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RESEARCH ARTICLE

Correlation between Cyp19A1 protein with estrogen and testosterone in sera of Iraqi autistic children

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Abstract

Autism spectrum disorder is a spectrum of behavioral anomalies characterized by impairment in social interactions and communication deficits. A potential role for hormonal dysfunction has been suggested in autism. This study conducted to detect correlation between cyp19a1 protein and testosterone, estradiol hormone among Iraqi autistic children. The study includes: 50 child (36male and14 female) aged < 5 - 10 years with confirmed diagnosis of autism using standard assessment, age and gender matched 25 confirmed healthy children (non autistic) used as controls. Serum was isolated and used for measuring the levels testosterone, estradiol and cyp19a1 by using enzyme linked immunosorbent assay. In the current results indicate a significant decrease ($P > 0.05$) in levels of serum levels of cyp19a1 and estradiol for autism compared with the apperantly healthy control group, Whereas level of testosterone in the autistic patient's serum showed a significantly increased level ($P < 0.05$) compared with healthy control. In addition, present results showed positive correlation between cyp19a1 and estradiol with significant difference ($P \leq 0.05$). While the correlation between cyp19A1 receptor and testosterone was negative with non-significant differences ($P \geq 0.05$). From this study concluded CYP19A1 reduction may be lead to reduced conversion of testosterone to estradiol resulting in elevated levels of testosterone as observed in ASD subjects.

INTRODUCTION

Autism is a behavior disorder with a neural developmental origin. It is defined by its behavioral properties in the editions of the Diagnostic and Statistical Manual of Mental Disorders (DSM). In the latest edition of the DSM, the DSM-IV-TR, autism is described by impaired functioning on three behavior domains: qualitative impairments in social interaction, qualitative impairments in communication, and the occurrence of stereotyped behaviors or restricted interests (1)

Autism affects males more than females; giving rise to the idea that the influence of steroid hormones on early fetal brain development may be one important early biological risk factor (2). The differences in circulating levels of gonadal hormones during fetal and infant development are responsible for most sexual dimorphism in adults. For normal male development to occur, sex hormones like testosterone act through estrogen receptors, which in turn also activate other genes and proteins. (3,4). Estrogen directly influences brain function through estrogen receptors located on neurons in multiple areas of the brain (5).

Estradiol, the most important estrogen, is formed from testosterone by the enzyme aromatase, also known as cytochrome P450, family 19 (CYP19A1). Estrogen is neuro-protective and plays an important role in emotional responses [3] and in frontal cortical activity during cognitive task performance in humans [6]. Estrogen acts through the binding to its receptor called estrogen receptor (ER).

CYP19A1 is responsible for estradiol biosynthesis. This protein is the key hydroxylating enzyme which converts androstenedione to estrogen and testosterone to estradiol. Aromatase is therefore considered a crucial protein in regulating levels of male and female sex hormones in various tissues (7).

Testosterone is a steroid hormone metabolized from cholesterol. In blood circulation, testosterone binds to the sex hormone binding globulin (SHBG) and is, thus, protected from metabolic degradation but is also biologically inactive. A minute fraction of testosterone is free and active. In adipose tissue and brain, CYP19A1 (aromatase) catalyzes the conversion of testosterone to the female sex steroid hormone estradiol. The effect is then mediated via estrogen receptors [8,9]. This study conducted to detect correlation between cyp19a1 protein and testosterone, estradiol hormone among Iraqi autistic childrens.

Patients and methods:

The Present study included 75 cases: 50 autistic patient's, 25 non autistic(healthy controls), Fifty patients (36 males and 14females) with Autism were selected for this study.The ages were ranged between 2-10 years. By analyzing of gender frequency, the majority of autistic children are males (72%) with a ratio (2.5:1), while the frequency of females (28%). The blood samples were collected from autistic children who were registered in Malak Al-Sagheer center, Al-Safa and Al-Rajaa Institute of Autism Care/ Baghdad. During the period from December 2014 to February 2015. Serum samples were collected from all studied groups to measure levels of CYP19A1 protein,estradiol and testosterone using an enzyme linked immunosorbent assay (ELISA) manufactured by cusbio-china ,humans (Germany) ,accubind (USA) respectively.

Statistical analysis

By using SPSS version 16.0, the differences in categorical variables between cases and control were compared with X^2 test. Logistic correlation was used to study the risk factors associated with the occurrence of autism

Results and discussion

It was noticed that serum level of (CYP19A1) was significantly decreased ($p < 0.05$) in autistic children (10.16± 2.47pg/ml) as compared with the healthy control (169.21± 22.17pg/ml), (Table 1).

Table (1): Mean of CYP19A1 level in studies group (Autism patients and Healthy control).

CYP19a1 / Studied groups	Mean	Range	SD	SE	P.value
Patients Autism	**10.16**	**117.81-0.11**	**17.50**	**2.47**	**P≤ 0.05**
Healthy Controls	**169.21**	**351.12-26.80**	**110.88**	**22.17**	

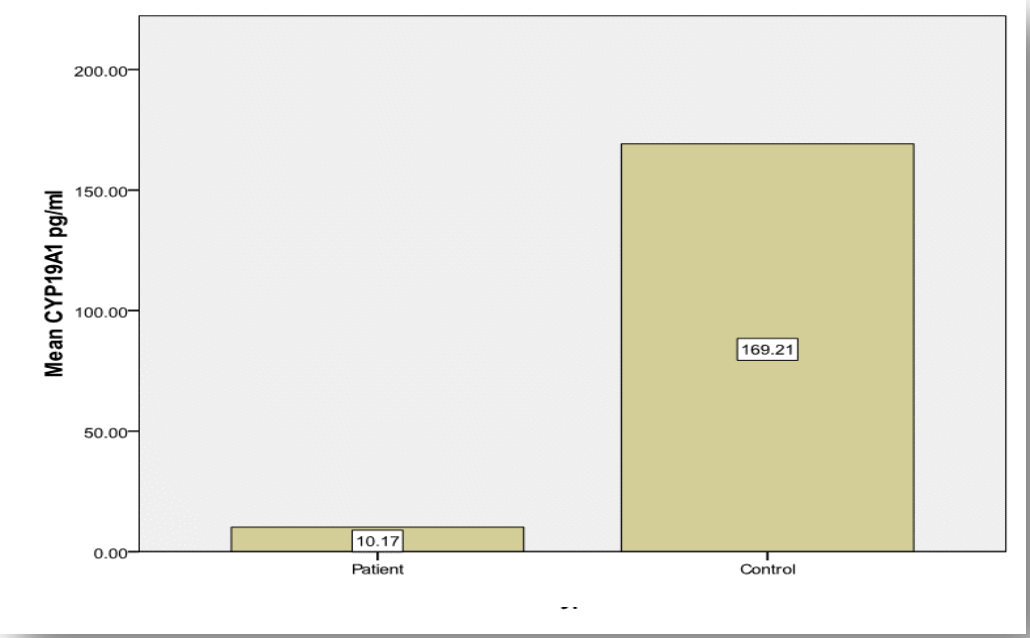

Figure (1): Mean of CYP19A1 in serum of studied groups.

In the current results showed reduction in Cyp19A1 in autistic children this agreement with Valerie Hu, which indicated that human with autism spectrum disorder have low levels of certain proteins Cyp19a1 (10). A recent study have reported the decrease in expression of CYP19A1 (11). The reduction of CYP19A1 could lead to reduced conversion of testosterone to estradiol resulting in increased levels of testosterone as observed in ASD (12).

A recent study, persent a significant decrease in CYP19A1 expression in ASD subjects due to alterations in ERβ transcriptional regulation in the brain of ASD subjects. Together, these findings suggest alterations in ER signaling in ASD [8].

In the present results showed that mean level of Estradiol hormone was significantly decreased in autistic children (11.25± 1.89 pg/ml) as compared With the healthy control (33.47 ± 2.35pg/ml), (Table 2).

Table 2: Mean of Estradiol hormone in Autism patients and Healthy control.

Estradiol / Studied groups	Mean	Range	SD	SE	C.S
Autism patients	**11.25**	**44.60-0.1**	**13.37**	**1.89**	**P≤ 0.05 H S**
Healthy control	**33.47**	**63.58-15.90**	**11.75**	**2.35**	

Table (2) showed highly significant decrease estrogen level this agreement with Sarachana *et. al.* (13) and Amanda *et.al.*, was findings reduced expression of estrogen as well as related with an enzyme (cyp19a1) that converts testosterone to estrogen could help explain the high testosterone levels in autistic individuals and higher autism rates in males (12).

The serum level of testosterone hormones was a significant increase in autistic children's group (4.92 ± 0.86) as compared with the healthy control group (1.87 ± 0.20) (Table 3).

Table 4-8: Mean of Testosterone hormone in Autism patients and Healthy control.

Testosterone / Studied groups	Mean	Range	SD	SE	C.S
Autism patients	**4.92**	**30.95-0.19**	**6.13**	**0.86**	**P≤ 0.05 H S**
Healthy control	**1.87**	**3.39-0.31**	**1.03**	**0.20**	

Table (3) Showed increase in serum Testosterone level in autistic children with highly significant, this results agree with Amanda *et.al.*(12) , Geier & Geier, 2007(14), Geier &Geier (2006) (15) , James *et.al* 2006 (16) . Barbeau *et.al.* note that a significant percentage of autistic children have elevated plasma testosterone levels, and suggests a role for sex hormones (11)**.**

In a previous study Tordjmann et al (1997) has not found significant differences in testosterone levels in autism because the studied group was formed with a very heterogeneous population, including pre-, and postpubertal subjects in both groups[17].

Correlation between parameters

In autistic patient's, inverse correlation was found between E2 and testosterone hormone (r = - 105) (p=0.48) , cyp19a1 and testosterone (r = -130 , p=0.991. In addition positive correlation between cyp19a1 and E2 hormone (r= 0.334* , p= 0.18) with highly significant difference (table 4).

Table 4 :Correlation between CYP19A1 and Estradiol, Testosterone hormone.

Parameters		Testosterone ng/ml	Estradiol pg/ml
CYP19A1 pg/ml	Pearson Correlation	-.161	.334*
	Sig. (2-tailed)	.263	.018
	No.	50	50

*. Correlation is significant at the 0.05 level (2-tailed).

The decrease in CYP19A1 could lead to reduced conversion of testosterone to estradiol resulting in increased levels of testosterone as observed in ASD subjects [4]. Our data are in agreement with a previous finding on reducing aromatase protein levels ASD subjects [6].

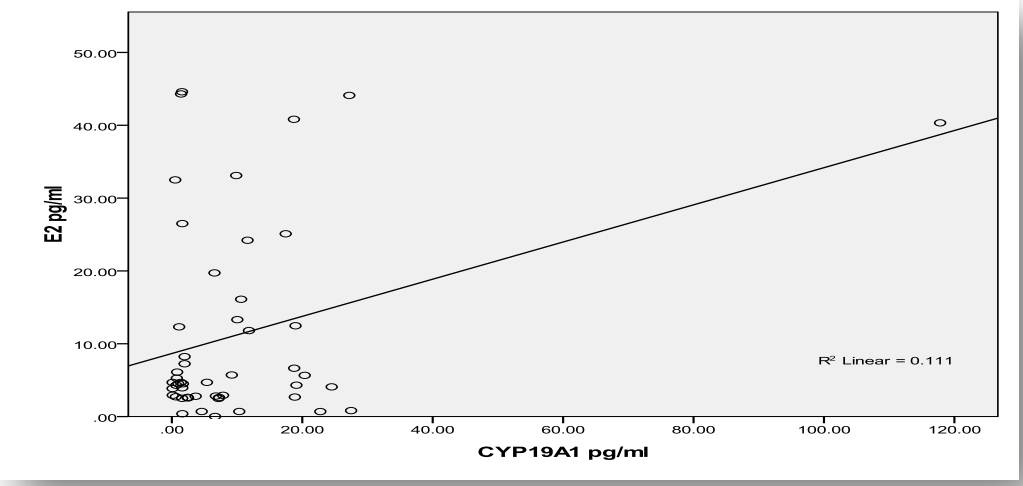

Fig. 2: Correlation between cyp19a1 and estradiol hormone.

Conclusion

From this study concluded CYP19A1 reduction may be lead to reduced conversion of testosterone to estradiol resulting in elevated levels of testosterone as observed in ASD subjects.

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