AUTISM

Definition:

Autism is defined as severe psychiatric disorder of childhood marked by severe difficulties in communication and forming relationships with other people, in developing language, repetitive, and limited patterns of behaviors and obsessive resistance to small changes in familiar surrounding ***(Chew et al, 2006).***

EPIDEMIOLOGY

ASD prevalence according the the Autism and Developmental Disabilities Monitoring (ADDM)2010 surveillance was 14.7 per 1,000 (one in 68) among children aged 8 years in the United States, also ASD prevalence was 23.7 per 1,000 (one in 42)among boys and 5.3 per 1,000 (one in 189) among girls ***(Jon et al, 2014).***

Prevalence of ASD are approximately four times more common in males than females ***(Fombonne, 2009).***

The number of children reported with autism spectrum disorders (ASDs) has continued to increase dramatically during the past 20 years for largely unknown reasons ***(MMWR, 2009).***

Although the increase may be partially due to changes in diagnostic criteria and general awareness, recent reports indicate that these factors alone are not sufficient explanation ***(Hertz-Picciotto & Delwiche, 2009; Leonard et al., 2010).***

Type of Autism:

Pervasive developmental disorder" in DSM-III as a generic term to include all shades and degrees of autism (the DSM-IV incorporated five diagnoses under pervasive developmental disorders: autism, Rett disorder, childhood disintegrative disorder (CDD), Asperger disorder (ASP), and not pervasive developmental disorder – not otherwise specified) ***(Johnson, 2007).***

The term "PDD-NOS" is used to describe individuals who meet some, but not all, of the DSM-IV-TR criteria for autistic disorder (ie, atypical autism) ***(Johnson, 2007).***

Individuals may fall into this category because of late age of presentation, atypical symptoms, or sub threshold symptoms.

In addition, some clinicians make an initial diagnosis of PDD-NOS (fig. 1) in children younger than 36 months regardless of the number or severity of symptoms because diagnostic accuracy is lower in younger children. There is significant discussion about the utility of this category of individuals and need for further clarification ***(Mandy et al., 2011 and Walker et al., 2004).***

Other objections have been raised about the DSM-IV/ICD-10 classification of pervasive developmental disorders. DSM-IV does not differentiate autistic disorder clearly from other pervasive developmental disorders, especially Asperger's syndrome ***(Volkman et al., 2009).***

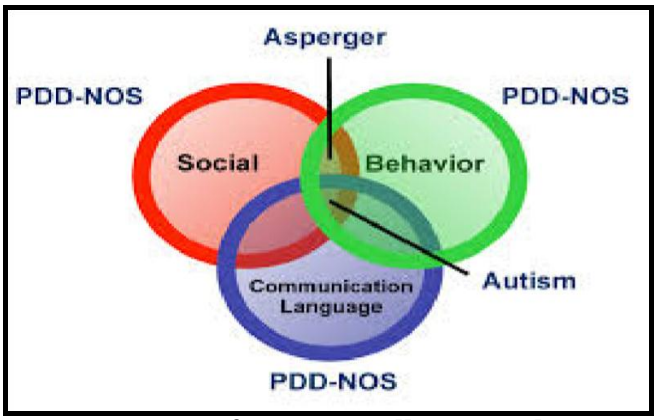

Fig. (1): Types-of autism (***Volkman et al, 2009).***

DSM-IV criteria for Asperger's syndrome ignore the abnormal use of language by individuals with Asperger's syndrome ***(Mayes et al., 2001).***

The DSM-IV-TR provides specific criteria to diagnose Asperger disorder ***(MMWR, 2007).***

In contrast to autistic disorder, individuals with Asperger disorder have better facility with the mechanics of verbal expression, higher levels of cognitive function, and greater interest in interpersonal social activity (often around their current obsessive preoccupation) ***(Volkman et al., 2009).***

There is some controversy regarding whether

- **Asperger disorder** is a form of high-functioning autism or a separate disorder ***(Sharma et al., 2011).***
- **Rett syndrome (RTT)** is a neurodevelopmental disorder that occurs almost exclusively in female ***(Rett, 1966).***

After a period of initially normal development, affected patients experience loss of speech and purposeful hand use, stereotypic hand movements, and gait abnormalities. Additional features include deceleration of head growth, seizures, autistic features, and breathing abnormalities ***(Neul et al., 2010).***

Most cases result from mutations in the MECP2 gen ***(Amir et al., 1999).***

Characteristic features of Rett syndrome include deceleration of head growth (in contrast to acceleration of head

growth, which occurs in other ASD), stereotypic hand movements, and dementia ***(Hagberg et al., 2000).***

- **Childhood disintegrative disorder**: The essential feature of Childhood disintegrative disorder (CDD), which is extremely rare, is a marked regression in multiple areas of functioning following a period of at least two years of apparently normal development. Apparently normal development is reflected in age-appropriate verbal and nonverbal communication, social relationships, play, and adaptive behavior. After the first two years of life (but before age 10 years), the child has a clinically significant loss of previously acquired skills in at least two of the following areas: expressive or receptive language, social skills or adaptive behavior, bowel or bladder control, play, or motor skills. Children with CDD are essentially identical to children with autistic disorder, save a history of normal development. CDD is often associated with an identified organic condition (eg, seizures, metabolic disorder, etc) ***(Hagberg et al., 2000).***

There is heightened interest in the potential etiologic role of non genetic factors, including exogenous exposures ***(Lawler, 2008; Landrigan, 2010; Hallmayer et al., 2011).***

Exogenous exposures that are known or suspected to interfere with neurodevelopment, including the heavy metals such as lead and mercury ***(Mendola et al., 2002; Palmer et al., 2009),*** have been suggested as important to examine in autism etiology. Studies have emerged that link prenatal exposure to endocrine disrupting chemicals and some solvents with neurodevelopmental outcomes in offspring ***(Laslo-Baker et al., 2004; Logman et al., 2005; Engel et al., 2010; Herbstman et al., 2010).***

Only a few studies have examined ASDs specifically; in studies of environmental contaminant levels around pregnancy, we and others reported associations with organochlorine pesticides ***(Roberts et al., 2007),*** hazardous air pollutants ***(Windham et al., 2006; Kalkbrenner et al., 2010),*** and proximity to freeways ***(Volk et al., 2011).***

Risk Factors:

- Fragile X – As many as 30 to 50 percent of patients with fragile X syndrome have features of autism ***(Demark, 2003).*** However, with cytogenetic techniques (not DNA analysis) and molecular analysis, fragile X syndrome is rarely found in patients with autism ***(Rogers et al., 2001).***
- Androgens may play a role in autism ***(Fombonne, 2003***), as subjects diagnosed with an ASD having a sex ratio of at least 4:1,

and the ratio is as high as 9:1 for Asperger's syndrome (AS). In addition, studies have revealed hormonal patterns consistent with significantly elevated androgen levels in subjects diagnosed with an ASD relative to controls ***(Geier et al. 2010, 2012).***

- Tuberous sclerosis complex - 17 to 60 percent of patients with tuberous sclerosis complex are also autistic; however, only 0.4 to 4 percent of patients with autism have tuberous sclerosis complex ***(Numis, 2011).***
- 15q chromosome duplications/triplications ***(Veltman, 2005).***
- 15q deletions (ie, Angelman syndrome) ***(Veltman, 2005).***
- Rett syndrome.
- Smith-Lemli-Opitz syndrome is an autosomal recessive disorder of cholesterol biosynthesis ***(Johnson et al., 2007).***

Other chromosomal "hot spots" include chromosome X, 2, 3, 7q, 17, and 22q ***(Baron-Cohen et al., 2006).***

Pathogenesis: (fig.2)

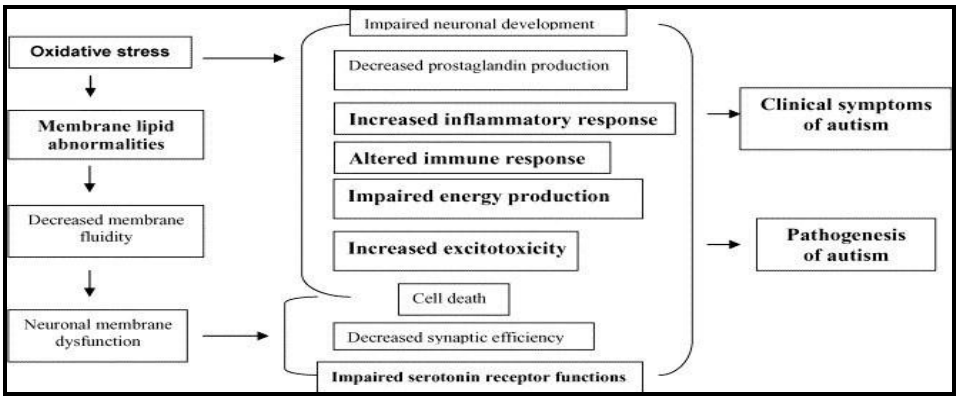

Fig. (2): Pathogenesis of autism ***(MMWR, 2009)***

The pathogenesis of ASD is incompletely understood. The general consensus is that ASD has a genetic etiology, which alters brain development, affecting social and communication development and leading to restricted interests and repetitive behavior ***(Muhle, 2004)***

Genetic factors:

There is increasing evidence for the role of genetic factors in the etiology of autism ***(Filipek et al., 2000)***. Evidence for the strong genetic contribution to development of ASD is derived from the following observations ***(Muhle, 2004):***

- Unequal sex distribution, with 4:1 male predominance

- Increased prevalence in siblings of patients with ASD compared to the general population
- High concordance rate among monozygotic twins (36 to 96 percent) ***(Hallmayer et al., 2011).***

Given the complexity of ASD and the diversity of clinical manifestations, it is likely that interactions between multiple genes are responsible for ASD and that epigenetic factors and exposure to environmental modifiers contribute to the variable expression ***(Bacchelli et al., 2006).***

Neurobiologic factors:

These abnormalities include diffuse differences in total and regional gray and white matter volumes, sulcal and gyral anatomy, brain chemical concentrations, neural networks, brain lateralization, and cognitive processing compared to individuals without autism ***(Chen et al., 2011).***

- **Parental age** : Advanced parental age (both paternal and maternal) has been associated with an increased risk of having a child with ASD ***(Reichenberg et al., 2006)***
- **Lack of association with immunizations**: some authors have attributed regressive autism to vaccine exposure (particularly

measles vaccine and thimerosal (a mercury preservative used in vaccines)). However, the overwhelming majority of epidemiologic evidence does not support an association between immunizations and autism ***(Deer, 2011).***

Diagnosis:

Accurate and appropriate diagnosis usually requires a clinician who is experienced in the diagnosis and treatment of autism ***(Johnson et al., 2007).*** Clinicians must rely on their clinical judgment, aided by guides to diagnosis ***(Filipek et al., 2000).*** At a minimum, the diagnostic evaluation should include documentation of whether the child's symptoms meet the DSMV-TR criteria for autism (table 1).

Diagnostic criteria for autistic disorder:

A1.Deficits in social emotional reciprocal relation, abnormal social approach and failure of normal back and forth conversation through reduced sharing of interests, emotions, and affect and response to total lack of initiation of social interaction.

A2. Deficits in nonverbal communicative behaviors used for social interaction; ranging from poorly integrated verbal and nonverbal communication, through abnormalities in eye contact and body ,

language or deficits in understanding and use of nonverbal communication, to total lack of facial expression or gestures.

A3. Deficits in developing and maintaining relationships, appropriate to developmental level (beyond those with caregivers); ranging from difficulties adjusting behavior to suit different social contexts through difficulties in sharing imaginative play and in making friends to an apparent absence of interest in people

B. RESTRICTED, REPETITIVE PATTERNS OF BEHAVIOR, INTERESTS, OR ACTIVITIES AS MANIFESTED BY AT LEAST 2 OF 4 SYMPTOMS:

B1. Stereotyped or repetitive speech, motor movements, or use of objects; (such as simple motor stereotypies, echolalia, repetitive use of objects, or idiosyncratic phrases).

B2. Excessive adherence to routines, ritualized patterns of verbal or nonverbal behavior, or excessive resistance to change; (such as motoric rituals, insistence on same route or food, repetitive questioning or extreme distress at small changes).

B3. Highly restricted, fixated interests that are abnormal in intensity or focus; (such as strong attachment to or preoccupation with unusual objects, excessively circumscribed or perseverative interests).

B4. Hyper- or hypo-reactivity to sensory input or unusual interest in sensory aspects of environment; (such as 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).

C. Symptoms must be present in early childhood (but may not become fully manifest until social demands exceed limited capacities)

D. Symptoms together limit and impair everyday functioning.

(MMWR, 2013)

Definitive diagnosis of ASD:

Role of primary care provider - The most important thing the primary care clinician can do is to listen to the parents and take their concerns seriously. Although primary care clinicians typically feel comfortable conducting the etiologic search (eg, identifying associated disorders, performing the medical history and examination, and coordinating genetic, metabolic, and neurologic evaluations as necessary), they usually seek the help of ASD specialists in making the definitive diagnosis of ASD ***(Zwaigenbaum et al., 2009)***

History:

The history for children who screen positive for ASD should include the following information ***(Johnson et al., 2007):***

- Review of the developmental history, with particular attention to early social-emotional and language milestones, play skills, behavior, and any regression
- Parental concerns regarding hearing, vision, and speech/language
- Specific information regarding early communicative behaviors, such as pointing, use of eye contact, and response to name
- History of repetitive, ritualized or stereotyped behaviors, such as hand flapping.
- Unusual visual behavior, or preoccupation with parts of toys
- Frequent tantrums and trouble tolerating change or transition
- History of possible seizures
- Self-injury
- Significant disturbance in eating (including pica) or sleep

A three-generation family history should be reviewed thoroughly, since autism spectrum disorders have a strong genetic component ***(Muhle et al., 2004)***. The following disorders should be asked about specifically ***(Volkmar et al., 2007):***

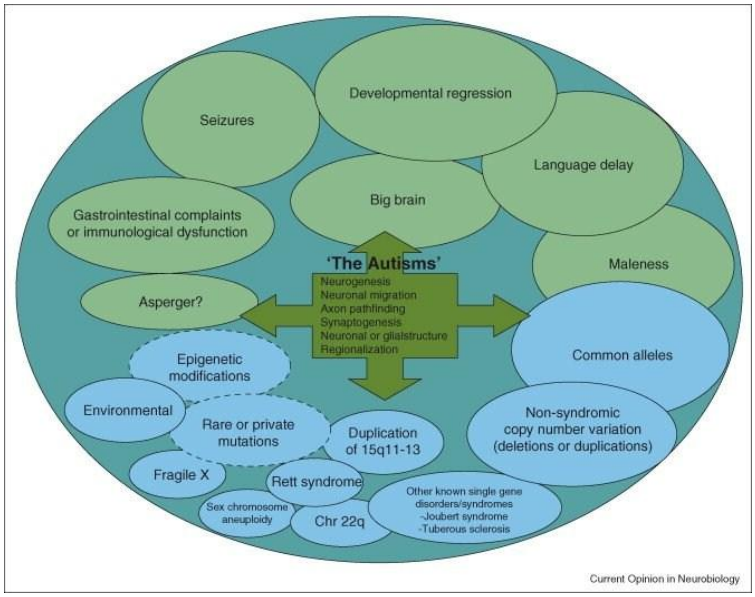

Fig. (3): Clinical picture of autism ***(Volkmar et al., 2007).***

Autism and other pervasive developmental disorders

- Language delay
- Intellectual disability (mental retardation)
- Fragile X syndrome, Rett disorder, Angelman syndrome, Prader-Willi syndrome, Smith-Lemli-Opitz syndrome
- Tuberous sclerosis complex
- Learning and attentional disorders
- Anxiety
- Obsessive-compulsive disorders

- Extreme shyness, social phobia, or mutism
- Mood disorders
- Schizophrenia
- Seizures
- Tic disorders

The psychosocial history should include information regarding the family supports and stresses ***(Volkmar F et al., 2007).***

Examination:

Extra time should be allotted for the examination because the communication deficits and behavioral symptoms may limit cooperation ***(Filipek et al., 2000).*** Important aspects of the examination include ***(Johnson et al., 2007):***

Measurements of growth parameters, including head circumference. Approximately one-fourth of children with isolated ASD have head circumference greater than the 97th percentile ***(Filipek et al., 2000).***

- Height and weight measurements are necessary in children who are being evaluated for ASD, since dietary obsessions and compulsions can result in poor weight gain or obesity.