INTRODUCTION

Autism is defined as a developmental disorder of brain function with many different causes ***(Rapin, 1997)***.

The major diagnostic criteria of autism comprises; failure of language development, severe impairment of interpersonal relationships, a restricted repertoire of activities, and onset before 3 years ***(Fenichel, 2001).***

Autism has a wide range of behavioral consequences that are broadly referred to as *pervasive developmental disorders* that include: Autistic disorder, Autism Spectrum Disorder (ASD) and Asperger's syndrome, the last two include children who have some features of autism, but do not meet the full criteria ***(Matson and Rivet, 2008)***.

The recent total prevalence of autism, Asperger's syndrome and related developmental disorders is estimated as 6.7 cases per 1,000 children, with male to female ratio (4:1) ***(CDC, 2007).***

It is believed that autism is a genetically based disorder requiring an environmental trigger to manifest ***(Muhle et al., 2004).*** There is little research concerning the role of environmental factors in disease expression; concerns about the role of mercury immunizations and other environmental toxins have been speculated ***(Weber and Newmark, 2007).*** Recent research has suggested that nutritional factors also play a major role in the development of autism ***(Curtis and Patel, 2008).***

In no area of developmental pediatric practice is there more controversy regarding the choice of treatment than related to children with autistic spectrum disorders (ASD) (***Levy and Hyman, 2008)***.

Autism is a complicated condition that may require an integrative treatment protocol involving many factors including behavioral and social therapy, pharmacotherapy, environmental control and nutritional therapy ***(Kidd, 2002).***

Vitamin D "The Sunshine Hormone":

Vitamin D is unique in the vitamin world in that it influences the entire body, from the bones to the brain. Ninety percent of human vitamin D stores come from skin production, not oral intake ***(Holick, 1987).***

Vitamin D deficiency is implicated in most of the diseases of civilization. Vitamin D's final metabolic product targets more than 200 human genes in a wide variety of tissues. Assessing serum 25-hydroxy-vitamin D [25(OH) D] is the only way to make the diagnosis and to assure treatment is adequate and safe ***(Cannell and Hollis, 2008).***

Ideal 25(OH) D levels are unknown but they are thought to be somewhere above 30 ng/mL (75 nmol/L) and probably closer 40 ng/mL (100 nmol/L) ***(Holick, 2007),*** and requires the daily ingestion of thousands – not hundreds – units to achieve ***(Cannell, 2007).***

Brain Functions and Vitamin D:

Accumulating data have provided evidence that

1 alpha, 25-dihydroxyvitamin D [1, 25-(OH) (2) D] is involved in brain function and its nuclear receptors are localized in neurons and glial cells ***(Garcion et al., 2002)***.

McGrath et al. (2001) concluded that hypovitaminosis D should be examined in more detail as a candidate risk factor for neurodevelopmental disorders naming it the "neglected neurosteroid". Furthermore they pointed out that calcitriol is a potent up-regulator of nerve growth factor and that vitamin D receptor is found in wide variety of brain tissues early in embryogenesis. It also offers neuroprotection, antiepileptic effects, immunomodulation, possible interplay with several neurotransmitter system and hormones, as well as regulation of behaviors ***(Kalueff et al., 2006).***

Autism and Vitamin D:

The apparent increase in the prevalence of autism over the last 20 years corresponds with increasing medical advice to avoid the sun, advice that has probably lowered vitamin D levels and would theoretically greatly lower activated vitamin D (calcitriol) levels in developing brains ***(Cannell, 2007).***

Children with vitamin D deficient rickets have several autistic markers that apparently disappear with high dose vitamin D treatment. Estrogen and Testosterone have very

different effects on calcitriol's metabolism (positive effect of Estrogen on calcitriol levels), differences that may explain the striking male/female sex ratios in autism ***(Cannell, 2007).***

Around 12-18 months, many infants stop drinking vitamin D fortified infant formula and begin consuming unfortified juices, which – interestingly – is also the time many autistic children rapidly deteriorate. Toddlers and young children who do not get regular sun exposure should take 1000-2000 IU vitamin D daily year round ***(Cannell and Hollis, 2008).***

Cornish (1998) found that children with ASD had dietary intake less than the recommended amounts for vitamin C, vitamin D, several B vitamins, iron and calcium.

Caregivers report that children with ASD like sameness of food items and have specific eating behaviors with more food preferences compared to typically developing children. Whenever a child's diet is limited in variety, the nutritional status of the child may be jeopardized due to inadequate intake of nutrients ***(Adams and Hollway, 2004).***

A placebo controlled three-month study of 20 autistic children found multivitamins with even low doses of vitamin D (150 units or 3.75 mcg) significantly improved sleep and gastrointestinal problems ***(Adams and Hollway, 2004).***

AIM OF THE WORK

Evaluation of 25(OH) cholecalciferol, parathyroid hormone and calcium status in Egyptian autistic children before and after 6 months period of oral vitamin D supplementation and assessment of the effect of the supplementation on the psychiatric test results.

AUTISM

A. Definition:

Autism is a brain development disorder that is characterized by impaired social interaction, verbal and non verbal communication, and restricted and repetitive behavior ***(APA, 2000).***

B. Historical perspective:

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 (αὐτός,) meaning self ***(Kuhn and Cahn, 2004).***

In ***1943, Leo Kanner***, a psychiatrist at Johns Hopkins University, first described autism in a small group of children who demonstrated extreme aloofness and total indifference to other people. In his words, "There is from the start an extreme autistic aloneness that, whenever possible, disregards, ignores, shuts out anything that comes to the child from the outside" ***(Frith, 2003).***

The terms "infantile autism" (onset before age 30 months) and "childhood-onset pervasive developmental disorder" (onset after 30 months) first appeared as a diagnostic labels in the Diagnostic and Statistical Manual of Mental

Disorders, Third Edition (DSM-III) under the umbrella of pervasive developmental disorders ***(APA, 1980).***

Pervasive developmental disorders are a group of neurodevelopment disorders of varying severity; affecting communication skills, social interaction, and behavior patterns. They are a set of disorders that cover the whole lifespan ***(Matson and Rivet, 2008)***.

It is now clear that the term infantile autism was, in many ways, a misnomer because autistic infants grow up to be autistic adults ***(Lewis, 2002).***

The DSM-IV ***(1994)*** and DSMIV-TR ***(2000)*** include five possible diagnoses under the umbrella of pervasive developmental disorders (Table-1) which have some concordance with the categories in the World Health Organization's International Classification of Disease, 10^{th} edition ***(WHO, 1992).***

Table (1): The Pervasive Developmental (Autistic Spectrum) disorder

DSM-IV Diagnoses*	ICD-10 Diagnoses†
Autistic disorder	Childhood autism
Asperger's disorder	Asperger's syndrome
Childhood disintegrative disorder	Other childhood disintegrative disorder
Rett's disorder	Rett's syndrome
PDD-NOS	Atypical autism Other PDD PDD unspecified
No corresponding DSM-IV diagnoses	Overactive disorder • With mental retardation • With stereotyped movements

PDD-NOS: Pervasive Developmental Disorders Not Otherwise Specified, PDD: Pervasive Developmental Disorders. ****American Psychiatric Association (1994).*** † ***World Health Organization (1992)***

Table (2): Differential diagnostic criteria of autism and non autistic pervasive developmental disorders

	Autism	**Asperger's**	**PDD-NOS**	**Rett's disorder**	**Childhood disintegrative disorder**
Age of recognition (months)	0-36 (3-5 years)	>36 (6-8 years)	Variable	5-30	>24
Regression	About 25% (social or communication)	No	Variable	Severe	Severe
Sex ratio (male:female)	2:1	4:1	M>F (variable)	F(?M)	M>F (variable)
Socialization	Poor, >2DSM-IV criteria	Poor	Variable	Varies	Very poor
Communication	Delayed, deviant, might be non-verbal	No early delay; qualitative and pragmatic difficulties later	Variable	Very poor	Very poor
Circumscribed interests	Variable (mechanical)	Variable (Facts)	Variable	NA	NA
Family history of similar conditions	Sometimes	Frequent	Unknown	Not generally	No
IQ range	Severe MR to normal	Mild MR to normal	Mild to severe MR	Severe MR	Severe MR
Seizures	Common (25% over lifespan)	Uncommon (roughly 10%)	Uncommon (roughly 10%)	Frequent	Common
Head growth deceleration	No	No	No	Yes	No
Outcome	Poor to fair	Fair to	Fair to	Very	Very poor

		good	good	poor	

NA=not applicable. IQ: intelligence quotient. MR=mental retardation. NOS=not otherwise specified.DSM-IV=Diagnostic and Statistical Manual of Mental Disorders, 4th edition ***(Volkmar and Cohen, 1992)***.

C. Epidemiology:

After intellectual impairment, ASDs are the most common developmental disability ***(CDC, 2007).***

Prevalence of autistic disorder is between ten and twenty per 10 000 children ***(Newschaffer et al., 2007).*** Estimates of autism spectrum disorders have been more consistent than have those for autistic disorder—perhaps because they are less sensitive to small differences in case definitions. These estimates are close to 60 per 10 000 children in in the year ***2007*** increasing to 1 case per 110 individual in the ***CDC report, (2009).***

The reported prevalence of autism has dramatically increased (Figure: 1), and some have called it an epidemic. A number of factors contribute to the apparent increase:

1. There is a true increase in the prevalence of this disorder.
2. There is increased case-finding resulting from increased awareness of this disorder on the part of the public, medical and other professionals.
3. Experts frequently refer to the recent "broadening" phenotype of ASD and the resulting inclusion of children with disorders that do not necessarily meet the criteria for

true autism as a potential influence on the increased numbers.

(Weber and Newmark, 2007)

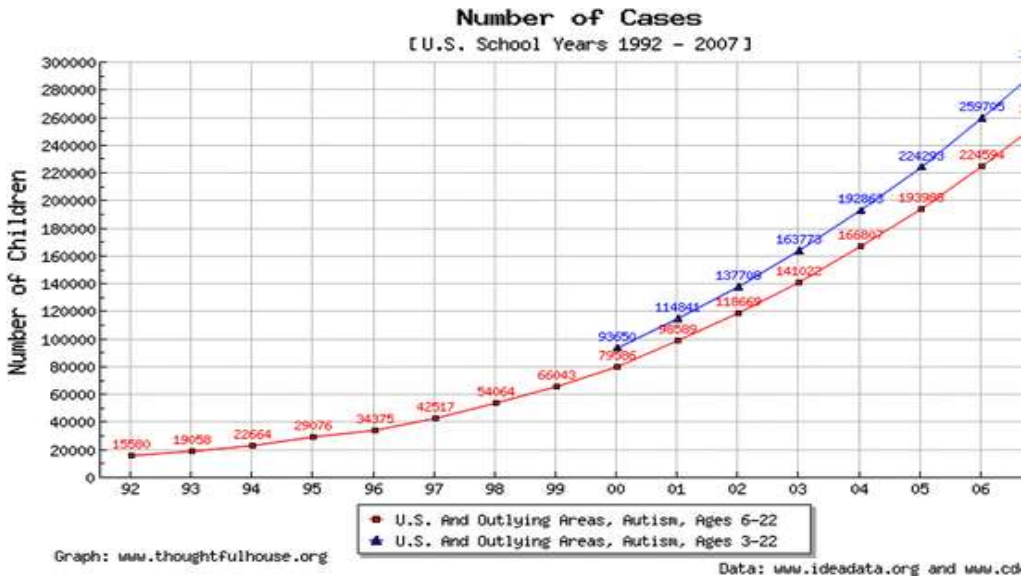

Figure (1): The near exponential increase in the number of cases of autism in the United States between the years 1992 and 2007.

There are no published available data on the prevalence of autistic spectrum disorders in Egypt ***(Meguid et al., 2008).*** However ***Seif Eldin et al. in 2008*** reported 33.6% prevalence of ASD among children with developmental disorders in Egypt.

Prevalence of autistic spectrum disorders in Saudi Arabia is 6:1000 (***Al-Salehi et al., 2009).*** A study conducted in Haifa, Israel, showed an incidence rate of 1:1000 and a male to female ratio of 4.2:1 ***(Michael et al., 2001).***

A study conducted in UAE found a weighted prevalence of 29 per 10,000 for PDD in the 3-year-old UAE national population ***(Eapen et al., 2007).***

Regardless of the study, the year conducted, or the reported rate of prevalence, more boys than girls are consistently found to be affected with ASDs, with male-to-female ratios ranging from 2:1 to 6.5:1 with a mean of 4:1 ***(CDC, 2007).*** The male-to-female ratio is even higher for high-functioning autism and AS (Asperger's syndrome), ranging from 6:1 to as high as 15:1 ***(Volkmar et al., 2005).*** But as severity of cognitive impairment increases, the male-to-female ratio decreases to 1.3 to 1 ***(Yeargin-Allsopp et al., 2003).***

D. Clinical characteristics:

The diagnosis of an ASD is based exclusively on developmental pattern and behavioral observation ***(Levy et al., 2009).***

Core symptoms of autism spectrum disorders affect domains of socialization, communication, and behavior (Table : 3). Results of prospective studies by ***Volkmar et al. in 2005*** of infants at risk (ie, younger siblings of affected children) have shown that deficits in social responsiveness, communication, and play can be present in those as young as age 6–12 months ***(Levy et al., 2009).*** Furthermore, ***Dawson et al. 1998*** noted that neonates normally have a remarkable interest in social

interaction (Figure 2). By contrast, in autism the human face is an object of little interest.

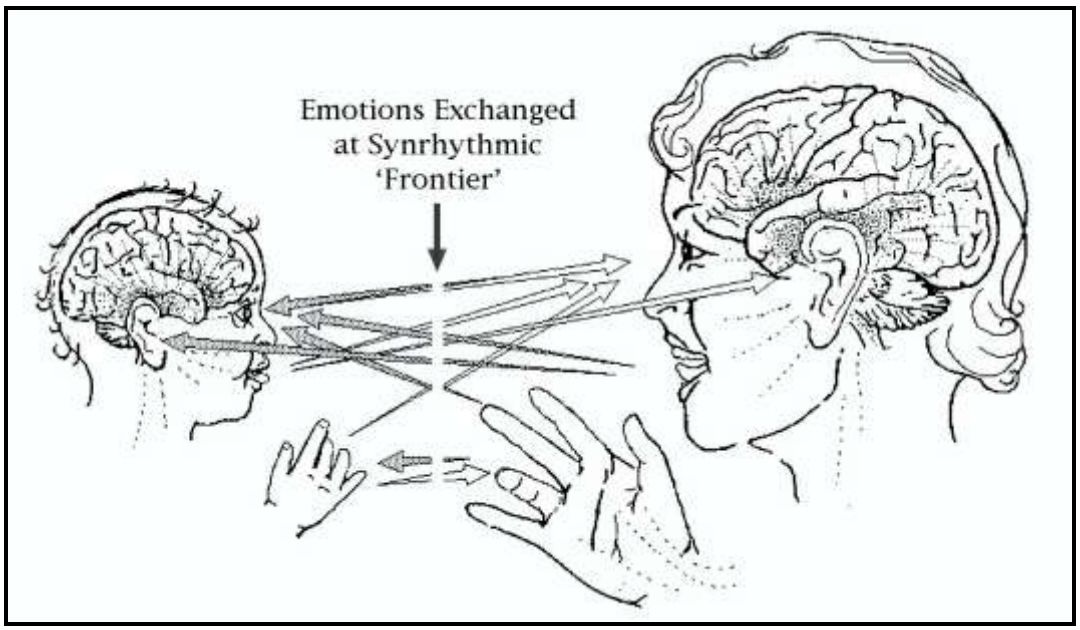

Figure (2): Normal social interaction in young infants involves eye contact, skin contact, and auditory connection ***(Dawson et al., 1998).***

Presentations can differ widely from one child to the next; some are perceived by parents as "different" during the first few months of life, others present with delayed speech development during the second year of life, and still others may appear to be normal only to regress and lose skills after the first year of life ***(Werner and Dawson, 2005).***

Table (3): Core domains of autism

Socialization
• Impaired use of non-verbal behaviors to regulate interactions
• Delayed peer interactions, few or no friendships, and little interaction
• Absence of seeking to share enjoyment and interests
• Delayed initiation of interactions
• Little or no social reciprocity and absence of social judgment
Communication
• Delay in verbal language without non-verbal compensation (eg, gestures)
• Impairment in expressive language and conversation, and disturbance in pragmatic language use
• Stereotyped, repetitive, or idiosyncratic language
• Delayed imaginative and social imitative play
Restricted, stereotyped, and repetitive patterns of behavior
• Preoccupation with stereotyped or restricted interests or topics
• Adherence to routines, rigidity, and perseverative behavior
• Stereotyped, repetitive motor mannerisms, and selfstimulatory behavior
• Preoccupation or fascination with parts of items and unusual visual exploration

(APA, 2000)

Symptoms and signs are discussed in detail in the DSMIV-TR (Table 4).

Table (4): Diagnostic Criteria for Autistic Disorder

A. A total of six (or more) items from (1), (2), and (3), with at least two from (1), and one each from (2) and (3):
   1. Qualitative impairment in social interaction, as manifested by at least two of the following:
      a. Marked impairment in the use of multiple nonverbal behaviors such as eye-to-eye gaze, facial expression, body postures, and gestures to regulate social interaction
      b. Failure to develop peer relationships appropriate to developmental level
      c. Lack of spontaneous seeking to share enjoyment, interests, or achievements with other people (e.g., by a lack of showing, bringing, or pointing out objects of interest)
      d. Lack of social or emotional reciprocity
   2. Qualitative impairments in communication as manifested by at least one of the following:
      a. Delay in or total lack of the development of spoken language (not accompanied by an attempt to compensate through alternative modes of communication such as gesture or mime)
      b. In individuals with adequate speech, marked impairment in the ability to initiate or sustain a conversation with others
      c. Stereotyped and repetitive use of language or idiosyncratic language
      d. Lack of varied, spontaneous make-believe play or social imitative play appropriate to developmental level
   3. Restricted repetitive and stereotyped patterns of behavior, interests, and activities, as manifested by at least one of the following:
      a. Encompassing preoccupation with one or more stereotyped and restricted patterns of interest that is abnormal either in intensity or focus
      b. Apparently inflexible adherence to specific, nonfunctional routines or rituals
      c. Stereotyped and repetitive motor mannerisms (e.g., hand or finger flapping, twisting, or complex whole-body movements)
      d. Persistent preoccupation with parts of objects

B. Delays or abnormal functioning in at least one of the following areas, with onset before 3 years old: (1) social interaction, (2) language as used in social communication, or (3) symbolic or imaginative play.

C. The disturbance is not better accounted for by Rett's Disorder or childhood disintegrative disorder.

(APA, 2000)

One unique characteristic of ASDs is the "unevenness" of skills. Abilities may be significantly delayed in some areas of development yet "advanced" in others, often because of exceptional focusing, memory, calculation, music, or art abilities ***(Williams et al., 2005),*** (figure 3)**.** Rarely, highly