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STUDY THE GENDER DIFFERENCES IN ADHD CHILDREN: IS THE RESPONSE TO CNS STIMULANTS A CASE OF ONE FITS BOTH?

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Abstract:-Attention-Deficit-Hyperactivity Disorder (ADHD) is one of the most prevalent disorders in school children worldwide, with social and academic functioning impairments and persistence into adulthood that appears to be more in boys than in girls (3:1). While CNS stimulants are the first line of treatment, improving up to 70-90% cases, their use had created controversies questioning their risks. Gender mind treatment criteria to test differences in response, side effects profile, dose of response, and dosing schedule were the aims of the current work. Consenting 21 males and 10 females have participated in the study, with mean age of 8.2+3, 8.4+2.2 years respectively, 100.8, 106.5 IQ respectively and no chronic comorbid physical or mental contra indications. They were screened by diagnostic tools (Mini International Neuropsychiatric Interview, Stanford Binet and Wechster Intelligence Scales, Vigil Continuous Performance Test, Conner's Parent and Teacher Rating Scales, and Stimulants Side effects Rating Scale). The dosage of the selected stimulant (Methylphenidate) was estimated based on the subjects' weight (0.75, 0.76 mg/kg respectively). Short-term follow-up of 6 weeks reevaluated improvement and side effects developed. Combined type of ADHD was the most prevailing variant, with higher severity in females, namely inattention, reflected in particular on Teacher Rating Scale of Conner. In the noted marked improvement, there were undetected statistically significant gender differences, however in the individual symptoms females recorded less improvement and showed more talk less and less interest as side effects. Conclusive evidences for the role of gender in ADHD require by passing methodological limitations as well as confounding factors.

Keywords: Children, Gender differences, ADHD.

INTRODUCTION

Attention-Deficit Hyperactivity Disorder (ADHD) is one of the most common disorders of childhood. Its incidence rate is 3-5% of pre-pubertal elementary school children (Hawi et al., 2000) that appears to be more common in boys than in girls in a ratio of 3:1 in the population studies and as 9:1 in clinics referred studies (Gershon, 2002). Girls with ADHD were more likely than boys to have predominantely inattentive type, and to show lower ratings on hyperactivity, impulsivity and externalizing problems, and less learning disabilities (Biederman *et al.*, 2005). Collins (1994) and many others referred to its gender-based biology that have led to better under-standing of its management. CNS stimulants gave marvelous responses in treatment of ADHD. They vary in their actions. Methylphenidate that has the shortest plasma half-life of about 2-3 hours, has practical advantages and is highly effective in 75% of cases (Dupaul and Rapport, 1993 and Biederman, 2003).

The present study endeavors to present key issues in pharmacological treatment of ADHD that might highlight various mechanisms and their implications for better understanding of diagnosis, treatment, and prognosis of this indespread disorder of childhood. The delayed recognition of the subjects incorporates elements of clinical excitement of valuable contributions and complex interactions between gender and behavioral abnormalities, cognitive deficits and therapeutic strategies via its hypotheses of whether there are differences between (a) the response, (b) side effects profiles, (c) dose of response, and (d) dosing to be related to gender of ADHD sufferers.

SUBJECTS AND METHODS

The 31 cases were selected from outpatients' clinic of the Institute of Psychiatry, Ain Shan University Hospitals; some were referred from the pediatric department from Research Institute of Ophthalmology with inclusion criteria fulfilling the DSM-Vadiagnostic criteria, between 5-15 years old, with no contra-indications to stimulant's therapy, both sexes were screened after consent of their parents. Those with IQ below 90, chronic general medical conditions, forms of pervasive developmental or tics disorder, epilepsy, previous poor response or intolerance to stimulants or non-consenting families were excluded. Tools for diagnosis comprised the use of the Mini International Neuropsychiatric Interview Scale for children (Sheehan et al., 1998) intelligence scales of Stanford Benit (Terman and Mereal, 1916) and Wechster for children (Wechster, 1991), attention profile using Vigil Continuous Performance Test (The Psychological Corporation Harcourt Brace and Company, 1998), ADHD symptoms and their severity were assessed by Conner (1997), translated and validated by El-Sheikh *et al*. (2003) and Zaki *et al*. (2005) and the Stimulant Drug Side Effects Rating Scale of Barkely (1997). Data were statistically analyzed according to Diagnostic and Statistical Manual of Mental Disorders (2013).

A pilot study involving 10 subjects (8 males, 2 females) was conducted to determine size and selection methods, inter-raters reliability and applicability of tools, and dose ranges of methyl phenidate (0.4-1 mg/kg). Full medical history including onset duration severity as well as full detailed scheme of treatment were obtained by the pediatrician with thorough clinical examination. Special clinical files were also done for all the studied cases with all their clinical findings for possible co-morbid pediatric illnesses, neurological conditions and contra indications for the use of methylphenidate including initial weight, and blood pressure. Absence of development abnormalities was emphasized during prenatal, natal, and postnatal periods such as bleeding during pregnancy, infections, obstetric complications, postnatal cyanosis, jaundice, pneumonia, or low birth weight. Also, developmental milestones abnormalities as delayed walking or talking, family history of consanguinity or similar conditions were ruled out.

Close follow-up of studied children at starting of the least effective doses initiation, titration and optimization till reaching the dose of response were guided by pediatrician, parents, and teachers whenever possible by the end of 6 week follow-up periods, reevaluation using Vigil continuous performance test, Conner's two rating scales for parents and teachers, and screening of possible side effects listed in the stimulants side effects rating scale were verified.

RESULTS

Demographic data of the study sample:

ADHD candidates of 21 males (67.7%) and 10 females (32.3%) were included. The females mean age was 8.2 (+3) years, with a minimum of 5 and maximum of 14 and males mean age was 8.4 (+ 2.2) years, with a minimum of 6 and maximum of 14 t=0.286, P=0.78). 25 (80.6%) of parents were non-consanguineous (x2 = 0.828, p=0.3). 4 (12.9%) cases had family history of similar conditions x2 = 0.662, p =0.3). There were no statistically significant difference between males and females regarding antenatal (x2 = 2.17, p=0.3), natal (x2 = 1.02, p=0.4), postnatal histories (x2 = 0.83, p=0.3), or developmental milestones (x2 = 3.17, p=0.5).

Clinical and Psychometric characteristics of the studied sample in relation to GENDER:

The study showed that the mean age of onset of ADHD was 4.4(+1.2) years with a minimum age of 2.5 and a maximum of 6 years, with no statistically significant difference between females and males (t= 0.298, p= 0.768). The combined type was diagnosed in 22 (70.9%), 16 (76.2%) were males, and 6 (60%) were females, the predominantly inattentive type was found in 7 (22.6%) subjects, whereas only 2 (6.5%) were males with the predominantly hyperactive impulsive type, the presentation of these variants was statistically insignificant in the studied sample (x2 = 3.186, p= 0.2). The psychiatric comorbidities were present in 18 (58.1%) cases, mostly the disruptive behavior disorder (oppositional defiant and conduct disorders) in 11 (35.4%) patients (5 were females and 6 were males), followed by specific phobic disorders (animal, darkness, and erythrophobia) in another 3 (9.6%) cases, then childhood depression in 2 (6.5%), and another 2 (6.5%) who were males encountered with multiple comorbid problems (of conduct, agoraphobia, social and specific phobias), again with x2= 2.62, p-value of 0.62 indicating no statistical significant differences. The mean IQ of the subjects enrolled was 100.8+5.8 for females and 106.5+9.5 for males, with t=1.75, p=0.09 (i.e.) with no significant discrimination. The attention profile of the studied children was initially assessed by the Vigil test, revealed that total omission, total comission, total error and total average delay in females and males with no statistically significant differences where t-values were 1.24, 1.57, 1.78, -0.39 respectively with p-values of 0.22, 0.12, 0.08, 0.69 reflecting cases attention profiles of even affection. Initial severity profiles of ADHD in the studied groups and their responses to medication were screened on Tables from (1-12) including side effects and dosages.

Table 1: Initial severity of ADHD symptoms in the studied premedicated sample using conner's rating scale in relation to gender.

Conner's parent rating scale (initial) subscales	Total		Gender				T- value	P-value
			Male		Female			
	Mean	S.D	Mean	S.D	Mean	S.D		
Oppositional	69.4	10.56	67.3	9.74	67.3	9.74	1.638	0.1
Inattention	74.5	8.38	72.3	7.63	72.3	7.63	2.197	0.03*
Hyperactivity	77.2	9.34	75.3	8.71	75.3	8.71	1.667	0.1
Anxious shy	63.4	13.69	62.9	10.97	62.9	10.97	0.299	0.7
Perfectionism	58.6	11.99	59.2	10.89	59.2	10.89	-0.383	0.7
Social problem	73.9	13.88	71.1	13.07	71.1	13.07	1.671	0.1
Psychosomatic	62.5	14.13	64.6	15.59	64.6	15.59	-1.162	0.2
ADHD index	76.5	7.84	73.6	7.13	73.6	7.13	3.347	0.002**
Conner global index (CGI)	79.8	8.18	77.0	7.32	77.0	7.32	3.200	0.003**
DSM_ IV inattention	76.3	10.07	73.3	9.46	73.3	9.46	2.668	0.01**
DSM_ IV hyperactive Impulsive	78.3	8.47	75.9	7.57	75.9	7.57	2.435	0.02*
DSM_ IV total	78.8	7.07	76.3	7.04	84.1	6.50	2.937	0.005**

* = significant; ** = highly significant

Table 2: Initial severity of ADHD symptoms in the studied premedicated sample on Conner's teacher rating scale in relation to gender.

Conner's teacher rating scale (initial) subscales	Total		Gender				T-value	P-value
			Male		Female			
	mean	S.D	mean	S.D	mean	S.D		
Oppositional	70.5	14.68	65.7	12.64	83.7	12.50	2.448	0.02*
Inattention	63.8	6.87	62.2	8.30	68.2	9.21	1.219	0.02*
Hyperactivity	72.8	12.36	67.3	9.12	88.0	4.00	4.314	0.001***
Anxious shy	77.2	10.73	75.1	10.90	83.0	8.75	1.292	0.2
Perfectionism	68.3	12.71	67.4	12.13	71.0	15.8	0.477	0.6
Social problem	64.5	12.00	63.6	13.38	67.0	8.16	0.465	0.6
ADHD index	70.7	12.51	65.4	10.05	85.0	4.69	3.678	0.003**
Conner global index (CGI)	75.0	13.30	69.5	11.22	90.0	0.00	3.557	0.004**
DSM_ Iv inattention	65.0	9.90	61.0	7.86	76.0	5.35	3.491	0.004**
DSM_ Iv hyperactive impulsive	73.3	12.80	68.4	11.21	86.7	3.94	3.127	0.008**
DSM_ Iv total	71.4	12.52	66.3	10.07	85.5	5.80	3.555	0.004**

* = significant; ** = highly significant; *** = very high significant

Table 3: Male patients' response to medication according to Conner's parent rating scale.

Conner's parents rating scale subscales	Premedicated male		Medicated male		Paired- T- value	P-value
	mean	S.D	mean	S.D		
Oppositional	67.3	9.74	58.6	9.37	4.762	0.000***
Inattention	72.3	7.63	57.00	8.07	7.050	0.000***
Hyperactivity	75.3	8.71	61.8	9.34	5.406	0.000***
Anxious shy	62.9	10.97	58.7	9.36	2.609	0.01**
Perfectionism	59.2	10.89	52.8	7.07	2.475	0.02*
Social problem	71.1	13.07	65.0	12.82	2.294	0.03*
Psychosomatic	64.6	15.59	59.6	9.15	1.873	0.08
ADHD index	73.6	7.13	58.0	7.06	6.983	0.000***
Conner global index (CGI)	77.0	7.32	60.9	7.02	7.563	0.000***
DSM_ Iv inattention	73.3	9.46	56.4	7.97	7.285	0.000***
DSM_ Iv hyperactive impulsive	75.9	7.57	62.0	11.59	5.355	0.000***
DSM_ Iv total	76.3	7.04	59.6	8.65	7.572	0.000***

* = significant; ** = highly significant; *** = very high significant

Table 4: Male patients' response to medication according to Conner's teacher rating scale.

Conner's teachers rating scale subscales	Premedicated male		Medicated male		Paired- T- value	P -value
	mean	S.D	mean	S.D		
Oppositional	65.7	12.64	60.1	9.61	1.702	0.1
Inattention	62.2	8.30	52.2	4.33	4.955	0.001***
Hyperactivity	67.3	9.12	55.3	6.00	3.884	0.003**
Anxious shy	75.1	10.94	67.8	9.08	2.226	0.05*
Perfectionism	67.4	12.13	66.9	7.99	0.115	0.9
Social problem	63.6	13.38	56.7	8.87	1.663	0.1
ADHD index	65.4	10.05	54.2	5.98	3.958	0.003**
Conner global index (CGI)	69.5	11.22	56.5	7.46	4.804	0.001***
DSM_ Iv inattention	61.0	7.86	51.0	4.54	3.527	0.005**
DSM_ Iv hyperactive impulsive	68.4	11.21	54.3	6.60	5.085	0.000***
DSM_ Iv total	66.3	10.07	53.4	4.84	4.391	0.001***

* = significant; ** = highly significant; *** = very high significant

Table 5: Female patients' response to medication according to Conner's parents rating scale.

Conner's parent rating scale subscales	Premedicated female		Medicated female		Paired- T- value	P -value
	mean	S.D	mean	S.D		
Oppositional	73.8	11.37	61.4	13.39	3.546	0.006**
Inattention	79.0	8.44	64.7	11.43	3.096	0.01**
Hyperactivity	81.1	9.84	66.3	11.00	3.240	0.01**
Anxious shy	64.5	18.85	59.8	10.34	0.847	0.4
Perfectionism	57.4	14.6	55.4	8.03	0.887	0.3
Social problem	79.8	14.36	72.9	16.08	2.754	0.02*
Psychosomatic	58.3	9.77	59.2	13.45	-0.227	0.8
ADHD index	82.5	5.72	63.7	9.27	4.887	0.001***
Conner global index (CGI)	85.8	6.76	67.4	9.53	4.968	0.001***
DSM_ Iv inattention	82.7	8.53	62.8	8.80	5.457	0.000***
DSM_ Iv hyperactive impulsive	83.3	8.44	63.3	8.93	5.246	0.001***
DSM_ Iv total	84.1	6.50	64.6	8.90	50785	0.000***

* = significant; ** = highly significant; *** = very high significant

Table 6: Female patient's response to medication according to Conner's teacher rating scale.

Conner's teacher rating scale subscales	Premedicated female		Medicated female		Paired- T- value	P -value
	mean	S.D	mean	S.D		
Oppositional	83.7	12.50	63.5	9.94	1.953	0.1
Inattention	68.2	9.21	61.5	9.88	1.676	0.1
Hyperactivity	88.0	4.00	68.0	11.88	2.828	0.6
Anxious shy	83.0	8.75	71.5	21.91	1.703	0.2
Perfectionism	71.0	15.79	59.0	11.48	1.782	0.2
Social problem	67.0	8.16	59.2	9.17	0.979	0.4
ADHD index	85.0	4.69	67.7	4.99	3.618	0.03*
Conner global index (CGI)	90.0	0.000	62.5	17.99	3.057	0.05*
DSM_ Iv inattention	76.0	5.35	61.7	11.70	3.105	0.05*
DSM_ Iv hyperactive impulsive	86.7	3.94	70.2	10.04	2.747	0.07
DSM_ Iv total	85.5	5.80	67.7	8.48	3.412	0.04*

* = significant

Table 7: Follow-up severity of ADHD symptoms in the medicated studied sample in relation to gender using Conner's parent rating scale.

Conner's parent rating scale (FU) subscales	Total		Gender				T-value	P-value
			Male		Female			
	mean	S.D	mean	S.D	mean	S.D		
Oppositional	59.5	10.71	58.6	9.37	61.4	13.39	0.683	0.5
Inattentive	59.5	9.80	57.0	8.07	64.7	11.43	2.167	0.03*
Hyperactivity	63.3	9.90	61.8	9.34	66.3	11.00	1.169	0.2
Anxious shy	59.1	9.52	58.7	9.36	59.8	10.34	0.292	0.7
Perfectionism	53.6	7.41	52.8	7.07	55.4	8.03	0.930	0.3
Social problem	67.5	14.24	65.0	12.82	72.9	16.08	1.477	0.1
Psychosomatic	59.5	10.50	59.6	9.15	59.2	13.45	-0.102	0.9
ADHD index	59.8	8.12	58.0	7.06	63.27	9.27	1.898	0.05*
Conner global index (CGI)	63.0	8.63	60.9	7.01	67.4	9.53	2.128	0.04*
DSM_ IV inattention	58.4	8.67	56.4	7.97	62.8	8.80	2.027	0.05*
DSM_ IV hyperactive impulsive	62.4	10.75	62.0	11.59	63.3	8.93	0.31	0.7
DSM_ IV total	61.2	8.93	59.6	8.65	64.6	8.90	1.485	0.1

* = significant

Table 8: Follow-up severity of ADHD symptoms of the medicated studied sample in relation to gender using Conner's teacher rating scale.

Conner's teacher rating scale (FU) subscales	total		Gender				T-value	P-value
			Male		Female			
	mean	S.D	mean	S.D	mean	S.D		
Oppositional	61.0	9.55	60.1	9.61	63.5	9.94	0.602	0.5
Inattention	54.7	7.24	52.2	4.33	61.5	9.88	2.625	0.02*
Hyperactivity	58.7	9.50	55.3	6.00	68.0	11.88	2.807	0.01**
Anxious shy	68.8	12.81	67.8	9.08	71.5	21.91	0.487	0.6
Perfectionism	64.8	9.34	66.9	7.99	59.0	11.48	-1.158	0.1
Social problem	57.4	8.77	56.7	8.87	59.2	9.17	0.483	0.6
ADHD index	57.8	8.39	54.1	5.98	67.7	4.99	4.029	0.001***
Conner global index (CGI)	58.1	10.81	56.4	7.46	62.5	17.99	0.955	0.3
DSM_ Iv inattention	54.5	8.05	51.9	4.54	61.7	11.70	2.445	0.02*
DSM_ Iv hyperactive impulsive	58.5	10.33	54.4	6.60	70.2	10.04	3.630	0.003**
DSM_ Iv total	57.2	8.82	53.4	4.84	67.7	8.84	4.101	0.001***

* = significant; ** = highly significant; *** = very high significant

Table 9: Follow-up attention profile of the medicated patients as scored using vigil test in relation to gender.

Vigil scores (fu)	Total		Gender				T-value	P-value
			Male		Female			
	Mean	S.D	Mean	S.D	Mean	S.D		
Total omission	13.3	13.01	11.1	9.49	18.1	18.15	1.422	0.1
Total commission	10.2	7.22	11.1	6.59	8.3	8.34	-1.030	0.3
Total error	23.5	16.94	22.2	14.08	26.4	22.50	0.639	0.5
Total average delay	585.1	65.00	568.9	53.93	619.2	75.75	2.124	0.04*

* = significant

Table 10: Responder/Non responders in the medicated studied sample in relation to gender.

Responder / non responder		Gender				T-value	P-value
		Male		Female			
		N	%	N	%		
Fu parent ADHA index	Non responder	2	9.5	5	50	10.064	0.03*
	Responder	13	90.4	5	50		
Fu parent Global index	Non responder	6	28.6	5	50	3.069	0.6
	Responder	15	71.4	5	50		
Fu parent DSM –IV inattention	Non responder	2	9.6	3	30	6.022	0.1
	Responder	19	90.4	7	70		
Fu parent DSM -IV hyperactive impulsive	Non responder	8	38.1	4	40	6.136	0.2
	Responder	13	61.9	6	60		
Fu parent DSM – IV total	Non responder	8	38.1	5	50	3.657	0.4
	Responder	13	61.9	5	50		

* = significant

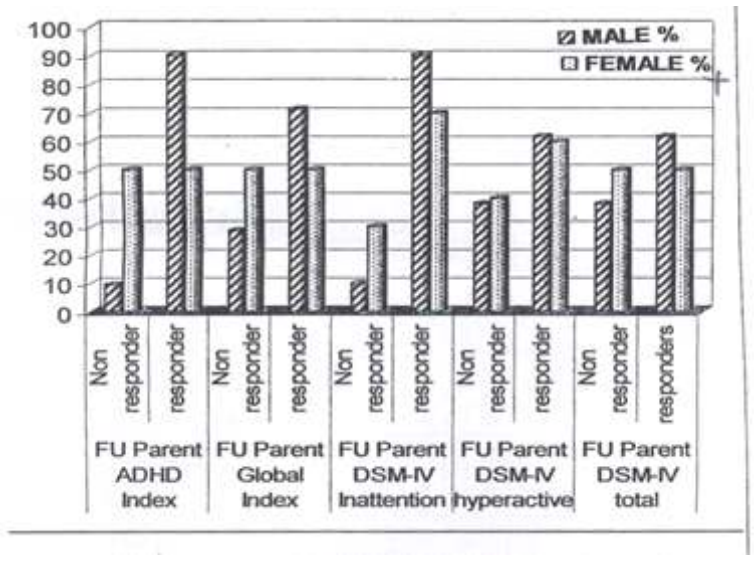

Fig. 1: Responder/Non responders in the medicated studied sample in relation to gender.

Table 11: Dose of response of methylphenidate in relation to gender.

Dose of response (mg/kg)	Min. dose	Max. dose	Mean dose	S.D	T-value	P-value
Female	0.5	1.0	0.76	0.16	0.055	0.9
Male	0.6	1.0	0.75	0.12		

Table 12: Lists the stimulant side effect profile or the medicated studied sample in relation to gender.

Side effect profile of the stimulant (methylphenidate)		Total		Gender				X2	P-value
				Female		Male			
		N	%	N	%	N	%		
Insomnia	Absent	28	90.3	9	90	19	90.5	0.467	0.6
	Temporary	2	6.5	1	10	1	4.8		
	Persistent	1	3.2	0	0	1	4.8		
Nightmares	Absent	29	93.5	10	100	19	90.5	1.018	0.6
	Temporary	1	3.2	0	0	1	4.8		
	Persistent	1	3.2	0	0	1	4.8		
Stare a lot	Absent	18	58.1	5	50	13	61.9	1.662	0.4
	Temporary	8	25.8	4	40	4	19		
	Persistent	5	16.1	1	10	4	19		
Talk less	Absent	25	80	6	60	19	90.5	5.886	0.05*
	Temporary	2	6.5	2	20	0	0		
	Persistent	4	12.9	2	20	2	9.5		
Uninterested in others	Absent	25	80.6	5	50	20	95.2	9.263	0.01**
	Temporary	2	6.5	2	20	0	0		
	Persistent	4	12.9	3	30	1	4.8		
Decrease appetite	Absent	10	32.3	3	30	7	33	0.034	0.9
	Temporary	12	38.7	4	40	8	38.1		
	Persistent	9	29	3	30	6	28.6		
Irritable	Absent	20	64.5	7	70	13	61.9	3.314	0.2
	Temporary	6	19.4	3	30	3	14.3		
	Persistent	5	16.1	0	0	5	23.8		
Stomach	Absent	16	51.6	4	40	12	57.1	1.255	0.5
	Temporary	9	29	3	30	6	28.6		
	Persistent	6	19.4	3	30	3	14.3		

Headache	Absent	24	77.4	7	70	17	81	1.827	0.4
	Temporary	4	12.9	1	10	3	14.3		
	Persistent	3	9.7	2	20	1	4.8		
Drowsiness	Absent	27	87.1	9	90	18	85.7	1.255	0.5
	Temporary	2	6.5	0	0	2	9.5		
	Persistent	2	6.5	1	10	1	4.8		
Sad	Absent	24	77.4	6	60	18	85.7	3.924	0.1
	Temporary	3	9.7	1	10	2	9.5		
	Persistent	4	12.9	3	30	1	4.8		
Prone to cry	Absent	22	71	7	70	15	71.4	3.668	0.2
	Temporary	4	12.9	0	0	4	19		
	Persistent	5	16.1	3	30	2	9.5		
Anxious	Absent	28	90.3	10	100	18	85.7	1.582	0.4
	Temporary	2	6.5	0	0	2	9.5		
	Persistent	1	3.2	0	0	1	4.8		
Bites finger	Absent	31	100	10	100	21	100		
	Temporary	0	0	0	0	0	0		
	Persistent	0	0	0	0	0	0		
Euphoria	Absent	30	96.8	10	100	20	95.2	0.492	0.7
	Temporary	0	0	0	0	0	0		
	Persistent	1	3.2	0	0	1	4.8		
Dizziness	Absent	29	93.5	9	90	20	95.2	0.308	0.5
	Temporary	0	0	0	0	0	0		
	Persistent	2	6.5	1	10	1	4.8		
Tics or involuntary movement	Absent	31	100	10	100	21	100		

DISCUSSION

Majewska (1992) indicated influence of sex hormones on physiology and development of males and females by regulating synthesis, enzymatic activity, neurotransmitters, receptors and effectors of neuronal functions. He confirmed potent effect of steroids in modulated GABA (A) receptors that controls chloride conductance in neurons which is a target for many psychotropic. The brain dopaminergic systems are sexually dimorphic (Konrad *et al*., 1991) where receptors for progesterone and estrogens exist (McEwen and Parsons, 1982). Sex differences in the cholinergic systems (Miller, 1983 and Luine, 1985), Serotoninergic activities (Arato *et al.,* 1991), glutamatergic-mediated neuronal excitability (Smith, 1989), and ? -endorphin or expression of pro-enkephalin m-RNA (Romano *et al*., 1990) with possible interactions in brain regions thereby influencing neurophysiology and psychopathology. The presence of y chromosome has made human male brain more vulnerable to neurodevelopmental problems than females and more proneness to prenatal complications, e.g. anoxia, toxemia, hemorrhage, and prematurity (McClure, 2000). He also pointed out to more liability of males to have obstetric complications as they more oxygen needs for their more lateralized brain activities than new born girls. These inferences might increase the incidence of developmental disorders in male brains among which is ADHD as well as specific reading and language delays, clumsiness etc. Backevalier and Hagger (1991) have shown that androgens may retard growth of cerebral cortex, slow its maturation, and impair learning.

Historical viewing of ADHD through all those particular set of lenses in the process of examining larger numbers of clinic-referred boys of ADHD has triggered the existing work. By adhering to meticulous and objective criteria of the examined sample of the 31 candidates with diagnosed attention problems, there were few differences. The non-random sampling of children with ADHD may be responsible in part for the later proved results. The assumption that many girls with ADHD are going undiagnosed and untreated as reported by Epstein et al. (1991) might stand against identifying detectable differences. ADD girls with less hyperactivity symptoms, no wonder, go unnoticed though are less attentive, even by teachers at schools. A strong male-biased referral patterns in schools and clinics across the countries were also reasoned by Quinn and Wigal (2004) in their struggle for appropriate help of ADHD subjects.

The clinical samples only capture those who have been referred for treatment, and are typically aggressive, hyperactive, impulsive children, who are predominantly boys, along with a less number of girls who exhibit similar patterns. The role of school psychologists, and pediatricians is crucial to represent the true prevalence and characteristics of ADHD subjects avoiding that bias, and therefore more early referrals, and less severe cases inclusions, and be diagnosed in the community settings. The role of pediatric in early detection and rational management including different pharmacological management, behavioral intervention, continuous assessment in follow-up and family guidance and evaluation of the outcome with the inter-referal and cooperative with the child psychiatric and psychologist. Parents and teachers alike continue to behave as if the behavioral and academic functioning of boys should receive a higher priority than that of girls.

Although, ADHD was labeled as "the diagnosis of the decade" for almost a full ten years (Todd, 2000), it remains to be better studied and reviewed from all of its aspects with good clinical methods. Gender weighed prevalences of ADHD, its different risk factors, postulated under pinnings need to be more studied. The limited clinically significant differences in treatment responses may be more evident if determined in adolescents and adults with same problem of ADHD where the modulation of biological effects of maturation, sex hormones, sex-role, expectations and social patterns are to be more clearly considered. Biederman et al. (2002) found that males and females manifested similar degree of impairment in social interactions, peer rejection and low self-esteem in their non-referred clinical sample. Girls suffered from major depressive episodes and are receiving medications for it more than boys because of their wider affection of lower self-esteem in comparison to boys as a consequence of ADD as noted by Quinn and Wigal (2004), Kennedy and Gorwood (2012) and Lam (2012).

Yet, since the above mentioned gender differences were less apparent than expected in the absence of gender-by-ADHD interaction, they can be attributed to many confounding factors than modification of ADHD effect by gender. The long-term outcomes of girls and boys may yield more statistically significant gender-by-ADHD interactions than it was anticipated in the findings of the present work. In the light of what were presented above, and all the previously mentioned studies, the need for more work to reduce the large gap in ADHD in pediatric practice and further elucidate the factors which could result in gender based referral bias and unfavorable responses, is to be recommended. To date, there have been no prospective studies are in the way to help mitigating the differences related to gender in ADHD subjects. A larger body of research examining the potential benefits of CNS stimulants, their risks, and dosages in ADHD subjects may objectively validate their different efficacy and safety, especially larger double-blind and single-blind studies with placebo controls, case reports, and open studies.

Supplementation of these studies with behavioral treatments may lead to more stable improvement in ADHD and more adherence to drug treatments. Nevertheless, the existing work offers distinct advantages of the use of CNS stimulants, their unlikely evoked side effects. Real world practice of treating ADHD cases co-morbid with other physical and mental illnesses represent other challenges of the therapeutic responses, medications interactions and variability in dose titrations. Clinicians may hesitate to prescribe CNS stimulants for ADHD patients with co-morbid diagnoses though the current guidelines from the American Academy of Pediatrics that recommend CNS stimulants and behavior-modifications as first-line therapy for the management of ADHD (APA, 2013).

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