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Review Article

Autism spectrum disorder and its differential diagnosis: A nosological update

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Abstract

Autism spectrum disorder (ASD) is a neurodevelopmental disorder, often presenting in early childhood with restricted and repetitive behaviors, interests and activities and significant impairment in social communication. The objective of this review is to sensitize mental health professionalsand cliniciansfor the varying clinical presentation of ASD, key differentiating features from other disorders, and updating diagnostic criteria as per recent nosological advances, as timely diagnosis and early intervention is significant for long term course and prognosis.

Keywords: Autism, autism spectrum disorder, ASD, differential diagnosis

Introduction

Timely diagnosis is vitally important as early intervention inautism may improve the outcome of behavioral problems, functional skills, and communication difficulties. To start comprehensive treatment at younger ages, clinicians are trying to diagnose these disorders at the earliest. International classification of diseases, tenth revision (ICD-10) classifies autism under Pervasive developmental disorder (PDD) [1] and Diagnostic and statistical manual of mental disorders,

4thedition (DSM IV) as Autism [2]. DSM-IV and ICD-10 included several subtypes of PDD: Autism, Asperger's Syndrome, Pervasive developmental disorder not otherwise specified (PDDNOS), Childhood disintegrative disorder, and Rett syndrome. Recently two major classificatory systems i.e., DSM-5 (American Psychiatric Association, 2013) [3] and ICD-11 (World Health Organization, 2018) [4] have classified autism into Autism spectrum disorder (ASD). It reflects the scientific consensus that four separate disorders are depicting a single condition with varying clinical presentation and severity in two broad domains. This spectrum approach allows room for individual variation in these symptom dimensions. DSM-5 has been the first classificatory system to have transcribed the spectrum concept from research to practice. The prior approach of categorically delineating ASD into different types of PDD had common core symptom presentation across different categories but had the poor predictive ability of outcome based on this categorization, making it a heterogeneous group for researchers and had no clear clinical ramifications in terms of management guidelines.

There are many overlapping features between ASD and other psychiatric and physical disorders as well as several differentiating features in terms of age of onset, clinical presentation, progression, treatment, and outcome. On the other side, it is not uncommon to have psychiatric comorbidity in patients with ASD. Until recently, there is a considerable delay between parents' recognition of problems in their child's development and the diagnosis of autism. Parents' overall satisfaction rating related to the process of referral and diagnosis is reportedly much higher on getting a confirmatory diagnosis at a younger age. Therefore, timely diagnosis of ASD has become more crucial for better prognosis and comprehensive management.

Though most of data related to classifications and diagnostic criteria's is available in standard literature, a comprehensive review encompassing the chronology of diagnostic criteria and the

subtle differences between them is lacking. The index article aims to provide a narrative review and nosological update on ASD, with focus on differentiation of ASD from other psychiatric disorders, which will help the mental health professionals and clinicians to identify the individuals with autism, thus also reducing the frequency of misdiagnosis.

In order to gain a grip on the historical underpinnings and fundamental differences between the subtypes of autism, initial section of the review discusses historical aspects of autism and aspergers syndrome differentials as per ICD-10 [1] and DSM-IV [2] classification, as in DSM-5 and ICD-11, autism and its subdivisions have been subsumed under the broader term of ASD. The various changes in DSM and ICD series are mentioned in Table-1 & 2 respectively. The term ASD is used throughout this article (consistent with the DSM-5 and ICD-11 diagnostic criteria) with respect to Autism, Asperger syndrome, Childhood disintegrative disorder, and PDDNOS.

Search Strategy

Electronic searches of PubMed, Science Direct, and Google Scholar databases were carried out with the aim of identifying published articles on nosological updates and differences, differential diagnosis of autism spectrum disorders and pervasive developmental disorders. The search was done using the following subject headings or free text terms and their combinations: Autism spectrum disorders, pervasive spectrum disorders, ASD, PDD nosology, differential diagnosis. The searches were carried out in August 2019 and were independently performed by the two authors. Next, a supplemental Google search using random combinations of the above terms was done to further screen the available literature. Cross-references of selected papers were also screened to identify relevant articles. Further, standard literature, notably ICD-8, 9, 10 and DSM-I, II, III, IV AND 5 were also reviewed. The search was restricted to articles in the English

language without any restriction on the date of publication. Any disagreement was sorted out through mutual discussion and consensus.

Historical aspects

Landmark in the area of autism is the case series reported by Kanner in 1943 where he reports in detail, 11 cases unique to existent literature at that time and sharing certain common features. [5] One or more of the following characterized the cases:

- Inability to relate themselves in the ordinary way to people an situations from the beginning of life
- "Autistic aloneness" (shutting out anything that comes from the outside)
- Failure to make an anticipatory posture in preparation to being picked up
- Delayed acquirement of ability to speak and the speech being meaningful
- Excellent rote memory
- Echolalia
- Repetition of personal pronouns as heard
- Anxiously obsessive desire of sameness
- Limitation in the variety of spontaneous activity
- Good relation to objects

In another landmark article, Lorna Wing provides a comprehensive account on Asperger's syndrome, detailing the clinical features described by Asperger seen in a set of cases [6]. One or more of the following characterized the cases:

- Speech: difficulty in using pronouns correctly
- Limited non-verbal communication
- Impairment of two-way social interaction

- Repetitive activities and resistance to change
- Clumsy and ill coordinated motor movements
- Excellent rote skills and intense interest in 1 or 2 areas

These two case series formed the foundation for the institution of a specific nomenclature within the classification systems. DSM-I and DSM-II gave such entities a common term of schizophrenic reaction, childhood type which in the later editions were termed as pervasive developmental disorders. ICD-8 was the first among the ICD series, which formulated a separate nomenclature for such entities giving the name infantile autism under the schizophrenia grouping. It was in ICD-10 the term pervasive developmental disorder was used. The label Asperger's disorder or Asperger's syndromecreated in DSM-IV and ICD-10 in the 1990s. As is evident, in the initial decades, such patients were considered to be belonging to the schizophrenic spectrum of disorders, only gaining separate status in the later editions of the classification systems.

Table-1: Changes in DSM series:

	DSM I (1952) DSM II (1968)	**DSM III (1980)**	**DSM IV (1994)**	**DSM 5 (2013)**
Nomenclature	Schizophrenic reaction, childhood type	Pervasive developmental disorders	Pervasive developmental disorders	Autism spectrum Disorders
Diagnostic Subcategories	-	Infantile Autism Childhood Onset PDD Atypical PDD	a. Autistic Disorder b. Asperger Disorder c. Childhood Disintegrative Disorder d. Rett syndrome e. PDD-NOS	None

PDD-Pervasive developmental disorder, PDD-NOS- Pervasive developmental disorder, not otherwise specified

Table-2: Changes in ICD series:

	ICD-8 (1967)	**ICD-9 (1975)**	**ICD-10 (1992)**	**ICD-11 (Proposed draft)**
Nomenclature	Infantile autism" under the schizophrenia grouping	Infantile Autism included in category of psychosis with onset in childhood	Pervasive developmental disorders	Autism Spectrum Disorder
Diagnostic Subcategories			a.Childhood autism b.Atypical autism c. Rett's syndrome d. Other childhood disintegrative disorder e. Overactive disorder associated with mental retardation and stereotyped movements f. Asperger's syndrome g. Other pervasive developmental disorders h.Pervasive developmental disorder, unspecified	6A02.0 to 6A02.Z (detailed in later section)

Nosological updates for Autism spectrum disorder (ASD)

DSM-5 Neurodevelopmental disorder working group concluded that there is no sufficient evidence regarding the difference in clinical presentation, etiology, outcome and response to treatment in between the various subcategories of autism, so they have been eliminated and replaced with a single diagnostic entity of "ASD" [7].

ASD as per DSM-5

ASD is characterized by the presence of both 1) deficits in social communication and social interaction, and 2) restricted repetitive behaviors, interests, and activities.

These changes in DSM-5 criteria's have generated considerable controversy, with a school of thought advocating that the revised DSM-5 criteria might underdiagnose individuals who would otherwise have earlier been diagnosed as autism (high functioning) according to ICD-10/DSM-IV [8]. Although, recently published data does not favor this concern [9].

Diagnostic Criteria of ASD as per ICD-11

In line with DSM-5, ICD-11 has also updated the diagnostic criteria for autism [4] and classified ASD under the broad heading "Neurodevelopmental disorders" in chapter 6A02. ASD is characterized by persistent deficits in the ability to initiate and to sustain reciprocal social interaction and social communication, and by a range of restricted, repetitive, and inflexible patterns of behavior and interests. The onset of the disorder typically occurs in early childhood and causes pervasive impairment in important areas of functioning. ASD is further classified based on the presence of intellectual development and impairment in functional language-

6A02.0-Autism spectrum disorder without disorder of intellectual development and with mild or no impairment of functional language

6A02.1-Autism spectrum disorder with disorder of intellectual development and with mild or no impairment of functional language

6A02.2-Autism spectrum disorder without disorder of intellectual development and with impaired functional language

6A02.3-Autism spectrum disorder with disorder of intellectual development and with impaired functional language

6A02.4-Autism spectrum disorder without disorder of intellectual development and with absence of functional language

6A02.5-Autism spectrum disorder with disorder of intellectual development and with absence of

functional language

6A02.Y-Other specified autism spectrum disorder

6A02.Z-Autism spectrum disorder, unspecified

Differential Diagnosis:

Broadly these are divided into two subheadings-

A. Differentialdiagnoses within Pervasive developmental disorders-These are briefly summarized as per former nosological systems (ICD-10 and DSM-IV TR) and compared in Table-3.

1. Childhood Autism:

It is manifest more commonly in boys, generally before the age of 3 years, presented with impaired development, restricted, repetitive behavior and abnormal social interaction and communication.

2. Atypical autism/Pervasive developmental disorder not otherwise specified (PDD-NOS)

This refers to atypical or non-specific presentation of autism as it differs from autism in terms either of age of onset (manifest after age of 3 years) or failure to completely fulfill diagnostic criteria in above mentioned three domains i.e.abnormalities in one or two of the three domains (social reciprocity, communication, and restrictive, stereotyped, repetitive behavior) and/or impaired development [10].

3. Asperger's syndrome

Individuals with Asperger's syndrome have higher verbal than non-verbal IQ and do not have any language delay, hence more commonly, diagnosis is delayed [11].

4. Childhood disintegrative disorder (CDD)

Childhood disintegrative disorder also termed 'Heller syndrome.' It presents after an apparently normal development for the first two years of life as a child withdraws from social engagement, with the loss of receptive and expressive language functions, and develops fecal and urinary incontinence. Gradual deterioration generally continues for several months, and in the majority it is idiopathic, but sometimes it is caused by cerebral lipoidosis or leukodystrophy [12].

Table-3: Differentials among PDD subtypes [14,15]

Feature	Autistic disorder	Asperger's syndrome	Rett's syndrome	CDD	PDD-NOS
Age at recognition	0-36 months	Usually >36 months	5-30 months	>24 months	Variable
Gender affected	Male > female	Male >> female	Female (rarely male)	Male > female	Male > female
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-ASD	Sometimes	Frequent	Not usually	No	Unknown
Seizure disorder	Common	Uncommon	Frequent	Common	Uncommon
Head growth deceleration	No	No	Yes	No	No
IQ	Severe MR to normal	Mild MR to normal	Severe MR	Severe MR	Severe MR to normal
Outcome	Poor to fair	Fair to good	Very poor	Very poor	Fair to good
Hand stereotypes	No	No	Characteristic feature	Present sometimes	No
Developmental regression	No	uncommon	Present in language	Evident in language, coordination, bladder, bowel function & other areas	No
Verbal IQ > nonverbal IQ	No	Characteristic feature	No	No	No

CDD- Childhood disintegrative disorder, IQ- intelligence quotient, MR- mental retardation, ASD-Autism Spectrum Disorder

5. Rett syndrome

It is a progressive developmental disorder commonly seen in girls, with relatively normal general and psychomotor development until 18 months of life. It presents with stagnation of further development and rapid deterioration of behavior and mental abilities, with loss of purposeful hand movements and emergence of characteristic “hand-washing” stereotypy or wringing movements, jerky ataxia of the trunk and limbs, and acquired microcephaly. Timely diagnosis of Rett syndrome is essential for prognostication [13,14].

B. Differential diagnoses with other psychiatric disorders

1. Social (pragmatic) communication disorder

It is characterized by difficulty in understanding the rules of social communication through language, storytelling, with a lack of conventional greetings, and responding to a second person's verbal and nonverbal cues. Since social communication deficits is one component of ASD, so the diagnosis of social (pragmatic) communication disorder is only made in the absence of restricted, repetitive behaviors, interests, and activities.

2. Language Disorders

Though language delay is a common reason for referral ofchildren with ASD, but non-autistic children of such referrals usually have severe receptive-expressive language disorder and sometimes have problems in social communication. Children with language disorders do not have restricted, repetitive patterns of behavior, interests, or activities or problems in nonverbal communication.

3. Sensory Deficits

Children with ASD are sometimes mislabeled as deaf. Deaf children usually have social interactions with peers and family members and consistently seek out nonverbal social communication and generally respond only to loud sounds, whereas children with ASD may ignore loud or normal sounds and respond to soft or low sounds. A comprehensive history should differentiate clearly, and rule out vision and hearing impairment, and clinicians should proceed for extensive ophthalmological and audiological investigations for further clarification [14].

4. Selective mutism

It usually starts before the age of 4 years and more commonly in girls and children with language impairment. Though they appear more withdrawn and less interactive in specific situations like schools, unlike autism, they usually have normal development, social reciprocity, strong parental bonding and do not have restricted or repetitive patterns of behavior [14, 16].

5. Intellectual Disability (ID)

Children with ASD present with specific impairment in social interactions rather than global impairment as seen in children with ID. About two-thirds of children with autism also have associated intellectual deficits. Inindividual with ID, additional diagnosis of ASD should be considered when social communication and interaction are significantly impaired relative to other nonverbal skills [14,17].

6. Childhood-Onset Schizophrenia

Negative symptoms of the schizophrenia (i.e., reduction in normal functions) such as restrictions in emotional expression, fluency of speech, and goal-directed behavior, etc. generally appear

similar to social and communication deficits of ASD. On contrary overall development remain normal in children with schizophrenia and sometimes these two disorders can co-occur [14,18].

7. Attention-deficit hyperactivitydisorder (ADHD)

Like children with ADHD, with ASD may alsopresent with hyperactivity, inattention, and impulsivity.On the other side, children with ADHD may sometime appear in their own world and socially disconnected, but they do not have restricted interests and repetitive behaviors and any impairment in reciprocal social interaction [14].

8. Landau–Kleffner Syndrome

It is also termed as‘acquired aphasia with epilepsy’. In this condition children usually have normal development, with intact non-verbal cognitive and motor functioning and later they develop receptive and expressive aphasia, social withdrawal, and behavioral abnormalities [19].

9. Depression

ASD and depression have a commonality in presentation like social withdrawal, lack of emotional response, and loss of interest in relationships, etc., but generally, depression starts in adulthood with a distinct change in premorbid personality and functioning. On the other side, depression is more commonly reported in children with “high-functioning autism” as they are more aware of ongoing difficulties [20]. A comprehensive history, detailed symptomatology, and mental status examination are important in differentiating both the disorders.

10. Emotional neglect or psychosocial deprivation

Sometimes children with emotional neglect or psychosocial deprivationpresent with language delay, restricted interests, and poor social skills, but unlike ASD, they have better social reciprocity and substantial improvement with brief psychosocial intervention [21].

11. Social Anxiety Disorder (Social Phobia)

In social anxiety disorder individual typically have adequate age-appropriate social relationships and social communication capacity, although they may appear to have impairment in these areas when first interacting with unfamiliar peers or adults.

12. Reactive attachment disorder (RAD)

Both ASD and RAD can manifest dampened expression ofpositive emotions, cognitive and language delays, and impairments in social reciprocity. Children with RAD have experienced a history of severe social neglect. The restricted interests and repetitive behaviors characteristic of ASD. Children with ASD regularly show attachment behavior typical for their developmental level, which was rarely or inconsistently in children with RAD.

Autism spectrum disorder in adults

Autism spectrum conditions in people without obvious developmental delay (eg, those with Asperger's syndrome) and with subtler difficulties tend to be recognized later [22]. Making a first diagnosis of autism spectrum conditions in adults can be challenging for practical reasons (eg, no person to provide a developmental history), developmental reasons (eg, the acquisition of learnt or camouflaging strategies), and clinical reasons (eg, high frequency of co-occurring disorders). First identification of autism spectrum conditions in adulthood is clearly established in DSM-5. Important features of the latest DSM-5 definition that support diagnosis in adulthood are that diagnostic behavioral descriptions apply to all ages; behavior contributing to a diagnosis can be current or historical; and criterion of a specific early age of onset is no longer required, being replaced by "symptoms must be present in the early developmental period (but may not become fully manifest until social demands exceed limited capacities, or may be masked by learned strategies in later life) [23].

To conclude, nosology and diagnostic criteria's have been updatedinthe newer versions of both the classificatory systems, ICD-11 and DSM-5. Asignificant overlap exists between ASD and other psychiatric and developmental disorders. The presentation of ASD can also change over time, as per the demands of the environment or comorbidity and some core behavioral symptoms may improve with time while some behaviors may persist for longer duration [24]. Behavioral and cognitive disturbances may co-occur with ASD, masking the underlying comorbid disorders, which may lead to misdiagnosis, thus delaying the definitive treatment. The complexity and heterogeneity of ASD at multiple levels are the major challenges for family, mental health professionals, researchers and policy makers. Clinical expertise and awareness of updated nosological criteria, meticulous history with thorough physical and mental status examination is vital for timely accurate diagnosis and comprehensive early intervention for every individual with ASD.

Conflict of interest: None declared

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