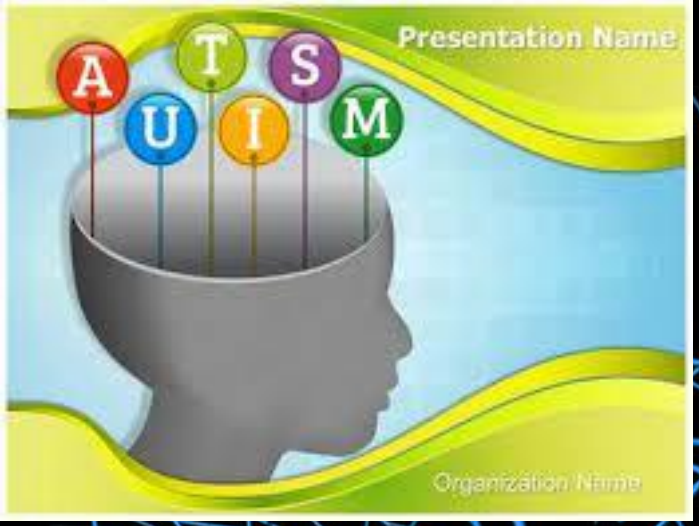

AUTISM ETIOLOGY

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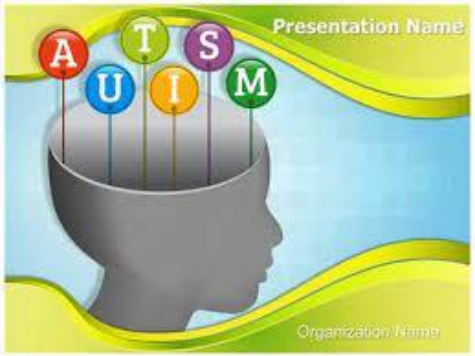
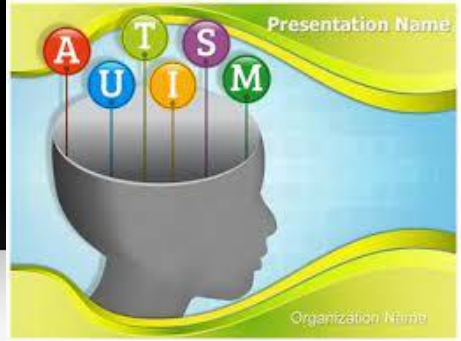
2022

History



- Although Leo Kanner first described a syndrome of “autistic disturbances” in 11 children who shared “unique” and previously unreported patterns of behavior, including socialremoteness, obsessiveness, stereotypy, and echolalia,
- The first set of formal diagnostic criteria for this disorder was not formulated until the 1970s

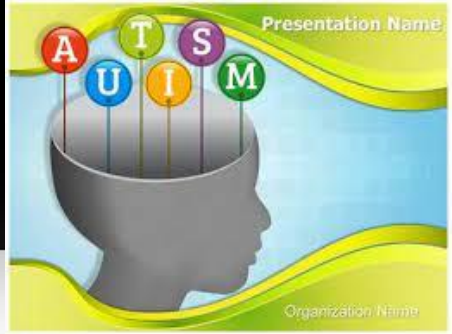


In the third edition of DSM the term “autism” was included for the first time and was clearly differentiated from childhood schizophrenia and other psychoses under a new diagnostic umbrella of pervasive developmental disorders (PDD)

The fourth edition of DSM : five possible diagnose sunder the PDD umbrella:

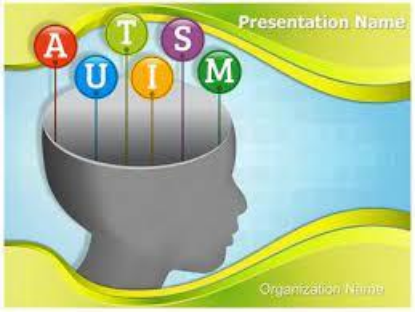
autistic disorder
Asperger syndrome
childhood disintegrative disorder
Rett syndrome
PDD-NOS/atypical autism

Epidemiology



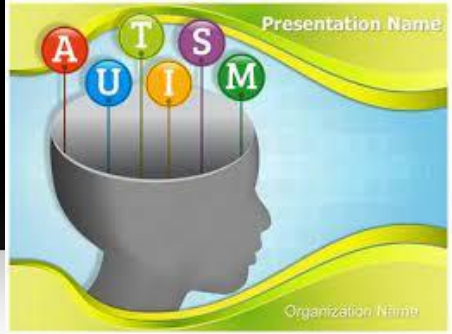
- The reported prevalence of autism has dramatically increased.
- In 2006 the reported prevalence in 8-year-olds in the United States was 9.0 per 1000
- In a 2007 parent-reported United States diagnostic survey, the prevalence for ASD was 11 per 1000
- In 2010 : 14 per 1000 or one in 68 child

Epidemiology



- In random adult survey in England, ASD prevalence was approximately 1 per 100
- In 2011 in Sweden, prevalence was highest in 13- to 17-year-olds (2.46%)
- In Norway, for 6- to 12-year-olds, autism prevalence is 0.6%
- A South Korean study estimated the highest prevalence of 1.9%, but the participation rate was 63%
- prevalence estimates in last two decades reaching 1-2 %.

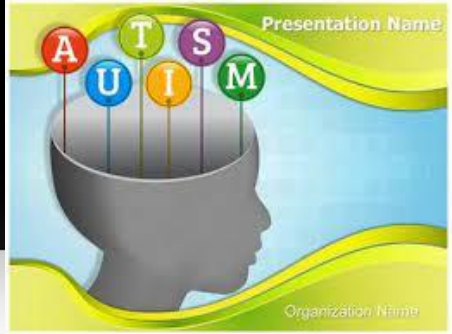
Factors contribute to the apparent increase



- Definitions, screening methods, diagnostic criteria, and completeness of sampling are important factors affecting prevalence results
- Autism prevalence was underestimated in the past
- Diagnostic criteria have evolved and broadened
- There is now co diagnosis with known medical disorders, such as Fragile X syndrome, Tourette syndrome (TS), and Down syndrome
- Growing public awareness among parents and teachers as well as availability of services and diagnostic screens
- Children earlier diagnosed as mentally retarded may have met current criteria for autism

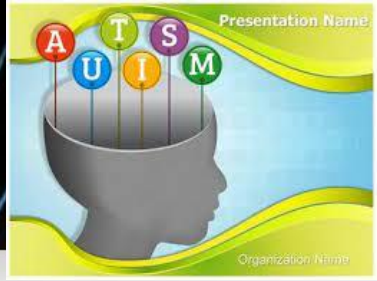
Bishop and associates found that up to 60% of adults previously diagnosed with developmental language disorder would meet more recent criteria for PDD

Fact



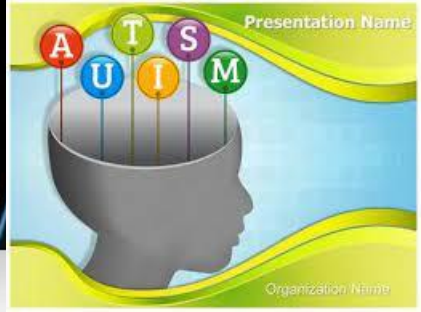
Although a substantial proportion of the increase seen in autism is due to factors such as a combination of better, more population-based studies and changes in the diagnostic criteria and age at diagnosis, the increase cannot be solely attributed to known factors, and there is likely to be a true increase in incidence

Epidemiology (sex)



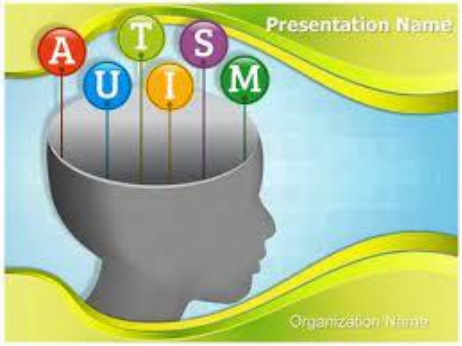
- Male to female ratio : 4 to 1 for the milder forms
- If severity of cognitive impairment increases, the male to female ratio decreases to 1.3 to 1.44
- An autism diagnosis is about 20 times more likely in siblings when one child had autism about 10.1% compared with 0.5% prevalence in siblings of controls
- A report from Japan found gender differences in the risk for subsequent siblings:
- General sibling risk was 10%, 7.7% if the proband was male and 20.0% if the proband was female
- Risk is 25% if there are already two siblings with ASD
- Monozygotic twin was diagnosed was 153 times that of control children with no autistic sibling

Etiology and Risk factors



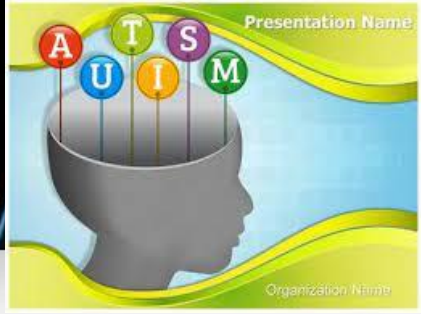
- Genetic
- Perinatal problem and Prematurity
- Parental Age
- Socioeconomic Factors
- Maternal risk factor
- Enviromental factors
- Vaccination ?

Genetic



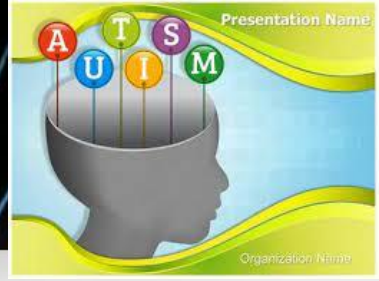
- Genome sequencing data indicates there are 100 genes associated with ASD, both common and rare (inherited and de novo), with many shared with other neurodevelopmental, psychiatric, and neurological conditions
- There is evidence that epigenetic mechanisms, such as DNA methylation,play a significant role in ASD etiology in combining genetic and environmental factors that dysregulate neurodevelopmental processes

Perinatal Problem and Prematurity



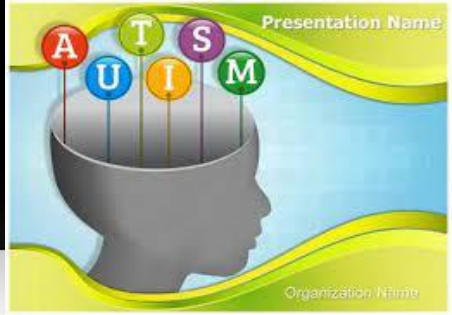
- Limperopoulos and associates found a 25% rate of positive screening for ASD at 18 to 24 months of age in 91 infants who were less than 1500 g and 31 weeks' gestation at birth
- NICU admission in term neonate
- prematurity, cesarean delivery, hypoxia ,abnormal presentation ,umbilical cord complications, fetal distress, birth injury or trauma, multiple birth, maternal hemorrhage, summer birth, low birth weight, small for gestational age, congenital malformation, low 5-min Apgar score, meconium aspiration, neonatal anemia, ABO or Rh incompatibility, and hyperbilirubinemia , intracranial hemorrhage ,neonatal seizure cerebral edema
- Hypoxia emerged as the most consistent factors associated with ASD risk

Parental Age



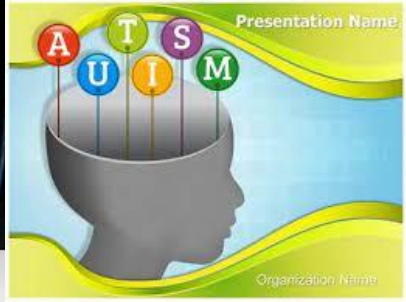
- In a large population of children born between 1989 and 1994, mothers older than 35 years were three times more likely to have an autistic child than women younger than 20 years
- One California study found that, when adjusted for age of the other parent and other covariates, the risk of autism increases by up to 40% for each 10-year increase in maternal age and by 20 to 25% for each 10-year increase in paternal age
- In another study, also from California, maternal age was linearly correlated with risk but increased paternal age was a risk factor only in mothers over 30-years-old.

Socioeconomic Factors



Some studies found that socioeconomic level does not affect risk, but in other studies, ASD prevalence was higher with increasing socioeconomic status Risk was also increased in multiple births and in black children

Maternal Risk Factors



- Maternal thyroid peroxidase antibody (TPOAb) increased risk by nearly 80%
- Maternal infection requiring hospitalization during any trimester of pregnancy
- Gestational or type 2 diabetes
- Preeclampsia ,hypertension
- Maternal prenatal stress in the first trimester
- Maternal obesity
- Vitamin D ,iron,zinc ,copper deficiency
- Children born within 1 year of an autistic sibling have increased risk over those born after longer intervals

Maternal Obesity

A recent review (across 32 articles and 36 cohorts) risk of mother weight showed : compared with mothers of normal weight, the offspring of obese and overweight mothers had a 17% increased risk of experiencing any neurodevelopmental disorder (OR 1.17, 95% CI 1.11–1.24) and a 36% increased risk for ASD (OR 1.36; 95% CI 1.08–1.70)

Sanchez CE, Barry C, Sabhlok A, Russell K, Majors A, Kollins SH, Fuemmeler BF (2018) Maternal pre-pregnancy obesity and child neurodevelopmental outcomes: a meta-analysis. Obes Rev

Sex Steroids

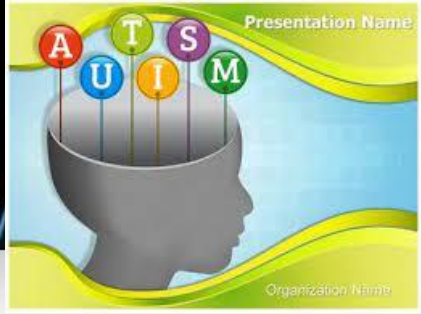
- High fetal exposure to sex steroids may contribute to ASD risk
- Fetal testosterone influences individual differences in typical development in eye contact behaviors,vocabulary size, restricted interests, mentalizing , empathy, systemizing, attention to detail, and autistic trait
- A genetic study of autism found evidence that single nucleotide polymorphisms in sex steroid synthesis genes (ESR2, CYP11B1, CYP17A1,CYP19A1) were associated with autism traits and autism with intellectual disability and good verbal skills
- Fetal testosterone exposure is one of several hypotheses which attempts to explain the male preponderanc of neurodevelopmental disorders, especially in ASD
- Maternal PCO and maternal hirsutism increased risk of ASD due to androgen excess

Prenatal sonography

Though not established in human studies, animal studies have linked ultrasound exposure in utero specially in first trimester to alterations in neuroanatomy and function, for example in the hippocampus

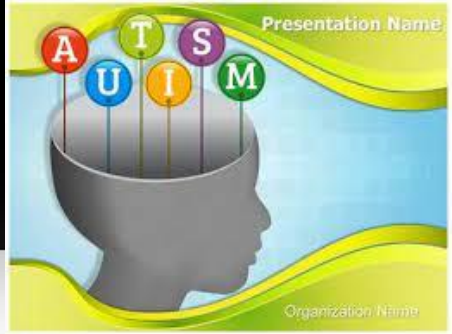
- Webb SJ, Garrison MM, Bernier R, McClintic AM, King BH,Mourad PD (2017) Severity of ASD symptoms and their correlation
- with the presence of copy number variations and exposure to first trimester ultrasound. Autism Res

Vaccination



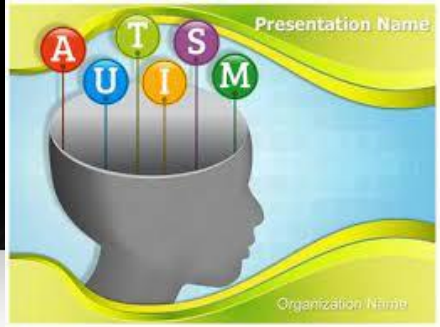
- Multiple studies concluded that there was no increase
- in risk of autistic disorder with exposure to the MMR vaccine
- Taylor and associates analyzed five methodologically
- sound cohort studies involving 1,256,407 children and
- five case-control studies of 9920 children and did not find any increased risk of autism associated with either childhood vaccines or the mercury-containing preservative thimerosol,which has not been used routinely since 2001

Maternal drugs and toxin



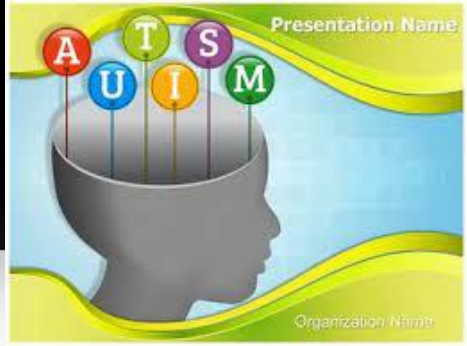
- Valporate
- SSRI ?
- Alcohol
- Smoking

Enviromental Factors



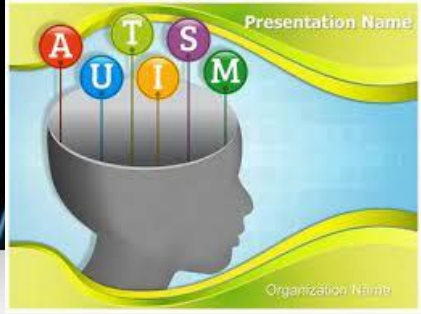
- Pesticides (organophosphate …)
- Air pollutants
- Heavy metals (lead ,mercury,nickel ,cadmium …)
- Non-persistent organic pollutants (phthalates and bisphenol, used primarily in the production of plastics)
- Persistent organic pollutants (DDT)
- Vitamin D deficiency may cause mutations as vitamin D contributes to repair of DNA damage

Other Factors



- Institutional deprivation
- Natural disasters
- Maternal migration

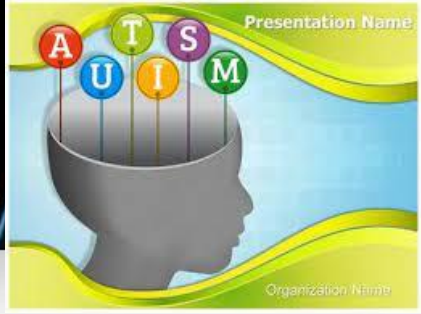
Protective Factors



- prenatal vitamin supplementation close to delivery might reduce the risk of autism in offspring, with folate (vitamin, B9, folic acid, folacin)
- pre and periconceptional folate supplementation
- Fatty acids including the omega-3 group are assumed to play a key role in neurodevelopment during early childhood
- maternal omega 3/omega 6 intake or status

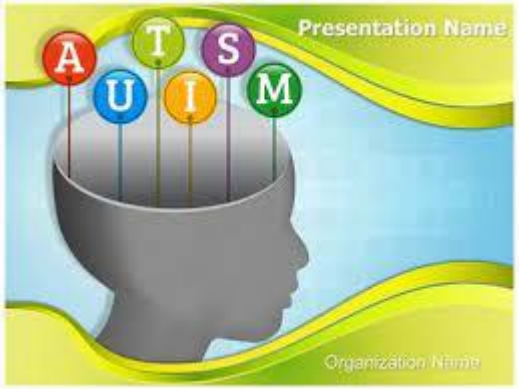
- Parity of four or more children was highlighted as a factor connected to decreased autism risk in one study

Brain Structure In Autism



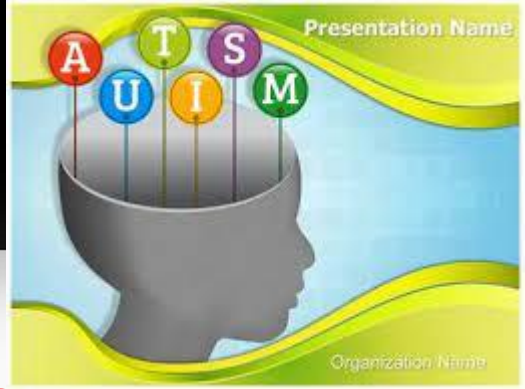
- Brain enlargement has been observed in children with(ASD), but the timing of this phenomenon and its relationship to the appearance of behavioral symptoms is unknown
- Brain MRI :decrease and increase globally in the cortical white matter volume or white matter microstructure in ASD

Nurotransmitters



- A comprehensive study of eight neurotransmitter receptors in the hippocampus demonstrated a reduction in the GABA-ergic system
- Serotonin system as central to ASD pathology disruption of the 5HT2a receptor binding throughout the cingulate cortex in adults
- Serotonin levels in blood platelets also have been
- shown to reflect ASD status
- Genetic changes in the serotonin system have also been reported in association with ASD pathology.

Take Home Message



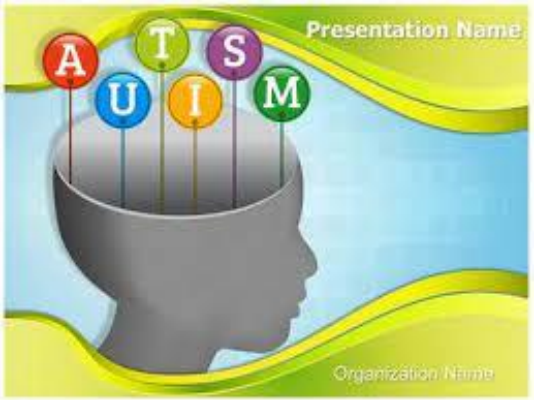
prevalence of autism has dramaticaiiy increased

Etiology is multifactorial

Most imporatant risk factors :

Genetic

Enviromental



THANKS FOR YOUR ATTENSION