Research Article

Understanding of Autism Spectrum Disorders

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Abstract
Late reports demonstrate that the rate of autism spectrum disorder (ASD) is significantly expanding, in spite of the fact that ASD etiology and pathogenesis are still far to be completely clarified. It is defined as a state of neurodevelopmental disorder characterized by a deficiency in social, verbal and nonverbal communication, for example, impaired eye to eye connection, outward appearance, and body motions in the initial 3 years of life. It's considered as multiple disorders due to hereditary and non-hereditary hazard factors. Serious investigations are in progress to distinguish hereditary, biochemical, electrophysiological or imaging markers that could add to screening as well as subgrouping determination in a clinical setting. educational and behavioral treatments play an important role in the management of ASD, pharmacological and interventional medications have likewise demonstrated some advantage in children with ASD.
Key Words: Autism Spectrum Disorders, tryptophan, DSM-5.

Introduction
Autism Spectrum Disorders is a complex neurodevelopmental disorder. It starts before three years old. ASD is described by unavoidable defect in social collaboration, impedance in verbal and nonverbal communication, and stereotyped forms of interests and exercises. The expanding rate of ASD in the pediatric population and the absence of fruitful therapeutic treatments make ASD a standout amongst the most difficult issue for medication [(1,2)]. The expression "spectrum" in ASD implies that every individual can be influenced in various ways, and indications can extend from mild to severe [(3).].

The predominance of ASD has expanded in the previous two decades. In spite of the fact that the expansion in prevalenceis cause changes in DSM-5 criteria and help for early detection of autism. Studies have demonstrated a male is most commonly affected 2~3 times than females. Likewise, a few studies have recommended the probability that the female has special protection from ASD [(4,5)].

Causes and Risk Factors:

1- Neurological Factors:

Different studies found a defect in brain development, neural designing and connectivity. The frontal and temporal lobe are the uniquely influenced cerebrum regions in ASD. The amygdala is a most important segment of the limbic system. It has 2 particular actions including eye stare and face expression. The defect of the amygdala cause fear processing, modulation of memory and eye stare when looking to them. Other than amygdala, nucleus accumbens (NAc) is a key structure which is connected with the social reward reaction in ASD [(6,7)].

2- Genetic Factors:

Hereditary causes including genetic and chromosomal abnormalities have been found in 10%~20% of people with ASD .family history with ASD subject have a 50 times with a repeat rate of 5%~8%[(8)]. Researchers are now closer to find the relation between autism and gender as the incidence is four times higher in young men than girls. Recently, they have discovered that PTCHD1 gene in the X-chromosome . Men acquire X chromosome from their mother and Y chromosome from their father. So, loss or mutation on this gene increasing the risk of autism in boys while girls are protected from autism by a second X chromosome[(9)]. De novo mutation associated with high incidence of autism. Genes with de novo mutation include CHD8, DYRK1A, GRIN2B, KATNAL 2,

RIMS1, SCN2A, POGZ, ADNP, ARID1B, ANK2,CUL3, TBR1and TBR1. Some of candidate gene play unique parts in the pathogenesis of a mental imbalance, by influencing cerebrum structure and function. These genes include Engrailed homebox 2 (EN2), Reelin, serotenin transporter gene (5HTT), GABRB3, FOXP2, AVPR1A, UBE3A, WNT2[10].

3- Prematurity:

low birth weight babies are probably going to be influenced by neurodevelopmental diseases, including autism, at a significantly higher rate than the overall public[11].

4- Cultural Factors:

ASD has been reported in the developed countries. Israeli born children showed higher rates of ASD than Ethiopian children. Furthermore, Israeli children of Ethiopian extraction showed rates of ASD at a much higher rate than the children born in Ethiopia[12].

5- Nutritional Factors:

a- Folic acid Deficiency:

There is a connection between folate digestion and ASD. Autoantibodies that inhibit folate entrance into the cerebrum have been related with ASD. they react to large dose of reduced folate known as folinic acid (leucovorin calcium). A portion of similar anomalies are additionally found in mothers of children with ASD and supplementing folate before and during pregnancy periods prevent the infant from getting ASD [13] .

b- Vitamin D Deficiency:

Vitamin D has a critical part in brain homeostasis, neurodevelopment and maturation. Numerous investigations proposed that vitamin D has a critical part as a neuroactive steroid, which can influence neuronal differentiation, axonal network and brain structure and action. Additionally, vitamin D deficiency within pregnancy is commonly associated with defect in the embryo (4).It was found that the symptoms of ASD children were signifecantrly improved following 4 months of vitamin D3 therapy [14] .

c- Iron Deficiency:

iron provide an essential part in subjective, conduct, and motor growth. A decrease of iron levels in the brain might be associated by changes in serotonergic , dopaminergic frameworks, cortical systems, and myelination. It is found that hemoglobin levels of children with ASD were lower than normal one. Also, Hemoglobin levels of sever autistic children were lower than those with mild to moderate autism [15].

6- trace elements and heavy metals:

Zn help in normal development and improvement within pregnancy, youth, and puberty. People with extreme Zn insufficiency can create neuropsychological changes. Cu toxicity cause harmful effect in the brain including irritability, learning and social issue. zinc keep up a balance of copper in the blood. that is why, the level of zinc was reported low in ASD while copper high and this leading to decrease of zinc/copper ratio which can be used as biomarker for autism [16].Mercury can specifically pass the blood brain barrier and deposit in high amounts particularly in the visual cortex, cerebellum, and spinal cord. Mercury additionally attached to the membranous organelles like, endoplasmic reticulum, mitochondria, and Golgi complex and disturb their actions. It was observed increase levels of mercury in the blood, RBC and brain tissue in autistic children [17] . Human exposure to aluminum has been detected in ASD. To-date the greater part of studies have utilized hair as their marker of human exposure to aluminum while aluminum in blood and urine have restricted degree. Pediatric vaccines that include an aluminum adjuvant are considered indirect exposure to aluminum.a new study support high deposition of aluminum in brain of autism [18].

Diagnostic criteria:

The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM 5) divided symptoms into two categories: the social communication and interaction domain, which includes deficits in verbal and nonverbal communication, and the repetitive behavior domain.

For diagnosis, the children should have three or more in the domain of social communication and interaction, and two symptoms in the repetitive behavior domain

a- **Social communication and interaction domain:**

1. **Deficits in social emotional reciprocity**

- Abnormal social approach

- Failure of normal back and forth conversation
- Reduced sharing of interests, emotions, affect and response
- Total lack of initiation of social interaction

2. Deficits in nonverbal communicative behaviors

- Poorly integrated verbal and nonverbal communication
- Abnormalities in eye contact and body-language
- Deficits in understanding and use of nonverbal communication
- Total lack of facial expression or gestures

3. Deficits in developing and maintaining relationships

- Difficulty making friends
- Apparent absence of interest in people
- Difficulties adjusting behavior to suit different situations

b- **Repetitive and restrictive behavior domain:**

1- Stereotyped or repetitive speech, motor movements, or use of objects

- Simple motor stereotypies
- Echolalia
- Repetitive use of objects
- Idiosyncratic phrases

2- **Excessive adherence to routines, ritualized patterns of behavior**

- Excessive resistance to change such as motoric rituals
- Insistence on same route or food
- Repetitive questioning or extreme distress at small changes

3- Highly restricted, fixated interests that are abnormal in intensity

- Strong attachment to and/or preoccupation with unusual objects
- Excessively circumscribed or preservative interests.

4- Hyper- or hypo-reactivity to sensory input

- Unusual interest in sensory aspects of environment
- Apparent indifference to pain/heat/cold
- Adverse response to specific sounds or textures
- Excessive smelling or touching of objects
- Fascination with lights or spinning objects [(19)].

Laboratory investigations:

a- **Blood tests** include (iron, vitamin D, thyroid function tests and zinc/copper ratio)

b- Chromosomal investigation:

conventional karyotyping analysis is helpful in catching genomic rearrangements such as reciprocal translocation, inversion, and complex rearrangements [(20)].

c- Genetic testing:

1- Gene expression in the tryptophan metabolic pathway by using microarray and RNA extraction for detection of gene expression in tryptophan metabolism. These genes include:

- SLC7A5 and SLC7A8, coding for tryptophan transporter subunits, expressed in both blood and brain.
- The mitochondrial isoform of tryptophanyl tRNA synthetase (WARS2).
- gene encoding the isoform 2 of Tryptophan hydroxylase (TPH2).
- several genes coding for enzymes involved in the kynurenine pathway include (AADAT, HAAO, and MAOA) [(21)].

2- Serum microRNA:

Act as a post-transcription regulator of gene expression and developing human brain. It is a noninvasive biomarker for ASD and detected by quantitive PCR [(22)].

***d*- Metabolic screening:**

there are many blood and urine tests that the researchers built up, the most exact one found that children with ASD had more elevated amounts of a compound called dityrosine and advanced glycation end product (AGEs) [(23)].

Management:

Early intervention

When the diagnosis is made, parents are urged to start early intervention. This consists of applied behavioral analysis (ABA), speech therapy, occupational therapy, psychomotor therapy and special education.

Medications for autism:

Many drugs have been tried in autism to alleviate symptoms.

Few drugs have proven to be useful. Other drugs are still in clinical trials. Recently, a dose from vasopressin can improve the behavioral changes in autism but still under trails [(19, 24)].

Conclusion

Understanding of autism spectrum disorder is necessary especially their causes and risk factors to facilitate finding a useful blood or urine tests for early detection of autism. This allow early intervention and early improvement in educational and social development.

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