REVIEW ARTICLE

SPECTRUM DISORDERS CURRENT KNOWLEDGE AUTISM WITH REFERENCE TO THE ROLE OF ANIMAL MODELS

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ABSTRACT:

Background: *Autism spectrum disorder (ASD) is a set of neurodevelopmental disorders which affects communication, cognition and behavior. It is termed as a "spectrum" disorder because of the wide variation in the type and severity of symptoms people experience. Symptoms generally appear in the first two years of life.*

Aim of the work*: To summarize evidence on the prevalence, etiology, pathogenesis, diagnosis and treatment of ASD and role of experimental animals.*

Observations: *Pathogenesis of ASD represents an area of great uncertainty and yet the many postulated mechanisms are poorly understood. Several theories to regarding ASD pathogenesis exist; neural connectivity, neural migration, and excitatory-inhibitory neural activity. Immune disturbances and glial cell dysfunction were also presumed to play a role. There is still no direct and definite mechanism explaining the pathogenesis of ASD. Diagnosis of ASD can be difficult but it is crucial to ensure receiving support and help as soon as possible. ASDs are generally not "curable," but the main goals of treatment are to lessen associated deficits and family distress, and to increase quality of life and functional independence. Medical, behavioral, or complementary and alternative lines of treatment are employed. Animal models of autism are being developed to meet the urging need for investigating the underlying causes of ASD and to find the proper medication to help treat the condition or control its symptoms.*

Conclusion: *The exact cause of autism spectrum disorder is so far unknown. Further work is needed to broaden the horizons on the understanding of ASD.*

Key words: *Autism spectrum disorders, etiology, pathogenesis, diagnosis, treatment, animal models.*

INTRODUCTION:

Autism spectrum disorders (ASD) describe a group of neuro-developmental conditions. ASD is characterized by; early-onset difficulties in social communication, restricted repetitive and stereotyped patterns of behaviors and narrow interests[1].

Prevalence:

The prevalence of ASD worldwide is estimated to be 1 case per 160 children [2&3]. ASD is more prevalent in developed countries and the United States has the highest rate of autism. ASD prevalence rate has been increasing but this may be attributed to improved detection and diagnostic criteria of the disorder[4]. Prevalence of ASD in the Arab world hasn't been accurately recorded and wasn't clearly known due to the stigma following the affected children. Some organizations have been established like in Saudi Arabia and Egypt to increase

awareness about ASD. Many steps are still needed to be taken to increase the ability of early detection and intervention[5].

Etiology:

It is largely agreed that autism is multifactorial with many risk factors contributing to its pathology including genetic and environmental factors.

Strong genetic component has been suggested first however its role couldn't be identified as definite and direct cause, and this led to the belief of a strong involvement of environmental factors[6].

Genetic contribution could be attained from many conditions like; the average estimation of concordance rate for identical twins is 60-90 % and ranges from 5-31% in dizygotic twins and non-twin siblings and so siblings of ASD individual are at a higher risk of having the disorder. Also, mothers suffering from depression and personality disorders, family history of psychological disorders have been mentioned as risk factors for occurrence of ASD. Phenylketonuria is one of many inborn errors of metabolism that was suggested to cause at least 5% of ASD cases. Many genetic conditions have also been mentioned as risk factors for ASD like; Down syndrome, Turner syndrome, Klinefelter syndrome, and Fragile X syndrome[7].

Many environmental risk factors have been associated with the etiology of ASD, but no single risk factor is identified clearly as a direct and definite cause. Environmental risk factors include chemicals, pesticides, heavy metals, drugs, dietary factors, infection, vaccination, and stress. These factors could affect the mother from preconception period passing by prenatal, post-natal periods to the early childhood period and even factors affecting the father[8].

Many factors have been related to increased incidence of ASD including; advanced parental age more than 35 years, the use of assisted reproductive technology, maternal nutrition during pregnancy for example food that is deficient in vitamin D, folic acid or omega 3, or higher levels of methanol and

Aspartame. Also, maternal body mass index whether obesity or underweight, many medications that may be taken by the mother during pregnancy or even before pregnancy especially both anti-epileptic and anti-depressant drugs out of which valproic acid showed the strongest association with neurodevelopmental disorders including ASD in the offspring[9].

Air pollution has emerged in the last decade as a potential risk factor for ASD. Polluted air usually contains hazardous substances such as chlorinated solvents and heavy metals like; mercury, lead, manganese that may be associated with increased incidence of ASD according to. Prenatal exposure to some pesticides such as organophosphates and organochlorines has been linked with increased occurrence of some ASD traits[10].

Depression, anxiety, and periods of great and long-lasting stress during 21-32 weeks of gestation may lead to increased risk of development of ASD. Maternal infection during the first trimester with infections like; rubella, measles, mumps, chicken pox, influenza, herpes, pneumonia, syphilis, varicella, zoster, and cytomegalo virus. Bacterial infection that needs hospitalization in the second trimester are known risk factors for ASD. Low birth weight or post-natal infections like meningitis, mumps, varicella and unknown fever in the first 30 days of life have also been associated with increased occurrence of ASD[11].

Pathogenesis:

Pathogenesis of ASD represents an area of great uncertainty and yet the many postulated mechanisms are poorly understood.

The neural connectivity theory suggests that ASD may develop due to either over-

connectivity or under connectivity. Over-connectivity is the result of increasing neuron numbers that induce cerebral overgrowth, while under- connectivity is associated with reduced intra-cortical integration. Another theory is neural migration which suggests that ASD may result from defective neural migration to the cerebral cortex during the first 6 months of pregnancy. Excitatory-inhibitory neural activity is another theory that suggests that the abnormality is caused by GABA or glutamate receptor dysfunction. Calcium signaling abnormalities and its effects on excitatory- inhibitory networks have also been postulated. Immune disturbances including suppression of cell mediated immunity and sub-normal levels of CD4 lymphocytes with many other immune related abnormalities were also postulated. A recent promising area of research on ASD pathogenesis is glial cell dysfunction. Although many theories on ASD pathogenesis have been suggested, there is still no direct and definite mechanism explaining the pathogenesis of ASD[12].

Diagnosis:

Diagnosis of ASD can be difficult because there is no reference test like a blood or medical test, but it rather depends on the healthcare giver experience and monitoring the development and behavior of the child.

ASD can be diagnosed at 18-month age or younger however, some children don't receive a definite diagnosis until much older. There are many early signs of ASD that can be detected in children like avoiding eye contact, less communication with other children and the surrounding people, and obvious discomfort following minor changes in routine.

It is crucial to diagnose ASD early to ensure receiving support and help as soon as possible and that can be achieved by several investigations for example:

- Developmental monitoring that is done by observing the child growth and whether the child meets the typical developmental milestones like in playing, behaving, learning and so on.
- Developmental screening which is a more formal way that is done by doctors, nurses and healthcare professionals using brief test or questionnaire to inquire about the child thinking, behavior, language and movement. These tests are recommended to be done during regular visits for normal children at ages 9, 18 and 30 months and specifically for ASD at 18 and 24 months. Additional screening may be done if the child is at a high risk of developing ASD (family history of ASD) or showing behaviors related to ASD.
- Comprehensive developmental evaluation: a screening tool done by healthcare professionals to determine whether the child is on the normal track or should be investigated more and it will decide if the child needs special treatment or early intervention services [13].

The criteria used to diagnose ASD are outlined in the Diagnostic and Statistical Manual of Mental Disorders (DSM) published by the American Psychiatric Association [14&15].

DSM-5 Autism Diagnostic Criteria:

A. **Persistent deficits in social communication and social interaction across multiple contexts, as manifested by the following, currently or by history:**

1. Deficits in social-emotional reciprocity, ranging, for example, from abnormal social approach and failure of normal back-and-forth conversation; to reduced sharing of interests, emotions, or affect; to failure to initiate or respond to social interactions.
2. Deficits in nonverbal communicative behaviors used for social interaction, ranging, for example, from poorly integrated verbal and nonverbal

communication; to abnormalities in eye contact and body language or deficits in understanding and use of gestures; to a total lack of facial expressions and nonverbal communication.

3. Deficits in developing, maintaining, and understanding relationships, ranging, for example, from difficulties adjusting behavior to suit various social contexts; to difficulties in sharing imaginative play or in making friends; to absence of interest in peers.

Severity is based on social communication impairments and restricted repetitive patterns of behavior. (**See the table**).

B. Restricted, repetitive patterns of behavior, interests, or activities, as manifested by at least two of the following, currently or by history:

1. Stereotyped or repetitive motor movements, use of objects, or speech (e.g., simple motor stereotypies, lining up toys or flipping objects, echolalia (meaningless repetition of another person's spoken words as a symptom of psychiatric disorder), idiosyncratic phrases (language occurs when the child uses standard words or phrases in an unusual, but meaningful way)).
2. Insistence on sameness, inflexible adherence to routines, or ritualized patterns or verbal nonverbal behavior (e.g., extreme distress at small changes, difficulties with transitions, rigid thinking patterns, greeting rituals, need to take same route or eat food every day).
3. Highly restricted, fixated interests that are abnormal in intensity or focus (e.g., strong attachment to or preoccupation with unusual objects, excessively circumscribed or perseverative interest).
4. Hyper- or hypo reactivity to sensory input or unusual interests in sensory aspects of the environment (e.g., apparent indifference to pain/ temperature, adverse response to specific sounds or textures, excessive smelling or touching of objects, visual fascination with lights or movement).

Severity is based on social communication impairments and restricted, repetitive patterns of behavior. (**See table I**)

C. 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).

D. Symptoms cause clinically significant impairment in social, occupational, or other important areas of current functioning.

E. These disturbances are not better explained by intellectual disability (intellectual developmental disorder) or global developmental delay. Intellectual disability and autism spectrum disorder frequently co-occur; to make comorbid diagnoses of autism spectrum disorder and intellectual disability, social communication should be below that expected for general developmental level.

Note: Individuals with a well-established DSM-IV diagnosis of autistic disorder, Asperger's disorder, or pervasive developmental disorder not otherwise specified should be given the diagnosis of autism spectrum disorder. Individuals who have marked deficits in social communi-cation, but whose symptoms do not otherwise meet criteria for autism spectrum disorder, should be evaluated for social (pragmatic) communication disorder.

Specify if:

- **With or without accompanying intellectual impairment**
- **With or without accompanying language impairment**
  - (Coding note: Use additional code to identify the associated medical or genetic condition.)

- **Associated with another neuro-developmental, mental, or behavioral disorder**
  - (Coding note: Use additional code[s] to identify the associated neuro-developmental, mental, or behavioral disorder[s]).
- **With catatonia** (abnormality of movement and behavior arising from a disturbed mental state)
- **Associated with a known medical or genetic condition or environmental factor.**

Table: Severity Levels for Autism Spectrum Disorder [16].

Severity level	Social communication	Restricted, repetitive behaviors
Level 3 "Requiring very substantial support"	Severe deficits in verbal and non-verbal social communication skills cause severe impairments in functioning. Very limited initiation of social interactions, and minimal response to social overtures from others. For example, a person with few words of intelligible speech who rarely initiates interactions, and when he or she does, makes unusual approaches to meet needs only and responds to only very direct social approaches.	Inflexibility of behavior, extreme difficulty coping with change, or other restricted / repetitive behaviors markedly interferes with functioning in all spheres. Great distress/difficulty changing focus or action.
Level 2 "Requiring substantial support "	Marked deficits in verbal and non-verbal social communication skills, social impairments apparent even with support in place, limited initiation of social interactions, and reduced or abnormal responses to social overtures from others. For example, a person who speaks in simple sentences whose interaction is limited to narrow special interests, and who has markedly odd nonverbal communications.	Inflexibility of behavior, difficulty coping with change, or other restricted /repetitive behaviors appear frequently enough to be obvious to the casual observer and interferes with functioning in a variety of contexts. distress and/or difficulty changing focus or action.
Level 1 "Requiring support"	Without support in place, deficits in social communication caused noticeable impairments. Difficulty initiating social interaction, and clear examples of atypical or unsuccessful response to social overtures from others .may appear to have decreased interest in social interactions. For example, a person who is able to speak in full sentences and engages in communications but whose to-and-fro conversations with others fails and his attempts to make friends are odd and typically unsuccessful.	Inflexibility of behavior causes significant interference with functioning in one or more contexts. Difficulty switching between activities. problems of organization or planning hamper independence.

Management

ASDs are generally not "curable," and different aspects of management aim to achieve better results. Most children with ASDs remain within the spectrum as adults and regardless of their IQ level they might find it challenging to have separate private lives and to be independent financially through proper employment. The main goals

when treating children with autism are to lessen associated deficits and family distress, and to increase quality of life and functional independence[17].

Goals of therapy in ASD include[18]:

- Improving communication and functional skills.
- Treat and manage comorbid conditions.
- Help decrease and relieve parents fear and stress.
- Eliminate unhelpful and disruptive behaviors.
- Improve social and learning skills.

Medical treatment:

There is still no known treatment of ASD. However, there are some medications are used to control core symptoms like hyperactivity, anxiety and depression and to adjust maladaptive behaviors that are seen more with children suffering from cognitive impairment like aggression, self-injury, impulsivity, decreased attention.

Risperidone and aripiprazole were approved by the FDA (Food and Drug Administration) for the treatment of ASD. They are atypical antipsychotics showed to be beneficial in treating aggression, irritability, and self-injury. Risperidone is approved for children from 5-16 years of age, but it has some side effects like weight gain. Aripiprazole is approved for children from 6-17 years of age. It also has some side effects including; drowsiness, weight gain, and some extrapyramidal symptoms. Small reports have suggested variable benefits of olanzapine, clozapine, ziprasidone. Other medications of different classes have been used, such as alpha-2 agonists, mood stabilizers, beta blockers, and selective serotonin reuptake inhibitors (SSRI) but there is no evidence of their efficacy against disruptive behavior of ASD[19].

Behavioral treatment:

It is recommended for preschool- to early school–aged children with ASD to have behavioral therapy for at least 25 hours per week. It is a structured plan that envolves teaching new skills through reinforcement of favorable behaviors, reducing unfavorable behaviors and encouragement of generalizing these skills. Cognitive behavioral therapy has helped to lessen anxiety symptoms in older children with ASD who have average to above-average IQ.

Targeted play is another way which has helped to improve social communication skills. Social skills training has showed some improvement in social skills and emotional recognition in school-aged children without intellectual dysfunction. Parent training and education programs enhance language skills and reduce disruptive behavior in children[20].

Complementary and alternative treatments:

There are a lot of complementary and alternative treatments that is tried by the families of ASD children for example there is massage therapy that can be carried out by parents and showed benefits on ASD symptoms like language, sleep and anxiety. Melatonin helps manage sleep disorders and improve daytime behavior. Vitamin B6 and manganese have been considered to be used in children with ASD to improve language, speech, and behavior however vitamin B6 could result in neuropathy as a side effect and manganese has diarrhea as a side effect. Horseback riding have shown ability to improve irritability, hyperactivity, and social communication skills[20].

Prognosis:

Prognosis of ASD is variable and depends for a large extent on the early diagnosis and intervention which is usually linked to a better outcome. Of individuals suffering from ASD about 75% showed poor outcomes and 25% showed better prognosis. Cases which acquire language before 6 years of age, have IQ more than 50 and have special

skills are predicted to show good prognosis[21].

Human rights:

Every human, including people with autism, have the right to attain the highest standard of physical and mental health. Nevertheless, autistic people have higher rates of unmet health-care needs compared to general population. Moreover, they are more vulnerable during humanitarian emergencies. Unfortunately, autistic people are often subject to stigma and discrimination, including unjust deprivation of health care, education and opportunities to engage and participate in their communities. Part of the problem arises from health-care providers' inadequate knowledge and understanding of autism. In addition, there is lack of awareness about ASD among general population [22].

ASD simulation in animals:

Animal models of autism are being developed to meet the urging need for investigating the underlying causes of ASD and to find the proper medication to help treat the condition or control its symptoms. Animal models of ASD can be divided into four groups.

1. Animals with specific deficiencies of neuropeptide receptors.
2. Models in which there is reproducing certain pathological conditions that may be associated with ASD.
3. Models with neonatal deficits in some brain zones and anomalies which have been found in some people with ASD.
4. Models of genetic abnormalities that lead to diseases associated with ASD.

Laboratory-bred rodents are used in modeling of the autistic symptoms and some experiments are done using other animals like monkeys and some birds. Rodents are very suitable because their behavior can be examined thoroughly, and their communication disorders can be detected. Also, many methods have been developed to influence the state of their nervous system[23].

Rats and mice behaviors can have a direct relation with the three core features of autism: deficits in social interaction (e.g., analysis of videotapes), deficits in communication (e.g., scent marking), and increased repetitive/stereotyped motor behaviors (e.g., self-grooming), and persistence on sameness and restricted interests (e.g., perseveration in the T maze or water maze). Rodents can also be tested for several other behaviors related to ASD such as enhanced anxiety and eye blink conditioning, and a deficit in sensorimotor gating (pre-pulse inhibition; PPI)[24].

Developed Animal models of ASD are many and each type represent a different suggested risk factors and pathology of ASD for example; there are models related to genetic factors that is concerned with abnormal genetic conditions associated with ASD like in fragile X mental retardation gene (Fmr1), neuroligin 3 and 4 genes (NLGN), mutations in the DLX, Reelin, Engrailed, and PTEN genes and many other models. Environmental factors model in which different environmental risk factors that may be contributing to ASD have been studied on animals.

In thalidomide and valproic Acid models, mothers taking these drugs during early pregnancy have shown an increased incidence of autism in their offspring. In mercury model, exposure to methyl mercury during childhood have been associated with many neurodevelopmental disorders[25].

No animal model can be valid in all situations, in all purposes. One of the most widely used animal models is the valproic acid (VPA) animal model of autism spectrum disorder (ASD). This model can demonstrate many of the behavioral and structural features observed in individuals with autism. Autism is diagnosed by two behavioral criteria: (a) deficiency in social communication and interaction, (b) restricted, repetitive patterns of behaviors, interests, or activities with other comorbid traits. Noticeably, prenatal VPA

exposure induces varying degrees and types of repetitive behaviors in animal models which validates an important behavior marker in clinical autism. Results from many studies showed marked decreases in social interaction of VPA-treated rats, consistent with other findings[26].

Several anatomic and behavioral features characteristic of human cases by exposing rodents' embryos to VPA have been showed. Cerebellum as an example was affected by reduction in its size in patients with ASD in comparison with control and that was demonstrated by Magnetic resonance imaging, smaller vermal lobules VI and VII have been displayed. Similar changes were found in brains from rat model of autism induced by prenatal exposure to VPA. There was decrease in the number of motor neurons of the motor nuclei (V, XII), and the VI and III cranial nerve nuclei were affected in the exposed rats. In the same way, another study found decreased number of cells in the posterior lobe of the cerebellum. Cerebellar anatomy changes in humans might be due to loss of neurons in the cranial nerve motor nuclei, as showed in rats. The amygdala is likely to be involved in the pathology of ASD, due to its involvement in social-emotional behavior. Rats exposed to VPA in had an abnormal handling of their fear memories and showed inability to extinguish them, which could be explained by the hyperactivity and hyper plasticity found in the lateral amygdala[26, 27, 27, 28&29].

Conclusion:

Autism spectrum disorders (ASD) are a diverse group of conditions. The abilities and needs of autistic people vary greatly. The exact cause of autism spectrum disorder is so far unknown. Further work is needed to broaden the horizons on the understanding of ASD.

Conflict of interest:

The authors declare no conflict of interest.

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المعرفة الحالية لاضطرابات طيف التوحد مع الإشارة إلى دور النماذج الحيوانية

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الخلفية: اضطراب طيف التوحد (ASD) هو مجموعة من الاضطرابات النمائية العصبية التي تؤثر على التواصل والإدراك والسلوك. يُطلق عليه اضطراب "الطيف" بسبب التباين الواسع في نوع وشدة الأعراض التي يعاني منها الأشخاص. تظهر الأعراض بشكل عام في العامين الأولين من العمر. من المتفق عليه إلى حد كبير أن التوحد متعدد العوامل مع العديد من عوامل الخطر التي تساهم في علم الأمراض بما في ذلك العوامل الوراثية والبيئية.

هدف العمل: تلخص هذه المراجعة الدليل على انتشار ومسببات المرض والتشخيص والعلاج لاضطراب طيف التوحد. وكذلك دور الطب التجريبي في هذا الصدد.

الملاحظات: تمثل عملية التسبب في اضطراب طيف التوحد مجالًا من عدم اليقين الكبير ، ومع ذلك فإن العديد من الآليات المفترضة غير مفهومة جيدًا. تم افتراض العديد من النظريات لشرح التسبب في مرض ASD. الاتصال العصبي ، والهجرة العصبية ، والنشاط العصبي الاستثاري المثبط. يفترض أيضًا أن الاضطرابات المناعية تلعب دورًا. يعد الخلل الوظيفي للخلايا الدبقية من المجالات البحثية الواعدة الحديثة حول التسبب في اضطراب طيف التوحد. على الرغم من اقتراح العديد من النظريات حول التسبب في مرض ASD ، إلا أنه لا توجد آلية مباشرة ومحددة تشرح التسبب في ASD. قد يكون تشخيص اضطراب طيف التوحد صعبًا ولكن من الضروري ضمان تلقي الدعم والمساعدة في أسرع وقت ممكن. لا تعد اضطرابات طيف التوحد "قابلة للشفاء" بشكل عام ، ولكن الأهداف الرئيسية للعلاج هي تقليل العجز المرتبط بالضيق الأسري ، وزيادة نوعية الحياة والاستقلال الوظيفي. يتم استخدام خطوط العلاج الطبية أو السلوكية أو التكميلية والبديلة. يتم تطوير نماذج حيوانية للتوحد لتلبية الحاجة الملحة للتحقيق في الأسباب الكامنة وراء اضطراب طيف التوحد وإيجاد الدواء المناسب للمساعدة في علاج الحالة أو السيطرة على أعراضها.

الخلاصة: إن السبب الدقيق لاضطراب طيف التوحد غير معروف حتى الآن. هناك حاجة إلى مزيد من العمل لتوسيع آفاق فهم ASD.