Assessment of Hypothalamic Pituitary Axis: Gonadotrophic Releasing Hormone Test in a Sample of Egyptian Children and Adolescents with Autism Spectrum Disorders

Thesis

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Candidate

Michael Botros Elkes Morcos

List of Contents

List of Abbreviations

Abbr.	Title
AAP	American academy of pediatrics guidelines
ABC	Autism behavior checklist
ABA	Applied Behavioral Analysis
ADDM	Autism and developmental disabilities monitoring
ADI-R	Autism diagnostic interview- revised
ADOS-G	Autism diagnostic observation schedule- generic
ADOS-T	Autism diagnostic observation schedule- toddler module
AIT	Auditory integration training
AQ	Autism spectrum quotient
ASD	Autism spectrum disorder
ASP	Asperger disorder
ATEC	Autism treatment evaluation checklist
ATs	Autistic traits
BMI	Body mass index
CAH	Congenital adrenal hyperplasia
CAM	Complementary and alternative medicine
CARS	Childhood autism rating scale
CAST	Childhood autism spectrum test
CDD	Childhood disintegrative disorder
CHAT	Checklist for autism in toddlers
CS	Cesarean section
CSBC-DP-	Communication and Symbolic Behavior Scales

ITC	Developmental Profile – Infant Toddler Checklist.
CY-POCS	Children's yale-brown obsessive compulsive scale
DHEA	Dehydroepiandrosterone
DSM IV	Diagnostic and statistical manual of mental disorders
ECLIA	electrochemiluminescence immunoassay
EIBI	Early intensive behavioral intervention
EMB	Extreme male brain theory
E-S	Empathizing – systemizing
ESDM	Early Start Denver Model
fE	Fetal estrogen
FSH	Follicular stimulating hormone
fT	Fetal testosterone
GARS	Gallium autism rating scale
GnRH	Gonadotropin releasing hormone
HBOT	Hyperbaric oxygen therapy
HPG	Hypothalamic pituitary gonadal axis
IEP	Individualized education program process
ITI	Intertrial Interval
LapCorp	Laporatory corporation of America
LH	Luteinizing hormone
M-CHAT	Modified checklist for autism in toddlers
MT	Metallothionein
NCCAM	National center for complementary and alternative medicine
NVD	Normal vaginal delivery

PANDAS	Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infection
PDD-NOS	Pervasive developmental disorder- not otherwise specified
Q-CHAT	Quantitative checklist for autism in toddlers
S^D	Discriminative Stimulus
SCQ	Social communication questionnaire
SDS	Standard deviation score
SQ	Systemizing quotient
STAT	screening tool for autism in two years old
TMS	Trans cranial magnetic stimulation
TV	Testicular volume

List of Tables

List of Figures

Abstract

Background: Autism Spectrum Disorders comprise an extremely heterogeneous class of neurodevelopmental disorders. Consonant with the heterogeneity of ASDs is the multiplicity of proposed causative factors, with candidates including genetic, hormonal, immunologic, and early life stress factors. Aim of the Work: The aim of this work is to study the male hormones (FSH, LH and total testosterone) in male autistic children and adolescents by doing gonadotrophic release hormone test. **Subjects and Methods:** This cross-sectional study was conducted on thirty male autistic children diagnosed according to the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM V) in child psychiatry clinic, pediatric hospital, Ain Shams University from March, 2016 to August, 2016. **Results:** According to Laboratory Corporation of America(LapCorp): FSH normal range in tanner I &II patients from 0.3 to 4.6 mIU/ml. LH normal range in patients with tanner I from 0 to 3.6 mIU/ml. and normal range in patients with tanner II from 0.3 to 4.8 mIU/ml. Testosterone in prepubertal males tanner stage 1 < 0.025 and in tanner stage 2 from 0.025 to 4.32 ng/ml. In pubertal males 2.4 to 8.3 ng/ml. **Conclusion:** Autistic patients were found to have high levels of FSH in 70% of patients, high levels of LH in 10% of patients and normal levels of testosterone and for severity, most of autistic patients with severe autism had higher FSH levels when compared to mild to moderate autistic patients; while LH levels were normal in both groups; while there is no relationship between autism severity and testosterone level. **Recommendations:** Early screening for autistic children for aggressive and abnormal sexual behavior.

Key words: autism, ASD, FSH, DSM V, tanner stage, testosterone

Introduction

Autism Spectrum Disorders comprise an extremely heterogeneous class of neurodevelopmental disorders. Consonant with the heterogeneity of ASDs is the multiplicity of proposed causative factors, with candidates including genetic, hormonal, immunologic, and early life stress factors ***(Schaafsma and Pfaff, 2014).***

Autism affects males more than females, occurring at a ratio at least 3:1. This sex difference may reflect a male vulnerability to develop autism, as individuals with autism tend to display a hypermasculine profile on many cognitive tasks ***(Baron-Cohen et al., 2005).***

Also, patients may have lower than expected 2^{nd} to 4^{th} digit ratios that correlate with higher ratios of fetal testosterone (fT) to fetal estrogen (fE). Some neuroanatomical studies comparing the brains of individuals with and without autism revealed structural differences associated with high levels of fT, including hemispheric asymmetries. 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 ***(Elbaz et al., 2014).***

Testicular androgens have a central role in human male development. In prenatal life, increased testicular

androgens around 4–6 weeks gestation masculinize the genitalia and initiate the sexual differentiation of the brain through hormonally dependent, sex-specific changes in the ultrastructure of the developing central nervous system (e.g., cell proliferation, cell death, patterns of cell migration, dendritic branching) ***(MacLusky et al., 1997).***

A series of clinical studies have examined androgen metabolites in patients diagnosed with an ASD. These studies have revealed hormonal patterns consistent with significantly elevated androgen levels in patients diagnosed with an ASD relative to controls ***(Geier et al., 2012).***

In light of evidence revealing significantly elevated androgen levels in subjects diagnosed with an ASD, and a significant relationship between elevated androgens and ATs, it was previously hypothesized that treatments specifically targeting elevated androgen levels in subjects diagnosed with an ASD might significantly improve ATs ***(Geier and Geier 2005).***

Aim of the Study

The aim of this work is to study the male hormones (FSH, LH and total testosterone) in male autistic children and adolescents by doing gonadotrophic release hormone test.

Autism

Definition:

Autism spectrum disorders (ASD) are a set of heterogeneous neurodevelopmental conditions characterized by early-onset difficulties in social communication and unusually restricted, repetitive behavior and interests ***(Lai et al, 2013).***

Epidemiology

ASD prevalence according 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).***

The reported prevalence of ASDs has increased markedly during the past 3 decades. The current ASD prevalence in children is estimated to be approximately 1.4% but has been reported to be as high as 2.6% ***(Stefan, 2015).***

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:

Autism is diagnosed clinically using diagnostic criteria described in the Diagnostic and Statistical Manual of Mental Disorders (DSM). The updated DSM, Fifth was published in May 2013, replacing the DSM, Fourth Edition-Text Revision (DSM-IV-TR; American Psychiatric Association 2000) with controversial changes made in the definition and criteria for The DSM-IV-TR categorized autism symptoms into three domains (social interaction; communication; and restricted, repetitive behaviors) with diagnostic sub-types denoted: autistic disorder, pervasive developmental disorder-not otherwise specified (PDD-NOS) and Asperger's disorder. Rett's Disorder and Childhood Disintegrative Disorder are also included in DSM-IV-TR Rett's Disorder is often associated with an underlying genetic etiology and Childhood Disintegrative Disorder has physical symptoms, such as bowel and bladder dysfunction, that accompany significant regression in developmental skills ***(Harstad et al., 2015).***

In contrast, the DSM-V consolidates the sub-types of autism into a single "autism spectrum disorder" (ASD) diagnosis and categorizes autism symptoms into only two domains: social communication and restricted, repetitive patterns of behavior, interests or activities.A number of concerns have been voiced about the changes to the DSM