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UNRAVELING THE MYSTERY OF AUTISM

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ABSTRACT: The scope for patients suffering from Autism Spectrum Disorder today is far brighter than what it was a century ago. A few of these individuals, after great efforts, can read, write and communicate reasonably well while living in their homes rather than support institutions. Nevertheless, a large segment of adults suffering from Autism cannot work full-time to earn their livelihood. To add to the misery, marriage and long-term relationships are out of reach for such patients. Autism Spectrum Disorder is now redefined as a constellation of symptoms manifested by defective social skills, impaired communication, stereotypical behavior and repetitive motor movements observed during early childhood. Although research in the area of childhood disorders has undergone an enormous development over the past 100 years, the etiology, pathogenesis, and biomarkers of Autism are still a matter of speculation. Autism research has witnessed blazing debates in recent years about the missed diagnosis and overlap of similar childhood disorders, which sometimes turned into academic rather than scientific face-offs. The Risk factors responsible for causing Autism, Classical Symptoms, the latest Diagnostic Criteria, and the Management Strategies have all been illustrated in this Review article with the help of self-explanatory flow-Charts. Furthermore, this interesting article is a humble compilation of the events that led to the unification of pervasive developmental disorders into a single disorder and unfolded how the concept of Autism spectrum disorder was sequentially evolved.

INTRODUCTION:

Preamble: Autistic behavior has existed since ancient times, though diagnostic criteria underwent continual modifications over the last century.

The clinical features displayed by young children in the early days till the beginning of the 19th century such as abnormal behavior, lack of social interaction, communication difficulties, self-centered behavior, intellectual shortcomings, stereotypic movements were taken as signs of mental retardation, dementia, idiocy, foolishness and/or schizophrenia. These form the classic symptoms of a child suffering from autism as per the latest guidelines of DSM-5 or ICD-11, as we know today. Today's scope for patients suffering from Autism Spectrum Disorder is far brighter than

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what it was a century ago. Some of these individuals, after great efforts, can read, write and communicate reasonably well while living in families rather than support institutions. The credit for this encouraging scenario goes to the pediatricians, psychiatrists, neurologists, psychologists, psycho-pharmacologists, scientists and government agencies for offering timely support in identifying precisely this neuro developmental disorder and providing necessary therapeutic guidance and remedies.

Nevertheless, a large segment of adults suffering from Autism is not in a position to work full-time to earn their livelihood even today, even in developed countries. Any chronic mental illness represents a substantial economic burden to the caregivers due to continuous health care demand, highly specialized training and trainer fees, expensive medicines and helplessness of the grown-up adult in income generation. To add to the misery, marriage and long-term friendship are beyond consideration for such patients, who exhibit abnormal social approaches, possess poor communication skills and believe in a non-flexible lifestyle. Considerable work needs to be done still to understand how to prevent the occurrence of Autism in the first place. Although research in the area of childhood disorders has undergone a radical development over the past 100 years, the etiology and pathogenesis of Autism is still a matter of speculation.

Thus, without reliable biomarkers, ASD continues to be diagnosed by observing the behavioral pattern exhibited by the child and by asking questions to caregivers. Since the eighteenth century till date, Autism research has witnessed blazing debates about the missed diagnosis and symptom overlap of similar childhood disorders, which sometimes turned into academic rather than scientific face-offs. Co-existing intellectual disability is a serious concern among pre-school children suffering from ASD. Furthermore, co-occurring problems such as attention deficit hyperactive disorder (ADHD), depression, childhood schizophrenia, cerebral palsy, Down's syndrome, Fragile X syndrome, Tourette's disorder, language disorders complicate further the diagnosis of Autism Spectrum Disorder (ASD) because of similarity in symptoms and behaviour¹.

The authors have outlined the characteristic features briefly of all these overlapping childhood disorders below so as not to confuse them with ASD. The risk factors responsible for causing Autism, classical signs and symptoms, diagnostic criteria, and the management strategies have all been illustrated with the help of self-explanatory flow-Charts in this Review article. Furthermore, this article is a humble compilation of the events that led to the unification of pervasive developmental disorders into a single disorder and unfolded sequentially how the concept of Autism spectrum disorder was evolved.

Evolution of the Concept of “Autism Spectrum Disorder”:

Autism and Mental Retardation: Autistic behavior has existed since ancient times, although diagnostic criteria underwent continual modifications over the last century. To understand the development of autistic symptoms, it is necessary to consider each behavior in the context of what is normal for the child's non-verbal mental age and the extent to which this behavior is delayed or atypical. The clinician, therefore, needs to have a good understanding of the normal milestones in the development of a child. Many symptoms of Autism are not unique to Autism and may represent some or the other form of childhood disorder (Mental retardation). The clinical features displayed by young children in the early days till the beginning of the 19th century, such as abnormal behavior, lack of social interaction, communication difficulties, self-centered behavior, intellectual shortcomings, stereotypic movements, were taken as signs of either mental retardation, dementia, idiocy, foolishness and/or schizophrenia. These form the classic symptoms of a child suffering from Autism as per the latest guidelines of DSM-5 or ICD-11, as we know today. Several scientists in various parts of the world offered different explanations for childhood abnormalities representing different aspects of Autism. The terms "idiocy" and "imbecility" are certified by the Oxford English Dictionary as early as the 16th century. Many of the "holy fools," or Orthodox Church ascetics, who roamed ancient Russia, in reality, displayed autistic behaviors, being notoriously nonverbal, impervious to social interactions, and indifferent to cold weather or pain².

Famous cases showed that some “idiots” had specific problems in social communication (consistent with Autism) rather than a mere global mental deficiency. The descriptions of children, who most likely suffered from Autism, can be traced as early as the 1700s with some reports of feral children and in the records of the training school for the intellectually disabled in the 1800s. Presumably, these feral children had either been abandoned or run away from their parents. One such case is Victor, the Wild Boy of Aveyron (1788-1828), a feral child who was discovered when he was about 12 years old. Victor might have been a child with Autism, abandoned by his parents, who displayed difficulty in initiating and maintaining social relationships³.

In 1887, Dr. John Langdon Down (British physician, best known for having described Down syndrome) presented 10 cases of “idiots’ savants,” *i.e.* children with exceptional abilities in a narrow field, such as calendar calculating. While these cases may or may not be all autistic, most of them would now satisfy criterion B for ASD in DSM-5 (*i.e.*, restricted and repetitive patterns of behavior, interest, or activities). Dr. Down, based on his clinical experience, proposed a classification of Mental Retardation into (i) congenital, (ii) accidental, and (iii) developmental. The latter type occurred in children, who did not have the usual “physical aspects” of retardation. Some of these children had developed normally until the period of second dentition, and then suddenly regressed, “lost their learned skills, speech and preferred to live in a world of their own, spoke in the third person, exhibited rhythmical and repetitive movements and showed apathy towards all relatives and friends”. This “Developmental Retardation” category probably corresponds to cases of both early-onset and late-onset Regressive Autism².

The Resemblance between Dementia and Schizophrenia: The first formal description of schizophrenia as a mental illness was made in 1887 by German psychiatrist Dr. Emile Kraepelin. He used the term “dementia praecox” to describe the symptoms of illness now known as schizophrenia. Dr. Kraepelin attributed dementia praecox to be primarily a disease of the brain in those early days. However, he was mistaken in believing that this disorder was a form of early dementia.

It is now well known that schizophrenia and dementia (memory loss) are distinct disorders. The term “Schizophrenia” derived from the Greek roots schizo (split) and phrene (Mind) was first introduced in 1908 by Swiss psychiatrist Paul Eugen Bleuler during a lecture delivered at a psychiatric conference in Berlin. Bleuler later expanded the concept of schizophrenia as a new mental disorder into a monograph published in 1911.

Autism before Official Recognition: Paul Eugen Bleuler (a Swiss psychiatrist), Hans Asperger (an Austrian child specialist), Leo Kanner (an Austrian-American psychiatrist and social activist), and Grunya Sukhareva (a Russian lady-psychiatrist) deserve the credit for designating the term “Autism” for the first time in the area of developmental disorders while working separately. In 1911, Bleuler considered Autism as a clinical sign of psychosis. The word “Autism” originated from the Greek word “autos”, synonymous with self-isolated or automatic movement⁴. Grunya Efimovna Sukhareva was the first physician to describe an Autism-like condition much before Hans Asperger and Leo Kanner as schizoid (eccentric) psychopathy in 1925. In 1959, she renamed the condition as Autistic (pathological avoidant) psychopathy. The original paper with the comprehensive report of Autistic characteristics in children was initially published in Russian and re-published in a German journal, the *Monatsschrift für Psychiatrie und Neurologie* a year later in 1926⁵.

In 1938, Hans Asperger accepted Bleuler's nomenclature “Autistic” in its current sense to depict unusual child behavior. Asperger described the unnatural behavioral pattern exhibited by four boys as “Autistic psychopathy”, now popularly known as “Asperger's Syndrome”. Asperger pointed out that these children were clumsy and different from normal children in terms of motor skills⁶. Leo Kanner used the term Autism in a medical report when he diagnosed Donald Triplett (the first patient) to be suffering from “Autism” in 1938. He published a paper in 1943, applying the term “infantile Autism” to 8 boys and 3 girls with peculiar behavioral features. These 11 children had problems in social interactions, experienced difficulties in adapting to the changes in routines

and showed echolalia. Kanner's report was groundbreaking and gave medical literature a window to this complex and enigmatic disorder⁷. Then, Bruno Bettelheim studied the effect of therapy sessions on a group of Autistic children and claimed that the problem in the children was due to the coldness of their mothers and put forth a hypothesis (which did not last long) with Kanner that Autistic children had frigid mothers. Bernard Rimland was a psychologist and also a father of a child suffering from Autism. He disagreed with Bettelheim, who had stated that the cause of Autism was rooted in parenting skills.

In 1964, Bernard Rimland published, "Infantile Autism the *Syndrome* and its *Implications* for a Neural Theory of Behavior" and in 1968, he created the first checklist for assessing symptoms suggestive of Autism. Several lines of research converged to suggest that Autism was a distinctive concept on its own and not the earliest manifestation of schizophrenia. By 1971, the first Journal devoted specifically to Autism was established with Leo Kanner nominated as its editor. The original name for the Journal also included the words "childhood schizophrenia" although, this term was later removed as it became clear that Autism and childhood schizophrenia were distinct conditions. In 1978, Rutter proposed a new definition of Autism that included delayed and deviant social and language abilities beyond general developmental level and restricted interests and repetitive behaviors; all with onset early in life⁸. The Erica Foundation (a Swedish non-profit organization) took the initiative in supporting children with mental illness by providing psychotherapy, integrative treatment and education in the early 1980s. Many parents still had confusion about these 3 mental disorders, *viz.* Autism, Mental Retardation and Psychosis.

Confusion between Childhood Schizophrenia and Autism: The term Autism was first used by Eugen Bleuler in 1908 to describe a schizophrenic patient, who had withdrawn into his world. Greek word "Autos" means self and the word Autism was used to mean self-admiration and withdrawal within one's world. Autistic disorder, however, did not find any place in the official book of the American Psychiatric Association (APA) popularly known as DSM-1 published in 1952.

Schizophrenia was labeled "Schizophrenic reaction" in DSM-1. The category of childhood schizophrenia appeared in DSM-II (an official manual of APA 1968), to describe children exhibiting schizophrenic symptoms together with severe disturbances in development⁸. Childhood schizophrenia is a rare mental disorder that does not differ from adulthood schizophrenia. Schizophrenia is a long-lasting serious mental illness, in which the patient gets cut off from reality. Schizophrenic patients experience hallucinations, delusions and exhibit abnormal behavior/speech, inflexibility and indifferent attitude. No wonder that for many years, children suffering from Autism received a diagnosis as Childhood Schizophrenia. The abnormal behavior of children suffering from both schizophrenia and Autism exhibited a similar pattern. Therefore, it was natural to have confusion between these two childhood-mental disorders.

Official Recognition of Autism: Several lines of research were further carried out, which resulted in including "Infantile Autism" for the first time as an official diagnostic category in the groundbreaking third edition of the Diagnostic and Statistical Manual (DSM-III; APA 1980). It took until 1980 for the DSM-III to officially differentiate Autism as a developmental disorder from childhood schizophrenia. DSM-III referred to the occurrence of Autistic behavior in infants, thereby accounting for peculiar and abnormal behavior of young children. The criteria described a pervasive lack of social responsiveness consistent with Kanner's first description of the condition. An additional diagnostic term, "residual infantile Autism", was included for cases that had once met the criteria but no longer did so. Another diagnostic category was also included to describe children who had an onset of Autism-like condition after a substantial period of normal development⁸. Despite the major advantage that DSM-III offered by providing official recognition of infantile Autism, its problems quickly became clear. The definition itself was monothetic (*i.e.*, all criteria must be met), and the diagnostic criteria were too rigid, which led to the revision of DSM 3, (the DSM-III-R of APA 1987)⁹. DSM-III-R (DSM-III Revised) provided a checklist in 1987 for diagnosing Autism. Lorna Wing, along with Christopher Gillberg at

Children's Neuro-Psychiatric Clinic in Sweden in the 1980s found that Wing's triad of symptoms: Disturbed mutual contact, disturbed mutual communication and limited imagination represented a child with Autism. Later on, in the 1990s, they added another feature, 'limited planning ability' making it a square. A significant conceptual change in DSM-III-R was to rename the condition from "infantile Autism" to "Autistic disorder". In DSM-III-R, a new polythetic set of 16 detailed criteria was provided. The criteria were organized into three major domains of dysfunction observed in Autism, viz. I) Qualitative impairments in reciprocal social interaction, II) Impairments in communication, and III) Restricted interests/resistance to change and repetitive movements. For diagnosis of Autistic disorder, a total of at least eight positive criteria were required, two from the social domain and at least one from each of the other two categories. DSM-III-R was created to provide greater clinical flexibility and the 'residual' category was labeled as Otherwise Specified (PDD-NOS) ⁸. The Autistic disorder has undergone continual refinement in every subsequent edition of the manual, since its first appearance in DSM-III. However, the DSM-III-R criteria for Autistic disorder suffered from certain demerits such as weak reliability, poor validity and lack of specificity. There was a substantial improvement in the definition and diagnostic criteria of Autism in the subsequent editions of DSM-IV and DSM-V.

The Sequence of Events in India Connected with Autism: The Viennese child-specialist A. Ronald used the term "abnormal child" for the first time in 1944 while working at Darjeeling (West Bengal) in India to reflect Autism. Ronald provided a summary of the identification, triggers, forms and management of "abnormal children" parallel to Kanner's flagship report ⁴. In 1959, the word "Autism" made its debut in Indian literature and several research papers devoted to childhood abnormalities were published during the 1960s. The first case report of Autism appeared in an Indian journal in 1962. There were a few publications in the 1960s and 1970s referring to infantile Autism. However, the Indian medical fraternity was unaware of Autism till the late 1970s. India witnessed a sudden spurt in Autism

related awareness since the late 1980s. The release of the film 'Rain Man', in 1988 focusing on an Autistic savant, who was gifted with a photographic memory and extraordinary calculating powers turned out to be a crucial juncture for Autism. This movie yielded a respectable international recognition for this childhood disorder (Autism) with Indian film-goers being no exception. This film won the best picture of the year award and was nominated for eight Oscars during 61st Academy Awards. Tito Mukhopadhyay, an 11-year-old boy of Bangalore (India) suffering from Autism, released his treatise, "Beyond the Silence: My Life, the World, and Autism", in 2000. The methods described in the book for training a child suffering from Autism adopted by Tito's mother aroused a lot of interest globally. From the late 1980s, cognizance of Autism in India has witnessed enormous growth in numerous domains ¹⁰.

The Shift from Pervasive Developmental disorders to Autism Spectrum Disorder: The DSM-4 published in 1994 specified criteria for the diagnosis of patients suffering from five Pervasive Developmental Disorders viz. Autistic disorder, Asperger's disorder, Childhood disintegrative disorder, Rett's disorder, and Pervasive developmental disorder-not otherwise specified (NOS). The DSM-5 (published by American Psychiatric Association) notified in May 2013 marks an important shift in the conceptualization of Autism from a multi-categorical diagnostic system to a single diagnosis based on multiple dimensions ¹¹. Autism was one of such developmental disorders, which attracted the attention of one and all given heavy stress suffered by the victim during his lifetime and his family and the social impact. Decades of research directed towards improvement and simplification of diagnostic criteria of Autistic disorder resulted in substantial changes from the specifications mentioned in DSM-4 while finalizing the fifth edition of DSM See **Fig. 1**. Paramount changes include i. The removal of different pervasive developmental disorders (PDDs), ii.) The creation of the "spectrum" diagnosis, iii.) And the merging of three core domains of Autism into two domains ¹². The DSM-5 Neurodevelopmental Disorders Work Group observed that there had been a lot of overlap and

confusion among clinicians and judiciary while diagnosing precisely the 5 pervasive developmental disorders as per diagnostic criteria specified in DSM-4. This confusion was obfuscating the efforts associated with treatment options. The separate PDDs as specified in DSM-4 showed some similarities and exhibited overlapping symptoms, which influenced proper therapy and insurance coverage¹³. Under the classification of the DSM-IV-TR, a majority of individuals suffering from Autism were diagnosed into the PDD-NOS category, which was unreasonable and ambiguous.

The Work Group addressed this concern by reclassifying these five maladies into a single diagnosis of Autism spectrum disorder. The creation of the Autism spectrum was an advance diagnostically, as it helped to remove pseudo-specificity and created an all-inclusive diagnosis for a very heterogeneous disorder⁴. A second major change in Autism diagnosis involved merging defective social interaction and communication (difficulties) into a single (the first) domain while preserving restricted and repetitive behaviors in the second domain⁴.

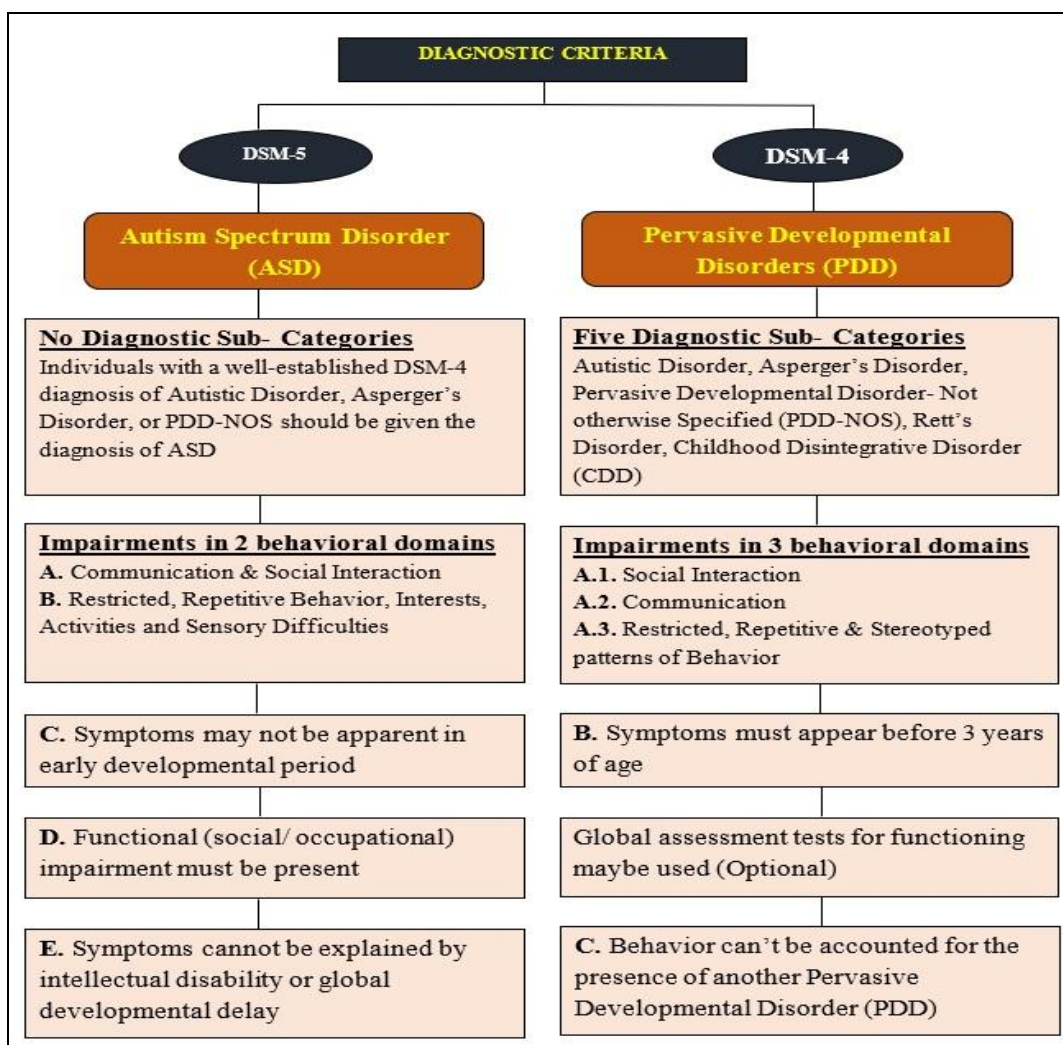


FIG. 1: DSM-4 VS. DSM-5 DIAGNOSTIC CRITERIA⁴

Thus, the new system of Autism Spectrum Disorder classification as per DSM-5 covers symptoms in two domains: The 'social communication and interaction domain', including deficits in verbal and non-verbal communication and the 'restricted, repetitive behavior domain'. See Fig. 2. The social-communication domain is monothetic and the restricted, repetitive behaviors domain is

polythetic. The DSM-5 criteria for ASD also introduced a series of specifiers to include descriptors that apply trans-diagnostically. Specifiers for Autism spectrum disorder include accompanying intellectual or language impairment or an association with a medical/ genetic condition / environmental factor; with another neuro developmental, mental/behavioral disorder; or

catatonia¹¹. Severity specifiers (ranging from levels, i) mild, ii) moderate, iii) severe) indicating a need for support, substantial support, or huge support, respectively are also provided. In DSM-5, the symptom presentation for Autism spectrum disorder must be evident during early development “but may not become fully manifest until social demands exceed limited capacities, or may be masked by learned strategies in later life”. Another

welcome addition to the DSM-5 Autism spectrum disorder classification is the requirement for mental health professionals to individualize assessments by determining how therapeutic intervention, compensation and current supports have improved or masked the symptoms⁴. The DSM-5 has lowered the threshold for diagnosing Autism spectrum disorder by emphasizing the importance of adaptive functioning and clinical assessment.

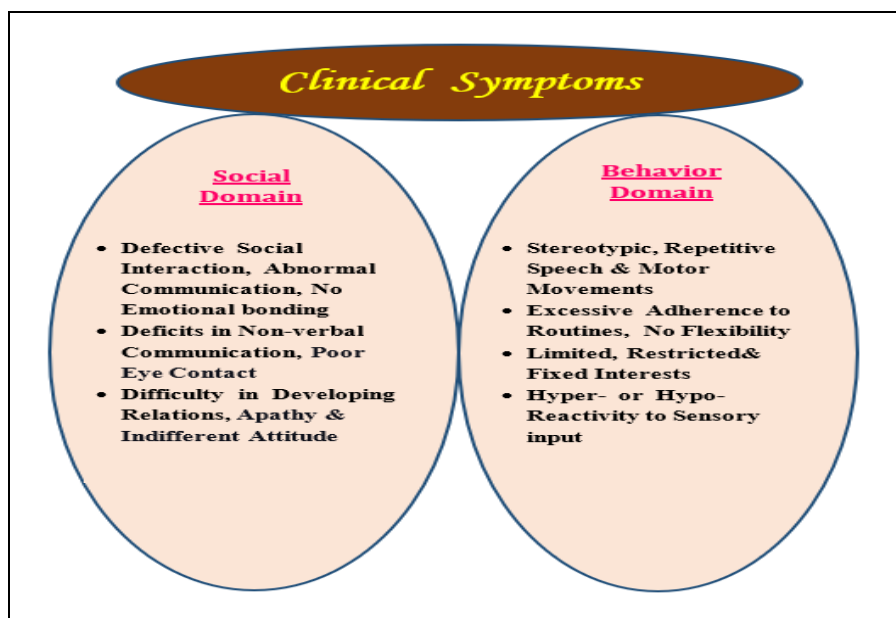


FIG. 2: CLINICAL SYMPTOMS OF ASD

ICD-11 Guidelines (Approved by WHO for Prospective Implementation from January 2022): The eleventh edition of the “International Classification of Diseases and Related Health Problems” (ICD-11), is in pipeline for prospective implementation by WHO from January 2022. This edition of ICD-11 guidelines has an updated chapter on “Mental, Behavioral and Neuro developmental Disorders”, which is in agreement with recent specifications made in the DSM-5. In the new edition of ICD-11, the category ‘neurodevelopmental disorders’ covers I) Disorders of intellectual development, II) Developmental speech or language disorders, III) Autism spectrum disorders (ASD), IV) Developmental learning disorders, V) Developmental motor coordination disorder, VI) Attention deficit hyperactivity disorder (ADHD), VII) Stereotyped movement disorder, and VIII) a residual category labeled as ‘Other neurodevelopmental disorders’⁴. The pervasive developmental disorders mentioned in the ICD-10, including childhood Autism, atypical

Autism and Asperger syndrome, have disappeared entirely and are now grouped under one category, namely ASD. The age of onset for ASD is now broader in the proposed guidelines and mentioned as an early developmental period rather than being specified as 3 years of age. As per the ICD-11, both ASD and ADHD may co-exist in the same individual. The recognition that ADHD and ASD can co-exist is also an important refinement that is extremely useful to clinicians. In both the DSM-5 and the ICD-11, grouping all these individuals together are now accompanied by adding different ‘specifiers’ to the ASD diagnosis in an attempt to take account of the enormous heterogeneity inherent in the disorder’s presentation. These specifiers include intellectual level, language level, medical, genetic, or mental health comorbidities¹⁴. The DSM-5 is regarded to be the “gold standard in ASD diagnosis” and the ICD-11 guidelines closely mirror the DSM-5 approach but do distinguish Autism with and without intellectual disabilities. ICD-11 guidelines for ASD have been substantially

refined to cover the limitations and experience of ICD-10, DSM-4 and DSM-5, including the life-long presentations of ASD.

Childhood Disorders: There are several childhood disorders that are likely to mystify or complicate Autism Spectrum Disorder. It is, therefore, necessary for health care professionals to be aware of the typical features of the childhood disorders discussed below.

Neuro-Developmental Disorders (NDDs): The term “neurodevelopmental” designates that the cause is situated neurologically before or during birth² influencing the child's normal development. Neurodevelopmental disorders (NDDs) are defined as a group of conditions with onset in the developmental period, inducing deficits that produce impairments in personal, social, academic, or occupational functioning in later life (DSM-5). NDDs comprise of intellectual disability (ID); Communication Disorders; Autism Spectrum Disorder (ASD); Attention-Deficit/Hyperactivity Disorder (ADHD); Neurodevelopmental Motor Disorders, including Tic Disorders; and Specific Learning Disorders¹¹. In all of these disorders, a child's normal growth is compromised to varying degrees. Childhood disorders such as Attention Deficit Hyperactivity Disorder (ADHD), Autism spectrum disorder (ASD), and Intellectual disability (ID) are typically complex, heterogeneous conditions that show considerable clinical overlap. There are both genetic and environmental contributions to their etiology, which are not yet fully elucidated¹⁵. Neurodevelopmental disorders are characterized by childhood delays in developmental domains, such as cognition, motor activities, executive functioning, language/communication, social functioning and adaptive behavior. The range of developmental deficits varies from child to child depending upon the specific limitations of learning, global impairments, defective social skills, or intelligence².

Intellectual Disability: Intellectual disability is a disability characterized by severe drawbacks in both intellectual functioning and adaptive behavior. Intellectual functioning is also called as intelligence or intellect of a person. The ICD-11 guidelines specify diagnostic criteria for a distinct category of intellectual developmental disorders.

Intellectual disability is a term used when there are limits to a person's ability to learn reason and function at a normal pace in daily life. Intellectual disability is characterized by deficits in general mental abilities, such as reasoning, problem-solving, planning, abstract thinking, judgment, academic learning, and learning from experience. These deficits result in impairments in communication, social participation, occupational functioning, adjust-ability in new settings and confidence levels. The diagnosis is used for individuals who cannot undergo systematic assessments of intellectual functioning, including children who are too young to participate in a standardized testing protocol. Levels of intellectual disability vary greatly in children, *i.e.*, Mild, Moderate, Severe, and Profound. When intellectual disability is associated with a genetic syndrome, there may be a characteristic physical appearance (*e.g.*, Down syndrome). Intellectual disability is categorized as a neurodevelopmental disorder and is distinct from neurocognitive disorders characterized by the loss of cognitive functioning¹¹. Intellectual disability is common among individuals suffering from Autism spectrum disorder. Assessment of intellectual ability may be complicated by social, communication and behavior deficits inherent to both the disorders¹¹. IQ (Intelligence Quotient) test is often applied to measure the intelligence of a person. Most people have an IQ in the range of 85-130. IQ below 75 is abnormal and above 125 is outstanding /rare (found in highly talented individuals). The average IQ of an Indian is 82, Russian: 97, American: 98, German: 99, British: 100. Japanese: 104, South Korean: 105, and Chinese: 106, Singaporean: 107.

Communication Disorders: Disorders of communication include deficits in language, speech and communication. Speech is the expressive production of sounds and includes an individual's articulation, fluency and voice and resonance quality. Language includes the form, function, and use of a conventional system of symbols (*i.e.*, spoken words, sign language, written words and pictures) in a rule-governed manner for communication. Communication includes any verbal or nonverbal behavior that influences another individual's behavior, ideas, or attitudes. The communication disorders include language

disorder, speech disorder, social (pragmatic) communication disorder and childhood-onset fluency disorder (stuttering). The first three disorders are characterized by deficits in the development and use of language, speech, and social communication, respectively. Speech disorders prevent people from forming correct speech sounds, while language disorders affect a person's ability to learn words or understand what others say to them. However, both speech and language disorders make it difficult for a person to express his thoughts and feelings to others. The core diagnostic features of language disorder are difficulties in the acquisition and use of language due to deficits in the comprehension or production of vocabulary, sentence structure, and discourse. The language deficits are evident in spoken communication, written communication, or sign language. Language learning is dependent on both receptive and expressive skills. Speech sound disorder is heterogeneous in its underlying mechanisms and includes phonological disorder and articulation disorder. A speech sound disorder is diagnosed when speech sound production is not what would be expected from a child of that age group and developmental stage. Furthermore, when the deficits are not the result of a physical, structural, neurological, or hearing impairment.

Social (pragmatic) Communication Disorder: Social (pragmatic) Communication Disorder is characterized by a primary difficulty with pragmatics, or the social use of language and communication, as manifested by deficits in understanding and following social rules of verbal and nonverbal communication in naturalistic contexts, changing language according to the needs of the listener or situation and following rules for conversations and storytelling. A childhood-onset Fluency Disorder is characterized by disturbances of the normal fluency and motor production of speech, including repetitive sounds or syllables, prolongation of consonants or vowel sounds, broken words, blocking, or words produced with an excess of physical tension. Like other neurodevelopmental disorders, communication disorders begin early in life and may produce lifelong functional impairments¹¹. Autism spectrum disorder is the primary diagnostic consideration for individuals presenting with social

communication deficits (Communication Disorders). The two disorders can be differentiated by the presence or absence of restricted/ repetitive patterns of behavior, interests/activities. Restricted/ repetitive behavior patterns, interests/activities are present in patients suffering from Autism spectrum disorder and absent in social (pragmatic) communication disorder¹¹.

Attention-Deficit Hyperactivity Disorder [ADHD]: ADHD is a neurodevelopmental disorder characterized by marked inattention, disorganization and/or hyperactivity (impulsivity) that interferes with functioning or development. Inattention and disorganization interfere with the ability to stay on task. The children suffering from ADHD frequently lose things and materials, which is unexpected at their age. Hyperactivity (impulsivity) signifies over-activity, fidgeting, inability to stay seated, intruding into other people's activities and lack of patience. In childhood, ADHD frequently overlaps with disorders that are often considered "externalizing disorders," such as Oppositional defiant disorder and Conduct disorder. ADHD begins in childhood, and symptoms are manifest before the child becomes 12 years old. ADHD often persists into adulthood, with resultant impairments in social, academic and occupational functioning¹¹. Individuals with ADHD and those with Autism spectrum disorder exhibit inattention, social dysfunction, and difficult-to-manage behavior. The social dysfunction, restlessness and peer rejection seen in individuals with ADHD must be distinguished from the social disengagement, isolation, and indifference to facial and tonal communication cues displayed by individuals with an Autism spectrum disorder. Children with Autism spectrum disorder may display tantrums because of resistance to tolerate a change in routine. In contrast, children with ADHD may misbehave during a major transition because of impulsivity or poor self-control. The increased aggression that may occur in ADHD must also be distinguished from the repetitive motor behavior that characterizes some cases of Autism spectrum disorder¹¹.

Motor Disorders: The neurodevelopmental motor disorders include Developmental Coordination Disorder, Stereotypic Movement Disorder, and Tic disorders¹⁶. Developmental Coordination Disorder

is characterized by deficits in the acquisition and execution of coordinated motor skills and is manifested by clumsiness and slowness. Individuals suffering from this disorder exhibit inaccuracy in performance of motor skills and frequent unprecedented falls or abnormal postures to prevent falls, which interfere with daily routine activities. Individuals with Autism spectrum disorder may not show any interest in tasks testing coordination skills, such as ball sports, thereby interfering with the diagnosis of coordinated motor competence. Co-occurrence of developmental coordination disorder and Autism spectrum disorder is common¹¹.

Stereotypic Movement Disorder: Stereotypic Movement Disorder is diagnosed when an individual makes repetitive, seemingly driven, and purposeless motor behaviors, such as hand flapping, body rocking, head banging, self-biting, or hitting. The movements interfere with social, academic, or other meaningful activities. If the behaviors cause self-injury, this should be specified as a part of the diagnostic description. Stereotypic movements may be a presenting symptom of Autism spectrum disorder and should be considered when repetitive movements and behaviors are being evaluated. Deficits of social communication and reciprocity as specified in the social domain (DSM-5) manifesting in Autism spectrum disorder are generally absent in stereotypic movement disorder¹¹.

Tic Disorders: Tic Disorders are characterized by the presence of motor or vocal tics, which are abrupt, sudden, rapid, recurrent, non-rhythmic movements/ vocalizations (sounds). For example, a child with tics may shrug his shoulders/flare nostrils/clench fists/ blurt out offensive words/blink repeatedly and rapidly even though there is no irritation in the eyes. The duration of Tic symptoms, age at onset, presumed etiology, and clinical presentation defines the specific type of Tic disorder, *viz.* Tourette's disorder, Persistent (Chronic) Motor or Vocal Tic disorder, Provisional (Transient) Tic disorder, other specified Tic disorder, and or unspecified Tic disorder. The Tic disorders are hierarchical in order (*i.e.*, Tourette's disorder, followed by persistent [chronic] motor or vocal Tic disorder, followed by provisional Tic disorder, followed by the other specified and

unspecified Tic disorders), such that once a Tic disorder at one level of the hierarchy is diagnosed, a lower hierarchy diagnosis cannot be made¹¹. Tic symptoms get reduced on relieving the stress of the child. The most notable Tic disorder is Tourette syndrome.

Tourette's Disorder: In Tourette's disorder both the brain and nerves show abnormalities, causing people to make uncontrollable repeated movements (physical) and sounds (verbal), also known as motor and vocal tics. The symptoms usually begin in childhood, can vary from mild to severe and change over time. Tic disorders are inherited. Tourette disorder shows a waxing-waning symptom phenomenon, which can cause problems to the child's physical, mental and emotional well-being¹⁶. There are no fool-proof tests to diagnose Tic disorders, therefore may be confused with ASD. Tourette Disorder is self-diagnosable and may last for years/entire life.

Specific Learning Disorder: Specific learning disorder (SLD) as the name implies is diagnosed when there are specific deficits in an individual's ability to perceive or process information efficiently and accurately. This neuro developmental disorder first manifests during the years of formal schooling and is characterized by persistent difficulties in learning basic academic skills such as reading, writing, rhyming, grammar, punctuations, controlling crayons and pencils, reciting poems, and/or arithmetic. The individual's academic performance is well below average. Specific learning disorders may occur in intellectually gifted children as well and may manifest only when the learning assessment procedures (e.g., timed tests) cannot be overcome by innate intelligence. For all individuals, specific learning disorders can produce lifelong impairments in activities dependent on the skills, including occupational performance. Having a learning disorder means that a child has difficulty in one or more areas of learning, even when overall intelligence or motivation is not affected. Types of learning disorders include Dyslexia (difficulty in reading/spellings), Dyscalculia (difficulty with math/numbers/calculations), Dysgraphia (difficulty in writing/graphics/drawing)¹¹. Children with SLD often experience difficulty in communicating and grasping what others have expressed. Although

learning disability is a lifelong challenge, one can improve to a large extent with appropriate support and intervention. Clinicians should take into account the clinical signs of Specific Learning Disorders (SLD) before arriving at the diagnosis of ASD.

Pervasive Developmental Disorders: The diagnostic category Pervasive Developmental Disorders (PDD) (DSM-4) represented a group of disorders characterized by delays in developing multiple basic functions, including socialization and communication skills. The pervasive developmental disorders included Autism, Asperger syndrome, Childhood disintegrative disorder (CDD) and Rett syndrome. Pervasive developmental disorder not otherwise specified (PDD-NOS) referred to the diagnosis of Autism applied to children who exhibited some symptoms but did not fully meet the criteria laid down in DSM-4 (Atypical Autism). The diagnostic category of Pervasive Developmental Disorders (PDD) is now merged into a single category of Autism Spectrum.

Autism Spectrum Disorder (ASD): Autism spectrum disorder is a complex, life-long neurodevelopmental disorder with the onset of symptoms in the early developmental period. Autism spectrum disorder (ASD) is a collective term for a group of heterogeneous disorders, characterized not only by defective reciprocal social skills and poor communication but also by limited imagination, restricted interests, and repetitive behavior patterns (DSM-5). These symptoms evoke severe impairments in social, occupational, and other important areas of everyday functioning. It is a developmental disability that affects the way patients communicate, behave, or interact with others. The core symptoms of ASD have a devastating impact on the child's functioning and quality of life and his family across the lifespan. Children suffering from ASD may avoid eye contact, repeat actions like turning around themselves and use the parent's hand instead of pointing to indicate an object they want. They may show no interest in people in their vicinity, including their parents, and show an inability to understand the feelings/intentions of others. The child suffering from Autism prefers to keep himself/herself isolated from the surrounding

interactions. As a consequence, these children would prefer toys, showing disregard to other children and adults. High Functioning Autism (HFA) is an Autism subcategory where the patient exhibits no intellectual disability but may have poor communication skills, indifferent attitude, no emotional bonding, and deficits in reciprocal social interaction. However, Intellectual Disability, ADHD, and Autism spectrum disorder frequently co-occur.

Asperger Syndrome (AS): Asperger syndrome can be looked upon as a mild Autistic disorder. People with this condition may be socially awkward but show an absorbing interest in certain topics. Generally, high functioning Autism patients suffer from Asperger syndrome. High functioning Autism signifies that these children suffering from Asperger syndrome show normal language skills, intellect, and cognitive functions. The children with AS take a firm stand on what they think is right and focuses on rules and routines. However, they do face difficulty in social interaction and do engage in repetitive behavior. Early diagnosis and behavioral intervention can help the child achieve full potential to lead a normal productive life. Asperger syndrome is an integral part of Autism spectrum disorder, though, on the mild side of the spectrum.

Childhood Disintegrative Disorder (CDD): Childhood disintegrative disorder, also known as Heller's Syndrome / Disintegrative Psychosis, is grouped under pervasive developmental disorders. It is a rare condition characterized by late-onset (beyond 3 years of age) developmental delays with severe and sudden reversals in previously acquired language, social function, and motor skills. An apparent period of fairly normal development is often noted before a regression in skills. The age at which this regression can occur varies but is typically seen after three years of reaching normal milestones. About half the children diagnosed with CDD show an abnormal electroencephalogram (EEG). CDD has some similarities to Autism and is sometimes considered a low-functioning form of it. In the DSM-5, CDD is merged into Autistic spectrum disorder.

Rett Syndrome: Rett syndrome is also known as RTS or Cerebroatrophic hyperammonemia. Rett

syndrome is an extremely rare genetic neuro developmental disorder that affects the way the brain develops in girls, causing a progressive loss of motor skills and speech. Rett syndrome is caused by a mutation in the methyl CpG binding protein 2 or MECP2 gene on the X-Chromosome. Despite being caused by a gene mutation, Rett syndrome is rarely inherited. Rett syndrome typically becomes apparent after 6-18 months of age. Infants seem normal and healthy during the first six months, but over time, they rapidly lose coordination, language, speech followed by a slowing of development, repetitive movements, loss of purposeful use of the hands, peculiar hand movements, slowed brain and head growth, problems with walking, seizures and intellectual disability. Apraxia (the inability to perform motor functions) is perhaps the most severely disabling feature of Rett syndrome, interfering with every body movement, including eye gaze and speech. Children with Rett syndrome often exhibit Autistic-like behaviors in the early stages.

Cerebral Palsy: Cerebral palsy (CP) represents a group of disorders that affect a person's ability to move, maintain balance, and posture. Cerebral palsy = Cerebral + Palsy. The term Cerebral reflects related to the brain. Palsy means weakness in using the muscles. It is a congenital disorder of movement, muscle tone, or posture. CP is the most common motor disability in childhood. CP is caused by abnormal brain development in the womb or damage to the developing brain usually before/during birth/premature delivery/maternal infections. The early signs shown by the child include Delays in rolling over/ sitting/ crawling/standing/walking *etc.* The clinical symptoms of CP comprise exaggerated reflexes, rigid limbs, and involuntary movements. A person suffering from CP may not be able to walk at all and may demand lifelong care. There are 4 types of Cerebral Palsy, *viz.* 1 Spastic CP, 2 Dyskinetic CP, 3 Ataxic CP and 4 Mixed CP. Related conditions such as intellectual disability; seizures; problems with vision, hearing, or speech; changes in the spine (such as scoliosis); or joint problems (such as contractures) may be present. All these conditions overlap to some extent with ASD features.

Down's syndrome: Down's syndrome is also known as trisomy ²¹. It is a genetic disorder caused

by abnormal cell division resulting in the presence of all or part of the third copy of chromosome 21 (extra genetic material) in the baby. It is usually associated with physical developmental delays, mild to moderate intellectual disability and characteristic facial features (A flattened face with almond-shaped eyes that slant up, short neck, and small ears). It is an incurable disorder. Early developmental delay signs overlap with ASD symptoms, thereby complicating the diagnosis of ASD.

Fragile X Syndrome (FXS): Martin-Bell syndrome is a rare inherited genetic condition causing intellectual and developmental disabilities. Each cell in the body contains thousands of genes. These genes determine many things about a person. For example, the looks of a person, his IQ, his adaptability, potential illnesses, *etc.* In addition, genes have instructions for making proteins in the cells. These proteins are essential for the proper working/functioning of the body. FXS is caused by a change in a gene called the fragile X mental retardation 1 (FMR1) gene. The FMR1 gene makes a protein called fragile X mental retardation protein (FMRP), which is needed for normal brain development. The altered (FMR1) gene makes an abnormal protein causing Fragile X syndrome. It affects both males and females, but females usually have milder symptoms. Symptoms include delays in talking, learning disabilities, developmental delays, and social/behavioral problems, anxiety, and hyperactive behavior. Physical features include large ears. A long face, a prominent jaw & forehead and flat feet. However, these disabilities vary in severity from one child to another. Fragile X syndrome overlaps in symptoms with ASD since intellectual and developmental abnormalities are seen in both of these disorders.

All the above childhood disorders exhibit some common symptom-pattern with Autism Spectrum Disorder and may co-occur with Autism.

Risk Factors Leading To Autism Spectrum Disorder: The traditionally acknowledged pathological and non-pathological conditions resulting in ASD include compromised immune system, mitochondrial dysfunction, intellectual disability, prenatal, perinatal, postnatal factors, adverse environment, gynecological interventions,

and defective genes, which work independently or in combination to alter the functional capacity of the brain ¹⁷. **Fig. 3.** illustrates the risk factors /causes associated with Autism.

Vaccines Controversy and Autism: The discovery of vaccines is considered a huge success story for community health. Yet, misconceptions exist around vaccines and ASD. The most controversial report highlighting “administration of measles-mumps-rubella (MMR) vaccine led to Autism” appeared in The Lancet in 1998 when Wakefield hypothesized that MMR vaccine could probably lead to the development of intestinal abnormalities, neurodevelopmental regression and Autism. This led to the development of tremendous fears in the minds of parents. Well-defined epidemiologic studies found no link of the MMR vaccine to Autism ¹⁸. A systematic survey conducted in all children, who had taken birth in Denmark from 1991-1998 observed no inter-connection between the age of the child during MMR vaccination, a dosing schedule of vaccination and the occurrence of Autism. These results demonstrating no correlation between

Autism and MMR vaccination were confirmed by ecological studies executed in Japan, UK, America, and Canada. Since the MMR vaccine was not a causative factor of Autism, the Wakefield paper was retracted by the Journal consequently. A recent study shows that the MMR vaccine is not associated with enhanced chances of developing ASD, even in children who are particularly susceptible to Autism, because of having an elder brother/ sister diagnosed with ASD ¹⁸. Adverse environments, infectious diseases, and genetic components are substantially involved in causing ASD. Vaccination is a time-tested healthcare strategy to counter fatal infectious diseases in children. The recommended schedule of childhood vaccines (like MMR, Diphtheria-pertussis-tetanus (DPT), etc.) varies greatly in different countries ¹⁹. The lack of MMR vaccine administration in children due to MMR controversy has led to the outbursts of measles in America and the recurrence of this disease in Europe ¹⁸. Well-designed investigations did not indicate any link between the MMR vaccine and the presence of either mercury or aluminum content in vaccines to Autism ¹⁹.

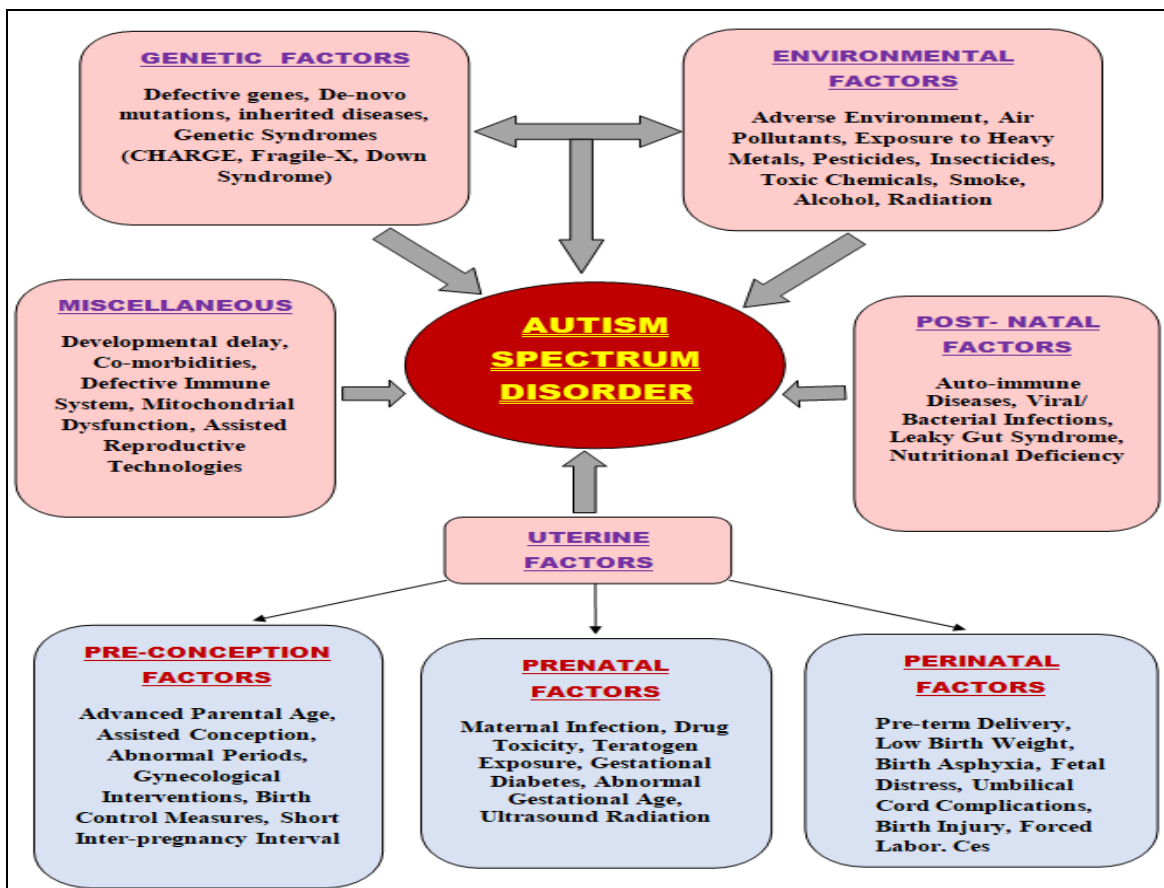


FIG. 3: RISK FACTORS RESPONSIBLE FOR ASD

On the other hand, Children following the prescribed vaccination schedule had lower chances of suffering from ASD than children with inadequate vaccination²⁰. Thus, vaccines appear to be crucial in preventing ASD owing to direct effects on the immune system producing protective antibodies and indirect effects of counter-acting the occurrence of childhood infections^{20, 21}. The vaccination approach has been a big accomplishment for mankind to overcome viral/bacterial infections.

Safety of Thimerosal as a Vaccine Preservative:

Thimerosal was amongst the most promising new organomercurials with bactericidal activity, which was used as a preservative in vaccines to enhance the shelf-life. Thimerosal (49% ethyl mercury) administered to children through childhood vaccines responsible for an epidemic of Autism, created a controversy in the 1990s²². As a preventive step, the USA switched over to a childhood vaccine program that did not contain thimerosal, with the exception of the multi-dose influenza vaccine. Nevertheless, Autism prevalence continued to rise irrespective of the presence or absence of thimerosal in the vaccine preparations. The findings of carefully planned epidemiologic investigations established zero risks of ASD linked to vaccines having thimerosal as an ingredient. The incidence of Autism did not differ when separate groups of children were administered the pertussis vaccine with or without thimerosal. The proposed interconnection between thimerosal and ASD was also rejected by the "Institute of Medicine" (IOM). Furthermore, several studies in the UK, USA and Italy countries found no correlation between the incidence of Autism and thimerosal intake in early childhood²¹. More recently, controlled observational studies in children subjected to both MMR and thimerosal-containing vaccines revealed that these were not endangered to the development of ASD^{21, 22}.

Comorbidities: Clinicians have long been aware that ASD is often accompanied by other difficulties. In addition to ASD, the earliest considerations are usually developmental delay, intellectual disability, language and motor difficulties. DSM-5 recognizes this complexity by allowing multiple diagnoses, even within psychiatry, such as ASD and ADHD. ADHD is the

most common comorbidity in children with ASD. When criteria for both ADHD and Autism spectrum disorder are met, both diagnoses should be given. This principle also applies to concurrent diagnoses of Autism spectrum disorder and developmental coordination disorder, anxiety disorders, depressive disorders, epilepsy, sleep disorders, and constipation¹¹. Anxiety in different forms such as social anxiety, generalized anxiety, and separation anxiety co-exist with ASD in younger children, which could be due to poor communication skills and defective social interaction. Adolescent girls, in particular, suffer from both phobias and depression along with ASD. Around (25%) children show irritability and aggression when suffering from ASD, unlike other developmental disorders. Autism spectrum disorder is frequently associated with intellectual impairment and structural language disorder (*i.e.*, an inability to comprehend and construct sentences properly). Specific learning difficulties (literacy and numeracy) are routinely observed in children with ASD¹¹.

Idiopathic intellectual disability, when co-occurring with ASD takes the form of minor physical aggression in toddlers and verbal aggression in adults. Other Comorbidities often associated with Autism, include schizophrenia, bipolar affective disorder, epilepsy, Down's syndrome, Tourette syndrome, hypothyroidism, intellectual impairment, metabolic disorders, and hypertension¹⁷. Avoidant-restrictive food intake disorder is a fairly frequent presenting feature of Autism spectrum disorder exhibited by extremely selective and narrow food preferences. Undisputedly, the co-occurrence of different disorders with ASD seems to be normal rather than the exception. ASD increasingly appears to be not a single disorder but a blend of common core symptoms accompanied by a large variability of symptoms characteristic of other disorders. In fact, instead of studying ASD as a distinct, no so logical entity, it should be studied as part of a continuum, which can embrace other neurodevelopmental disorders²³.

Management of Autism Spectrum Disorder:

Although no medicine has been recognized to treat ASD, several medicines have been proposed to ameliorate co-morbid conditions and ASD-associated symptoms such as self-harm, aggressive

episodes, irritability, unusual conduct, in-attention, anxiety, depression, hyperactivity and insomnia. Complementary therapies such as cognitive behavioral therapy, Speech therapy, music therapy, educational therapy, psychotherapy, occupational therapy and nutritional therapy have shown partial benefits when applied individually as per the specific needs of the child¹⁰. Most importantly, compassionate care coupled with assurance and reassurance by the parents and friends is crucial. No single therapy works completely for all kinds of patients. Different treatment approaches have been practiced to address different aspects of social behavior, communication deficits, physical disabilities, specific symptoms, and comorbidities. Therefore, designing appropriate routine and behavioral support by a psychotherapist tailored for

each child as per its symptoms is essential for providing a comfortable life. Several substances targeting immune dysfunction, neuroinflammation, glutamate/GABA imbalance, NMDA receptors, and neuropeptides are undergoing clinical trials with variable success. Stem cell therapy aimed at preventing neuro-degeneration, modulating the immune system and improving brain function is also being investigated. To help the unfortunate child and improve the quality of life of concerned families, an integrative approach combining drug therapy and non-drug therapy offers a great promise. See **Fig. 4**. However, along with the therapeutic management, the cooperation of family members backed by society is necessary for enhancing the quality of life of a child suffering from ASD¹⁰.

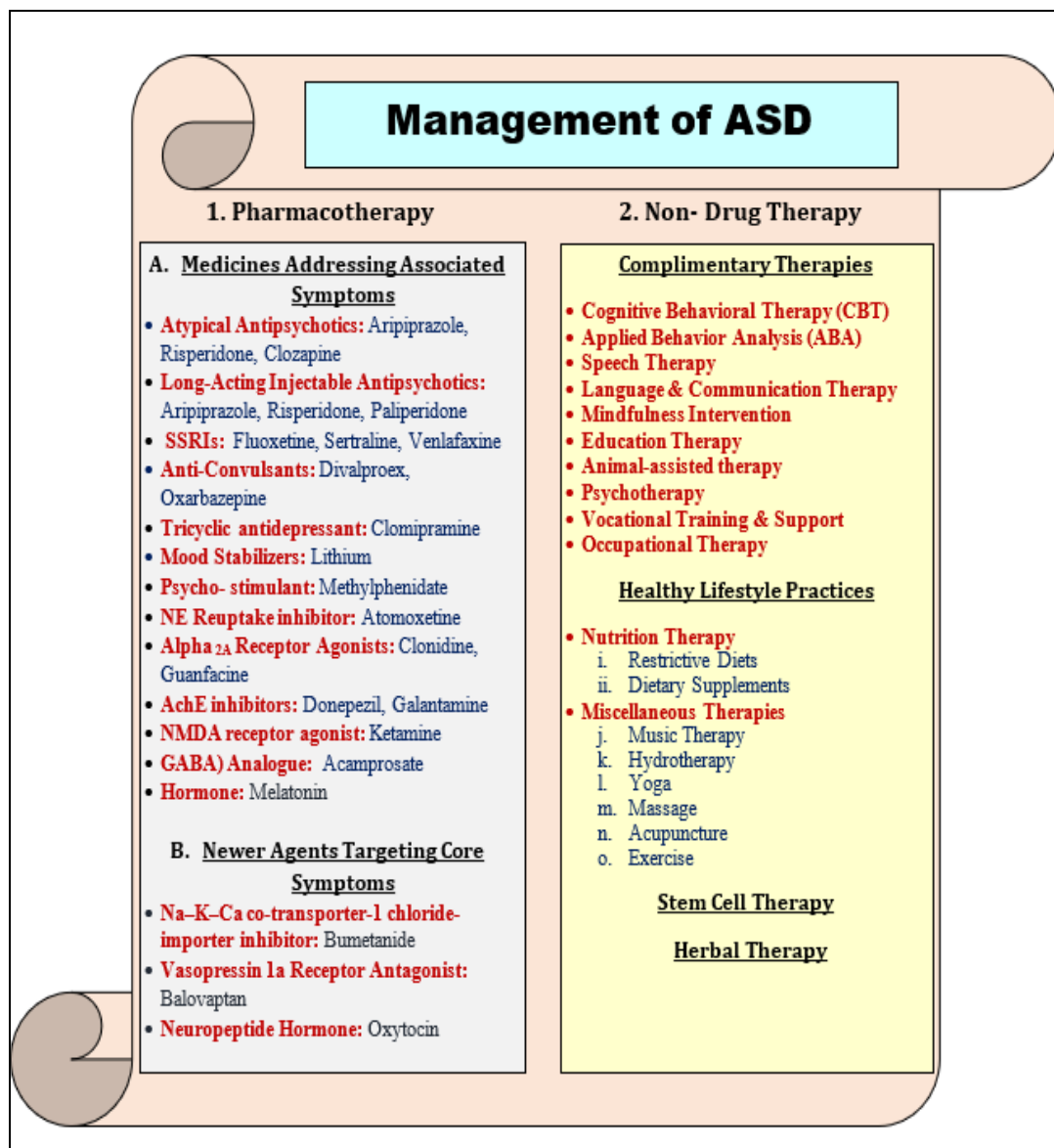


FIG. 4: MANAGEMENT OF ASD

Autism in Media: Since the 1970s, fictional portrayals of individuals with Autism have become popular. Public perception of Autism is often based on these fictional portrayals in novels, biographies, movies, and television series. Even with steps forward, the media is still criticized for not representing all aspects of the Autism spectrum.

Although many portrayals in popular media are meant to spread awareness, some have perpetuated unrealistic stereotypes. Mainstream media tends to focus on a single part of the Autism spectrum. The “Autistic savant,” a person with Autism, who has exceptional skill or brilliance in some limited field, is the most common theme.

<u>Autism in International Media</u>	<u>Autism in Indian Media</u>
<ul style="list-style-type: none"> • Silence (1974) • The Boy Who Could Fly (1986) • Rain Man (1988) • I Am Sam (2001) • The Black Balloon (2008) • The Horse Boy (2009) • Ocean Heaven (2010) • Temple Grandin (2010) • Girls With Autism (2015) • The A Word (2016) • A Boy Called Po (2016) • Atypical (2017) • The Good Doctor (2017) • Please Stand By (2018) 	<ul style="list-style-type: none"> • Anjali (1990) • ApnaAsman (2003) • Koi Mil Gaya (2003) • Main Aisa Hi Hoon (2005) • AAP Ki Antara (2009) • Barfi (2012) • Haridas (2013) • Hey Jude (2018)

FIG. 5: PORTRAYAL OF AUTISM IN MEDIA

The most popular representations of Autism in the media include movies such as “Rain Man” and TV shows such as the Good Doctor. Every performance does have nuances that make their portrayal of the Autism spectrum unique, but there are some recycled depictions. One common theme throughout these movies and TV shows is the repeated portrayal of males with savant syndrome. Rain Man portrayed a man with Autism having extraordinary ability in card counting and “The Good Doctor” represented a medical resident with incredible memory and skills. Although portraying a character with savant abilities and ASD is not inaccurate, it only represents about 10 percent of individuals on the Autism spectrum. Perhaps this is the method by which media can make Autism more “accessible” or more “relatable” to the general public. The media needs to capture a holistic portrayal of Autism better so that all ranges of the spectrum are included. Media portrayal has and always been directly linked to public mindset and perception. In regards to the Autism spectrum, the gradual increase in representation of people with Autism has allowed for greater recognition of the community. But recognition and baseline understanding is not enough. Mainstream media needs to do better at accurately representing the

entire Autism spectrum. We need to start seeing characters on TV and in movies which reflect the breadth of experiences of people with Autism. However, within the past few years, a variety of networks have begun introducing more diverse characters with Autism. With the release of these new productions, mainstream media appears to be moving towards a more holistic portrayal of the Autism community.

Organizations Working to Improve the Quality of Life of Autism Patients: Various governmental and non-governmental organizations are working worldwide to increase public awareness about Autism, the day-to-day issues, of patients and their families across the Autism spectrum. These organizations advocate for appropriate services for patients of all age groups and provide the latest information regarding treatment, education, research, and advocacy. The mission of some of these organizations is to apply research findings to overcome the challenges of Autism. These organizations use science to address the social, educational, and treatment concerns of self-advocates parents, Autism professionals, and caregivers. In addition to funding research, they disseminate new and useful information to as many

members of the Autism community as possible and direct all research and programs initiatives toward enhancing the quality of life of individuals suffering from Autism. Apart from these

organizations, various web resources are also available for supporting Autism patients, their families and educators of children with Autism Spectrum Disorder.



FIG. 6: ORGANIZATIONS WORKING FOR AUTISM PATIENTS

Future Perspectives: It's just natural for every parent to aspire for a brilliant child and strive for optimal nurturing during the early years of development. Child growth-related botheration, childhood diseases, and neurodevelopmental disorders are all deceptive tortuous conditions difficult to diagnose at the right stage. This review article has humbly dealt with the evolution of the concept of Autism Spectrum Disorder (ASD) juxtaposing several childhood disorders that exhibit similar symptom patterns. The term neurodevelopmental disorder reflects some form of abnormality in brain development. Furthermore, neurological and psychiatric conditions are pathologically and clinically altogether distinct.

Neurodevelopmental disorders are typically heterogeneous and multifactorial in origin. The segment of overlap among neurological, psychiatric, and neurodevelopmental disorders alongside their constituent symptom dimensions is very large. Childhood neurodevelopmental disorders such as attention deficit hyperactivity disorder (ADHD), Autism spectrum disorder (ASD), childhood schizophrenia, and intellectual disability (ID) typically are complicated conditions that not only show considerable clinical overlap but often co-exist. Overall, the authors recommend an open and flexible approach in clinical practice while dealing with these disorders since the child's

entire future life is at stake. Experts from a wide range of disciplines (e.g., child psychiatrists, psychologists, pediatricians, neurologists, gynecologists, speech and language therapists, occupational therapists, *etc.*) need to be consulted for accurate diagnosis and treatment of children suffering from these baffling disorders. Multi-disciplinary professional expertise and combined diagnostic facilities for children facing developmental disorders in general and Autism spectrum disorder, particularly at a multi-specialty center, can help ensure precise assessment and intervention across all neuro-developmental domains to explicitly recognize the overlaps.

The assessments of these disorders and comorbid conditions, which appear to be a rule rather than an exception need to extend beyond core diagnostic criteria, the constraints of a structured interview, social context, and individual's current strengths and weaknesses (e.g., cognitive ability, quality of parenting, income, overall intellect, classroom environment, *etc.*), to devise a comprehensive management plan. Gaps between the latest research findings in this area and clinical practice need to be bridged. ASD has often been studied as a distinct nosological entity and not as part of a continuum, which can embrace other neuro-developmental disorders. Besides, forethought is imperative for developmental change associated with the child's

growth, maturity, middle-age, and old age, while finalizing the treatment schedule. Medical classifications that are based on etiology and biomarkers have important advantages, such as clear targets for intervention. In the case of mental disorders, this is not possible because the etiology of mental disorders is multi-dimensional and incompletely understood. Autism is currently one of the most visible and widely discussed developmental human conditions with no clue about the biomarkers. Over the last century, research in Autism Spectrum Disorder (ASD) has constantly grown. However, the etiology and neurochemistry of this disorder are still a matter of speculation. Furthermore, there is no satisfactory animal model to study ASD pathogenesis. ASD continues to be diagnosed based on the symptoms and behavior of the patient since no reliable biomarker has been singled out to date. As a result, promising remedies for ASD core symptoms are still lacking.

As a whole, we deem that the existing data support the hypothesis that the mechanisms underlying ASD etiology result from the effects of diverse gene-environment interactions, with possible cumulative or even multiplicative effects not only at the individual level but also through the generations. Nevertheless, the authors opine that recent developments in understanding gene-environment interactions are opening up new research vistas, which might eventually lead to a leap forward in our comprehension and treatment of this disorder.

Despite the positive role of the organizations supporting ASD patients and awareness attempts of media, there are persisting needs for better coordination between healthcare systems, service providers, special training schools, residential and employment facilities for gifted individuals, and support measures available for disabled ASD patients. It is anticipated that the crucial advances in high-risk genes and aberrant neuronal circuitry would lead to innovative breakthroughs. Large and heterogeneous sample sizes are needed to identify the interconnection between the effects of adverse environmental exposure during critical (conception, prenatal and postnatal) developmental periods of an embryo within the uterus and the dynamic role of protective factors.

These well-designed investigations would offer new avenues to disentangle the mystery of the development of ASD. Future challenges include understanding the influence of sex differences better, how to learn from these differences, how to apply best what we know about the dimensions that significantly impact the lives of ASD patients in different countries, cultures, and populations. Furthermore, amendments based on “Autistic voices” and input from adolescents suffering from Autism and their families in newer versions of DSM and ICD would surely go a long way in improving the quality of life of the ASD community. We know today much more than what we did many years ago; nonetheless, the west will have plenty to learn and a long journey to travel.

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