INTRODUCTION

Autism Spectrum Disorder (ASD) represent a group of neuro developmental disorders typified by impairment in verbal& non-verbal communication, social withdrawal and stereotypical behaviors which may or may not be associated with cognitive deficits, self-injurious behaviors and other neurological comorbidities ***(Salmi et al., 2013).***In addition to the core features of ASD, children with ASD may also exhibit concomitant problems such as tantrum, aggression, hyperactivity and anxiety ***(White et al., 2009).***A dramatic rise in prevalence of autism spectrum disorder has occurred over the past two decade ***(Fombonne, 2009).*** In many countries the prevalence of ASD becomes 1 in 68 or 14.7 per 1000 ***(Center for Disease Control, 2012).***

Many parameters including hormones, neurotransmitters, and immunological mediators may be involved in the severity and pathogenesis of autism. Oxytocin (OT) is involved in the regulation of repetitive and affiliative behaviors, which is the key features of autism; it is believed that oxytocin may play a role in autism ***(Ruggeri et al., 2014).***Oxytocin has generally been associated with positive social behaviors such as social recognition, social contact, pair bonding, and parenting ***(Hammockand Young, 2005).***Oxytocin is synthesized primarily in the brain's para-ventricular and supra optic nuclei. OT is transported by neuro-secretory axons to the posterior

hypothalamus before being sent to the pituitary for peripheral release, or projected to various regions of the brain and central nervous system involved in reproductive, social, and aggressive behaviors ***(Donaldson et al., 2009).***Oxytocin releasing occurs into blood and within distinct brain regions in response to stress and some social stimuli, and it also believed to have an-anti-depressant like effect ***(slattery, 2010).***

Aim of the Study

The aim of the present study is to assess the level of serum oxytocin hormone in an Egyptian sample of children with Autism spectrum disorder (ASD) and to study its relation to the severity of symptoms of the disease.

Chapter 1

AUTISM

Definition

Autism is a neurodevelopmental disorder that is characterized by deficits in social interaction, social communication, restricted and repetitive interests, and behavioral patterns ***(Breentani et al., 2013).***It is also characterized by impaired language and social skills, and restricted areas of interest. Additional features may include poor eye contact, repetitive behavior, sensory modulatory dysfunction, and varying levels of cognition and motor disturbances ***(Breentani et al., 2013).***The symptoms gradually begin after the age of six months, become notcibale by age two or three years and continue through adulthood ***(Rogers, 2009).***ASD causes severe impairment of the quality of life and different disability which is highly intense ***(Kogan et al., 2009; Tchaconas and Adesman, 2013)***.The intensity of impairments is worsened by the high incidence of disorders associated with a diagnosis of ASD, such as seizures, intellectual impairment, and Fragile X ***(Mefford et al., 2012).***

Historical overview

The New Latin word autismus (English translation autism) was coined by the Swiss psychiatrist Eugen Bleuler in 1910 as he was defining symptoms of schizophrenia. He

derived it from the Greek word autos (meaning self) ***(Kuhn, 2004).*** Leo Kanner apsychiatrist at the Johns Hopkins Hospital first used autism when he introduced the label early infantile autism in a 1943 report of 11 children with striking behavioral similarities ***(Frith, 2003).***In Kanner's first paper nearly all the characters described, notably "autistic aloneness" and "insistence on sameness", are still regarded as typical of the autistic spectrum of disorders ***(Happe, 2006).*** In 1980, DSM-III differentiates autism from childhood schizophrenia. In 1987, the DSM-III-R diagnosed autism according to a check list. In May 2013, the DSM-5 updated the classification for PDDS which included PDD-NOS, Autism, Asperger Syndrome, Rett Syndrome, and CDD, has been replaced with the term of ASD ***(Baker, 2013).***

Epidemiology

Autism spectrum disorder (ASD) are the most common developmental disability ***(CDC, 2007).*** Most recent reviews tend to estimate a prevalence of 1–2 per 1,000 for autism and close to 6 per 1,000 for ASD ***(Newschaffer, 2007).*** Underestimation in the rate of ASD may be because of inadequate data ***(Carronna, 2008).***CDC's most recent estimation is that 1 out of every 68 children, or 14.7 per 1,000, has an ASD ***(CDC, 2010).***

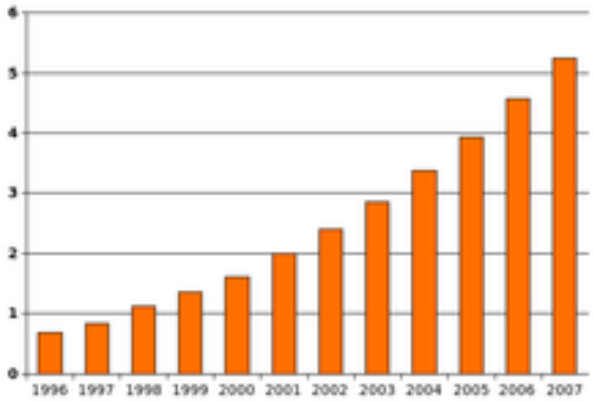

Figure (1): Reports of autism cases per 1,000 children grew dramatically in the US from 1996 to 2007.

The prevalence of autism has dramatically increased as shown in (Figure 1), and some have called it an epidemic. This increase is due to changes in diagnostic practices, referral patterns, availability of services, age at diagnosis, and public awareness ***(Fombonne, 2009).*** ASD is considered the fastest growing developmental disorder in the USA, it affect 1 in every 68 children ***(Developmental Disabilities Monitoring Network Suurveillance Year 2010, 2014).*** ASD shows a marked male bias in prevalence, with approximately four affected males for every affected female ***(Werling and Geschwind, 2013).*** The sex ratio averages 4.3:1 and is greatly modified by cognitive impairment: it may be close to 2:1 with intellectual disability and more than 5.5:1 without ***(CDC, 2007).***

There is ***(Seif Eldin et al., 2008)*** concluded that the prevalence rate of autism in children in Egypt was 33.6% . ***(Abd Elhameed, Abd Elbaky and Kamel, 2011; El-Baz,***

Ismael and Nour El-Din, 2011; Amr et al., 2012) about autism in Egypt found that Paternal age over 35 years associated with increased risk of autism. Most patient present at age of one and half years and the rest at age 2 years,3 and 4years with decreasing frequency. Most cases are presented with delayed speech. High rate occur in males than female. Most cases were in school of special needs. All studied developmental milestone were delayed. History of threatened abortion, caesarian section, low birth weight, post natal hypoxia were associated with increased risk of autism. Thirty one percent of patient had diffuse epileptogenic pattern in EEG.

Etiology

No definite cause of autism has been identified, but it is believed to be multifactorial as both genetic and environmental factors ***(Bailey et al., 2009).*** Environmental factors are likely to play a major role in the increased prevalence of autism ***(Deth et al., 2008).*** Genetic factors remain important, because it is indicated by high rates among twins and siblings ***(Bohm and Stewart, 2009).***

1) Genetic factors

The relative risk of a second child having this diagnosis is 20–50 times higher than the population base rate ***(O'Roak and State, 2008).*** Many genes have been associated with autism

by sequencing the genomes of affected individuals and their parents ***(Sanders et al., 2015).***

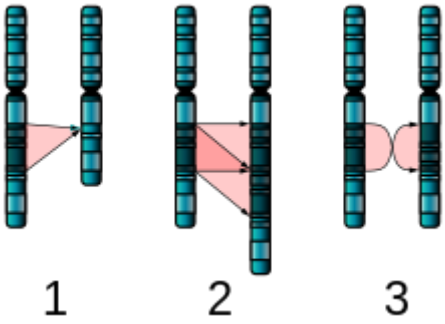

Figure (2): Deletion (1), duplication (2) and inversion (3) are all chromosome abnormalities that have been implicated in autism.

Autism has a strong genetic basis as shown in figure (2), although the genetics of autism are complex ***(Abrahams and Geschwind, 2008).***Monozygotic twins are concordant for autism spectrum disorder than dizygotic twins by 60-90% ***(Bailey et al., 2009).***There is a discovery that a a gene called MET doubles the risk of occurring autism in children ***(Campbell et al., 2006).***There is expected unbalanced chromosomal abnormalities are found predominantly in children with autism and accompanying dysmorphology ***(Takahashi & Miles 2009).*** The presence of a syndrome in an individual l patient with autism may be a key factor in the pathogenesis of the disorder in that patient, but not be the only factor ***(Smith et al., 2009).*** In Fragile X syndrome 1% to 3% of children on the basis of an autism diagnosis have fragile X syndrome, at least half the children with fragile X syndrome have some autistic behaviors, including avoidance of eye

contact, language delays, repetitive behaviors, sleep disturbances, self-injurious behaviors, hyperactivity, inattention, and sound sensitivities ***(Harris et al., 2008).*** Sotos syndrome is associated with the major features of behavioral problems, learning disability, congenital cardiac anomalies, neonatal jaundice, renal anomalies, scoliosis, and seizures ***(Buxbaum et al., 2007).*** In Tuberous sclerosis complex (TSC) 25%-50% of mentally retarded individuals have autism diagnostic criteria but only 1.1%-1.3% of individuals diagnosed with ASD have TSC ***(De Vries et al., 2007).*** In phenylketonuria autistic symptoms in untreated children with PKU improve after initiation of dietary therapy ***(Filipek, 2005).***

In Mitochondrial disorders although mitochondrial respiratory chain has been reported in individuals with autism on rare occasions, elevated plasma concentrations of lactate have been frequently noted ***(Corriea, 2006).*** Mitochondria play an important role in regulating developmental processes ***(Matson & Liu, 2002).*** So it is important to consider the nuclear action of mitochondria l genomes in autism pathogenesis ***(Smith et al., 2009).*** Complexity arises due to interactions among multiple genetic, environmental, and epigenetic factors which do not change DNA but are heritable and influence gene expression ***(Rapin and Tuchman, 2008).***

2) Epigenetic

Epigenetic processes may increase the risk of autism. Epigenetic changes occur as a result of chromosomal histone modification or modification of the DNA bases. Such modifications are known to be affected by environmental factors, including nutrition, drugs, and mental stress ***(Miyake, 2012).***

3) Enviromental factors

Prenatal exposure to rubella or cytomegalic virus is called the principle non genetic cause of autism ***(Meyer et al., 2007).*** Infection-associated immunological events in early pregnancy may affect neural development more than infections in late pregnancy ***(Meyer et al., 2007).*** There are theories that some agent cause birth defects have also been suggested that increase risk of autism such as exposure to valporic acid ***(Chomiak and Turner, 2013).*** It is hypothesized that folic acid taken during pregnancy could play a role in reducing cases of autism by epigenetic mechanism ***(Lyall et al., 2014).*** Congenital malformation, abnormal fetal, presentation, fetal, distress, trauma, low birth weight, maternal hemorrhage, high paternal age; mother above 30 years and fathers above 35 years were associated with increased risk of autism ***(Gardener et al., 2011).*** High prevalence rates of autism among preterm than normal gestational age by using the Modified Checklist for Autism Toddlers (M-CHAT) ***(Limperopoulos et al., 2008).***

Evidences for and against association of autism with viral infection after birth had been presented ***(Libbey et al., 2005).***

4) Thyroid disorder

Thyroid problems that lead to thyroxine deficiency in the mother in weeks 8–12 of pregnancy lead to produce changes in the fetal brain Leading to autism ***(Roman, 2007).***

5) Diabetes disorder

Diabetes in the mother during pregnancy is a significant risk factor for autism; a 2009 meta-analysis and a 2014 review found that gestational maternal diabetes was significantly associated with an increased risk of ASD ***(Xu and Guiferg, 2013).***

6) Vitamin D deficiency

Vitamin D deficiency leads to weakness in natural defenses against mutations ***(Kinney et al., 2009).*** Evidencing the role of vitamin D deficiency as a causative agent for autism, a paper reported that 10 patients with autism had the lowest vitamin D levels of any of the groups studied ***(Humble et al., 2010).***

7) Immune system disorder

In mothers with autistic children there is maternal immunoglobulin reactivity against fetal brain proteins ***(Singer***

et al., 2008; Braunschweig et al., 2008). When maternal autoimmune disease is present, antibodies circulating to the fetus may lead to the development of autism spectrum disorders ***(Ashwood et al., 2006).*** Interactions between the immune system and the nervous system begin early during embryogenesis, and successful neurodevelopment depends on a balanced immune response. It is possible that aberrant immune activity during critical periods of neurodevelopment is part of the ***(Fox et al., 2012).*** Families with autism show clustering of autoimmune disorders ***(Croen et al., 2005).*** Several immunological diseases occur at an increased rate among primary family members of individuals with autism ***(Mouridsen et al., 2007).*** Independent studies have also suggested that persons with autism have a greater family history of autoimmune disease compared to controls ***(Bauer et al., 2007).***

8) Lead problems

Lead poisoning has been suggested as a possible risk factor for autism, as the lead blood levels of autistic children is higher than control ***(Zafeiriious, 2007).***

9) Maternal stress and autism

The maternal prenatal exposure to stress,financial problems, death of a husband or job loss may be factors that

lead to increase the risk of autistic disorders in the offspring ***(Kinney et al., 2008).***

Pathophysiology

Autism's symptoms result from maturation-related changes in various systems of the brain. How autism occurs is not well understood. Its mechanism can be divided into two areas: the pathophysiology of brain structures and processes associated with autism, and the neuropsychological linkages between brain structures and behaviors ***(Penn, 2006).*** The behaviors appear to have multiple pathophysiologies ***(London, 2007).***Several pathophysiological mechanisms had been suggested in the process of understanding autism as immune dysfunction theory, channelopathy, and other mechanisms ***(Onore et al., 2012).***The theory of unbalanced excitability – inhibitory network in autism states that mutations involving Gamma Amino Butyric Acid (GABA) receptor gene contribute in abnormal central nervous system excitability which may partially explain pathophysiological basis of autism ***(Schmitz and Rezaie, 2008).***

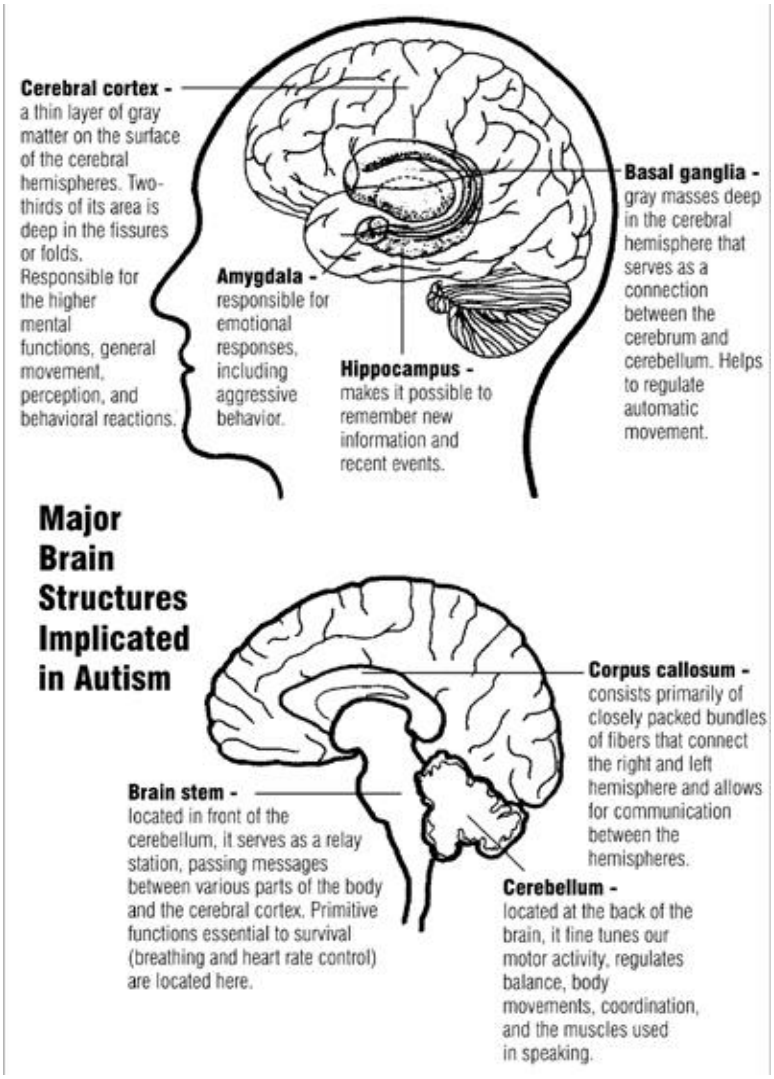

Figure (3): Autism affects the amygdala, cerebellum, and many other parts of the brain ***(Amaral et al., 2008).***

Autism appears to result from developmental factors that affect many or all functional brain systems as shown in figure (3), and to disturb the timing of brain development more than the final product ***(Amaral et al., 2008).***

Macrocephaly is noted by age 2–3 years in 20% of children with autism spectrum disorder. Brain growth accelerates at 12 months ***(Minshew and Williams, 2007).***Neuroimaging studies**,** have shown overgrowth in cortical white matter and abnormal patterns of growth in the frontal lobe, temporal lobes, and limbic structures such as the amygdala. These brain regions are implicated in development of social, communication, and motor abilities that are impaired in autism spectrum disorder ***(Pardo and Eberhart, 2007).***Numerous studies have reported abnormal connectivity in those with ASD ***(Wan and Schlaug, 2010).(Wegiel et al., 2008)*** have revealed neuronal developmental heterochronicity in early childhood, resulting in selective developmental delay of the growth of neurons in some subcortical structures and the cerebellum during the most critical stage of development of social behaviors and communication skills .Functional magnetic resonance imaging stated that the functional abnormalities in a network involved in emotional and interoceptive awareness might be at the basis of altered emotional experiences and impaired social abilities in ASD ***(Ebisch et al., 2011).***The reduced size of neurons and their nuclei in the cortex of autistic subjects reported is an indicator of reduced or impaired functional connectivity between distant cortical regions ***(Casanova et al., 2006).***There is at present a convergence of findings stemming from structural neuroimaging studies indicating a reduction in size of the corpus callosum in patients with autism ***(Frazier and Hardan,***