria. Assessment for ASD should entail both a parent interview and a direct observation of the individual. Parent interview should inquire about social and communicative functioning, especially in the context of peers, and the presence of repetitive and stereotyped behaviors and interests. This should also include a thorough developmental history, emphasizing early social development to confirm stability of symptoms from early childhood forward. Observation should directly assess social and communicative behavior through play- or interview-based methods, also monitoring atypical behaviors (e.g., motor mannerisms, sensory behaviors) or rigid or repetitive interests or behavioral routines. It is helpful to observe a child across structured and unstructured contexts, as high-functioning children with ASD often appear more typical in highly structured or stereotyped interactions, such as greeting routines or standardized testing. The social disability is often most evident when guidance for social behavior is minimized and predictability is reduced. An interview should address peer and romantic relationships, interests and hobbies, recreational activities, insight into the perspective of others (including the impact of one's own behavior on others), comprehension of figurative language, and insight into the nature of social relationships and emotional experiences. Because individuals with ASD may under-report or misperceive status of social relationships, accounts should be verified independently by parents or educators. Given high co-morbidity of anxiety and depression, especially among high-functioning adolescents and adults with ASD, attention should also

be paid to mood symptoms. Assessment of mental health status, including integrity of thought process, is also indicated.

Standardized self-report, parent/teacher report, and direct observation measures have been developed to screen for and diagnose ASDs. Though many are effective for this purpose, none, to-date, reliably distinguish among individual ASDs, such as discriminating Asperger syndrome from Autistic Disorder (Campbell, 2005; Lord and Corsello, 2005). The current “gold standard” diagnostic protocol for autism spectrum disorders consists of a parent interview, the Autism Diagnostic Interview – Revised (Lord et al., 1994), and a semi-structured conversation/play-based interview, the Autism Diagnostic Observation Schedule (Lord et al., 2000). Both instruments require specific training to administer and score reliably. Differential diagnosis among ASDs continues to rely on the judgment of experienced clinicians.

Children thought to be at risk for ASD should be referred for a multidisciplinary assessment by a team with specific experience in the assessment of ASDs (Klin, Saulnier et al., 2005). This practice ensures that complementary disciplines are employed to differentiate ASD from disorders with overlapping symptoms, such as expressive language disorder. Interdisciplinary assessment should entail thorough developmental and health history and include minimally the disciplines of psychology, speech and medicine. Psychological assessment should assess cognitive (or developmental) function, motor control, and adaptive functioning. Assessment of adaptive skills is important to document functional deficits among individuals with intact cognitive function (Klin et al., 2007). Psychological assessment of cognitive or developmental function should be employed to provide a frame of reference for gauging social and communicative function and play to facilitate differential diagnosis of cognitive impairment versus ASD. Speech and language assessment should measure language production, language comprehension, nonverbal communication and gesture (including gaze and joint attention in young children), pragmatic and figurative language, prosody, rhythm, volume, and content of speech (Paul, 2005). In addition to these discipline specific assessments formal diagnostic evaluation should also be included using standardized diagnostic assessments. Depending on the age of the patient and presenting concerns, specialists in the areas of motor function (e.g., occupational or physical therapists), behavior modification, neurology, psychopharmacology, academic preparation, or vocational training should be consulted in the context of the evaluation.

4.2 Additional assessments

Genetic screening for various inherited metabolic disturbances is now considered best practice. Genetic testing should assess for conditions known to be associated with inherited disorders, such as fragile X syndrome, or inherited disorders that may have broader impact on physical health, such as phenylketonuria. Audiological evaluation is indicated to rule out contribution of auditory dysfunction to social and language impairments; brain stem auditory evoked response can be applied for individuals unable to comply with other methods of audiological assessment. Neurologic consultation is appropriate if seizure activity is suspected, if late onset is observed, or if other indications of gross neurological dysfunction or soft signs are observed. EEGs and brain imaging, such as sMRI, are not recommended in all cases as they are neither diagnostic nor prescriptive in most cases; they may, however, be appropriate on a case-by-case basis if other factors suggest brain dysfunction beyond that associated with ASD (Minshew et al., 2005).

5. Treatment and intervention

5.1. Treatment objectives

Difficulties in social interaction and communication represent major challenges for effective learning (National Research, 2001). Recent studies using eye tracking methods suggest that as much as 90 percent of social-affective information is lost to the developing child with attendant problems in areas such as joint attention, selective attention, and other skills important for successful learning (Klin et al., 2002). Likely as a consequence of this lack of social engagement and difficulties learning, numerous problem behaviors develop that pose further challenges for effective learning. Essentially the goals for treatment of the child with autism or a related disorder are to minimize, as much as possible, those effects of autism which negatively impact learning and, to the extent possible, support normative developmental processes and learning skills (NRC, 2001). Goals for the individual child should be based on that child's individual pattern of strengths and weaknesses. A mandate, in the U.S. and other countries, for universal childhood education marked a major shift in service provision for this population.

5.2. Psycho-Educational Approaches

Children with autism and related conditions typically need intensive, well structured educational services. A series of model service delivery programs have been developed (see NRC, 2001 for a review). Most of these adopt a teaching approach based in principles of applied behavior analysis although other programs are more eclectic or more developmentally based. Data suggest that early, sustained intervention is most effective. Children with significant cognitive impairment or behavioral difficulties present the greatest challenges for programs and typically need a highly structured classroom setting with much individual attention. As children make gains, mainstream settings become more important and peers can be important models for learning and behavior change. Services of many different specialists including special educators, psychologists, speech therapists, and occupational or physical therapists are often needed. Because of the prognostic importance of language-communication skills, this is typically an area of attention with a focus on social and functional communication in addition to basic language, such as vocabulary (Paul, 2005). For children with no spoken language, augmentative systems or assistive technologies may be indicated (Mirenda, 2008). Explicit teaching of social skills with extrinsic reinforcement is required, as children with ASD tend not to acquire these abilities through imitation or observation (Kransny et al., 2003). Behavioral interventions address problem behaviors and help children profit from intervention programs (Powers, 2005); these can be effective for addressing maladaptive behaviors in home, academic, and community settings. In the past, insight oriented psychotherapy was frequently utilized for more able individuals, but, presently, more emphasis is placed on counseling and problem-focused therapies from cognitive-behavioral perspectives (Volkmar and Wiesner, 2009).

5.3. Pharmacological interventions

Drug treatments can help decrease problem behaviors such as self-injury, aggression, repetitive -stereotyped movements, and irritability-overactivity (Scahill and Martin, 2005). The core aspects of the condition (social-communication problems) have not proven to be drug responsive. Since individuals are often enrolled in behaviorally-based programs behavioral data can frequently be obtained and used to assist in monitoring drug response. As with any medication, use must balance risk and side effects, e.g. sedation or weight gain. The major tranquilizers (neuroleptics) have been most extensively studied and an elegant double-blind, placebo control study by the RUPP group demonstrated significant benefit of the atypical neuroleptic, risperidone, within two weeks (McCracken et al., 2002). Although frequently prescribed, the efficacy of other classes of medicine, e.g., the SSRIs has been

more controversial. These agents have many potential theoretical benefits but appear to work better in adolescents and adults as compared to children. (King et al., 2009). The stimulant medications may help with attentional issues although rates of side effects are relatively high and may lead to treatment discontinuation (Jahromi et al., 2009). Various other agents have been studied with limited empirical support. These include naltrexone, mood stabilizers, and beta blockers. For individuals with Asperger's disorder and, perhaps, higher functioning autism there appears to be a significant increase in risk of depression in adolescence and young adulthood, and it is important for the clinician to be alert to this potential. (Volkmar and Wiesner, 2009)

A host of alternative treatments are frequently used. These include various diets and vitamin therapies. Various somatic treatments have not proven particularly useful. While most alternative and complementary medicine treatments have relatively little risk others, such as chelating agents, have significantly increased risk including death (Jacobson et al., 2005).

5.4. Developmental Course

The diagnosis of autism and related disorders in infants and young children is an area of active investigation (Chawarska et al., 2008). Not all required diagnostic features may be present until around age 3 (often the repetitive behaviors are last to develop). Children with Asperger's disorder usually do not come to attention until enrolled in preschool due to their preserved language and relative proficiency with adults. Children with autism and related conditions frequently make major developmental gains in the elementary school years particularly if they had received early and intensive interventions. Behavior problems may also increase during this time (Loveland and Tunali-Kotoski, 2005). In adolescents some individuals make major gains while others lose skills; the latter pattern may be associated with the onset of seizure disorder (Shea and Mesibov, 2005). A progression in social skills development has been noted by Wing (Wing, 1997) with children moving from a more aloof and disinterested to a passive and finally to a more eccentric, one-sided social style.

5.5. Prognosis

ASDs tend to be life-long conditions. Most optimal outcomes involve adults who lead happy, fulfilling lives and maintain gainful employment despite eccentricities or socially oddities. The prognosis of the condition appears to be improving for ASD, with perhaps 15 percent or more of cases now able to achieve adult independence and self-sufficiency. Early and intensive intervention and mandates for school service appear to be involved in improved overall prognosis (Howlin, 2005). Planning for adulthood should begin in adolescence with consideration of capacities for independent living and vocational skills. Factors predicting long-term outcome in autism include nonverbal cognitive ability in the normal range, the presence of some functional language by age 5, and adaptive skills.

For Asperger's disorder and PDD-NOS the prognosis is even better than for autism although there is increased risk for other mental health problems including depression and anxiety disorders. (Towbin, 2005; Klin, McPartland et al., 2005). For Rett's and CDD the outcome is poor (Volkmar et al., 2005; VanAcker, Loncola, and Acker, 2005).

6. Future developments in treatment and research

Evident in the research reviewed above, the field has made great strides in elucidating the underpinnings of autism and related conditions since study commenced less than 70 years ago. Recent advances have resulted in increased recognition and earlier detection and intervention enabling enrollment of children into empirically-validated interventions. An increasing array of therapies exists, recently including medications specifically approved for ASD. Despite extensive research into brain and genetic mechanisms, specific etiologies for

ASD remain elusive. Likewise, the interaction between these intrinsic factors and environmental influences remains unclear. In both cases, this likely reflects a relatively crude diagnostic method reliant upon observed behavior and probable conflation of distinct disorders with variable etiologies despite grossly similar phenotypes. Researchers are applying increasingly comprehensive genetics assays and more sophisticated brain imaging methods, enabling examination of time course and connectivity among brain regions in terms of both brain structure and functional activity. These methods are being applied in a complementary fashion to examine gene-brain-behavior relationships and to examine responsiveness to intervention which, in turn, may result in more effective matching of intervention strategies with individuals. Given these factors, it is likely that the observed improvements in quality of life and prognosis for individuals on the autism spectrum can be expected to continue in coming years.

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Table 1
Differential Diagnostic Features of Autism and Nonautistic Pervasive Developmental Disorders

Feature	Autistic Disorder	Asperger's Disorder	Rett's Disorder	Childhood Disintegrative Disorder	Pervasive Developmental Disorder-NOS
Age at recognition (months)	0-36	Usually >36	5-30	>24	Variable
Sex ratio	M>F	M>F	F (?M)	M>F	M>F
Loss of Skills	Variable	Usually not	Marked	Marked	Usually not
Social skills	Very poor	Poor	Varies with age	Very poor	Variable
Communication skills	Usually poor	Fair	Very poor	Very poor	Fair to good
Circumscribed Interests	Variable (Mechanical)	Marked (Facts)	NA	NA	Variable
Family history - similar problems	Sometimes	Frequent	Not usually	No	Sometimes
Seizure disorder	Common	Uncommon	Frequent	Common	Uncommon
Head growth decelerates	No	No	Yes	No	No
IQ range	Severe MR to normal	Mild MR to normal	Severe MR	Severe MR	Severe MR to normal
Outcome	Poor to good	Fair to good	Very poor	Very poor	Fair to good

Adapted, with permission, from Lippincott-Raven Publishers, Nonautistic Pervasive Developmental Disorders, F. R. Volkmar & D. Cohen, in *Psychiatry*, R. Michaels, et al., editors, Chapter 27.2, page 4.

Table 2**ICD-10 Criteria for Childhood autism (F84.0)**

A.	Abnormal or impaired development is evident before the age of 3 years in at least one of the following areas:
1.	receptive or expressive language as used in social communication;
2.	the development of selective social attachments or of reciprocal social interaction;
3.	functional or symbolic play.
B.	A total of at least six symptoms from (1), (2), and (3) must be present, with at least two from (1) and at least one from each of (2) and (3).
1.	Qualitative impairments in social interaction are manifest in at least two of the following areas:
a.	failure adequately to use eye-to-eye gaze, facial expression, body postures, and gestures to regulate social interaction;
b.	failure to develop (in a manner appropriate to mental age, and despite ample opportunities) peer relationships that involve a mutual sharing of interests, activities, and emotions;
c.	lack of socio-emotional reciprocity as shown by an impaired or deviant response to other people's emotions; or lack of modulation of behavior according to social context; or a weak integration of social, emotional, and communicative behaviors;
d.	lack of spontaneous seeking to share enjoyment, interests, or achievements with other people (e.g., a lack of showing, bringing, or pointing out to other people objects of interest to the individual).
2.	Qualitative abnormalities communication as manifest in at least one of the following areas:
a.	delay in, or total lack of, development of spoken language that is not accompanied by an attempt to compensate through the use of gestures or mime as an alternative mode of communication (often preceded by a lack of communicative babbling);
b.	relative failure to initiate or sustain conversational interchange (at whatever level of language skill is present), in which there is reciprocal responsiveness to the communications of the other person;
c.	stereotyped and repetitive use of language or idiosyncratic use of words or phrases;
d.	lack of varied spontaneous make-believe play or (when young) social imitative play.
3.	Restricted, repetitive, and stereotyped patterns of behavior, interests, and activities are manifested in at least one of the following:
a.	an encompassing preoccupation with one or more stereotyped and restricted patterns of interest that are abnormal in content or focus; or one or more interests that are abnormal in their intensity and circumscribed nature, though not in their content or focus;
b.	apparently compulsive adherence to specific, nonfunctional routines or rituals;
c.	stereotyped and repetitive motor mannerisms that involve either hand or finger flapping or twisting or complex whole-body movements;
d.	preoccupations with part-objects or nonfunctional elements of play materials (such as their odor, the feel of their surface, or the noise or vibration they generate).
C.	The clinical picture is not attributable to the other varieties of pervasive developmental disorders; specific development disorder of receptive language (F80.2) with secondary socio-emotional problems, reactive attachment disorder (F94.1), or disinhibited attachment disorder (F94.2); mental retardation (F70–F72) with some associated emotional or behavioral disorders; schizophrenia (F20) of unusually early onset; and Rett's syndrome (F84.12).