GENETIC POLYMORPHISMS AND THERAPEUTIC RESPONSE TO ATOMOXETINE IN EGYPTIAN CHILDREN WITH ATTENTION-DEFICIT HYPERACTIVITY DISORDER

By

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ABSTRACT

Background: Attention Deficit Hyperactivity Disorder (ADHD) is highly prevalent in school age children worldwide and we need to improve response to atomoxetine drug (non stimulant) which used for treatment of ADHD.

Objective: This study was undertaken to Study of possibly existing genetic polymorphisms of (CYP2D6, CYP2C19) the main enzymes involved in atomoxetine metabolism and their relations with therapeutic response to atomoxetine in a sample of Egyptian children with ADHD disorder, and try to correlate their phenotype-genotype status.

Patients and Methods: 150 children (100 cases+ 50 control) attended to outpatient pediatric neurology clinic in Bab Al Sha'reya hospital of Al-Azhar University were evaluated by history, general and systemic examination stressing on neuro- psychatric examination, DSM-5 criteria for diagnosis of ADHD , Conner's Abbreviated Rating Scale for the follow up of ADHD and genetic polymorphisms of CYP2D6 and CYP2C19 study by using (PCR) / (RFLPS) techniques.

Results: There was genetic polymorphisms of the CYP2D6 and CYP2C19 enzymes in ADHD children that possibly influence the response to atomoxetine, $P < 0.001$.

Conclusion: These results suggest that CYP2D6, CYP2C19 poor metabolizers taking atomoxetine optimal doses are likely to have greater efficacy, greater increases in side effects and some differences in tolerability compared with CYP2D6, CYP2C19 extensive metabolizers taking similar dose.

Keywords: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), Polymerase Chain Reaction (PCR), Restriction Fraction Length Polymorphisms (RFLPS), cytochrome p450 2D6(CYP2D6), cytochrome p450 2C19(CYP2C19).

INTRODUCTION

Attention deficit hyperactivity disorder (ADHD) is a mental disorder of the neurodevelopmental type **(Sroubek And Kelly 2013).**

ADHD symptoms begin by age six to twelve years, are present for more than six months, and cause problems in at least two settings (such as school, home, or recreational activities **(Dulcan and lake ,2011).**

It affects about 5–7% of children when diagnosed via the Diagnostic and Statistical Manual of Mental Disorders – fifth Edition (DSM-5) criteria **(American Psychiatric Association, DSM-5, 2013).**

The cause of most cases of ADHD is unknown; however, it is believed to involve interactions between genetic and environmental factors. Certain cases are related to previous infection or trauma to the brain **(Thapar et al., 2012).**

The management of ADHD typically involves counseling or medications either alone or in combination. While treatment may improve long-term outcomes, it does not get rid of negative outcomes entirely **(Shaw et al., 2012).**

Medications used include stimulants, atomoxetine, alpha-2 adrenergic receptor agonists, and sometimes antidepressants **(Bidwell et al., 2011).**The long-term effects of ADHD medication have yet to be fully determined **(Kiely and Adesman, 2015).**

Psychostimulant drugs such as methylphenidate (MPH) and amphetamines are first-line treatments for this disorder, but they are effective only in 70% of the cases **(Biederman and Spencer, 2008).**

Atomoxetine, due to its lack of addiction liability, may be preferred in those who are at risk of recreational or compulsive stimulant use **(Kooij et al., 2010).**

Atomoxetine was the first non-stimulant drug to be approved for use in ADHD. Atomoxetine is a selective norepinephrine reuptake inhibitor and it is thought to exert its therapeutic effect by increasing the concentration of synaptic norepinephrine. Because it is a non-stimulant, atomoxetine has the advantages of having less potential for abuse, and it is not scheduled as a controlled substance, Atomoxetine is primarily metabolized through the CYP2D6 enzymatic pathway **(Marian et al., 2011).**

Cytochrome P450 2D6 (CYP2D6) enzyme is responsible for the metabolism of many commonly drugs, including atomoxetine, antidepressants, antipsychotics, analgesics, and beta-blockers. The CYP2D6 gene is highly polymorphic - more than 100 alleles have been described **(Hicks et al.,2015).**

CYP2D6*1 is the wild-type allele and is associated with normal enzyme activity and the normal "extensive metabolizer" phenotype. The CYP2D6 alleles *2, *33, and *35, among others, are also considered to have normal activity **(Ingelman-Sundberg et al., 2007).**While the most common non-functional and reduced function CYP2D6 alleles include CYP2D6*3, *4, *5, and *6 and CYP2D6*10, *17 and *41 **(Swen et al., 2011).**

Cytochrome P450 2C19 (CYP2C19) along other CYP enzymes, forms the metabolite N-Des methyl atomoxetine. Although this metabolite has substantially less pharmacological activity compared to atomoxetine, and is present at much lower plasma concentrations, one study found that genetic polymorphisms of the CYP2C19 gene also influenced the pharmacokinetics of atomoxetine **(Choi et al., 2014).**

With global rise in ADHD diagnosis, the international drug consumption of stimulants has been increasing in the past decade **(Singh, 2008),** Therefore, identifying genetic and/or biological markers predicting drug response has turned into a public health concern.

Pharmacogenetic studies would hopefully lead to individualized treatment protocols in the near future by providing a panel of informative genetic markers to check before starting a pharmacotherapy.

AIM OF THE WORK

The aim of this work is to study possibly existing genetic polymorphisms of (CYP2D6, CYP2C19) the main enzymes involved in Atomoxetine metabolism and their relations with therapeutic response to atomoxetine in a sample of Egyptian children with ADHD disorder and try to correlate their phenotype-genotype status.

PATIENT AND METHODS

This is a case control study which was conducted up on 100 cases with ADHD which selected from children followed at pediatric neurology outpatient clinic at Bab Al Sha' ryea university hospital, their ages ranged from 6 to 12 years, Matched with 50 normal healthy children served as a

control during the period from December 2016 till November 2017.

Subjects were classified as:

Group A: Hundred (100) children with ADHD, which divided into two

Sub groups:

Group (A1): Fifty (50) children with ADHD responding to Atomoxetine drug.

Group (A2): Fivty(50) children with ADHD not responding to Atomoxetine drug.

Group B: Apparently healthy control group of Fivty (50) children.

Inclusion criteria

Any child with ADHD on atomoxetine treatment their ages ranged from 6 to 12 years old, both sexes were present.

Exclusion Criteria:

1. Age of the patients more than 12 ys and less than 6ys.
2. Any neuropsychiatric disease such as epilepsy, metabolic disorders, and sleep disorders.
3. Symptoms and signs of mental retardation.
4. Simultaneous administration of other medications and its side effects as antidepressant, sedatives, antiepileptic and antipsychotic drugs.

Financial Disclosure Funding:

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Etical Consideration:

1. A written informed consent was obtained from patients or their legal guardians.
2. Approval by the ethical Committees of pediatrics department, Faculty of Medicine Al-Azhar university was obtained before the study .
3. The authors declared no potential conflicts of interest with respect to the research , authorship, and publication of this article.
4. All the data of the patients and results of the study are confidential and the patients have the right to keep it.

Each patient and control was subjected to:

1. History taking.
2. General and systemic examination stressing on neuropsychatric examination.
3. Diagnostic and Statistical Manual of Mental Disorders - fifth edition (DSM5) for diagnosis of ADHD.

4. Conners parent rating scale for detection of severity of ADHD and for follow up (Arabic version).
5. Application of clinical pharmacological testing in children by atomoxetine capsule which was initiated at a total daily dose of approximately 0.5 mg/kg and increased after a minimum of 3 days to a target total daily dose of approximately 1.2 mg/kg administered either as a single daily dose in the morning or as evenly divided doses in the morning and late afternoon/early evening for **8** weeks and Patients were assessed weekly and doses titrated for efficacy and tolerability .
5. Blood samples obtained from all groups to detect genetic polymorphisms of (CYP2D6 *1 & CYP2D6 *2 &CYP2C19 *1 & CYP2C19 *2) by using Polymerase Chain Reaction (PCR) / Restriction Fraction Length Polymorphisms (RFLPS) techniques that done at Molecular Genetics Department at National Research Centre at El Dokki, Cairo, Egypt.

Genotyping for CYP2D6:

- Genotyping for CYP2D6*1 and CYP2D6*2 alleles was performed by the PCR-RFLP method.
- PCR amplification of CYP2D6 was done using the following primers:

  Forward primer:
  5'-GCTGGGGCCTGAGACTT-3'

  Reverse primer:
  5'-GGCTATCACCAGTGCTGGTGCT-3'
- The PCR products were digested with HhaI enzyme and separated on 2% Agarose gel.
- Since the restriction site is absent in the mutant allele (CYP2D6*2), the PCR products are not digested by the restriction enzyme.
- In the CYP2D6*1 (wild-type) allele the restriction enzymes HhaI splice the PCR product (1029 bp) into 414, 372, 111, 91, 41 bp (Figure 4)
- Pattern after gel electrophoresis:
  1. CYP2D6*1/ CYP2D6*1: 414, 372, 111, 91, 41 bp
  2. CYP2D6*1/ CYP2D6*2: 786, 414, 372,111, 91,41 bp
  3. CYP2D6*2/ CYP2D6*2: 786, 111, 91,41 bp

Genotyping for CYP2C19:

- Genotyping for CYP2C19* 1 and CYP2C19*2 alleles was performed by the PCR-RFLP method.
- PCR amplification of CYP2C19 was done using the following primers:

  Forward primer:

  5'-AATTACAACCAGAGCTTGGC-3'

  Reverse primer:

  5'-TATCACTTTCCATAAAAGCAAG-3'
- The PCR products were digested with SmaI enzyme and separated on 2% Agarose gel.
- Since the restriction site is absent in the mutant allele (CYP2C19*2), the PCR products are not digested by the restriction enzyme.
- In the CYP2C19*1 (wild-type) allele the restriction enzymes SmaI splice the PCR product (169 bp) into 120 bp, 49 bp (Figure 5)
- Pattern after gel electrophoresis:

  1. CYP2C19*1/ CYP2C19*1: 120, 49 bp
  2. CYP2C19*1/ CYP2C19*2: 169, 120, 49 bp
  3. CYP2C19*2/ CYP2C19*2: 169 bp.

STATICAL ANALYSIS

Data Were collected, coded, revised and entered SPSS version 22 (IBM© Corp., Armonk, NY, USA). Numerical data were expressed as mean and standard deviation. Qualitative data were expressed as frequency and percentage. The collected data were tabulated and analyzed using the suitable statistical methods":

1. Student t test which used to compare between 2 means and standard deviations of 2 groups.
2. "Z" test which used to compare between2 percentages of 2 groups.

The level of significance:
P > 0.05 means no significance.
P<0.05 means significant.
P<0.01 means high significant.
P<0.001 means high significant.

RESULTS

The results of this work summarized in the following tables and figures:

Table (1): Comparison between ADHD cases and control according to conners score n=150.

Conners score / Groups	X± SD	Minimum	Maximum	T	P
Group A N=100	63.03±6.98	49	78	16.36	0.005
Group B N=50	38.4±5.71	30	49		

X = mean **SD= Standard deviation**

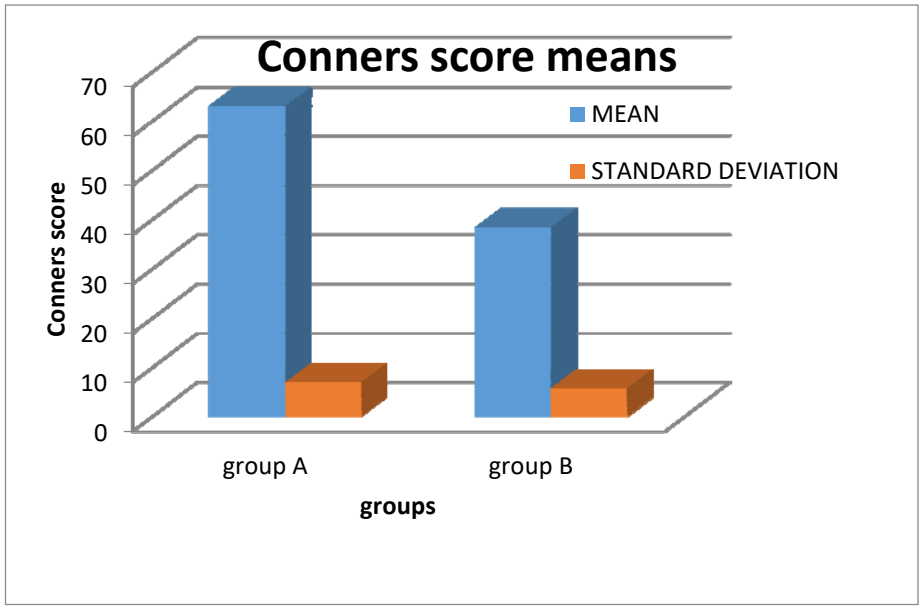

Figure (1): Means of conners score between ADHD cases & control

Table (1) and figure (1) show: The mean and standard deviation among ADHD cases were more than of control group ,there was statically positive significant difference between ADHD cases and control group as regard conners score means, p <0,05.

Table (2): Comparison between ADHD cases as regard DSM -5 combined type n=100

DSM-5	+ve	-ve	Total	Test of

combined / Groups							significance	
	No	%	no	%	no	%	Z	P
Group A1	19	38.0	31	62.0	50	100.0	.415	0.003
Group A2	32	64.0	18	36.0	50	100.0	.415	0.003
Total	51(51%)		49 (49%)		100 (100%)		----------	

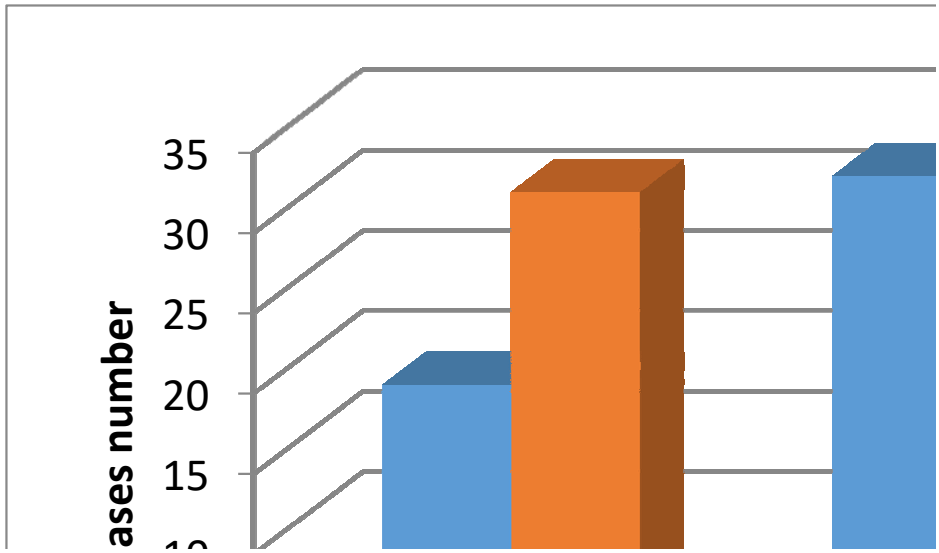

Figure (2): DSM -5 combined type among the study

Table (2) and Figure (2) show that: The number and percentage of positive DSM-5 combined type was higher in group **A2** than group **A1**, there was statically positive significant difference between group **A1** and group **A2,** p<0,01.

Table (3): Comparison between ADHD cases as regard DSM -5 inattentive type n=100

DSM-5 inattentive / Groups	+ve		-ve		Total		Test of significance	
	No	%	No	%	No	%	Z	P
Group A1	35	70.0	15	30.0	50	100.0	.387	0.006
Group A2	22	44.0	28	56.0	50	100.0	.387	0,006
Total	57(57%)		43(43%)		100 (100%)		----------	

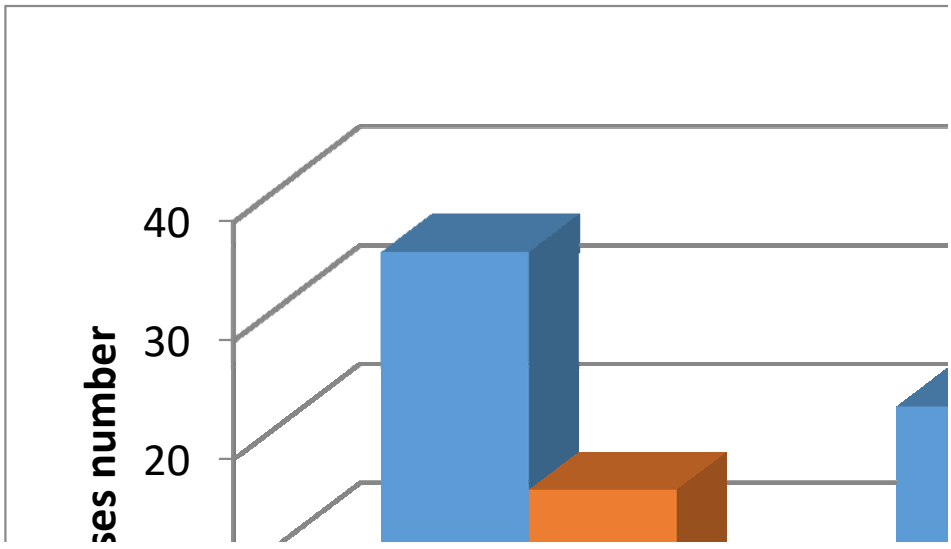

Figure (3): DSM -5 inattentive type among the study

Table (3) and Figure (3) show : The number and percentage of positive DSM-5 inattentive type was higher In group A1 than other group A2, there was statically positive significant difference between groupA1 and group A2, P< 0,01.

Table (4): Comparison between ADHD cases as regard DSM -5 hyperactive- impulsive type n=100

DSM-5 hyperactive / Groups	+ve		-ve		Total		Test of significance	
	No	%	No	%	No	%	Z	P
Group A1	35	70.0	15	30.0	50	100.0	.513	0.0005
Group A2	19	38.0	31	62.0	50	100.0	.513	0.0005
Total	54 (54%)		46(46%)		100(100%)		----------	

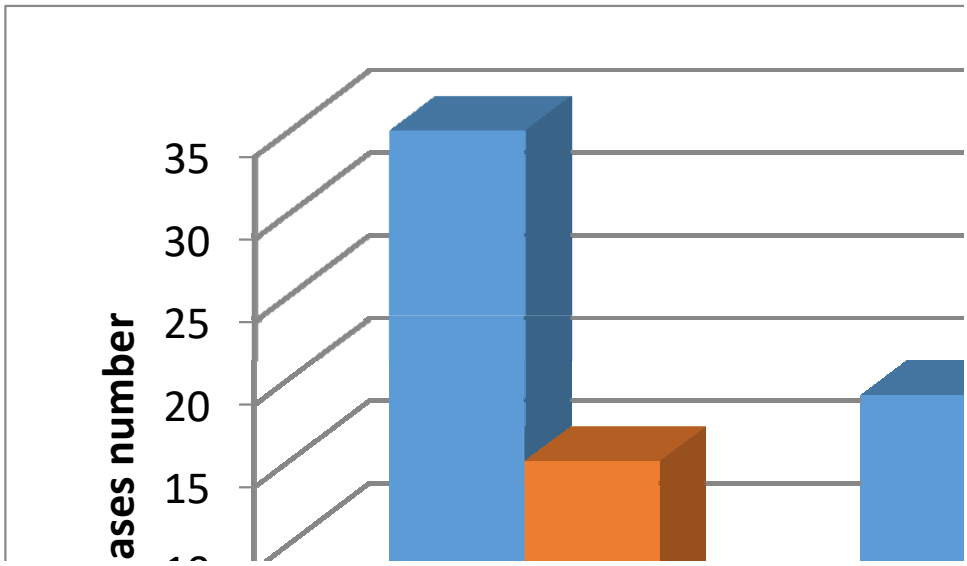

Figure (4): DSM -5 hyperactive-impulsive type among the study

Table (4) and Figure (4) show : The number and percentage of positive DSM-5 hyperactive–impulsive type was higher In group **A1** than other group **A2** , there was statically highly positive significant difference between group **A1** and group **A2**, P < 0,001

Table (5): Frequency of wild alleles of (CYP2D6 & CYP2C19) and their correlations

Groups \ Wild alleles	Allele frequency		Sign P value
	CYP2D6	CYP2C19	
	Wild type	Wild type	
Group A1	**20**	**35**	**0.0006**
Group A2	**16**	**32**	**0.0007**
Group B	**24**	**36**	**0.0003**

CYP2D6 (wild type): CYP2D6*1*1 & CYP2C19 (wild type): CYP2C19*1*1

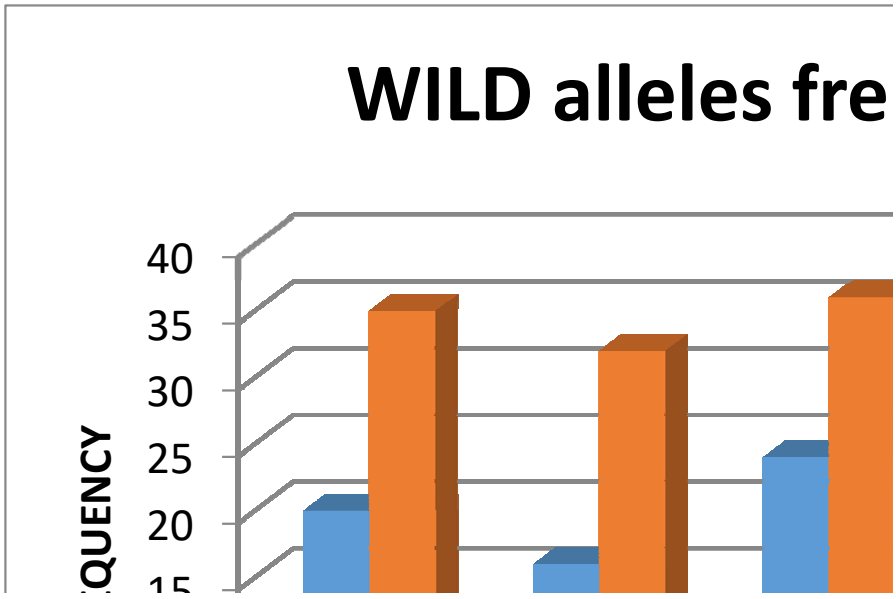

Figure (5): Frequency of wild alleles of (CYP2D6 & CYP2C19)

Table (5) and figure (5) show: The frequency of CYP2D6 (wild allele) was more in group **A1** than other groups , the frequency of CYP2C19 (wide allele) was more in group **B** than other groups ,there was statically highly positive significant difference between wild alleles in the three studied groups ,$p<0.001$.

Table (6): Frequency of mutant alleles of (CYP2D6 & CYP2C19) and their correlations

Mutant alleles / groups	Allele frequency		Significance
	CYP2D6	CYP2C19	
	mutant type	mutant type	P value
Group A1	**48**	**24**	0.172
Group A2	**35**	**27**	0.0001
Group B	**38**	**17**	0.004

CYP2D6 (mutant type): (CYP2D6*2*2 + CYP2D6*1*2)
CYP2C19(mutant type): (CYP2C19*2*2 + CYP2C19*1*2).

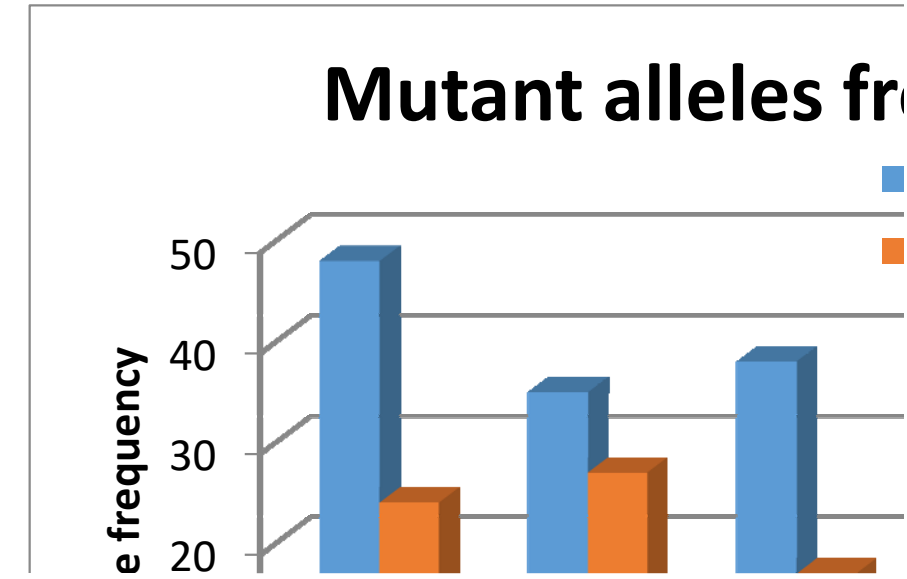

Figure (6) : Frequency of mutant alleles of (CYP2D6 & CYP2C19)

Table (6) and figure (6) show: The frequency of CYP2D6 (mutant alleles) was more in group **A1**Than other groups , the frequency of CYP2C19 (mutant alleles) was more in group **A2** than other groups ,there was statically positive significant difference between mutant alleles in groups (**A2&B**) $p<0.01$.

Table (7): Comparison between percentage and number of subjects the three studied groups as regard CYP2D6 allel*2 &CYP2D6 allel *1 polymorphisms.

Phenotype / Groups	PM		EM		HEM		Allele	
	No	%	No	%	No	%	Wild type	Mutant type
Group A1	0	0	18	36.0	12	24.0	40%(20)	60%(30)
Group A2	0	0	1	2.0	33	66.0	32%(16)	68%(34)
Group B	0	0	12	24.0	14	28.0	48%(24)	52%(26)

(PM) Poor metabolizer (no functional allels)& (EM) homozygous extensive metabolizer (two functional allels) &(HEM) heterozygous extensive metabolizer (one functional allel) & wild =(CYP2D6*1*1) Mutant = (CYP2D6*2*2 + CYP2D6*1*2).

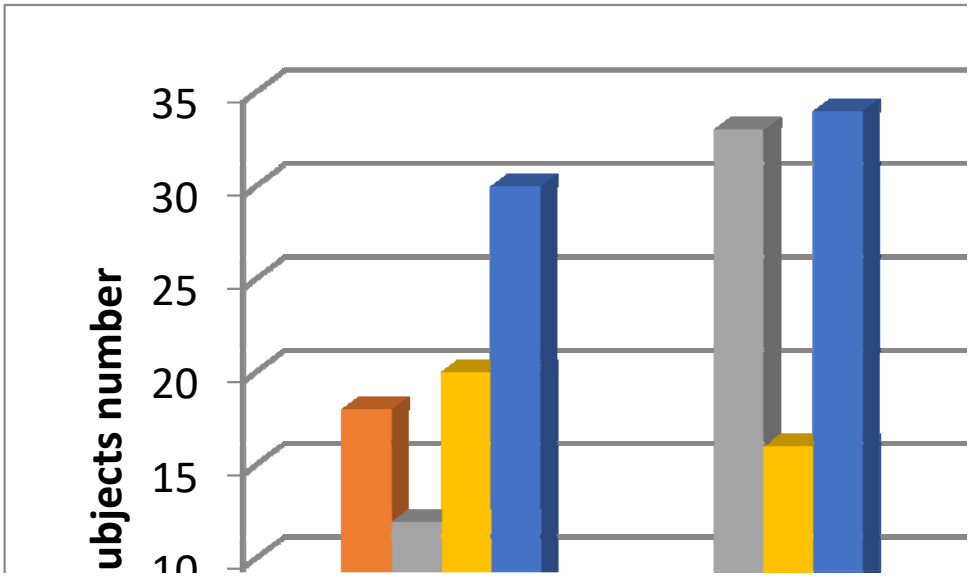

Figure (7): Number of subjects as regard CYP2D6 allel*2 & CYP2D6 allel *1 polymorphisms.

Table (7) and Figure (7) show: The percentage of **(PM)** phenotype was zero in three studied groups ,the percentage of **(EM)** Phenotype was more in group **B** than other groups , the percentage of **(HEM)** Phenotype was more in group **A2** than other groups, the percentage of wild allele was more in group **A1 ,** the percentage of mutant allel was more in group **A2.**

Table (8): Comparison between percentage and number of subjects the three studied groups as regard CYP2C19 allele*2&CYP2C19 allele*1 polymorphisms

Phenotype / Groups	PM		EM		IM		Allele	
	No	%	No	%	No	%	Wild type	Mutant type
Group A1	9	18.0	35	70.0	6	12.0	70%(35)	30%(15)
Group A2	9	18.0	32	64.0	9	18.0	64%(32)	36%(18)
Group B	3	6.0	36	72.0	11	22.0	72%(36)	28%(14)

(PM) Poor metabolizer (no functional allels)& (EM) homozygous extensive metabolizer (two functional allels) &(IM) Intermediate metabolizer (one normal function and one no function allele) & wild =(CYP2C19*1*1) &Mutant = (CYP2C19*2*2 + CYP2C19*1*2)

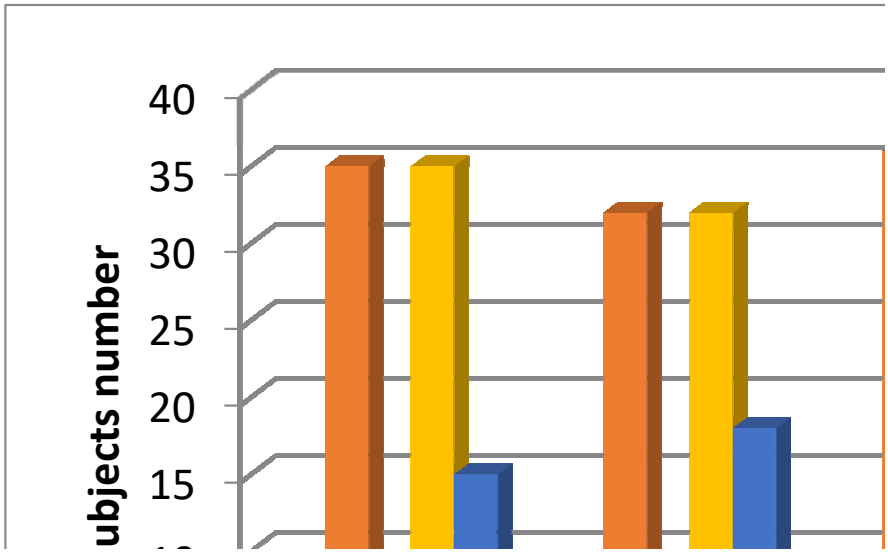

Figure (8): number of subjects as regard CYP2C19 allele*2&CYP2C19 allele*1 polymorphisms

Table (8) and Figure (8) show: The percentage of **(PM)** phenotype were equal in group **A1** and group **A2**, ,the percentage of **(EM)** Phenotype was more in group **B** than other groups , the percentage of **(IM)** Phenotype was more in group **B** than other groups, the percentage of wild allele was more in group **B** and the percentage of mutant allel was more in group **A2.**

DISCUSSION

This is case control study aimed to study genetic polymorphisms and therapeutic response to atomoxetine in Egyptian children with ADHD.

The role of genetic polymorphisms in inter individual variability of atomoxetine response in Egyptian children has not been elucidated.

In our study the most common ADHD type according to DSM -5 criteria is in attentive type(57%) followed by hyper active type (54%) then combined type(51%) In agreement with our results **Biederman et al., 2005,** reported the predominantly of inattentive type of ADHD **Alobaidi and Ali, 2009,** also found the predominantly of inattentive type of ADHD .

In agreement with our results one small study of 100 children with ADHD receiving atomoxetine therapy found that the presence of at least one nonfunctional or reduced function CYP2D6 allele led to an increase in adverse effects, such as gastrointestinal problems and sleep disorders, and a late response to treatment (longer than 9 weeks). The study concluded that CYP2D6 genotyping before atomoxetine treatment may be beneficial in preventing overdosing or early cessation of treatment because of initial adverse effects (**Ter Laak et al., 2010).**

However, another study found genotyping to be unnecessary, because during the routine clinical management of ADHD, investigators were able to adjust the dose of atomoxetine in children and adolescents who had normal or reduced CYP2D6 activity,so that their treatment was comparable in safety and efficacy without knowing what their CYP2D6 genotype was **(Trzepacz al., 2008).**

In agreement with our results **Michelson et al., 2007**, that prove that Variations in plasma atomoxetine exposures can occur because of genetic variation or as a consequence of co administration with drugs that inhibit CYP2D6 and CYP2D6 poor metabolizers taking atomoxetine in doses up to 1.8 mg/kg/day are likely to have greater efficacy, greater increases in cardiovascular tone, and some differences in tolerability compared with CYP2D6 extensive metabolizers taking similar doses.

In agreement with our results (**Trzepacz et al., 2008)**, that was 1365 children with ADHD, 87x PM, 1239x EM# (genotyped for *3*8). Atomoxetine for 10 weeks.

Patients were assessed weekly and doses titrated for efficacy and tolerability at the discretion of investigators. Initial dose 0.5 mg/kg per day. Maximum dose 1.8 mg/kg per day. Concomitant medications allowed with the exclusion of medications for other psychiatric conditions. Compared to EM PM: - Mean modal dose decreased from 1.26 mg/kg/day to 1.14 mg/kg/day (S) - Mean final dose decreased from 1.50 mg/kg/day to 1.35 mg/kg/day (S) - No increase in response rate (≥ 25% reduction in ADHD symptoms) with 81.6% and 84.9% for EMs and PMs respectively (NS) - No larger decrease in ADHD symptoms with 52% and 59% for EMs and PMs respectively (NS) - Larger decrease in inattention score with 49% and 57% for EMs and PMs respectively (S) - No effect on incidence of treatment-emergent adverse events (including decreased appetite) with 57.5% and 54% for EMs and PMs respectively (NS) - No differences between groups for discontinuation due to any adverse event with 2.4% and 5.8% for EMs and PMs respectively (NS) - No effect on height, DBP, SBP, QTc-interval. - Weight loss increased from a 1.0% weight increase to a 2.5% decrease (S) - Smaller increase in mean pulse rate with 8.5% and 13.4% for EMs and PMs respectively (S) - Predicted AUC at t=8-10 weeks increased from approximately 3 to 25 µg.hour/ml (29%) .

As regard concomitant use of CYP2D6 inhibitor (fluoxetine) with atomoxetine we found In children and adolescents up to 70 kg body weight administered strong CYP2D6 inhibitors or in patients who are known to be CYP2D6 PMs, atomoxetine should be initiated at 0.5 mg/kg/ day and only increased to the usual target dose of 1.2 mg/kg/day if symptoms fail to improve after 4 weeks and the initial dose is well tolerated.

If the initial dose is not increased this is comparable to a decrease to 42% of the normal recommended dose, this agree with USA full prescribing Information about atomoxetine.

There is one study (**Choi et al., 2014)** done on genetic poly morphisms of CYP2C19 and atomoxetine response and our study also agree with its results that found a great phenotype - genotype correlations

CONCLUSION

Pharmacogenitics studies have important role in atomoxetine response variability and the results

suggest that CYP2D6, CYP2C19 poor metabolizers taking atomoxetine in optimal doses are likely to have greater efficacy, greater increases in side effects and some differences in tolerability compared with CYP2D6, CYP2C19 extensive metabolizers taking similar dose.

Results suggest genotyping is of almost importance during routine clinical management.

RECOMMENDATIONS

We recommend the following :

1. Further wide scale studies on prevalence of CYP2D6 & CYP2C19 alleles to achieve better results ,altogether with serum level of drug of interest .
2. Genotyping is helpfull before prescription of important drugs during routine clinical management.

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تعدد الأشكال الجينية والاستجابة العلاجية للاتوموكستين فى الأطفال المصريين المصابين باضطراب نقص الانتباه وفرط الحركة

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الهدف : دراسة تعدد الأشكال الجينية لانزيم سيتوكروم ب 450 المسئول عن التمثيل الدوائى للاتوموكستين وربط ذلك بالاستجابة العلاجية للاتوموكستين ومعرفة الجرعات المناسبة لكل مريض ومدى الاستجابة.

المنهجية : تم إجراء الدراسة على 100 طفلا فى سن المدارس والذين تتراوح أعمارهم من سن 6 سنوات إلى سن 12 سنه والمترددون على عيادة أعصاب الأطفال فى مستشفى باب الشعرية الجامعى وذلك بعد اخذ موافقة كتابية من آباء الأطفال وموافقة لجنة الأخلاقيات بقسم الأطفال وكلية الطب جامعة الأزهر.

وهؤلاء الأطفال من بين الأطفال تم تشخيصهم باضطراب فرط الحركة وضعف الانتباه وفق المعايير الخاصة بالاضطراب فى الدليل الإحصائى الخامس للاضطرابات النفسية ومقياس كونرز 48 سؤال تقدير الوالدين الخاص أيضاً بالاضطراب ثم تم إعطاؤهم دواء الاتوموكستين الذى يستخدم لعلاج هذا الاضطراب بجرعات نصف إلى واحد ونصف مجم لكل كجم فى اليوم كبسولة بالفم صباحا مرة واحدة او مرتين صباحا وعصرا وقد لوحظ أن الاستجابة العلاجية للتوموكستين متفاوتة بين المرضى فتم تقسيم المرضى الى مجموعتين مجموعة تستجيب للاتوموكستين (50) طفل ومجموعة لا تستجيب (50) طفل.

تم مقارنة هاتين المجموعتين التجريبيتين بمجموعه ثالثة ضابطه (50) طفل أعمارهم أيضاً ما بين 6 إلى 12 سنه وتم اخذ عينات دم من كل الأطفال موضوع الدراسة

(150) طفل لقياس تعدد الأشكال الجينية لإنزيم ستوكروم بواسطة التحليل الكمى النوعى وتقييد طول الجين المتعدد الشكل

النتائج : يغلب على المرضى غالبا اضطراب فرط الحركة من نوع سيطرة نقص الانتباه وعدد الذكور (68)% وعدد الإناث (32) % ويغلب وجود شكل الجين الأولى الخاص بالتمثيل الدوائى الطبيعى للاتوموكستين فى كل المجموعات اما النوع المتغير للجين والمتعدد الشكل فيغلب فى المجموعة التى لا تستجيب للاتوموكستين وهذا يدل على أن وجود تعدد شكل جينى فى انزيمى السيتوكروم ب450 موضوع الدراسة يؤثر بشكل كبير على درجة الاستجابة العلاجية للا توموكستين

الاستنتاجات والتوصيات : إن قياس تعدد الأشكال الجينية قبل إعطاء الاتوموكستين أمر مهم لتحديد نوعية استجابة المريض للدواء ومعرفة الجرعة المناسبة لكل مريض وتقليل ظهور الأعراض الجانبية للدواء