Pervasive developmental disorders

Etiological, diagnostic and treatment conundrum

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ABSTRACT

Pervasive developmental disorders are severe childhood psychiatric disorders that afflict millions of children worldwide. Despite availability of tremendous data on these disorders, there is a paucity of information among clinicians including mental health professionals. Pervasive developmental disorders, caused by multiple neurobiological and environmental etiologies, are characterized mainly by impaired social interactions, impaired communication and language, and abnormal repetitive interests and behaviors. A clear understanding of the underlying pathophysiological mechanisms of pervasive developmental disorders requires routine developmental surveillance, extensive clinical diagnostic workup and laboratory investigations. The children with pervasive developmental disorders need a multimodal treatment approach. In Arabian Gulf countries, research is warranted to explore different aspects of these disorders.

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Autistic disorder (AuD), one of the prototypical and putative subtypes of pervasive developmental disorders (PDDs), is characterized by severe and pervasive deficits in several developmental areas including reciprocal social interactions, communication and language skills, and cognitive abilities.[1,2] These lifelong pervasive deficits together with stereotyped behavior, interests, and restricted activities are usually evident in the first years of life that are not compatible with the individual's developmental level or mental age. Pervasive developmental disorders are heterogeneous in nature and are caused by biologic/genetic-environment interactions. Additionally, lack of theory of mind reflecting executive function deficits and the theory of weak central coherence also collectively explains social communication deficits, perseveration and rigidity, and the uneven pattern of intellectual abilities found in children with autism and other PDDs.[3] According to the major classifications of mental disorders (**Table 1**), PDDs are categorized into 5[1] and 8 subtypes.[4] Each PDD has specific diagnostic criteria and guidelines and can be differentiated from the other. However, the distinction between AuD, Asperger disorder (AD) and atypical autism with low intelligence quotient (IQ) and high IQ is most difficult.[5,6] Furthermore, even the anchoring diagnostic criteria of each PDD may not pass validation analysis. For example, lack of early language delay in AD is not a valid discriminating variable among PDD subtypes.[7] Clumsiness as a diagnostic feature of AD may not be applicable to a group of intelligent children with AD.[8] Moreover, AD is also associated with developmental motor milestone delays and lower receptive language abilities, which may cause further difficulties in distinguishing it from other PDDs. Patients with high functioning AuD again posit diagnostic difficulties in particular with PDD not otherwise specified-atypical autism. Whether or not childhood disintegrative disorder (CDD) should be considered a separate diagnosis is debatable.[9] To complicate the diagnostic issue further, PDDs are often

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Table 1 - Pervasive developmental disorders as seen in ICD-10 and DSM-IV.

ICD-10 categories [F84]	DSM-IV categories [299.00]
1. Childhood autism [F84.0]	1. Autistic disorder [299.00]
2. Atypical autism [F84.1]	5. Pervasive disorder not otherwise specified [atypical autism] [299.80]
3. Rett's syndrome [F84.2]	2. Rett's disorders [299.80]
4. Other childhood disintegrative disorders [F84.3]	3. Childhood disintegrative disorder [299.10]
5. Overactive disorder associated with mental retardation and stereotyped movements [F84.4]	
6. Asperger syndrome [F84.5]	4. Asperger disorder [299.80]
7. Other pervasive developmental disorders [F84.8]	
8. Other pervasive disorders [F84.9]	

ICD - International Classification of Diseases
DSM - Diagnostic and Statistical Manual [of Mental Disorders]

Table 2 - Comorbidity of PDDs.

Medical conditions	Psychiatric disorders
1. Congenital rubella	1. Mental retardation
2. Phenylketonuria	2. Anxiety disorders
3. Down's syndrome	3. Mood disorders including mania
4. Fragile X syndrome	4. Sleep disorders
5. Turner syndrome	5. ADHD
6. XYY syndrome	6. Obsessive-compulsive disorder
7. Tuberous sclerosis	7. Tourette's disorder
8. Neurofibromatosis	8. Childhood schizophrenia
9. Megalencephaly [Cole-Hughes syndrome]	9. Catatonia
10. Velocardiofacial syndrome	10. Developmental disorders
11. Infantile spasms and other related conditions	
12. Cerebral lipoidosis	
13. Joubert syndrome	
14. Congenital blindness	
15. Pyridoxine dependency	
16. Schilder's disease	
17. Metachromatic leukodystrophy	

PDD - pervasive development disorder
ADHD - attention deficit hyperactivity disorder

associated with mental retardation-dual disability[10] and a variety of medical diseases and psychiatric disorders-dual/poly diagnoses)[11] (**Table 2**). The comorbid conditions may not be typical of PDDs[12] but could be related more to the mental subnormality. Individuals with PDDs need a multimodal treatment approach together with suitable rehabilitation.

This review will mainly focus on AuD, the most severe form and prototypical of PDDs. However, a brief comparative account of other PDDs will also be provided. As a corollary, this review will familiarize the concerned clinicians to identify early and intervene sustainedly for reasonably improving the outcome and prognosis of children with PDD's. It would also act as a stimulus for conducting basic applied research on PDD's.

Origins of PDD. In 1943, Leo Kanner first described early infantile autism also know by several names including Kanner's syndrome and highlighted its salient features in terms of impaired social interactions, failure to use language for communication, obsessive desire for sameness, and good cognition. Later, rigorous neurophysiological assessments of a proportion of autistic children revealed a variety of cognitive deficits.[13,14] However, their first degree relatives do not show any evidence of cognitive and social impairments.[15] Infantile autism was later conceptualized as a PDD that tends to improve with maturation. Kanner considered infantile autism as an "inborn autistic disturbance of affective contact" reflecting genetic component. Soon after, he realized the etiological significance of faulty parental influences reflecting psychological causation, which was not sustained by subsequent studies. As a corollary, neurobiological mechanisms and developmental-maturational etiologies proposed by several researchers largely explained infantile autism.[16] Likewise, the diagnosis of AuD was shrouded in controversies. Autistic children were wrongly given a variety of diagnoses including childhood psychosis, childhood schizophrenia, symbiotic psychosis and atypical personality disorder. However, later studies provided empirical data differentiating autism from childhood schizophrenia. In 1980, infantile autism was included in the Diagnostic and Statistical Manual [of Mental Disorders] (DSM)-III under PDDs category, which was retained in DSM-IIIR and also found place in International Classification of Diseases (ICD)-9. Subsequently, PDDs were reported to be conceptually identical in ICD-10 and DSM-IV.[17] In another development, AuD, based on Wing's social dimension, was subtyped into aloof, passive and finally active-but-odd.[18] Among the 3 subgroups, only the first 2 were later validated.[19]

In 1994, Hans Asperger described a syndrome in a group of children with impaired social interactions and communication abilities, later known by his name as Asperger syndrome.[20] In contrast to AuD, there are no clinically significant delays in language, cognition or age-appropriate self-help skills and adaptive behavior in AD. However, social interactions are impaired and AD children are further characterized by curiosity about the environment. Subsequently, there were many case reports and epidemiological research exploring AD, which was also included in 2 major psychiatric classifications.[1,4,21] In 1966, Andreas Rett described Rett's disorder (RD) among brain-damaged female children and highlighted its characteristic features, 1) normal developmental history in the first few months of life, 2) loss of previously acquired skills, 3) development of characteristic midline hand stereotypes, 4) gait and truncal ataxia and apraxia, 5) pseudomicroencephaly, 6) muscle tone abnormalities, 7) seizures and electroencephalographic (EEG)

abnormalities, 8) respiratory problems, 9) elevated blood ammonia, and 10) diffuse atrophy with reactive proliferation of the astroglia in brain biopsy studies. The elevated blood ammonia was not found to be a consistent finding in subsequent case reports.[16] In 1908, Theodore Heller described childhood disintegrative psychosis, also known as disintegrative psychosis or dementia infantilis. This syndrome is characterized by a marked regression in multiple areas of functioning following a period of at least 2 years of apparently age appropriate normal development. There is a clinically significant loss of previously acquired skills in at least 2 areas 1) expressive or receptive language, 2) social skills or adaptive behavior, 3) bowel or bladder control, 4) play or motor skills 5) social and communicative deficits, and 6) restricted, repetitive, and stereotyped patterns of behavior, interests, and activities. The 5th subtype is PDD not otherwise specified (atypical autism) that does not meet the criteria for AuD because of late age onset, atypical symptomatology, or subthreshold symptomatology, or all of these.[1] Overall, PDDs are not uncommon disorders of childhood and need continuing research because many of their aspects are yet to be well understood. Notably, PDD main subtypes are considered on a continuum and differ only by degree of impairment.[22]

Nosological refinements. DSM-I and DSM-II did not recognize autism as an independent disorder because it was viewed as a childhood form of schizophrenic reaction or schizophrenia. Infantile autism together with other subtypes of PDDs when differentiated from childhood schizophrenia were included in DSM-III. The ICD-9, most consistent with DSM-III, also included infantile autism, disintegrated psychosis and others under the category of psychoses with origins specific to childhood. However, the term "pervasive developmental disorders" was not considered in ICD-9. Because of certain critical reasons including age of onset, developmental issues, and vague criteria for social and language assessment, DSM-III diagnostic subcategories of PDDs were questioned and therefore, only 2 categories - AuD and PDD not otherwise specified (NOS) were considered in DSM-III R along axis-II. Infantile autism was substituted by AuD as it was known to persist in adolescents and adults. Although the term "pervasive" remained debatable, it was included in ICD-10 and was also retained in DSM-IV because the spectrum of these disorders affects most areas of development and central nervous system (CNS) maturation.[23] Unlike ICD-9, the ICD-10 considered 8 diagnostic categories under PDDs (**Table 1**). Likewise, DSM-IV recognized RD, CDD, AD, and PDD not otherwise specified-atypical autism. Furthermore, the AuD was placed along axis-I in DSM-IV and its diagnostic criteria were further refined and reduced in number.

Epidemiological parameters of PDDs. There is converging epidemiological evidence that the prevalence of AuD is 2-5 cases per 10,000 children (**Table 3**). The most consistently reported prevalence rate of childhood autism concluded from several surveys is 5 per 10,000 individuals,[24] which is now reported to increase up to 7 to 13 per 10,000 children.[25,26] This trend could be attributed to broad diagnostic criteria, comprehensive case ascertainment, earlier age under consideration, true increase in prevalence, geographical distribution, provision of child health services, and enhanced awareness among concerned clinicians.[26,27] A Norwegian study did not confirm this epidemiological trend.[28] The estimated prevalence of AD is 3.6 per 1,000 children of age 7-16 years. This figure inflated to 7.1 per 1,000 children when high index of suspicion children were also included.[29] Rett's disorder is exclusively described in females with a prevalence of 1 in 10,000 to 1 in 15,000. The reported prevalence of PDD-NOS is 10-12/10,000 children.[30] However, the prevalence of all forms of PDDs is approximately 18.7 per 10,000.[26] With the exceptions of RD and CDD, other forms of PDDs are more common than AuD. Autistic disorder preferentially afflicts males, the male to female ratio is

Table 3 - Prevalence of pervasive developmental disorders.

Sources	Country	AuD	AD	PPD-NOS
1.Lotter, 1966[142]	UK	4.5/10,000		
2.Treffert, 1970[143]	USA	2.5/10,000		
3.Wing et al, 1976[144]	UK	4.8/10,000		
4.Gillberg, 1984[145]	Sweden	2/10,000		
5.Steinhausen et al, 1986[146]	Germany	1.9/10,000		
6.Bryson et al, 1988[147]	Canada	10/10,000		
7. Tanoue et al, 1988[148]	Japan	13.9/10,000		
8.Ritvo et al, 1989[149]	USA	4/10,000		
9.Turner et al, 2000[24]	UK	5/10,000		
10.Tanguay et al, 2000[96]	USA	5/10,000	10/10,000	
11.Cascio & Kilmon, 1997[30]	USA			10-12/10,000
12.Ehlers & Gillberg, 1993[29]	Sweden		3.6-7.1/10,000	
13.Sponheim & Skjeldal, 1998[28]	Norway	4-5/10,000		

UK - United Kingdom, USA - United States of America, AuD - Autistic disorder, AD - Asperger disorder, PPD-NOS - pervasive developmental disorder not otherwise specified

variable but the most consistent reported one is 2.5 to 1. In some studies, the reported ratio is 3 to 3.8:1,[24,26] which covaries with mental retardation. The overall higher incidence of autism among boys is attributed to their lower threshold for neuronal insult. Males have more severe autistic features on several measures of early social development as compared to their counterparts.[31] Whether or not AuD is realistically more common among upper social class families having highly intelligent and educated parents is debatable. Autistic disorder is now frequently reported among low socioeconomic families. This discrepant finding could be attributed to differential access to physicians having expertise in diagnosing AuD. Regarding AD, a male to female ratio was 4:1 that dropped to 2.3:1 when possible cases were also considered.[29] In another review on AD, the projected male to female ratio was 8:1.[32] Further, RD afflicts only female gender while CDD and atypical autism are more common in males.

Etiological considerations. Etiologically, PDDs are heterogeneous. There is converging evidence suggesting the tremendous significance of biological factors underlying PDDs. For instance, PDDs are more often comorbid with mental retardation, medical and genetic diseases, seizure disorders, psychiatric disorders, and other developmental deficits.[33,34] However, these psychomedical conditions like megalencephaly may not be specific to autism or other PDDs.[35] Likewise, psychiatric symptoms such as impulsivity and hyperactivity,[36] the 2 core features of attention deficit hyperactivity disorder (ADHD) may not be related specifically to PDDs. However, these conditions may share some etiological underpinnings. Alternatively, some investigators have attempted to explain PDDs by cognitive-developmental system theory.[37] The authors would examine critically the neurobiology of PDDs as vast literature supports the relevance of organic etiology of PDDs. The neurobiological factors could be as follows, 1) genetic and perinatal, 2) neuroanatomical, 3) neurochemical, and finally 4) immunological.

Gene and environment. Several family and twin studies provided strong evidence that genetic factors are important determinants of AuD.[38,39] The estimated incidence of autism in siblings is 2.5% to 3%, which is much higher than the general population. Additionally, the families of children with PDDs are shown to have an array of psychopathologies including cognitive, language, and social deficits, mood and anxiety disorders,[40] which could be expression of a similar genetic predisposition to autism. Tourette's syndrome, having a strong genetic component, is also reported to comorbid with PDDs.[41] Further, genetic support came from autistic twin studies, which found 36% to 89% concordance rates in monozygotic twins while 0% concordance rate in dizygotic twins.[42] Notably, AuD and other PDDs are inherited through several mechanisms which may encompass X-linked (RD), autosomal recessive with reduced penetrance and variable expression, and chromosomal abnormalities such as tetrasomy 15, deletion of the long arm of chromosome 8, fragile site at Xq27 and XYY karyotypes.[43,44] Higher-(AD) and lower-(AuD) functioning PDD children may have separate genetic mechanisms.[45] However, AuD, CDD and RD share similar genetic transmissible mechanisms.[46,47] Furthermore, variations in severity dimension across PDDs is found to be correlated with familial and genetic factors.[48] The genetic etiology of autism and specific language impairment is linked to a region on chromosome 7 (7q3), chromosome 2 (2q), and other genes 3, 7, 15, 18, 19, and X and other susceptibility loci.[38,49,50] Investigators have also reported duplication of chromosome 15 (15q11-q13) in autism and partial epilepsy,[51,52] both conditions may involve gamma-aminobutyric acid (A) receptor dysfunction. The role of adenosine deaminase alleles [ADAs], in particular ADA2, should be explored because ADA1 and ADA2 alleles are implicated in purine metabolism, immune responses, and peptidase activity that may be altered in some autistic children.[53] Additionally, PDDs coexist with genetically determined medical disorders (**Table 2**) that have variable prevalence of 7% to 37%, attributable to different diagnostic criteria, etiological relations with PDDs, and definition of medical conditions.[38,54-56] In addition to their own salient clinical features, the genetic conditions also manifest features of PDDs that are stereotypes, lack of eye to eye gaze, echolalic speech, restricted play and perseverative interests. Therefore, children presenting with these genetic disorders should always be screened for PDDs. Although the revelation of exact genetic interrelationship may be difficult, abnormal tuberous sclerosis gene mutation may directly influence the development of autism.[54,57] However, autism may not have cause-effect relationship with mental retardation or infantile spasms, the 2 conditions commonly encountered in patients with tuberous sclerosis. Further, it is highlighted that autistic children are exposed to a variety of prenatal, perinatal and neonatal complications, which are maternal bleeding after first trimester, maternal use of medications during pregnancy, fetal distress, neonatal anemia, and delayed cry together with lower obstetrical optimality scores. Burd et al found 5 obstetrical risk factors including decreased birth weight, low maternal education, delayed prenatal care, previous termination of pregnancy, and increasing father's age for autism.[58] Notably, an abnormal fetus vulnerable to develop autism may lead to these obstetrical complications, hence the relationship may be both reciprocal and very complex too. Autism may be caused by gene-environment interaction, whereby very early fetal development (approximately day 20-24) may be faulty, in particular gene abnormalities due to adverse environmental exposures during pregnancy.[59] Overall, the causative role of environmental factors in autism and other PDDs is explored scarcely, therefore, further research is warranted.

Neuroanatomical substrates of PDDs. The evidence towards neuronal dysfunctions underlying AuD and

other PDDs is derived from different studies that have utilized neuroimaging methods, histological techniques, neuropsychological testing, brain autopsies, evoked-potential techniques, and regional cerebral blood flow measurements.[38,60-62] As a corollary, the most probable neuronal areas implicated in autism are the mesial and frontal temporal lobes (late prenatal-early postnatal origin), the brainstem (early prenatal origins) and diencephalic structures, cerebellar hemisphere and vermis, and the left hemisphere.[38,63] Reportedly, high functioning autism (AD), is not a medial temporal lobe amnestic disorder that is characterized by an impairment in explicit memory (remembering a shopping list) and intact implicit memory (a woman seems familiar although you can not remember having met her before).[64] The amygdala has been equated with social brain network that is disturbed in PDDs and metabolically less active in autism.[60] The dilatation of temporal horn of the left lateral ventricle (15%) together with increased cell-packing density in the amygdala and hippocampus was shown in children with autism.[38] Furthermore, as also supported by animal experiments, the mesial temporal lobe is found to be damaged in children with autism who had herpes simplex encephalitis, oligodendroglioma, and agenesis of left temporal lobe. Based on these results, the researchers hypothesized that the loss of Purkinje cells in the cerebellum eliminates the inhibitory control of the deep cerebellar nuclei resulting into dysregulation of many behavioral functions observed in autistic spectrum disorders. The aforesaid abnormal findings in left mesial temporal lobe structures, cerebellum, and left cerebral cortex suggest that there exists a defect in neuronal migration, which occurs before the 6th month of gestation and clinically covariates with communicative and language difficulties, cognitive impairments, prosody, and comprehension of emotional cues found in PDD children.[16]

Neurochemical perturbations in PDDs. The neurochemical hypothesis of AuD implicates the etiological role of serotonin, dopamine, gamma aminobutyric acid, N-methyl-D-aspartate, and endogenous opioids.[38,52,65] Approximately 33% of autistic children and 50% of mentally retarded patients are demonstrated to have hyperserotonemia in their blood.[38] According to researchers, a neurochemical diathesis in terms of hyperserotonemia may reflect either elevated or decreased serotonin in the CNS and so serotonergic antagonist and agonist are tried in children with PDDs with variable results. Excessive CNS dopamine neurotransmission is associated with hyperactivity and stereotypes as seen in autistic children who respond therapeutically to dopamine antagonists. Further research is needed to identify which subtypes of dopamine receptors [D1-D5] and transporters are involved in the etiology of PDDs. Opioid addicts during intoxication and withdrawal phase manifest some autism-like features that suggest the role of enkephalins and endorphins in autism. Likewise, children exposed prenatally to opioids were later found to manifest autistic spectrum disorder features. In accordance to opioid theory, some drugs such as naltrexone were used in autism with encouraging results. The pathogenetic role of exogenous opioids originating from the bowel has also been considered in autism.[66] Autism may be a disorder linked to the disruption of the G-alpha proteins that affect retinoid receptors in the brain. Furthermore, G-alpha proteins disrupted disorders including night blindness, pseudohypoparathyroidism, adenoma of thyroid or pituitary gland are found in those parents whose children are at risk for developing PDDs.[67] The MECP2 gene, which encodes methyl-CpG-binding protein 2 is implicated in X-linked RD.[68]

Immunological basis of PDDs. The immune system, as also activated by infectious and genetic factors in animal models, may be disturbed in neurodevelopmental disorders including PDDs, mental retardation and schizophrenia.[69] A subgroup of autistic children were shown to have a decreased immunological response and their mothers were found to have antibodies to the leukocyte antigen in sera and also on their CNS cells. Maternal antibodies directed against fetal nervous tissue may damage the CNS resulting in the development of autism.[16] The children with AuD were demonstrated to have increased production of proinflammatory cytokines-interleukin (IL-1) receptor antagonist and interferon (IFN) gamma, products of inflammatory response system that could play a role in the pathophysiology of AuD.[70] In another study involving children with autistic spectrum disorders, researchers showed excessive innate immune responses in terms of tumor necrosis factor-alpha [TNF-alpha]-one of the proinflammatory cytokines that were stimulated by lipopolysaccharide and other stimulants of phytohemagglutinin.[71] Overproduction or underproduction of certain cytokines in genetically predisposed individuals for developing PDDs may cause neurodevelopmental arrest or neurotoxicity.[72] Early impaired immunological tolerance, one of the immunological injury hypotheses related to cognitive deficits as revealed in PDDs, is also implicated in their pathogenesis.[73] Like DR beta 1 gene located close to C4B gene, a deficient form of C4B-one of the major histocompatibility complex genes, termed as C4B null allele (no C4B protein expressed) has been found with increased frequency in autism. C4B encodes a product that is involved in eliminating pathogens such as viruses and bacteria from the body.[74] Additionally, the demonstration of autoantibodies (IgG isotype) to neuron-axon filament proteins [anti-NAFP], glial fibrillary acidic protein [anti-GFAP] and myelin basic protein (anti-MBP) in autistic children further bolsters the autoimmune pathology in this disorder.[75] Further, a serological association between measles virus antibody (measles-IgG) and human herpesvirus-6 antibody (HHV-6-IgG) and brain autoantibodies was reported, which supports the hypothesis that a virus-induced autoimmune pathology may cause autism.[76] Likewise, autoantibodies are also found against serotonin receptors

in autism.[16] The association of several disorders caused by viruses including congenital rubella, herpes simplex encephalitis, and cytomegalovirus infections with autism suggests its possible viral etiopathogenesis. Moreover, increased spring birth rate among autistic children susceptible to maternal winter influenza also suggests the viral etiology of AuD.[66] Children with autistic spectrum disorders were also demonstrated to have lymphocytic colitis with affected epithelium.[77] Maldigestion of gluten and casein resulting in the production of opioid-type peptides/exorphins is implicated in the etiopathogenesis of autism.[78] The administration of certain vaccines may contribute to autism,[78,79] but a recent study reported negative association of measles-mumps-rubella vaccination with bowel symptoms or development of regression among autistic children.[80]

Phenomenology and diagnostic features of PDDs. According to DSM-IV,[1] there are essential and associated diagnostic features of all types of PDDs, which are most consistent with the diagnostic guidelines of its counterpart.[4] These children with PDDs present with a variety of clinical behavioral patterns (**Table 4**), which encompass 3 major areas including reciprocal social interactions, communication and language skills, and finally activities, interests, and play. Most importantly, the developmental regression in those areas manifest at 24-months[81] and the period of normal development in almost all PDDs must not extend past age 3 years.[16] Further, children with PDDs are reported also to manifest executive dysfunctions and impaired imaginative creativity.[82] Additionally, they have the inability to understand false beliefs[83] and difficulty in face recognition.[84] Children with PDDs also have subtle mindreading deficits.[85] According to Dawson and associates, they also manifest certain maladaptive behaviors subserving some functions including self-injurious behavior (no specific reasons), stereotypes (nonsocial reasons), and aggression (attentional reasons).[86] The severity of repetitive behaviors in autistic adults parallels the sensitivity of the 5-HT1d receptor, as manifested by sumatriptan elicited Gh response.[87] Reportedly, the diagnosis of autism is more stable at 2-years compared to other PDDs.[88,89] Beside moderate mental retardation and receptive and expressive language dissociation, children with PDDs may have a range of other behavioral symptoms such as hyperactivity, short attention span, impulsivity, temper tantrums, tics, sleep problems, appetite and mood disturbances.[90,91] Curiously, they may not be afraid of real dangers as compared to harmless objects. Later, individuals with PDDs tend to develop depression when they realize their serious impairments and negative life events and up to 25% also develop seizure disorders.[16,92] A proportion of patients with PDDs are reported to manifest catatonic features, which needs further clarification regarding their etiologies, neuropathology, and early signs of vulnerability.[93]

Table 4 - Abnormal behavioral patterns in pervasive developmental disorder.*

1. Failure to cuddle
2. An indifference or aversion to affection or physical contact
3. A lack of eye to eye contact, facial expression, body postures and gesture or socially directed smiles
4. A failure to respond to the parents' voices
5. Lack of peer relationships appropriate to developmental level
6. Lack of showing, bringing, or pointing out objects of interest
7. Lack of social and emotional reciprocity
8. Apparently deaf appearance
9. Lack of spoken language and no alternative nonverbal communication
10. In individual with adequate speech, impaired ability to initiate or sustain a conversation
11. Stereotyped and repetitive use of language
12. Lack of varied, spontaneous make-believe play or social imitative play
13. Intense preoccupation with one or more stereotyped and restricted patterns of interest
14. Inflexible adherence to specific, nonfunctional routines or ritual
15. Hand or finger flapping or twisting, or complex whole-body movements
16. Persistent preoccupation with parts of objects
17. Clinging mechanically to a specific person
18. Willingness to be passively engaged in social activities
19. Later more interested in social interaction in unusual ways
20. Expect other people to answer ritualized questions in specific ways
21. Little sense of other people's boundaries
22. Inappropriate intrusion in social interaction
23. Tasks involving long-term memory may be excellent
24. Information tends to be repeated over and over again
*3 major components - social interactions, communication and language, restricted interests, behavior, activities and play

Screening scales and laboratory tests for PDD. In addition to the aforesaid clinical diagnostic cues, there are several instruments for systematically assessing and diagnosing children with possible PDDs,[94] which are the Childhood Autism Rating Scale, the Autism Diagnostic Interview-Revised and the Autism Diagnostic Observation Schedule, pre-Linguistic Autism Diagnostic Observation Schedule, Autism Spectrum Screening Questionnaire, and the Checklist for Autism in Toddlers (CHAT) and KIDIES.[2,16,95-99] Most of these scales including Social Reciprocity Scale support the notion of "broader autism phenotypes".[100] Some scales just assess individual dimension, such as social skills of children with comorbid developmental disorders.[10] Overall, these psychological instruments, using dimensional as well as spectrum approach, are very useful in the early identification, diagnosis, and treatment of children with PDDs. Further from the perspectives of diagnosis, treatment and research, each child with PDDs should take the following, 1) detailed developmental, psychiatric and medical evaluation, 2) comprehensive neurological and psychological assessment, 3) physical examination including measurement of head circumference, presence or absence of minor physical anomalies, adenoma sebaceum, and pigmented skin patches, 4) hearing and visual acuity tests, 5) various laboratory analyses including serological examination, blood chemistry, tests for inborn error of metabolism, 24-hour urine collection for mucopolysaccharidoses, uric acid, and calcium, 6) cytogenetic analysis, 7) EEG,

8) evoked potential measurements, and 9) neuroimaging.[16,42,46,101] These investigations will help in identifying several medical conditions plus understanding brain glucose metabolism reflecting neuronal network dysfunctions underlying PDDs. Finally, brain autopsy studies may reveal neuropathological findings in different areas of the brain including cerebellum. In accordance with some researchers, the authors suggest that there should be a continuing search for ultimate diagnostic indicator(s) in terms of genetic, metabolic, immunologic, or neurologic that will distinguish individual PDD and other developmental disabilities.[102]

Differential diagnostic conundrum of PDDs. Each child with impaired social interactions, communication difficulties and marked restricted activities together with make believe play should have only one distinctive diagnosis of PDD (**Table 5**). Hence, AuD should be differentiated from 1) RD that has been diagnosed only in females with a characteristic pattern of head growth deceleration, loss of previously acquired purposeful hand skills, and the appearance of poorly coordinated gait or trunk movements. Additionally, they may exhibit transient difficulties in social interactions, 2) CDD has a distinctive pattern of developmental regression following at least 2 years of normal development, 3) AD that lacks delay in language development and characterized by pedantic speech.[103] Notably, children with AD are reported to have a good outcome in terms of education, employment, autonomy, marriage, reproduction, need for continuing medical and institutional care.[104] Hence, AD has been considered a separate entity rather than a high functioning subtype of AuD.[105] Further, children with AD are reported to have better social and language skills as compared to high functioning autistic children with equal IQ.[106] The diagnosis of AD is usually confirmed late, namely 11 years as compared to autism, namely 5.5 years.[107] Despite all these differential indicators, some investigators still suggest that AD may simply be "high-IQ autism" and rejects separate names for the disorder,[108] and 4) Pervasive developmental disorder not otherwise specified, namely atypical autism, which is characterized by late onset, atypical manifestations, or subthreshold symptomatology, or all of these.[1] Beside the aforesaid clinical parameters, event-related potential [P3] and other relevant tests could further help in differentiating several subtypes of PDDs.[109] Pervasive developmental disorders should also be differentiated from, 1) periods of normal developmental regression which are neither severe nor prolonged,[16] 2) fragile X syndrome, which is characterized by less severe impairments in social skills, communications, and cognitive functioning,[110] 3) childhood schizophrenia that usually develops after years of normal development and is characterized by active-phase symptoms of prominent delusions or hallucinations lasting for at least one month. Children with AuD may later develop schizophrenia, 4) schizotypal personality disorders are characterized by deficits in interpersonal relationships only, 5) selective mutism, the appropriate communication skills in certain contexts and social interactions coupled with diverse patterns of behaviors are preserved, 6) expressive and mixed receptive-expressive language disorders, there is only language impairment, 7) severe or profound mental retardation poses a diagnostic challenge and an additional diagnosis of PDD is made only when there are qualitative deficits in social interactions and communicative skills plus the specific restricted behaviors, 8) stereotypic movement/or habit disorders

Table 5 - Differentiation between pervasive developmental disorders.

Variables	AuD	AD	RD	CDD	PDD-NOS
Prevalence	<common	common	rare	rare	>common
Sex	m++	m++++	fe++++	m+	m++
Verbal mental age/skills	lower	higher	higher	higher	lower
Delay in early language development	++	--	--	--	++
Theory of mind	----	---	---	--	--
Mindreading deficits	+++	+++	++	++	++
Beta-endorphin	higher	normal	normal	normal	normal
Genetic vulnerability	++	++++	+	+	++
Social skills	poor	poorer	poor	poor	poor
Clumsiness*	--	++	--	--	--
Pedantic speech	--	++	--	--	--
Face recognition	deficits	--	--	--	<deficits
Psychosis/violence	++	++++	+++	+++	++
Depression	+	++++	+/-	+/-	+
Severity	>severe	<severe	>severe	>severe	severe
Diagnostic stability	stable	<stable	<stable	<stable	?stable
Diagnosis made	early	late	early	early	early
Outcome**	poorer	good	poorer	poorer	poor

AuD - autistic disorder, AD - Asperger disorder, RD - Rett's disorder, CDD - childhood disintegrative disorder, PDD-NOS - pervasive developmental disorder not otherwise specified, + = yes, - = no, +/- = yes or no, m - male, fe - female,
*AD children with higher intelligence are less clumsy
**outcome in terms of education, employment, autonomy, marriage, reproduction, need for continuing medical and institutional care

are not diagnosed in the background of AuD that is also characterized by motor stereotypes, 9) Landau-Kleffner (L-K) syndrome that is characterized by acquired aphasia (developmental dysphasia), seizures, subsequent inability to comprehend spoken language, and impaired expressive language together with EEG abnormalities in terms of continuous spike and wave activity but no impairment in social interactions.[16,66,111,112] The epileptiform activity may play a causative role in 33% of children with autism.[112] Moreover, nonverbal communication is intact and there is no intellectual deterioration in L-K syndrome, 10) reactive attachment disorder, which is characterized by disturbed sociability attributed to grossly inadequate care but it is completely reversible with appropriate psychological treatment, 11) children with infantile epilepsy, reported to have autistic spectrum disorders, are further characterized by right brain lesions and EEG abnormalities.[113,114] and 12) ADHD, which is mainly characterized by hyperactivity, impulsivity and attentional difficulties and some authors suggest its inclusion in the PDD category.[115]

Onset, course and prognosis of PDDs. With the possible exception of CDD and RD, the onset of other PDDs is usually insidious, slow, and chronic. However, the course of PDDs may be either progressive or continuous or regressive or fluctuating.[24,116] The clinical features related to social interaction, more subtle and difficult to define, may occur during early infancy and childhood. However, the autistic features developing after the age of 2 years are easily identifiable. Approximately 33% of autistic children may develop normally for the first 2 years of life.[112] Later, the course of PDDs is characterized by developmental gains in social functioning as the child reaches school age. Language skills and overall intellectual level are the strongest factors related to ultimate prognosis. Comorbid medical conditions and emerging psychiatric disorders in terms of depression, schizophrenia, anxiety, aggression, self-injuriousness, and intellectual level will further predict the prognosis of PDDs. There is paucity of follow-up studies on PDDs, hence, the outcome prediction of PDDs is murky. However, according to some researchers, only a small percentage of individuals with AuD reach adult age so as to live and work independently. Some degree of partial independence is possible in about one-third of cases. Like other PDDs, the highest functioning adults with AuD typically continue to exhibit minor problems in social interaction and communication and language with markedly restricted interest and activities.[104] Moreover, autistic children are reported to have lifelong severe disabilities in several domains of functioning.[24] Similar predictions but with relatively less severe disabilities could apply to other PDDs.[106] Coplan has presented a triaxial model comprising of age, degree of intelligence, and severity of autistic symptoms for counseling parents of autistic children regarding its prognosis.[117] In the light of pausity of follow-up data, there is a definite need for carrying out longterm studies on PDDs.

Management strategies of PDDs. The treatment of children with PDDs should be aimed at controlling behavioral manifestations and improving language development, social skills and overall learning. The treatment plan must be tailored according to individual needs, however, special education and language therapy are the essential components of a multidisciplinary approach. The management of PDDs could be grouped into, 1) nonpharmacological approaches, and 2) pharmacological treatments (**Table 6)**.

Nonpharmacological approaches. Children with PDDs including AuD require special education in a structured setting for acquiring learning skills and avoidance of solitary engagements with the purpose of ultimately leading an independent good quality of life.[16] Computer intervention programs may now help teach people with AuD or AD.[118] Both high IQ and younger age determine their placement in regular education classrooms.[119] Sign language and speech therapy improves communication skills and meaningful language development.[120] Behavioral modeling, role play and supervised group activities minimize the severe problems related to social interactions, emotional reciprocity, social rules and attention. Additionally, family therapy and social support networks have therapeutic effects among autistic children and those with other developmental disorders.[121] A day treatment model comprising of structured activities was found to be effective in all abnormal domains of children with PDDs.[122] Further, peer-mediated intervention may help PDD children develop interpersonal relations in appropriate social contexts.[123] Auditory integration training may or may not improve their behavioral oddities.[124] Intensive behavioral modification programs such as shaping and prompting will help in eliminating abnormal behavior while establishing desired behavior. Additionally, they may need positive reinforcement in terms of appropriate rewards. Some studies have reported benefits in only 42% of autistic children who received intensive behavioral training. They also show improvement in symptom severity and posttreatment IQ scores.[16,125] Individual psychotherapy may help higher functioning autistic persons only. With the increasing

Table 6 - Management strategies of pervasive developmental disorder.

Nonpsychopharmacological therapies	Psychopharmacological therapies
1. Special education	1. Conventional antipsychotics
2. Sign language and speech therapy	2. Novel/atypical antipsychotics
3. Family therapy	3. Traditional antidepressants
4 Social support network	4. Specific serotonin reuptake inhibitors
5. Role play	5. Mood stabilizers
6. Peer-mediated and group therapy	6. Psychostimulants
7. Individual psychotherapy	7. Opioid antagonists
8. Behavioral modification	8. Antiepileptics and steroids
9. Genetic counseling	9. Secretin and other treatments

understanding of genetic mechanisms of PDDs, concerned parents may require genetic counselling.[126]

Pharmacological treatment of PDDs. Prior to drug therapy, PDD individuals must have detailed baseline clinical and laboratory work-up. Thereafter, clinical progress could be monitored every 6 months with periodic drug withdrawals. In addition, the 3 domains involving theory of mind, joint attention, and affective reciprocity could be used in assessing the effectivity of pharmacological and psychotherapeutic interventions among children with autistic spectrum disorders.[127] Notably, psychotropics are of greater use in only those children who manifest symptoms such as temper tantrum, aggressive spells with assaultiveness, self-injurious behavior, hyperactivity, motor stereotypes, anxiety (65%), and depression.[16,92,128,129] In PDD patients, antidepressants were the most common prescribed drugs (32.1%), followed by stimulants (20.2%), and neuroleptics (16.5%).[130] Antipsychotics improve targeted symptoms in PDD individuals, but tend to cause discomforting side-effects in particular tardive dyskinesia.[128,129,131] Haloperidol when combined with behavior therapy facilitates speech development. The daily recommended dose of haloperidol in autistic children is 0.016 to 0.217mg/kg. Another antipsychotic drug, pimozide has been found to be effective in hypoactive/normoactive autistic children. The daily dose of pimozide is 1.0 to 9.0mg. Children could develop cardiotoxicity if pimozide is given at more than 0.3mg/kg of body weight.[16] Risperidone, atypical antipsychotic and most commonly recommended medication, is effective in the treatment both of children and adults with autism and other PDDs. Risperidone is a serotonin 2A-dopamine D2 antagonist, which reduces repetitive behavior, aggression, anxiety or nervousness, depression, irritability, and overall behavioral symptoms of PDDs. No adverse effects except mild, transient sedation, weight gain, hypersalivation, stereotypes and reversible withdrawal dyskinesia have been observed.[132] Antidepressants including clomipramine, desipramine, fluvoxamine, sertraline, and fluoxetine were found to be effective in controlling different symptoms such as obsessive-compulsive, angry moods, repetitive aggression, and social interactional problems observed among patients with PDDs. However, these medications should be given in the lowest therapeutic doses in children so as to prevent adverse effects including acute urinary retention, constipation, behavioral toxicity and seizures.[16,133,134] Another antidepressant, venlafaxine, a norepinephrine reuptake inhibitor, was found to be effective in improving several domains of autistic spectrum disorder and associated features of ADHD.[135] Psychostimulants, effective in ADHD, decrease hyperactivity and also improve attention when given to individuals with PDDs. However, these medications are associated with insomnia, behavioral toxicity and worsening of stereotypes. In open trials, methylphenidate, 10-50 mg/day, decreased hyperactivity in autistic children and at the same time produced no major side-effects. Fenfluramine, a serotonin depleter and a known anorexic, given in daily dose of 1.250-2.068 mg/kg, was found to be effective in 33% of autistic children with brain hyperserotonemia.[16,131] This anorexic drug improves stereotypes, hyperactivity, social interactions and language. However, this drug has adverse effect on learning. Notably, controlled trials of fenfluramine in autistic children found no better results over placebo. In light of opioid dysregulation hypothesis, in open trials naltrexone improved stereotypes, hyperactivity, withdrawal, self-injurious behavior and language in autistic individuals. However, controlled investigations found naltrexone to be effective only in reducing hyperactive behavior but there were no adverse effect on learning.[128-130] Clonidine is an a_2-adrenergic agonist and its daily transdermal dose is 0.005 mg/kg. It reduces noradrenergic drive in autistic children that results in improvement in stereotypes, social withdrawal, hyperactivity, and temper tantrums. Other miscellaneous drugs include buspirone, mood stabilizers, and beta-blockers, which have produced reduction in symptoms in open trials, therefore, need further controlled investigations.[16,128-131,136] Beside the use of genomeceuticals, restriction of diet in particular casein and gluten, supplementation with exogenous enzymes and probiotic bacteria are also recommended for the treatment of autism.[78] Approximately one-third of patients with autism showing epileptiform activity may need antiepileptic drugs, steroids, and even neurosurgery.[112] Finally, secretin, that received tremendous media hype following its therapeutic success in a autistic child, is a peptide gastrointestinal hormone that stimulates pancreatic secretion. Subsequently, it was not found to be effective in autism or PDDs compared to placebo.[137] However, some researchers have reported that secretin has a few clinically meaningful effects on speech and behavior of children with PDDs.[138] One placebo-controlled cross-over study found efficacy of porcine secretin on measures of positive affect and activity level.[139] Overall, there is no specific drug treatment for individuals with lifelong PDDs, therefore, further research is needed for developing new effective drugs with a better clinical profile.

In conclusion, PDDs are clinically well defined childhood disorders with no specific etiopathogenesis.[140] Therefore, the management of patients with PDDs is symptomatic and includes both psychotherapeutic and pharmacological interventions. The genetic-environmental causal models may shed further light on the pathophysiology of PDDs and help in developing drugs that are more specific for children with PDDs. In Arabian Gulf countries, there is a dearth of literature on PDDs,[141] therefore, further research is needed.

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