Androgen Levels in Egyptian Autistic Children and Adolescents Relation to Disease Severity

Thesis

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INTRODUCTION

Autism is prevalent neurodevelopmental disorder characterized by impairment in social relatedness and communication, repetitive behaviors, abnormal movement patterns, and sensory dysfunction ***(Eigsi & Shapiro, 2003).***

Though symptoms of autism may be present from birth, they may also manifest between 12 months and 24 months of age ***(Werner & Dawson, 2005).*** Its emergence in early life, its chronic course affecting all intellectual elements , the lack of successful treatment ***(Bailey et al, 1996)*** and the increasing incidence make it one of the most serious psychiatric illness ***(Stokstad, 2001)***

Autism affects males more than females occurring at a ratio at least 3:1 ***(Centers for Disease Control and Prevention, 2007).*** This sex difference may reflect a male vulnerability to develop an autism as individuals with autism tend to display a hypermusculine profile on many cognitive tasks ***(Baron-Cohen, 2002)*** also, may have lower than expected 2nd to 4th digit ratios which correlate with higher ratios of fetal testosterone to fetal estrogen ***(Lutchmay et al.,2004).***

Some neuroanatomical studies comparing the brains of individuals with and without autism revealed structural differences associated with high levels of free testosterone (FT), including hemispheric asymmetries ***(Herbert et al.,2005).***

Finally, girls with abnormally high FT levels as a result of congenital adrenal hyperplasia (CAH) have a higher number of autistic traits than their unaffected sisters ***(Knichmeyer et al, 2006).*** Clinical examination of patients with autism has revealed that on average, girls with autism show a significant delay in the onset of menarche ***(Knichmeyer, et al 2006)*** **(**since excess androgens have been linked to menstrual problems) ***(Caufriez, 1991)*** and are more likely to display elevated rates of testosterone-related disorders than neurotypical controls ***(Ingudomnukul et al., 2005).*** Other studies have shown elevated blood androgen metabolites in patients with autism in comparison with controls ***(Geier et al., 1997).***

AIM OF THE WORK

We examined blood androgens levels in a group of children with autism in comparison to reference values of Egyptian controls and their relations to autistic severity. In addition the risk for association of androgen with autism was estimated.

AUTISM

Definition:

Autism is a severe neurodevelopmental disorder characterized by impaired communication, social interaction and imagination that is often accompanied by repetitive and stereotyped behavior ***(Moy et al., 2006).*** It develops before the 36th month of age and persists into adulthood causing life long disability with higher prevalence in males more than females about male: female 3:1 (***Ashwood and Van De Water, 2001)***.

Autism is recognized now as a heterogeneous syndrome with a broad range of behavioral symptoms and severity. The spectrum of autism-related disorders is collected under the umbrella of pervasive developmental disorders (PDDs) ***(American Psychiatric Association, 1994).*** All of them demonstrate characteristic deficits in communicative and social skills, varying however, in pervasiveness, severity and onset. This group comprises autistic disorder (previously referred to as classic autism). Asperger's syndrome, Rett's disorder, childhood disintegrative disorder, and pervasive developmental disorder-not otherwise specified (PDD-NOS) ***(Korvatska et al., 2002)***.

Historical Review:

The history of autism goes as far back as 1911 with ***Eugen Bleuler*** a Swiss psychiatrist first coined the term. However, that term applied to adult schizophrenia. ***(Marinelli et al., 2003).***

In 1943, ***Leo Kanner*** (a doctor from Johns Hopkins University) first described 11 cases of what he termed autistic disturbance of affective contact. In these cases, there was an inability to relate to people in usual ways. Kanner also noted unusual responses to the environment, which could include both stereotyped behavior and resistance to change or insistence on sameness, as well as unusual aspects of the child's communication skills, such as tendency to echo language (echolalia). Kanner believed that the condition was not associated with mental retardation because the children looked intelligent and did well on some parts of intelligence quotient (IQ) tests.

In 1944, ***Hans Asperger***, independent of Kanner, wrote about a group of children he called autistic psychopaths. In most aspects they resembled the children of ***Kanner's*** description. The difference was that he did not mention echolalia as a linguistic problem but that the children talked like little grown-ups. In addition, he mentioned their motor activity which was more clumsy and different from normal children.

As time went on, it became clear that most children function in the mentally retarded range. However, consistent with ***Kanner's***

original observation, it continues to be the case that marked scatter in skills -with occasional "splinter skills"- is often observed. ***Kanner*** mentioned that parents were unusually well

educated or successful in their occupations. This led to the notion that autism might somehow result from pathological patterns of care. Considerable evidence suggests this is not the case. There is no particular bias in terms of social class distribution of autism if factors that control for case ascertainment are controlled for. It is also the case that parents of autistic children do not exhibit specific deficits in parenting or other aspects of childcare and are not likely to have other psychiatric disabilities at an increased rate, with the exception of mood disorders and a range of developmental difficulties. Autism and schizophrenia remained linked in many researchers' minds until the 1960s. It was only then that medical professionals began to have a separate understanding of autism in children from the 1960s through the 1970s, research into treatments for autism focused on medications such as LSD (*Lysergic acid diethylamide*), electric shock, and behavior change techniques. The latter relied on pain and punishment. During the 1980s and 1990s, the role of behavior therapy and the use of highly controlled learning environments emerged as the primary treatments for many forms of autism and related conditions. Currently, the cornerstone of autism therapy is behavior therapy. Other treatments are added as needed. In the early 1960s, a growing body of evidence began to accumulate to suggest that the condition resulted from a neuropathlogical process. A landmark in classification occurred in 1978 when ***Micheal Rutter*** proposed a definition of autism based on:

1. Social delay and deviance (not just due to mental retardation).
2. Communication problems (not just due to mental retardation).
3. Unusual behavior such as stereotyped movements and mannerisms (insistence on sameness).
4. Onset before the age of 30 months ***(Volkmar et al., 1994).***

Rutter's definition and the growing body of work on autism were influential in the definition of the condition of DSM-III. In DSM-III, the condition was first recognized and placed in a new class of disorders -the pervasive developmental disorders**.** Successive editions of the World Health Organization's "International Classification of Diseases" (ICD) and the American Psychiatric Association's "Diagnostic and Statistical Manual of the Mental Disorders" (DSM) have reflected changing ideas of autism and related disorders. Almost 50 years after Kanner's first description, the latest versions of ICD (ICD10) ***(World Health Organization, 1992)*** and DSM-IV ***(American Psychiatric Association, 1994)*** provided virtually identical definitions of autism and autistic-like disorders ***(Volkmar et al., 1994)***.

In both systems, the overall construct of autistic and autistic-like behavior problems has been given the name pervasive developmental disorders. The term "pervasive" was meant to emphasize that in autism, development was disturbed over a range of different domains, in contrast to the relatively

more delineated difficulties of the specific developmental disorders and the centrality of cognitive problems in mental retardation. The term "developmental" implies that individuals with these conditions suffer from disturbances in the normative unfolding of multiple developmental competencies, including social relations and communication. These disorders have their onset in the first years of life, and developmental disorders have important implications throughout the life span ***(Sophie, 2002)***.

Epidemiology of autism:

A. Prevalence of Autism:

Autism was initially felt to be a fairly rare illness (less than 5 in 10,000), but over the last twenty years there has been an explosive increase in incidence, growing on average around 25% per year in some areas ***(Jepson, 2003)***. Studies show prevalence rates ranging from 10 to 20 per 10,000 children ***(Dalton et al., 2004)***. In the United states, it is currently believed to affect 1 out of every 250 individuals on average (up to 1 in 150 in some areas) ***(Jepson, 2003).***

B. Sex Ratio:

Studies based on on both clinical and epidemiological samples have suggested a higher incidence of autism in boys than in girls with male: female ratio of 3: 1 ***(Fombonne, 2003)***.

C. Social Class:

Although early studies supported Kanner's impression of an association between autism and a higher socioeconomic status, most epidemiological studies published in the 1980s and 1990s have faild to reveal such association. Autism is clearly seen in all social classes ***(Volkmar et al., 2004)***.

Etiology of autism:

In 10-30% of cases, there is an identifiable etiology (secondary autism). Some of the frequently quoted causes are herpes simplex encephalitis which involves one or both temporal lobes, intra-uterine cytomegalovirus or rubella infections, intra-uterine exposure to thalidomide or valproate, chromosomal anomalies like fragile-X or Angelman syndromes, genetic disorders such as inadequately treated phenylketonuria (PKU), tuberous sclerosis or Cornelia de Lange syndrome, and many others ***(Gillberg and Colman, 1996)***. In the majority of cases, there is no obvious cause (primary autism) ***(Cohen and Volkmar, 1997)***.

The causes of autism are multifactorial ***(Dalton et al., 2004)***. Autism is caused when a child with an appropriate genetic susceptibility is exposed to a number of environmental insults resulting in a complex series of interactions in several body systems, primarily the central nervous system (brain), the gastrointestinal system (the gut) and the immunological system

(body defense) **(Fig. 1).** Each child with autism is a unique individual and has unique biochemistry that has some how become disordered ***(Jepson, 2003)***. Causes of autism include:

1-Brain Testosterone Theory

Simon Baron-Cohen proposed a model for autism based in his empathising-systemising (E-S) theory. His team ,at the Autism Research center in Cambridge;UK,measured testosterone levels in the amniotic fluid of mothers while pregnant. This is presumed to reflect levels in the babies themselves. The team found that the babies with higher fetal testosterone levels had a smaller vocabulary and made eye contact less often when they were a year old**. *(Baron-Cohen, 2002).***

His group has looked at the original 58 children again, at age four. The researchers found that the children with higher testosterone in the womb are less developed socially, and the interests of boys are more restricted than girls**. *(Auyeung et al.,2009).***

Baron-Cohen theorized that high fetal testosterone levels push brain development towards an improved ability to see patterns and analyze systems. Males supposedly tend to be better at these tasks than females. But the high levels are thought to inhibit the development of communication and

empathy, which are allegedly typical female skills. ***(Mottron et al .,2003).***

2-Genetic causes:

The neuroanatomic findings in monozygotic twin pairs with autism support the role of genetic liability in autism (***Kates et al., 2004***). The recurrence risk for autism after the birth of an autistic child is 60 to 150 times more than the populate. Epidemiologically based, same gender twin studies have reported higher concordance rates for autism among identical twins than among non identical twins. The mode of genetic transmission is unclear. The marked fall-off in rates of autism that occurs from identical to non identical twins or siblings suggests that a small number of interacting genes rather than one single gene is involved, with estimates of genes involved ranging from 2 to 20. (***Cook, 2001***). The genes of autism have been found to affect different steps of cortical development, including proliferation of neuronal progenitor cells, neuronal migration and maintaining integrity of the pial surface ***(Mochida and Walsh, 2004)***. Several full genome searches for susceptibility loci in autism using affected sibling pairs have been performed. Although several areas of the genome (i.e., on chromosome 7q, 1, 2, 6, 13 and 16) have been identified as regions of interest, currently no specific variation in a specific gene has been firmly established as a susceptibility gene for autism ***(Cook, 2001)***. The most promising may be the findings

of deletions and duplications in chromosome 15 affecting the transport of the neurotransmitter serotonin ***(Cook et al., 1997)*** but many other chromosomal loci are also being considered ***(Gillberg, 1998)*** such as HLA genes and their products ***(Lee et al., 2006)***.

3-Metallothionien (MT) dysfunction:

MT is a family of proteins that controls the copper/zinc ratio in the body. MT dysfunction in autism was described by ***William Walsh,*** who took extensive biochemical analyses of over 500 autistic patients, and discovered that almost universally, these children have abnormal copper/zinc ratio with high body copper and low body zinc. Other functions of MT in the body include development of brain neurons, detoxification of heavy metals, maturation of the gastrointestinal tract (GI), anti-oxidation, boosting immune function and delivery of zinc to cells. Because MT synthesis is enhanced by estrogen and progesterone, it would explain the male sex predominance (3: 1) seen in autism. MT dysfunction could be caused by a genetic defect, or an environmental insult that disables MT ***(Jepson, 2003)***.

4-Mitochondrial Causes:

A likely etiological possibility in autism may involve a mitochondrial dysfunction with concomitant defects in neural oxidative phosphorylation within the central nervous system

(Lombard, 1998). Autism may be a disorder of fatty acid metabolism due to a possible dysfunction of mitochondrial long chain acyl CoA dehydrogenase enzyme responsible for the beta oxidation of unsaturated fatty acids in the mitochondria ***(Clark-Taylor, 2004).*** This hypothesis is supported by a frequent association of lactic acidosis and carnitine deficiency in autistic patients. Also, because the mitochondria are vulnerable to wide array of endogenous and exogenous factors which appear to be linked by excessive nitric acid production ***(Lombard, 1998).***

In ***2005, Mostafa and coworkers*** reported that brain energy metabolism of many autistic children is low due to summation of several factors including low plasma polyunsaturated fatty acids (PUFAs) and/or disturbed mitochondrial function as evidenced by decreased serum carnitine and increased plasma lactate levels ***(Mostafa et al .,2005).***

There are autistic children who come from families with patterns of maternal inheritance of psychiatric disabilities. This opens up the possibility of errors of mitochondrial DNA ***(Gillberg, 2000).*** Mitochondrial DNA (mtDNA) is strictly maternally inherited and does not recombine. Mitochondrial DNA mutates more than 10 times more rapidly than nuclear DNA. It has a greater exposure to oxidative stress because it is exposed to oxygen free radicals generated by oxidative phosphorylation and there is an absence of a protective histone coat. In addition, mtDNA has no effective repair system for DNA damage ***(Gillberg***

and Coleman, 2000). In Rett syndrome, a pathologic role of mitochondria has also been proposed based on ultrastructural abnormality in mitochondrial number and size in skin and muscle biopsies ***(Singer and Naidu, 2001)***. Strategies to augment mitochondrial function either by decreasing production of endogenous toxic metabolites, reducing nitric oxide production, or stimulating mitochondrial enzymes activity may be beneficial in treatment of autism ***(Lombard, 1998)***.

5-Neurobiologial Causes

The three principal neurotransmitter types in the brain are:

1- The monoamine neurotransmitters, which are the catecholamines (dopamine, nor epinephrine, and epinephrine), serotonin, acetylcholine and histamine.

2- The amino acid neurotransmitters, which include the inhibitory actions of γ-aminobutyric acid (GABA) and the excitatory glutamate.

3- The neuropeptide neurotransmitters as corticotropin-releasing factor, somatostatin release-inhibiting factor, neurotensin and cholecystokinin ***(Nestler et al., 2001)***.

Synaptic transmission of multiple neurotransmitters needs the neurobiological effect of Acetyl L-Carnitine **(*Traina et al., 2004).***